ICAHN Construction Toolkit

Section Two – Relevant Publications

Articles and Additional Reading List

2014 FGI Sustainable Design

ASHE-FGI Monograph Room Ventilation

CDC Developing a Water Management Program to Reduce Legionella Growth and Spread in Buildings

CDC Vaccine Storage and Handling Toolkit 2019

IHI Evidence Based Design White Paper 2009

National Academies of Sciences. Engineering, and Medicine 2019. Management of Legionella in Water Systems.

NIOSH Selecting, Evaluating, and Using Sharps Disposal Containers

Role of the Physical Environment in the 21st Century Hospital

Sustainable Design Guidelines for Hospitals and Outpatient Facilities

A White Paper

FGI
FACILITY GUIDELINES INSTITUTE

February 5, 2014

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This publication accompanies the 2014 edition of the *Guidelines for Design and Construction of Health Care Facilities*.

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Purpose of This Document

Many organizations have developed or are in the process of developing sustainable building rating systems, standards, or building codes that apply to the health care sector. However, few of these standards include substantial input from health care facility administrators, clinicians, and design professionals who specialize in health care projects. The cyclical revision process for the Facility Guidelines Institute's *Guidelines for Design and Construction of Hospitals and Outpatient Facilities* offers an opportunity to develop minimum guidelines for sustainable design of health care environments that can be vetted by members of the Health Guideline Revision Committee who are stakeholders in the design of acute and ambulatory health care facilities. The guidelines in this paper are intended to help facilities achieve organizational sustainability goals while balancing the needs of patients, visitors, and staff with the fiscal pressures currently affecting the health care industry.

These minimum guidelines, which are intended to apply to both new construction and renovation of existing facilities, will be referenced as a white paper in the 2014 edition of the FGI *Guidelines for Design and Construction of Hospitals and Outpatient Facilities*. Until the white paper is used to inform proposals for the 2018 *Guidelines* revision cycle, it will be posted on the FGI website at www.fgiguidelines.org/resources for reference and free download.

Note: The content of this white paper has been written to correlate with the content of the 2014 edition of the FGI *Guidelines for Design and Construction of Hospitals and Outpatient Facilities* and attempts to avoid repeating information found in the *Guidelines*. One example of this is environment of care features, which are discussed in some detail in Chapter 1.2 of the 2014 edition.

An excerpt from the* Health Guidelines Revision Committee Operations Manual*:

Interim White Papers
White papers are reports prepared at the direction of the HGRC Steering Committee. White papers are usually topics of interest to the health care community and used to provide additional information on a topic in the *Guidelines* (e.g., the PHAMA white paper written during the 2010 revision cycle) or recommendations for changing the content of the *Guidelines* (e.g., the medical oncology white paper prepared during the 2010 cycle). In the latter case, the white paper will be retired once the content has become part of the Guidelines document.

Contents

Introduction

1 Building Site

- Mandatory Requirements
- Performance Option
- Prescriptive Option

2 Energy Use

- Mandatory Requirements
- Performance Option
- Prescriptive Option

3 Indoor Environmental Quality

- Mandatory Requirements

4 Water Supply

- Mandatory Requirements
- Performance Option
- Prescriptive Option

5 Airborne Emissions, Effluent, and Pollutant Controls

- Mandatory Requirements

6 Materials and Resources

- Mandatory Requirements
- Performance Option
- Prescriptive Option

7 Waste

- Mandatory Requirements

Sustainable Design Guidelines for Hospitals and Outpatient Facilities

A green building, also known as a sustainable or high-performance building, is an environmentally sustainable building that is designed, constructed, and operated to minimize its total environmental impacts. The green building guidelines in this document are applicable to health care facilities (specifically acute care hospitals and ambulatory care facilities) and balance the needs of patients, visitors, and staff with the fiscal pressures in the health care industry and organizational sustainability goals.

This document covers the following specific aspects of sustainable design:

1. Building site
2. Energy use
3. Indoor environmental quality
4. Water supply
5. Airborne emissions, effluent, and pollutant controls
6. Materials and resources
7. Waste

The sections are designed to present mandatory requirements along with two potential paths for further action that allow the user to choose the appropriate path for a specific design and construction project:

(1) **Mandatory requirements** are items that must be completed for compliance.

(2) The **performance path** leads to design and construction of a building intended to achieve a specified level of *performance* based on a benchmark minimum and a process of comparison. The goal of the performance approach is to allow maximum flexibility to support achievement of a desired goal in a way that coordinates better with the overall needs and strategies of the health care organization.

(3) The **prescriptive path** is intended to achieve approximately the same or better result as the performance path, but by complying with a series of *prescriptive* measures rather than using a process to determine how to achieve the desired outcome. The prescriptive path has little flexibility, unless an exception is noted, and users are expected to comply with each specific requirement.

A facility can comply with these guidelines by meeting the mandatory requirements and the requirements for either the performance path or the prescriptive path for each of the eight sections. If the design of a facility follows the performance path, this can be demonstrated with calculations and documentation certified by a licensed professional that verify achievement of the desired level of performance. The benchmark used to calculate the improved performance outcomes of a building shall be clearly outlined in the documentation.

References: The following documents were used for reference in preparation of these guidelines:

- ASHRAE 62.1-2013: *Ventilation for Acceptable Indoor Air Quality*
- ANSI/ASHRAE/IES 90.1-2010: *Energy Standard for Buildings Except Low-Rise Residential Buildings*
- ANSI/ASHRAE/ASHE 170-2013: *Ventilation of Health Care Facilities*

- ASHRAE *Advanced Energy Design Guide for Large Hospitals*
- ASHRAE *Advanced Energy Design Guide for Small Hospitals and Healthcare Facilities*
- California Green Building Code, Hospitals section
- DOE-2, DOE Building Energy Codes Program COMcheck™ tool
- Green Globes® CIEB-HC (Continual Improvement for Existing Buildings – Healthcare)
- Green Globes® NC (New Construction)
- Green Guide for Health Care™
- LEED® for Healthcare
- SPC 189.3P: Proposed Standard for the *Design, Construction and Operation of Sustainable High-Performance Health Care Facilities*

1 BUILDING SITE

In addition to the mandatory requirements, either the performance option (Section 1.2) or the prescriptive option (Section 1.3) shall be implemented.

1.1 Mandatory Requirements

1.1.1 Erosion and sedimentation control plan. An erosion and sedimentation control (ESC) plan shall be prepared for all construction activities associated with the project.

1.1.1.1 The ESC plan shall conform to the erosion and sedimentation requirements of the 2003 EPA Construction General Permit (CGP) *or* local erosion and sedimentation control standards and codes, whichever are more stringent.

1.1.1.2 The plan shall describe the measures to be implemented to accomplish the following objectives:

a. Prevent loss of soil during construction caused by storm water runoff and/or wind erosion, including protecting topsoil by stockpiling for reuse.

b. Prevent sedimentation of storm sewer or receiving streams.

c. Prevent pollution of the air with dust and particulate matter.

- The CGP shall outline the provisions necessary to comply with Phase I and Phase II of the National Pollutant Discharge Elimination System (NPDES) program.
- Although the CGP only applies to construction sites greater than one acre, the requirements shall be applied to all projects.

Information about the EPA CGP (including a copy of the document) is available at http://cfpub.epa.gov/npdes/stormwater/cgp.cfm.

1.1.2 Site utilization

1.1.2.1 A site access plan shall be completed to minimize site disruption associated with the project's construction phase.

Aspects of site location such as accessibility to patients and proximity to public transportation should be reviewed in evaluating the site utilization plan. The existing built environment should be assessed as part of the site access plan.

1.1.2.2 Temporary construction facilities, designated staging areas, access roads, and construction parking shall be planned within new building and paving footprints to minimize site disturbance.

1.1.2.3 Measures shall be established to protect priority sensitive areas of the site, including prohibiting staging, stockpiling and soil compaction.

1.1.2.4 Disturbance to protected wetlands and habitats of endangered species shall be prevented.

1.1.2.5 Storage shall be provided for fuels, and measures shall be established for handling fuels, to prevent spills and discharge into waterways.

1.1.3 Brownfield remediation. If the site is a brownfield:

1.1.3.1 A Phase 1 environmental site assessment shall be performed as determined by a local, state, or federal agency. See ASTM E1527-05: *Standard Practice for Environmental Site Assessments: Phase I Environmental Site Assessment Process*.

1.1.3.2 Documentation for remediation of the site shall be completed to the residential level as defined in the EPA Regional Screening Levels (RSL) for Chemical Contaminants at Superfund Sites. (www.epa.gov/region9/superfund/prg).

1.2 Performance Option

1.2.1 Parking capacity. A written plan shall address the following:

1.2.1.1 A combination of programs, such as telemedicine, mailed prescriptions, carpooling, and coordination with local mass transit (including shuttles), to reduce vehicular traffic and encourage pedestrian and cyclist traffic to the site

1.2.1.2 The anticipated number of parking spaces required and the number of spaces reduced based on the services to be provided as outlined in the functional program.

1.3 Prescriptive Option

1.3.1 Parking capacity. Parking capacity shall be sized to meet, but not exceed, minimum local zoning requirements *or* health department regulatory authority for licensing requirements, whichever is the overriding requirement.

Parking needs may vary according to the needs of the functional program and the location of the facility (urban, suburban, or rural sites). Consideration should be given to the following:

Designate 5 percent of a facility's total parking spaces as preferred parking for carpools or vanpools.

Provide electric vehicle charging stations at 1 percent of new parking spaces.

2 ENERGY USE

In addition to the mandatory requirements, either the performance option (Section 2.2) or the prescriptive option (Section 2.3) shall be implemented.

2.1 Mandatory Requirements

2.1.1 Measurement and verification plan

2.1.1.1 A measurement and verification (M&V) plan shall be developed and implemented consistent with one of the following options in the *International Performance Measurement and Verification Protocol* (IPMVP®), Volume III: Applications, Part I: Concepts and Options for Determining Energy Savings in New Construction:

a. Option D: Whole Building Calibrated Simulation

b. Option B: ECM (Energy Conservation Measure) Isolation

The January 2006 edition of IPMVP can be found at www.evo-world.org/index.php?option=com_content&view=article&id=272&Itemid=504&lang=en.

2.1.1.2 At minimum, metering that provides consistent and reliable data shall be provided for the following electrical and mechanical systems (as applicable to the scope of the project):

a. Gas

- Main gas line to the site
- Each natural gas boiler
- Kitchen gas

b. Electricity

- Consumption (kWh) and demand (kW) for each source of electricity to the building
- Output from each automatic transfer switch
- Energy consumption for pump and fan for each motor with a variable frequency drive (VFD)

c. Thermal energy

- All steam purchased from off-site sources, including recovered condensate
- Steam produced by each steam boiler
- Hot water produced by each hot water boiler
- Chilled water output for each water chiller

d. Energy source (fuel oil, propane, etc.) for each device listed

- Each steam or hot water boiler
- Each generator not used for emergency purposes only

2.1.2 Interior lighting sensors and controls

2.1.2.1 Occupancy light sensor controls

a. The following spaces shall be equipped with occupant sensor(s) that automatically turn lighting off within 30 minutes of all occupants leaving the space but allow "manual off" control:

- Offices 250 sq. ft. (25 m2) or smaller
- Classrooms of any size
- Lecture, training, or vocational rooms of less than 1,000 sq. ft. (100 m2)
- Multipurpose rooms of less than 1,000 sq. ft. (100 m2)
- Conference rooms and meeting rooms less than 1,000 sq. ft. (100 m2)
- Meeting centers
- Storage, including environmental services room, clean workroom or clean supply room, soiled workroom or holding room, equipment and supply storage rooms, and furniture storage areas.
- Staff lounge facilities or changing areas
- Small toilet rooms
- Examination rooms (except those where patient may lie motionless for observation for an extended period)

- Mechanical, electrical, control, and IT rooms. In some large mechanical/electrical spaces, two levels of lighting shall be provided, only one of which is connected to the motion sensor.

  This requirement is to accommodate an employee who may be working steadily in the space without moving and thus will not trigger a motion detector.

b. All occupancy sensor controls shall be either "manual on" or bi-level "automatic on" and shall be programmed to a low light level combined with multi-level circuitry and "manual on" switching for higher light levels.

c. Where such occupancy sensors are installed in an area with daylight and daylighting controls are used, the occupancy sensors shall work in conjunction with the daylighting controls.

2.1.2.2 Multilevel lighting controls

a. The general lighting of any enclosed space 100 sq. ft. or larger shall have multilevel lighting controls.

b. Multilevel controls shall have at least one control step that is between 30 and 70 percent of design lighting power and allows the power of all lights to be manually turned off.

2.1.2.3 Automatic controls for lighting in daylight zones. Lighting in all daylight zones where the combined daylight zone per enclosed space is greater than 250 square feet (23.22m2), including daylight zones under skylights and daylight zones adjacent to vertical fenestration, shall be provided with controls that automatically reduce lighting power in response to available daylight by *one* of the following methods:

a. Continuous daylight dimming, or

b. A combination of stepped switching and daylight-sensing automatic controls, which are capable of incrementally reducing the light level in steps and turning lights off automatically

Note: Perimeter spaces in which patient care is delivered, such as exam rooms, shall have overrides to these lighting controls.

2.1.2.4 Exterior lighting systems. Exterior lighting systems shall comply with the following:

a. ANSI/ASHRAE/IES Standard 90.1: *Energy Standard for Buildings Except Low-Rise Residential Buildings*

b. Sections 5.3.3.2 and 5.3.3.3 of ANSI/ASHRAE/USGBC/IES 189.1-2011: *Standard for the Design of High-Performance, Green Buildings Except Low-Rise Residential Buildings*

Exceptions:

- Specialized signal, directional, and marker lighting associated with site wayfinding and transportation
- Advertising signage or directional signage
- Lighting integral to equipment or instrumentation and installed by its manufacturer

- Lighting that is in use for no more than 60 continuous days and is not re-installed any sooner than 60 days after being uninstalled
- Lighting for material handling, transportation areas, and associated storage areas
- Roadway lighting required by regulatory authorities

c. All permanently installed outdoor luminaires employing lamps rated over 100 watts shall have a lamp efficacy of at least 60 lumens per watt.

2.1.3 Controls for outdoor lighting

2.1.3.1 Area lighting. All permanently installed outdoor lighting, including lighting of building facades, parking lots, canopies, and pick-up/drop-off zones, shall be controlled by a photo-control or astronomical time switch that automatically turns off the outdoor lighting when daylight is available.

Exception: Lighting for steps or stairs that require illumination during daylight hours

Exception: Lighting for emergency department entrances and exits

2.1.3.2 Garage lighting. Two levels of lighting shall be provided in parking garages.

a. Thirty percent of the total fixtures shall be controlled by a daylight sensor.

b. The balance of the fixtures shall be controlled by a combination of daylight sensor and occupancy sensor.

2.2 Performance Option

Buildings shall be designed to achieve an ENERGY STAR® rating of at least 75, modeled in accordance with Appendix G of ASHRAE 90.1-2010 as modified by the design assumptions in Appendix 1, using the most current version of DOE-2 (www.doe2.com), EnergyPlus (www.energyplus.gov), eQuest (www.doe2.com/equest) software, or other industry-accepted software.

Use EPA Target Finder to estimate energy use for a design project. Target Finder calculates a rating based on a comparison of projected energy use with that of facilities of similar size in the ENERGY STAR database. See www.energystar.gov/index.cfm?c=evaluate_performance.bus_portfoliomanager.

Note: Notwithstanding this requirement, in no circumstances shall building energy systems be designed to use more energy than allowed by local codes or that conflicts with the needs of the care population being served.

2.3 Prescriptive Option

Buildings shall be designed according to the following climate-specific design strategies that are prescriptive and do not require modeling to demonstrate energy savings:

2.3.1 Roofing materials

2.1.3.1 For buildings of at least 90,000 square feet, roofing shall be provided based on the climate zone as recommended in the American Society for Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) *Advanced Energy Design Guide for Large Hospitals*. Components addressed in the recommendations include insulation and the solar reflectance index (SRI).

2.1.3.2 For buildings of 90,000 square feet or less, roofing shall be provided based on the climate zone as recommended in the ASHRAE *Advanced Energy Design Guide for Small Hospitals and Healthcare Facilities*. Components addressed in the recommendations include insulation and the solar reflectance index (SRI).

2.3.2 Joints and other openings

2.3.2.1 Joints and other openings in the building envelope that are potential sources of air leakage shall be caulked, gasketed, weather-stripped, or otherwise sealed to limit infiltration and exfiltration.

2.3.2.2 Before the building is occupied, the building envelope shall be tested for thermal and airflow leakage and any deficiencies discovered shall be corrected as part of the envelope commissioning process.

2.3.3 Variable speed drives. Individual motors serving variable flow systems and having a motor speed exceeding 3 horsepower shall have controls and/or devices (such as variable speed control) that will result in pump motor demand of no more than 30 percent of design wattage at 50 percent of design flow.

2.3.4 Hydronic variable flow systems. HVAC chilled and hot water pumping shall be designed for variable fluid flow and shall be capable of reducing pump flow rates to no more than the larger of the following:

2.3.4.1 50 percent or less of the design flow rate, *or*

2.3.4.2 The minimum flow required by the equipment manufacturer for the proper operation of equipment served by the system.

2.3.5 Pipe insulation. Pipe insulation shall comply with the requirements of the latest edition of ASHRAE 90.1.

2.3.6 Economizers. Systems shall have air-side or water-side economizers where required for the facility's climate zone in ASHRAE 90.1.

2.3.7 Heat recovery. Air-side heat recovery shall be provided in accordance with the ASHRAE *Advanced Energy Design Guide for Large Hospitals*.

2.3.8 Building commissioning. Building commissioning shall be performed in accordance with the American Society for Healthcare Engineering (ASHE) *Health Facility Commissioning Guidelines*.

2.3.9 Appliance efficiency. All equipment and appliances shall be Energy Star-labeled if Energy Star is applicable to that equipment or appliance.

2.3.10 Equipment efficiency. Equipment shall comply with the provisions for cooling and heating equipment efficiencies in the ASHRAE *Advanced Energy Design Guide for Large Hospitals*.

2.3.11Lighting power density. Lighting shall comply with the climate zone-specific targets for lighting power density in the ASHRAE *Advanced Energy Design Guide for Large Hospitals*.

3 INDOOR ENVIRONMENTAL QUALITY

Note: There is no prescriptive or performance option for this criterion.

3.1 Mandatory Requirements

3.1.1 HVAC system design. HVAC systems shall be designed and installed using the DOE Building Energy Codes Program COMcheck™ tool (www.energycodes.gov) or a similar program or a life cycle analysis that determines how much energy the system will use.

3.1.2 Ventilation rates

3.1.2.1 Ventilation rates shall meet the minimum requirements of the latest edition of one of the following, whichever is more stringent and applicable to the building type:

a. Relevant local licensing requirement for ventilation

b. ASHRAE 62.1: *Ventilation for Acceptable Indoor Air Quality*

c. ANSI/ASHRAE/ASHE 170: *Ventilation of Health Care Facilities*

3.1.2.2 Mechanical ventilation systems shall be designed using the ventilation rate procedure in ASHRAE 62.1 *or* ventilation requirements of the applicable local code, whichever is more stringent.

a. Mechanical ventilation systems shall be designed so spaces can be operated with a reduced airflow when they are unoccupied but required differential pressures, temperature, and humidity control can still be maintained.

b. Mechanical ventilation systems shall have sensors and monitoring to assure adequate ventilation for minimal temperature and moisture control.

c. Mechanical ventilation systems shall be able to revert to occupied status in a reasonable time frame.

3.1.3 Air distribution system duct sealing for leakage control. Duct sealing and leakage testing shall be performed and comply with the provisions for same in the ASHRAE *Advanced Energy Design Guide for Large Hospitals*.

3.1.4 Dampers for air supply and exhaust equipment. Outdoor air supply and exhaust/relief equipment shall be installed with dampers that automatically close upon fan shutdown.

3.1.5 Indoor air quality. Buildings shall comply with or be below requirements in sections 6 through 8 of ANSI/ASHRAE/ASHE Standard 170.

3.1.5.1 Outdoor air delivery monitoring. A permanently mounted device to measure direct total outdoor airflow shall be provided to measure the system minimum outdoor airflow rate.

a. The device shall be capable of measuring flow within ±15 percent of the minimum outdoor airflow rate.

b. The device shall be capable of being used to send an alarm to the building operator or a signal to a building central monitoring system when flow rates are out of compliance.

Exception: Constant volume air supply systems that use a damper position feedback system are not required to have a direct total outdoor airflow measurement device.

3.1.5.2 Environmental tobacco smoke

a. Signage stating no smoking is allowed in the building shall be posted within 10 feet

(3 m) of each building entrance.

b. Any exterior designated smoking areas shall be located a minimum of 25 feet (7.5 m) from building entrances, outdoor air intakes, and operable windows.

3.1.5.3 Building entrances. Main entrances and service entrances shall employ an entry mat system that reduces the intrusion of particulate matter into the interior environment.

3.1.5.4 VOC emission requirements for adhesives and sealant, paints, coatings, and primers, floor covering materials, patient room furniture and ceiling and wall systems

a. Acceptable emissions levels shall be determined in accordance with the California Department of Public Health *Standard Method for the Testing and Evaluation of Volatile Organic Chemical Emissions from Indoor Sources Using Environmental Chambers*, Version 1.1, and shall meet the limit requirements therein. The determination of emissions shall be based on:

> See www.calrecycle.ca.gov/greenbuilding/specs/section01350 for the CDPH *Standard Method* cited.

- Minimum room volume, clear floor area, natural light, and window area to floor area ratio of a private patient room as prescribed in the FGI *Guidelines for Design and Construction of Hospitals and Outpatient Facilities*
- Provision of outside air at a rate of 2.0 air changes per hour as prescribed in Table 7-1 of ANSI/ASHRAE/ASHE 170: *Ventilation of Health Care Facilities*

b. Office furniture systems and seating installed prior to occupancy shall be tested in accordance with, and shall not exceed the VOC limit requirements in Section 7.6.2 of ANSI/BIFMA e3: *Furniture Sustainability Standard and Tools* (www.bifma.org/?page=e3standard).

c. Composite wood, wood structural panel, and agrifiber products shall not contain any added urea-formaldehyde resins.

> Composite wood and agrifiber products are defined as particleboard, medium-density fiberboard, wheatboard, strawboard, panel substrates, and door cores.

3.1.6 Lighting control. For requirements, see Section 2.1.2 (Lighting sensors and controls) under Mandatory Requirements for Energy Use.

3.1.7 Acoustics. For acoustic planning and design requirements, see the FGI *Guidelines for Design and Construction of Hospitals and Outpatient Facilities*, 2014 edition.

4 WATER USE

In addition to the mandatory requirements, either the performance option (5.2) or the prescriptive option (5.3) shall be implemented.

4.1 Mandatory Requirements

4.1.1 Medical equipment. Potable water shall not be used for once-through cooling for any medical equipment.

4.1.2 Irrigation water. Irrigation systems shall be designed to use only captured rainwater, recycled wastewater, recycled gray water, or water treated and conveyed by a public agency specifically for non-potable uses for irrigation.

Exception: Use of irrigation systems to establish landscaping when first planted shall be permitted.

Use of xeriscaping should be considered to avoid the need for irrigation.

4.1.3 Measurement and verification plan

4.1.3.1 A measurement and verification plan shall be developed and implemented consistent with one of the following options as specified in volumes cited of the *International Performance Measurement and Verification Protocol* (IPMVP®) to provide for long-term continuous measurement of potable cold water uses in the facility.

a. Option D: Whole Building Calibrated Simulation, Savings Estimation Method 2 in IPMVP Volume III (April 2003)

b. Option B: Retrofit Isolation in IPMVP Volume I: Concepts and Options for Determining Energy and Water Savings (January 2012)

4.1.3.2 The following water uses (as applicable to the project) shall be metered:

a. Main water to site

b. Fire suppression water system

c. Special deduct meters, including those for cooling tower makeup, boiler system makeup, boiler blowdown, other hydronic loop makeup, irrigation, and emergency medical equipment cooling

4.2 Performance Option

4.2.1 Plumbing fixtures and fittings and water reduction

4.2.1.1 Aggregate water consumption shall be reduced by 20 percent based on consumption of all fixtures and fittings in the building.

4.2.1.2 The following shall be used as baseline benchmarks for consumption:

a. Toilet	1.6 gpf (6 lpf)
b. Urinal	1.0 gpf ((3.8 lpf)
c. Hand-washing station faucet	2.2 gpm at 60 psi (8.3 lpm at 415 kPa)
d. Showerhead	2.5 gpm at 80 psi (9.5 lpm at 550 kPa)

4.3 Prescriptive Option

4.3.1 Plumbing fixtures and fittings and water reduction. Plumbing fixtures (toilets and urinals) and fittings (faucets and showerheads) shall comply with the following:

4.3.1.1 Toilets—flushometer valve

a. For single-flush fixtures, maximum flush volume as determined in accordance with ASME A112.19.2 shall be1.28 gal (4.8 L).

b. For dual-flush fixtures, effective flush volume as determined in accordance with

ASME A112.19.14: *Six-Liter Water Closets Equipped with a Dual Flushing Device* and the draft U.S. EPA WaterSense Specification for Flushometer Valve Toilets shall be 1.28 gal (4.8 L).

4.3.1.2 Toilets—tank type: Tank-type toilets shall comply with the performance criteria of the U.S. EPA WaterSense Specification for Tank-Type Toilets.

4.3.1.3 Urinals: Maximum flush volume as determined in accordance with ASME A112.19.2 shall be 0.5 gal (1.9 L).

a. Non-water urinals shall comply with ASME A112.19.19: *Vitreous China Nonwater Urinals* or IAPMO Z124.9: *Plastic Urinal Fixtures* as appropriate.

b. Equip all urinals (but not toilets or bedpan washers) with sensor operators.

4.3.1.4 Public sink faucets: Maximum flow rate shall be 0.5 gpm (1.9 L/min) when tested in accordance with ASME A112.18.1/CSA B125.1: *Plumbing Supply Fittings*.

4.3.1.5 Public metering self-closing faucet: Maximum water use shall be 0.25 gal (1.0 L) per metering cycle when tested in accordance with ASME A112.18.1/CSA B125.1.

4.3.1.6 Patient toilet room sink faucets: Maximum flow rate shall be 1.5 gpm (5.7 L/min) when tested in accordance with ASME A112.18.1/CSA B125.1.

4.3.1.7 Patient toilet room and staff showerheads: Maximum flow rate shall be 2.0 gpm (7.6 L/min) when tested in accordance with ASME A112.18.1/CSA B125.1.

4.3.1.8 Hand-washing station sink faucets: Maximum flow rate shall be 2.2 gpm (8.3 L/min) when tested in accordance with ASME A112.18.1/CSA B125.1

4.3.2 Vacuum pumps and air compressors. No potable water shall be used for vacuum pumps and air compressors.

4.3.3 Sterilizers. Sterilizers shall be provided with water recovery provisions.

5 AIRBORNE EMISSIONS, EFFLUENT, AND POLLUTANT CONTROLS

Note: There is no prescriptive or performance option for this criterion.

5.1 Mandatory Requirements

5.1.1 Bi-products of combustion. All combustion systems shall be designed using processes that comply with the local jurisdiction's air quality management district regulations.

5.1.2 Oil interceptors. Oil interceptors shall be established at all drains from parking areas and central plant areas as described in one of the following, whichever is more stringent:

5.1.2.1 Technologies and strategies described in this section for waste water discharge, spill prevention, and hazardous waste containment; or

5.1.2.2 Local regulations for waste water discharge, spill prevention, and hazardous waste containment

5.1.3 Wastewater discharge. Systems shall be designed to allow testing of wastewater discharge.

5.1.4 Spill prevention. To minimize the risk of leakage and spills, above- and below ground containment areas that comply with the following regulations shall be provided for storage of fuels and chemicals:

5.1.4.1 U.S. EPA Spill Prevention, Control, and Countermeasures (SPCC) rule (www.epa.gov/oem/content/spcc)

5.1.4.2 All applicable state and local administrative codes pertaining to storage tanks

5.1.5 Hazardous waste containment. All outdoor hazardous waste holding areas shall be designed in accordance with 40 CFR Part 264: *Standards for Owners and Operators of Hazardous Waste Treatment, Storage, and Disposal Facilities* (EPA Resource Conservation and Recovery Act).

5.1.5.1 Secondary containment systems shall be provided for all generators, whether otherwise required or not, to prevent spills and migration of waste to soil and ground or surface water.

5.1.5.2 Covered enclosures shall be provided to prevent precipitation from increasing the risk of contaminated liquids migrating to the soil and ground or surface water.

6 MATERIALS AND RESOURCES

In addition to the mandatory requirements, either the performance option (7.2) or the prescriptive option (7.3) shall be implemented.

6.1 Mandatory Requirements

6.1.1 Areas for recyclables

6.1.1.1 For new building projects, there shall be designated spaces that serve the entire building and are dedicated to the collection and storage of non-hazardous materials for recycling, including paper, corrugated cardboard, glass, plastics, and metals at both the point of service and pickup area(s).

6.1.1.2 The size and functionality of the recycling areas shall be coordinated with the anticipated collection services to maximize the effectiveness of the dedicated areas.

6.1.2 Reduced impact materials. Calculations for compliance shall only include materials permanently installed in the project.

6.1.2.1 The building assembly shall comply with either the performance or prescriptive option for specification of products and materials.

6.1.2.2 The interior fit-out shall comply with either the performance or prescriptive option for specification of products and materials.

6.2 Performance Option

6.2.1 Life cycle assessment (LCA)

6.2.1.1 Life cycle assessment for building assembly

a. A minimum of two alternatives that conform to the owner's project requirements shall be developed for the structural system and building envelope in accordance

with the following:

- ISO 14040 (*Environmental management -- Life cycle assessment -- Principles and framework*)
- ISO 14044 (*Environmental management -- Life cycle assessment – Requirements and guidelines*)

b. Each building structure and envelope alternative shall have a common design, including building size and use; common construction requirements; and materials appropriate for the locale.

c. The assemblies shall include all structural elements, insulation, and sheathing/envelope, roof/ceiling, and intermediate floors (including interstitial space).

Examples of life cycle assessment tools suitable for completing building assembly LCAs include the following:

- Athena Impact Estimator for Buildings, Version 4.2 or later (www.athenasmi.org/our-software-data/impact-estimator/)
- GaBi (www.gabi-software.com/america/solutions/building-lca/)
- SimaPro (www.simapro.co.uk/)
- CMLCA (http://cml.leiden.edu/software/software-cmlca.html)

Building service life and maintenance should be considered when evaluating a building assembly.

6.2.1.2 Life cycle assessment for interior fit-out

a. This assessment shall be performed in accordance with ISO Standards 14040 and 14044 for a minimum of two alternative interior fit-outs (including finishes and furnishings) that conform to the owner's project requirements.

b. Each interior fit-out alternative shall provide building service life compliant with the owner's project requirements.

The interior fit-out should include all finishes, furnishings, interior non-bearing partitions, millwork/casework, and interior doors, windows, and openings.

Building service life and maintenance should be considered when evaluating an interior fit-out.

6.3 Prescriptive Option

6.3.1 Building assembly (including structure and envelope)

6.3.1.1 Based on the building application and specification of comparable products (based on cost), 10 percent or more of the material and product specifications for the building assembly shall comply with one or more of the following:

a. **Environmental Product Declarations (EPDs).** Any EPD® used shall recognize Product Category Rules; conform to ISO Standards 14040, 14044, 14025 (*Environmental labels and declarations – Type III environmental declarations – Principles and procedures*) and 21930 (*Sustainability in building construction -- Environmental declaration of building products*), or EN 15804 (*Sustainability of*

construction works – Environmental product declarations – Core rules for the product category of construction products); at minimum include cradle-to-gate scope; and conform to the requirements for either industry-wide or product-specific EPDs:

- **Industry-wide (generic) EPD.** Products specified for the building assembly shall have third-party verified Type III EPDs, including external verification in which the manufacturer is explicitly recognized as a participant by the program operator.
- **Product-specific EPD.** Products used for the building assembly shall have publicly available product-specific, third-party verified Type III EPDs, including external verification. "Product-specific" means manufacturer-specific for a product family.

b. **Third-party certifications.** Products specified shall meet the requirements of multiple-attribute standards developed by an approved standard development organization using a consensus process. Examples of such standards include:

- NSF Sustainability Assessment Standards (http://www.nsf.org/business/sustainability_ncss/index.asp?program=SustainabilityNcs)
- UL Environment Standards (http://www.ul.com/global/eng/pages/solutions/standards/accessstandards/sustainabilitystandards/)
- Sustainable Forestry Initiative certifications (http://www.sfiprogram.org/getting-certified/benefits-of-sfi-certification/)

c. **Product life cycle**

- Products specified shall have a third-party certified life cycle product assessment based on ISO 14040 and 14044 and minimally covers cradle-to-gate scope.
- Compliance documentation shall include the life cycle assessment completed by a manufacturer or third party with results verified and/or certified by a third party.

6.3.2 Interior fit-out (including interior finishes and furniture)

6.2.3.1 Based on the building application and specification of comparable products (based on cost), 10 percent or more of the materials and products specified for the interior fit-out assembly shall comply with one or more of the following:

a. **Environmental Product Declarations.** These shall be EPDs that use recognized Product Category Rules; conform to ISO Standards 14040, 14044, 14025, and 21930 or EN 15804; at minimum include cradle-to-gate scope; and conform to the requirements for industry-wide or product-specific EPD:

- **Industry-wide (generic) EPD.** Products specified for the interior fit-out shall be third-party, certified Type III Environmental Product Declarations (EPDs), including external verification where the manufacturer is explicitly recognized as a participant by the program operator.
- **Product-specific declaration.** Products specified for the interior fit-out shall be products with a publicly available product specific third-party, certified Type III EPDs, including external verification.

"Product-specific" means manufacturer-specific for a product family.

b. **Third-party certifications.** Products specified shall be based on a multiple-attribute standard developed by an approved standard development organization using a consensus-based process. Examples include:

- NSF Sustainability Assessment Standards
- UL Environment Standards
- Sustainable Forestry Initiative certifications

c. **Product life cycle**

- Products specified shall have a third-party certified life cycle product assessment based on ISO 14040 and 14044 and minimally covers cradle-to-gate scope.
- Compliance documentation shall include the life cycle assessment completed by a manufacturer or third party with results verified and/or certified by a third party.

7 WASTE

Note: There is no prescriptive or performance option for this criterion.

7.1 Mandatory Requirements

7.1.1 Mercury reduction and waste. Building products that contain intentionally added mercury shall not be specified. When there is no alternative, products that minimize mercury content shall be specified.

7.1.1.1 In facilities delivering dental care, amalgam separation devices shall be installed that meet or exceed the requirements of ISO-11143: *Dentistry – Amalgam separators*.

7.1.1.2 An area shall be provided for storing mercury-containing products (e.g., lamps) to be recycled.

7.1.1.3 All illuminated exit signs shall be Energy Star-qualified, UL-certified LED lamps.

7.1.1.4 All fluorescent lamps shall be low-mercury lamps.

Fluorescent lamps other than compact fluorescent lamps (CFLs) should have armor sleeves to reduce and contain breakage.

Maximum Mercury Content of Lamps

Lamp	*Maximum content*
T-8 fluorescent, 8-foot	10 mg mercury
T-8 fluorescent, 4-foot or shorter	3.5 mg mercury
T-8 fluorescent, U-bent	6 mg mercury
T-5 fluorescent, linear	2.5 mg mercury
T-5 fluorescent, circular	9 mg mercury
Compact fluorescent, non-integral ballast	3.5 mg mercury
Compact fluorescent, integral ballast	3.5 mg mercury, ENERGY STAR-qualified
High-pressure sodium, up to 400 watts	10 mg mercury
High-pressure sodium, above 400 watts	32 mg mercury

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7.1.2 Construction waste management. A construction waste management plan shall be developed and implemented.

7.1.2.1 At minimum, materials shall be identified that can be recovered, reused, and/or recycled and plan to divert them from disposal in landfills or incinerators.

7.1.2.2 The disposal method shall be identified for each material, and whether materials will be sorted or co-mingled on-site shall be determined.

7.1.2.3 At least 50 percent of non-hazardous construction and demolition debris shall be recovered, reused, recycled, and/or salvaged.

7.1.3 Hazardous waste

7.1.3.1 For requirements, see Section 5.1.5 (Hazardous waste containment) under Airborne Emissions, Effluent, and Pollution Controls in this document.

7.1.3.2 Management of hazardous waste disposal shall comply with all applicable state and federal regulations.

7.1.3.3 Certification shall be made that waste minimization activities have been undertaken as stated in 40 CFR 262.27 (Waste minimization certification).

ASHE Monograph

Literature Review: Room Ventilation and Airborne Disease Transmission

Farhad Memarzadeh, PhD, PE

ASHE®

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Jointly published by

ASHE

FGI
FACILITY GUIDELINES INSTITUTE

© 2013 ASHE
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This monograph can be downloaded from under the Resources tab of both the ASHE and the FGI websites. Paper copies can be purchased from www.ashestore.com.
ASHE catalog #: 055584

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Abstract

This literature review explores the role that ventilation, assessed by air changes per hour (ACH), plays in infection transmission and disease control. The *American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) Position Document on Airborne Infectious Diseases* (2009) notes the dilution effect that ACH has on infectious disease transmission. The Wells-Riley equation supports the premise that increasing the volume of "clean" air dilutes the room air and thus exposes people in the room to fewer potentially infectious particles. ACH is the only variable in the Wells-Riley equation that can be quantified by direct measurement. Our knowledge of the effect of the many other variables (e.g., infectious dose, relative humidity, temperature, host susceptibility, chain of transmission) on disease transmission is limited.

The majority of studies conducted to assess the role of ventilation in infection transmission and disease control have been either observational or based on animal models that are not particularly applicable to the study of human disease. Case studies on aircraft and other vehicles, schools, and "sick" buildings and hospitals, as well as some animal studies, suggest that regardless of actual ACH, ventilation rate is just one of many factors that affect the transmission of infectious disease.

The ability to precisely predict particulate movement is needed to increase our understanding of how airborne disease organisms move within ventilated facilities. A recently published empirical study (Faulkner et al. 2013) indicates that in some situations there may be limits to the improvements in the environment that can be achieved by increasing ACH in the occupied zones of rooms.

Existing ventilation guidelines that recommend specific ACH rates for some defined spaces are often based on experiential and observational evidence rather than on hard data. Nonetheless, ACH has been shown to be an important environmental control in preventing the transmission of infectious disease in public spaces. Considerably more research is needed—in conjunction with rigorous and sustained space-specific risk assessments—before standard ventilation recommendations are changed in any way.

Room Ventilation and Airborne Disease Transmission

The relationship between air changes per hour (ACH) and infection transmission, in a closed environment or outdoors, is enigmatic. ACH is a measure of how many times the air in a defined space is replaced. Air change rate (ACR) and ACH are often used interchangeably. Examples of technical definitions for ACH include:

- The ratio of the total volume of air passing through the zone to and from the outdoors per unit of time to the volume of the zone
- The ratio of the volumetric flow rate of air into the space to the interior volume of the space
- The ratio of air supply into a zone (i.e., a room or space) to the volume of the zone
- The number of times the air in a defined space is replaced

Several studies have shown a direct relationship between ACH and infectious disease transmission, while others suggest an indirect relationship (Artenstein et al. 1967; Aintablian, Walpita, and Sawyer 1998; Booth et al. 2005; Chen and Li 2008; Sawyer et al. 1994; Suzuki et al. 2002; Mastorides et al. 1999; Huynh et al. 2008). This inconsistency suggests that modes of transmission vary by setting and circumstances and that transmission may result from a combination of factors. Memarzadeh (2011a, 2011b) and Li and colleagues (2007, 2005) recently conducted studies and comprehensive

reviews of the extensive literature on airborne and droplet infectious disease transmission.

Li and colleagues (2007) posed two questions that sum up why more specific investigation is needed to determine the relationship between ACH and infectious disease transmission.

1. Is there sufficient evidence to support the ventilation rate and/or airflow pattern as a contributing cause(s) for the spread of airborne infectious diseases?
2. If so, is there sufficient evidence to support minimum ventilation requirements to minimize transmission of airborne infectious diseases in different settings (nosocomial or otherwise)?

Li and colleagues (2007) came to these conclusions:

1. There is strong and sufficient evidence to demonstrate an association between ventilation and air movements in buildings and the transmission and spread of infectious diseases such as measles, *Mycobacterium* tuberculosis (M. tb), chickenpox (varicella), influenza, smallpox, and severe acute respiratory syndrome (SARS).
2. There are insufficient data to support minimum ventilation requirements for specific public spaces (e.g., hospitals, isolation rooms, schools, offices) in relation to the spread of infectious disease via airborne and droplet routes.

Research has identified many variables that influence disease transmission and the possible interactions that affect a pathogen's ability to be transmitted or to remain viable and virulent (e.g., necessary infecting dose, susceptibility of the host, infectivity of the pathogen, environmental factors) (WHO 2009). Despite this knowledge, no definitive quantitative analysis establishes either a minimum or an optimum ACH in relation to other variables that may affect infection transmission for any specific functional area or protocol. In single-use facilities such as school buildings, laboratories, offices, and airplanes, the ACH is often determined non-scientifically on the basis of factors such as comfort, seasonal changes in temperature and humidity, and reduction of noxious odors or volatile organic compounds (VOCs).

Most researchers agree that a facility housing several different functions should employ an ACH parameter that maximizes comfort and reduces

odors and disease transmission. Depending on the facility, other factors may also influence the determination of an appropriate ACR. For example, Memarzadeh (1998) showed that "controlling the humidity in animal rooms is more significant in managing the production of ammonia (from animal urine) than is the use of high air change rates." This finding allowed for a decrease in the ACR from 15 to as low as 5, while improving the welfare of the animals.

Faulkner and colleagues (2013) performed an empirical study to determine the effects of ACH on particulate concentrations in the occupied zone and ventilation outlet of an empty ventilated chamber given a known particulate density in the incoming ventilation air. The results indicated that in some situations the advantages of increasing ACH may be limited.

These parameters will likely differ depending on the function of the space. Most studies do not account for the amount of time an infected individual spent in the space (Memarzadeh 2011a, 2011b). Most experts now agree that in mechanically ventilated spaces, the ACH should be determined on the basis of a risk assessment of the use and conditions of the space. Memarzadeh (2010) provides a novel methodology to approximate how much air displacement and containment leakage might occur during a momentary positive pressure reversal in a facility that is designed to sustain directional airflow even under failure conditions. This methodology can be used to quantify contaminant migration across a boundary in room types such as airborne-infection isolation (AII) rooms and protective environment (PE) rooms that use sustained differential air pressure to prevent infectious particle transmission.

Memarzadeh and Xu (2012) discuss the importance of applying a scientific analysis to disease transmission and designing a ventilation system based on a site-specific risk analysis. Conditioned ventilation air can cost $4 to $8/cfm/year, which is a substantial cost for large biomedical facilities that use high air-exchange rates to maintain healthy environments. Increasing the air exchange rate of a typical 70-square-meter laboratory from 6 ACH to 14 ACH can increase the annual heating, ventilation, and air conditioning (HVAC) energy cost by around $8,000 (Memarzadeh 2009). Because so many factors affect disease transmission, Memarzadeh and Xu (2012) suggest that a ventilation system based on a thorough risk assessment can reduce infection risk without necessarily increasing ventilation airflow rate.

Chain Model of Disease Transmission

To become infectious, a microorganism must have the following:

1. A portal of entry
2. A host
3. A portal of exit

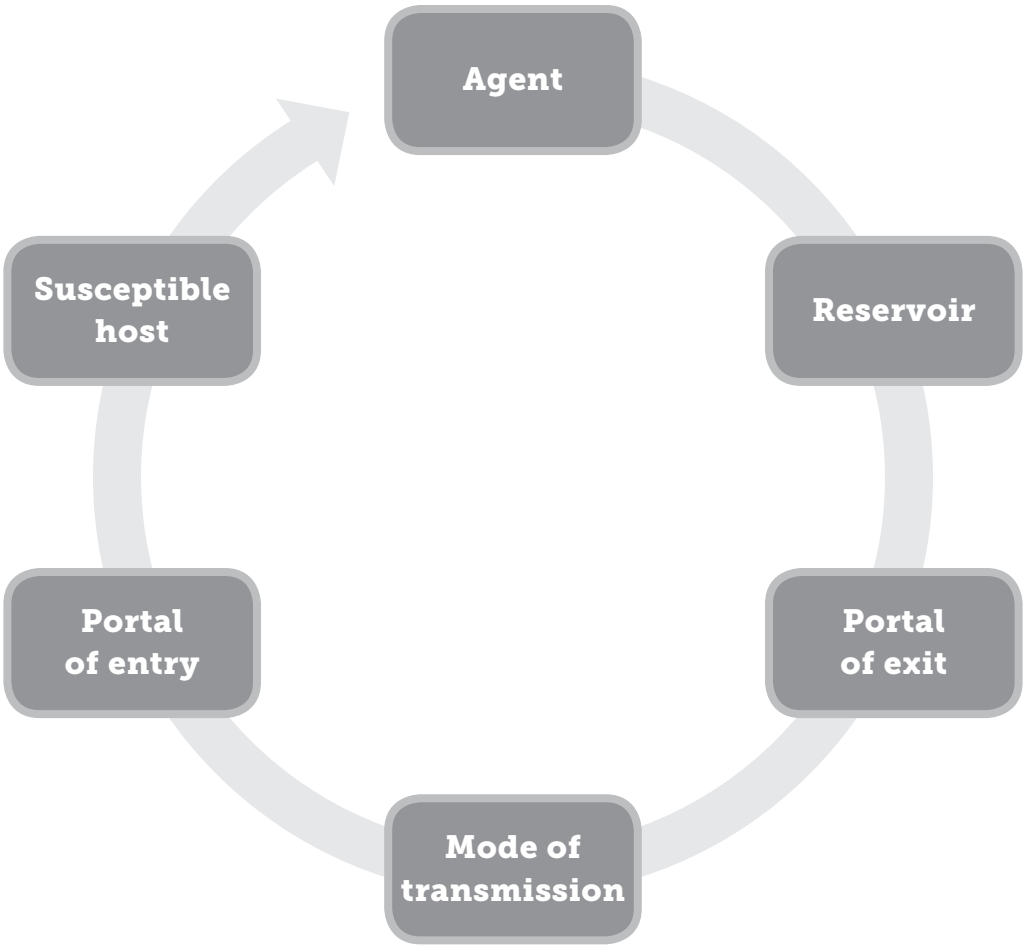
These are the critical components of the chain of disease transmission represented in Figure 1.

- The agents are disease-causing organisms such as bacteria, fungi, viruses, and protozoa.
- A reservoir is any place an infectious agent can survive, grow, or multiply.
- The portal of exit is the path by which an infectious agent leaves the reservoir.
- The mode of transmission is the means by which an organism is transferred from one carrier to another by either direct transmission (direct contact between infectious host and susceptible host) or indirect transmission (which involves an intermediate carrier such as an environmental surface or a piece of medical equipment).
- The portal of entry is the route through which the pathogen enters its new host.
- A susceptible host is a person who can get sick when exposed to a pathogen.

Furthermore, disease transmission is dependent on factors such as the following (Green 1969):

- Dose (adequate number of pathogenic organisms)
- Virulence of the organism
- Susceptibility of the host (i.e., whether the host is immune-compromised, has lowered immunity, or is unvaccinated)
- Viable mode of transmission (a sufficient number of the organism is transferred from source to host)
- The correct portal of entry into the host

Figure 1: Chain Model of Disease Transmission



Transmission of a microorganism can occur by more than one route. In an enclosed environment, the chain of transmission is influenced by the ventilation conditions. Numerous variables can affect each factor and the microorganism's ability to move to the next level of infection. In the chain of transmission, a microorganism must leave one host or reservoir to be transmitted to another. This suggests that there is a spatial component to the chain of transmission, whether transmission occurs through direct or indirect contact or via an airborne route. The airborne transport of microorganisms represents a possible weak link in the infection transmission route. This is where infection control measures (i.e., providing barriers to transmission) may have the greatest chance of breaking the infection cycle (Fletcher et al. 2004).

Environmental infection control strategies must be based on the principles of the chain of disease transmission, regardless of the disease of concern.

The presence of microbes in the environment does not necessarily lead to infection or even cross-transmission. For an infection to develop, the chain of transmission must be intact, and there must be a susceptible recipient.

While evidence and data are sufficient to support an association between ventilation flows and the transmission of airborne pathogens, airborne pathogen transmission is poorly understood. It is extraordinarily difficult, if not impossible, to trace airborne infectious disease transmission routes using standard epidemiological techniques. Not only does airborne evidence rapidly disappear, but the many factors that can affect the spread of disease make it extremely difficult to rule out any single route of infection.

Airborne infectious disease outbreaks are difficult to investigate, primarily because the path of transmission is transient. It is difficult to pinpoint the time of infectious particle release (exhalation or procedural) and to locate the source/index person and infected persons, and the exact states of the HVAC system operating conditions at the time of transmission are often unknown.

Existing Standards and Ventilation Risk Assessment

Risk assessment is essential to determining the most efficient, cost-effective ACH for any particular space or combination of spaces and should be done early in the design process and remain an ongoing process (Memarzadeh and Xu 2012).

ASHRAE (2003) suggests the following steps be part of any risk assessment:

1. Identify the risks.
2. Estimate the level of exposure to the risks.
3. Estimate the probability of risk occurrence.
4. Determine the value of the potential loss.
5. Rank the risks.
6. Identify vulnerabilities.

The Facility Guidelines Institute's *Guidelines for Design and Construction of Health Care Facilities* (FGI 2010) weighs the susceptibility of occupants against the degree of environmental contamination for hospital settings. This consideration can also be applied to other building types.

Disease Transmission Terms

Masago and colleagues (2008) and Jones and colleagues (2009) have clarified the terminology used to describe the complexity of disease transmission (see Table 1). Their definitions not only help us understand Masago and Jones's methodology for risk assessment, which is examined later in this monograph, they also help us evaluate other studies on disease transmission. Masago and Jones make a clear distinction between how the terms are used in models of disease transmission and how they are applied in a real-world situation such as an outbreak. This is important because it is extremely difficult to conduct controlled experiments in this field. Predictive modeling that incorporates numerous variables is more practical and can provide mitigating solutions for real-world scenarios.

Many terms (e.g., *high*, *low*, *adequate*, *inadequate*) used to describe ACH, ventilation rates, HVAC systems, filtration, number of particles, types of spaces, and other variables that are part of or affected by a ventilation system can be misleading as they are subjective and cannot be quantified in relation to airborne disease transmission.

Table 1: Comparison of Some Disease Transmission Terms

(Proposed by Masago et al. [2008] and Jones et al. [2009])

Term	Modeling	Real World
Exposure	The individual actually received some dose.	The individual was exposed to the source of the contaminant but it is not known whether he or she really received a dose. A clinical test can be used to look for evidence of exposure.
Infection	The microorganism has begun its replication in the host. This can be measured by antibody response or identification of the biological agent at the site of replication.	Infection is usually synonymous with disease (impairment of the person's health status or some function), although disease does not always manifest as a clinical condition.
Contagion	It is possible to estimate the probability of transmission from an infected individual to a susceptible individual based on exposure scenarios and the characteristics of the microorganism. Estimates of very low risks can be made.	Very high levels of disease transmission can be evaluated through investigations, but risk of contagion is generally addressed as yes or no without quantification of probability.
Sputum vs. saliva	Sputum is the material that is brought up into the mouth from the lungs with persistent deep coughing and includes some saliva. Saliva is the liquid produced in the mouth that aids in digestion. Saliva is easier to collect and measure. In the mouth, the sputum mixes with saliva. The numbers of bacilli can be 100 times higher in sputum than in saliva.	
High or low Adequate or inadequate Critical or non-critical	These terms can refer to air changes per hour, ventilation rates and HVAC systems, filtration, number of particles, and spaces.	

Risk factors for most infectious agents are difficult to quantify. Many elements must be considered, including the susceptibility of people exposed. For example, measles is highly contagious. However, immunization against this virus virtually eliminates susceptibility even if the exposure involves household contact. Other risk variations among individuals may be due to genetics, health status, or gender. Risk factors may also be related to the local environment, such as age and operational status of the ventilation equipment (Memarzadeh 2011b).

Temperature and relative humidity are important factors to consider when performing a risk assessment and developing control measures. Their role in surface survival of pathogens is well known (Memarzadeh 2011a). Other risk factors related to socio-adaptive behaviors include compliance with use of standard operating procedures involving personal protective equipment (PPE), decontamination of environmental surfaces, adherence to isolation precautions, and use of respiratory hygiene strategies (e.g., covering one's mouth and nose when sneezing or coughing, wiping down surfaces with disinfectant, proper discarding of contaminated disposables such as tissues). Although the presence of a risk factor for a particular pathogen increases the chances an illness will be contracted, it does not always lead to an illness. On the other hand, the absence of any single risk factor or the existence of a protective factor does not necessarily protect against infectious illness (Memarzadeh 2011b). It is crucial to find a balance between reducing infectious disease transmissibility and maintaining occupant comfort.

Existing standards and guidelines suggest that the risk of infectious airborne transmission can, in part, be controlled mechanically. They recommend setting barriers to break the chain of infection (Siegel et al. 2007). However, ACH is not the sole determinant of disease transmission, and the ACH differs among buildings and spaces based on function and natural or mechanical ventilation schemes. The World Health Organization (WHO) guideline on natural ventilation discusses the difficulties in developing ventilation guidelines for infection control due to insufficient data to recommend a minimum ventilation flow rate for infection control against droplet nuclei (WHO 2009).

Role of Ventilation in Disease Transmission

Ventilation can reduce the concentration of airborne pathogens by removing or diluting airborne droplet nuclei. Studies have shown that tuberculin conversion among health care workers was strongly associated with inadequate

ventilation in general patient rooms and with type and duration of work but not with ventilation in respiratory isolation rooms (Menzies et al. 2000).

Menzies and colleagues (2000) found an association between tuberculin conversion of a non-infected individual exposed to an infectious source of tuberculosis (TB) and an ACH of less than 2 in general or non-isolation patient rooms. Conversion was not associated with the ventilation rates in respiratory isolation rooms. However, regardless of the ACH, the time to conversion was the same. This finding may indicate that ACH is relatively unimportant in respiratory isolation rooms (Menzies et al. 2000). It is generally accepted that a higher ventilation rate can dilute the contaminated air inside a space more rapidly than a lower ventilation rate, and presumably also decrease the risk of transmission to individuals in the space. However, studies of TB outbreaks suggest that while ventilation is an important determinant of disease transmission, the identification of other contributing factors makes it difficult to generalize ventilation rate as the cause. These studies were largely based on questionnaires and retrospective observations (Menzies et al. 2000).

Some studies have demonstrated that air dilution or replacement does not protect personnel from exposure to concentrated bursts of aerosols in biological laboratories. In fact, Crane (1994) notes an observation by Chatigny and West (1976) that increasing ventilation rates from 6 to 30 ACH has a minimal effect on aerosol concentration of microorganisms in the first few minutes after release.

The maximum ventilation rate (above which there is no further reduction of infection risk) is not known. Although the minimum ventilation flow rate may be used in an effort to reduce energy consumption (Masago et al. 2008), it is unclear what the optimal level is.

Since most ventilated rooms have incomplete mixing under steady state operating conditions, contaminant concentrations will vary considerably throughout the room. This is especially true for particulates because, depending on their size and other properties, they may be less likely to follow air flow patterns. A complex interaction of the particulate inertia, drag forces from airflow, and gravity dictates movement and deposition of particulates in confined spaces. Under steady state conditions, one could conduct a mass balance analysis to determine the mass of particulates entering the chamber through the air inlet and the mass of particulates exiting the chamber through the exhaust air, then assume that the remainder of the particulate mass is removed from the air by deposition onto the floor via gravity or by colliding with and adhering to walls and other surfaces. Some of the particu-

late mass would remain suspended in the air within the room to maintain a certain room concentration. A recent empirical study by Faulkner and colleagues (2013) showed that the advantages of increasing ACH in terms of improving environments in the occupied zone of rooms may have limits, a finding that warrants further investigation.

There has never been a major infectious disease outbreak in a hospital that could be directly attributed to ventilation. Thus, the status quo seems to be effective in controlling the spread of some diseases. We should be cautious in making blanket changes to the existing ventilation standards without conducting more targeted research.

Since more than 1 billion passengers travel by air annually, many studies have looked at ventilation and infection rates in aircraft cabins. Some have indicated that the risk of catching an infectious illness on commercial aircraft may be reduced if the cabin ventilation rates are increased and/or the cabin air is refreshed more frequently. The studies suggest that risk of disease transmission within the aircraft cabin seems to be affected by cabin ventilation and efforts to increase ventilation will reduce risk (Aviation Health Working Group 2001b; WHO 1998; Withers and Christopher 2000). It is interesting to note that no peer-reviewed scientific work has compared the relationship between cabin air quality and aircraft ventilation rates and heightened health risks with other modes of transport or with office buildings (Mangili and Gendreau 2005; National Research Council 2002; GAO 2004; U.S. House of Representatives 2003; Aerospace Medical Association 1997; Rayman 1997).

In addition to air exchange, negative pressurization is often used in spaces such as AII room and biocontainment laboratories to prevent contaminants from flowing out of the room. However, aerosol transmission can occur between persons within or between these rooms for several reasons. The individuals may not be aware that they are infectious (such as in an emergency room or a school); they may be asymptomatic carriers; or a mechanical failure may occur in a building that is not equipped to deal with a total air handling system shutdown.

ASHRAE (2001) Standard 62-2001 notes that study results can be inconsistent because the ventilation rate and CO2 concentrations used to measure contaminants are only surrogates for the actual agents that might be causing the symptoms. Seppänen, Fisk, and Mendell (1999) conducted a comprehensive review of 20 studies done in work settings to examine the relationship between ventilation rates and occupant health. This review found a consistent

relationship between ventilation rates below 10 l/s per person and increased symptoms among occupants. In some studies, ventilation rates greater than 10 l/s per person, even up to 20 or 30 l/s per person, were associated with further significant reductions in occupant symptoms.

Apte, Fisk, and Daisey (2000) corroborated these findings in an analysis of a large data set of adults in office buildings. This study found statistically significant, dose-dependent increases of up to a factor of six in the risk of building-related lower respiratory and mucous membrane irritation symptoms when average workday indoor CO2 concentrations increased by 420 ppm above outdoor levels, which was still below the ASHRAE 62-2001 [133] standard of 1,000 ppm.

Mechanics of Disease Transmission

Prior to the 2003 worldwide severe acute respiratory syndrome (SARS) epidemic, there was strong evidence that ventilation and indoor environmental surfaces are an important determinant of nosocomial disease transmission (Bean et al. 1982). In the early 20th century, the work of Wells (1934), Wells and Stone (1934), and Duguid (1945) demonstrated that airborne particles can remain airborne for as long as one week after initial aerosolization. This early work was the basis for the airborne droplet nuclei theory for infectious disease transmission used to date (Wells 1934; Wells and Stone 1934).

According to the Centers for Disease Control and Prevention's (CDC) *Guidelines for Environmental Infection Control in Health-Care Facilities* (CDC and HICPAC 2003), only TB, measles (rubeola virus), and chickenpox should be considered true airborne infectious diseases. However, other infectious agents, such as SARS-CoV, are sometimes considered opportunistic because they could be transmissible over short distances (e.g., 1 to 2 meters) in favorable environmental conditions.

The 2003 SARS epidemic began in China when SARS-CoV emerged, likely in circulation among animals, and was spread person to person. The epidemic drew attention to the potential contribution of mechanical ventilation as one outbreak involved a combination of insufficient ACH, environmental survival of the virus, and ambient conditions that led to airborne dispersal over a large area (Li et al. 2005). When patients infected with the virus were admitted to health care facilities, transmission occurred where there were lapses in use of PPE and/or close contact in enclosed environments.

When someone with SARS coughs or sneezes, others may become infected by inhaling droplets in the air or touching surfaces where droplets may have been deposited. This indicates that SARS-CoV can be transmitted via both airborne and contact mechanisms. The SARS virus may live on hands, tissues, and other surfaces for up to six hours in these droplets and up to three hours after the droplets have dried. Live virus has been found in the stool of people with SARS, where it has been shown to live for up to four days. The virus may be able to live for months or years when the temperature is below freezing. Booth and colleagues (2005) reported that SARS-CoV RNA can be detected in the air, and in some cases the airborne virus can be grown in culture, demonstrating extended viability outside the infected host (Xiao et al. 2004). The SARS outbreak was initially thought to be spread through contaminated droplets. Most transmission in health care facilities appeared to be related to contact and droplet spread over distances of 1 to 2 meters.

Hanley and Borup (2010) provide examples of disease transmission in buses and taxis in which air conditioning and/or natural ventilation are available (Daisey, Angell, and Apte 2003; Daisey and Angell 1998; Olsen et al. 2003; Olsen and Dossing 1982; Ko, Thompson, and Nardell 2004; McFarland et al. 1993). Passengers shedding virus in these spaces are a probable source of aerosol transmission. The studies showed via contour maps that movement in or out of a vehicle, time spent in the vehicle, temperature and humidity of the vehicle, and physical contact with contaminated objects (e.g., money) are all factors in transmitting infection.

A study by Han and colleagues (2009) is significant in the study of airborne transmission of viral disease. An outbreak of influenza A pandemic (H1N1) occurred in June 2009 among members of a tour group in China who had traveled in the same bus for seven hours. Apparently, the index case-patient noticed flu-like symptoms prior to arriving in China. Secondary cases developed in 30 percent of the tour group members who had talked with the index case-patient and in one other passenger who had sat within two rows of the index case-patient. Tour group members who had not talked with the index case-patient did not become ill. Other kinds of contact, such as dining at the same table and receiving chewing gum from the index case-patient, played no role during this outbreak. Per this investigation, H1N1 pandemic virus infection was found to be caused by transmission during coughing or vocalization by an index case-patient, which indicates droplet transmission.

Wells's Quantum Theory of Disease Transmission

In 1955, Wells introduced the quantum theory of disease transmission. He proposed a hypothetical infectious dose unit, the quantum of infection, which is defined as the number of infectious airborne particles (one or more) required to infect a susceptible person (Wells 1934; Wells and Stone 1934; Wells 1955). Wells suggested that the number of people infected may follow a discrete probability distribution. Using a Poisson distribution line to calculate the frequency of infection in a population, he indicates that 63.2 percent of a population may become infected if a susceptible person breathes in one quanta of contagion (Beggs et al. 2003).

Beggs and colleagues (2003) indicate that because the overall infectivity of any airborne pathogen depends as much on the immunological state of the susceptible individuals as on the physical and biological characteristics of the agent, it is impossible to directly measure the quanta present in any outbreak. It is, however, possible to indirectly determine the quanta if the physical parameters associated with the outbreak are known. The epidemiological models discussed in the sidebar have been used to determine the quanta of infection associated with outbreaks of TB, measles, and other airborne infections.

Beggs and colleagues (2003) compared quanta production rate data for TB and measles outbreaks from a variety of sources and noted that a vast range of quanta production rates are associated with TB outbreaks. It appears that for normal pulmonary TB patients the quanta production rate is quite low (1.25 quanta/h) (Riley et al. 1962). The much higher TB quanta production rates (> 2,000 quanta/h) appear to be associated with outbreaks that involve large amounts of aerosolised infectious agent (Kantor, Pobletem, and Pusateri 1998; WHO 2001) such as occurred in an Arkansas hospital in 1985 during the irrigation of a hip abscess teeming with M. tb bacilli (Hutton et al. 1990). The high quanta value attributed to the school measles outbreak (Riley, Murphy, and Riley 1978) indicates the highly infectious nature of this disease (Wells 1995; Beggs et al. 2003).

Wells (1934) and Wells and Stone (1934) established that the primary mode of airborne infection was via droplet nuclei, while a host of other investigations showed that particles are generated when an infected person coughs, sneezes, talks, vomits, defecates, or undergoes medical procedures such as suctioning, endotracheal intubation, or cough induction by chest physiotherapy (Yu et al. 2004; Yu et al. 2005; Morawska 2006). Most of the studies rely on the Wells-Riley equation (Wells 1955; Riley, Murphy, and Riley

Mathematical Models of Infectious Disease Transmission

Mathematical models of infectious disease transmission are used to better understand the dynamics of a real-world situation and to test hypotheses about the variables involved. Models make assumptions that quantify certain features of the scenario while at the same time limiting their applicability to all scenarios. However, the most common disease-transmission models have been successfully used to plan control and mitigation measures against future epidemics of an infectious disease.

All of the accepted models assume that (1) all susceptible individuals have an identical pulmonary ventilation rate, (2) the air in the room space is completely mixed and the infectious agent is evenly distributed throughout the room space, and (3) all susceptible individuals are equally vulnerable to the infectious agent (Beggs et al. 2003). However, in reality, complete air mixing and even distribution of the airborne infectious agent is never completely achieved.

Although all of the models can be used to predict the number of new cases of a disease over time for a given number of susceptible individuals and infectors and specified ventilation conditions, they are not universally applicable (Beggs et al. 2003).

Susceptible-Infected-Recovered Model

One of the first and simplest transmission models was the Susceptible-Infected-Recovered (SIR) model formulated in the 1920s. The basic theory for the dynamics of transmission describes a population divided into three classes or states: susceptible (S), infectious (I), and recovered (R). The model assumes that the population is closed (i.e., no one enters or leaves the population and there is a permanent immunity).

Over time and with better understanding of the epidemiology of infectious disease, many extensions of the SIR model have been created to account for factors such as contact rates among different age groups, speed of the disease's outbreak, demographic effects (crude birth rates and crude death rates in many developing countries are large enough to affect the population dynamics of infection), spatial effects (how populations are geographically dispersed), and stochastic effects. Other models, such as agent-based and spatial-transmission models, provide a means to assess location of hosts and their typical movement as well as a quantitative description of the infection process.

The Wells-Riley Model

Most of the published studies performed to quantify the risk of airborne transmission in enclosed spaces stem from the work of Wells (1955) and Riley and colleagues (1978), referred to as the Wells-Riley equation. This model includes Wells's quantum theory of disease transmission and addresses the probability of a susceptible person becoming infected by inhaling a quanta of infection.

The Wells-Riley equation predicts the infection rates of persons who shed infectious particles within a building. When an infected person coughs or sneezes, a percentage of the expelled microbes become droplet nuclei that have the potential to cause disease if they gain access to mucosal membranes of a susceptible person, either directly or indirectly (CDC 2010).

The probability of infection through infectious droplet nuclei is inversely correlated to the ventilation rate. The parameters used in the Wells-Riley equation include ventilation rate, generation of droplet nuclei from the source (quanta/minute), and duration of exposure.

The Wells-Riley analysis has been applied to numerous risk analysis studies for disease transmission, but the model has limitations (Wells 1955). For example, the analysis assumes air is well mixed and concentration of bioaerosols is uniform. Thus, it does not account for other influences, such as distance between infected and susceptible people or the stochastic effects inherent in a small population. The result is the quantification of the average risk only rather than including the expected range (Noakes and Sleigh 2008). Perhaps the biggest limitation of the Wells-Riley model is the representation

of the infectious dose. This parameter cannot fully capture the complex interaction between infectors, pathogens, and potential hosts (Noakes and Sleigh 2009).

The Mass Action Model

The Mass Action (MA) model (Riley 1974) has been used to determine the dynamics of diseases with short incubation periods, such as measles. In the MA equation, the number of infectious transmissions per infected case is a function of the number of susceptible individuals in the population. This scenario is characterized by an increased number of infected cases in successive time periods. Simultaneously, the number of susceptible individuals in the population decreases, leading to a slow reduction of susceptible individuals.

Gammaitoni and Nucci's Model

The Gammaitoni and Nucci (GN) epidemiological model (Gammaitoni and Nucci 1997a, 1997b) is based on Wells's experiments and includes the change of quanta level in a room space over time. Gammaitoni and Nucci took into consideration that the previous models neglect differences in susceptibility and assume that the rate at which quanta of infection are added to the air by infectious persons is constant; the latent period of the disease is longer than the time scale of the model, the number of infective persons in the room is constant; droplet nuclei are instantaneously and evenly distributed in the room; droplet nuclei are removed by fresh-air ventilation of the room; ultraviolet irradiation is at a constant rate; fresh air is at the same temperature and pressure as the air already present in the room; the number of infected persons is proportional to the number of encounters between susceptible persons and quanta of infection; and the encounter rate is proportional to both the number of susceptible persons and quanta of infection in the room (law of mass action). The GN model indicates that a certain number of persons exposed to a source of TB infection will be infected in spite of all precautions, but if the infection rate is known this number can be kept low by increasing the disinfection rate and decreasing the time of exposure.

Beggs and colleagues (2003) compared the applicability of the various models. He noted that although any of the models can be used to make reasonable predictions under different circumstances, their limitiations can lead to inadequate protection measures when performing a risk assessment (Beggs et al. 2003).

1978) that predicts the infection rates of persons who shed infectious particles within a building (see sidebar on page 14). While the technology and the proposed causative factors for disease transmission have progressed considerably, almost every peer-reviewed scientific publication on infection control and HVAC recommends further study to quantify the most appropriate ACH standard.

The work of Menzies and colleagues (2000), Schulman and Kilbourne (1962), and Hoge and colleagues (1994) provided direct, strong evidence in support of the Wells-Riley equation. The rate of increase for new cases of airborne contagion in a group breathing the same atmosphere expresses the contagion potential as inversely proportional to the sanitary ventilation per susceptible occupant (Wells 1955). This means that the subsequent analysis using the Wells-Riley equation is justified.

Knibbs and colleagues (2011) used the GN model to estimate airborne transmission risk. The GN model is capable of incorporating non–steady-state quanta levels. Sze To and Chao (2010) conducted a comprehensive review and comparison of the Wells-Riley and dose-response models. While the Wells-Riley model is quick and does not require interspecies extrapolation of infectivity, dose-response models can consider disease transmission routes besides airborne. These models can also calculate the infectious source strength of an outbreak in terms of the quantity of the pathogen rather than a hypothetical unit. Sze To and Chao point out that current risk models do not account for spatial distribution of airborne pathogens, which is a critical factor in infection risk assessment of respiratory disease. Infection risk assessment models of respiratory diseases must be further developed to make them more universal in their application.

There are many well-documented observational studies in the literature for airplanes, taxis, schools, and so on (Hanley and Borup 2010; Daisey, Angell, and Apte 2003; Daisey and Angell 1998; Olsen et al. 2003; Olsen and Dossing 1982; Ko, Thompson, and Nardell 2004; McFarland et al. 1993), but none quantitatively shows the effects of any single or combined variable other than ACH for airborne transmission via a ventilation system. It is widely conjectured that, more often than not, infections occur via a combination of airborne and contact transmission. Although there is little evidence that ventilation directly reduces the risk of disease transmission, many studies suggest that insufficient ventilation increases the risk.

There is clear and undisputed evidence that using higher ventilation rates in conjunction with other preventive measures reduces the risk of disease transmission. A WHO (2009) report on the use of natural ventilation notes that where droplet nuclei are an important mode of disease transmission, average quanta production rates in subjects are usually < 1 quanta/minute. With a quanta production rate of 10 quanta/minute, the estimated risk of infection with 15 minutes of exposure in a room with 12 ACH is 4 percent, and with 24 ACH it is 2 percent. This illustrates the importance of adequate ventilation.

Evidence of Relationship Between ACH and Disease Transmission

Unfortunately, most studies showing a relationship between ventilation and infection transmission are not current (i.e., most were published between 1945 and 2009). A few significant studies published between 2009 and 2012

expand our knowledge of disease transmission, but these are still not conclusive in a quantitative sense.

A comprehensive literature review by Li and colleagues (2007) of 40 studies found 10 studies that were conclusive and 12 studies that were partly conclusive in favor of the relationship between ACH and airborne transmission. Among the 10 conclusive studies, several showed an association between airflow patterns and the spread of diseases (Bloch et al. 1985; Gustafson et al. 1982; Hutton et al. 1990; Wehrle et al. 1970), including several that examined clusters of SARS-CoV (Li et al. 2005; Yu et al. 2005; Wong et al. 2004). Infectious agents included in this review also involved the measles, M. tb, chickenpox, influenza, smallpox, and cold viruses.

In these studies, a few secondary cases or even a large number of cases at a considerable distance from the index patient were shown to be transmitted via an airborne route. All the outbreaks investigated in the five studies occurred in hospitals or pediatric offices, highlighting the importance of air environments in health care settings. As the first conclusive study, Wehrle and colleagues (1970) used smoke tests to show the airflow pattern and dispersion of virus-laden aerosols from the index patient's room in a three-story hospital. The heat emitted from the radiators used for space heating introduced the upward flows through the stairwell as well as above the semi-open windows (for ventilation). Such air currents carried virus-laden aerosols into other rooms in the upper floors and subsequently caused infection and disease (Langmuir 1980).

These 10 studies demonstrated the role of building ventilation and airflows in relation to the spread or control of airborne infectious diseases. However, data were insufficient to specify or quantify the minimum ventilation requirements in hospital and non-hospital environments in relation to the spread of airborne infection. One exception is the work of Menzies and colleagues (2000), which showed an association between tuberculin conversion and ventilation of general or non-isolation patient rooms of less than 2 ACH. In light of this study and the ambiguous results of the many other studies related to ventilation and disease transmission, it is not surprising that the current design requirements for isolation rooms, operating theaters, and general hospital areas are not based on solid evidence (CDC 1994). Further studies are necessary to determine the ventilation requirements in non-hospital environments such as offices, homes, and schools. It may be beneficial for schools, residential homes for the elderly, institutions for the mentally ill, or prisons to have a higher ventilation rate during influenza peak seasons. Further work is also required to develop practical,

robust, and valid methods for measuring indoor bioaerosols due to their low concentration and mobility.

Of the 12 studies that were partly conclusive, three were outbreaks of M tb. (Calder et al. 1991; Edlin et al. 1992; Ehrenkranz and Kicklighter 1972), three studied SARS-CoV (Li et al. 2005; Olsen et al. 2003; Yu et al. 2004), two were measles outbreaks (Riley, Murphy, and Riley 1978; Remington et al. 1985), and four were on chickenpox, anthrax, and rhinovirus (Hoge et al. 1994; Riley et al. 1962; Moser et al. 1979). In addition, Leclair and colleagues (1980) provided incomplete ventilation data but strong epidemiological evidence for airborne transmission.

Knibbs and colleagues (2011) found that current outdoor air-exchange rates of 4.9 ACH in the lung function laboratory and 23.8 ACH in an emergency department isolation room limited infection risks of influenza, tuberculosis, and rhinovirus to 0.1 to 3.6 percent. For all scenarios, risk decreased rapidly as air exchange increased.

These studies imply that room ventilation is a key determinant of airborne disease transmission if no other factors are taken into account. Despite this, ventilation guidelines in hospitals do not take into account robust scientific evidence related to the prevention of airborne transmission.

Variables Involved in Disease Transmission

It is well documented that no single factor is responsible for the spread of infectious disease, regardless of the offending microorganism. Viruses that can be transmitted by the airborne and/or droplet route include SARS-CoV (FGI 2010), enteric viruses of intestinal origin (e.g., norovirus), chickenpox, measles, mumps and rubella viruses, and M. tb. There has been occasional spread of rabies virus due to aerosolization of laboratory viral strains (Aitken and Jeffries 2001).

Brundage and colleagues (1988) and Fisk (2001) cite evidence that low ventilation rates and other building characteristics (i.e., closed ventilation systems, tight buildings) can lead to increased rates of respiratory-transmitted diseases caused by viruses.

The involvement of numerous interacting and interrelated factors in the spread of infectious disease is also well documented. Among these factors are the effects of aerosol droplet and contact transmission dynamics; the nature of the dust levels; the health and condition of individuals' naso-pharyngeal

mucosal linings; patient susceptibility; the population density in a particular location; the ventilation of the location; temperature; humidity; geographic location; length of exposure; number of infected people producing contaminated aerosols; ventilation rate; infectious particle settling rate; nature of the infectious agent (e.g., enveloped or non-enveloped virus); presence of surrounding organic material; exposure to UV light or antiviral/microbial or fungal chemicals; microorganism resistance to antibiotic, antiviral, or antifungal therapy; type and degree of invasive procedures; spatial considerations such as seating or sleeping arrangements; contact with a carrier; persistence of pathogens within hosts; immuno-epidemiology; evolution; spread of resistance; and the role of host genetic factors. Regardless of the route or interaction of any of these factors, not every exposure to an infectious microbe will necessarily result in a symptomatic infection or an asymptomatic infection that creates a carrier situation leading to further infections of susceptible hosts (Memarzadeh 2001b). See also Figure 1 on page 5.

Spatial Considerations and Dispersion Factors

The puzzle of disease transmission is further complicated by the modes of transmission, the physical mechanisms of transmission, individual behaviors, and the lack of evidence for the effect of spatial and particle dispersion factors. Building ventilation systems help prevent building-associated illness by diluting and removing unknown airborne microbial contaminants.

Data on disease transmission and dilution factors have primarily come from populations that are relatively dense or in a poorly ventilated space. Incidents and data have been extrapolated from a variety of locations and circumstances to derive hypotheses for disease transmission.

It has been noted that in most studies of disease transmission, the duration of exposure is not taken into account (Memarzadeh 2011a, 2001b). However, some observational studies in overcrowded situations indicate that duration of exposure is important. A study of an overcrowded Russian prison, in which susceptible prisoners share enclosed spaces with infectious prisoners for very long periods, found that this arrangement appears to ensure the spread of TB (WHO 2001). From a 1950 study of nurses working in a TB ward, Riley and colleagues (1959) concluded that airborne M. tb bacilli were not very numerous in the ward and that it would take the better part of a year for a tuberculin-negative nurse working on a TB ward to convert to positive.

Beggs and colleagues (2003) conclude from this and other evidence that if a susceptible person remains in the presence of persons with open pulmonary

TB for long enough they will inevitably become infected, even when the quanta production rate is relatively low. Beggs and colleagues (2003) also suggest that ventilation rate expressed as ACH can be very misleading. Absolute ventilation rate, measured in m^3/s or m^3/min, more accurately predicts the potential to transmit disease to susceptible individuals in a more crowded enclosed space.

Chen and Zhao (2010) believe that a systemic and general analysis of factors that influence dispersion in a ventilated room, such as ventilation rate, indoor air humidity, indoor air temperature, ventilation pattern, droplet nuclei size, and exhaled initial velocity, may be helpful to understand the dispersion characteristic of exhaled droplets in an indoor environment.

The dilution effect of the ventilation system has been examined in depth (Cole and Cook 1998; Nardell et al. 1991; Rudnick and Milton 2003). The results of these studies have been used to develop guidelines and standards that specify minimum ventilation dilution recommendations to reduce the risk of airborne transmission of infectious diseases in different indoor environments (CDC 1994; FGI 2010). Air dilution, along with pressure differentials, air filtration, and other mechanical options can keep the risk of M. tb transmission low by reducing exposure to high concentrations of infectious airborne particles. CITC (2007) notes that the more effective the mixing of air, the better the dilution of infectious particles.

Beggs (2003) identified many epidemiologic studies that incorporated the ventilation dilution effect and developed different risk assessment models based on the perfectly mixed assumption inherent in the dilution concept. But most experts agree that evidence is insufficient to suggest a minimum ACH in most situations. There is evidence that low ventilation rates and other building characteristics can lead to increased incidence of respiratory diseases caused by viruses (Brundage et al. 1988; Fisk 2001).

The importance of spatial considerations dilution, and dispersion as evidenced in a Center for Advancing Microbial Assessment (CAMRA) report (Rayman 1997; Jones et al. 2009) has also been shown in a study by Chao and Wan (2006). Richmond-Bryant (2009) studied the characteristics of the spatial velocity and particle concentration profiles that might result in health care workers' exposure to a pathogenic agent in an AII room. Chen and Zhao (2010) note that this and other studies neglected to consider droplet evaporation when doing the simulations. Design of the ventilation system appears to play a significant role in particle transmission as well.

Computational fluid dynamics (CFD) in conjunction with optical measurement methods has incorporated factors such as evaporation features of aerosols to examine dispersion characteristics of expiratory aerosols within an enclosure with a ceiling-return and a unidirectional downward flow. One study showed that small aerosols had settling times of less than 20 seconds in downward flow, but the time increased to 32 to 80 seconds in ceiling-return flow. Lateral dispersion was increased to more than 2 minutes in ceiling-return flow, where there was a combination of turbulent dispersion and bulk-flow transport mechanisms. The significance of aerosol transport by bulk flow was about an order of magnitude stronger than that by turbulent dispersion. However, results also show that aerosols could be dispersed for considerable distances solely by turbulence if they were suspended longer. Large aerosols settled within a very short time due to heavy gravitational effects. The results demonstrated that the dispersion of expiratory aerosol in indoor environments could be controlled by manipulating the ventilation airflow patterns and provided new insights in designing proper bed spacing in hospital ward environments (Chao and Wan 2006).

Memarzadeh and Xu (2012) and Memarzadeh, Olmsted, and Bartley (2010) note that although the respiratory flows of infected individuals are one of the main sources of infectious airborne pathogens in hospitals, there are few studies on how exhalation flows interact with the room ventilation system. All previous studies focused on the contaminants exhaled or released from a standing or seated person. They note that small pressure differences induced by natural forces such as thermal buoyancy due to air temperature differences, the wind, or mechanical fans can move air from one room to another. Air filtration aims to reduce airborne concentrations to well below infectious doses. The spatial position of the patient in relation to others in the room appears to affect risk of transmission. In a hospital setting, patients lie in bed much of the time. The direction of an exhalation jet from a standing or seated person and that from a lying person can be different (e.g., the latter may be lying face up). The upward thermal plume generated by a standing or seated person is much stronger than that generated by a lying person. Thus, some differences between the behaviors of breathing flows in hospital and other indoor environments are expected. The exhalation jet from a lying patient can behave differently in different ventilation systems and can be affected by other factors, such as the mode of contaminant release and the thermal plume generated by the human body or other heat sources. Understanding how different ventilation systems affect breathing flows from a patient lying supine is useful for developing an effective ventilation method to minimize

the risk of cross-infection via airborne transmission. Droplet nuclei 5 µm in diameter exhibit a settling velocity of 1 meter/hour (88 feet per minute) in still air and can follow the exhalation flows as well as the ambient air flows in a hospital ward.

Small droplets may also participate in short-range transmission, but they are more likely than larger droplets to evaporate to become droplet nuclei, at which point they have the potential for long-range airborne transmission. True long-range aerosol transmission becomes possible when the droplets of infectious material are small enough to remain airborne almost indefinitely and to be transmitted over long distances. Pathogens that are not routinely transmitted via the droplet route can be dispersed into the air over short distances. For example, although Staphylococcus aureus is most commonly transmitted via the contact route, viral upper respiratory tract infection has been associated with increased dispersal from the nose into the air over a distance of 4 feet under both outbreak and experimental conditions. This is known as the *cloud baby* and *cloud adult* phenomena (Bassetti et al. 2005).

It is generally accepted that the respiratory flows of infected individuals contribute to the dissemination of infectious airborne pathogens. Memarzadeh and Xu (2012) examined the transport mechanism, the particle path, and a suggested control strategy for reducing airborne infectious disease agents. Most studies on the transmission of infectious disease particles have focused primarily on ACH and how this measure provides a dilution factor for possible infectious agents. The results of this study suggest that in an enclosed and mechanically ventilated room (e.g., an isolation room), the dominant factor in the transmission and control of contaminants is the path between the contaminant source and exhaust. Contaminants are better controlled when this path is uninterrupted by an air stream. This study illustrates that the ventilation system design (when it conforms to the hypothesized path principle) may be a more important factor than flow rate (i.e., ACH). A secondary factor is the distance from the contaminant source. This study provides evidence and support for previous findings that moving away from the patient generally reduces the infection risk in a transient (coughing) situation, although the effect is more pronounced under higher flow rate.

Airborne Particle Transmission

Airborne particles can contain disease-causing microorganisms. Typically, particle sizes for biologic aerosol particles are 0.02 to 0.3 µm for viruses, 0.5

to 10 µm for bacteria, and 0.5 to 30 µm for fungi. Pathogen-laden droplets expelled by an infected person dry out in the room air and produce fine particles and droplet nuclei that can suspend in the air.

Although the liquid evaporates, the residual droplet nuclei may remain in the air for long periods of time depending on particle size, velocity, and density; force of expulsion; humidity; and rate of air flow. Air currents, aided by the ventilation system, help to spread them over a wide area. The disease-causing organisms are inhaled by or come to rest near a susceptible person, who is subsequently infected through mucous membrane contact with contaminated hands or materials. Droplet nuclei are so small that they bypass the innate host defense mechanisms of the human upper respiratory tract and are deposited in the alveoli in the lungs (Fletcher et al. 2004).

Experimental studies with smallpox conducted by Downie and colleagues (1965) and investigations by Yu and colleagues (2004) during the 2003 global SARS outbreaks suggest that droplets from patients could reach persons located 1.83 meters [6 feet] or more from their source.

Particle movement in air is determined by Stokes's settling law, which governs how quickly a sphere falls under the opposing forces of gravity downward and air friction upward. The result is microbes contained in fluids that rapidly fall out of the air. Larger droplets with more mass are more strongly influenced by gravity and less so by air flows and move more ballistically, falling more quickly. Smaller droplets with less mass are less influenced by gravity and can be transported as a cloud over greater distances by air flows. These complex air movements make the route and suspension time of an infectious particle very difficult to determine once it has left the infectious host.

There is essential agreement that particles with an aerodynamic diameter of 5 µm or less are aerosols, whereas particles of 20 µm are large droplets. Studies show that 80 to 90 percent of particles from human expiratory activities are smaller than l µm (Papineni and Rosenthal 1997). When reviewing the literature, it is important to verify the size of the particles being studied and the investigators' definitions.

Sneezing can introduce as many as 40,000 droplets, which can evaporate to produce droplets of 0.5 to 12 µm (Olsen et al. 2003; Riley et al. 1962), while in a patient with active M. tb coughing naturally, the infectious particle size was 2.1 to 3.3 µm (Fennelly et al. 2004). These particles can be expelled at a velocity of 100 m/s (≈20,000 FPM) and reach distances of several meters. A cough can generate about 3,000 droplet nuclei (Fitzgerald and Haas 2005), the same number as talking for five minutes; a single sneeze can generate

100,000 floating bioaerosol particles, many containing viable microorganisms (Duguid 1945). Although a single cough typically produces a small percent of this amount, coughs occur about 10 times more frequently than sneezes. Some studies have shown that an M. tb–infected patient can produce 1 to 249 bacilli an hour, while a person in the infectious stage of a cold may produce 6 to 200 droplet nuclei per hour containing viable viruses that remain airborne longer than 10 minutes (Fitzgerald and Haas 2005).

Infectious bioaerosols may exist as single or aggregate cells, spores, viruses, or infectious material carried by an inanimate disseminating agent. When viable infectious droplets or droplet nuclei are present, any aerosol-generating activity—such as making a bed or walking around—exacerbates the movement of these particles. True long-range aerosol transmission becomes possible when the droplets of infectious material are sufficiently small to remain almost indefinitely airborne and to be transmitted over long distances.

Droplet transmission is a form of contact transmission, and some infectious agents transmitted via the droplet route also may be transmitted via the direct and indirect contact routes. However, in contrast to contact transmission, respiratory droplets carrying infectious pathogens transmit infection when they travel directly from the respiratory tract of the infectious individual to susceptible mucosal surfaces of the recipient, generally over short distances, necessitating mucous membrane protection.

Most pathogens have the potential for being transmitted by large droplets. Examples of pathogens that can be transmitted by large droplets but are not considered true airborne infections include SARS-CoV, whooping cough (Bordetella pertussis), influenza virus, adenovirus, rhinovirus, Mycoplasma pneumoniae, group A streptococcus, and bacterial meningitis (Neisseria meningitidis). Evidence exists that Chlamydia psittaci and Chlamydia pneumonia are transmitted by airborne droplet nuclei (Riley et al. 1962).

Microorganisms are also hygroscopic. A 1.5 µm hygroscopic particle, which is an average size in coughs and sneezes, may increase to 2.0 µm in diameter when passing through the nose and to 4.0 µm in the saturated air of the nasopharynx and the lung (Knight 1993). The larger size may affect retention in the lung. Thus, the relative humidity can have a profound effect on the transport of the particles as a result of change in size, viability, and airborne duration. Gravitational, thermal, and electrostatic fields profoundly affect their aerodynamic behavior (Riley et al. 1962).

Dust has been implicated as a vector in airborne transmission of infectious disease as well as an irritant and allergen. A variety of studies indicate that

most exposures to airborne dust in nonindustrial indoor environments range from 15 to 200 lg/m3. The dust can be described as consisting of a relatively inert base with the addition of biologically active compounds such as allergens or toxic chemicals (Knight 1993; Armstrong, Sherertz, and Llewellyn 1990; Gyntelberg et al. 1993, 1994; Hauschildt, Mølhave, Kjærgaard 1999; Hedge et al. 1989; Hodgson and Collopy 1990; Kjærgaard and Brandt 1993; Lebowitz, Quackenboss, and Kryzanowski 1990; Skov, Valbjørn, and Gyntelberg 1989; Wallace 1996; Mølhave et al. 2000).

A relatively transient condition known as *organic dust toxic syndrome*, which can result in chronic obstructive pulmonary disease in long-duration exposures (Vogelzang et al. 1998), occurs within hours of a high-dose inhalation of endotoxin, fungal spores, and mycotoxins (Von Essen et al. 1990). Mølhave and colleagues (2000) conducted an exploratory study on the effects of dust on the eyes. The results imply that even relatively low concentrations of office dust may have an effect. It is possible that the effects accumulate over repeated daily exposures, resulting in a sensitization of the exposed individuals. The authors suggest that among healthy nonsensitized subjects, a continuum of risk factors may exist. They believe that although it isn't possible to draw final conclusions on the effects of dust, the dust interacts with other variables to cause a reaction. Bacterial endotoxins, present in house dust and airborne particulate matter, are thought to cause a range of flu-like symptoms (Rylander et al. 1989, 1992). The most commonly measured microbiological contaminants measured in schools were allergens in deposited dust (e.g., house dust mite allergen, fungi, bacteria). The levels of these allergens were high enough to cause allergy symptoms in allergic occupants. Evidence of a dose–response relationship was reported (Smedje, Norback, and Edling 1997).

Effects of Ventilation System Design

A ventilation system design study by Memarzadeh, Wilson, and Ramesh (2011) shows how ventilation system design affects particle movement in an AII room. The study indicated that low exhaust and high ventilation flow removed the most particles. With a lying patient, 12 ACH removed more particles than did 16 ACH with high exhaust. This can be explained by the flow pattern above the patient, which is determined by the downward forced convection from the ceiling diffusers above the bed and the upward flow of the cough from the mouth of the lying patient. With greater downward flow (16 ACH rather than 12 ACH) from the ceiling diffuser, the upward movement of droplets carried by the cough of a lying patient could be suppressed

and thus have difficulty reaching high exhausts. The authors concluded that low exhaust removes more particles and decreases the number of particles remaining around a bed than other exhaust locations do. Increasing ventilation flow from 12 to 16 ACH generally helps to remove particles from an isolation room (except in cases of high exhaust and a lying patient coughing), but not necessarily a breathing zone. The number of particles in a bathroom resulting from a cough in a main room is dependent on air-current particle distribution and bathroom location.

Numerous aircraft studies indicate that ventilation is one of the most critical factors in airborne disease transmission (Moser et al. 1979; Aviation Health Working Group 2001a; National Research Council 1986; WHO 1998; Select Committee on Science and Technology 2000; Kenyon et al. 1996). Fernstrom and Goldblatt (2013) reviewed many of the aerobiological variables (e.g., particle size, particle type, duration that particles can remain airborne, distance that particles can travel, meteorological and environmental factors), as well as the common origins of infectious particles. They state that "practitioners of all kinds agree that the airborne transmission of infectious disease is a problem. Just how big or urgent a problem, however, continues to be debated" (Fernstrom and Goldblatt 2013). Studies also have stated that one air change per hour of well-mixed air in any space is thought to remove 63 percent of the airborne organisms in that space (Nardell et al. 1991; Riley and Nardell 1989). The recirculation of cabin air is known not to be a risk factor for contracting upper respiratory tract infections (Zitter et al. 2002), but airborne transmission becomes widespread in passenger cabins with no ventilation (Moser et al. 1979; National Research Council 1986; WHO 1998).

While a 2003 study by Olsen and colleagues showed a spatial component to a SARS transmission aboard an aircraft, another aircraft incident led the CDC to perform an aggressive investigation on M. tb transmission aboard an aircraft in 2007. From this investigation, they developed a risk analysis methodology (the first study of its kind, to our knowledge) that provides a tool to calculate the risk of infection in the real world. The incident resulting in this study occurred when a multidrug-resistant tuberculosis (MDR) infected traveler flew from Atlanta to Paris and then from Prague to Montreal. Each of the transatlantic flights lasted approximately eight hours. The traveler was hospitalized upon his return to Atlanta. The CDC developed a quantitative microbial risk assessment tool to determine the risk of infection to the 80 people within five rows surrounding the infected person during the flights. In this CAMRA study, the investigators (Rayman 1997; Jones et al. 2009)

used computational fluid dynamics to show that the seating pattern in different sizes of aircraft (Boeing 747, Boeing 767, Airbus 310), the location of the air inlets, the overhead baggage compartments, and the air flow pattern all affect the magnitude of the exposures and risk to passengers as a result of the stable eddies within each row and the advective velocity toward the cabin rear. Passengers seated next to the source case had the highest doses.

The CAMRA study showed that the range of bacilli emission from the patient is one of the components that drive the risk. In the human respiratory tract, about 20 percent of particles in the 1 to 4 µm range that are inhaled via the nose deposit in the alveolar region and may be expelled via the sputum and saliva from coughing and sneezing. In the CAMRA risk analysis methodology, concentration in the saliva and the amount and size distribution of particles emitted by coughing were used to determine the concentration of M. tb in the aircraft. The analysis predicted the removal of M. tb from the breathing zones of seated passengers within five minutes of emission, resulting in the conclusion that the concentration of M. tb. would not build up in the aircraft cabin for cough frequencies of 10 to 12 per hour. The doses due to a series of coughs are additive. The study examined two parameters derived from data of symptomatic patients: M. tb concentration in sputum and saliva and number of coughs per hour (Yeager et al. 1967). Using 20 ACH based on the Ko, Thompson, and Nardell (2004) estimate, and assuming that the particles are well mixed, the study determined that the particles are emitted at the air-exchange rate of 4.2 m^3/hour or 2.4 cfm. Decay rate of the M. tb in air or aerosol was not considered. Air inhalation rate for each passenger was set at 0.54 m^3/hour. This model assumes passengers are exposed to equal amounts of M. tb cells. The model provides a useful tool for estimating the probability of risk of exposure to an individual based on their location and distance from the source or index case. The risk of infection on average ranged from 1/1000 to 4/10,000, with detectable average ranges of bacilli in the saliva. However, with nondetectable bacilli, the risk was seen as ranging from less than 2/100 million to approximately 6/billion. The concentrations were assumed on the basis of data from symptomatic patients. This study supported the hypothesis that ventilation may be an important determinant of airborne infection risk on airplanes (Zitter et al. 2002).

Natural vs. Mechanical Ventilation Systems

Escombe and colleagues (2007) examined the effect of natural ventilation in hospitals. Comparisons were made between older hospital buildings that used open windows for ventilation versus newer hospitals that used

mechanical ventilation. A carbon dioxide tracer gas was used to establish the number of air changes in various sizes of rooms, with and without open windows and doors. Infection risk for M. tb was predicted using the Wells-Riley equation (see sidebar on page 14). The risk of airborne spread was far lower in rooms with open windows than in the expensive mechanically ventilated rooms. Low-cost natural ventilation seems to be a better option than negative pressure ventilation in tropical countries. The main drawback is possible contamination of adjacent areas when airflow is inward. In addition, the epidemiology of transmission of TB in the facilities studied by Escombe and colleagues is unknown as this investigation did not include contacts of patients with active TB to discern if there was less occupational transmission of M. tb with high ACH.

Levin (1989, 2007) also suggests that the tuberculosis infection rate was not actually reduced by opening windows as suggested in Escombe and colleagues' investigation because infection rates were merely calculated using the Wells-Riley equation. While it is important to consider the ventilation rate provided by mechanical ventilation systems, the rate through open windows must take into account window size, number of windows, and location in a room as modified by indoor–outdoor temperature differences and wind direction and velocity.

Modes of Transmission

Many people assume that infectious diseases are spread via airborne transmission and they associate that process with natural or mechanically created air currents. This assumption is inherently flawed because in addition to the complexity of airborne transmission, strong evidence suggests that infection transmission may occur via other routes. Transmission of infectious particles may occur through a ventilation system, but there are clear incidents of transmission from water reservoirs or particle settling on surfaces and being acted upon by the surrounding atmosphere via hydro- and hygroscopic factors—temperature and relative humidity and dust, for example. The infectious agent may also undergo a physical change caused by evaporation, dehydration, rehydration, effects of UV light, or any number of other physical parameters.

From a biological perspective, infectious diseases are caused by microbial, viral, or fungal pathogens, each of which has unique attributes that affect transmission (Tang et al. 2011). The pathogens are dependent on physical factors such as cell or particle size, route of entry into the body, physical

state of the infectious agent, virulence, and individual recipient susceptibility. Each of these factors, in turn, may be affected by a multitude of other variables.

Infectious disease is transmitted between animals and humans or in a person-to-person pattern, though acquisition typically requires prolonged or repeated contact in an indoor environment, as opposed to casual contact. Diseases can be spread from a single source (index source) such as an individual. The relationship between the incubation period and the pattern of onset of illness determines whether the disease arose from a single source or represents ongoing or propagated transmission (Sartwell 1995).

There are three primary routes of transfer: (1) direct contact and fomites, which are inanimate objects that transport infectious organisms from one individual to another (Boone and Gerba 2007); (2) large droplets (generally with a mass median aerodynamic diameter [MMAD] of > 10 µm); and (3) particles with MMAD < 10 µm, sometimes termed *droplet nuclei*. Clinically applicable distinctions are made between short-range droplet transmission (i.e., between individuals, generally 1 meter apart) and long-range routes (i.e., within a room, between rooms, or between distant locations, generally distances greater than 1 meter). Recent work by Xie and colleagues (2007) identifies large droplets as those larger than 5 to 100 µm at the original time of release. Nicas, Nazaroff, and Hubbard (2005) show by modeling that emitted large droplets will evaporate to 50 percent of their initial value and that if the initial diameter is < 20 µm, this process will happen instantaneously. However, large droplets released in short-range aerosols (e.g., sneezing) are sometimes confused with airborne transmission, but such released particles do not typically transmit over long distances. Clinically applicable distinctions are also made between short-range airborne infection routes (between individuals, generally less than 1 meter [3.28 feet] apart) and long-range routes (within a room, between rooms, or between distant locations, generally greater distances than 1 meter [3.28 feet]). Some infectious agents (e.g., SARS) may transmit primarily by large droplets, but under some situations they may be transmitted through air in various modes (FGI 2010). Roy and Milton (2004) classified aerosol transmission of diseases on the basis of the agent's capacity to be transmitted and to induce disease through fine-particle aerosols and other routes.

A particle's size is a consequence of the process that led to its generation, and thus it is dependent on the source. The content of an infectious agent expelled by an infected person depends, among other factors, on the location within the respiratory tract from where the droplets originate.

Pathogenic organisms usually reside in the tonsil, larynx, and lung and seldom at the front of the mouth. To assess the potential for infection via airborne or droplet route, an understanding of the localities from which droplets originate during various expiratory activities and the numbers of droplets arising from each site is needed (Daisey and Angell 1998). Breathing, coughing, singing, and sneezing by an infected person can generate pathogen-containing particles of saliva and mucus with diameters < 10 μm (Daisey and Angell 1998; Gold and Nankervis 1989). Studies have suggested that droplets larger than 20 μm rapidly settle onto surfaces (Gold and Nankervis 1989), while droplets between 0.5 and 20μm remain in the air for long periods and are more likely to be captured in the respiratory tract and produce infection (McCluskey, Sandin, and Greene 1996). If particles carrying pathogens are inhaled by a susceptible individual and deposited in a suitable location in the respiratory tract, infectious disease may occur (Remington et al. 1985).

WHO's 2009 ventilation guidelines (Atkinson et al. 2009) determined minimum ventilation rate requirements based on the effect of air-change rate on decay of droplet nuclei concentration and estimation of the effect of ventilation rate on infection risk for known airborne diseases using the Wells–Riley equation. These underlying principles indicate that the higher the ventilation rate, the more rapid the decay of particles (e.g., droplet nuclei) in the room air.

Chen and Zhao (2010) recommend that when reviewing the literature and designing CFD analysis to study droplet dispersion as related to indoor disease transmission, the transient process whereby a droplet becomes a droplet nucleus due to evaporation should not be ignored.

Influenza is transmitted primarily through close contact, such as during exposure to large respiratory droplets, direct contact, short-range exposure to infectious aerosols, or a combination of these routes (Brankston et al. 2007). However, the relative contribution and clinical importance of each of these modes of transmission have not been established.

Klontz and colleagues (1989) performed a highly cited study that looked at an influenza outbreak in aircraft. They looked at two military aircraft with fully functioning ventilation systems that had 15 ACH in the passenger cabin and directional airflow from ceiling to floor with minimum horizontal airflow. Within 72 hours of deplaning, 56 percent of the passengers on both planes became ill. A significant difference in risk of acquiring influenza was observed between the two aircraft and appeared to be related

to the number of symptomatic persons on board. The epidemiologic data show that secondary transmission of influenza to family members and roommates occurred in the days following the initial cases. Movement on the plane was not mentioned as a possible factor in transmission. It is difficult to draw conclusions regarding the mode of transmission in this study due to the lack of controlled scientific evidence to support any single or combined factor(s).

One of the major studies to define influenza as an airborne pathogen was a classic observation by Moser and colleagues (1979). The authors investigated an opportunistic outbreak of influenza due to a lack of outdoor air coming into the enclosed space of a grounded aircraft. The ventilation system was inoperative for more than three hours, and 72 percent of passengers were infected with influenza. This outbreak was attributed to poor ventilation but could also have been caused by close contact with the index case. The occurrence of infection increased with time spent on the aircraft. In addition, the aircraft was unique in that half of it was used for cargo and half for passengers. In short, this case study provides no clear evidence for a single mode of transmission or that ventilation was the primary factor. The passengers were moving around and probably touching surfaces that contaminated their hands, and there was no air circulation. Thus, those who became ill may have been infected via any of the common modes of transmission.

Another cluster of disease on an airplane involved (MDR-TB, as reported by Kenyon and colleagues (1996), in which highly infectious TB transmission was limited to proximity of the index patient when the ventilation system was effective. The CDC conducted epidemiological studies of M. tb transmission in airplanes and found that although the airplane environment contributes to the risk of infection transmission, other indoor factors are also involved, although the relative importance of any factor is unknown (Bassetti et al. 2005; Memarzadeh, Wilson, and Ramesh 2011). The results from numerous studies related to modes of transmission suggest that the mode probably differs according to the setting and environmental conditions. This hypothesis has led to the belief that implementing engineering control methods in health care facilities could reduce hospital-acquired infections (Tellier 2006). However, a review of the same evidence by Brankston and colleagues (2007) reinforced that a hierarchy of administrative, environmental, and PPE controls are effective in mitigating cross-transmission of influenza. This review also concluded that "the airborne route of transmission [is] unlikely to be of significance in most clinical settings."

Additional Research Is Needed

A great deal of additional research is needed to make valid conclusions regarding the number of air changes per hour needed to reduce disease transmission. More accurate and comprehensive models that account for mixing, room volume, occupant density, proximity, host susceptibility, and the pathogenicity of infectious agents need to be developed (Beggs et al. 2003). Further measurement is also required of bioaerosols at different concentrations and different airflow rates. A broader variety of mechanical and natural ventilation, HEPA filtration, and UV germicidal irradiation strategies in offices, homes, schools, prisons, long-term health care facilities (e.g., nursing homes), laboratories, and acute health care facilities need to be evaluated under controlled experimental conditions rather than in observational and retrospective studies to determine the best approaches for reducing infectious disease transmission. Strategies may differ according to the disease and the particular set of circumstances, thus giving rise to improved risk assessment methodologies.

Future research should integrate the role of the ventilation system, the health status of the occupants, spatial relationships among them, and duration of exposure, thus requiring a multidisciplinary approach.

Conclusion

In summary, there are insufficient data to specify or quantify the minimum ventilation requirements in public spaces, including hospitals, office buildings, aircraft, and schools in relation to the spread of airborne infection. Further studies are needed to determine ventilation requirements in hospital and non-hospital settings. Practical, robust, and valid methods must be developed for measuring indoor bioaerosols, due to their low concentration and mobility. These studies may be applicable to the ventilation design of future buildings and renovations. The 2013 study by Faulkner and colleagues indicated that in some situations the advantages of increasing ACH may be limited in terms of providing better environments in the occupied zones of rooms.

Although the presence of a risk factor for a particular pathogen increases the chances of contracting an illness, it does not always lead to an illness. On the other hand, the absence of any single risk factor or the existence of a protective factor does not necessarily guard against getting an infection (Memarzadeh and Xu 2012). It is crucial to find a balance between reducing

infectious disease transmissibility and maintaining occupant comfort and ventilation rates.

The variables affecting the relationship between ACH and infection transmission are so many and the evidence for the causative or associated role of ACH in disease transmission is so incomplete that it is not easily possible to determine the direct effect of ventilation on disease transmission. As yet, no single prescribed ACH rate for any particular set of circumstances—or as a function of any other variable—is known to fully prevent disease transmission. However, there is sufficient evidence from studies of natural ventilation and controlled indoor ventilation to suggest that ACH plays a role in controlling disease transmission. Therefore, the most prudent course of action is to carefully consider a risk assessment and look at evidence-based factors to determine the best ACH for a space.

To provide a sound basis for setting standards, more studies are needed in which the relationship between symptoms and measured exposures to multiple specific pathogens/pollutants is investigated. Furthermore, quantitative information is needed on the relationship between exposure and health response for specific pollutants suspected to cause health symptoms.

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www.ashe.org

June 5, 2017

Version 1.1

Developing a Water Management Program to Reduce *Legionella* Growth & Spread in Buildings

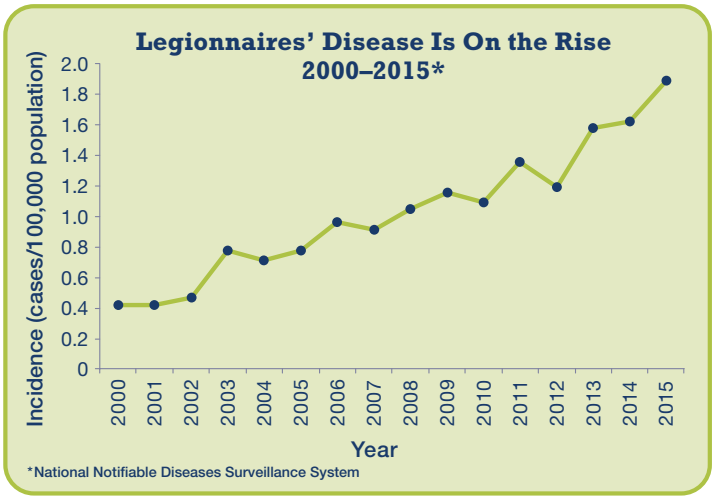
A PRACTICAL GUIDE TO IMPLEMENTING INDUSTRY STANDARDS

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Foreword

Legionnaires' disease is a serious type of pneumonia caused by bacteria, called *Legionella*, that live in water. *Legionella* can make people sick when they inhale contaminated water from building water systems that are not adequately maintained. Unfortunately, Legionnaires' disease is on the rise in the United States. To reverse this trend, we are asking for your help to manage the risk of exposure to *Legionella* from water in your building.

Your building may need a water management program to reduce the risk for Legionnaires' disease associated with your building water system and devices. This water management program should identify areas or devices in your building where *Legionella* might grow or spread to people so that you can reduce that risk. *Legionella* water management programs are now an industry standard for large buildings in the United States (ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta).



In the United States, reported cases of Legionnaires' disease have increased by nearly four and a half times since 2000. More illness occurs in the summer and early fall but can happen any time of year.

This toolkit will help you develop and implement a water management program to reduce your building's risk for growing and spreading *Legionella*. If you already have a program, this toolkit will help you assess and strengthen it. Included are practical resources to help you ensure that your water management program is comprehensive, effective, and in line with industry standards. This toolkit also highlights special considerations for healthcare facilities.

Because building water systems vary in their design and complexity, examples in this toolkit are only meant to help you understand the process. You should develop a water management program to reduce *Legionella* growth and spread that is specific to your building.

We welcome your feedback on this toolkit by emailing RDB@cdc.gov.

For additional information about Legionnaires' disease, visit www.cdc.gov/legionella.

This toolkit can also be found online at www.cdc.gov/legionella/WMPtoolkit.

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Table of Contents

Foreword ii

How to Use This Toolkit 1

Identifying Buildings at Increased Risk 2

Glossary 3

Introduction to *Legionella* Ecology 4

Elements of a Water Management Program 6

Establish a Water Management Program Team 7

Describe Your Building Water Systems Using Text 8

Describe Your Building Water Systems Using a Flow Diagram 10

Identify Areas Where *Legionella* Could Grow & Spread 11

Control Measures & Corrective Actions: The Basics 12

Decide Where Control Measures Should Be Applied 13

Decide How to Monitor Your Control Measures 14

Establish Ways to Intervene When Control Limits Are Not Met 15

- Corrective Action Examples 15
- Contingency Response Examples 18

Make Sure the Program Is Running as Designed & Is Effective 21

Document & Communicate All the Activities of Your Water Management Program 22

Special Considerations for Healthcare Facilities 23

- Elements of a Water Management Program 23
- Identifying & Investigating Legionnaires' Disease Cases 24

References & Resources 26

Appendix A 29

Appendix B 30

How to Use This Toolkit

If you've never developed a *Legionella* water management program (a plan to reduce the risk of *Legionella* growth and spread), you might not be sure where or how to start. This toolkit will provide guidance to help you develop, implement, and evaluate a *Legionella* water management program for your building. You do not have to have training or certification in any specific hazard analysis, risk assessment, or risk management methodologies to use this toolkit. However, you may need to seek help from an expert in some cases. Be sure to follow all relevant federal, state, and local laws, regulations, and ordinances. If anything in this toolkit conflicts with these policies, always adhere to the policies.

Where do we start?

The first step is to determine if you even need a program. You can use the worksheet on page 2 to find out if your entire building or parts of it are at increased risk for *Legionella* growth and spread. If you learn that you need to develop a program, this toolkit will explain what steps you should take and give several examples to clarify the process.

Do we really need a water management program to prevent *Legionella* growth and spread?

If you answer **YES** to any of the questions on page 2, then yes! Developing and implementing a program means that you are helping to protect people from getting Legionnaires' disease, a serious type of pneumonia (see Appendix A for more information on this disease).

Is this toolkit full of scientific terms?

You might come across some technical terms that are unfamiliar. The glossary on page 3 and the introduction to *Legionella* ecology on pages 4–5 should help you with these terms.

Will this toolkit tell us everything that we need to do?

No. Because every building is unique, only you have access to all the information that is needed to develop and implement a program specific to your building. An example of a building is included to help illustrate some of the steps. It's important to know that these examples are not comprehensive and you will need to create a program specific to your building water system and devices.

This toolkit looks really long. What's the bottom line?

You need to actively identify and manage hazardous conditions that support growth and spread of *Legionella*. As you work through the toolkit, you'll learn about the importance of identifying and controlling hazardous conditions that increase the chance of *Legionella* growth and spread. The bottom line is that you need to:

- Identify building water systems for which *Legionella* control measures are needed
- Assess how much risk the hazardous conditions in those water systems pose
- Apply control measures to reduce the hazardous conditions, whenever possible, to prevent *Legionella* growth and spread
- Make sure the program is running as designed and is effective

Is there anyone who can help us develop our program?

Yes. As you'll learn in the toolkit, it's recommended that you form a water management team. Your team should include a variety of people who bring different skills to the table (learn more on page 7). You might already have all the expertise you need on staff, but sometimes you will need to get outside help. In some cases, you may need to train your in-house personnel or hire professionals with specific experience in *Legionella* bacteria in building water systems, such as a certified industrial hygienist, a microbiologist, or an environmental health specialist. Blueprints could come in handy, too.

What do all of the gray boxes mean?

The gray boxes throughout the document highlight program elements that are especially relevant for healthcare facilities. The content found outside of the gray boxes is also applicable to these types of facilities.

Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

Identifying Buildings at Increased Risk

Survey your building (or property) to determine if you need a water management program to reduce the risk of *Legionella* growth and spread.

If you answer YES to any of questions 1 through 4, you should have a water management program for *that building's* hot and cold water distribution system.

Healthcare Facilities

Yes ____ No ____ 1. Is your building a healthcare facility where patients stay overnight or does your building house or treat people who have chronic and acute medical problems† or weakened immune systems?

Yes ____ No ____ 2. Does your building primarily house people older than 65 years (like a retirement home or assisted-living facility)?

Yes ____ No ____ 3. Does your building have multiple housing units and a centralized hot water system (like a hotel or high-rise apartment complex)?

Yes ____ No ____ 4. Does your building have more than 10 stories (including basement levels)?

Devices in buildings that can spread contaminated water droplets should have a water management program even if the building itself does not. If you answer NO to all of questions 1 through 4 but YES to any of questions 5 through 8, you should have a water management program for *that device*.

Yes ____ No ____ 5. Does your building have a cooling tower*?

Yes ____ No ____ 6. Does your building have a hot tub (also known as a spa) that is not drained between each use?

Yes ____ No ____ 7. Does your building have a decorative fountain?

Yes ____ No ____ 8. Does your building have a centrally-installed mister, atomizer, air washer, or humidifier?

If you answer NO to questions 1 through 8, you should still maintain water systems according to manufacturer recommendations. On properties with multiple buildings, prioritize buildings that house or treat people who are at increased risk for Legionnaires' disease (see Appendix A to learn who is at increased risk).

The building standards discussed in this toolkit do not apply to single-family or small multiple-family residences (e.g., duplexes), even those with the devices in questions 6 through 8, but residents do need to take steps to protect themselves from waterborne diseases.

Homeowners should follow local and state guidelines for household water use, and owners of the devices in questions 6 through 8 should follow the manufacturer's instructions regarding cleaning, disinfecting, and maintenance.

Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

†Burns, cancer, solid organ or bone marrow transplant, kidney disease, diabetes, or chronic lung disease

*For a definition of a cooling tower, visit www.cti.org/whatis/coolingtower.shtml.

Glossary

Biofilm (slime): Germs and the slime they secrete that stick to and grow on any continually moist surface; provides housing, food, and security for many different types of germs, including *Legionella*

Building water systems: Includes hot and cold water distribution and all devices that use water people can be exposed to, such as hot tubs, decorative fountains, and cooling towers

Control: To manage the conditions within your building according to your water management program

Control measures: Things you do in your building water systems to limit growth and spread of *Legionella*, such as heating, adding disinfectant, or cleaning

Control limits: The maximum value, minimum value, or range of values that are acceptable for the control measures that you are monitoring to reduce the risk for *Legionella* growth and spread

Control points: Locations in the water systems where a control measure can be applied

Contingency response: Reaction to control measures that are persistently outside of control limits or events that pose an immediate risk to control of your building water systems; required for all instances when Legionnaires' disease occurs, but may also be appropriate for unexpected events such as equipment failure or acts of nature that disrupt the water system

Corrective action: Actions taken to reestablish control when monitoring or measurement values are outside control limits

Dead legs: Piping that is subject to low or no flow due to design or decreased water use such as capped pipes or unused faucets

Disinfectant: Chemical or physical treatment used to kill germs, such as chlorine, monochloramine, chlorine dioxide, copper-silver ionization, ultraviolet light, or ozone

Hazardous conditions: Anything that, if not controlled, can contribute to the growth and spread of *Legionella* to a person

Healthcare facility: A place where patients stay overnight for medical care or where people with chronic or acute medical problems* are treated; this may include inpatient or outpatient care areas

Heterotrophic plate counts: A measure of the number and variety of bacteria that are common in water; a high count may indicate a high microbial load and the need for corrective action, but cannot be substituted for *Legionella* testing

***Legionella*:** Bacteria that can cause Legionnaires' disease

Legionnaires' disease: A serious type of pneumonia caused by *Legionella*

Residual: The amount of disinfectant available in water to kill germs

Scale and sediment: The mineral build-up in a water system that uses up disinfectant and supports germ growth and/or survival

Stagnation: When water does not flow well; areas of stagnant water encourage biofilm growth and reduce temperature and level of disinfectant

* Burns, cancer, solid organ or bone marrow transplant, kidney disease, diabetes, or chronic lung disease

Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

Introduction to *Legionella* Ecology

Legionella pneumophila

Legionella is found naturally in freshwater environments, like lakes and streams, but generally the low amounts in freshwater do not lead to disease. *Legionella* can become a health problem in building water systems. To pose a health risk, *Legionella* first has to **grow** (increase in numbers). Then it has to be **aerosolized** so people can breathe in small, contaminated water droplets.

Where can *Legionella* grow and/or spread?

***Legionella* can grow in many parts of building water systems that are continually wet, and certain devices can then spread contaminated water droplets. Examples include:**

- Hot and cold water storage tanks
- Water heaters
- Water-hammer arrestors
- Expansion tanks
- Water filters
- Electronic and manual faucets*
- Aerators
- Faucet flow restrictors
- Showerheads* and hoses
- Pipes, valves, and fittings
- Centrally-installed misters*, atomizers*, air washers*, and humidifiers*
- Nonsteam aerosol-generating humidifiers*
- Infrequently used equipment, including eyewash stations*
- Ice machines*
- Hot tubs*
- Decorative fountains*
- Cooling towers*
- Medical devices* (such as CPAP machines, hydrotherapy equipment, bronchoscopes)

*These devices can spread *Legionella* through aerosols or aspiration

Factors external to buildings that can lead to *Legionella* growth

- **Construction:** Vibrations and changes in water pressure can dislodge biofilm and free *Legionella* into the water entering your building.
- **Water main breaks:** Changes in water pressure can dislodge biofilm and free *Legionella* into the water, while dirt and other materials can be introduced into the water and use up disinfectant.
- **Changes in municipal water quality:** Changes in water quality can increase sediment, lower disinfectant levels, increase turbidity, or cause pH to be outside recommended ranges. Changes in disinfectant type can impact how you should monitor your program.

Factors internal to buildings that can lead to *Legionella* growth

- **Biofilm:** Protects *Legionella* from heat and disinfectant; provides food and shelter to germs; grows on any surface that is constantly moist and can last for decades
- **Scale and sediment:** Uses up disinfectant and creates a protected home for *Legionella* and other germs
- **Water temperature fluctuations:** Provide conditions where *Legionella* grows best (77°F–108°F); *Legionella* can still grow outside this range
- **Water pressure changes:** Can cause biofilm to dislodge, colonizing downstream devices
- **pH:** Disinfectants are most effective within a narrow range (approximately 6.5 to 8.5)

  Many things can cause the hot water temperature to drop into the range where *Legionella* can grow, including low settings on water heaters, heat loss as water travels through long pipes away from the heat source, mixing cold and hot water within the plumbing system, heat transfer (when cold and hot water pipes are too close together), or heat loss due to water stagnation. In hot weather, cold water in pipes can heat up into this range.

- **Inadequate disinfectant:** Does not kill or inactivate *Legionella.*

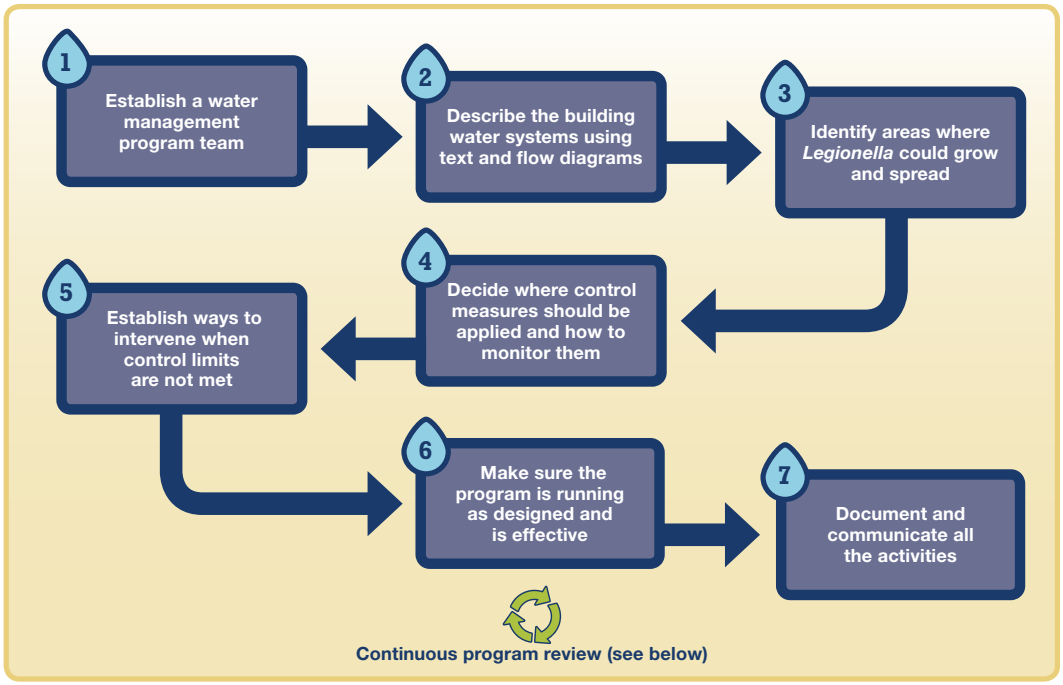
  Even if the water entering your building is of high quality, it may contain *Legionella*. In some buildings, processes such as heating, storing, and filtering can degrade the quality of the water. These processes use up the disinfectant the water entered with, allowing the few *Legionella* that entered to grow into a large number if not controlled.

- **Water stagnation:** Encourages biofilm growth and reduces temperature and levels of disinfectant.

  Common issues that contribute to water stagnation include renovations that lead to 'dead legs' and reduced building occupancy, which can occur in hotels during off-peak seasons, for example. Stagnation can also occur when fixtures go unused, like a rarely used shower in a hospital room.

Elements of a Water Management Program

Developing and maintaining a water management program is a multi-step, continuous process. The key steps, listed here, are explained in more detail throughout the toolkit with the associated step number appearing on the page where the specific step is discussed.



Program Review

You need to **review** the elements of your program at least once per year. Make sure you also review and revise your program when any of the following events occur:

- Data review shows control measures are persistently outside of control limits
- A major maintenance or water service change occurs, such as:
  - New construction
  - Equipment changes (e.g., new hot tub chlorinator pump)
  - Changes in treatment products (e.g., disinfectants)
  - Changes in water usage (e.g., high and low season for hotel)
  - Changes in the municipal water supply
- One or more cases of disease are thought to be associated with your system(s)
- Changes occur in applicable laws, regulations, standards, or guidelines

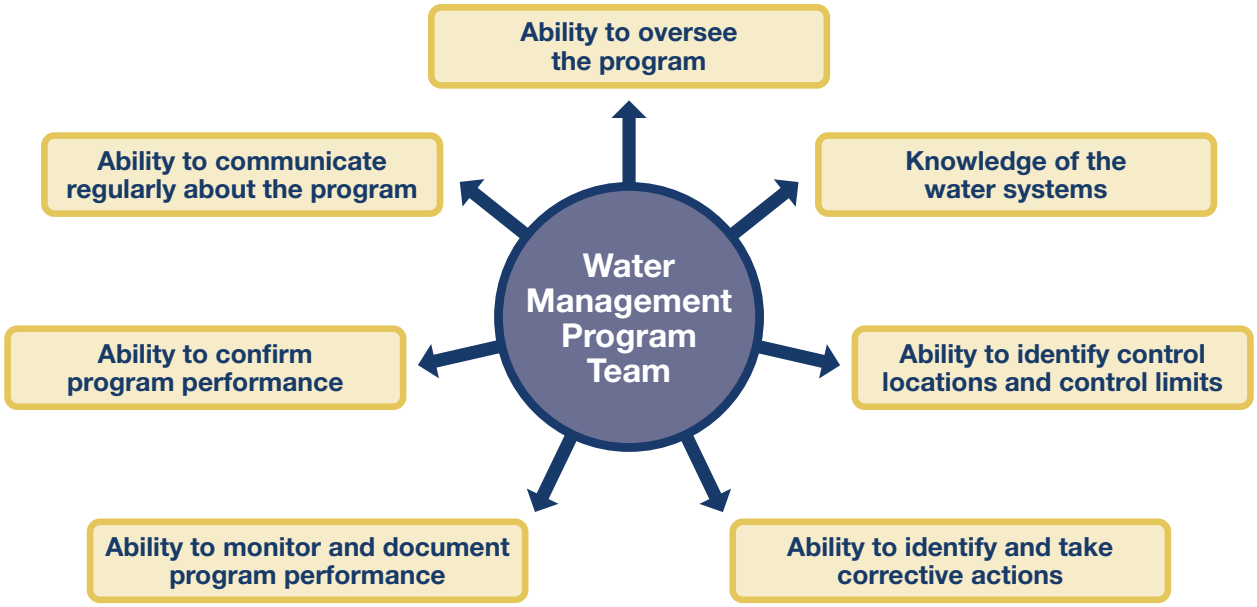
If an event triggers you to review and update your water management program, remember to:

- Update the process flow diagram, associated control points, control limits, and corrective actions
- Update the written description of your building water systems
- Train those responsible for implementing and monitoring the updated program

Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

Establish a Water Management Program Team

Certain skills, described in the diagram below, are needed to develop and implement your water management program. These skills would typically be provided by a combination of people, some of whom may have multiple skills (examples shown below).



Consider who among your employees, partners, and outside experts can provide these skills so that you can develop the most effective program possible. Those who might be part of your water management program team include:

- Building owner
- Building manager/administrator
- Maintenance or engineering employees
- Safety officers
- Equipment or chemical suppliers
- Contractors/consultants (e.g., water treatment professionals)
- Certified industrial hygienists
- Microbiologists
- Environmental health specialists
- State and local health officials

Healthcare Facilities

The team should also include:

- Someone who understands accreditation standards and licensing requirements
- Someone with expertise in infection prevention
- A clinician with expertise in infectious diseases
- Risk and quality management staff

In some cases, you may need to train your in-house personnel or hire professionals with specific experience in *Legionella* bacteria in building water systems.

Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

2 Describe Your Building Water Systems Using Text

EXAMPLE: BUILDING A

You will need to write a simple description of your building water system and devices you answered YES to on page 2. This description should include details like where the building connects to the municipal water supply, how water is distributed, and where pools, hot tubs, cooling towers, and water heaters or boilers are located. An existing as-built diagram of the plumbing system and fixtures may be useful in developing this description. Below is a description of the water systems* for an example building (Building A). You will see how this text gets turned into a diagram in the next section (page 10).

1. **Water enters** the basement of the property via a 4-inch main from the municipal water line at Maple Street. Water is immediately drawn off to charge the fire suppression system. The rest of the water is sent through cold water distribution. There is backflow prevention throughout the system, including between the cold water distribution and the city water main and between the cold water distribution and the fire suppression system.

   Note: *Problems with entering water are usually beyond the building manager's control, such as main breaks or construction that disrupts water service. However, an essential part of a water management program is monitoring water and responding to changes coming in from the municipal water line. You can contact your drinking water provider to report any changes you notice in the quality of water being delivered to your building.*

Healthcare Facilities

Be sure to include descriptions of water sources relevant to:

- Patient care areas
- Clinical support areas
- Components and devices that can expose patients to contaminated water

You should also develop an ongoing dialogue with your drinking water provider so that you are aware of changes that may affect your building's water supply.

2. **Cold water is distributed** directly to the lit decorative fountain in the lobby, the cooling tower on the roof, the hot tub and pool on the first floor, ice machines on floors 2, 4, 6, 8, and 10, and shower and faucet fixtures in rooms on all 12 floors. All internal plumbing consists of 2-inch copper and polyvinyl chloride (PVC) piping. There is backflow prevention between cold water distribution and the utility lines that serve the cooling tower and hot tub/pool room.

   Note: *In warm climates, water in pipes that typically carry cold water may reach a temperature that allows for growth of* Legionella*. Detectable residual disinfectant added by your water provider helps to limit growth of* Legionella *and other germs. Additionally, decorative fountains with submerged lighting and devices such as cooling towers and ice machines may contain areas where cold water can be heated to temperatures that allow* Legionella *to grow. Swimming pools do not usually generate hazardous conditions because they rarely reach adequate temperature for growth or generate water droplets small enough to be inhaled.*

3. **Cold water is heated** to 140°F by two joined 120-gallon water heaters. The heaters supply a 500-gallon storage tank. Cold water is also delivered to an 80-gallon water heater in the basement that serves the kitchen and staff break room.

   Note: *Even water heaters set to the correct temperature may contain zones of lower temperature water where cold and hot water mix or where excessive sediment blocks heating elements. Most residual disinfectants are reduced by heating the water.*

*Examples of water systems not included in Building A that may be of concern include, but are not limited to, recycled or reused water, eyewash stations, and solar water heaters.

Disclaimer: Example content is provided for illustrative purposes only and is not intended to be relevant to all buildings.

Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

2

4. **Hot water is distributed** to plumbing fixtures in the basement through floor 5 from the joined water heaters in the basement on a direct (non-recirculating) line. Hot water is distributed to floors 6 through 11 from the storage tank with a recirculating line designed to return to the joined water heaters in the basement. Note that hot water is tempered (mixed with cold water) at the fixtures by thermostatic mixing valves.

   Note: *Water in direct hot and cold water pipes can pose multiple hazardous conditions. First, the process of heating the water can reduce disinfectant levels. Second, if hot water is allowed to sit in the pipes (stagnation), it might reach a temperature where* Legionella *can grow and could encourage sediment to accumulate or biofilm to form. With recirculating hot water pipes, the greatest risk is that returning water with reduced or no disinfectant cools to a temperature where* Legionella *can grow. If this happens,* Legionella *in the return line can travel to central distribution points and contaminate the entire plumbing system of the building.*

5. **Hot, cold, and tempered waste water is discarded** through the sanitary sewer line.

   Note: *It is not known at this time if* Legionella *can grow and spread in sources such as harvested rainwater or reclaimed graywater (i.e., bath, laundry).*

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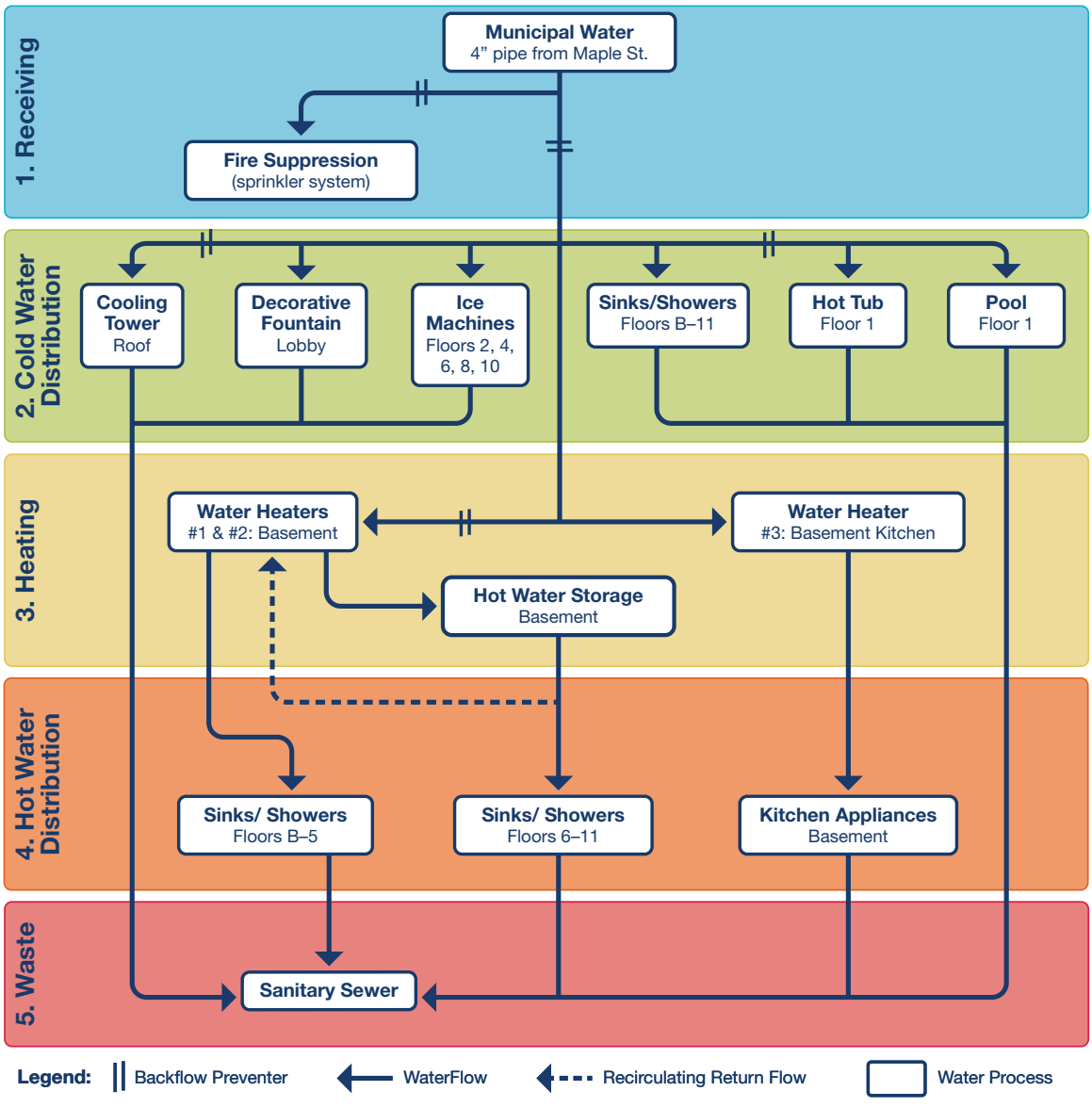
Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

2 Describe Your Building Water Systems Using a Flow Diagram

EXAMPLE: BUILDING A

In addition to developing a written description of your building water systems, you should develop a process flow diagram. Below is an example of a process flow diagram for Building A. Note that this diagram does not need to be as detailed as your building plans. In fact, it's best if the process flow diagram can be understood easily by all members of your team.



Disclaimer: Example content is provided for illustrative purposes only and is not intended to be relevant to all buildings.

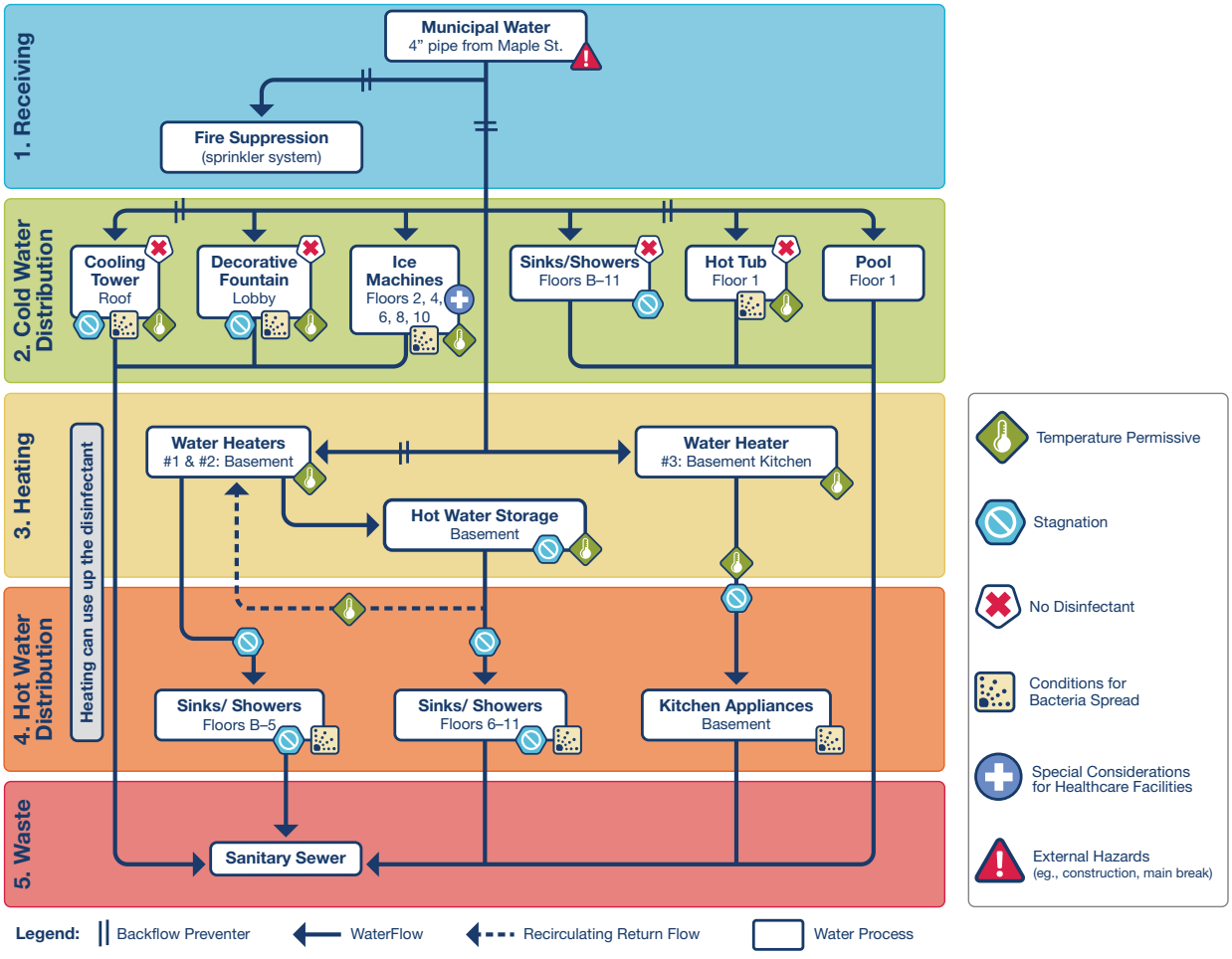
Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

3

Identify Areas Where *Legionella* Could Grow & Spread

EXAMPLE: BUILDING A

Once you have developed your process flow diagram, identify where potentially hazardous conditions could occur in your building water systems. The below diagram points out locations and types of hazardous conditions you could expect in Building A. Each potentially hazardous condition should be addressed individually with a control point, measure, and limit.



Healthcare Facilities

Think about:

- Areas where medical procedures may expose patients to water droplets, such as hydrotherapy
- Areas where patients are more vulnerable to infection, such as bone marrow transplant units, oncology floors, or intensive care units

In Building A, the ice machine is included to illustrate that patients with problems swallowing may be at increased risk for *Legionella* spread by aspiration.

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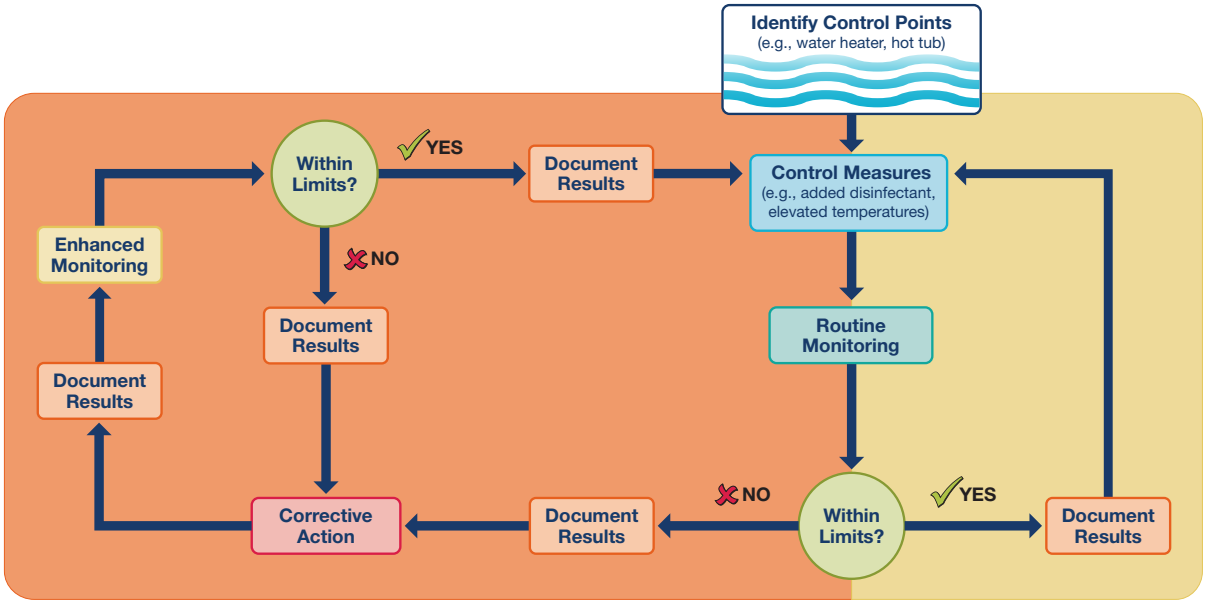
Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

3 Control Measures & Corrective Actions: The Basics

The diagram below shows the process of implementing and monitoring control measures. If you find that a control limit (i.e., temperature levels, disinfectant levels) is not being met, you need to take corrective actions to get conditions back to within an acceptable range. The right side, in yellow, illustrates the routine process of monitoring control measures to make sure they are within limits. The left side, in orange, shows the process of what to do if control measures are found to be outside of their limits.



Remember, any time there is a suspected case of Legionnaires' disease associated with your building you should:

- Contact your local and/or state health department or work with them if they contact you
- Notify anyone who could be affected by the growth and spread of *Legionella* in your building if the health department asks you to
- Decontaminate the building water systems if necessary (you may need to get additional help from outside experts)
- Review the water management program and revise it, if necessary

Healthcare Facilities

In addition to the steps listed above that you would take in all buildings, if a case of healthcare-associated Legionnaires' disease is discovered in a healthcare facility:

- Make sure the person with expertise in infection prevention on your team is aware
- **Important:** Tell clinicians so they can test patients with healthcare-associated pneumonia for Legionnaires' disease with both culture of lower respiratory secretions and the *Legionella* urinary antigen test
- Report the case to your local and/or state health department; a full investigation may be needed

For more details on identifying and investigating Legionnaires' disease cases in healthcare facilities, see page 24.

Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

4

Decide Where Control Measures Should Be Applied

Control measures and limits should be established for each control point. See the diagram on the next page for the types of monitoring that could occur in Building A. You will need to monitor to ensure your control measures are performing as designed. Control limits, in which a chemical or physical parameter must be maintained, should include a minimum and a maximum value.

Examples of chemical and physical control measures and limits to reduce the risk of *Legionella* growth:

- Water quality should be measured throughout the system to ensure that changes that may lead to *Legionella* growth (such as a drop in chlorine levels) are not occurring.
- Water heaters should be maintained at appropriate temperatures.
- Decorative fountains should be kept free of debris and visible biofilm.
- Disinfectant and other chemical levels in cooling towers and hot tubs should be continuously maintained and regularly monitored. Surfaces with any visible biofilm (i.e., slime) should be cleaned.

Healthcare Facilities

Clinicians should test patients with healthcare-associated pneumonia (pneumonia with onset ≥48 hours after admission) for Legionnaires' disease. This is especially important among patients at increased risk for developing Legionnaires' disease (see Appendix B), among patients with severe pneumonia (particularly those requiring intensive care), or if any of the following are identified in your facility:

- Other patients with healthcare-associated Legionnaires' disease diagnosed in the past 12 months
- Positive environmental tests for *Legionella* in the past 2 months
- Current changes in water quality that may lead to *Legionella* growth (such as low chlorine levels)

The preferred diagnostic tests for Legionnaires' disease are culture of lower respiratory secretions on selective media and the *Legionella* urinary antigen test.

Additionally, certain commonly-encountered changes in building water system design or management might require increasing the extent and frequency of monitoring. It's a good idea to anticipate additional hazardous conditions that could be associated with scheduled or unanticipated changes in water quality, such as:

- System start up
- System shut down
- Regularly scheduled maintenance
- Renovations, construction, and installation of new equipment on your property
- Equipment failure
- Water main break or other service interruptions

Anti-scald Regulation

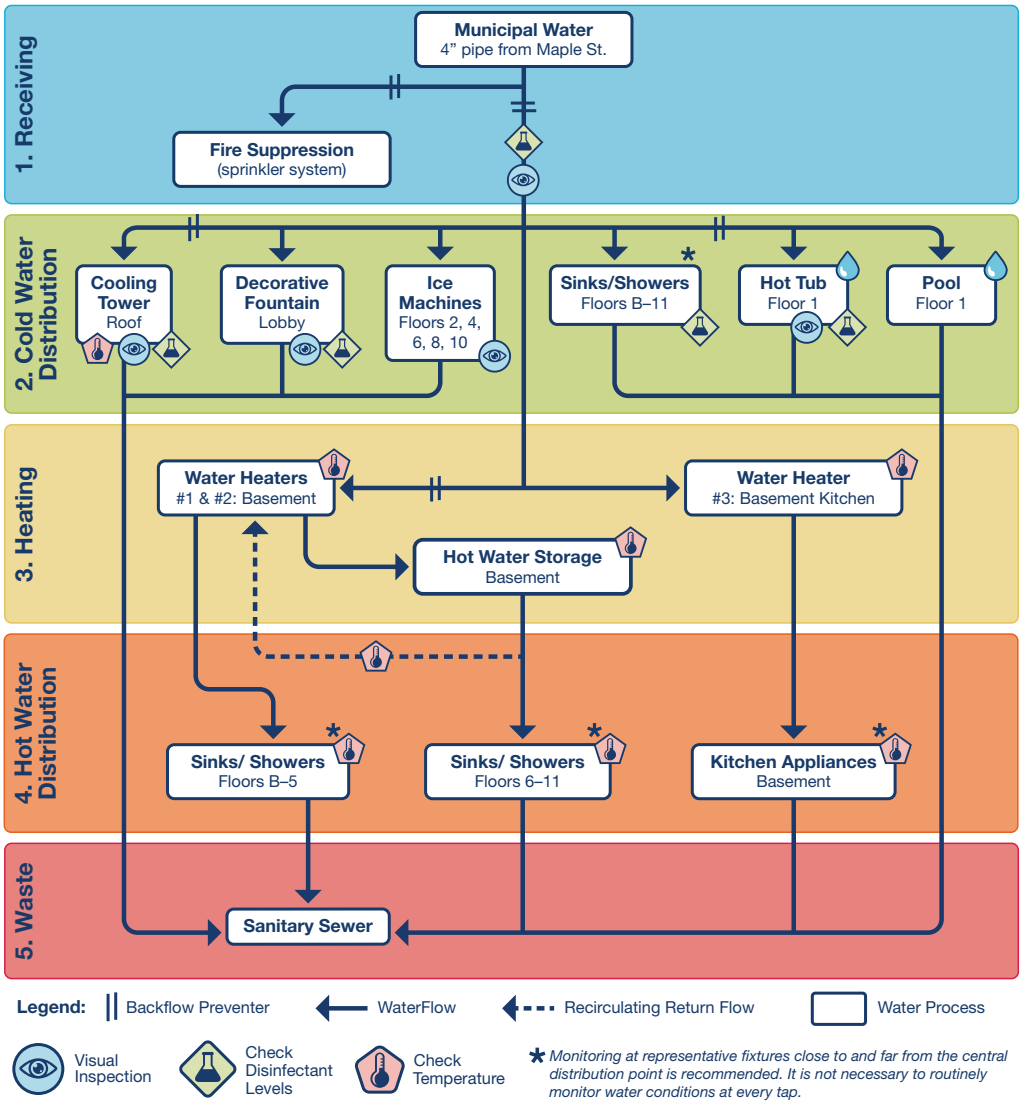
You should follow local and state anti-scald regulations. However, maximum temperatures allowed by your state may be too low to limit *Legionella* growth. Engineering controls that mix hot and cold water together at or near the point of use can reduce the risk of scalding while allowing water in pipes to remain hot enough to limit *Legionella* growth.

Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

4 Decide How to Monitor Your Control Measures

EXAMPLE: BUILDING A

The diagram below shows which types of monitoring could occur at different locations within Building A's water system to reduce the risk of growth and spread of *Legionella*.



Disclaimer: Example content is provided for illustrative purposes only and is not intended to be relevant to all buildings.

Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

Note: *In addition to whatever you do to prevent* Legionella*, state and local regulations may exist that govern the design, construction, operation, and maintenance of public aquatic facilities (e.g., pools and hot tubs). See CDC's Model Aquatic Health Code at www.cdc.gov/mahc/index.html for helpful information, but this document is not a substitute for state and local regulations.*

Note: *Heterotrophic plate counts can aid in your monitoring program as an indicator of water quality, but should not be used as a control measure.*

5

Establish Ways to Intervene When Control Limits Are Not Met

CORRECTIVE ACTION EXAMPLES

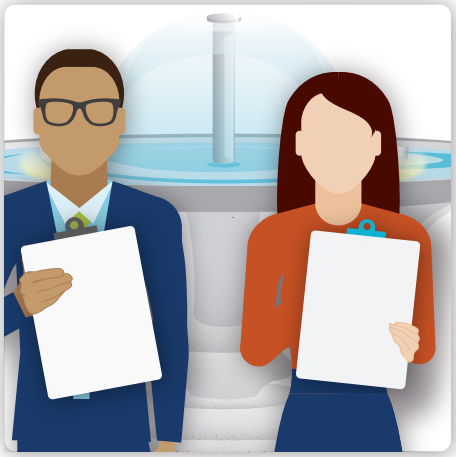
Building water systems are dynamic. You should plan for your monitoring results to vary over time and be prepared to apply corrective actions. **Corrective actions** are taken in response to systems performing outside of control limits. The following are examples of corrective actions.

Example 1—Biofilm growth in the decorative fountain

1. During her weekly inspection of the fountain in the first floor lobby, Michelle Patterson notes that the fountain walls have accumulated a slimy growth.

2. As dictated by her water management program, Michelle immediately shuts off the fountain, drains it to the sanitary sewer, and scrubs it with a detergent recommended by the manufacturer.

3. She then follows the program's start up procedure to refill the fountain with water and checks the residual disinfectant levels to make sure that they are within control limits.



4. Michelle documents her observations and the performance of interim cleaning in her log book. She informs her supervisor.

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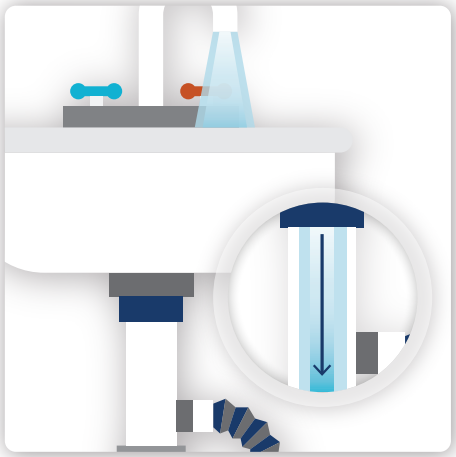
5 Example 2—Unoccupied floor

1. The eighth floor of the building is being renovated and is closed to the public. Jason Hernandez understands that this may cause a temporary hazardous condition because water usage will decrease, which means that stagnation is possible.



2. After discussing the issue with his supervisor, Jason counteracts the potential for stagnation by daily flushing of the sinks and fixtures with hot and cold water in several rooms including those at the end of the hall, which are farthest from the vertical pipe serving that floor (riser).

3. Jason also increases the frequency of measuring temperature and chlorine levels on the eighth floor from weekly to daily for the duration of the renovation.

4. He documents the method and duration of flushing and records his daily temperature and chlorine readings in his log book. He reviews his documentation with his supervisor.

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Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

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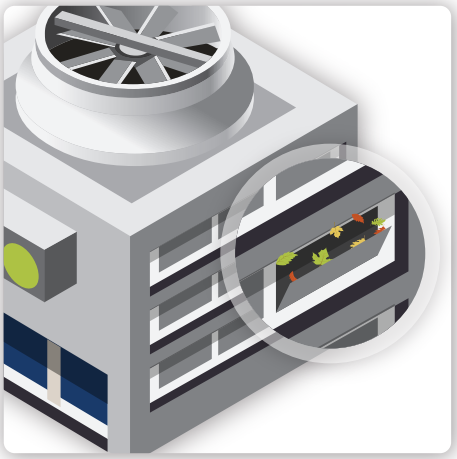
Example 3—Debris in the cooling tower



1. During weekly inspection of the cooling tower, Michelle discovers that leaf litter has accumulated in the reservoir.

2. Upon further investigation, she finds that a panel has become dislodged, allowing windblown debris to enter.

3. After replacing the panel and skimming out the debris, Michelle checks the disinfectant levels and performs a heterotrophic plate count as an indicator of water quality.

4. She documents her actions in her log book. She also makes a note to check the disinfectant levels daily for a week to make sure that the cooling tower remains within control limits. She reviews her actions and documentation with her supervisor.

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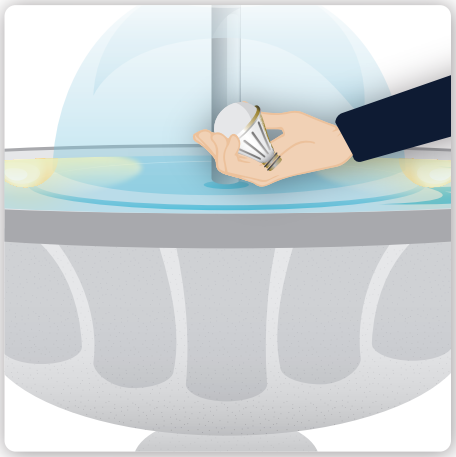
5 CONTINGENCY RESPONSE EXAMPLES

Even the most closely monitored systems will sometimes require adjustments, as shown in the following examples. You should be prepared to respond, even to unexpected problems, based on your knowledge of the building water systems and how *Legionella* grows and spreads. You may need to initiate a customized contingency response to gain control of a building water system. **Contingency responses** may involve several steps and often require follow up. A contingency response is always required when a case of Legionnaires' disease has been linked to a building and is also appropriate in other situations.

Example 1—Biofilm growth in the fountain

1. During the annual review of the water management program, supervisor Anson Cho notes that Michelle and Jason performed six interim cleanings of the lobby fountain due to excessive biofilm growth in the past year.

2. Upon further review of the logs, he discovers that the biofilm growth was observed near the inner wall where incandescent lighting illuminates the water.



3. Anson decides to replace the incandescent bulbs with LED bulbs to prevent the lights from heating the water to a temperature that allows biofilm to grow.

4. After three months of routine inspections show that this corrective action reduces biofilm growth and eliminates the need for interim cleaning, Anson amends the water management program to specify use of only LED bulbs in the fountain and he informs the owner.

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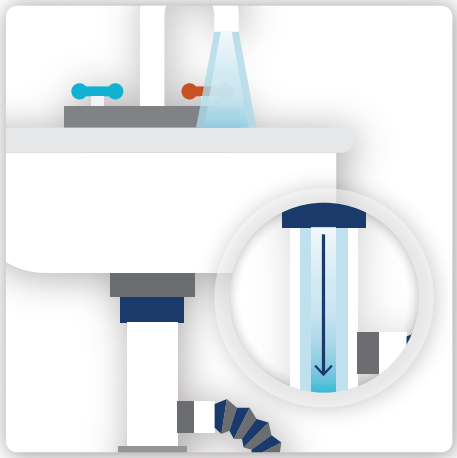
5

Example 2—Water main break

1. Jason receives several complaints from building occupants of foul-tasting water. He also notes a brownish tint to the water entering the building during his daily visual inspection. Jason immediately contacts the water provider and discovers that there was a water main break nearby but that a boil water advisory was not issued. He sends a notice to building occupants about the main break and that they should limit water usage for the next 4 hours while facilities clear the line.



2. To improve building water quality, Jason flushes the water at multiple sinks and fixtures near the entry until the water runs clear and falls within established water quality parameter control limits. He also flushes fixtures in areas where he received taste and odor complaints and at pre-determined flushing locations per the water management program.

3. Jason increases the frequency of measuring chlorine levels at the taps from weekly to daily to ensure that adequate residual disinfectant is moving through the system.

4. Jason informs his supervisor, documents his actions, and records chlorine readings in his log book.

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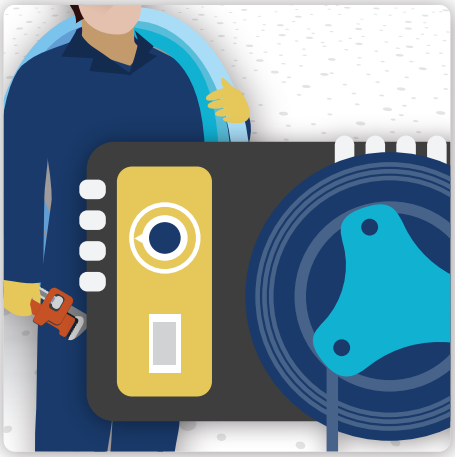
5 Example 3—Broken chlorinator in the hot tub

1. Michelle notes chlorine levels of zero within the hot tub during her daily inspection. On further inspection she notices that disinfectant in the automatic delivery system reservoir is full.

2. Michelle immediately closes the hot tub and calls the pool contractor.



3. The contractor arrives the next day to discover that the chlorinator pump has malfunctioned and replaces the unit.

4. Michelle documents the action and follows the water management program's protocol for start up, which includes cleaning the hot tub, shocking it with a high dose of disinfectant, and back-flushing the filter. Michelle also recommends that the supervisor amend the water management program to include a daily check of equipment operation and disinfectant levels in the reservoir, in addition to the daily visual inspection and chlorine measurements, so that such equipment failures may be detected more quickly in the future.

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6

Make Sure the Program Is Running as Designed & Is Effective

Verification: Are we doing what we said we would do?

Your program team should establish procedures to confirm, both initially and on an ongoing basis, that the water management program is being implemented as designed. This step is called "verification." For example, if you said you would test the hot tub daily for chlorine and record and communicate those results, have you been doing that? If you found a problem, did you take the action included in your program?

People should not verify the program activity for which they are responsible. For example, if one person is responsible for maintaining the hot tub and another is responsible for the cooling tower, they could verify each other's work, not their own.

Healthcare Facilities

Water management program teams that include infection control staff may also choose to use their facility's routine surveillance for healthcare-associated Legionnaires' disease to validate their program. To look for healthcare-associated cases, histories for all patients with diagnosed Legionnaires' disease should be reviewed for possible healthcare exposures and certain patients with healthcare-associated pneumonia (see gray box on page 13) should be tested for Legionnaires' disease.

Validation: Is our program actually working?

Now that you have a water management program, you need to be sure that it is effective. Your program team should establish procedures to confirm, both initially and on an ongoing basis, that the water management program effectively controls the hazardous conditions throughout the building water systems. This step is called "validation."

Environmental testing for *Legionella* is useful to validate the effectiveness of control measures. The program team should determine if environmental testing for *Legionella* should be performed and, if so, how test results will be used to validate the program. Factors that might make testing for *Legionella* more important include:

- Having difficulty maintaining the building water systems within control limits
- Having a prior history of Legionnaires' disease associated with the building water systems
- Being a healthcare facility that provides inpatient services to people who are at increased risk for Legionnaires' disease (see Appendix B)

If the program team decides to test for *Legionella*, then the testing protocol should be specified and documented in advance. You should also be familiar with and adhere to local and state regulations and accreditation standards for this testing.

Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

7 Document & Communicate All the Activities of Your Water Management Program

Documentation

Now that you have done all of the work required to create your water management program, write it down. This information will be important to improve your program and if you or others want to review your records. Your written program should include at least the following:

- Program team, including names, titles, contact information, and roles on the team
- Building description, including location, age, uses, and occupants and visitors
- Water system description, including general summary, uses of water, aerosol-generating devices (e.g., hot tubs, decorative fountains, cooling towers), and process flow diagrams
- Control measures, including points in the system where critical limits can be monitored and where control can be applied
- Confirmatory procedures, including verification steps to show that the program is being followed as written and validation to show that the program is effective
- Document collection and transport methods and which lab will perform the testing if environmental testing is conducted

Communication

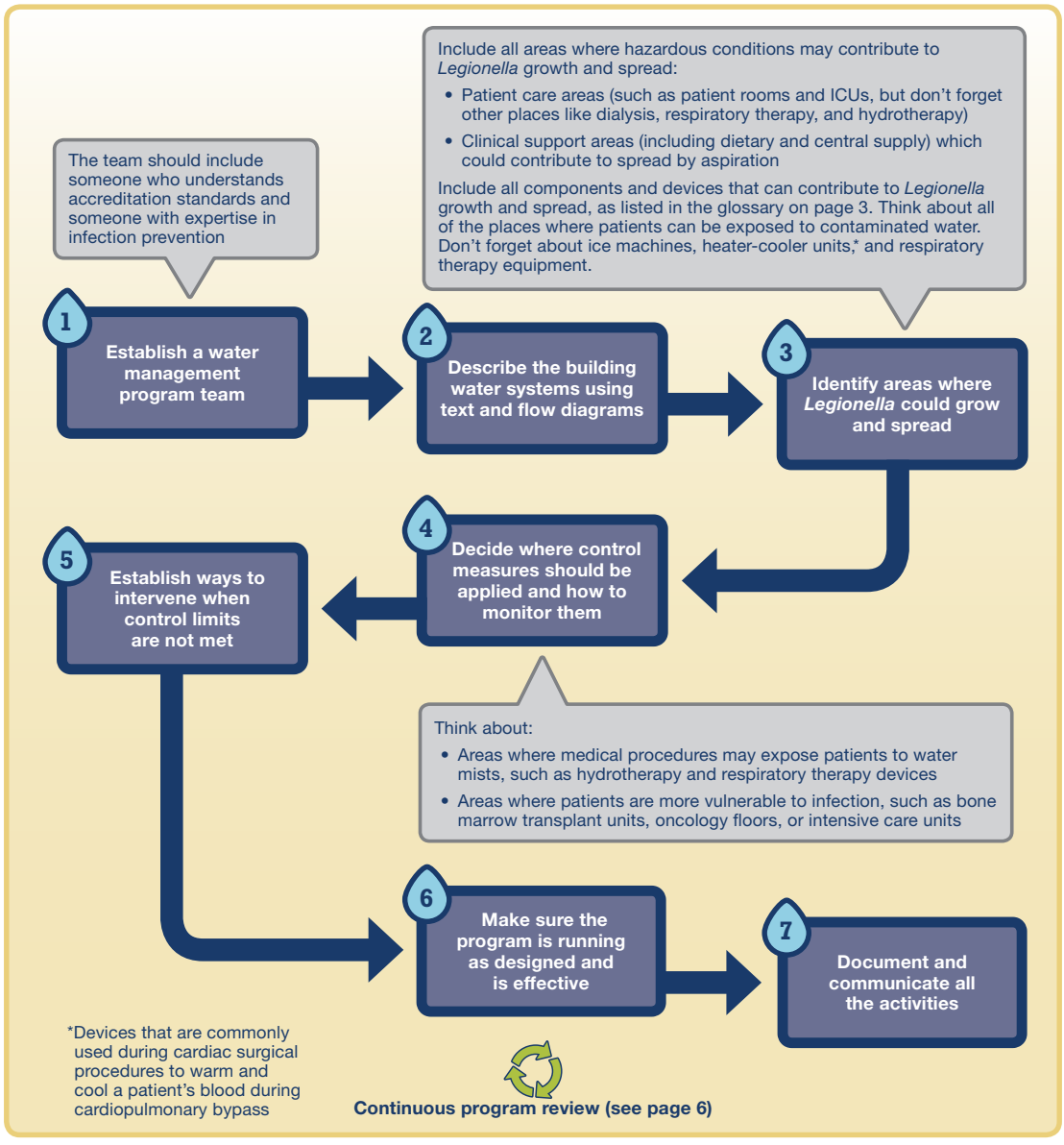
You have worked hard to develop your water management program and you have carefully documented all aspects of it. Resist the temptation to put it on a shelf and walk away. Consider notifying building occupants that you have a plan in place to keep the building water systems safe, just as you would for an elevator inspection. Be sure to communicate with your employees and colleagues about your program on a regular basis and train those responsible for implementing and monitoring the program. Use this communication as an opportunity to identify strategies for improving the management and efficiency of your water systems.

Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

Special Considerations for Healthcare Facilities

ELEMENTS OF A WATER MANAGEMENT PROGRAM

Developing and maintaining a water management program in healthcare facilities requires a few more considerations than the ones explained on page 6. All healthcare facilities should have a *Legionella* water management program.



Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

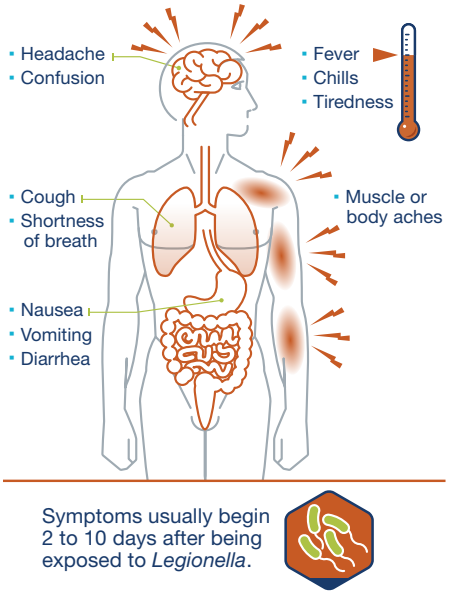
Note: *ASHRAE 188 Normative Annex A applies to accredited healthcare facilities that have a Certification Board of Infection Control and Epidemiology (CBIC) certified infection preventionist or a master's-level epidemiologist.*

IDENTIFYING & INVESTIGATING LEGIONNAIRES' DISEASE CASES

Healthcare facilities are often uniquely positioned to identify and respond to cases of Legionnaires' disease. A healthcare facility's water management program to limit *Legionella* growth and spread should include the actions to take when a patient is diagnosed with Legionnaires' disease or environmental triggers occur. If you decide to conduct a full investigation of the source of an infection, key elements should be included, as noted on the next page. A full investigation following a diagnosis of Legionnaires' disease can help determine whether the infection was acquired in the facility or the community.

Clinicians should test patients with healthcare-associated pneumonia (pneumonia with onset ≥48 hours after admission) for Legionnaires' disease. This is especially important among patients at increased risk for developing Legionnaires' disease (see Appendix B), among patients with severe pneumonia (particularly those requiring intensive care), or if any of the following are identified in your facility:

Legionnaires' disease symptoms



Symptoms usually begin 2 to 10 days after being exposed to *Legionella*.

- Other patients with healthcare-associated Legionnaires' disease diagnosed in the past 12 months
- Positive environmental tests for *Legionella* in the past 2 months
- Current changes in water quality that may lead to *Legionella* growth (e.g., low residual disinfectant levels, temperatures permissive to *Legionella* growth, nearby construction, areas of stagnation)

Other patients, besides those with healthcare-associated pneumonia, should also be tested for Legionnaires' disease (see Appendix B). The preferred diagnostic tests for Legionnaires' disease are culture of lower respiratory secretions on selective media and the *Legionella* urinary antigen test.

Perform a full investigation for the source of *Legionella* when:

- ≥1 case of **definite** healthcare-associated Legionnaires' disease (a case in a patient who spent the entire 10 days prior to onset of illness in the facility) is identified at any time
- ≥2 cases of **possible** healthcare-associated Legionnaires' disease (cases in patients who spent part of the 10 days before symptoms began at the same facility) are identified within 12 months of each other (note that under certain circumstances, during a cooling tower outbreak for example, the interval may be shorter)

Key elements of a full public health investigation include:

- Working with healthcare facility leaders*
- Performing a retrospective review of cases in the health department surveillance database to identify earlier cases with possible exposures to the healthcare facility
- Developing a line list of possible and definite cases associated with the healthcare facility
- Working with infection control and clinical staff to actively identify all new and recent patients with healthcare-associated pneumonia and test them for *Legionella* using both culture of lower respiratory secretions on selective media and the *Legionella* urinary antigen test
- Obtaining postmortem specimens, when applicable
- Considering recommendations for restricting water in the facility or other immediate control measures
- Performing an environmental assessment to evaluate possible environmental exposures
- Performing environmental sampling, as indicated by the environmental assessment
- Decontaminating possible environmental source(s)
- Subtyping and comparing clinical and environmental isolates, if available
- Working with healthcare facility leaders to determine how long heightened disease surveillance and environmental sampling should continue to ensure the outbreak is over
- Working with healthcare facility leaders to review and possibly revise the water management program, if indicated

* Leaders may include infection control practitioners, facility managers, hospital administrators, quality assurance staff, or others.

Reference: ASHRAE 188: *Legionellosis: Risk Management for Building Water Systems* June 26, 2015. ASHRAE: Atlanta. www.ashrae.org

Note: *ASHRAE 188 Normative Annex A applies to accredited healthcare facilities that have a Certification Board of Infection Control and Epidemiology (CBIC) certified infection preventionist or a master's-level epidemiologist.*

References & Resources

There are many references and resources that can help you develop and implement your *Legionella* water management program, some of which are listed below.

Standard

Standard 188—Legionellosis: Risk Management for Building Water Systems (ANSI Approved)
ASHRAE
Published 2015
www.techstreet.com/ashrae/products/1897561

Guidelines

Guideline 12—Minimizing the Risk of Legionellosis Associated with Building Water Systems
ASHRAE
Published 2000
www.techstreet.com/ashrae/products/232891
(currently under revision)

Legionellosis Guideline: Best Practices for Control of *Legionella*
Cooling Technology Institute
Published 2008
www.cti.org/downloads/WTP-148.pdf

Model Aquatic Health Code Guidance
Centers for Disease Control and Prevention
Published 2014
www.cdc.gov/mahc/index.html

Laboratory Resources

ELITE Program
Centers for Disease Control and Prevention and Wisconsin State Laboratory of Hygiene
wwwn.cdc.gov/ELITE/Public/EliteHome.aspx

Planning Guides & Toolkits

Emergency Water Supply Planning Guide for Hospitals and Healthcare Facilities
Centers for Disease Control and Prevention, American Water Works Association
Published 2012
www.cdc.gov/healthywater/pdf/emergency/emergency-water-supply-planning-guide.pdf

Drinking Water Advisory Communication Toolbox
US Department of Health & Human Services, Centers for Disease Control and Prevention, Environmental Protection Agency, American Water Works Association
Published 2013
www.cdc.gov/healthywater/pdf/emergency/drinking-water-advisory-communication-toolbox.pdf

Investigation Tools for Clusters and Outbreaks of Legionnaires' Disease
Centers for Disease Control and Prevention
www.cdc.gov/legionella/outbreak-toolkit

Healthcare Resources

Sehulster LM, Chinn RYW, Arduino MJ, Carpenter J, Donlan R, Ashford D, et al. **Guidelines for Environmental Infection Control in Health-care Facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC).** *MMWR*. 2003;52 (RR-10): 1–42.
www.cdc.gov/mmwr/preview/mmwrhtml/rr5210a1.htm

Kohn WG, Collins AS, Cleveland JL, Harte JA, Eklund KJ, Malvitz DM. **Guidelines for Infection Control in Dental Health-Care Settings—2003.** *MMWR*. 2003;52(RR-17):1–61.
www.cdc.gov/mmwr/preview/mmwrhtml/rr5217a1.htm

Tablan OC, Anderson LJ, Besser R, Bridges MD, Hajjeh R. **Guidelines for Preventing Health-care-associated Pneumonia, 2003: Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee.** *MMWR*. 2004;53(RR-3):1–36.
www.cdc.gov/mmwr/preview/mmwrhtml/rr5303a1.htm

Prevention of Healthcare-associated *Legionella* Disease and Scald Injury from Potable Water Distribution Systems
Veterans Health Administration
Published 2014
www.va.gov/vhapublications/ViewPublication.asp?pub_ID=3033

Legionnaires' Disease Information

Legionnaires' Disease Website
Centers for Disease Control and Prevention
www.cdc.gov/legionella

Laws

Safe Drinking Water Act
Environmental Protection Agency
www.epa.gov/sdwa

Literature Reviews

Technologies for *Legionella* Control in Premise Plumbing Systems
Environmental Protection Agency
www.epa.gov/ground-water-and-drinking-water/technologies-legionella-control-premise-plumbing-systems

Appendix A

LEGIONNAIRES' DISEASE

Legionnaires' (LEE-juh-nares) disease is a very serious type of pneumonia (lung infection) caused by bacteria called *Legionella*. If you develop pneumonia symptoms and may have been exposed to *Legionella*, see a doctor right away. Be sure to mention if you have used a hot tub, spent any nights away from home, or stayed in a hospital in the last two weeks.

Legionnaires' Disease Can Cause Pneumonia Symptoms

Signs and symptoms of Legionnaires' disease can include:

- Cough
- Muscle aches
- High fever
- Shortness of breath
- Headache

Doctors use chest x-rays or physical exams to check for pneumonia. Your doctor may also order tests on a sample of urine and sputum (phlegm) to see if your lung infection is caused by *Legionella*.

Legionnaires' Disease Is Serious, but Can Be Treated with Antibiotics

Legionnaires' disease is treated with antibiotics (drugs that kill bacteria in the body). Most people who get sick need care in a hospital but make a full recovery. However, about 1 out of 10 people who get Legionnaires' disease will die from the infection.

Certain People Are at Increased Risk for Legionnaires' Disease

Most healthy people do not get Legionnaires' disease after being exposed to *Legionella*. Being 50 years or older or having certain risk factors can increase your chances of getting sick. These risk factors include:

- Being a current or former smoker
- Having chronic lung disease, such as emphysema or chronic obstructive pulmonary disease (COPD)
- Having a weakened immune system from diseases like cancer, diabetes, or kidney failure
- Taking medication that weakens your immune system

Legionella Are Usually Spread through Water Droplets in the Air

In nature, *Legionella* live in fresh water and rarely cause illness. In man-made settings, *Legionella* can grow if water is not properly maintained. These man-made water sources become a health problem when small droplets of water that contain the bacteria get into the air and people breathe them in. In rare cases, someone breathes in *Legionella* while they are drinking water and it "goes down the wrong pipe" into the lungs. In general, Legionnaires' disease is not spread from one person to another. However, this may be possible in rare cases.

Legionnaires' disease, a type of severe pneumonia, is caused by breathing in small droplets of water that contain *Legionella*.

Commons Sources of Infection

Outbreaks of Legionnaires' disease are often associated with large or complex water systems, like those found in hospitals, hotels, and cruise ships.

The most likely sources of infection include:

Water used for showering (potable water)

Cooling towers (parts of large air conditioning systems)

Decorative fountains

Hot tubs

cdc.gov/legionella CS260481 03/07/2016

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Appendix B

What Clinicians Need to Know about

LEGIONNAIRES' DISEASE

Legionnaires' disease is a sometimes fatal form of pneumonia that is on the rise in the United States. Unfortunately, this disease is also underrecognized and underdiagnosed. Clinicians are in a unique position to make sure cases are detected, allowing rapid investigation by public health officials and prevention of additional cases.

Diagnosis and Testing

Clinical features of Legionnaires' disease include cough, fever, and radiographic pneumonia. Signs and symptoms for Legionnaires' disease are similar to pneumonia caused by other pathogens; the only way to tell if a pneumonia patient has Legionnaires' disease is by getting a specific diagnostic test. Indications that warrant testing include:

- Patients who have failed outpatient antibiotic therapy for community-acquired pneumonia
- Patients with severe pneumonia, in particular those requiring intensive care
- Immunocompromised patients with pneumonia*
- Patients with a travel history (patients who have traveled away from their home within 10 days before the onset of illness)
- All patients with pneumonia in the setting of a Legionnaires' disease outbreak
- Patients at risk for Legionnaires' disease with healthcare-associated pneumonia (pneumonia with onset ≥48 hours after admission)

* Clinicians may also consider testing for Legionnaires' disease in patients with other risk factors for this infection (see page 2).

Testing for healthcare-associated Legionnaires' disease is especially important if any of the following are identified in your facility:

- Other patients with healthcare-associated Legionnaires' disease diagnosed in the past 12 months
- Positive environmental tests for *Legionella* in the past 2 months
- Current changes in water quality that may lead to *Legionella* growth (such as low chlorine levels)

Infection control staff may have more information about these situations in your facility.

The preferred diagnostic tests for Legionnaires' disease are culture of lower respiratory secretions (e.g., sputum, bronchoalveolar lavage) on selective media and the *Legionella* urinary antigen test. Serological assays can be nonspecific and are not recommended in most situations. Best practice is to obtain both sputum culture and a urinary antigen test concurrently. Sputum should ideally be obtained prior to antibiotic administration, but antibiotic treatment should not be delayed to facilitate this process. The urinary antigen test can detect *Legionella* infections in some cases for days to weeks after treatment. The urinary antigen test detects *Legionella pneumophila* serogroup 1, the most common cause of Legionnaires' disease; isolation of *Legionella* by culture is important for detection of other species and serogroups and for public health investigation. Molecular techniques can be used to compare clinical isolates to environmental isolates and confirm the outbreak source.

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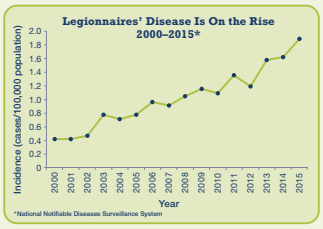
Order both a culture of a lower respiratory specimen and a urinary antigen test when testing patients for *Legionella*.



In the United States, reported cases of Legionnaires' disease have grown by nearly four and a half times since 2000. More than 6,000 cases of Legionnaires' disease were reported in 2015, but this number is likely an underestimate as the illness is thought to be underdiagnosed.

More illness occurs in the summer and early fall, but Legionnaires' disease can happen any time of year.

Treatment

If your patient has Legionnaires' disease, see the most recent guidelines for treatment of community-acquired pneumonia (http://bit.ly/CommunityPneumonia) and hospital-acquired pneumonia (http://bit.ly/HospitalPneumonia). Macrolides and respiratory fluoroquinolones are currently the preferred agents for treating Legionnaires' disease.

Reporting

Make sure your infection control department or lab are promptly reporting cases of Legionnaires' disease to your local health department. Timely identification and reporting of cases is important, as this allows public health officials to quickly identify and stop potential clusters and outbreaks by linking new cases to previously reported ones.

Etiology

Legionnaires' disease is a severe form of pneumonia that often requires hospitalization and is fatal in about 10% of cases overall, and in 25% of healthcare-associated cases. Legionnaires' disease is caused by *Legionella* bacteria. There are at least 60 different species of *Legionella*, and most are considered capable of causing disease. However, most disease is caused by *L. pneumophila*, particularly serogroup 1.

Transmission

While *Legionella* is found in natural, freshwater environments, it can become a health concern in human-made water systems (e.g., plumbing system of large buildings, cooling towers, certain medical devices, decorative fountains, hot tubs) where conditions allow it to multiply and come in contact with vulnerable persons. People contract *Legionella* by inhaling aerosolized water droplets containing the bacteria, or, less commonly, by aspiration of contaminated drinking water. *Legionella* is usually not transmitted from person to person; however, a single episode of person-to-person transmission has been reported. Fortunately, most people exposed to the bacteria do not become ill.

Risk Factors

Risk factors for developing Legionnaires' disease include:

- Age ≥50 years
- Smoking (current or historical)
- Chronic lung disease, such as emphysema or COPD
- Immune system disorders due to disease or medication
- Systemic malignancy
- Underlying illness, such as diabetes, renal failure, or hepatic failure

Prevention

The key to preventing Legionnaires' disease is maintenance of the water systems in which *Legionella* may grow. If *Legionella* is found in a healthcare facility's water system, the facility should work to eliminate the bacteria. CDC encourages all building owners, and especially those in healthcare facilities, to develop comprehensive water management programs to reduce the risk of *Legionella* growth and spread. Learn more about how to develop a water management program at www.cdc.gov/legionella/WMPtoolkit.

Timely reporting of Legionnaires' disease cases is important for controlling clusters and outbreaks.

Commons Sources of Infection

Outbreaks of Legionnaires' disease are most often associated with large or complex water systems, like those found in hospitals, long-term care facilities, hotels, and cruise ships.

The most likely sources of infection include:

Water used for showering (potable water)

Cooling towers (parts of large air conditioning systems)

Decorative fountains

Hot tubs

Vaccine Storage and Handling Toolkit

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

January 2019

CS296544-B

Table of Contents

Introduction 2

SECTION ONE: Vaccine Cold Chain 4

SECTION TWO: Staff and Training 6

SECTION THREE: Vaccine Storage and Temperature Monitoring Equipment 8

SECTION FOUR: Vaccine Inventory Management 16

SECTION FIVE: Vaccine Preparation 19

SECTION SIX: Vaccine Transport 21

SECTION SEVEN: Emergency Vaccine Storage and Handling 25

Glossary 27

Resources 29

Disclaimer: This document provides best practices and Centers for Disease Control and Prevention (CDC) recommendations on storage, handling, and transport of vaccines and diluents. It also provides information on vaccine storage and handling requirements related to the Vaccines for Children program. Use of trade names and commercial sources in this toolkit is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services (DHHS), the U.S. Public Health Service (PHS), or CDC.

Introduction

Proper vaccine storage and handling are important factors in preventing and eradicating many common vaccine-preventable diseases. Yet, each year, storage and handling errors result in revaccination of many patients and significant financial loss due to wasted vaccines. Failure to store and handle vaccines properly can reduce vaccine potency, resulting in inadequate immune responses in patients and poor protection against disease. Patients can lose confidence in vaccines and providers if they require revaccination because the vaccines they received may have been compromised.

This toolkit provides information, recommendations, and resources to assist you in properly storing and handling your vaccine supply. The Centers for Disease Control and Prevention (CDC) Vaccine Storage and Handling Toolkit brings together best practices from the Advisory Committee on Immunization Practices (ACIP) General Best Practice Guidelines for Immunization,* product information from vaccine manufacturers, and results of scientific studies. Implementing these best practices and recommendations will help protect your patients, safeguard your vaccine supply, and avoid the unnecessary costs of revaccinating patients and replacing expensive vaccines.

For specific, detailed storage and handling protocols for individual vaccines, always refer to the manufacturers' product information and package inserts,* or contact the manufacturer directly.

Vaccines for Children Program

The Vaccines for Children (VFC) program provides vaccines at no cost to eligible children. VFC providers are important partners in making sure VFC-eligible children receive viable, properly handled vaccine.

This toolkit provides general background information on many of the VFC storage and handling requirements and illustrates best practices essential to safeguarding the public vaccine supply.

If you are a VFC provider or receive other vaccines purchased with public funds, consult your state or local immunization program (referred to throughout this document as "immunization program"*) to ensure you are meeting all mandatory storage and handling requirements that are specific or tailored to your jurisdiction.

You may see vendors use terms such as "VFC-compliant," "CDC-compliant," or "satisfies VFC requirements" in their marketing materials or on their websites. In this context, "compliance" and related terms may lead consumers to incorrectly believe that CDC or the VFC program has independently assessed and verified the quality of these products. CDC/VFC is not authorized to assess, validate, verify, or endorse the products or services of private companies. Should you encounter this type of language in vendor marketing materials, please keep in mind that neither CDC nor the VFC program has validated any product or service for compliance with CDC or VFC program requirements or standards.

*ACIP recommendations: www.cdc.gov/vaccines/hcp/acip-recs/index.html

Manufacturers' package inserts: www.immunize.org/packageinserts/

Immunization programs: www.cdc.gov/vaccines/imz-managers/awardee-imz-websites.html

Introduction

How to Use the Vaccine Storage and Handling Toolkit

This toolkit outlines CDC recommendations for vaccine storage and handling.

This list shows the icons you will see throughout the toolkit and their meanings:

ICON	DESCRIPTION
	CDC Recommendation – CDC recommends this as a minimal action to protect your vaccine supply.
	CDC Best Practice – CDC recommends best practices as additional actions, practices, and procedures to enhance protection of your vaccine supply.

Additional CDC vaccine storage and handling information is available at:

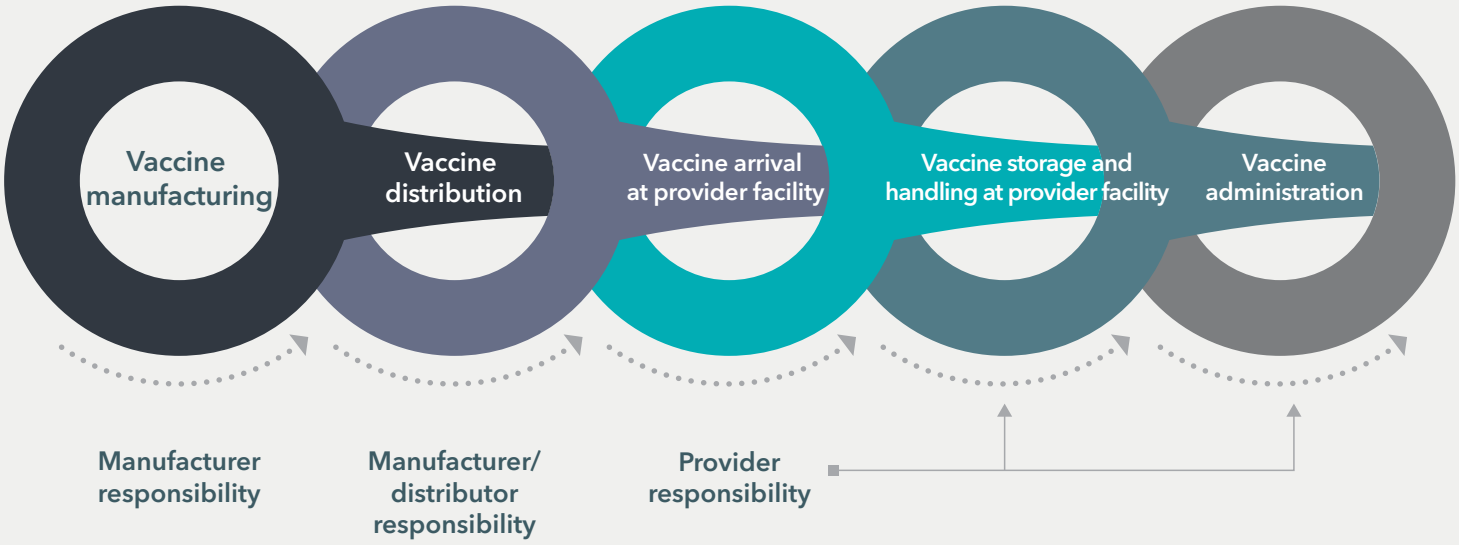
- Vaccine storage and handling home page:
  www.cdc.gov/vaccines/recs/storage/default.htm
  (sign up for notifications about updates)
- Educational webinars and continuing education for health care providers:
  www.cdc.gov/vaccines/ed/courses.html
- Contact information for state/local immunization programs:
  www.cdc.gov/vaccines/imz- managers/awardee-imz-websites.html
- E-mail specific questions to CDC: NIPInfo@cdc.gov

Proper vaccine storage and handling play critical roles in efforts to prevent vaccine-preventable diseases. Vaccines exposed to storage temperatures outside the recommended ranges may have reduced potency, creating limited protection and resulting in the revaccination of patients and thousands of dollars in wasted vaccine.

Proper storage and handling begin with an effective vaccine cold chain.

A cold chain is a temperature-controlled supply chain that includes all vaccine-related equipment and procedures. The cold chain begins with the cold storage unit at the manufacturing plant, extends to the transport and delivery of the vaccine and correct storage at the provider facility, and ends with administration of the vaccine to the patient.

Cold Chain Flowchart



If the cold chain is not properly maintained, vaccine potency may be lost, resulting in a useless vaccine supply.

Vaccines must be stored properly from the time they are manufactured until they are administered. Potency is reduced every time a vaccine is exposed to an improper condition. This includes overexposure to heat, cold, or light at any step in the cold chain. Once lost, potency cannot be restored.

Exposure to any inappropriate conditions can affect potency of any refrigerated vaccine, but a single exposure to freezing temperatures (0° C [32° F] or colder) can actually destroy potency. Liquid vaccines containing an adjuvant can permanently lose potency when exposed to freezing temperatures.

When the cold chain fails

Assuring vaccine quality and maintaining the cold chain are shared responsibilities among manufacturers, distributors, public health staff, and health care providers.

An effective cold chain relies on three main elements:

- A well-trained staff
- Reliable storage and temperature monitoring equipment
- Accurate vaccine inventory management

Results of a cold chain failure can be costly.[1,2,3] ACIP's *General Best Practice Guidelines for Immunization* states, "vaccine exposed to inappropriate temperatures that is inadvertently administered should generally be repeated."[4]

A break in the cold chain can mean extra doses for patients, increased costs for providers, and damage to public confidence in vaccines.

More importantly, patients refusing revaccination can remain unprotected from serious, vaccine-preventable diseases.

Vaccine appearance is not a reliable indicator that vaccines have been stored in appropriate conditions. For example, inactivated vaccines—even when exposed to freezing temperatures—may not appear frozen, giving no indication of reduced or lost potency.

By following a few simple steps and implementing CDC-recommended storage and handling practices, providers can ensure patients receive high-quality vaccine that has not been compromised.

1. Department of Health and Human Services, Office of Inspector General. Vaccines for Children Program: Vulnerabilities in Vaccine Management, June 2012, oig.hhs.gov/oei/reports/oei-04-10-00430.asp.
2. Gazmararian JA, Oster NV, Green DC, Schuessler L, Howell K, et al. Vaccine storage practices in primary care physician offices: assessment and intervention. *Am J Prev Med* 2002;23(4):246–53.
3. Bell KN, Hogue CJR, Manning C, Kendal AP. Risk factors for improper vaccine storage and handling in private provider offices. *Pediatrics* 2001;107(6):1–5.
4. Centers for Disease Control and Prevention. ACIP's *General Best Practice Guidelines for Immunization*, https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html.

Vaccine storage and handling practices are only as effective as the staff that implements them. Staff that is well-trained in general storage and handling principles and organization-specific storage and handling standard operating procedures (SOPs) is critical to ensuring vaccine supply potency and patient safety.

Staff Training

All staff members who receive vaccine deliveries as well as those who handle or administer vaccines should be trained in vaccine-related practices and be familiar with your facility's storage and handling SOPs. If you are a VFC provider or have vaccines purchased with public funds, contact your immunization program* for specific state requirements related to training, policies, and procedures.

Online Training Resources

CDC's *You Call the Shots*: Vaccine Storage and Handling† is a free, online training module focused on storage and handling requirements.

Check with your immunization program* and professional organizations to see what vaccine storage and handling training resources they offer.

Storage and Handling SOPs

CDC recommends your facility develop and maintain clearly written, detailed, and up-to-date storage and handling standard operating procedures (SOPs). SOPs will help your facility stay organized, serve as a reference and training tool, and assure proper vaccine management. SOPs help ensure proper procedures are followed and problems are identified, reported, and corrected. SOPs should also provide guidance for emergencies such as equipment malfunctions, power failures, or natural disasters.

Storage and handling plans and SOPs should contain plans and information for three major areas (see the **Vaccine Storage and Handling SOP Worksheet**):

- General information—include contact information for vaccine manufacturers, equipment service providers, and important facility staff, as well as job descriptions, regularly used forms, and staff training requirements
- Routine storage and handling SOPs—include information for all aspects of vaccine inventory management, from ordering to monitoring storage conditions
- Emergency vaccine storage, handling, and transport SOPs—outline steps to be taken in the event of equipment malfunctions, power failures, natural disasters, or other emergencies that might compromise vaccine storage conditions

Worksheets to assist you in developing your organization's routine and emergency SOPs are located in the resources section.

Train staff on routine vaccine storage and handling and emergency SOPs. Keep SOPs near vaccine storage units and make sure staff knows where to find them. Document all training completed with dates and participant names.

Storage and handling training should be completed:

- As part of new employee orientation
- Annually as a refresher for all staff involved in immunization and vaccine storage and handling activities
- Whenever new vaccines are added to inventory
- Whenever recommendations for storage and handling of vaccines are updated

*Immunization programs: www.cdc.gov/vaccines/imz-managers/awardee-imz-websites.html

†You Call the Shots: Vaccine Storage and Handling: www.cdc.gov/vaccines/ed/youcalltheshots.html

Vaccine Coordinator Recommendations

Designate a primary vaccine coordinator. This person will be responsible for ensuring all vaccines are stored and handled correctly and should be an expert on your facility's storage and handling SOPs.

Coordinator responsibilities should include:

- Ordering vaccines
- Overseeing proper receipt and storage of vaccine deliveries
- Documenting vaccine inventory information
- Organizing vaccines within storage units
- Setting up temperature monitoring devices
- Checking and recording minimum/maximum temperatures at start of each workday‡
- Reviewing and analyzing temperature data at least weekly for any shifts in temperature trends
- Rotating stock at least weekly so vaccines with the earliest expiration dates are used first
- Removing expired vaccine from storage units
- Responding to temperature excursions (out-of-range temperatures)
- Maintaining all documentation, such as inventory and temperature logs
- Organizing vaccine-related training and ensuring staff completion of training
- Monitoring operation of vaccine storage equipment and systems
- Overseeing proper vaccine transport (when necessary) per SOPs
- Overseeing emergency preparations per SOPs:
  - Tracking inclement weather conditions§
  - Ensuring appropriate handling of vaccines during a disaster or power outage‖

Coordinator responsibilities may be completed by the coordinator or delegated to appropriate staff. Ensure the coordinator has trained the delegate(s) and documented competency for the specific task(s) assigned.

Staff Training and SOP Best Practices

- Review and update SOPs annually.
- Appoint an alternate vaccine coordinator to act in the absence of the primary coordinator.
- The alternate coordinator, like the primary coordinator, should be an expert in routine and emergency SOPs.

‡This is a VFC provider requirement.

§The Federal Emergency Management Agency (FEMA) offers a wide range of information on disaster preparedness: www.fema.gov/.
The Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA) offers information concerning the storage and use of temperature-sensitive biological products that have been involved in a temporary electrical power failure or flood conditions: www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/.

‖The National Oceanic and Atmospheric Administration (NOAA) provides up-to-date information on U.S. weather conditions:
www.weather.gov/
www.goes.noaa.gov/

SECTION THREE: Vaccine Storage and Temperature Monitoring Equipment

It is important your facility has proper storage and monitoring equipment that is set up correctly, maintained appropriately, and repaired as needed. This equipment protects patients from inadvertently receiving compromised vaccine and your facility against costs of revaccinating patients, replacing expensive vaccines, and losing patient confidence in your practice.

Vaccine Storage Units: Refrigerator and Freezer Recommendations

There are several types of vaccine storage units available. Purpose-built units are specifically designed to store vaccines. However, household-grade units are also an acceptable option for vaccine refrigeration under the right conditions.

- **Use purpose-built or pharmaceutical-grade units designed to either refrigerate or freeze**. These units can be compact, under-the-counter style or large.

Purpose-built units, sometimes referred to as "pharmaceutical-grade," are designed specifically for storage of biologics, including vaccines. These units often have:

- Microprocessor-based temperature control with a digital temperature sensor (thermocouple, resistance temperature detector [RTD], or thermistor)
- Fan-forced air circulation with powerful fans or multiple cool air vents promoting uniform temperature and fast temperature recovery from an out-of-range temperature.

Household-grade units can be an acceptable alternative to pharmaceutical-grade vaccine storage units. As the name implies, these units are primarily designed and marketed for home use. However, the freezer compartment of this type of unit is not recommended to store vaccines and there may be other areas of the refrigerated compartment that should be avoided as well. If your facility provides frozen vaccine, a separate freezer unit is necessary.

Do not store any vaccine in a dormitory-style or bar-style combined refrigerator/freezer unit under any circumstances.

These units have a single exterior door and an evaporator plate/cooling coil, usually located in an icemaker/freezer compartment. These units pose a significant risk of freezing vaccines, even when used for temporary storage. (Note: Not all small storage units are dormitory- or bar-style units. Compact, purpose-built units for biologics can be used to store vaccines.)

Storage unit doors

A door that is not sealed properly or left open unnecessarily not only affects the temperature in a unit, it also exposes vaccines to light, which can reduce potency of some vaccines. Consider using safeguards to ensure the doors of the unit remain closed—for example, self-closing door hinges, door alarms, or door locks.

Storage Unit Best Practices

To fully ensure the safety of vaccines, equipment should include a recommended unit with enough space to accommodate your maximum inventory without crowding.

Storage Unit Placement

Good air circulation around the outside of the storage unit is important. Place a storage unit in a well-ventilated room, leaving space between the unit, ceiling, and any wall. Nothing should block the cover of the motor compartment. The unit should be firm and level, with the bottom of the unit above the floor. Make sure the unit door opens and closes smoothly and fits squarely against the body of the unit. If not secured properly, unit doors pose a particular risk to maintaining appropriate internal temperatures of vaccine storage units. Studies find most units work best when placed in an area with standard indoor room temperatures, usually between 20° C and 25° C (68° F and 77° F). Check the manufacturer-supplied owner's manual for additional guidance on placement and spacing.

You may see vendors use terms such as "VFC-compliant," "CDC-compliant," or "satisfies VFC requirements" in their marketing materials or on their websites. In this context, "compliance" and related terms may lead consumers to incorrectly believe that CDC or the VFC program has independently assessed and verified the quality of these products. CDC/VFC is not authorized to assess, validate, verify, or endorse the products or services of private companies. Should you encounter this type of language in vendor marketing materials, please keep in mind that neither CDC nor the VFC program has validated any product or service for compliance with CDC or VFC program requirements or standards.

Stabilizing Temperatures in New and Repaired Units

It may take two to seven days to stabilize the temperature in a newly installed or repaired refrigerator and two to three days for a freezer.

Before using a unit for vaccine storage, check and record the minimum and maximum temperatures each workday for two to seven days. If temperatures cannot be recorded digitally, check and record temperatures a minimum of two times each workday. Once you have two consecutive days of temperatures recorded within the recommended range, your unit is stable and ready for use.

Temperature Ranges

Refrigerators should maintain temperatures between 2° C and 8° C (36° F and 46° F).* Freezers should maintain temperatures between -50° C and -15° C (-58° F and +5° F). Refrigerator or freezer thermostats should be set at the factory-set or midpoint temperature, which will decrease the likelihood of temperature excursions.

Consult the owner's manual for instructions on how to operate the thermostat. Thermostats are marked in various ways and, in general, show levels of coldness rather than temperatures. The only way to know the temperature where vaccines are stored is to measure and monitor it with a temperature monitoring device.

Temperature Monitoring Device (TMD)

Every vaccine storage unit must have a TMD. An accurate temperature history that reflects actual vaccine temperatures is critical for protecting your vaccines. Investing in a reliable device is less expensive than replacing vaccines wasted due to the loss of potency that comes from storage at out-of-range temperatures.

- **CDC recommends a specific type of TMD called a "digital data logger" (DDL).** A DDL provides the most accurate storage unit temperature information, including details on how long a unit has been operating outside the recommended temperature range (referred to as a "temperature excursion"). Unlike a simple minimum/maximum thermometer, which only shows the coldest and warmest temperatures reached in a unit, a DDL provides detailed information on all temperatures recorded at preset intervals.

Many DDLs use a buffered temperature probe, which is the most accurate way to measure actual vaccine temperatures. Temperatures measured by a buffered probe match vaccine temperatures more closely than those measured by standard thermometers, which tend to reflect only air temperature.

Temperature data from a DDL can either be downloaded to a computer using special software or retrieved from a website. The software or website may also allow you to set the frequency of temperature readings. Reviewing DDL data is critical for vaccine viability, so it is important to decide whether independent software or a website program works best for your facility.

- **Keep the data for three years so it can be analyzed for long-term trends and/or recurring problems.** Those receiving public vaccine may need to keep records longer as required by state regulations.

- **Use a DDL or other appropriate TMD for:**
  - Each vaccine storage unit
  - Each transport unit (emergency or non-emergency)

Have at least one backup TMD in case a primary device breaks or malfunctions.

- **Use DDLs with the following features:**
  - Detachable probe that best reflects vaccine temperatures (e.g., a probe buffered with glycol, glass beads, sand, or Teflon®)†
  - Alarm for out-of-range temperatures
  - Low-battery indicator†

*Probes that are permanently embedded in a buffer are acceptable as long as the temperature monitoring system for the entire unit can be calibration-tested.

†Since these devices are typically battery-operated, have a supply of extra batteries on hand.

- Current, minimum, and maximum temperature display‡
- Recommended uncertainty of +/-0 .5° C (+/-1° F)
- Logging interval (or reading rate) that can be programmed by the user to measure and record temperatures at least every 30 minutes

Use DDLs with a current and valid Certificate of Calibration Testing.

Certificate of Calibration Testing

Calibration testing is done to ensure the accuracy of a temperature monitoring device's readings against nationally accepted standards.

A DDL's Certificate of Calibration Testing should include:

- Model/device name or number
- Serial number
- Date of calibration (report or issue date)
- Confirmation that the instrument passed testing (or instrument is in tolerance)
- Recommended uncertainty of +/-0 .5° C (+/-1° F) or less

To determine if a Certificate of Calibration Testing or Report of Calibration was issued by an appropriate entity, check to see if the certificate indicates one or more of the following items about calibration testing:

- Conforms to International Organization for Standardization (ISO)/International Electrotechnical Commission (IEC) 17025 international standards for calibration testing and traceability
- Performed by a laboratory accredited by International Laboratory Accreditation Cooperation (ILAC) Mutual Recognition Arrangement (MRA) signatory body
- Traceable to the standards maintained by the National Institute of Standards and Technology (NIST)
- Meets specifications and testing requirements for the American Society for Testing and Materials (ASTM) Standard E2877 Tolerance Class F or higher
- Refers to another acceptable accuracy validation method, such as comparison to other traceable reference standards or tests at thermometric fixed points

Calibration testing should be done every one to two years or according to the manufacturer's suggested timeline. TMDs can experience a "drift" over time, affecting their accuracy. This testing ensures the accuracy of the device continues to conform to nationally-accepted standards.

Mishandling a TMD can affect its accuracy. If a TMD is dropped, hit against the side of a storage unit, or is potentially damaged in any way, its accuracy should be checked against another calibrated TMD. If there is any question about accuracy, the device should be replaced or sent for calibration testing.

Monitoring Vaccine Temperature and Vaccine Equipment

Monitoring vaccine storage equipment and temperatures are daily responsibilities to ensure the viability of your vaccine supply and your patients. Implementing routine monitoring activities can help you identify temperature excursions quickly and take immediate action to correct them, preventing loss of vaccines and the potential need for revaccination of patients.

Certain types of TMDs have significant limitations and should not be used to measure temperatures in a vaccine storage unit. These devices can be difficult to read and, because they only show the temperature at the exact time they are checked, may fail to detect temperatures outside the recommended range.

CDC does not recommend the following TMDs:

» Alcohol or mercury thermometers, even if placed in a fluid-filled, biosafe, liquid vial

» Bimetal stem TMDs

» TMDs used for food

» Chart recorders

» Infrared TMDs

» TMDs that do not have a current and valid Certificate of Calibration Testing

Please note: Some devices sold in hardware and appliance stores are designed to monitor temperatures for household food storage. They are not calibrated and not accurate enough to ensure vaccines are stored within the correct temperature range. Using these devices can pose a significant risk of damaging vaccines.

‡Battery changes may affect temperature accuracy and may warrant checking against a known, calibrated TMD. Check with the device's manufacturer for specific information on battery changes.

Power Supply

Food and beverages should never be stored in the unit with vaccines.

Even with appropriate equipment and temperature monitoring practices in place, power disruption can result in destruction of the entire vaccine supply. Precautions should always be taken to protect the storage unit's power supply.

- **Plug in only one storage unit per electrical outlet to avoid creating a fire hazard or triggering a safety switch that turns the power off.**
- **Use a safety-lock plug or an outlet cover to prevent the unit from being unplugged.**
- **Post "DO NOT UNPLUG" warning signs at outlets and on storage units to alert staff, custodians, electricians, and other workers not to unplug units.**
- **Label fuses and circuit breakers to alert people not to turn off power to a storage unit.**
- **Use caution when using power outlets that can be tripped or switched off and avoid using:**
  - Built-in circuit switches (may have reset buttons)
  - Outlets that can be activated by a wall switch
  - Multioutlet power strips

If built-in circuit switches or power strip surge protection must be used, make sure the power strip is rated to carry the maximum current as specified by the manufacturer of the refrigerator or freezer. Contact the unit manufacturer for any additional questions or guidance regarding circuit switches, power strips, or surge protection.

If the entire storage unit is affected by a temperature excursion because of a power supply issue or unit malfunction, refer to your facility's emergency SOPs.

Organizing and Storing Vaccine

Correctly organizing and placing vaccines in a storage unit helps prevent conditions that could reduce vaccine potency or cause vaccine failure.

Temperature Monitoring

Regular checks provide an opportunity to inspect the storage unit, reorganize any misplaced vaccines, and remove any expired vaccines. Check the temperature each time vaccines are accessed in the unit.

Review storage unit temperature readings and review continuous DDL software or website information weekly for changes in temperature trends that might require action.

If there appears to be any fluctuation in temperature, troubleshoot the problem based on additional information provided in this toolkit, manufacturer manuals, and/or your office storage and handling SOPs.

- **Store vaccines in their original packaging with lids closed until ready for administration.** Vials and manufacturer-filled syringes should always be stored in their original packaging. Loose vials or syringes may be exposed to unnecessary light, potentially reducing potency, and may be more difficult to track for expiration dates. They may also impact inventory management and increase the risk of administration errors because they may be confused with other vaccines. For certain purpose-built units, it is recommended that vaccine be stored outside of the packaging. If this is the case, follow the manufacturer's guidance for vaccine storage.
- **Check and record storage unit minimum and maximum temperatures at the start of each workday.**

  Record:

  - Minimum/maximum temperature
  - Date
  - Time
  - Name of person who checked and recorded the temperature
  - Any actions taken if a temperature excursion occurred
  - If a reading is missed, leave a blank entry in the log.

Temperature Excursions

Temperature excursions or inappropriate storage conditions for any vaccine require immediate action. Any temperature reading outside the recommended ranges in the manufacturers' package inserts* is considered a temperature excursion. In general, manufacturers analyze information about the magnitude of the temperature excursion and the total amount of time that temperatures were out of range, as well as information about the vaccine in question, to determine whether a vaccine is likely to still be viable.

CDC recommends the following steps in the event of a temperature excursion:

1. Any staff who hears an alarm or notices a temperature excursion on the DDL should notify the primary or alternate vaccine coordinator immediately or report the problem to their supervisor.
2. Notify staff by labeling exposed vaccines, "DO NOT USE," and placing them in a seperate container apart from other vaccines (do not discard these vaccines).

Organizing and Storing Vaccine

To confirm vaccines are stored correctly and to minimize the risk of administration errors, implement the following practices:

» Store each type of vaccine or diluent in its original packaging and in a separate container.
» Position vaccines and diluents two to three inches from the unit walls, ceiling, floor, and door. If using a household-grade unit, avoid storing vaccines and diluents in any part of the unit that may not provide stable temperatures or sufficient air flow, such as directly under cooling vents, in deli, fruit, or vegetable drawers, or on refrigerator door shelves. The instability of temperatures and air flow in these areas may expose vaccines to inappropriate storage temperatures.
» Label shelves and containers to clearly identify where each type of vaccine and diluent is stored.
» Store vaccines and diluents with similar packaging or names or with pediatric and adult formulations on different shelves.
» Whenever possible, store diluent with the corresponding refrigerated vaccine. Never store diluent in a freezer.
» Avoid placing or storing any items other than vaccines, diluents, and water bottles inside storage units.
  - If other medications and biological products must be stored in the same unit as vaccines, they must be clearly marked and stored in separate containers or bins from vaccines.
    — Potentially contaminated items (e.g., blood, urine, stool) should be properly contained and stored below vaccines due to risk of contamination from drips or leaks.
    — The freezer of a household-grade unit may be used for non-vaccine, medical storage, so long as the use does not compromise the temperature range within the refrigerator compartment where vaccine is stored.
» Arrange vaccines and diluents in rows and allow space between them to promote air circulation.
» Place vaccines and diluents with the earliest expiration dates in front of those with later expiration dates.

*Manufacturers' vaccine package inserts: www.immunize.org/fda/

BEST PRACTICES

Place water bottles on the top shelf and floor and in the door racks. Putting water bottles in the unit can help maintain stable temperatures caused by frequently opening and closing unit doors or a power failure.

Water bottles are not recommended for use with certain pharmaceutical-grade and purpose-built units. For such units, follow the manufacturer's guidance.

How to Store Vaccines

3. The vaccine coordinator, supervisor, or if necessary, the person reporting the problem should begin to document the event with the following information[§]:
   a. Date and time of the temperature excursion
   b. Storage unit temperature as well as room temperature, if available (including minimum/maximum temperatures during the time of the event, if available)
   c. Name of the person completing the report and description of the event[‖]:
      — General description of what happened
      — The length of time vaccine may have been affected, if using a DDL
      — Inventory of affected vaccines
      — List of items in the unit (including water bottles) other than vaccines
      — Any problems with the storage unit and/or affected vaccines before the event
      — Other relevant information
4. Implement your facility SOPs to adjust unit temperature to the appropriate range. At a minimum, check the TMD to make sure it is appropriately placed in the center of the vaccines.
5. Contact your immunization program and/or vaccine manufacturer(s) per your SOPs for further guidance on whether to use affected vaccines and for information about whether patients will need to be recalled for revaccination. Be prepared to provide documentation of the event (e.g., temperature log data) to ensure you receive the best guidance.
6. Complete your documentation of the event, including:
   a. Action taken
      — What you did with vaccine and how long it took to take action
      — Whom you contacted and instructions received
      — What you did to prevent a similar future event
   b. Results
      — Final disposition of affected vaccines (e.g., shortened expiration date per manufacturer, discarded, or returned)
      — Other comments

[§]The Immunization Action Coalition has developed a Temperature Monitoring Log and a Vaccine Storage Troubleshooting Record to support these activities.

[‖]Responses from vaccine manufacturers to events depend on information given by the provider to the manufacturer. If different information about the same event is provided to the same manufacturer, this can lead to different recommendations on whether vaccine can be used or whether patients need to be revaccinated. In addition, each event is unique, and manufacturer recommendations based on existing stability data cannot be applied to future events that may appear to be similar.

Regular Maintenance of Vaccine Storage Units and Temperature Monitoring Devices

Storage units and TMDs need regular maintenance to ensure proper operation.

Never allow vaccines to remain in a malfunctioning unit for an extended period of time. If you believe your your unit has failed, implement your emergency SOPs.

Conduct routine maintenance for all vaccine storage units and related equipment so that your equipment functions at maximum efficiency.

- Check seals and door hinges.
- Clean coils and other components per manufacturer direction.
- Defrost manual-defrost freezers.
- Clean the interior of each unit to discourage bacterial and fungal growth. Do so quickly to minimize the risk of a temperature excursion.
- Test any backup generator quarterly and have it serviced annually.

Troubleshooting Equipment Problems

Adjusting Storage Unit Temperatures

Storage unit temperatures may need to be adjusted over time. In some situations, thermostats may need to be reset in summer and winter, depending on room temperature.

Temperature adjustments should:

- Be made by the primary or alternate vaccine coordinator, based on information from the TMD and temperature monitoring log.
- Be done at a time that is not during a busy workday when the unit door is being frequently opened and closed.

Remember that temperatures within any storage unit will vary slightly, even with normal use. Therefore, before making any adjustment:

- Confirm the unit is securely plugged into a power source.
- Check the temperature inside the storage unit.
- Wait 30 minutes, without opening the door, to allow the temperature to stabilize and then check it again to determine if the thermostat should be adjusted.

If you believe there could be an issue with your TMD, use your backup device to confirm the temperature.

If you confirm that an adjustment is needed:

1. Refer to the owner's manual for detailed instructions.
2. Make a small adjustment toward a warmer or colder setting by turning the thermostat knob slowly to avoid going outside the correct temperature range.
3. Once the adjustment is made, allow the temperature inside the unit to stabilize for 30 minutes without opening the door.
4. Recheck the temperature.
5. Repeat these steps as needed until the temperature has stabilized at around 5° C (40° F) for a refrigerator or between -50° C and -15° C (-58° F and +5° F) for a freezer.
6. Consider placing additional water bottles in the unit to help improve temperature stability.

Do not leave vaccines in a storage unit that does not maintain temperatures within the recommended range. If you are unable to stabilize the temperature in your unit within the required range, or temperatures in the unit are consistently at the extreme high or low end of the range, your vaccine supply is at high risk. Use your SOPs to identify an alternative unit with appropriate temperatures and sufficient storage space until the primary unit can be repaired or replaced.

If you are using a combination storage unit, note that adjustments to the freezer temperature can adversely affect the refrigerator compartment temperature, possibly resulting in frozen vaccines in the refrigerator.

Repeated Alarm Alerts

If the temperature alarm goes off repeatedly, do not disconnect the alarm until you have determined and addressed the cause. Do basic checks of the unit door, power supply, and thermostat settings. If the alarm continues to trigger or the temperature remains out of range, transfer vaccines to a backup unit as directed by your SOPs. A repair technician should check your equipment to determine the need for repair or replacement.

Proper vaccine inventory management is essential for appropriate vaccine ordering and stock rotation, and ensures your facility has the vaccines your patients need. Vaccines are expensive, so making sure they are unpacked, stored, prepared, administered, and transported correctly is critical.

Never leave a vaccine shipping container unpacked and unattended. If vaccines and diluents get too warm, they cannot be used. Be sure all staff knows that vaccine deliveries require immediate attention.

Vaccine Delivery

Scheduling and Receiving Deliveries

Maintaining the cold chain is the first step in vaccine inventory management. Staff members who might accept vaccine deliveries should be trained to immediately notify the vaccine coordinator or alternate coordinator when deliveries arrive. Vaccines must always be immediately checked and stored properly upon arrival.

Unpacking Deliveries

Vaccines and diluents must be carefully unpacked, stored at recommended temperatures, and documented immediately after they arrive. Do not place an unopened and/or unpacked shipment box in a vaccine storage unit because the cool packs shipped with the vaccine may make the packaged vaccine too cold if placed inside the storage unit.

Immediately examine shipments for signs of damage and to guarantee receipt of the appropriate vaccine types and quantities.

- Examine the shipping container and vaccines for signs of physical damage.
- Check the contents against the packing list to be sure they match.
  - For frozen vaccines, the packing list will show the maximum time vaccines can be in transit based on shipment date.
- If the shipment includes lyophilized (freeze-dried) vaccines, make sure they came with the correct type and quantity of diluents.
- Immediately check both vaccine and diluent expiration dates to ensure you have not received any expired or soon-to-expire products.
- Immediately check the cold chain monitor (CCM), a device used to monitor vaccine temperatures during transport, if one was included, for any indication of a temperature excursion during transit.

Vaccine Inventory Accounting

Stock Counts

Stock records are used to determine the type and amount of vaccines your facility should stock to meet the needs of your patients. At least once a month and before placing any vaccine order, count all vaccine and diluent doses to make sure the number of doses in the storage unit matches the number of doses documented in the stock record. Always check expiration dates while counting stock and remove any expired doses immediately.

Stock Records

Use a stock record to account for and document every dose of vaccine. This record will help you keep track of your inventory and can be in either paper or electronic form. This record should be updated weekly and include the vaccine delivery information below:

- Date of delivery and initials of the person who unpacked the box
- Vaccine and diluent name and manufacturer
- Number and expiration date for each lot
- Number of doses received
- Condition of each vaccine and diluent upon arrival
- CCM reading if included in the shipping container
- Number of doses used
- Balance of remaining doses after subtracting the amount used

Note: State and local programs that have an immunization information system (IIS) with vaccine inventory accounting functions will require VFC providers to use the IIS to track their inventory.

Tally Sheets

Tally sheets can help keep stock records up to date. Place tally sheets outside the storage unit door (or another easily accessible location), and have staff use tick marks to keep a count of every dose removed from the unit.

If the numbers in the storage unit do not match the doses documented in the stock record, enter the correct number based on your count on a separate line below the old balance on your stock record. Make a note next to the new entry indicating that your count confirmed the new balance and sign it. Use the corrected balance for calculating stock quantities in the future.

If you receive multiple doses of the same vaccine in the same presentation from the same lot with the same expiration date, you can document these doses as one entry on the stock record. Indicate the total number of doses received, regardless of how many vials or syringes the doses came in. For example, if you receive 10 single-dose vials of the same vaccine with the same lot number and expiration date, you can make a single entry on the stock record, noting that 10 doses were received.

If there are discrepancies between the contents and the packing list or other concerns about the contents, immediately notify the vaccine manufacturer. If you are a VFC provider or receive vaccines purchased with public funds, contact your immunization program.*

Diluents should be documented on a separate stock record and should equal quantities of corresponding vaccines.

At the end of each month, determine the total number of vaccine and diluent doses used that month and the amount of stock still available. At the end of each year, use your stock record to determine the number of doses received for the year and add up your monthly dose counts to get a total number of doses used. This information will help you determine your facility's needs and guide you in ordering so you can minimize future waste and reduce the need for transfer and transport of vaccines. It will also help to make sure you have a sufficient supply to meet your patients' needs.

Vaccine Ordering

Order and stock only enough vaccine to meet patient needs.†

Storing a larger volume than your facility needs can increase the risk of wasting vaccines if they expire before they can be used or they are compromised in some way (e.g., due to mechanical failure of a storage unit).

Most facilities should also reorder based on patient needs after checking stock count. Vaccine orders usually arrive within one to two weeks, but there can be delays. When possible, avoid placing last-minute or rush orders to lessen the risk of running out of vaccines.

Arranging your stock

The vaccine coordinator (or other designated person) should rotate vaccine and diluent stock at least once a week, as well as each time your facility receives a vaccine delivery. This will ensure that vaccines expiring sooner are used first.

Stock Rotation and Removal

Vaccine stock should be rotated and checked for expired doses regularly. Any expired vaccines and diluents should be removed immediately to avoid inadvertently administering them. Arrange stock for each vaccine type so that doses with the earliest expiration dates are placed in front of those with later expiration dates.

Contact your immunization program* to find out if expired vaccines purchased with public funds can be returned.

*Contact your immunization program for details about specific state or local regulations impacting this activity.

†An adequate supply of vaccine varies for most providers, facilities, or immunization programs. It is recommended that reordering is done when stock has been reduced to a four week inventory.

Understanding Expiration Dates

Determining when a vaccine or diluent expires is a critical step in maintaining proper storage and handling. Understanding vaccine expiration dates can help save your practice time and money.

When the expiration date has only a month and year, the product may be used up to and including the last day of that month. If a day is included with the month and year, the product may only be used through the end of that day.

In some instances, such as the examples for beyond use date (BUD) below, vaccines must be used before the expiration date on the label.

Beyond Use Dates

Some vaccines have a beyond use date (BUD), which is calculated based on the date the vial is first entered and the storage information in the package insert.

The BUD replaces the manufacturer's expiration date and should be noted on the label along with the initials of the person making the calculation. Examples of vaccines with BUDs include:

Reconstituted vaccines have a limited period for use once the vaccine is mixed with a diluent. This period or BUD is listed in the package insert.
Multidose vials might have a specified period for use once they have been entered with a needle. For example, the package insert may state that the vaccine must be discarded 28 days after it is entered. If the vial is entered on 06/01/2019, the BUD is 06/29/2019. The vaccine should not be used after the BUD.
Manufacturer-shortened expiration dates may apply when vaccine is exposed to inappropriate storage conditions. The manufacturer might determine the vaccine can still be used, but will expire on an earlier date than the date on the label.

Vaccine Disposal

General vaccine disposal guidelines for:

- **Expired or compromised vaccine**—sometimes unused vaccine and diluent doses, unopened vials, expired vials, and potentially compromised vaccine may be returned for credit, even if they must be discarded. Contact your immunization program* and/or the vaccine manufacturer for vaccine-specific information.
- **Open and broken vials and syringes, manufacturer-filled syringes that have been activated, and vaccine predrawn by providers**—these cannot be returned and should be discarded according to your state requirements.
- **Empty vaccine vials**—most are not considered hazardous or pharmaceutical waste and do not require disposal in a biomedical waste container.†† However, check and comply with your state requirements regarding disposal.

Medical waste disposal requirements may vary from state to state because they are set by state environmental agencies. Contact your immunization program* or state environmental agency for guidance to ensure your facility's vaccine disposal procedures comply with state and federal regulations.

*Contact your immunization program for details about specific state or local regulations impacting this activity.

††While vials are not usually considered hazardous or pharmaceutical waste, an empty RV dispensing tube or oral applicator is considered medical waste and should be disposed of in a medical waste container.

Preparing Vaccine for Administration

Vaccine preparation is the final step in the cold chain before administration. Handling vaccines with care is equally as important as storing them properly.

Vaccine administration

- Prepare vaccines in a designated area away from any space where potentially contaminated items are placed.
- Only prepare vaccines when you are ready to administer them.
- Always check expiration dates and confirm that you have selected the correct vaccine.
- Only administer vaccines you have prepared. This is a quality control and patient safety issue and a best practice standard of medication administration.

Different types of vaccine vials

Single-Dose Vials

A single-dose vial (SDV) contains one dose and should be used one time for one patient. SDVs do not contain preservatives to help prevent microorganism growth. Never combine leftover vaccine from one SDV with another to obtain a dose.

Only open an SDV when ready to use. Before you remove the protective cap, always check the vial to make sure you have the correct vaccine. Once you remove the cap, you must use the vaccine because it may not be possible to determine if the rubber seal has been punctured. Discard any unused SDVs without a protective cap at the end of the workday.

Multidose Vials

A multidose vial (MDV) contains more than one dose of vaccine. Because MDVs typically contain a preservative to help prevent the growth of microorganisms, they can be entered or punctured more than once. Only the number of doses indicated in the manufacturer's package insert should be withdrawn from the vial. After the maximum number of doses have been withdrawn, the vial should be discarded, even if there is residual vaccine or the expiration date has not been reached.

MDVs can be used until the expiration date printed on the vial unless the vaccine is contaminated or compromised in some way or there is a BUD noted in the package insert.

Never use partial doses from two or more vials to obtain a dose of vaccine.

Manufacturer-Filled Syringes

A manufacturer-filled syringe (MFS) is prepared and sealed under sterile conditions by the manufacturer. **Activate an MFS (i.e., remove the syringe cap or attach the needle) only when ready to use.**

An MFS does not contain a preservative to help prevent the growth of microorganisms. Once the sterile seal has been broken, the vaccine should be used or discarded by the end of the workday.

Reconstitution of Vaccine

Lyophilized (freeze-dried) vaccines are in either powder or pellet form and must be mixed with a liquid (diluent) in a process known as "reconstitution" before being administered.

Diluents vary in volume and composition and are specifically designed to meet volume, pH balance, and the chemical requirements of their corresponding vaccines. Refer to the manufacturer's package insert for guidance on storage and handling.

Diluents are not interchangeable unless specified by the manufacturer.

- Some diluents contain an antigen or an adjuvant needed for vaccine effectiveness. Even if the diluent is composed of sterile water or saline, use only the diluent supplied with the vaccine to reconstitute it.

Always check expiration dates on both diluents and vaccines before reconstituting them.†

Never use a stock vial of sterile water or normal saline to reconstitute vaccines.

Never administer vaccine reconstituted with the wrong diluent.

- If an incorrectly reconstituted vaccine has already been administered, contact your immunization program* or the vaccine manufacturer for revaccination guidance.

Predrawing Vaccine

Predrawing vaccines can result in waste if more are drawn up than needed.

Draw up vaccines only at the time of administration. Once vaccines are inside syringes, it is difficult to tell them apart, which can lead to administration errors. However, there may be rare instances when the only option is to predraw vaccine.

Predrawn syringes must be stored at the manufacturer-recommended temperatures throughout the clinic day. If vaccines must be predrawn:

- Set up a separate administration station for each vaccine type to prevent medication errors.
- Draw up vaccines only after arriving at the clinic site or mass vaccination event. Drawing up doses days or even hours before administering them is not a best practice because general-use syringes are not designed for storage.
- Each person administering vaccines should draw up no more than one MDV or 10 doses at one time.
- Monitor patient flow to avoid drawing up unnecessary doses.
- Predraw reconstituted vaccine into a syringe only when you are ready to administer it. If a predrawn vaccine is not used within 30 minutes of being reconstituted, follow manufacturer guidance for storage conditions and time limits. A manufacturer may specify that an unused reconstituted vaccine can only be stored in the vial for a specified amount of time.
- Discard any remaining vaccine in predrawn syringes at the end of the workday.

Never transfer predrawn reconstituted vaccine back into a vial for storage.

As an alternative to predrawing vaccines, use manufacturer-filled syringes for large vaccination clinics.

* Immunization programs: www.cdc.gov/vaccines/imz-managers/awardee-imz-websites.html

† If you are a VFC provider or have other vaccines purchased with public funds and must transfer vaccine to another facility so it can be used before it expires, contact your immunization program* for guidance on vaccine transport.

Transport, as described in this section, involves the movement of vaccine between providers or other locations over a shorter distance and time frame and is appropriate for events such as an emergency, off-site clinic, or to ensure vaccines that are about to expire can be used rather than wasted.

Vaccine Transport Situations

Vaccine transport to off-site or satellite facilities is different from both shipping and emergency transport. Shipping usually involves a professional carrier and a longer distance and time frame for moving vaccines between locations. Emergency transport usually involves relocating vaccines to protect them when a facility's ability to store vaccines is compromised (e.g., because of power loss). Depending on the situation, some transport recommendations may be the same, but there are also some differences.

Vaccine Transport

Vaccines from your supply should not be routinely transported. In instances where the transport of vaccine from your supply is necessary, take appropriate precautions to protect your supply. Vaccines should only be transported using appropriate packing materials that provide the maximum protection.

Protecting your vaccine supply

- » Vaccine that will be used at an off-site or satellite facility should be delivered directly to that facility.
- » If delivery to the specific site is not possible, then vaccine can be transported in a stable storage unit and monitored with a TMD. If the facility doesn't have the capacity to refrigerate the vaccines, then a portable vaccine storage unit or qualified container and packout may be used with a DDL.
- » Develop an emergency plan or SOPs for transporting vaccines and include procedures and protocols for packing and transport.

Partially used vials cannot be transferred between providers OR across state lines.*

- **The total time for transport alone or transport plus clinic workday should be a maximum of 8 hours (e.g., if transport to an off-site clinic is 1 hour each way, the clinic may run for up to 6 hours).**
- **Transport diluents with their corresponding vaccines to ensure there are always equal amounts of vaccines and diluents for reconstitution.**
- **Your facility should have a sufficient supply of materials needed for vaccine transport of your largest annual inventory. Appropriate materials include:**
  - Portable vaccine refrigerator/freezer units (preferred option)
  - Qualified containers and packouts
  - Hard-sided insulated containers or Styrofoam™ (Use in conjunction with the *Packing Vaccines for Transport during Emergencies*† tool. This system is only to be used in an emergency.)
  - Coolant materials such as phase change materials (PCMs) or frozen water bottles that can be conditioned to 4° C to 5° C
  - Insulating materials such as bubble wrap and corrugated cardboard—enough to form two layers per container
  - TMDs for each container

Soft-sided containers specifically engineered for vaccine transport are acceptable. Do not use commercially available soft-sided food or beverage coolers because most are poorly insulated and likely to be affected by room or outdoor temperatures.

The same shipping materials the vaccines were initially shipped in should rarely, if ever, be used as they are not meant for reuse. This could put the cold chain and, ultimately, the viability of the vaccine, at risk.

* Contact your immunization program for details about specific state or local regulations impacting this activity.

† Packing Vaccines for Transport during Emergencies: www.cdc.gov/vaccines/hcp/admin/storage/downloads/emergency-transport.pdf

Transport of Vaccines

It is always safest to have vaccines delivered directly to a facility with a vaccine storage unit ready to receive the shipment, but this is not always possible. If necessary, vaccines may be transported using a portable vaccine refrigerator with a temperature monitoring device placed with the vaccines. If a portable vaccine refrigerator is not available, qualified containers and packouts with a TMD in each container can be used. For transport to an off-site clinic, bring only what is needed for the workday.

Transport System Recommendations

	Emergency Transport	Transport for Off-Site Clinic, Satellite Facility, or Relocation of Stock
Portable Vaccine Refrigerator or Freezer	Yes	Yes
Qualified Container and Packout	Yes	Yes
Conditioned Water Bottle Transport System†	Yes	No
Manufacturer's Original Shipping Container	Yes (last resort only)	No
Food/Beverage Coolers	No	No

Coolants for Transport

PCMs at 4° C–5° C (39° F–41° F) can also be purchased to maintain proper temperatures. Follow the manufacturer's instructions‡ for use to reduce the risk of freezing vaccines during transport.

Do not use frozen gel packs or coolant packs from original vaccine shipments to pack refrigerated vaccines. They can still freeze vaccines even if they are conditioned or appear to be "sweating."

In emergency situations, a system using conditioned water bottles can be used. Manufacturers' original shipping containers may also be used as a last resort in an emergency situation.

The *Packing Vaccines for Transport during Emergencies*† tool describes a system in which properly conditioned frozen water bottles can be used as a coolant when transporting vaccine during emergency situations.

Transport Planning and Preparation

Improper packing for transport is as risky for vaccines as a failed storage unit.

Include vaccine packing and transport protocols in your routine and emergency storage and handling SOPs. At a minimum, include the following procedures and protocols:

For all staff-facilitated transport:

- Identify trained staff to pack vaccines as well as primary and backup vehicles and drivers for transport in advance.
- Consider renting a refrigerated truck if you have a large quantity of vaccines or need to transport vaccines an extended distance.
- Take an inventory of your vaccines and record actions to protect the vaccines during transport.
- Open unit doors only when necessary and only after completing all preparation for packing and moving vaccines.

Emergency Transport

In addition to the actions outlined in Transport Planning and Preparation, during an emergency also:

» Contact the alternative vaccine storage facility before packing any vaccine to confirm it can accept your vaccines for storage.

» Note any protective measures in place at the time of the event (water bottles, battery-powered TMD, transport to alternative facility, etc.).

» Only open the unit door when you are ready to pack or power has been restored.

» If an emergency can be anticipated (e.g., weather event), suspend vaccination activities before the onset of emergency conditions to allow more time for packing and transport.

†Packing Vaccines for Transport during Emergencies: www.cdc.gov/vaccines/hcp/admin/storage/downloads/emergency-transport.pdf

‡Manufacturers' vaccine package inserts: www.immunize.org/fda/

- If using a company or personal vehicle, only transport vaccines inside the passenger compartment (not in the trunk or bed of a truck, which may be too hot or too cold).
- Move transport containers directly to a vehicle that is already at a comfortable temperature, neither too hot nor too cold.
- Avoid leaving containers in areas where they are exposed to direct sunlight.
- Check vaccine temperature upon arrival at the alternative vaccine storage facility and store vaccines at recommended temperatures immediately.
- Check with your immunization program[§] for additional guidance and resources on emergency transport of vaccines, particularly in major emergencies.

Transporting Opened Multidose Vials

If absolutely necessary, a partially used vial may be transported to or from an off-site/satellite facility operated by the same provider, as long as the cold chain is properly maintained. However, **a partially used vial cannot be transferred from one provider to another or across state lines.**

Transporting Diluents

Transport diluents with their corresponding vaccines so there are always equal amounts of vaccines and diluents for reconstitution. Follow the manufacturer's guidance[‡] for specific temperature requirements.

If diluents stored at room temperature (20° C to 25° C [68° F to 77° F]) are going to be transported with refrigerated vaccines, they should be refrigerated in advance for as long as possible so they do not raise the container temperature when placed with refrigerated vaccines.

Never freeze diluents—not even during transport.

Place an insulating barrier like bubble wrap between the diluents and conditioned water bottles or phase change materials.

Transporting Frozen Vaccines

If frozen vaccines must be transported, use a portable vaccine freezer unit or qualified container and packout that maintains temperatures between -50° C and -15° C (-58° F and +5° F).

Follow these steps for transporting frozen vaccines:

- Place a TMD (preferably with a buffered probe) in the container as close as possible to the vaccines.
- Immediately upon arrival at the destination, unpack the vaccines and place them in a freezer at a temperature range between -50° C and -15° C (-58° F and +5° F) . Any stand-alone freezer that maintains these temperatures is acceptable.
- Record the time vaccines are removed from the storage unit and placed in the transport container, the temperature during transport, and the time at the end of transport when vaccines are placed in a stable storage unit.

Do not use dry ice, even for temporary storage. Dry ice might expose the vaccines to temperatures colder than -50° C (-58° F).

Temperature Monitoring During Transport

Use a continuous TMD, preferably a DDL, for monitoring and recording temperatures while transporting vaccines:

- The TMD should have an accuracy of +/-0 .5° C (+/-1° F).
- Place buffered probe material in a sealed vial directly with the vaccines.
- Keep the TMD display on top of vaccines so you can easily see the temperature.

[§]Immunization programs: www.cdc.gov/vaccines/imz-managers/awardee-imz-websites.html

[‡]Manufacturers' vaccine package inserts: www.immunize.org/fda/

Temperature Monitoring After Transport

Immediately upon arrival at the destination, vaccines should be stored in an appropriate storage unit with a TMD. Be sure to follow these guidelines for monitoring and recording storage unit temperature:

- If the device displays min/max temperatures, this information should be checked and recorded.
- If the device does not display min/max temperatures, then the current temperature should be checked and recorded a minimum of two times (at the start and end of the workday).

If vaccines cannot be stored in an on-site storage unit, they should be kept in the portable vaccine storage unit using the following guidance:

- Place a TMD (preferably with a probe in a thermal buffer) as close as possible to the vaccines, and check and record temperatures hourly.
- Keep the container closed as much as possible.
- For off-site clinic use, remove only one multidose vial or 10 doses at a time for preparation and administration by each person administering vaccines.

SECTION SEVEN: Emergency Vaccine Storage and Handling

Emergencies like equipment failures, power outages, severe weather conditions, or natural disasters usually happen without warning and may compromise vaccine storage conditions. In addition to vaccine transport planning, you should make additional plans to prepare for emergencies.*

Emergency Equipment Backup Options

Alternative Storage Facility

No piece of vaccine storage equipment is infallible. At some point, equipment will fail because of a power outage, breakdown, or normal wear and tear.

- **Establish a working agreement with at least one alternative storage facility even if you have a generator as backup equipment.** Make sure you have 24-hour access to this facility. Hospitals, long-term care facilities, state depots, the Red Cross, fire stations, packing plants, and commercial pharmacies are some of the facilities that may be able to assist you.

Your facility may also choose to have a backup storage unit so that vaccine may not have to be packed and/or moved to an alternative storage facility if the primary storage unit fails.

Accessing Your Building after Hours

Emergency situations can arise outside of normal business hours, so maintain a relationship with your facility's building manager and/or security staff. Ensure all staff members are familiar with emergency SOPs, including after-hours roles and responsibilities. **Your facility's storage and handling SOPs should include instructions for accessing your vaccine storage units when the building is closed with a building map/diagram and locations of:**

- Spare batteries
- Flashlights
- Keys
- Locks
- Circuit breakers
- Emergency transport equipment and materials

Keep information on after-hours building access and security procedures with the SOPs, with building management and security staff, if appropriate, and also make sure relevant staff has copies of this information available at home.

Vaccines may remain inside a nonfunctioning unit as long as appropriate temperatures are maintained. Monitor your DDL to determine when additional action should be taken.

Generators and backup battery power sources

Having an on-site generator(s) prevents the need to transport vaccines to an alternative storage facility during a power outage.

» Keep sufficient fuel on hand to continuously run the generator for at least 72 hours.

» A generator should be tested quarterly and serviced annually.

A backup battery power source can be used in lieu of a generator.

» Backup battery power sources should be tested quarterly and serviced annually.

» Check the manufacturer's guide for testing procedures and maintenance schedules.

If an alternative vaccine storage facility is not available

If you cannot find an alternative vaccine storage facility within a reasonable distance, or if you cannot reach your alternative facility, you can use qualified containers and packouts and portable vaccine refrigerator/freezer units (if power source is available) using the *Packing Vaccines for Transport during Emergencies system*. Always place a TMD with the vaccines and carefully monitor the TMD to ensure vaccines remain within the appropriate temperature range. Temporary storage containers should remain closed, and vaccines can only be stored safely for as long as the containers are validated to maintain proper storage temperatures.

*The Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA) offers information concerning the storage and use of temperature-sensitive biological products that have been involved in a temporary electrical power failure or flood conditions: www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ProductSecurity/ucm147243.htm.

Power Outages

Monitoring Unit Temperature during a Power Outage

If your storage unit has an external temperature monitoring display that you can check without opening the unit door, take the following steps:

- Record room temperature (if possible) and the temperature inside the unit as soon as the power goes out.
- Record minimum and maximum temperatures reached inside the unit during the outage.
- Temperature excursions should be avoided, if possible, by using emergency plans and SOPs for transport and alternative storage. However, if temperatures have fallen outside of the recommended range, follow your procedures for temperature excursions.

If you cannot monitor the temperature inside the unit without opening the door and you do not have an alternative facility with power where the vaccines can be stored or other emergency vaccine storage SOPs, wait until power is restored and then take the following steps:

- Record the room temperature (if possible) and the temperature inside the unit.
- If using a DDL, document the length of time the power was off and the minimum and maximum temperatures during that period.
- If temperatures inside the unit have already fallen outside of the recommended range, follow your procedures for temperature excursions. Even if an excursion has occurred, move your vaccines to an alternative storage unit or location where they can be stored at appropriate temperatures, if possible. Make sure to separate and mark these vaccines "Do NOT Use" until a decision can be made about whether the vaccines can still be used.

During a power outage, only open the storage unit door if:

» Power is restored.

» It is determined that the vaccines need to be packed in separate storage containers and/or transported to an alternative storage facility.

Buffered temperature probe	Temperature probe designed to prevent false readings by protecting the thermometer from sudden changes in temperature that can occur when opening a refrigerator door. A probe is "buffered" by immersing it in a vial filled with liquid (e.g., glycol, ethanol, glycerin), loose media (e.g., sand, glass beads), or a solid block of material (e.g., Teflon®, aluminum).
Beyond use date (BUD)	The date or time after which a vaccine should not be administered, stored, or transported. The BUD should never exceed the manufacturer's original expiration date.
Calibration	Professional measurement of the accuracy of a temperature monitoring device's readings against nationally accepted standards.
Cold chain monitor (CCM)	Generally, a single-use device that monitors the temperature inside a vaccine shipping container. CCMs should be thrown away after being checked. CCMs are stored in a separate compartment of the shipping container (a CCM may not be included when vaccines are shipped directly from the manufacturer).
Conditioned water bottles	Frozen water bottles that have been submerged under lukewarm water until the ice block inside can spin freely.
Digital data logger (DDL)	An electronic device that records data digitally over time or in relation to location either with a built-in or external instrument or sensor.
Diluent	A diluting agent (e.g., a liquid) added to reconstitute lyophilized vaccine before administration. Manufacturers of these vaccines also supply the matching diluent.
Dormitory-style (bar-style) storage unit	A combination refrigerator/freezer unit with one exterior door and an evaporator plate (cooling coil), which is usually located inside an icemaker compartment (freezer) within the refrigerator. These units have been shown to pose a significant risk of freezing vaccines, even when used for temporary storage.
Fan-forced air circulation	Technology using powerful fans or multiple cool air vents inside the unit that promote uniform temperature and fast temperature recovery.
Household-grade storage unit	A storage unit that is primarily sold for home use.
Lyophilized	Freeze-dried; usually referring to a vaccine that is freeze-dried into a powder or wafer.
Minimum/maximum temperature	A vaccine storage unit's coldest and warmest temperature readings during a set period of time.

Glossary

Phase change materials (PCMs)	Engineered packing supplies that help control container temperatures during vaccine transport or shipping.
Potency	A vaccine's strength or effectiveness; in the context of this toolkit, potency refers to a vaccine's response to environmental conditions.
Presentation	Type of packaging for a vaccine (e.g., single-dose vial, multidose vial, manufacturer-filled syringe, etc.).
Purpose-built /pharmaceutical-grade units	Units that are specifically designed to store vaccines.
Qualified container and packout	A type of container and supplies specifically designed for use when packing vaccines for transport. They are "qualified" through laboratory testing under controlled conditions to ensure they achieve and maintain desired temperatures for a set amount of time.
Standard operating procedures (SOPs)	A set of step-by-step instructions compiled by an organization to help workers carry out complex routine or emergency operations. SOPs aim to achieve efficiency, quality output, and uniformity of performance, while reducing miscommunication and preventing failure to comply with industry regulations and best practices.
Stand-alone storage unit	A storage unit that operates independently of any other device or system for its desired function (i.e., a refrigerator that only functions as a refrigerator or a freezer that only functions as a freezer).
Temperature excursion	Any temperature reading that is outside the recommended range for vaccine storage as defined by the manufacturer's package insert.
Tolerance	Compliance with nationally accepted standards for the calibration limits of temperature monitoring equipment. The equipment can either be considered "in" or "out" of tolerance.
Traceability	An unbroken chain of measurements and associated uncertainties.
Uncertainty	The quantification of the doubt about the measurement result.

REFERENCE: Purpose-Built Vaccine Storage Units

Numerous vaccine storage units have entered the market that are designed specifically for the storage of vaccines. These units can take many physical forms. Some look like traditional stand-alone units, while others can take the form of dispensing or vending units, either with or without doors. Although these units may be similar to pharmaceutical-grade or medical-grade units, they are unique in that they are designed and tested to keep vaccines in appropriate storage conditions. If you are a VFC provider, your immunization program determines which purpose-built units meet VFC program requirements. Always check with your immunization program before purchasing any unit that will be used to store VFC vaccines. Features and considerations related to these types of units include the following:

VFC Vaccine Management

- Purpose-built units must have the ability to allow the user to separate public and private vaccine stock physically or virtually
- If stock is separated virtually, an inventory printout† must be accessible upon request.
- If unable to physically remove expired vaccine from a purpose-built unit immediately, the unit must be able to make expired vaccine inaccessible.

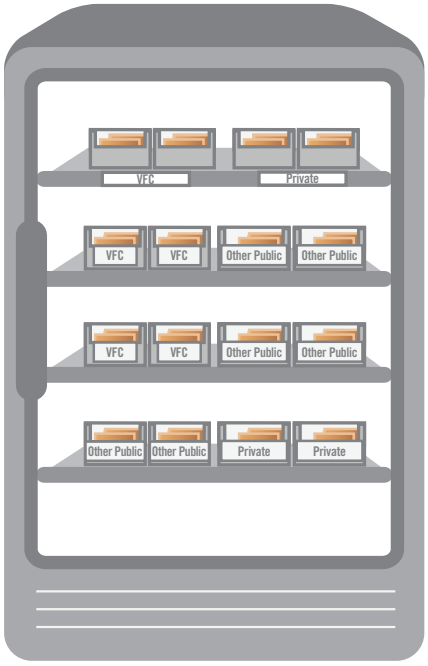
†The inventory printout should be used to answer storage and handling and inventory sections of the site visit reviewers guide.

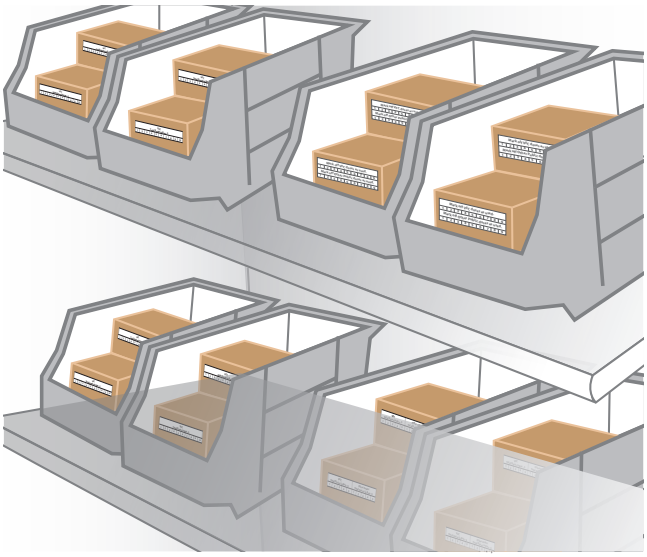
Temperature Monitoring

- Many purpose-built units have multiple temperature probes or sensors. It is important that these probes or sensors have current Certificates of Calibration.
- Many of the purpose-built closed or doorless units may utilize air sensors (non-buffered probes). Since these units have very limited exposure to ambient air, the use of a buffered probe is not essential.
- Many purpose-built units will have built-in digital data loggers with electronic interfaces that will allow you to track the continuous temperatures and/or provide min/max temperatures. If you are a VFC provider, always check to make sure that these satisfy the VFC program data logger requirements.

Vaccine Storage

- Many purpose-built units have undergone testing and temperature mapping so that the probe is in the most appropriate location.
- Although purpose-built units can have multiple temperature probes, a backup DDL is still needed for transport to a backup facility in an emergency.
- Many purpose-built units do not need water bottles to serve as thermal ballast.





WORKSHEET: Vaccine Storage and Handling SOPs

Complete the following checklist and forms and store this information in an easily accessible area near the vaccine storage unit.

CHECKLIST OF GENERAL INFORMATION

» Up-to-date contact information
- Primary vaccine coordinator
- Alternate vaccine coordinator
- Additional staff to assist in emergencies
- Immunization program
- Vaccine manufacturers
- Refrigerator and freezer maintenance and repair companies
- Temperature monitoring device (TMD) companies
- Utility/power company
- Vaccine storage unit alarm company (if applicable)
- Generator repair company (if applicable)
- Sources for qualified containers and packouts

» Descriptions of the roles and responsibilities of the primary and alternate vaccine coordinators

» Information for each storage unit, including serial number, links to equipment websites, installation dates, and routine maintenance and repair records

» Samples of all vaccine-related forms used in your facility

» Protocols for staff education and training

CHECKLIST FOR ROUTINE STORAGE AND HANDLING

Protocols for:
- Ordering and accepting vaccine deliveries
- Unpacking deliveries
- Managing inventory
- Storing each vaccine and diluent
- Placing vaccines and diluents in storage units
- Handling vaccines prior to administration
- Disposing of vaccines and supplies
- Monitoring storage unit and temperature
- Maintaining storage equipment and TMDs
- Responding to storage and handling problems
- Transporting vaccines to off-site/satellite facilities

CHECKLIST FOR EMERGENCY VACCINE STORAGE, HANDLING, AND TRANSPORT

All contact information in Checklist for General Information as well as up-to-date contact information for:
- Alternative vaccine storage facility (one or more)
- Transportation of vaccines

Vaccine storage unit specifications (type, brand, model number, serial number)

Diagram of facility showing important elements, including doors, flashlights, packing materials, batteries, circuit breakers

Keep a copy of emergency SOPs with emergency supplies and at multiple off-site locations such as homes of vaccine coordinator and alternate coordinator and with building manager, security staff, and alternative storage facility.

Protocols for:
- Monitoring vaccines during a power outage
- Packing vaccines and diluents for emergency transport
- Transporting vaccines to and from an alternative vaccine storage facility
- Assessing whether vaccine can be used after an emergency
- Accessing your building and facility after hours

WORKSHEET: Vaccine Storage and Handling SOPs

Store emergency information with emergency supplies.

STAFF CONTACT LIST			
Name	Title	Telephone Numbers home/cell/other	E-mail Address
	Primary Vaccine Coordinator		
	Alternate Vaccine Coordinator		

EMERGENCY STAFF CONTACT LIST			
Name	Title	Telephone Numbers home/cell/other	E-mail Address
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			
11.			
12.			
13.			
14.			
15.			

List contacts in order of preference. Determine whether all or certain persons on the list should be contacted or if the first person reached is sufficient.

WORKSHEET: Vaccine Storage and Handling SOPs

GENERAL RESOURCES CONTACT LIST			
Resources	Contact Person Name/Title	Telephone Numbers home/cell/other	E-mail Address
Local Health Department Immunization Program			
State Health Department Immunization Program			
Vaccine Manufacturers			
Refrigerator Repair Company			
Freezer Repair Company			
Utility/Power Company			
Temperature Monitoring Device Company			
Vaccine Storage Unit Alarm Company (if applicable)			
Generator Repair Company (if applicable)			

ALTERNATIVE VACCINE STORAGE FACILITIES			
Alternative Vaccine Storage Facility Name/Address	Contact Person Name/Title	Telephone Numbers home/cell/other	E-mail Address
1.			
2.			
3.			
4.			

TRANSPORTATION TO ALTERNATIVE VACCINE STORAGE FACILITIES			
Emergency Resources Name/Address	Contact Person Name/Title	Telephone Numbers home/cell/other	E-mail Address
Refrigeration Company			
Refrigeration Company (alternative)			
Private Vehicle			
Private Vehicle (alternative)			

WORKSHEET: Vaccine Storage and Handling SOPs

PACKING MATERIAL SUPPLIERS CONTACT LIST

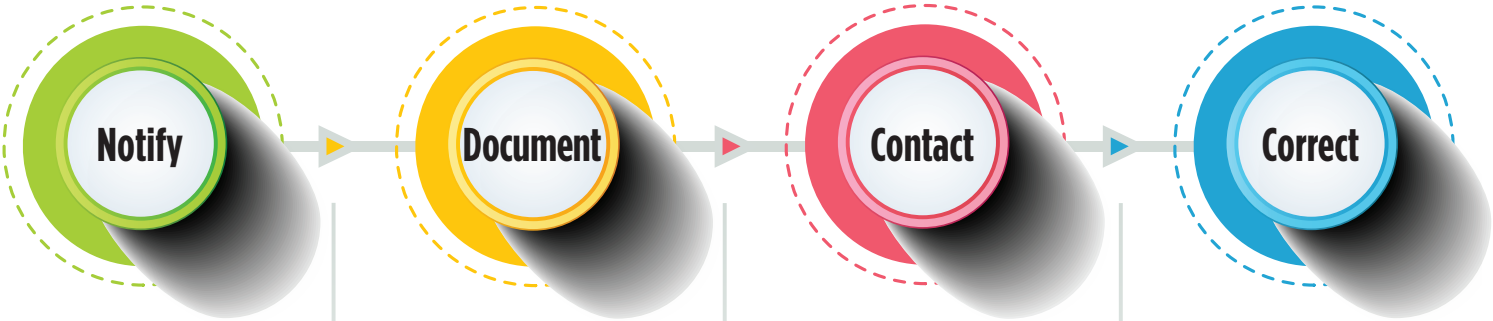
Emergency Resources	Company Name	Contact Person Name/Title	Telephone Numbers home/cell/other	E-mail Address
Portable vaccine refrigerator/freezer units				
Qualified containers and packout materials				
Qualified containers and packout materials (alternative)				
Packing materials				
Packing materials (alternative)				

VACCINE STORAGE UNIT SPECIFICATIONS

Type of Unit (Refrigerator or Freezer)	Brand	Model Number	Serial Number
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			

Handling a Temperature Excursion in Your Vaccine Storage Unit

Any temperature reading outside ranges recommended in the manufacturers' package inserts is considered a temperature excursion. Identify temperature excursions quickly and take immediate action to correct them. This can prevent vaccine waste and the potential need to revaccinate patients.



Notify

» Notify the primary or alternate vaccine coordinator immediately or report the problem to a supervisor.

» Notify staff by labeling exposed vaccines, "DO NOT USE," and placing them in a separate container apart from other vaccines in the storage unit. Do not discard these vaccines.

Document

» Document details of the temperature excursion:

- Date and time
- Storage unit temperature (including minimum/maximum temperatures during the time of the event, if available)
- Room temperature, if available
- Name of the person completing the report
- General description of the event (i.e., what happened)
- If using a digital data logger (DDL), determine the length of time vaccine may have been affected
- Inventory of affected vaccines
- List of items in the unit other than vaccines (including water bottles)
- Any problems with the storage unit and/or affected vaccines before the event
- Other relevant information

Contact

» Contact your immunization program and/or vaccine manufacturer(s) for guidance per your standard operating procedures (SOPs).

» Be prepared to provide the immunization program or manufacturer with documentation and DDL data so they can offer you the best guidance.

Contact manufacturer for excursions:	
Dynavax	1-844-375-4728
GlaxoSmithKline	1-888-825-5249
Massachusetts Biological Labs	1-888-825-5249
MedImmune	1-877-633-4411
Merck	1-800-672-6372
Pfizer	1-800-438-1985
Sanofi Pasteur	1-800-822-2463
Seqirus	1-855- 358-8966

Correct

» If the temperature alarm goes off repeatedly, do not disconnect the alarm until you have determined and addressed the cause.

» Check the basics, including:

- Power supply
- Unit door(s)
- Thermostat settings

» If the excursion was the result of a temperature fluctuation, refer to the section, "Vaccine Storage and Temperature Monitoring Equipment," in CDC's Vaccine Storage and Handling Toolkit for detailed guidance on adjusting storage unit temperature to the appropriate range.

» If you believe the storage unit has failed, implement your emergency vaccine storage and handling SOPs. Never allow vaccines to remain in a nonfunctioning unit following a temperature excursion.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Fahrenheit to Celsius and Celsius to Fahrenheit Conversion

°F	°C	°F	°C	°F	°C
-22	-30	**21**	-6.1	**64**	17.8
-21	-29.4	**22**	-5.6	**65**	18.3
-20	-28.9	**23**	-5	**66**	18.9
-19	-28.3	**24**	-4.4	**67**	19.4
-18	-27.8	**25**	-3.9	**68**	20
-17	-27.2	**26**	-3.3	**69**	20.6
-16	-26.7	**27**	-2.8	**70**	21.1
-15	-26.1	**28**	-2.2	**71**	21.7
-14	-25.6	**29**	-1.7	**72**	22.2
-13	-25	**30**	-1.1	**73**	22.8
-12	-24.4	**31**	-0.6	**74**	23.3
-11	-23.9	**32**	0	**75**	23.9
-10	-23.3	**33**	0.6	**76**	24.4
-9	-22.8	**34**	1.1	**77**	25
-8	-22.2	**35**	1.7	**78**	25.6
-7	-21.7	**36**	2.2	**79**	26.1
-6	-21.1	**37**	2.8	**80**	26.7
-5	-20.6	**38**	3.3	**81**	27.2
-4	-20	**39**	3.9	**82**	27.8
-3	-19.4	**40**	4.4	**83**	28.3
-2	-18.9	**41**	5	**84**	28.9
-1	-18.3	**42**	5.6	**85**	29.4
0	-17.8	**43**	6.1	**86**	30
1	-17.2	**44**	6.7	**87**	30.6
2	-16.7	**45**	7.2	**88**	31.1
3	-16.1	**46**	7.8	**89**	31.7
4	-15.6	**47**	8.3	**90**	32.2
5	-15	**48**	8.9	**91**	32.8
6	-14.4	**49**	9.4	**92**	33.3
7	-13.9	**50**	10	**93**	33.9
8	-13.3	**51**	10.6	**94**	34.4
9	-12.8	**52**	11.1	**95**	35
10	-12.2	**53**	11.7	**96**	35.6
11	-11.7	**54**	12.2	**97**	36.1
12	-11.1	**55**	12.8	**98**	36.7
13	-10.6	**56**	13.3	**99**	37.2
14	-10	**57**	13.9	**100**	37.8
15	-9.4	**58**	14.4	**101**	38.3
16	-8.9	**59**	15	**102**	38.9
17	-8.3	**60**	15.6	**103**	39.4
18	-7.8	**61**	16.1	**104**	40
19	-7.2	**62**	16.7		
20	-6.7	**63**	17.2		

°C	°F	°C	°F
-30	**-22**	13	**55.4**
-29	**-20.2**	14	**57.2**
-28	**-18.4**	15	**59**
-27	**-16.6**	16	**60.8**
-26	**-14.8**	17	**62.6**
-25	**-13**	18	**64.4**
-24	**-11.2**	19	**66.2**
-23	**-9.4**	20	**68**
-22	**-7.6**	21	**69.8**
-21	**-5.8**	22	**71.6**
-20	**-4**	23	**73.4**
-19	**-2.2**	24	**75.2**
-18	**-0.4**	25	**77**
-17	**1.4**	26	**78.8**
-16	**3.2**	27	**80.6**
-15	**5**	28	**82.4**
-14	**6.8**	29	**84.2**
-13	**8.6**	30	**86**
-12	**10.4**	31	**87.8**
-11	**12.2**	32	**89.6**
-10	**14**	33	**91.4**
-9	**15.8**	34	**93.2**
-8	**17.6**	35	**95**
-7	**19.4**	36	**96.8**
-6	**21.2**	37	**98.6**
-5	**23**	38	**100.4**
-4	**24.8**	39	**102.2**
-3	**26.6**	40	**104**
-2	**28.4**		
-1	**30.2**		
0	**32**		
1	**33.8**		
2	**35.6**		
3	**37.4**		
4	**39.2**		
5	**41**		
6	**42.8**		
7	**44.6**		
8	**46.4**		
9	**48.2**		
10	**50**		
11	**51.8**		
12	**53.6**		

SAMPLE: Stock Record and Tally Sheet

STOCK RECORD

Instructions: Use the monthly stock record to document inventory from new vaccine/diluent shipments and track weekly accounts of doses used. At the end of each month, count inventory in storage unit(s) and compare with recorded balance. If physical count and recorded balance are different, record the actual (physical count) balance next to the previous recorded balance. Note the cause of the discrepancy or if it is unknown. Start a new stock record every month, listing at the top the previous month's balance as the new month's starting balance.

Vaccine Type: PPSV23 Month and Year: August 2018

Date Received or Usage Tallied	Person Receiving Shipment*	Arrival Condition**	Vaccine or Diluent Name	Manufacturer	Vial Type (SDV, MDV, MFS)***	Lot Number	Expiration Date	Expiration Date After Reconstitution	Doses Received/ Balance Forward	Doses Used†	Balance (Doses)††
08/02/18	BEGINNING BALANCE FOR THE MONTH								2	N/A	2
08/09/18										1	1
08/15/18	LST	G	PPSV23	Merck	MDV	03958	02/15/19	N/A	5	3	3
08/23/18										1	2
08/29/18										0	2
								Vaccine Totals	7	5	2

* The initials of the person who unpacked and checked the vaccines/diluents upon arrival
** G = vaccines/diluents arrived in good condition
? = condition of vaccines/diluents questionable and state and local health department immunization program and vaccine manufacturer(s) contacted. Document details/outcome on reverse side of stock record.
*** SDV = Single-dose vial
MDV = Multidose vial
MFS = Manufacturer-filled syringe
† Includes number of doses administered, wasted, unusable, expired, or transferred.
†† Enter the sum of "Total Doses Received/Balance Forward" minus "Total Doses Used."

Physical Stock Check (In Doses)	2
Difference ("Balance" minus Physical Stock)	0
Balance Carried Forward (In Doses)	2

Some state or local health department immunization programs have developed their own stock record for immunization providers. Contact program staff for information. If stock records are not available from your state or local health department or an immunization information system (IIS), this stock record may be used.

TALLY SHEET

Instructions: Place a copy of this sheet on or near the refrigerator and freezer doors. Record the week (by date or week number). Write the vaccine/diluent names and indicate the storage location (refrigerator = R, freezer = F). Make a tick mark in the appropriate box for each dose of vaccine/diluent removed from the unit (i.e., each dose administered, wasted, unusable, expired, or transferred). At the end of the week, add the tick marks for each vaccine/diluent and update the totals on the appropriate stock record. File the completed tally sheet and replace with a new sheet.

Week: August 19—23, 2018 (Week 3)

Storage Location (R or F)*	Vaccine or Diluent Name	Doses Administered		Doses Wasted	Doses Expired	Doses Unusable**	Doses Transferred (Viable)***	Total
F	VAR	𝍸 III	(8)					8
R	DTaP	𝍸 𝍸 II	(12)					12
R	HepB	𝍸 𝍸 II	(12)					12
R	IPV	𝍸 𝍸 II	(12)		II			14
R	HepA (pediatric)	II	(2)					2
R	PPSV23	I	(1)					1

* R = Refrigerator F = Freezer
** Some unusable doses (VFC vaccines or other vaccines purchased with public funds) may need to be returned to your state or local health department immunization program.
*** Viable vaccine doses transferred to your state or local health department immunization program or another facility.

Some state or local health department immunization programs have developed their own tally sheets for immunization providers. Contact program staff for information. If tally sheets are not available from your state or local health department immunization program or an immunization information system (IIS), this tally sheet may be used.

Instructions: Use the monthly stock record to document inventory from new vaccine/diluent shipments and track weekly accounts of doses used. At the end of each month, count inventory in storage unit(s) and compare with recorded balance. If physical count and recorded balance are different, record the actual (physical count) balance next to the previous recorded balance. Note the cause of the discrepancy or if it is unknown. Start a new stock record every month, listing at the top the previous month's balance as the new month's starting balance.

Vaccine Type: _____ Month and Year: _____

Date Received or Usage Tallied	Person Receiving Shipment*	Arrival Condition**	Vaccine or Diluent Name	Manufacturer	Vial Type (SDV, MDV, MFS)***	Lot Number	Expiration Date	Expiration Date After Reconstitution	Doses Received/ Balance Forward	Doses Used†	Balance (Doses)††
	BEGINNING BALANCE FOR THE MONTH									**N/A**	

* The initials of the person who unpacked and checked the vaccines/diluents upon arrival

** G = vaccines/diluents arrived in good condition
? = condition of vaccines/diluents questionable and state and local health department immunization program and vaccine manufacturer(s) contacted. Document details/outcome on reverse side of stock record.

*** SDV = Single-dose vial
MDV = Multidose vial
MFS = Manufacturer-filled syringe

† Includes number of doses administered, wasted, unusable, expired, or transferred.

†† Enter the sum of "Total Doses Received/Balance Forward" minus "Total Doses Used."

Vaccine Totals	
Physical Stock Check (In Doses)	
Difference ("Balance" minus Physical Stock)	
Balance Carried Forward (In Doses)	

Some state or local health department immunization programs have developed their own stock record for immunization providers. Contact program staff for information. If stock records are not available from your state or local health department or an immunization information system (IIS), this stock record may be used.

Tally Sheet

Instructions: Place a copy of this sheet on or near the refrigerator and freezer doors. Record the week (by date or week number). Write the vaccine/diluent names and indicate the storage location (refrigerator = R, freezer = F). Make a tick mark in the appropriate box for each dose of vaccine/diluent removed from the unit (i.e., each dose administered, wasted, unusable, expired, or transferred). At the end of the week, add the tick marks for each vaccine/diluent and update the totals on the appropriate stock record. File the completed tally sheet and replace with a new sheet.

Week: _____

Storage Location (R or F)*	Vaccine or Diluent Name	Doses Administered	Doses Wasted	Doses Expired	Doses Unusable**	Doses Transferred (Viable)***	Total

* R = Refrigerator F = Freezer

** Some unusable doses (VFC vaccines or other vaccines purchased with public funds) may need to be returned to your state or local health department immunization program.

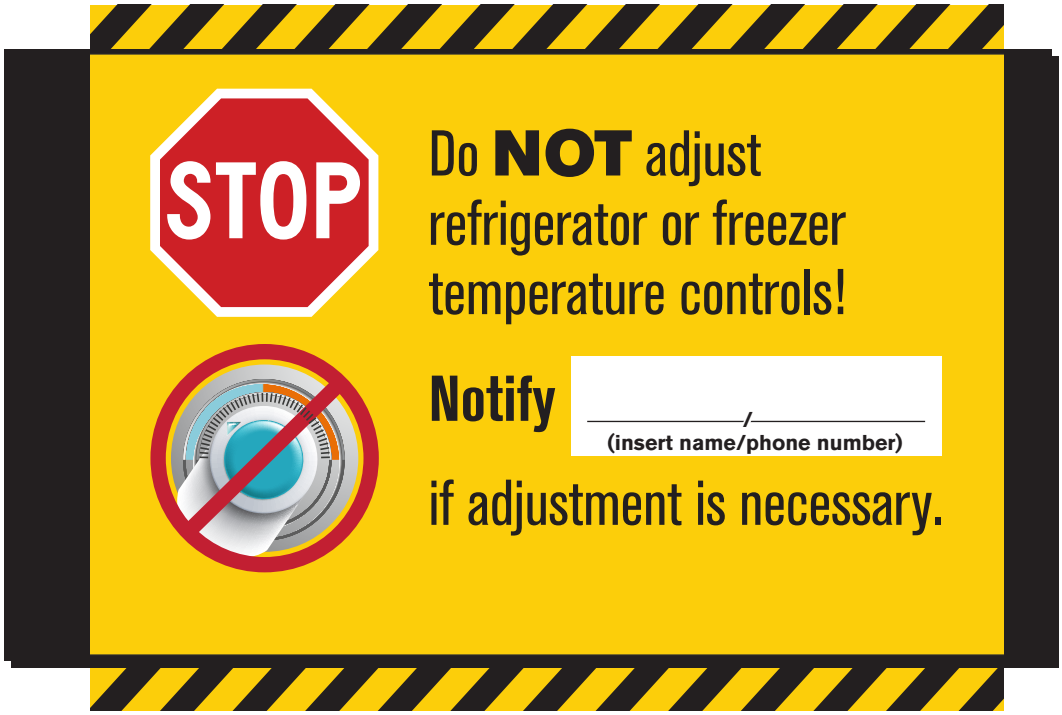
*** Viable vaccine doses transferred to your state or local health department immunization program or another facility.

Some state or local health department immunization programs have developed their own tally sheets for immunization providers. Contact program staff for information. If tally sheets are not available from your state or local health department immunization program or an immunization information system (IIS), this tally sheet may be used.

HANDLE WITH CARE: Protect Your Vaccine | Protect Your Patients

- Keep your storage units and vaccines within the appropriate temperature ranges.
- Check and record storage unit min/max temperatures at start of each workday. If your device does not display min/max temperatures, then check and record current temperature a minimum of 2 times (at start and end of workday). Also check current temperature before accessing and administering vaccine.
- Take immediate action if temperatures are out of range.
- Keep vaccines in their original packages.
- Many vaccines should be protected from light (consult manufacturer's product information).
- Check expiration dates and rotate your vaccine stock to keep most recent expiration dates at the front.

WARNING LABELS: Do Not Adjust Refrigerator Controls



WARNING LABELS: Do Not Adjust Freezer Controls

STOP

Do **NOT** adjust
FREEZER
temperature controls!

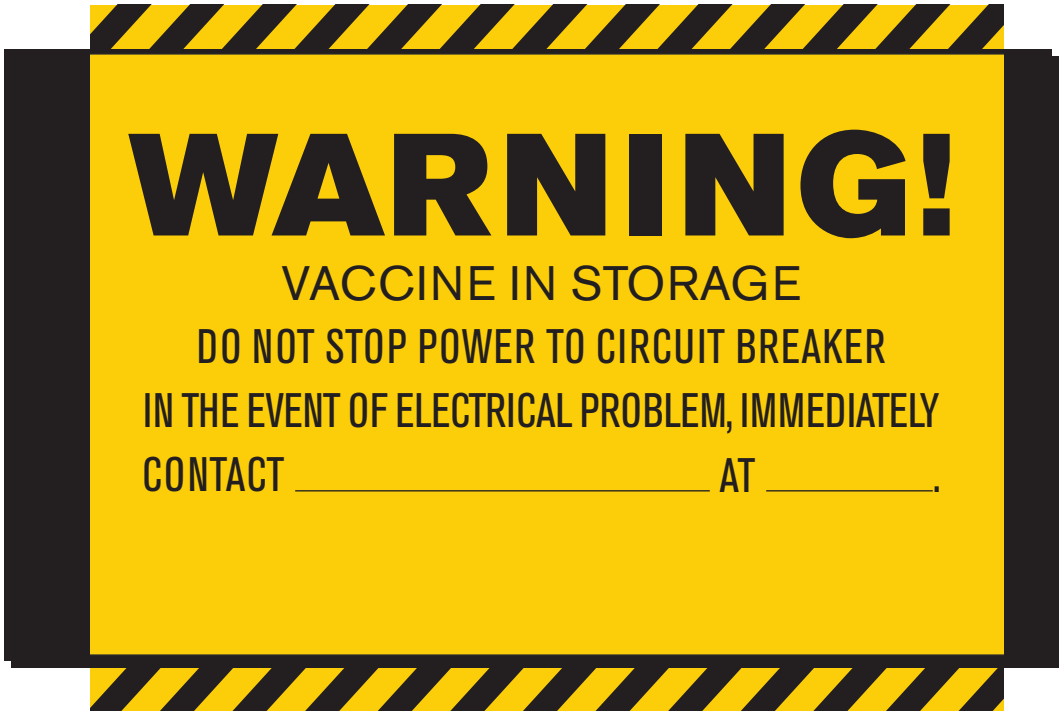
Notify _____/_____
(insert name/phone number)
if adjustment is necessary.

ALTO

¡ NO cambie la
temperatura del
CONGELATOR!

Comuníquese con
_____/_____
(inserte nombre y número de teléfono aqui)
si hay necesidad de
cambiar la temperatura.

WARNING LABELS: Warning! Do Not Stop Power to Circuit Breaker



WARNING LABELS: Warning! Do Not Unplug Refrigerator

WARNING!

DO **NOT** UNPLUG THE **REFRIGERATOR** OR BREAK CIRCUIT.

VACCINE IN STORAGE.

IN THE EVENT OF ELECTRICAL PROBLEM, IMMEDIATELY CONTACT: _____/_____.

(insert name/phone number)

¡AVISO!

NO DESCONECTE EL **REFRIGERADOR** NI CORTE EL CIRCUITO.

¡CONTIENE VACUNAS!

SI HAY UN PROBLEMA CON LA ELECTRICIDAD, COMUNIQUESE INMEDIATAMENTE CON:

_____.

(inserte nombre y número de teléfono aqui)

WARNING LABELS: Warning! Do Not Unplug Freezer

WARNING!

DO **NOT** UNPLUG THE **FREEZER** OR BREAK CIRCUIT.

VACCINE IN STORAGE.

IN THE EVENT OF ELECTRICAL PROBLEM, IMMEDIATELY CONTACT: _____/_____.

(insert name/phone number)

¡AVISO!

NO DESCONECTE EL **CONGELADOR** NI CORTE EL CIRCUITO.

¡CONTIENE VACUNAS!

SI HAY UN PROBLEMA CON LA ELECTRICIDAD, COMUNIQUESE INMEDIATAMENTE CON:

_____/_____.

(inserte nombre y número de teléfono aqui)

TRANSPORT LABELS: Refrigerate/Freeze Upon Arrival

TRANSPORT LABELS: Open Immediately: Refrigerate/Freeze Upon Receipt

TRANSPORT LABELS: Fragile: Handle with Care

TRANSPORT LABELS: Perishable: Rush

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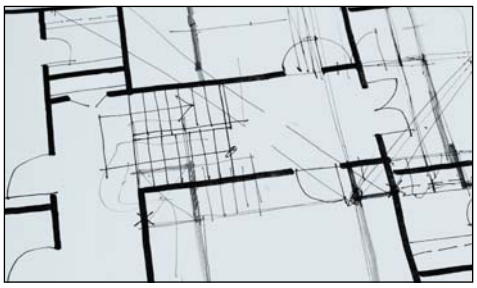

Innovation Series 2009

Using Evidence-Based Environmental Design to Enhance Safety and Quality

The Institute for Healthcare Improvement thanks The Center for Health Design, our colleagues in this important work to improve the safety and quality of health care.

The Center for Health Design.

18

The Institute for Healthcare Improvement (IHI) is a not-for-profit organization leading the improvement of health care throughout the world. IHI helps accelerate change by cultivating promising concepts for improving patient care and turning those ideas into action. Thousands of health care providers participate in IHI's groundbreaking work.

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How to cite this paper:

Sadler BL, Joseph A, Keller A, Rostenberg B. *Using Evidence-Based Environmental Design to Enhance Safety and Quality.* IHI Innovation Series white paper. Cambridge, Massachusetts: Institute for Healthcare Improvement; 2009. (Available on www.IHI.org)

Acknowledgements:

The authors would like to thank Maureen Bisognano, Jim Conway, Pat Rutherford, Sue Gullo, Don Goldmann, and Andrea Kabcenell of the Institute for Healthcare Improvement for their generous advice and comments in the development of this paper.

The authors also thank IHI staff members Jane Roessner, PhD, and Val Weber for their editorial review and assistance with this paper.

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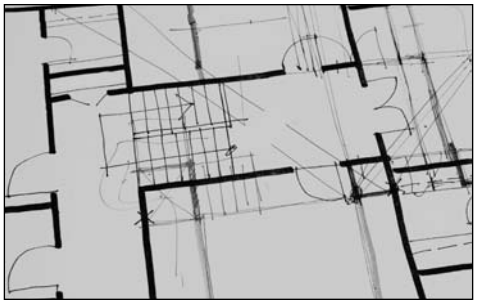

Innovation Series 2009

Using Evidence-Based Environmental Design to Enhance Safety and Quality

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Executive Summary

The Institute for Healthcare Improvement (IHI) has had a long history of looking outside, as well as inside, the health care sector for ideas and possible solutions, and has recognized the need to build bridges between different and often disconnected disciplines. One recent example is the effort to bridge the gap between the world of safety and quality, and the world of the physical environment in which care is provided. The purpose of this paper is to show health care leaders how, as part of an integrated improvement strategy, evidence-based environmental design interventions can measurably enhance the care they provide, improve the perceptions of the experience of that care by patients, families, and staff, and actually have a positive economic impact on their organizations.

The paper begins by establishing a connection between the physical environment in which patients receive their care and its safety and quality. The published literature in evidence-based environmental design, including references to two major reviews of that literature, is also described. A series of relatively low-cost recommendations are presented that virtually any health care organization should consider implementing. The paper also offers recommendations that are best addressed as part of new facility construction or major renovation. Examples of interventions for unit-specific microsystems are proposed, along with a facility checklist that any organization can use as a guide to determine whether its environment is actually helping or hindering care and the care experience.

In economic terms, the paper describes how to balance initial, one-time capital expenditures with ongoing operating cost savings and revenue enhancement through market differentiation. A suggested framework for calculating the economic return on investment of an intervention or group of interventions is included.

This paper aims to help bridge the gap between the worlds of safety and quality improvement and architectural and environmental design. Similar to experiences in safety and quality improvement, usually no single environmental design intervention will produce significant and sustainable results. Design interventions should be part of an integrated set of changes containing several components that are implemented together.

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Introduction

One Person's Perspective

"I try to think of a perfectly designed hospital and it would be more reliable—fewer drop-offs, fewer mistakes. There would be more precision—promises kept. It would be peaceful, healing—a quiet place—where patients can use their limited energy to get better, instead of having to fight the environment. And, most especially, the loved ones of patients are there all the time.

There would be a sense of things in their place, a place for everything. I think it would be simpler. I think the clutter and complexity and the machines and the bells and whistles need to be managed out of the care. I think it would feel more like home probably and therefore it has to be more customized. And somehow all of this needs to rest on science because we are in a technical enterprise that has to use knowledge and machines and drugs correctly. So underneath all is a confidence that we are going to do the right thing every single time."

—Donald Berwick, MD, President and CEO, Institute for Healthcare Improvement

In: *Transforming Hospitals: Designing for Safety and Quality*. [video] Rockville, MD: Agency for Healthcare Research and Quality; September 2007.

Connecting Evidence-Based Environmental Design to Quality Improvement

Increasing evidence indicates a correlation between the physical environment in which patients receive their care and the safety and quality of that care, as well as the patient's perception of that care. Similarly, there is a growing understanding of the connection between the environments in which people work and job satisfaction and stress.

A significant body of evidence shows that the physical environment is a critical component in programs to improve safety and quality for patients and provide a safer working environment for staff.[1] As part of a comprehensive quality improvement program, the physical environment can help reduce preventable harm to patients, such as hospital-acquired infections and falls, and must be carefully considered when designing new or renovated facilities.

Patients' perceptions of their care experience should become much more important in light of the publicly available Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) data mandated by the Centers for Medicare and Medicaid Services (CMS). In an article assessing patient perception of care in American hospitals, the authors examined several domains of the patient experience. The component that received the lowest composite score (52 percent) was a quiet room.[2] With the baby boomer generation reaching an age where they will be consuming more

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health care resources, they will be demanding quality care provided in physical environments that also help them get better and feel better.

The physical environment can also have a significant impact on revenue enhancement and operating cost avoidance, making it a sound long-term investment. As described by the research review mentioned above,[1] design interventions such as single patient rooms contribute to fewer healthcare-acquired infections, and ceiling-mounted patient lifts contribute to dramatically reduced caregiver back injuries. For example, at Peace Health in Eugene, Oregon, a 60-month study in two units where ceiling lifts were installed as part of a "no lift" policy showed an 83 percent reduction in annual work injury costs related to patient lifting. As a result, Peace Health included ceiling lifts in all 309 patient rooms in a subsequently constructed hospital in Riverbend in order to be "lift ready." They predict that they will realize a return on this investment in 2.5 years.[3]

With the widespread dissemination of HCAHPS patient satisfaction scores, there could be a strong revenue incentive to make prudent evidence-based environmental design interventions that reduce errors, noise, anxiety, confusion, and stress. These are all attributes of the care experience that patients and families understand and care about. It is likely that these attributes will influence patients' willingness to recommend a particular hospital or physician. The business case for evidence-based design should become significantly enhanced over time.

Further, many hospital facilities have simply come to the end of their useful lives, while, in several states, seismic and other safety requirements are mandating significant facility upgrades. In the US, we have entered a major hospital construction boom. It is projected that the already strong health care construction sector will have grown by 13 percent to a total of $53.8 billion in 2008 and will continue to experience a high growth rate through 2011.[4] In the year 2011, this figure is projected to reach $67 billion.[5] Despite the current national economic crisis (indeed, several health care providers have put construction projects on hold), health care construction remains more active than at any time since the federally funded Hill Burton program 50 years ago.

Evidence-Based Environmental Design: What the Literature Tells Us

Several recent studies have established the relationship between the physical design of hospitals and key outcomes. A multidisciplinary team completed a comprehensive review of the world's literature on evidence-based environmental design.[1] After screening an extensive series of cross-referenced keyword searches, all identified literature was evaluated using two criteria: 1) the study should be empirically based and examine the influence of environmental characteristics on patient, family, or staff outcomes; and 2) the quality of each study in terms of its research design and methods, and whether the journal in which the study was published was peer-reviewed. The review team then

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organized their review of approximately 1,000 articles into three categories: 1) *patient safety issues* such as infections, medical errors, and falls; 2) *other patient outcomes* such as pain, sleep, stress, depression, length of stay, spatial orientation, privacy, communication, social support, and overall patient satisfaction; and 3) *staff outcomes* such as injuries, stress, work effectiveness, and satisfaction.

Ulrich and colleagues state, "Compared to 2004, the body of evidence has grown rapidly and substantially…It is now widely recognized that well designed physical settings play an important role in making hospitals less risky and stressful, promoting more healing for patients, and providing better places for staff to work."[1]

A second comprehensive review, focused on the pediatric evidence-based design literature, assessed 320 articles individually for quality, rigor, and relevance.[6] A majority of the articles assessed were controlled observational (cohort or case control) studies without control groups, surveys, or case studies. The authors of this review conclude, "A growing body of research shows that the physical design of pediatric health care settings contributes to positive or negative clinical, developmental, psychosocial, and safety outcomes among patients and families. The physical environment is a key component of providing patient- and family-centered care and increasing safety and overall quality of care in pediatric settings."

In late 2008, The Joint Commission released the report, *Guiding Principles for the Development of the Hospital of the Future*. It contains a chapter on the design of the physical environment which relies on much of the same published research and includes a series of general principles that are fully consistent with the analysis and recommendations of this white paper.[7]

- Incorporate evidence-based design principles that improve patient safety, including single patient rooms, decentralized nursing stations, and noise-reducing materials, in hospital construction.
- Address high-level priorities, such as infection control and emergency preparedness, in hospital design and construction.
- Include clinicians, other staff, patients, and families in the design process to maximize opportunities to improve staff workflow and patient safety, and to create patient-centered environments.
- Design flexibility into the building to allow for better adoption to the rapid cycle of innovation in medicine and technology.
- Incorporate "green" (environmentally conscious) principles in hospital design and construction.

Similar to experience in quality improvement, frequently no single environmental design intervention will produce significant and sustainable measurable results. Interventions should be part of an integrated set of changes containing several components that, when implemented together, will lead to improvement. For example, installing alcohol-based hand gel dispensers in all patient rooms and high-volume treatment areas will not alone improve hand hygiene compliance by nurses, physicians, and other caregivers. But, when part of a comprehensive program that also includes education, competency

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checks, behavioral change techniques and accountability, such dispensers can have a significant impact. Installing hydraulic ceiling-mounted lifts alone will not reduce workforce injuries but, when part of a comprehensive "no lifts" education and standards program, ceiling lifts can help to dramatically reduce patient lift injuries.[3] The installation of sound-absorbing ceiling tiles in patient rooms will not alone improve a patient's ability to sleep, but, when part of an integrated noise reduction plan, can make a measurable difference.

Similar to the debate about the rigor and type of published studies in evidence-based medicine, there is not complete consensus about the persuasive power of studies in evidence-based design in terms of their causal effects. In the two comprehensive literature reviews mentioned above,[1, 6] the authors describe the types of categories of research and their relative strengths.

In conclusion, the literature tells us that ample evidence now exists in support of many evidence-based design interventions and that they can significantly enhance the ability of hospitals to achieve safety and quality goals if implemented in an integrated way with other quality improvement and change strategies. In addition to published studies, The Center for Health Design's research initiative, the Pebble Project, is a joint effort with several health care providers and suppliers to provide researched and documented examples of health care facilities whose physical design has made a difference in their safety, quality, and efficiency.[8]

Design Recommendations for Existing and Newly Built Facilities

We offer the following design recommendations based on the strength of the evidence in the literature,[1, 6] our opinion about their inherent reasonableness, and their impact on safety, quality, or cost. An extensive discussion regarding these design recommendations as well as the supporting references can be found in the literature reviews referenced earlier.[1, 6] Only one key reference per recommended design intervention is provided in the tables below. These recommendations can be implemented in virtually any facility undergoing minor renovations and at relatively low cost (see Table 1). Other strategies require greater financial investment and significant physical modifications; they are best implemented as part of a major renovation or a new construction project (see Table 2).

In addition, Appendix A includes a list of questions that hospital leaders should consider when evaluating new construction or renovation projects.

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Table 1. Design Interventions for Existing Health Care Facilities

Design Intervention	Quality and Business-Case Benefits	Literature in Direct Support of Intervention (key references only)
1. Install alcohol-based hand gel dispensers at each patient bedside and at all points of patient care	Reduced infections, improved hand hygiene compliance	[9] Randle J, Clarke MC, Storr J. Hand hygiene compliance in healthcare workers. *Journal of Hospital Infection.* 2006;64(3):205-209.
2. Install noise-mitigation materials such as sound-absorbing ceiling tiles as part of a noise reduction plan	Reduced patient and staff stress, reduced patient sleep deprivation, increased patient satisfaction	[10] Blomkvist V, Eriksen CA, Theorell T, Ulrich RS, Rasmanis G. Acoustics and psychosocial environment in coronary intensive care. *Occupational and Environmental Medicine.* 2005;62:1-8.
3. Utilize music and art as positive distractions during procedures	Reduced patient stress, pain, medication use, and anxiety	[11] Walworth DD. Procedural-support music therapy in the healthcare setting: A cost-effectiveness analysis. *Journal of Pediatric Nursing*. 2005;20(4):276-284. [12] Ulrich RS, Gilpin L. Healing arts: Nutrition for the soul. In: Frampton SB, Gilpin L, Charmel P, eds. *Putting Patients First: Designing and Practicing Patient-Centered Care.* San Francisco: Jossey-Bass; 2003:117-146.
4. Include effective wayfinding systems	Reduced staff time spent giving directions, reduced patient and family stress	[13] Carpman J, Grant M. *Design That Cares: Planning Health Facilities for Patients and Visitors* (2nd edition). Chicago: American Hospital Publishing; 1998.
5. Improve task lighting in pharmacy and medication rooms	Reduced medication errors	[14] Buchanan TL, Barker KN, Gibson JT, Jiang BC, Pearson RE. Illumination and errors in dispensing. *American Journal of Hospital Pharmacy*. 1991 Oct;48(10):2137-2145.

It is difficult to provide an "average" cost estimate for each design intervention, due to a series of variables, including age of the building and utility systems if the building has been updated; degree to which the building complies with building codes and regulations; regulatory climate and codes

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governing renovation; building construction (materials, structural bay spacing and construction, floor-to-floor heights, accessibility to areas not readily visible, etc.); and nature and complexity of utility systems behind walls and ceilings.

Some minor facility improvements can trigger additional seemingly unrelated work, particularly if the infrastructure is outdated. For example, an additional hand washing sink might be relatively simple to install in a new facility, but could require the plumbing system to be updated in an older one. In such circumstances, the addition of a surface-mounted dispenser for alcohol-based hand gel might provide similar benefits.

These relatively low-cost design interventions should be considered and carefully evaluated as part of any organization's improvement efforts. They have the potential to significantly improve care and raise patient satisfaction scores. Further, when undertaking new construction or major renovations, there are additional design interventions that should be considered (see Table 2).

Table 2. Design Interventions for Health Care Facilities as Part of New Construction or Major Renovation

Design Intervention	Quality and Business-Case Benefits	Literature in Direct Support of Intervention (key references only)
1. Build private patient rooms	Reduced infections, increased privacy, increased number of actual usable beds, increased patient satisfaction	[15] Chaudhury H, Mahmood A, Valente M. Advantages and disadvantages of single- versus multiple-occupancy rooms in acute care environments: A review and analysis of the literature. *Environment and Behavior.* 2005;37(6):760-786.
2. Provide adequate space for families to stay overnight in patient rooms	Increased patient and family satisfaction, reduced patient and family stress	[16] Rashid M. A decade of adult intensive care unit design: A study of the physical design features of the best-practice examples. *Critical Care Nursing Quarterly.* 2006;29(4):282-311.
3. Design rooms to minimize transfers and handoffs such as acuity-adaptable rooms or combining transitional care rooms with medical-surgical or ICU rooms	Reduced intra-hospital transfers, reduced errors, increased patient satisfaction, reduced unproductive staff time	[17] Hendrich A, Fay J, Sorrells A. Effects of acuity-adaptable rooms on flow of patients and delivery of care. *American Journal of Critical Care.* 2004 Jan;13(1):35-45.

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Design Intervention	Quality and Business-Case Benefits	Literature in Direct Support of Intervention (key references only)
4. Build larger patient bathrooms with double-door access and handrails	Reduced patient falls, reduced staff back injuries	[18] Hignett S, Evans D. Spatial requirements in hospital shower and toilet rooms. *Nursing Standard.* 2006 Sep 27-Oct 3;21(3):43-48.
5. Install improved air handling systems such as HEPA filters in areas treating immunosuppressed patients	Reduced airborne-caused infections	[19] Oren I, Haddad N, Finkelstein R, Rowe JM. Invasive pulmonary aspergillosis in neutropenic patients during hospital construction: Before and after chemoprophylaxis and institution of HEPA filters. *American Journal of Hematology.* 2001;66(4): 257-262.
6. Install ceiling-mounted lifts in the majority of patient rooms	Reduced staff back injuries	[20] Miller A, Engst C, Tate RB, Yassi A. Evaluation of the effectiveness of portable ceiling lifts in a new long-term care facility. *Applied Ergonomics.* 2006 May; 37(3):377-385.
7. Provide access to natural light in patient and staff areas	Reduced patient anxiety and depression, reduced length of stay, reduced staff stress	[21] Walch JM, Rabin BS, Day R, Williams JN, Choi K, Kang JD. The effect of sunlight on postoperative analgesic medication use: A prospective study of patients undergoing spinal surgery. *Psychosomatic Medicine.* 2005 Jan-Feb;67(1):156-163.
8. Build decentralized nursing stations	Increased staff time spent in direct patient care	[22] Howard L, Malloch K. Centralized and decentralized nurse station design: An examination of caregiver communication, work activities, and technology. *Health Environments Research and Design Journal.* 2007;1(1):44-57.

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Design Interventions for Specific Care Areas

Many quality improvement teams are focusing their efforts on a particular care unit in the hospital or in the medical office practice setting. Below are several recommended design interventions for six care areas which we believe will help to enhance safety and quality improvements underway.

Operating Room

Studies show that design characteristics of the operating room (OR) impact staff functioning and communication, as well as patient safety. Ventilation and filtration in the operating room environment can have an impact on surgical site infections, but various opinions abound regarding which ventilation and filtration systems are most effective. For example, numerous studies have been conducted discussing the advantages and disadvantages of the use of laminar flow (i.e., very even, smooth, low-velocity airflows that are used in clean-rooms and other settings) along with HEPA filters and automatically closing doors to reduce the incidence of surgical site infections.[23] Additional information can be found in the Centers for Disease Control and Prevention *Guidelines for Environmental Infection Control in Health-Care Facilities*.[24] There is a need for more research in this area.

Operating rooms tend to be crowded with a lot of equipment, monitors, carts, tables, and people over long periods of time. These environments tend to be noisy, with no access to natural light. These factors, along with the physically intense nature of the work performed, make the environment very stressful for nurses and physicians. It is important to improve working conditions for staff by reducing noise levels and by using ergonomic design of work areas. However, such design interventions must be considered within the greater context of variable design drivers. For example, most sound-absorbing materials are not easily cleaned and thus may be inappropriate for use in the surgical environment. Similarly, short-term solutions for reducing neck and back problems experienced by surgical nurses as well as guidelines for operating room design have been suggested based on an ergonomic evaluation of nursing work areas in the operating room.[25] Some suggestions include adjustable-height footstools, better monitor placement, and ergonomically designed instrument tables to help reduce neck and back torsion experienced by surgical nurses as they attempt to obtain an unobstructed view of the operating field and reach for instruments on instrument tables.

Intensive Care Unit

Communication and collaboration are key factors in the effective treatment of high-risk and critically ill patients. Ensuring communication and collaboration among families, patients, and the care team requires providing space for family support within the patient environment, maintaining privacy, and minimizing noise. An opportunity exists to improve outcomes by providing different levels of care without having to move patients from room to room as their acuity improves—known as an "acuity-adaptable patient room"—thus minimizing handoffs, reducing the potential for patient slips and falls

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to occur, and reducing the incidence of staff injuries related to patient lifting. An acuity-adaptable room requires more than just an architectural solution; it also requires cultural and operational changes in order for caregivers to support a one-room/multiple-acuity care model. Reductions in medication errors, falls, and patient transfers have been shown using an acuity-adaptable model.[17] The impact of modifying room acoustics was assessed by periodically changing sound-reflective ceiling tiles to sound-absorbing ceiling tiles within an intensive coronary care unit and revealed that patients' sleep patterns were better with sound-absorbing ceiling tiles in place.[10]

Having family members present during cardiopulmonary resuscitation is becoming a common practice in pediatrics. One study determined parents' perception of the effects of their presence during resuscitation efforts of their child. The findings from this study revealed that family presence during cardiopulmonary resuscitation should be encouraged and supported.[26] A design implication for supporting this practice is providing adequate space for families on the unit.

Emergency Department

Within an emergency department (ED) there can be an underlying conflict between the patient's need for privacy and the ED team's need to directly visualize and monitor a patient. A study conducted in a university medical center's ED found that time to initial physician assessment was higher for chest pain patients placed in rooms farther from the staff work area or placed in rooms with doors (rather than curtains).[27] This study suggested that visual and/or auditory barriers might impede timely intervention by physicians. On the other hand, lack of perceived privacy may impact patient trust and their ability to discuss health problems freely with their physicians. The seriousness of the problem is underscored by a study of an emergency department where five percent of the patients examined in curtained spaces reported withholding portions of their private history and refused parts of their physical examination because of lack of privacy.[28] It is important to optimally balance these issues of patient safety and patient privacy through design, for example, by providing enclosed treatment rooms for privacy and HIPAA compliance while also placing and configuring nurse stations to maximize room visibility.

Efforts to improve patient flow in the emergency department often focus on increasing the size of the ED, but this alone is inadequate and is not necessarily the best solution. Interventions to improve flow must look system-wide to understand how bottlenecks at different points in the care system create a "back up," which then manifests in the ED. When Virtua Health, a participating organization in The Center for Health Design's Pebble Project, started designing their new replacement facility in Voorhees, New Jersey, improving patient flow was an integral goal of their planning process. They used Lean and Six Sigma techniques to identify current problems in the system and then used future state mapping and other methods to identify the physical designs that would result in improved flow and a better patient experience in their hospital. Some environmental characteristics that they examined carefully in their quest to improve flow included the following:

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- *Travel distances* and frequency of trips for different individuals in alternative designs, with a goal of minimizing non-value-added trips and reducing fatigue
- *Departmental adjacencies* that are most efficient
- *Wayfinding ease*, including getting to the hospital as well as understanding how the patient moves through it
- *Single patient rooms* to optimize use of beds to which patients could be transferred

Innovative environmental design also has the potential to reduce the frequency of patients who choose to leave the ED without being seen. A patient's fear that he or she will not receive timely care might be impacted by the ED's design. Is the environment crowded, unattractive, and noisy such that it adds to the stress of waiting and makes the waiting time seem longer? A crowded and noisy emergency waiting room conveys the wrong message to an already stressed patient. Waiting room configuration as well as positive distractions such as views to nature or artwork can help distract patients and reduce stress. A study conducted at New York City's Weill Cornell Medical College examined the relationships between the attractiveness of the physical setting and actual and perceived waiting times, quality of care, anxiety, and staff-patient interaction in seven specialty outpatient practices in Manhattan. The study found that the more attractive the environment, the higher the perceived quality of medical care, the higher reported reduction of anxiety, and the more positive the reported interaction with staff. Also, patients in more attractive physical environments perceived shorter waiting times than patients in less attractive environments.[29]

Medical-Surgical Nursing Unit

A literature review of studies linking the physical environment of hospitals with patient and staff outcomes identified a large number of studies that point to the fact that private patient rooms are superior to semi-private patient rooms for several reasons.[1] In addition to the infection control advantages discussed earlier, other benefits include fewer patient transfers and associated medical errors; less noise (thus improved sleep); better patient privacy and confidentiality; better communications between staff and patients; superior accommodation of family; and consistently higher satisfaction with the overall quality of care delivered.

There is also some evidence that greater family presence in single patient rooms (due to better accommodation of family needs) helps prevent patient falls and other adverse events.[17] Innovations such as acuity-adaptable single patient rooms minimize patient transfers, and the time saved translates into increased caregiver time with the patient at the bedside.[17] Many new health care facilities are incorporating designs based on the findings from other industries such as the aeronautical industry, where standardization has shown to significantly reduce human error. Standardization in patient room design helps to minimize unnecessary variability in design details (e.g., location of gases) between patient rooms that could potentially lead to errors. These are promising new health care design interventions that need to be validated through research.

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Other design features in the patient unit—such as decentralized nursing stations and alcoves with views into patient rooms—increase visibility and access to patients, potentially improving communications and reducing adverse events. For example, reducing distances that caregivers routinely walk to access supplies and patient rooms also reduces staff fatigue and stress.

Noise is a persistent problem on most patient floors. The first step to reducing unwanted noise levels is to conduct a noise audit to determine sources, and then identify design strategies that will reduce or remove noise. Studies show that sound-absorbing ceiling tiles can help control acoustics on patient units which, in turn, results in improved speech intelligibility and reduced staff and patient stress. Several studies have shown that other design features such as access to nature and sunlight improve the perception of pain, accelerate patient recovery, and increase overall patient satisfaction with quality of care. Space for the family in the patient room and the attractiveness of the facility are linked to patient satisfaction and willingness to recommend the health care organization to others. Overall attractiveness of the facility, access to nature and sunlight, and the availability of staff respite areas are also associated with greater staff satisfaction.

Medical Office Setting

Redesigning the clinical office practice to embody many environmental design interventions can lead to increased patient and family satisfaction (e.g., minimizing noise, providing positive distractions), improved provider-to-patient communication (e.g., technology improvements, spatial organization of the room), and enhanced organizational efficiency (e.g., electronic health records, improving visual access).[30] Improving access to the medical office practice by addressing geographic proximity issues, establishing convenient access to the clinic from parking areas, and providing clear wayfinding systems within the facility create a more positive patient experience.[30] The design of waiting areas has a direct correlation to patient satisfaction. In one study, waiting areas that were considered to have higher physical attractiveness were associated with reduced patient anxiety, higher perceptions of quality care, and shorter perceived wait times.[29] Technology is increasingly providing additional ways to improve communications between providers and patients. The spatial organization of the exam room and orientation of computer screens that allow patients to see the information on the screen affects patient and clinician communication as well as the sense of connection experienced by the patient. Wait times can be reduced by implementing decentralized nurse stations, information kiosks, and the use of electronic medical records.[30]

Neonatal Intensive Care Unit

Several studies focusing on environmental factors within neonatal intensive care unit (NICU) settings have been identified in a literature review published by the National Association of Children's Hospitals and Related Institutions.[6] Among the environmental factors identified to have an effect on NICU patients were loud noise, high light levels, and infectious pathogens.

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Infants exposed to excessive noise levels in the NICU have been shown to have poor auditory system development, poor auditory attention, and increased stress. Many studies show that interventions to reduce noise levels can be extremely beneficial to infants in a NICU. Altering the noise levels within the infant's incubator can be an efficient way to alter the noise environment and does not require facility renovations. Interventions that have demonstrated physiological benefits for infant development and convalescence include covering the incubator, installing a sound-absorbing panel in the incubator, and placing sound-absorbing foam next to the infant.

As in other areas of the hospital environment, sound-absorbing acoustical ceiling tiles are effective in reducing noise and reverberation and can be used in the NICU. One hospital, constructing a developmental NICU, included sound-absorbing flooring, wall panels, ceiling tiles, and privacy curtains.[31] They also included new and more advanced equipment. The researchers found that the renovations and new equipment resulted in significant decreases in noise levels.

Infants are sensitive to light exposure and therefore the environment of the NICU impacts physiological outcomes and visual development among preterm infants. Cycled lighting (i.e., reduced light levels in the night) and providing focused lighting over incubators helps improve sleep and developmental outcomes among infants.[6]

The single family room design in the NICU provides a controlled and safe environment for the infant, and privacy and the opportunity to personalize for the family. In addition, each infant receives appropriate lighting, sound, and level of care for his/her particular developmental state.[6] Single family rooms are also linked to fewer nosocomial infections.[1] Several studies on staff perceptions and performance in an open bay versus a private room model suggest staff perceive that the private room model improved the quality of the physical environmental conditions, interaction with infants' families, and overall patient care. While concerns have been raised by caregivers and parents that private rooms can be visually and acoustically isolating, these issues can be addressed satisfactorily through good design.

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Checklist for Providing an Optimal Healing Environment

Based on the published research and the experience of many organizations, we recommend that any health care organization use the following checklist to assess whether they are providing a physical environment that promotes optimal healing.

Table 3. Checklist of Physical Design Elements to Promote an Optimal Healing Environment

Environmental Design Element	Implemented		Comments
	Yes	No	
1. Build private patient rooms			
2. Provide adequate space for families to stay overnight in patient rooms			
3. Install alcohol-based hand gel dispensers:			
In patient rooms			
In patient care areas			
4. Meet World Health Organization recommended noise level standards:†			
Perform noise audit			
Develop noise reduction plan (e.g., eliminate audible paging)			
Implement noise reduction plan			
5. Optimize lighting in medication prep areas			
6. Minimize unnecessary patient transfers (e.g., acuity-adaptable rooms)			
7. Provide wider doors in patient bathrooms			
8. Install optimal air filtration systems (i.e., protect immunosuppressed patients)			
9. Install ceiling-mounted patient lifts to reduce staff injuries:			
In patient rooms			
In patient care areas			
10. Install clear, effective wayfinding systems			

†Berglund B, Lindvall T, Schwela DT, eds. *Guidelines for Community Noise.* Geneva: World Health Organization; 1999. Available at: http://whqlibdoc.who.int/hq/1999/a68672.pdf

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Environmental Design Element	Implemented		Comments
	Yes	No	
11. Install "positive distractions" (to reduce patient anxiety): Music			
Art and interactive art			
Architectural features			
12. Provide choices for patients:			
Control lighting			
Control privacy			
Control music and visual images			

In addition to these elements of the physical environment, the materials hospitals use and the way energy is consumed also contribute to positive or negative outcomes. In October 2007, the Global Health and Safety Initiative was launched to create a social movement designed to develop synergies between "three safeties": patient safety, worker safety, and environmental safety and sustainability. The core assumption is that these safeties can be improved, as well as health care facilities themselves, by how we build, the products we buy, and by how we operate. As part of this work, an open source searchable database of recommended best practices for evidence-based design was developed from focus groups conducted by Kaiser Permanente and others.[32]

The Business Case: Balancing One-Time Capital Costs and Ongoing Operating Savings

In light of mounting pressure to improve quality and safety, and growing evidence that design of the physical environment can contribute to both, why haven't all hospitals rushed out and implemented these evidence-based design interventions? Some have. For those that haven't, the barriers are often perceived to be economic.

Balancing One-Time Capital Costs and Ongoing Operating Savings

Central to the business case is the need to balance one-time construction costs against ongoing operating savings and revenue enhancements. The first attempt to analyze this balance was published in 2004 by a multidisciplinary team that reviewed published research and the actual experience of health care organizations that used evidence-based design in portions of their construction projects. Many of these were pioneering hospitals, called Pebble Project partners, which were part of a collaborative learning program sponsored by The Center for Health Design.

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The authors designed a hypothetical *Fable Hospital*™. (The name *Fable* was chosen because it had not then been built.) When they analyzed the operating cost savings that resulted from reducing infections, eliminating unnecessary patient transfers, minimizing patient falls, lowering drug costs, lessening employee turnover rates, and improving market share and philanthropy, they concluded that, with effective management and monitoring, the financial operating benefits would continue for several years, making the additional innovations a sound long-term investment. Additional initial capital investments were recovered within three years. In short, there was a compelling business case for using evidence-based design to build better, safer hospitals.[33]

In addition to the reduction in worker back injuries mentioned above, Sadler, Dubose and Zimring[34] have described cost savings resulting from fewer infections, fewer medications errors, reduced falls, and reduced lengths of stay. Additional cost-effective interventions that improve a facility's sustainability and environmental efficiency have been described extensively and are beyond the scope of this paper. They include such areas as toxic wastes, use of mercury, and the overall carbon footprint.[35]

The Challenge of Moving from "Light-Green" to "Dark-Green" Dollars

To fully realize the business-case impact of the costs avoided by reducing infections or patient falls, organizations must estimate, capture, and reflect these in their financial statements. Similarly, organizations must capture the costs of reduced nursing turnover that requires less recruiting and training expenditures.

The movement of theoretical savings ("light-green" dollars) to actual savings to the hospital as reflected in its financial statements ("dark-green" dollars) is a key success factor to make the business case actually accomplish its objectives. This is true of any quality improvement intervention, whether or not connected to environmental changes, and was first described by an interdisciplinary team at the Institute for Healthcare Improvement.[36] Documenting actual cost savings in financial forecasts can be invaluable in convincing boards of trustees that evidence-based design investments are cost effective.

Emerging pay-for-performance methodologies that reward hospitals for quality and refuse to pay hospitals for harm they cause to patients (e.g., infections and falls) will further strengthen the business case. At the same time that the costs of unnecessary harm are increasing, public and employer expectations are growing. The emerging practice of not reimbursing organizations for hospital-acquired conditions and the public reporting of comparable patient satisfaction scores adds more weight to the revenue side of the business case. While Medicare has driven much of the initial reimbursement and transparent public-reporting requirements, Medicaid and commercial payers are rapidly adopting the same or similar practices.

A suggested framework that hospitals can use to calculate the return on investment of a specific evidence-based environmental design intervention is included in Appendix B. Each organization will need to incorporate the latest relevant evidence and its best judgment about the cost and revenue impacts of the interventions being considered.

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Conclusion

Hospital leaders and boards face a new reality: they can no longer tolerate allowing environmentally preventable patient hospital-acquired conditions such as infections and falls; injuries to staff; unnecessary intra-hospital patient transfers that can increase errors; or increased patient and family anxiety, stress, and length of stay caused by noisy, confusing care environments.

Leaders need to understand the clear connection between constructing well-designed healing environments and improved health care safety and quality for patients, families, and staff, as well as the compelling business case for doing so. The physical environment in which people work and patients receive their care is one of the essential elements in reducing a number of preventable hospital-acquired conditions.

As part of their management and fiduciary responsibilities, hospital leaders and boards should include cost-effective, evidence-based environmental design interventions in all their improvement programs or risk suffering the economic consequences in an increasingly competitive and transparent environment. Implemented successfully, responsible use of evidence-based design will improve patient safety and quality, enhance workforce recruitment and retention, and produce a significant multi-year return on investment.

The effectiveness of any evidence-based environmental design intervention will rarely occur in isolation from other important proven process improvements. The experience with IHI's 100,000 Lives and 5 Million Lives Campaigns has shown that effective change packages are usually an integrated set of improvements that are best implemented together. Building a new hospital or renovating an existing one also provides a unique opportunity to transform the culture and processes of the overall organizational enterprise to maximize the investment.

Imagine a health care environment where there are no needless infections, no needless falls, no needless patient transfers, no needless noise, no needless sleep deprivation, no needless lack of patient control, no needless physical barriers to communication, no needless confusion, no needless anxiety, and no needless workforce injuries, fatigue and inefficiency. Creating these environments is now within our grasp. All we need is the creativity, courage, and discipline to utilize cost-effective design interventions that work. Hospital leaders have an opportunity and an obligation to assure that, whether patients are in their care for an hour, a day, a week, or a year, they are providing care in an optimal healing environment.

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Appendix A.
How to Utilize Evidence-Based Environmental Design: Ask an Additional Question

Traditionally, hospital leaders have asked five questions when considering a major building project:

1. Urgency: Is the expansion/replacement actually needed now to fulfill the hospital's mission? What is the cost, in strategic terms, of not proceeding?
2. Appropriateness: Is the proposed plan the most reasonable and prudent in light of other alternatives?
3. Cost: Is the cost per square foot appropriate in light of other projects being built in the region?
4. Financial impact: Has the financial impact of additional volume, depreciation expense, and revenue assumptions been reasonably analyzed and projected?
5. Sources of funds: Is the anticipated combination of additional operating income, reserves, borrowing, and philanthropy reasonable and enough to support the project?

Now leaders should also ask a sixth question:

6. Impact of evidence-based design interventions: How will the proposed project incorporate all relevant and proven evidence-based design interventions to optimize patient safety, quality, and satisfaction, as well as workforce safety, satisfaction, productivity, and energy efficiency?[33]

Appendix B. A Proposed Framework for Calculating Return on Investment

The following four-step framework can be helpful in calculating the return on investment (ROI) of an evidence-based environmental design intervention. While healthcare-acquired infections is the example used, the framework may be applied to any intervention.

STEP 1: Identify your improvement goal (e.g., reduce healthcare-acquired infections (HAIs) to "x" number per year). Calculate the current scope of the problem in your facility to establish a baseline.

STEP 2: Estimate improvement costs. Identify the specific evidence-based environmental design strategies as well as clinical and administrative strategies needed to reach your improvement goal. Identify the associated initial and lifecycle costs for each strategy.

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Design Intervention	Initial Cost	Lifecycle Cost	Calculations/Comments
Provide 100% single patient rooms		Increased square feet (SF) with associated housekeeping, energy, and replacement furnishings costs	Single patient rooms are now the standard. However, these rooms are estimated to be __SF larger resulting in an average increase of __SF for an average inpatient unit, which could increase lifecycle operational costs.
Separate sink for staff in patient room		Increased operational plumbing maintenance costs	Separate staff sinks are now standard for new hospital construction. There may be minimal increased lifecycle operational costs.
Alcohol-based hand gel dispensers in all patient rooms		Replacement and maintenance costs and gel refill costs	Initial cost = (Total number of devices per patient room) x (Number of rooms)
Clinical and administrative interventions		Training costs	Include all incremental operating costs
Total Estimated Improvement Costs			

STEP 3: Calculate revenue improvement through cost avoidance. To understand the full impact of using evidence-based environmental design strategies, incorporate the financial impact of these improvements into the hospital's annual capital and operating budgets. Using estimated costs calculated in Step 2, determine the total cost avoided if the improvement goal is achieved.

Example:

(Number of HAIs avoided per year) x (Cost of average HAI) = Total Annual Cost Avoided

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Additional revenue improvements may be projected because of fewer HAIs:

- Increased capacity for more patient admissions: Reducing the number of patients with HAI and their associated longer length of stay will increase the capacity for admitting additional patients and their associated revenue.
- Avoided non-reimbursement for certain HAIs: Hospitals are no longer reimbursed for a growing list of healthcare-associated conditions that harm patients, many of which are HAIs.
- Reduced litigation and settlement costs: There may be fewer associated litigation and settlement costs for HAI patients who sue because of harm.
- Improved bond rating: A hospital's credit rating and ability to raise capital may be improved by implementing evidence-based design features that improve the safety and quality of patient care; improve the retention, satisfaction, safety and efficiency of staff; and thereby improve the organization's bottom line.[37]

STEP 4: Calculate the ROI. Compare the total annual cost avoidance identified in Step 3 with the total initial cost of the planned interventions in Step 2 to identify the ultimate financial savings over interim points along the hospital's lifecycle. For Year 2 and 5 costs, assume that you will have the same annual costs and cost avoidance for each year or you can project costs adjusted for inflation.

Variables	Initial Year	Year 2	Year 5
Cumulative revenue improvement through cost avoidance	Annual cost avoidance	Annual cost avoidance x 2	Annual cost avoidance x 5
Cumulative cost of improvements	Initial cost	Initial cost + Annual cost	Initial cost + (Annual cost x 4)
Savings	Cost avoidance – Cost of improvements	Cost avoidance – Cost of improvements	Cost avoidance – Cost of improvements

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STEP 5: Embed the business case in the fabric of the organization. While the above steps will help you create a business case for evidence-based design, to be successful in implementation the leadership team should also do the following:

- Select an architect with a proven understanding of and experience in evidence-based design, who will work with your organization to find fiscally responsible solutions that look beyond the initial capital cost.
- Communicate performance-improvement targets and progress internally to all appropriate stakeholders.
- Communicate performance-improvement targets and progress externally to increase public awareness and recognition that can differentiate the organization in the marketplace and increase market share.
- Share lessons learned and publish results. In so doing, contribute to needed knowledge about the financial and clinical impact of evidence-based design.

For a more in-depth examination of the full range of steps the leadership team and board could follow to ensure successful implementation of evidence-based design, see the article by Zimring and colleagues.[38]

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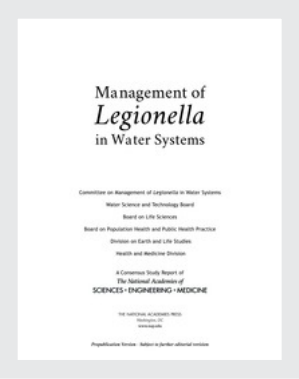

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SUGGESTED CITATION

National Academies of Sciences, Engineering, and Medicine 2019. *Management of Legionella in Water Systems*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25474.

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Management of *Legionella* in Water Systems

Committee on Management of *Legionella* in Water Systems

Water Science and Technology Board

Board on Life Sciences

Board on Population Health and Public Practice

Division on Earth and Life Studies

Health and Medicine Division

A Consensus Study Report of

The National Academies of

SCIENCES • ENGINEERING • MEDICINE

THE NATIONAL ACADEMIES PRESS

Washington, DC

www.nap.edu

Prepublication Version - Subject to further editorial revision

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THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW Washington, DC 20001

This activity was supported by the Alfred P. Sloan Foundation under Grant No. G-2016-7288; Centers for Disease Control and Prevention under Contract No. 200-2011-38807, TO# 59; Department of Veterans Affairs under Contract No. VA250-16-C-0012; and Environmental Protection Agency under Contract No. EP-C-14-005, TO# 22 and EP-C-14-005/68HE0C18F0876. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the views of the organizations or agencies that provided support for the project.

International Standard Book Number-13:
International Standard Book Number-10:
Digital Object Identifier: http://doi.org/10.17226/25474

Additional copies of this publication are available from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.

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Printed in the United States of America

Cover credit:

Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2019. *Management of* Legionella *in Water Systems*. Washington, DC: The National Academies Press. doi: http://doi.org/10.17226/25474

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Preface

Legionnaires' disease arrived on the scene in dramatic fashion during the 1976 Philadelphia outbreak that included 182 cases of pneumonia and 29 deaths. Almost 40 years later, major outbreaks at a community level (Flint, Michigan), in healthcare facilities (such as the Quincy, Illinois veterans home), and due to cooling towers (New York City) have again catapulted *Legionella* into national headlines. *Legionella* is now the number one cause of reported waterborne disease in the United States, transmitted through contaminated water that is aerosolized and exposing those nearby via inhalation into the respiratory tract.

The bacteria in the genus *Legionella* occur naturally in water but have optimal growth at warm temperatures. Wherever there are water and pipes eventually one can find *Legionella* including in many human-made building water systems. However, its exact niche and the factors influencing it to bloom are only now being elucidated. *L. pneumophila* is the species (among many) most often diagnosed as the cause of Legionnaires' disease. For every case associated with an outbreak there are nine more sporadic cases. Are these patients exposed in hospitals, from cooling towers, or within residences or commercial buildings such as hotels? Who is responsible for monitoring and controlling the bacteria and the disease? These are complex issues and despite major gains in knowledge about the bacteria, its ecology, its transmission, and Legionnaires' disease, there remains great uncertainty about how to control *Legionella* in water systems.

The National Academies of Science, Engineering, and Medicine were asked by the U.S. Centers for Disease Control and Prevention (CDC), the U.S. Department of Veterans Affairs (DVA), the U.S. Environmental Protection Agency (EPA), and the Alfred P. Sloan Foundation to address the state of the science with regard to *Legionella* including its ecology, disease diagnosis, amplification within water systems, quantification, prevention and control, policy and guidance, and all associated research needs.

This study was established under the auspices of the Water Science and Technology Board (WSTB) of the National Academies. The WSTB convened a Committee to address the management of *Legionella* in water systems that included 13 individuals with various backgrounds and expertise in *Legionella*. Over the course of two years, the Committee conducted a scientific literature review on the state of the science, covering the biology, taxonomy, and ecology of the bacteria; outbreaks and disease surveillance; environmental data from all types of building water systems; control methods; and rules and guidelines for addressing *Legionella* contamination. It conducted some original data analyses, and formulated conclusions and recommendations meant to improve management of *Legionella* contamination of water systems and consequently better control Legionnaires' disease in the United States.

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The Committee recognizes that *Legionella* is only one of a number of pathogens found in water distribution systems and in building premise plumbing. Some of these other pathogens may be as serious as *Legionella*, such as *Mycobacterium avium* (and other non-tuberculous mycobacteria). The control of *Legionella* may have unintended consequences on these other organisms, as discussed briefly in Chapter 4. However, it was not the purpose of this Report to consider organisms beyond *Legionella*.

During its six committee meetings, the Committee heard from experts involved in characterizing, monitoring, and remediating *Legionella* as well as from those knowledgeable about *Legionella* control policies from Australia, Canada, and Europe. I would like to thank the following individuals for giving formal presentations to the Committee including Sam Posner, Laura Cooley, Jason Kunz, and Brian Raphael, CDC; Shantini Gamage, Gary Roselle, and Oleh Kowalskyj, DVA; Eric Burneson, EPA; Paula Olsiewski, Sloan Foundation; Janet Stout, Special Pathogens Lab; Tim Keane, *Legionella* Risk Management, Inc.; Jennifer Clancy, ESPRI; Christopher Crawford, New York City Department of Health and Mental Hygiene; Jessica Evans, NSF International; David Krause, Forensic Analytical Consulting Services; Alvin Bartels, the Netherlands; David Cunliffe, Australia; Martin Exner, Germany; John V. Lee, England; and Gary Klein, Gary Klein and Associates. The Committee also thanks the many individuals that spoke during open-mic sessions or submitted written comments to the Committee during the course of the study.

This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report: Zia Bukhari, American Water; Anne Camper, Montana State University; Elizabeth Casman, Carnegie Mellon University; Jennifer Clancy, ESPRI; David Fisman, University of Toronto; Marian Heyman, Connecticut Department of Public Health; Sophie Jarraud, Lyon Medical School; Richard Miller, University of Louisville; Norman Pace, University of Colorado; and Caitlin Proctor, Purdue University.

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by Rhodes Trussell, Trussell Technologies, Inc., and Glen Daigger, One Water Solutions, LLC. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

Joan B. Rose, *Chair*
Committee on Management of *Legionella* in Water System

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Contents

SUMMARY 1

1 INTRODUCTION 11

2 DIAGNOSIS, ECOLOGY, AND EXPOSURE PATHWAYS 31

3 QUANTIFICATION OF LEGIONNAIRES' DISEASE AND *LEGIONELLA* 95

4 STRATEGIES FOR *LEGIONELLA* CONTROL AND THEIR APPLICATION IN BUILDING WATER SYSTEMS 175

5 REGULATIONS AND GUIDELINES ON *LEGIONELLA* CONTROL IN WATER SYSTEMS 245

ACRONYMS 285

APPENDIX Biographical Sketches of Committee Members and Staff 289

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Summary

Legionnaires' disease afflicts and kills more people in the United States than any other reportable waterborne disease. It is caused by bacteria of the *Legionella* genus, with the majority of diagnosed cases (from 80 to 90 percent) linked to *Legionella pneumophila*. Humans are primarily exposed to *Legionella* through inhalation of contaminated aerosols into the respiratory system. Patients infected with *Legionella* can develop pneumonia (classic Legionnaires' disease) or a milder flu-like condition called Pontiac fever; both conditions are referred to as legionellosis. Legionnaires' disease can be fatal, with between 3 and 33 percent of *Legionella* infections leading to death. Those at higher risk for developing Legionnaires' disease include the elderly, males, smokers, and the immunosuppressed. In the United States, the reported incidence of Legionnaires' disease increased more than five-fold from 2000 to 2017 (Figure S-1). Worldwide, the actual burden of Legionnaires' disease is generally acknowledged to be underreported, by as much as eight- to ten-fold.

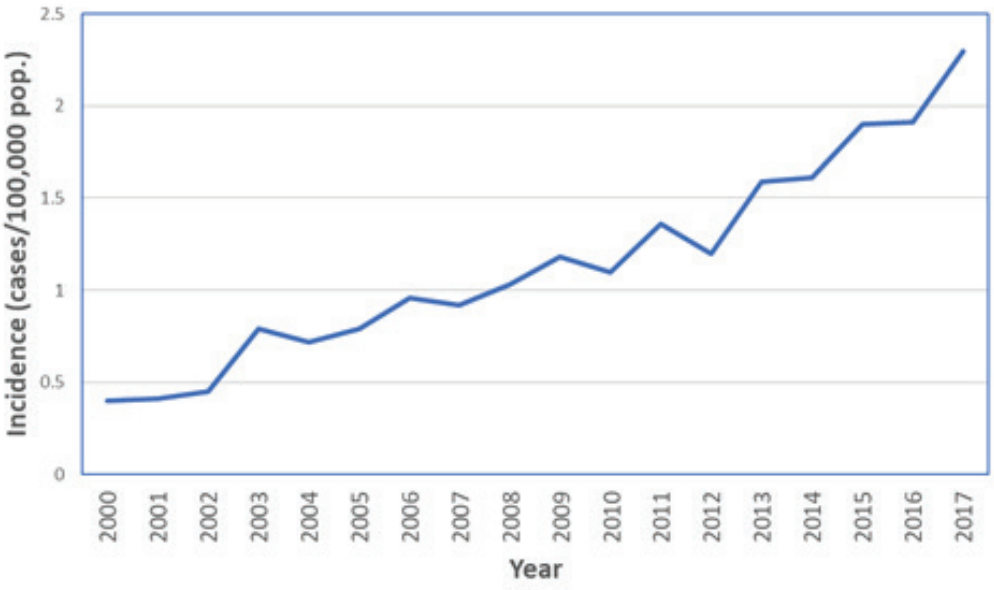

FIGURE S-1 Increasing incidence of legionellosis in the United States from 2000 to 2017. SOURCE: Adapted from Shaw et al. (2018) with 2016 and 2017 data from the National Notifiable Disease Surveillance System.

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Management of Legionella in Water Systems

Legionella bacteria reside in many natural environments including rivers, lakes, and soils. They grow optimally inside protozoan hosts, such as free-living amoebae associated with microbial biofilms that coat wet surfaces. Hence, it is not surprising that these bacteria can be found in a variety of engineered systems that support biofilm growth, including drinking water distribution systems, building plumbing systems, faucets, showerheads, cooling towers, hot tubs, and fountains. These water systems are sometimes characterized by warm temperatures, stagnant water, excess nutrients due to pipe corrosion, and a lack of chemical disinfectants—conditions that promote the growth of biofilms, their associated protozoa, and consequently *Legionella*. When these built environments generate contaminated aerosols, humans in the vicinity can be exposed to *Legionella* via inhalation or aspiration. Most of our knowledge of Legionnaires' disease comes from investigations of disease outbreaks, instances where two or more people are infected at the same time by the same source. However, the vast majority of Legionnaires' disease cases (greater than 95 percent) are sporadic cases for which the primary exposure source is never identified.

In the 40 years since the discovery of *L. pneumophila*, much has been learned about its ecology, whereas less progress has been made in preventing Legionnaires' disease or understanding the ecology of different species of pathogenic *Legionella*. Methods for monitoring both the disease incidence and *L. pneumophila* in water samples have evolved considerably, for both culture-based and molecular techniques. Yet, treatment of water systems to reduce colonization by *Legionella* continues to be complicated by the microbe's complex ecology and the diversity of systems in which *Legionella* can thrive. Moreover, although the Safe Drinking Water Act has been effective in reducing disease rates of waterborne enteric organisms in the United States, it has had little impact on managing *Legionella* in water systems and buildings.

In late 2017, the National Academies of Sciences, Engineering, and Medicine convened an expert committee (the Committee on Management of *Legionella* in Water Systems) to review the state of the science with respect to *Legionella* contamination of water systems and issue a report that addresses the following:

- **Ecology and Diagnosis**: Describe the microbial ecology of water supplies (from the source to the tap and within built systems) as it relates to *Legionella*. What strains of *L. pneumophila* are of most concern and how can their diagnosis be improved (e.g., in terms of increased specificity, simplicity, and speed)?
- **Transmission via Water Systems:** What are the primary sources and routes of human exposure to *Legionella*? What features/characteristics of water systems make them more or less likely to support growth of *Legionella?*
- **Quantification:** Considering surveillance data, case studies of outbreaks, hospital data, other routine testing of water systems, what is known about the concentration of *Legionella* in water systems *and* the prevalence of Legionnaires' disease over the last 20 years? How uncertain are these estimates and what can be done to reduce this uncertainty? How can quantitative risk assessment be improved?
- **Prevention and Control:** What are the most effective strategies for preventing and controlling *Legionella* amplification in water systems? What are the best methods to prevent exposure to *Legionella,* especially in at-risk populations? Is there a minimum level of contamination required to cause disease? What are the benefits, risks, gaps in implementation, and barriers to uptake of *Legionella* control programs?
- **Policy and Training Issues:** What policies, regulations, codes, or guidelines affect the incidence, control, quantification, and prevention of Legionnaires' disease? How might they be built upon to better protect the public? How can *Legionella* control be best balanced with other water priorities?

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ORGANIZATION OF THIS REPORT

Chapter 2 discusses Legionnaires' disease, the life history and complex ecology of *Legionella* in both natural and built water environments, and common exposure pathways. Chapter 3 focuses on the surveillance of Legionnaires' disease in the United States, methods to detect *Legionella*, and the results of environmental *Legionella* monitoring in different built water systems. Chapter 4 considers the many strategies used to control *Legionella*, including the use of heat, biocides, flow control, plumbing materials, aerosol formation prevention, and distal devices, along with their application in several typical built environments. Finally, Chapter 5 takes on the array of laws, regulations, codes and standards, and guidance documents that relate to *Legionella* management, both in the United States and abroad. This final chapter makes suggestions for how these various policy tools can be strengthened to better protect the public from legionellosis. Each chapter ends with conclusions and recommendations that synthesize more technical and specific statements found within the body of each chapter. The most important conclusions and recommendations are repeated in this summary.

DIAGNOSIS, ECOLOGY, AND EXPOSURE PATHWAYS

Since its discovery in the 1970s, more than 61 species of *Legionella* have been described, half of which have been isolated from patients. In North America and Europe, *L. pneumophila* is the most dominant *Legionella* species isolated from patients. Other species can lead to disease, including *L. micdadei, L. bozemanii, L. dumoffi* and *L. longbeachae.* In Oceania and parts of Asia, disease due to *L. longbeachae* approaches or exceeds that for *L. pneumophila.* The various species of *Legionella* differ in their virulence, infectivity, and preferred growth conditions (e.g., protozoan hosts and environmental factors). Yet what is known about legionellae ecology is almost exclusively based on studies with *L. pneumophila.* Similarly, a troublesome aspect of Legionnaires' disease diagnosis is the overreliance on the urinary antigen test, which only detects *L. pneumophila* serogroup 1.

L. pneumophila can adapt to environmental change by differentiating into replicative, transmissive, filamentous, mature infectious, and viable-but-not-culturable-like (VBNC-like) cells—forms that differ in their infectivity and their response to water treatment technologies. Even more complicated is that as pathogenic legionellae grow to high concentrations in free-living protozoa, infectious bacteria may be released within aerosols in various forms: as free cells, cells within biofilm fragments, or cells associated with free-living protozoan trophozoites, cysts, or expelled vesicles. A deeper understanding of *Legionella* ecology and of the genetic traits that equip *Legionella* strains to colonize engineered water systems, to survive in aerosols, and to thrive in the human lung is required. The following conclusions and recommendations for research are found in Chapter 2.

There is a need to better understand the mechanistic pathways for the development of Pontiac fever, and what roles the pathogen, endotoxins, *Legionella*-harboring amoebae, or other exposures play in disease pathogenesis. Because Pontiac fever is associated with less mortality, focused studies examining this clinical entity have been limited to date. There is a need to develop improved diagnostic tools for Pontiac fever (including molecular methods) that would enhance overall *Legionella* epidemiology and outbreak investigation.

Protocols should be developed to generate, identify, enumerate, and report distinct *Legionella* cell types. The capacity of *L. pneumophila* to resist detergents, heat, chemical disinfectants, and antibiotics,

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Management of Legionella in Water Systems

as well as predatory amoebae and white blood cells depends on its growth phase. The resilience and infection potential differ by orders of magnitude for replicative, stationary or transmissive phase, and the mature infectious form of *L. pneumophila*.

Whether *L. pneumophila* persistence within built water systems is promoted by the bacterium's differentiation into an apparent viable-but-non-culturable state that is both resilient and reversible remains an urgent question with implications for public health. To date, studies of VBNC-like *L. pneumophila* are largely descriptive. Protocols to generate and isolate pure populations of VBNC-like cells for physiological, biochemical, genetic, molecular, and infection studies are needed.

Ecological studies have almost exclusively focused on the impact of environmental conditions on growth, survival, and inactivation of *L. pneumophila*. To clarify whether the ecological principles observed for *L. pneumophila* also apply to other pathogenic *Legionella* species, research on the ecology of *L. longbeachae*, *L. micdadei*, *L. dumoffi,* and other pathogenic *Legionella* species is warranted. The ecological conditions responsible for *L. pneumophila* growth in environments such as cooling towers, wastewater treatment plants, soils, and hot springs are largely unexplored compared to building water systems (i.e., premise plumbing).

Whether legionellae persist within free-living protozoa versus growing to high numbers appears to be influenced by many poorly understood factors, including temperature, species of bacterial prey available, presence of host symbionts, and host cell form. **Direct observations and metagenomic studies of microbial diversity are required to identify the protozoa that control the growth of pathogenic *Legionella* in various environments.** Microcosm studies could investigate how nutrients and biocides affect the life stages of the host protozoa (e.g., by triggering encystation), identify the key host species, and elucidate the role of other free-living protozoa that might feed on the primary hosts of legionellae.

QUANTIFICATION OF *LEGIONELLA* AND LEGIONNAIRES' DISEASE

Chapter 3 addresses Legionnaires' disease rates from surveillance systems and the occurrence of *Legionella* bacteria in various water systems including the methods used to detect *Legionella* in clinical and environmental samples. Monitoring of both Legionnaires' disease and *Legionella* bacteria in the environment is fraught with difficulties, including which pneumonia patients are tested to diagnose the cause of their infection, where and when to sample in the environment, what detection methods to use, and how to interpret the data. More and improved environmental monitoring is needed to examine (1) the national occurrence of Legionnaires' disease and *Legionella* concentrations in different built environments, (2) the environmental conditions and amplification niches for the bacteria, and (3) the sources of exposure for both sporadic and outbreak-associated Legionnaires' disease.

Surveillance data show that Legionnaire's disease rates have been rising in the United States and in Europe over the past 20 years. Current incidence rates are understood to be a substantial underestimate of the actual disease burden for many reasons, including the lack of adequate diagnostic testing among pneumonia patients in most U.S. hospitals and the virtual absence of diagnosis for outpatients. Using data from previous studies and current surveillance systems, **the Committee estimates that the number of persons with Legionnaires' disease ranges from 52,000 to 70,000 in the United States each year.**

By reviewing dozens of *Legionella* studies from various building types from around the world, the Committee found the available *Legionella* occurrence data are highly variable and sparse, making

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comparisons among studies difficult and detection of spatial and temporal trends almost impossible. Available data suggest that cooling towers, hot tubs, showers, and wastewater treatment plants can be hot spots for growth of *Legionella* and exposures. Several studies that recorded concentrations of culturable *Legionella* were compiled to determine if and when concentration could be indicative of outbreaks of Legionnaires' disease. **A *Legionella* concentration of 5 x 10^4 colony-forming units per liter (CFU/L) should be considered an "action level", that is, a concentration high enough to warrant serious concern and trigger remediation. A lower action level may be necessary to protect those at higher risk for legionellosis, such as hospital patients, particularly those in intensive care, cancer, and solid-organ transplant units.** Additional conclusions and recommendations about Legionnaires' disease surveillance, environmental monitoring data, and quantitative microbial risk assessment are found below.

There is an urgent need to develop better clinical tools that will capture more cases of Legionnaires' disease and identify pathogenic *Legionella* beyond *L. pneumophila* serogroup 1. Hospitals in both rural and urban areas should have access to on-site urinary antigen testing to facilitate more targeted antimicrobial therapy and to increase disease recognition. Efforts to develop standardized molecular methods for *Legionella* diagnoses (including non-*pneumophila* species and serogroups other than serogroup 1) should be prioritized by research laboratories and federal agencies. Finally, the U.S. Department of Health and Human Services should target research funding to multi-center prospective studies of clinical respiratory samples using these new assays to better understand prevalence and diversity of the *Legionella* species and serogroups causing disease.

An improved understanding of sporadic, community-acquired cases of Legionnaires' disease is critical to reducing the rising rates observed over the past 20 years. **Determining the most common sources of sporadic disease will require well-funded, population-based studies in multiple jurisdictions (e.g., cities, counties, states).** Such studies would require the recruitment of multiple medical centers with an adequate number of *Legionella* cases each year, willingness and capacity to collect clinical samples for *Legionella* culture, personnel with knowledge of how to sample the most likely sources of exposure for legionellosis patients, and laboratory capacity to reliably grow *Legionella* from clinical and environmental samples.

Regional Centers of Excellence for prevention and control of legionellosis could serve as a backbone to strengthen the capacity of state health departments to detect and investigate cases of Legionnaires' disease. Such centers could be modeled on the Integrated Food Safety Centers of Excellence and the Centers of Excellence for Vector Borne Diseases, with modifications to include the relevant disciplines needed for *Legionella* applied research and control. These centers could promulgate best practices for prevention and control measures and they could train and assist building managers as they create water management plans. They could also help coordinate the in-depth, multiple-jurisdiction studies of environmental exposures recommended above.

A systematic study to compare culture methods for *L. pneumophila* (and other pathogenic legionellae) with quantitative polymerase chain reaction (qPCR), viability-qPCR, and reverse transcriptase qPCR is needed to determine comparability. qPCR and its variants offer a more rapid method to quantify *Legionella* in the environment, and could be used consistently to inform decisions on decontamination and restoration of affected systems, to investigate the bacteria's ecology and exposure pathways, and as a quality control method. With side-by-side comparisons of methods in a broad range of settings, it may be that PCR-based or other simplified methods or test kits could be shown to be useful predictors of human health risk and adequacy of remediation.

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Management of Legionella in Water Systems

There is a good framework to perform quantitative microbial risk assessment (QMRA) for various *L. pneumophila* exposures. QMRA can be used to determine *Legionella* concentrations in building water systems that correspond to certain Legionnaires' disease risk levels; such information can be used, for example, to inform design and permitting decisions about pipe length, setback distances for large industrial cooling towers, and building-level hydraulic design to maintain acceptable microbial quality. To further advance QMRA, additional knowledge is needed about the impact of virulence and strain differences, phenotypic alterations in potency and aerosol survival, and generation rate of aerosols from various devices. Data on exposures, especially for cooling towers, are lacking.

STRATEGIES FOR *LEGIONELLA* CONTROL AND THEIR APPLICATION IN BUILDING WATER SYSTEMS

Chapter 4 focuses on strategies for *Legionella* control in building water systems. The controls considered are temperature control, disinfection, hydraulic management, nutrient limitation, choice of plumbing materials, distal devices, and prevention of aerosols. The chapter then discusses how specific controls are applied to building water systems, considering large engineered systems such as potable water supply, wastewater treatment, and reclaimed water systems, large institutional buildings and households, cooling towers and humidifiers, and hot tubs. The chapter also discusses several emerging issues, such as potential conflicts among strategies for green building design, water and energy conservation, and more prospective *Legionella* control strategies.

For any given building water system, multiple strategies can be successfully employed and should be used. The effectiveness of many of the controls are interdependent; for example, optimal hydraulics is required for effective delivery of thermal control and chemical disinfectant while reactivity of the plumbing materials and the water source chemistry could lead to disinfectant decay. Different strategies available for controlling *Legionella* in water systems are feasible at different stages of a building's life cycle, with some being most important during initial construction (e.g., the choice of plumbing materials) while others are implemented during ongoing operation and maintenance (e.g., disinfection and flushing). The conclusions and recommendations below highlight key takeaways with respect to *Legionella* control strategies for various building and device types.

For all types of buildings, hot-water heater temperature should be maintained above 60°C (140°F), and the hot-water temperature to distal points should exceed 55°C (131°F). Maintaining temperature outside *Legionella's* preferred growth range is the paramount *Legionella* control strategy for all buildings that provide hot water and has been proven successful by numerous longitudinal field studies. Temperature control is most effective in large, complex hot-water systems that are hydraulically balanced, with dead-end pipes removed and faulty devices that compromise the distribution of hot water identified and replaced.

There is growing evidence that, compared to free chlorine, a monochloramine residual better controls *Legionella* risk from building water systems, although the reasons for the improved performance are not yet clear. It is possible that amoebae trophozoites are more sensitive to monochloramine, causing the amoebae to encyst and thus preventing the proliferation of *Legionella* within their host. Additional research is needed to examine the precise action of monochloramine on *Legionella* persistence and growth within pipe biofilms.

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Research is needed to better understand the persistence of distribution system disinfectant residuals within building plumbing. Public water supplies that maintain a disinfectant residual and manage hydraulics to prevent stagnation are helping to reduce *Legionella* exposure from the distribution system. Nonetheless, it is unclear to what extent the disinfection residual can achieve *Legionella* control within premise plumbing, for both single-family homes and small buildings as well as larger buildings.

Guidance about *Legionella* is needed for homeowners, especially consumers from at-risk segments of the population. In particular, there is a need to identify plumbing configurations and devices that inadvertently increase risk of *Legionella* proliferation as well as accessible, practical control options such as flushing taps after periods of disuse. Residential water systems can benefit from most of the control strategies discussed in Chapter 4, yet they are almost never formally implemented because of a lack of understanding or awareness on the part of homeowners and occupants.

Low-flow fixtures should not be allowed in hospitals and long-term care facilities because of these buildings' high-risk occupant populations. Low-flow fixtures have been promoted to conserve water and, in some cases, energy. Because of their lower flow, however, these fixtures, primarily low-flow faucets but also showers, increase water age and restrict disinfectant levels, including the disinfection provided by elevated water temperatures. As such, low-flow fixtures present a greater risk for *Legionella* development in the plumbing systems that feed them.

New designs are needed to help advance control of *Legionella* in cooling towers and humidifiers. Humidifier designs that produce water droplets within the temperature range conducive to *Legionella* growth should be avoided for use in new buildings, and existing units of these types should be replaced during building renovations. Strategies relying on disinfectants should consider using alternate types of biocides at regular intervals, since bacteria can regrow in cooling towers when biocide use is infrequent and irregular. Finally, cooling tower manufacturers should collectively design new systems that can operate at condenser water temperatures whereby the temperature going to the cooling tower will be greater than 60°C.

Green buildings have exacerbated many of the problems with *Legionella* by lengthening water residence times (which leads to loss of disinfectant residual) and lowering hot-water temperatures in premise plumbing. Criteria for certifying green buildings, energy-conserving features, and water-conserving features should be modified to take into account risk factors for *Legionella* growth. Substantial water conservation can still be potentially achieved while protecting public health with more overt management of water age, for example, through routine flushing.

REGULATIONS AND GUIDELINES ON *LEGIONELLA* CONTROL IN WATER SYSTEMS

Unlike Australia, Canada, and many European countries, the management of *Legionella* in water systems in the United States occurs on an *ad hoc* basis, ranging from no requirements at all to regulations that require some buildings to have water management plans that include *Legionella* monitoring of water samples along with treatment. The federal Safe Drinking Water Act does not provide any substantial control of *Legionella* in water systems.

Regulations in the Unites States that affect *Legionella* management (by requiring water management plans or monitoring of water systems for *Legionella*) currently cover healthcare facilities in New

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Management of Legionella in Water Systems

York State, cooling towers in New York City and New York State, healthcare facilities within the Veterans Health Administration, and hospitals and healthcare facilities receiving Medicare or Medicaid funds. All other buildings and private residences are formally protected from *Legionella* only through the application of building and plumbing codes. The following recommendations are made to develop a more comprehensive policy for *Legionella* management in the United States.

Expand the Centers for Medicare & Medicaid Services (CMS) Memorandum to Require Monitoring for *Legionella* in Environmental Water Samples. The CMS memo of 2017 requires that hospitals and long-term care facilities receiving CMS funding develop and implement water management plans. This memo has appropriately targeted buildings in which the mortality rates of Legionnaires' disease are high because of the vulnerable patient population. Routine quantitative *Legionella* monitoring programs would enable these institutions to assess the effectiveness of their water management programs. Such enhanced data collection from within hospital systems could help refine the data thresholds needed for prevention. This emphasis on *Legionella* monitoring is supported by international regulations, by the Veterans Health Administration (VHA) directive and the New York State regulations, and by guidance from the American Industrial Hygiene Association (AIHA).

Register and Monitor Cooling Towers. Regulations and guidelines requiring the registration of cooling towers provide a demonstrable public health benefit with minimal regulatory burden to building owners and managers. Cooling tower registries enable a rapid public health response to community clusters of legionellosis cases, including timely remediation of possible sources of infection, and they can also be used to assess the contribution of cooling towers to overall disease incidence. In addition, regulations requiring ongoing *Legionella* monitoring of cooling towers have been shown to reduce cooling tower colonization rates in jurisdictions where they have been implemented (e.g., Quebec and Garland, Texas).

Require Water Management Plans in All Public Buildings Including Hotels, Businesses, Schools, Apartments, and Government Buildings. The standard of care specified for water management plans should be considered best management practice for all public buildings. The recommendation here is to codify what are currently voluntary standards for managing public buildings. ASHRAE 188, AIHA (2015), and other guidance documents are available to help create a water management plan that can meet this requirement. Ideally, this requirement would be codified by either local jurisdictions with authority (such as building inspectors) or state authorities (such as departments of environmental protection or health). Once codified, the requirements could be supported by insurance companies; that is, without a water management plan, a building would not qualify for insurance.

Require a Temperature of 60°C (140°F) at Hot-Water Heaters and 55°C (131°F) to Distal Points. Optimal operating temperatures at critical points in the hot-water system are based on an international consensus that maintaining minimum temperatures across the different parts of a hot-water system is the first barrier to implement to restrict *Legionella* growth. Monitoring temperature at the distal points of hot-water systems would be necessary to verify that this requirement is being met. These temperature requirements could be codified by changing building and plumbing codes or by modifying the CMS memo. There is also the possibility of these requirements being incorporated into guidance documents as they undergo revision in the future.

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The recommendations discussed above are not prioritized; accomplishing any one of them would lead to important legionellosis risk reduction, with a cumulative effect as more of them are accomplished. The recommendations differ substantially in their necessary implementation schedule, which entities would provide oversight, their cost, and what other capacities need to be in place to support them. In particular, the additional monitoring requirements will necessitate the development of guidelines to interpret monitoring data. QMRA could play an important role by, for example, being used to develop routine operational targets for different types of building water systems to determine that the risk of legionellosis is acceptably low. Finally, it will be important to expand training and education on legionellosis and on the prevention and control of *Legionella* amplification in water systems. Education and training are particularly needed for those designing water systems, those overseeing municipal water supplies, those developing and implementing plumbing codes, those responsible for maintenance of water operations and premise plumbing, and those in government who are responsible for the safety of buildings, cooling towers, and the potable water supply.

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1
Introduction

The leading cause of reportable waterborne disease outbreaks in the United States today is Legionnaires' disease, a pneumonia caused by the *Legionella* bacterium. *Legionella* was first documented as a cause of human disease in 1976, after an outbreak of pneumonia of unknown origin was described among members of the American Legion who had attended a conference at the Bellevue-Stratford Hotel in Philadelphia. Of the nearly 2,000 conference attendees, 182 people developed clinical disease and 29 died from their illness. This large outbreak generated national alarm, as public health experts, laboratory scientists, and clinicians raced to define the pathogen (Winn, 1988). A subsequent epidemiological investigation revealed a relationship between the attack rate and the time spent in the hotel lobby and consequently, the route of exposure was surmised to be airborne. The high attack rate coupled with disease severity may have reflected the prevalence of pre-existing conditions among those exposed: of the 94 hospitalized cases, 58 had pre-existing conditions (Fraser et al., 1977). Once the etiologic agent was identified, antibody titers of hotel employees suggested they had been exposed to the bacterium intermittently over a long period.

In 1978 Dr. Joseph McDade and colleagues at the U.S. Centers for Disease Control and Prevention (CDC) discovered the etiologic agent of the Philadelphia outbreak (McDade et al., 1979). The bacterium responsible was named *Legionella pneumophila*, reflecting the patients initially diagnosed with disease and the respiratory complications seen with infection. The first to isolate *Legionella* species (spp.) is thought to be Hugh Tatlock in 1943 (Tatlock, 1944); subsequently, in 1959 F. Marilyn Bozeman isolated these bacteria from individual human cases. Retrospectively, the Philadelphia infectious agents were determined to be similar to the *L. pneumophila* seen previously by Bozeman in 1959 (Bozeman et al., 1968), as judged by immunological assay and similarity of guanine-cytosine DNA composition (McDade et al., 1979).

As news of the Philadelphia outbreak and the identification of *L. pneumophila* as a human pathogen spread, legionellosis became recognized throughout the world. *Legionella* spp. were retrospectively linked to previous enigmatic outbreaks of respiratory disease, including one dating back to 1957 in Minnesota. Thus, legionellosis was present in the United States for years prior to its detection in 1978 (Osterholm et al., 1983; Thacker et al., 1978). Another retrospective study linked *L. pneumophila* to a previously undiagnosed cluster of patients in a county health department facility in Pontiac, Michigan, struck by a "flu-like," less severe form of the illness associated with fever, headaches, and myalgias—a syndrome termed Pontiac fever (Glick et al., 1978). As culture techniques were improved and adopted by the microbiology community, the number of reported *Legionella* spp. grew to include *L. micdadei*, *L. bozemanii*, and *L. longbeachae*, among others. At the time of this publication, more than 61 *Legionella* spp. have been identified, of which more than half are associated with human disease (Cunha et al., 2016).

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Management of Legionella in Water Systems

In the period following the Philadelphia outbreak, knowledge surrounding legionellosis expanded rapidly (see Figure 1-1). In the first few years after the outbreak, scientists identified the pathogen, procedures critical for laboratory isolation, common environmental sites of exposure (e.g., air conditioning units, cooling towers, potable water), and the underpinning to new methods for diagnosis (e.g., the urinary antigen test) (Berdal et al., 1979; Feeley et al., 1978; Politi et al., 1979; Shands et al., 1985). Importantly, epidemiologic and laboratory animal models demonstrated the benefits of macrolides and flouroquinolones as antibiotic therapy for legionellosis (Fraser et al., 1978). Epidemiologic studies also identified *Legionella* spp. as primarily waterborne pathogens. In the 1976 Philadelphia outbreak, the hotel's cooling tower was the source of water droplets contaminated with *Legionella* that spread through the air in and around parts of the hotel. Subsequently, many *Legionella* outbreaks have been linked to water exposures, including clusters caused by potable water sources in hospitals (Broome et al., 1979; Tobin et al., 1980, 1981). A timeline of *Legionella*-related events since 1943 is provided by Figure 1-1. Medical and epidemiological terms related to Legionnaires' disease and used throughout this report are defined in Box 1-1.

CLINICAL DISEASE AND EPIDEMIOLOGIC STUDIES

Legionnaires' disease is caused by bacteria of the *Legionella* genus—small aerobic Gram-negative rods that are facultative intracellular pathogens. Humans are primarily exposed to *Legionella* through inhalation into the respiratory system, after which the organism replicates in pulmonary macrophages and monocytes. Incubation periods are thought to range from two to twelve days, but may be longer, particularly in immunosuppressed patients. Patients with *Legionella* pneumonia have fever, cough, shortness of breath, and myalgias (i.e., soreness or aching of the muscles)—common symptoms in other respiratory infections. Unlike most people with community-acquired pneumonias, however, patients with Legionnaires' disease more frequently have gastrointestinal symptoms and altered mental status and neurologic abnormalities. Patients with Pontiac fever present with fever, myalgias, chills, and headache, but by definition do not have pneumonia; most patients recover without treatment. Because both diseases have symptoms that are similar to other infections, the legionellosis diagnosis may be delayed or missed, which can lead to severe consequences in those with *Legionella* pneumonia.

Legionellosis is most common among the elderly and those who are immunosuppressed. Incidence is also higher in men and in people who smoke cigarettes. While disease from non-*pneumophila Legionella* spp. is more common in immunosuppressed patients, the majority of reported cases are caused by *L. pneumophila* and most frequently serogroup 1 (although this varies by country). *Legionella* spp. have been found on every continent (Aranciba et al., 2014; Beauté, 2017; Carvalho et al., 2008; Chaudhry et al., 2017; Chedid et al., 2005; Guo et al., 2015; Wolter et al., 2016; Yu et al., 2002), but most currently available epidemiologic data focus on legionellosis in large metropolitan areas in developed regions. In the United States, incidence of Legionnaires' disease increased more than five-fold from 2000 to 2017 (see Figure 1-2).

Legionnaires' disease is acquired by exposure to contaminated aerosols of water generated by manufactured devices such as showerheads and faucets, cooling towers, fountains, hot tubs, and other building water systems. Despite numerous reports of common-source outbreaks in the community, through travel or through hospital exposures, and despite improvements in epidemiologic and laboratory tools, the vast majority of *Legionella* cases remain sporadic, community-acquired cases for which the primary exposure source is never identified.

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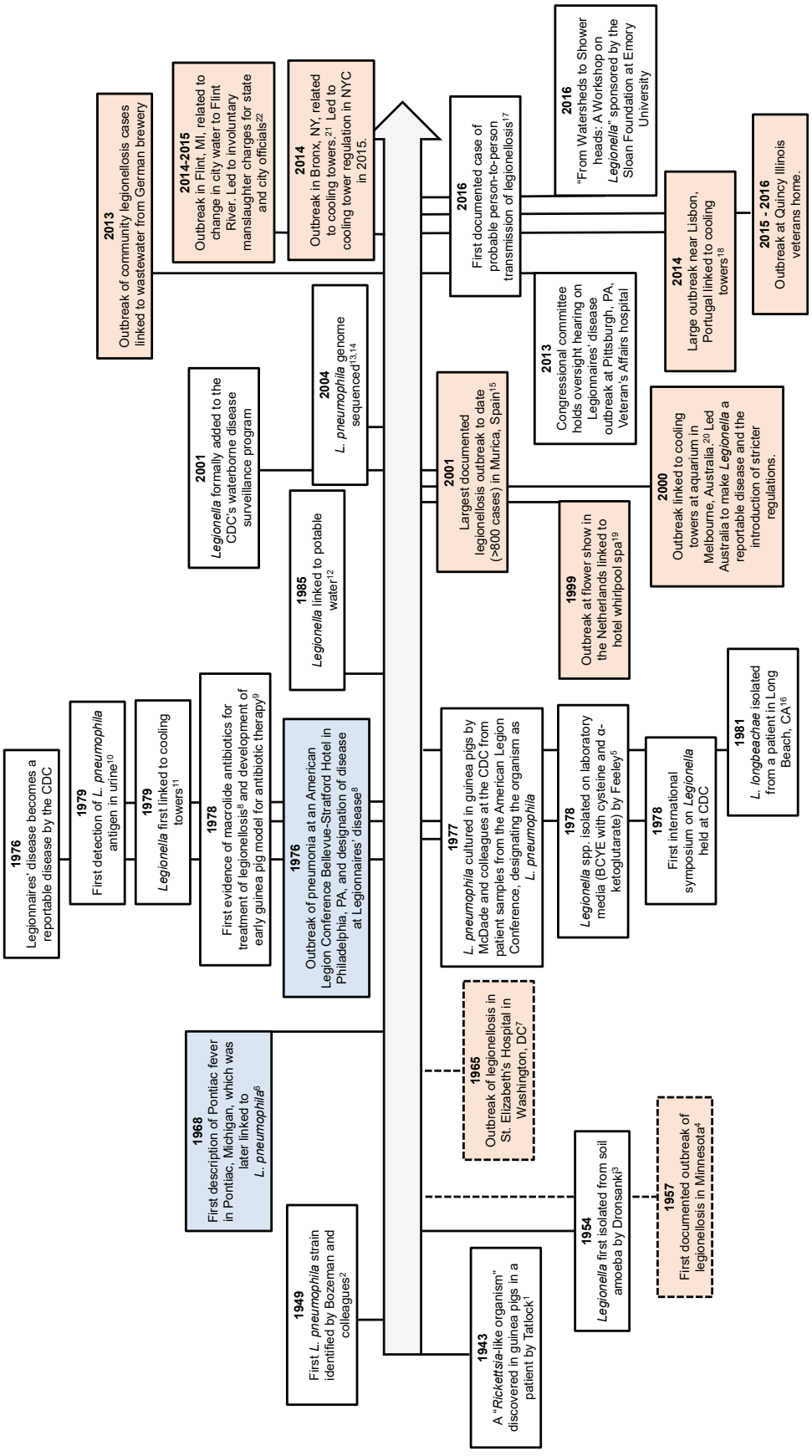

FIGURE 1-1 Timeline of important *Legionella* related events.
NOTES: Broken lines are outcomes determined through retrospective analysis. First *Legionella* spp. reported by Tatlock was *Tatlockia micdadei*, a synonym for *Legionella micdadei*. Blue indicates first reported cases of *Legionella* pneumonia and Pontiac fever respectively; orange indicates a large and historically significant outbreak. Citations indicated are listed at the end of the chapter. Timeline not to scale.

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BOX 1-1
Legionnaires' Disease Definitions

Attack rate: The proportion of exposed people who become ill with (or who die from) a disease in a population initially free of the disease.

Case: An individual with a specified disease, illness, or condition who meets specific clinical, laboratory, and/or epidemiologic criteria.

Cluster: Cases of a disease, illness, or other health-related condition, grouped together in time and/or place.

Disability-adjusted life years (DALYs): A common health metric used to quantify the number of healthy years lost to disability, illness, and/or death due to a particular disease. Often used to compare the health burden of different diseases or in diseases among specific populations and to inform public health policy or decisions.

Disease burden: Measure of a health problem's impact that combines financial cost, mortality, morbidity, and/or other indicators.

Incidence: The occurrence of new cases of a given medical condition or illness in a population within a specified period of time.

Legionellosis: Disease caused by *Legionella* bacteria. Legionellosis includes both lung infections (Legionnaires' disease) and milder syndromes (Pontiac fever).

Legionnaires' disease (also known as *Legionella* pneumonia): Lung inflammation caused by *Legionella* infection, in which the lung's air sacs fill with inflammatory cells fighting the infection. Patients with pneumonia have evidence of lung involvement on radiologic images and have positive cultures or other tests (e.g., urinary antigen) for *Legionella*.

Mortality rate: a measure of the frequency of occurrence of death in a defined population (e.g., all individuals diagnosed with a specific disease) during a specified interval.

Nosocomial: A disease originating or acquired in the hospital, most commonly in reference to infections.

Outbreak: The occurrence of cases of disease or illness in excess of what would normally be expected in a defined community, geographical area, or season (World Health Organization definition).

Pontiac fever: A self-limiting "flu-like" illness caused by exposure to *Legionella* bacteria, defined by lack of pneumonia. Named after site (Pontiac, Michigan) of first description.

Sporadic: A disease or illness that occurs infrequently and irregularly. With regard to *Legionella*, those cases not associated with an outbreak.

Waterborne disease: A disease transmitted or propagated by contaminated water.

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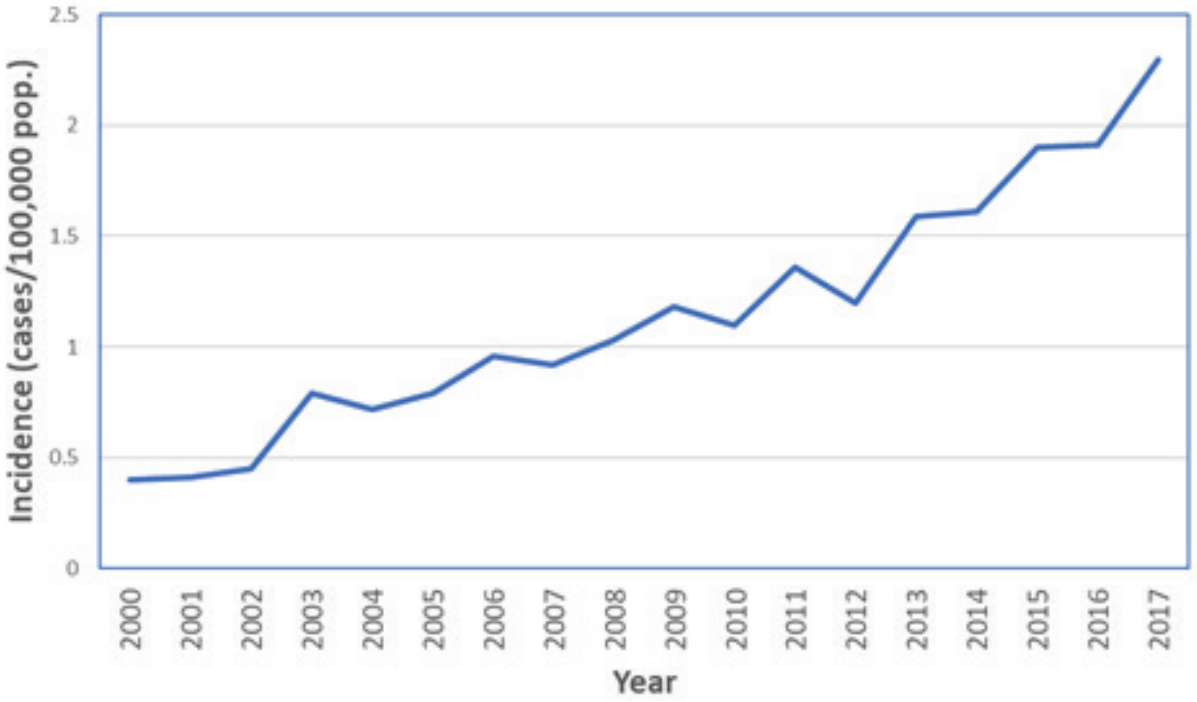

FIGURE 1-2 Increasing incidence of legionellosis in the United States from 2000 to 2017. SOURCE: Adapted from Shaw et al. (2018) with 2016 and 2017 data from the National Notifiable Disease Surveillance System (NNDSS).

The medical establishment has not optimized the diagnosis of Legionnaires' disease for many reasons. When patients present with pneumonia, most physicians choose empiric therapies that adequately treat the disease, so these cases are never counted. If a patient is tested using the urinary antigen test on site, results for infections caused by *L. pneumophila* serogroup 1 can be received in one day. However, when a patient is culture-tested for *Legionella*, it can be at least a week or longer before the results are known, making it difficult to diagnose cases in a timely manner. Worldwide, the actual burden of Legionnaires' disease is generally acknowledged to be underreported by as much as eight- to ten-fold (Dooling et al., 2015; Mercante and Winchell, 2015; Phin et al., 2014; St-Martin et al., 2013; von Baum et al., 2008).

Among common waterborne pathogens, *Legionella* is now the most common cause of reported drinking water-associated outbreaks (see Figure 1-3). Etiologic shifts from the 1970s to the modern era likely reflect successful efforts mandated by the Safe Drinking Water Act of 1974 to control fecal and enteric bacterial pathogens and parasites (primarily *Cryptosporidium* spp. and *Giardia lamblia*).

Waterborne infections account for $3 to 4 billion in excess costs in the United States per year (Adam et al., 2017). Nearly $1 billion per year goes to the top five primarily waterborne diseases (i.e., giardiasis, cryptosporidiosis, Legionnaires' disease, otitis externa, and non-tuberculous mycobacterial infections), including $430 million in hospitalization costs to Medicare and Medicaid (Collier et al., 2012). Proven *Legionella* cases are estimated to lead to a median cost of $26,000 to $38,000 per admission (Collier et al., 2012). European data paint a more ominous picture; Cassini and colleagues (2018) suggest that *Legionella* spp. are one of the top five pathogens leading to the most disability-adjusted life years (DALYs) and one of only four infections (including HIV, tuberculosis, and invasive pneumococcal disease) considered to have both a high population and high individual burden of disease (see Figure 1-4). Numerous sources worldwide have documented increasing incidence of *Legionella* cases, suggesting little progress in decreasing risk for *Legionella*. Incidence is generally thought to be underestimated, such that the true financial and human costs of legionellosis are also likely underestimated.

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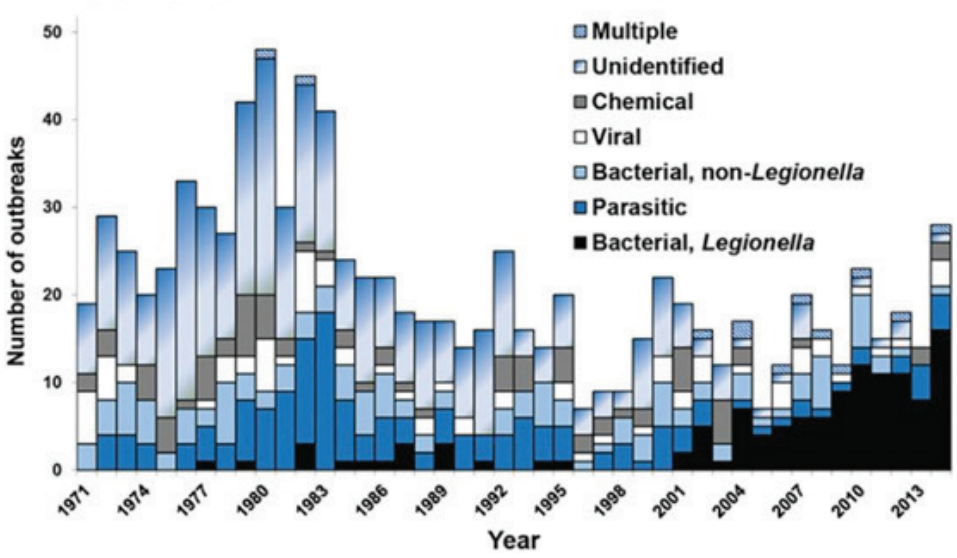

FIGURE 1-3 Etiology of reported drinking water associated outbreaks in the United States (n=298) by year, 1971 to 2014. SOURCE: Benedict et al. (2017).

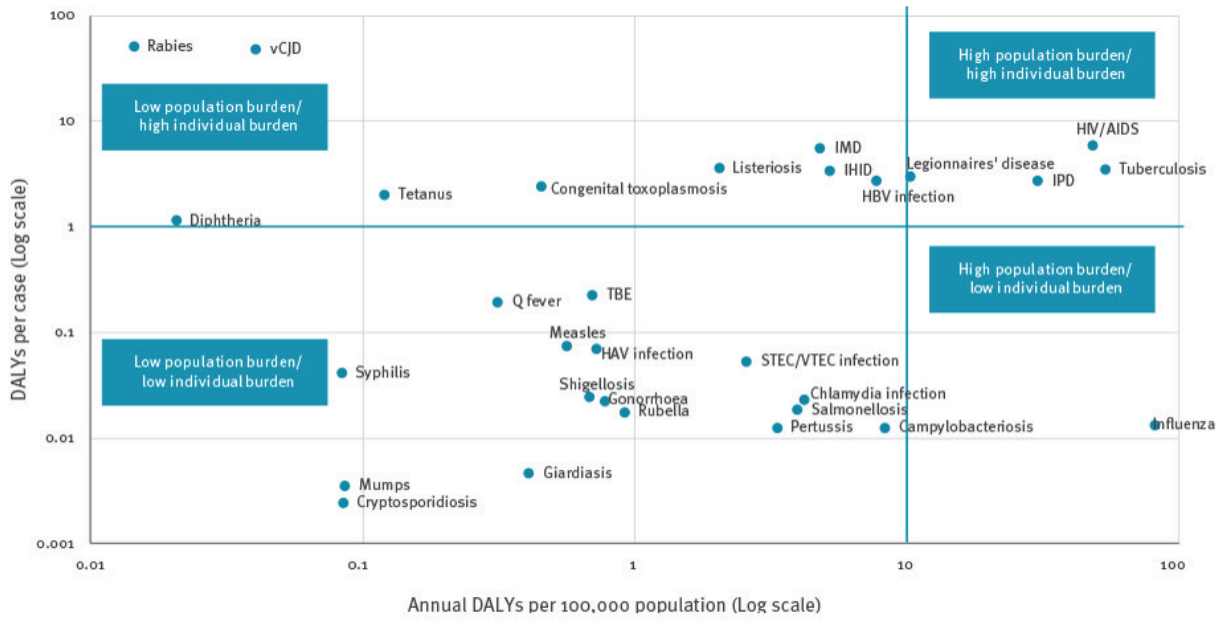

FIGURE 1-4 Scatterplot of the burden of selected infectious diseases in disability adjusted life years (DALYs) per case and DALYs per 100,000 population per year, European Union/European Economic Area countries, 2009 to 2013. SOURCE: Cassini et al. (2018).

NOTE: EU/EAA: European Union/European Economic Area; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HIV/AIDS: Human immunodeficiency virus infection; IHID: Invasive *Haemophilus Influenzae* disease; IMD: Invasive meningococcal disease; IPD: Invasive pneumococcal disease; STEC/VTEC: Shiga toxin/verocytotoxin-producing *Escherichia coli*; TBE: Tick-borne encephalitis; vCJD: variant Creutzfeldt-Jakob disease. Diseases were arbitrarily subdivided according to burven in DALYs per 100,000 population and DALYs per case.

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Table 1-1 lists waterborne bacterial pathogens associated with human sinopulmonary disease. Acquiring pneumonia from waterborne pathogens is uncommon, as most lead to gastrointestinal illness. Nonetheless, pneumonia can occur from waterborne pathogens, most notably *Legionella* spp., *Pseudomonas* spp., and non-tuberculous mycobacteria. Some of the listed bacteria grow opportunistically in building water systems, but only *Legionella* causes a reportable illness. Hundreds of organisms associated with waterborne disease are not discussed in detail in this report, including common waterborne pathogens such as *Pseudomonas* spp., non-tuberculous mycobacteria, *Campylobacter* spp., *Cryptosporidium,* and some *E. coli* infections. Nor does this report discuss other clinical illnesses linked to water, including otitis externa (an ear infection involving the external ear canal), diarrheal disease and their etiologic agents, and skin and soft-tissue infections, among others. Finally, Table 1-1 does not include a large number of important viruses, fungal spp., and parasites causing sinopulmonary infections that have been linked to water sources.

BUILT ENVIRONMENT IS A MAJOR ECOLOGICAL NICHE

Legionella bacteria naturally reside in many freshwater and soil environments, such as lakes, streams, and sediments, and many different species potentially cause disease. However, it is the unchecked growth of pathogenic legionellae in human-made water systems that typically leads to human exposures and causes disease. Humans are exposed to *Legionella* after inhaling or aspirating contaminated water aerosolized from a variety of sources.

L. pneumophila appears to grow poorly as individual, free-living cells in natural environments; instead, its growth is optimal within amoebae (Kuiper et al., 2004) and other free-living protozoa that are associated with biofilms (Buse et al., 2012; Hellinga et al., 2015). Indeed, the bacterial growth requirements are consistent with a natural, parasitic lifestyle. For example, replicating *Legionella* require external sources of certain amino acids and minerals (Reeves et al., 1981; States et al., 1985), low levels of oxygen (optimum below 1 mg/L) (Mauchline et al., 1992), and a temperature range between 25°C and 43°C (Garrity et al., 2005). During the *Legionella* life cycle, its physiological state switches between infectious and replicative forms as well as more hardy, dormant cell forms. Although *Legionella* can survive and persist in the absence of a host cell, in nature significant amplification appears to require protozoan hosts (Fields et al., 2002). Sometimes pathogenic legionellae replicate within free-living amoebae to levels that elevate risks to the people who are exposed (Ashbolt, 2015b; Declerck, 2010).

Accordingly, the ecology of *L. pneumophila* is directly linked to that of protozoa, whose primary habitat is biofilm (Declerck, 2010). A biofilm is a community of microorganisms within a self-produced hydrated gel matrix attached to moist soil, sediment, and other solid surfaces that accumulates organic and inorganic material (Characklis and Marshall, 1990). Biofilms typically form on all moist surfaces, including engineered surfaces such as pipes, tanks, appurtenances, filters, and gaskets—virtually everything that contacts water. Biofilm communities growing on pipes can include bacteria/archaea (including round, rod-shaped, filamentous, and appendaged forms), fungi, and higher organisms such as amoebae, ciliates, nematodes, larvae, and crustaceans (see Figure 1-5). The pipe material can exert a strong influence on the composition and activity of the biofilm's microbial community. Both surface materials and temperature influence the complex interactions among *Legionella*, host amoebae, and biofilm community members. (More detailed discussion on this ecology is found in Chapter 2.) In general, at moderate to warm temperatures, surfaces wetted with water that contains nutrients provide a favorable habitat for biofilm growth, grazing protozoa, and *Legionella* growing within the protozoa.

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TABLE 1-1 Common Waterborne Bacterial Pathogens Associated with Human Sinopulmonary Disease

Pathogen	Associated Disease(s)	Source*	Comments
Acinetobacter spp.	bacteremia, pneumonia, skin and soft-tissue infections	Healthcare-acquired	• High resistance to chlorine (Karunmathil et al., 2014) • Associated with hospital outbreaks • Can grow in building water systems
Aeromonas spp.	bacteremia, pneumonia, skin and soft-tissue infections	Community-acquired	• Primarily *A. hydrophila* • Can grow in building water systems
Burkholderia cepacia complex	bacteremia, pneumonia	Healthcare-acquired	• Can grow in building water systems • More frequent in patients with weakened immune systems
Burkholderia pseudomallei	bacteremia, pneumonia, skin and soft-tissue infections	Healthcare-acquired	• Associated with hospital outbreaks • Resistance to multiple forms of disinfection • Can grow in building water systems
E. coli and other selected Enterobacteraciae spp.	bacteremia, pneumonia, diarrhea, gastroenteritis	Both	• Consider in community wells or if fecal contamination is present • Associated with groundwater and surface water contamination • Multidrug-resistant Enterobacteraciae associated with pneumonia in hospital water systems (e.g., *Klebsiella pneumonia*)
Legionella spp.	pneumonia	Both	• Common cause of outbreaks • Species vary by location and host; *L. pneumophilia* make up majority • Largest number of cases are community-acquired with no source identified • Can grow in building water systems • Non-water-based exposures can also lead to legionellosis • Pontiac fever patients do not have pneumonia
Methylobacterium spp.	bacteremia, pneumonia	Healthcare-acquired	• Primarily occurs in patients with compromised immune systems • Can grow in building water systems
Non-tuberculous mycobacteria	bacteremia, pneumonia	Both	• Primarily *Mycobacterium avium-intracellulare*, but others also reported (Falkingham, 2011) • Can grow in building water systems • High resistance to chlorine
Pseudomonas spp.	bacteremia, pneumonia, skin and soft-tissue infections	Both	• Primarily *P. aeruginosa* • Can grow in building water systems
Stenotrophomonas maltophilia	bacteremia, pneumonia, skin and soft-tissue infections	Healthcare-acquired	• Known intrinsic resistance to multiple antibiotics • More frequent in patients with weakened immune systems • Can grow in building water systems

*Probable source location designation (community or healthcare associated) is based on published data regarding documented water source links.

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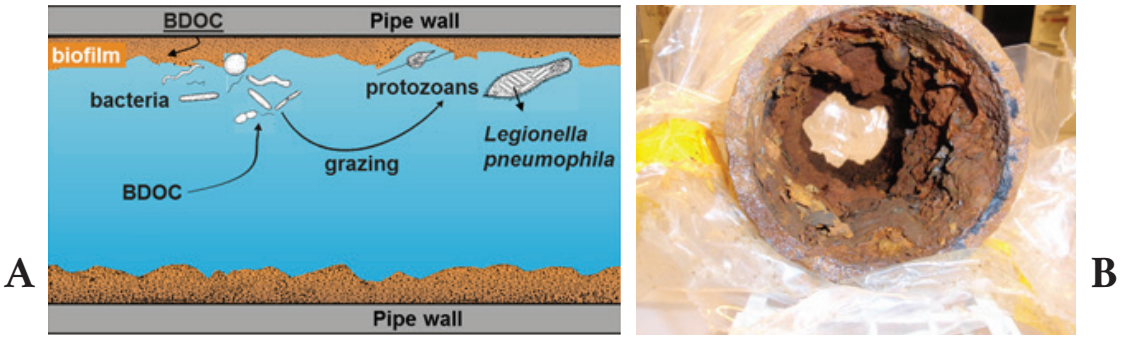

FIGURE 1-5 (A) Schematic of a biofilm growing on pipe walls, including the various microbial cells associated with the biofilm. (B) Corroded iron pipe showing the uneven surface that promotes the accumulation of biofilms.
NOTE: BDOC =biodegradable dissolved organic carbon. BDOC can leach out of plastic pipe walls and can also be provided by microorganisms.
SOURCE: Courtesy of Paul van der Wielen.

The main mode of human exposure to *Legionella* is via inhalation of aerosols. Aerosols are small (typically <100 µm) drops of liquid formed by the action of turbulence on fluids, although only those less than 10 µm can reach deep into the human lung. Any materials suspended within the liquid, such as bacteria and protozoa, can be transported within these droplets. The aerosol particles have a large surface area-to-volume ratio and may selectively accumulate hydrophobic materials, including bacteria (Parker et al., 1983). Aerosolization is distinct from volatilization, which is a chemical phase change wherein either a dissolved solute, or the solvent itself, exits the liquid to form a true vapor state.

Sites with both biofilm growth and potential for aerosolization are possible sources of Legionnaires' disease risk. Many such areas exist in the built environment, including components of heating, ventilation, and air conditioning (HVAC) systems such as cooling towers and humidifiers; indoor plumbing (called premise plumbing) including outlets such as showerheads and faucets; and spas, hot tubs, and Jacuzzis (collectively called hot tubs in this report) (see Figure 1-6). Additional known sources of infection are fountains, misters, nebulizers, car washes, and industrial wastewater treatment plants.

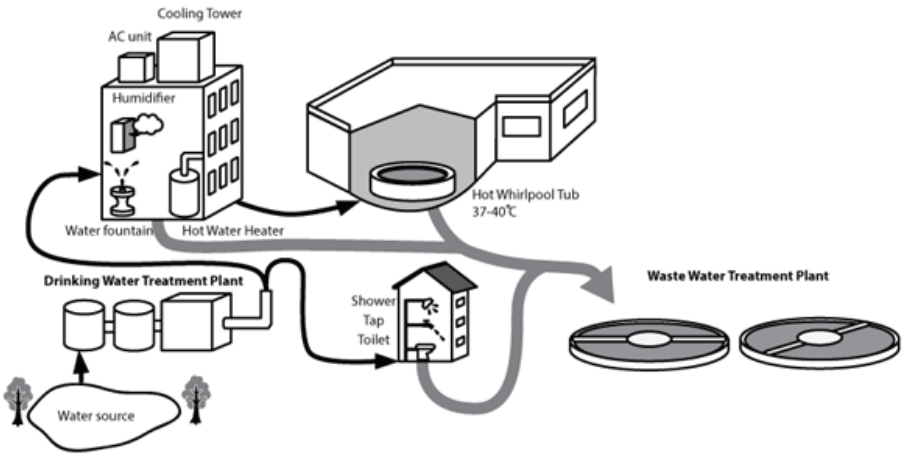

FIGURE 1-6 Built locations where *Legionella* growth can occur. NOTE: Thinner black arrows indicate water pathways to premise plumbing and thicker grey arrows indicate wastewater. SOURCE: Adapted from Exner (2018) by Kyoko Kurosawa.

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Management of Legionella in Water Systems

Building- and industrial-scale (e.g., power plants, industries) wet cooling towers have been implicated in many outbreaks of Legionnaires' disease (see Figure 1-7). Cooling towers remove heat from recirculating water used in water-cooled chillers, heat pumps, air compressors and other equipment. Heat is rejected from recirculating water in the cooling tower primarily through evaporation. Under certain conditions, biofilms can develop within water-associated piping, heat exchangers and other component surfaces. Furthermore, the warm temperatures of the bulk water in cooling towers are also conducive to *Legionella* growth. These towers may generate bacteria-laden aerosols that drift away from the building or facility and then are inhaled by people working and living in the building as well as passersby. Exposure can also occur indoors if the downdraft from cooling towers is transported into building interiors, via air intakes or infiltration. In the United States, there are estimated to be two million cooling towers including both individual and industrial towers.[1]

Legionella can also contaminate drinking water, either in distribution systems or premise plumbing. In the United States, more than 322 million people are served by 152,000 public drinking water systems with more than 1.2 million miles of water supply mains. The total length of premise plumbing, which refers to all piping downstream of the service line connection and within buildings, is thought to be more than 6 million miles (NRC, 2006). Compared with the main distribution system, premise plumbing uses relatively long sections of small diameter tubing with about ten times more surface area per unit length (NRC, 2006). Thus, premise plumbing provides extensive interior surface area for biofilm growth. Moreover, because of stagnation, premise plumbing is frequently devoid of a disinfectant residual. If water in the pipes becomes enriched with pathogens such as *Legionella*, occupants may be exposed to aerosols created by showerheads or faucets (see Figure 1-8). Other home appliances such as hot-water heaters (see Figure 1-9) and humidifiers (see Figure 1-10) can also provide habitats for biofilm growth and enrichment. In 2018, there were estimated to be over 127 million households in the United States.[2]

Biofilm and *Legionella* growth can also be enhanced by water age, which depends on the building type and use, occupancy, and water use. Indeed, the water residing in premise plumbing has a much wider age distribution than the water entering a home from the distribution system (NRC, 2006). Although in the United States the average hotel occupancy is about 66 percent, it can fluctuate seasonally between less than 50 percent to more than 75 percent,[3] creating significant potential for water stagnation. There are over 5 million hotel rooms in the country[4]. Green buildings may provide additional areas for growth of pathogens because of lower hot-water temperatures, lower flows, and longer building water ages (Rhoads et al., 2016).

[1] See https://energytrendswatch.com/2017/11/21/cooling-towers-not-so-cool/.
[2] See https://www.statista.com/statistics/183635/number-of-households-in-the-us.
[3] See https://www.statista.com/statistics/206546/us-hotels-occupancy-rate-by-month.
[4] See https://www.statista.com/statistics/245864/us-hotel-rooms-by-chain-scale-segment.

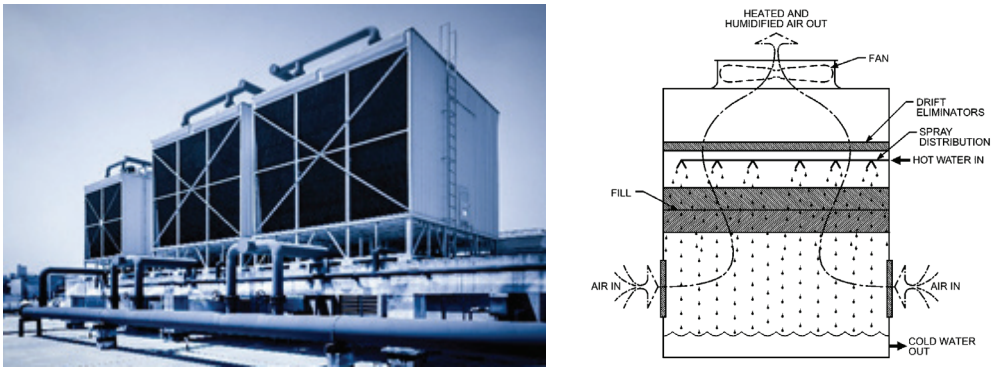

FIGURE 1-7 Photo and schematic of a cooling tower. SOURCES: Shutterstock and ASHRAE (2016).

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FIGURE 1-8 A faucet and a fine-mist showerhead showing the potential for aerosolization. SOURCE: Shutterstock.

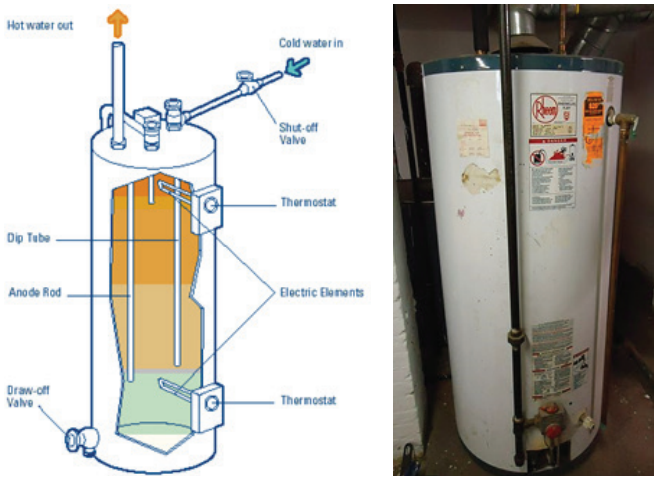

FIGURE 1-9 Schematic of an electric hot water heater and photo of a gas hot-water heater. SOURCES: https://buildingsfieldtest.nrel.gov/electric_resistance_water_heaters. © Government of Yukon (diagram) and WikiCommons (photo).

FIGURE 1-10 A hot tub, a humidifier, and a fountain. SOURCE: Shutterstock.

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Management of Legionella in Water Systems

In addition to the premise plumbing and fixtures typical of residential and commercial buildings, healthcare and medical facilities provide additional opportunities for both biofilm colonization and aerosolization due to specialized medical devices, such as dental units and hydrotherapy units. Moreover, compared with the general public, their susceptible patient populations are at risk of Legionnaires' disease of greater intensity or severity. In the United States there are more than 6,200 hospitals, with more than 930,000 beds[5]. In 2015 there were about 1.7 million nursing home beds in the United States[6]. According to the American Dental Association, there are almost 200,000 dentists in the United States[7].

Another major type of built environment that can generate *Legionella* risk are recreational water features, both outdoor and indoor. These include swimming pools, hot tubs, hot-spring baths, fountains (see Figure 1-10), and water parks, as biofilms can form on surfaces and contaminated aerosols can be generated. Recreational sources have resulted in several Legionnaires' disease outbreaks (Leoni et al., 2018). In the United States, there are an estimated 9 million swimming pools and 5 million hot tubs.[8]

Other less common locales in the built environment can provide conditions suitable for biofilm growth, and hence colonization by pathogens such as *Legionella* and their protozoan hosts. Among these locales are interior water features such as green walls and waterfalls (den Boer et al., 2002; Haupt et al., 2012) and external building features that introduce additional wetted and irrigated surfaces including green walls or roofs, particularly when collected or harvested water is used for domestic purposes (Hamilton et al., 2017). Irrigating, lawn sprinkling, and spray washing with stagnant water from hoses or fixtures may be of concern as well, especially when using recycled water treated to non-potable standards (Hamilton et al., 2018; Johnson et al., 2018). In several countries, wastewater treatment plants receiving industrial wastewaters with temperatures higher than 25°C have also been identified as sources of Legionnaires' disease (e.g., Loenenbach et al., 2018; Olsen et al., 2010) and Pontiac fever (e.g., Castor et al., 2005; Gregersen et al., 1999).

ORIGIN OF THE STUDY

In the 40 years since the discovery of *L. pneumophila*, much has been learned about its ecology; in contrast, less progress has been made toward preventing Legionnaires' disease or understanding the ecology of different species of pathogenic *Legionella* and their protozoan hosts. Most knowledge regarding Legionnaires' disease comes from investigations of disease outbreaks, in which two or more people are infected at the same time by the same source. Yet, only 4 percent of Legionnaires' disease cases are associated with known outbreaks and are thoroughly investigated (Hicks et al., 2011). Whether outbreaks accurately represent the exposure route of the numerous sporadic cases that go unreported remains unclear. Thus, improved monitoring of Legionnaires' disease in patient populations and of *Legionella* presence in water systems is critical to better understanding the disease burden and the likelihood for particular water systems to be sources of infection.

Though monitoring the disease incidence and the presence of *L. pneumophila* in water samples has evolved considerably over the past 20 years, controversies associated with each persist. For Legionnaires' disease, a urine antigen test or a (more difficult) sputum test are considered diagnostic, and yet such tests are not commonly performed for hospital patients with pneumonia. Furthermore, the urine antigen test only detects one of the 14 known serogroups of *L. pneumophila.* Because of these reasons, among others, the number of cases of Legionnaires' disease is grossly underestimated in the United States as well

[5] See https://www.aha.org/statistics/fast-facts-us-hospitals.
[6] See https://www.statista.com/statistics/323196/number-of-licensed-nursing-home-beds-in-the-us.
[7] See https://www.ada.org/en/science-research/health-policy-institute/data-center/supply-and-profile-of-dentists.
[8] See http://www.apsp.org/Portals/0/2016%20Website%20Changes/2015%20Industry%20Stats/2015%20Industry%20Stats.pdf.

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Management of Legionella in Water Systems

as in other countries that conduct surveillance. Water systems have traditionally been sampled using culture-based methods, which can take many days to detect growth and can be biased toward certain bacterial types. Polymerase chain reaction (PCR) methods exist, but their ability to differentiate between viable and nonviable organisms is still evolving. If routine monitoring of water systems for *Legionella* is to become standard practice for determining the risk of Legionnaires' disease for a given building or water system, accurate and quantitative microbiologic environmental testing is needed. Finally, although there is general agreement about the levels of detected *Legionella* that require remedial actions within a water system, there is no consensus on whether there is a threshold level of detected *Legionella* below which there is no risk of infection.

The treatment of water systems to reduce colonization by *Legionella* is further complicated by the bacterium's complex ecology. *Legionella* have developed multiple strategies to survive in the environment, including entering into a viable-but-non-culturable-like state, multiplying within a variety of protozoa including amoebae, and persisting within microbial biofilms. Indeed, its evolution of mechanisms to avoid digestion by its natural predatory hosts is thought to account for the virulence of certain strains of *Legionella* within human lung macrophages. Compared with bacteria in suspension, biofilms are relatively resistant to biocides and disinfectants, a primary means of treating built water systems. Other treatment methods involve raising water temperature beyond the growth range for the bacterium and host protozoa, reducing organic carbon levels in source water, altering pipe materials to discourage biofilm formation, and maintaining flow regimes in premise plumbing.

At best, a patchwork of laws, codes, policies, and guidance documents dictate how *Legionella* is managed in U.S. water systems and buildings. Healthcare facilities that are part of the Veterans Health Administration (VHA) system or that receive funding from the Centers for Medicare & Medicaid Services (CMS) must manage for *Legionella* contamination, but with varying requirements and oversight. Regulations to register, monitor, and treat cooling towers were put in place in New York City in the wake of the Bronx legionellosis outbreaks in the summer of 2015. New York State regulations now require all general hospitals and residential healthcare facilities to perform an environmental assessment, prepare and implement a sampling and management plan to test their potable water systems for *Legionella*, and institute control measures in the event of an exceedance. Similar and more widespread regulations for both cooling towers and buildings have existed in Australia, Canada, and some European countries for the past few years, and some are thought to have reduced the risk of Legionnaires' disease.

Beyond those buildings affected by the VHA and CMS requirements, management of legionellosis in the United States is mainly dictated via voluntary guidance documents from the American Industrial Hygiene Association, the American Society of Heating, Refrigerating, and Air-Conditioning Engineers, and the National Sanitation Foundation International, among others. Hence, *Legionella* management can be enforced only for a small subset of vulnerable buildings across the country. There is no federal law specifically targeting *Legionella.* The Surface Water Treatment Rule of the Safe Drinking Water Act only indirectly addresses *Legionella* via the requirement for maintaining a disinfectant residual in public water supply distribution systems that use surface water sources, and it does not extend to groundwater supplies or to building premise plumbing.

STUDY PURPOSE AND APPROACH

Following a May 2016 workshop on *Legionella* attended by representatives from around the world with expertise in public health, microbiology, and environmental engineering (Emory University, 2016), participants representing the National Academies of Sciences, Engineering, and Medicine sought to

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commence a consensus study on *Legionella* that could address the shortcomings previously mentioned. CDC, VHA, the U.S. Environmental Protection Agency (EPA), and the Sloan Foundation provided the funding for a project to address the Committee on Management of *Legionella* in Water Systems' statement of task (see Box 1-2).

BOX 1-2
Statement of Task

There are many questions and gaps in information concerning *Legionella pneumophila* and Legionnaires' disease that the proposed National Academies of Sciences, Medicine, and Engineering project would confront. An ad hoc committee of the National Academies will review the state of science with respect to *Legionella* contamination of water systems and issue a report that addresses the following:

Ecology and Diagnosis: Describe the microbial ecology of water supplies (from the source to the tap and within built systems) as it relates to *Legionella*. What strains of *L. pneumophila* are of most concern and how can their diagnosis be improved (e.g., in terms of increased specificity, simplicity, and speed)?

Transmission via Water Systems: What are the primary sources and routes of human exposure to *Legionella*? What features/characteristics of water systems make them more or less likely to support growth of *Legionella*?

Quantification: Considering surveillance data, case studies of outbreaks, hospital data, other routine testing of water systems, what is known about the concentration of *Legionella* in water systems and the prevalence of Legionnaires' disease over the last 20 years? How uncertain are these estimates and what can be done to reduce this uncertainty? How can quantitative risk assessment be improved?

Prevention and Control: What are the most effective strategies for preventing and controlling *Legionella* amplification in water systems? What are the best methods to prevent exposure to *Legionella*, especially in at-risk populations? Is there a minimum level of contamination required to cause disease? What are the benefits, risks, gaps in implementation, and barriers to uptake of *Legionella* control programs?

Policy and Training Issues: What policies, regulations, codes, or guidelines affect the incidence, control, quantification, and prevention of Legionnaires' disease? How might they be built upon to better protect the public? How can *Legionella* control be best balanced with other water priorities?

Research: For the sections above, what additional information gaps exist and what knowledge must be gathered to fill these gaps?

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Management of Legionella in Water Systems

ORGANIZATION OF REPORT

Chapter 2 discusses the diagnosis of Legionnaires' disease, the life history and complex ecology of *Legionella* in both natural and built water environments, and common exposure pathways. These active areas of research will require continued investment in order to improve the management of *Legionella* in water systems.

Chapter 3 focuses on the surveillance of Legionnaires' disease in the United States and Europe, as well as the environmental monitoring of *Legionella* that is becoming more common in built water systems. The need for a quantitative threshold of *Legionella* concentration above which action must be taken, and the role of quantitative microbial risk assessment, are extensively discussed in this chapter.

Chapter 4 considers the many strategies used to control *Legionella*, including the use of heat, biocides, flow control, aerosol formation prevention, and distal devices, along with their application in several typical built environments. The chapter also describes what is known about the efficacy of different control methods and their potential unintended consequences.

Finally, Chapter 5 reviews the array of laws, regulations, codes, standards, and guidance documents that relate to *Legionella* management, both in the United States and abroad. It includes suggestions for how these various policy tools can be strengthened to better protect the public from legionellosis.

Each chapter ends with conclusions and recommendations that synthesize more technical and specific statements found within the body of each chapter. The most important conclusions and recommendations are compiled in the report summary.

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2
Diagnosis, Ecology, and Exposure Pathways

Humans coexist with an abundance of microbes, organisms so small they are invisible to the naked eye. The vast majority are benign and many are beneficial, yet everyone can name microbes that cause disease. Although it is convenient to classify microorganisms as either friend or foe, such a distinction masks more complex interactions that dictate whether the human–microbe encounter promotes disease or health. In general, the impact of exposure to a particular microbe depends on the balance of three factors: the quantity of microorganisms, their capacity to cause harm, and the strength of an individual human's defenses (see Figure 2-1).

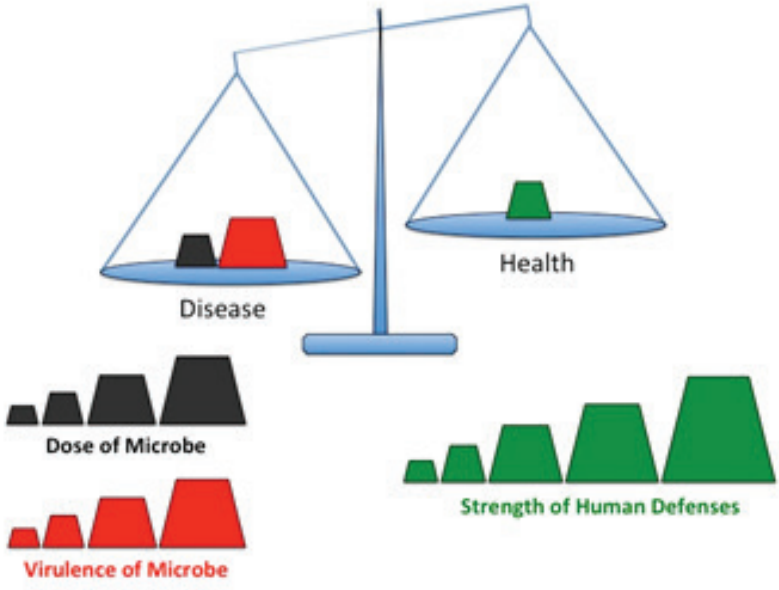

FIGURE 2-1 Consequence of exposure to microbial pathogens. The outcome of a host-microbe interaction depends on multiple factors: the dose, or quantity, of microbes; their virulence, or capacity to cause harm; and the strength of the human defenses. In the example shown, a robust immune response would tip the balance in health's favor. SOURCE: Adapted from Swanson et al. (2016). American Society for Microbiology, Copyright 2016; adapted with permission. No further reproduction or distribution is permitted without the prior written permission of the American Society for Microbiology.

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Management of Legionella in Water Systems

To tip the balance toward infection, all microbes, including *Legionella*, must surmount multiple challenges. First, microbes need to encounter a susceptible host. For *Legionella*, aerosols of contaminated water or soil can disperse these bacteria, exposing people in the vicinity. Second, the microbe has to enter the host. When inhaled or aspirated, aerosols (less than 10 μm in diameter) can carry *Legionella* into aveoli in the lungs. Third, to initiate an infection, microbes must breach inborn defensive barriers. In the case of Legionnaires' disease, a respiratory tract damaged by cigarette smoke, for example, offers an increased opportunity to establish infection. Finally, to cause disease, the infecting microbe needs to inflict damage. The trauma may be direct, such as when a bacterial toxin punctures host cells, or an indirect effect of a hyperactive inflammatory response, for example. Legionnaires' disease injures lung tissue and protective lung macrophages, a consequence of not only factors released by virulent bacteria, but also a robust inflammatory response that wreaks collateral damage. Bearing in mind these four prerequisites to infection, one can understand why combinations of exposure, *Legionella* loaded with an arsenal of virulence factors, and/or impaired human immune defense barriers create opportunities for some *Legionella* strains to establish severe lung infections. How the interplay among host defenses, *Legionella pneumophila* biology, and the ecology of engineered water systems alter the balance between health and disease is the focus of this chapter.

HUMAN HOST

The majority of Legionnaires' disease cases (from 80 to 90 percent in Europe and the United States) are linked to *L. pneumophila* (Beauté et al., 2013; Cross et al., 2016; Dooling et al., 2015; von Baum et al., 2008; Yu et al., 2002). However, since its discovery in the 1970s, more than 61 species and 3 subspecies of *Legionella* have been described, half of which have been isolated from patients (e.g., Hazel et al., 1987; Jaeger et al., 1988; Khodr et al., 2016; Vaccaro et al., 2016). In people with weakened immune systems, species other than *L. pneumophila* that are frequently isolated include *L. micdadei, L. bozemanii, L. dumoffi* and *L. longbeachae* (Cunha et al., 2016; Rucinski et al., 2018). In Oceania and parts of Asia, disease due to *L. longbeachae* approaches or exceeds that for *L. pneumophila* (Whiley and Bentham, 2011).

Human and financial burdens due to *Legionella* are substantial. *Legionella* species (spp.), particularly *L. pneumophila*, can cost from $26,000 to $38,000 per hospital admission (Collier et al., 2012). More importantly, *Legionella* infections can be morbid, leading to prolonged hospitalization and often intensive care admission. Mortality rates of legionellosis range between 2.9 and 33 percent (Burillo et al., 2017; Cunha, et al., 2016; Gargano et al., 2017; Greenberg et al., 2006; Mykietiuk et al., 2005). Death is more likely for people who are immunocompromised (del Castillo et al., 2016; Han et al., 2015; Lanternier et al., 2017; Pedro-Botet et al., 1998; Sivagnanam et al., 2017), admitted to the intensive care unit (Chidiac et al., 2012; Cunha et al., 2016; von Baum et al., 2008), receive delayed antibiotics (Heath et al., 1996), or who develop hospital-acquired legionellosis (Jesperson et al., 2010; Soda et al., 2015; Stout et al., 2003).

As introduced in Chapter 1 and further explained in Chapter 3, *Legionella* pneumonia is a significantly underreported disease (Beauté et al., 2013; Jong et al., 2010; Neil and Berkelman, 2008). Incidence varies even when legionellosis is reported, likely because of differences in local ecology, water sources, temperature and weather patterns (Fisman et al., 2005; Ricketts et al., 2018), testing availability (Pierre et al., 2017), and surveillance of and methods for reporting incident cases. In the Etiology of Pneumonia in the Community (EPIC) study evaluating community-acquired pneumonia, *Legionella* pneumonia was the eighth most common pathogen identified for patients requiring hospital admission in five hospitals in Nashville, Tennessee, and Chicago, Illinois (Jain et al., 2015). Even this high ranking was conservative, as the EPIC study data only included assessment of *L. pneumophila* serogroup 1 and excluded high-risk

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Management of Legionella in Water Systems

immunosuppressed patients or those with prior hospitalization. The Competence Network for Community-Acquired Pneumonia (CAPNETZ) study in Germany, which used culture, urinary antigen, and polymerase chain reaction (PCR) testing of samples, found that 97 out of 941 (9.6 percent) of all community-acquired pneumonia cases were due to legionellosis, the majority of which were attributed to *L. pneumophila* (von Baum et al., 2008). Non-*pneumophila* presentations of legionellosis, limited testing, use of empiric therapy, and lack of consensus for the epidemiological definition of presentations such as Pontiac fever (Tossa et al., 2006) further contribute to underreporting (Whiley et al., 2014). Furthermore, rates of disease caused by non-*pneumophila Legionella* spp. and non-serogroup 1 *L. pneumophila*, for which there are more limited diagnostic modalities, are also thought to be underestimated (Benin et al., 2002; Lode et al., 1987; Muder and Victor, 2002). Serological testing of blood donors indicates that exposure to *Legionella* may be higher than generally appreciated, with seroprevalence ranging between 4 and 22 percent and up to approximately 40 percent in some cities or among those with high-risk occupations (Borella et al., 2008; Coniglio et al., 2009; Nadaraja et al., 1987; Rudbeck et al., 2008; Valciņa et al., 2015).

Increasing Incidence

Studies worldwide have shown increasing incidence of *Legionella* cases (Beauté, 2017; Burillo et al., 2017; Neil and Berkelman, 2008). In the United States, reported cases increased five-fold from 2000 to 2017 (see Figure 1-2). The causes of this increase are not well characterized, but are thought to be multifactorial. Methods to detect *Legionella* in clinical samples are now both easier to perform (e.g., urinary assays) and more readily available outside of large academic laboratories, making their use increasingly common (Pierre et al., 2017). Community-acquired pneumonia national guidelines (Bradley et al., 2011; Mandell et al., 2007) and prediction tools (Cunha, 1998; Fiumefreddo et al., 2009; Miyashita et al., 2017) have both helped increase awareness of *Legionella*. However, these guidelines, aimed at community practioners, were created to streamline diagnostic work-up and antibiotic management. Indeed, most current guidelines recommend that even low-risk patients receive empiric antibiotics that include either a macrolide (in combination with a beta-lactam or cephalosporin or as the primary agent, depending on host risk factors) or a respiratory flouroquinolone (moxifloxacin or levofloxain) (Yu et al., 2004). These agents not only target many common causes of pneumonia, such as *Streptococcus pneumonia* and *Moraxella catarhallis*, but also cover atypical pneumonia pathogens including *Mycoplasma pneumoniae* and *Legionella* spp. Although such guidelines promote prompt administration of appropriate empiric therapy for patients with pneumonia, providers of such early antibiotic therapy may actually be less apt to pursue diagnostic testing for legionellosis. This tendency is particularly true for mild cases, as some guidelines only recommend testing for patients who have severe disease or are admitted to the intensive care unit (Mandell et al., 2007).

Changing demographics, such as the aging population, may contribute to the rise in disease incidence as well. From 1970 to 2018, the median age in the United States has increased by nearly ten years, such that Americans aged 65 and older now make up a larger portion of the U.S. population (CDC, 2013). And the number of elderly Americans is predicted to increase. Immune senescence of both innate and adaptive immunity plays an important role in increased risk among the elderly population (Boe et al., 2017). Enhanced survival of high-risk patients (e.g., those with an underlying condition such as cancer, cardiac disease, or lung disease) may also contribute to the increased incidence trend. Likewise, the increasing number of patients with compromised immunity due to immunosuppressive therapies and prolonged survival among higher-risk immunosuppressed patients may contribute to increasing legionellosis incidence. Although likely an underestimate, current data suggest that at least 2.7 percent

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Management of Legionella in Water Systems

of Americans consider themselves immunosuppressed (Harpaz et al., 2016), indicating nearly 9 million at-risk individuals in the United States by this criterion alone. With the increasing number of agents that modify immune responses, improvements in survival, and the number of conditions that are currently treated with immunosuppressive therapy, this susceptible population is expected to increase. Specific immuncompromised populations are known to be growing. For example, the United Network of Organ Sharing reported a doubling of the number of patients receiving a solid organ transplant over the past 20 years[1]. Likewise, the National Cancer Institute estimates that the number of cancer survivors will increase by 30 percent over the next decade.[2]

Increasing population density in cities served by aging, centralized water systems (and including more cooling towers) may elevate the risk of legionellosis. Indeed, the American Society of Civil Engineers gave the U.S. water infrastructure a "D" rating (ASCE, 2017), noting that many pipes laid in the mid-20th century are now beyond their expected lifespan, increasing their risk for main breaks and intrusion, corrosion-enhanced biofilm development, and colonization with *Legionella*. Exposure in daily life may be more frequent due to increasing contact with water products and water devices, particularly those ideally suited for *Legionella* growth (e.g., cooling towers; hosing, faucets, and showerheads; hot tubs, Jacuzzis, and spas [collectively called hot tubs in this report]; humidifiers; fountains).

Additionally, climatic changes, including increased rainfall and global temperatures, have been linked to increasing disease incidence, either directly or through increased use of water sources linked to legionellosis. Most climate work has focused on the effects of temperature and rainfall events. Clear seasonality to *L. pneumophila* exposure has been established by multiple studies (European Centre for Disease Prevention and Control, 2013; Marston et al., 1994). For example, a PCR screen of more than 44,000 respiratory specimens over a recent eight-year period in Rochester, MN, documented annual peaks during the warm, humid months (Rucinski et al., 2018). Likewise, risk of disease increased during warm, wet periods in the mid-Atlantic region of the United States, as well as The Netherlands, Spain, and Taiwan (Chen et al., 2014; Fisman et al., 2005; Garcia-Vidal et al., 2013, reviewed by Walker 2018; Hicks et al., 2007; Karagiannis et al., 2009; Simmering et al., 2017). Cassell et al. (2018) suggests that precipitation is associated with the risk of sporadic Legionnaires' disease, noting a 48 percent increased risk of legionellosis two weeks after a 5-mm average increase in rainfall. With increasing global temperatures, more precipitation and flooding in some regions, and rising sea levels, there is concern that *Legionella* and other waterborne infections will continue to increase.

Worldwide, the actual burden of Legionnaires' disease is generally acknowledged to be underreported as a consequence of the generally low rate of diagnostic testing coupled with the reliance on a diagnostic test that is highly specific for a single serogroup of *L. pneumophila* (Dooling, 2015; Mercante and Winchell, 2015; Phin et al., 2014; St-Martin et al., 2013; von Baum et al., 2008). During a three-year period in Germany, about 10 percent of Legionnaires' disease patients were infected with species other than *L. pneumophila* (von Baum et al., 2008). Over a ten-year period in Denmark, 40 percent of the Legionnaires' disease cases that were confirmed by laboratory culture were caused by *L. pneumophila* that were not serogroup 1 (St-Martin et al., 2013). Similarly, in the United States, for the Legionnaires' disease cases reported from 2011 to 2013 to the Centers for Disease Control and Prevention's (CDC) Active Bacterial Core Surveillance network, 9 percent of the 140 culture-confirmed cases were due to non-serogroup 1 *L. pneumophila* (Dooling et al., 2015). Also troubling is the higher mortality among patients infected with these non-serogroup 1 strains compared with serogroup 1 *L. pneumophila* (Marston et al., 1994; Mercante and Winchell, 2015; St-Martin et al., 2013). These differences could be because of differences in those at risk for these pathogens or because of the lack of commonly available diagnostic tools, which delays identification. Finally, sole reliance on the urine antigen test hampers efforts to recognize

[1] See https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#.
[2] See https://www.cancer.gov/ about-cancer/understanding/statistics.

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Management of Legionella in Water Systems

and interrupt outbreaks, as epidemiological investigations require discriminatory genetic tests of clinical and environmental *L. pneumophila* isolates (Mercante and Winchell, 2015).

Risk Factors for *Legionella* Disease

Numerous factors are linked to increased risk of legionellosis, varying from host factors to exposure factors. Indeed, in large outbreaks not everyone who is exposed to *Legionella* develops disease (Bartram, 2007; Phin et al., 2014). Male adults are at higher risk (Cunha et al., 2016; MacIntyre et al., 2018; WHO, 2018). Indeed, in the United States the incidence of reported cases of legionellosis in men (2.31/100,000) was approximately 50 percent higher than in females (1.50/100k) in 2016. Age is also commonly identified as a risk factor for legionellosis, with most studies suggesting risk begins increasing at approximately age 40 to 50 years (Bartram, 2007; Farnham et al., 2014; Sopena et al., 2007). Data on children are more sparse, but suggest that children may be less likely to develop severe infections (Greenberg et al., 2006; Muldoon et al., 1981; Yu and Lee, 2010). In one review of case reports, the majority of children who became ill had other at-risk diseases (e.g., cancer) and more than half were under the age of one (Greenberg et al., 2006). More than 70 percent of pediatric legionellosis cases may be hospital-acquired, suggesting either less clinical disease or underdiagnosis in the community (Alexander et al., 2008). Neonates may be at highest risk for hospital-acquired legionellosis because of both increased exposures and their weaker immune status (Levy and Rubin, 1998). Although infrequently reported, water births have been linked to some cases of neonatal legionellosis (Frazin et al., 2001; Ganseth et al., 2017).

Populations with jobs that increase occupational exposure to water are also at risk of legionellosis (Principe et al., 2017). Among these populations are water-service providers, maintenance workers, wastewater and cleaning personnel, and workers in industries that use industrial water sprayers (e.g., paper and textile mills, plastic molding factories).

Another classical demographic risk factor for legionellosis is impaired immunity, either through anatomic changes to the airway or weakened barriers to respiratory pathogens. Indeed, age-related immune senescence is thought to be an important reason why rates are higher among older patients. Smoking is a clear dose-dependent risk factor and possibly contributes to the higher incidence of cases reported for males than females. Smoking also changes the airway epithelium, perturbs pulmonary cilia function, decreases airway clearance, and alters the aerodigestive microbiome, factors each thought to increase the risk for bacterial pneumonias, including those caused by *Legionella* spp. (Arcavi et al., 2004; Gao et al., 2014; Morris et al., 2013). Not only are those who smoke at higher risk than those who have never smoked, but those who have smoked more than 20 cigarettes per day for more than 20 years have a risk 25 times greater than that of non-smokers as well as a higher incidence of disease during outbreaks (Che et al., 2008). Risk and severity of illness may be further increased by smoking-related complications such as chronic obstructive pulmonary disease or emphysema (El-Ebiary et al., 1997). Even exposure to second-hand smoke has been suggested to increase risk (Wang et al., 1995).

Another population vulnerable to *Legionella* pneumonia is patients at increased risk of aspiration, such as those with neuromuscular diseases, the elderly, and neonates (Blatt et al., 1993; Wei, 2014). (Indeed, studies suggest that episodes of silent aspiration are significantly more common among elderly patients when compared to age-matched controls [Kikuchi et al., 1994]). Researchers have hypothesized that the "microaspiration" that occurs during drinking or with particular clinical conditions may deliver *Legionella* to the lung and cause pneumonia (Lee and Ryu, 2018; Marrie et al., 1991). The oropharynx (Jaresova et al., 2006) and dental plaques (Tesauro et al., 2018) may also be colonized with *Legionella,* which would increase the likelihood of aspiration. Still, exposure pathways related to aspiration are

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Management of Legionella in Water Systems

more difficult to investigate unless clearly linked to feeding tubes or other mechanical methods associated with tap water and aspiration (Dournon et al., 1982; Marrie et al., 1991; Muder et al., 1992; Venezia et al., 1994; Yu, 1993).

Patients with known impaired immune function, including those with organ dysfunction, are also at increased risk for legionellosis. Patients undergoing treatment for cancer and those who have received a solid organ transplant may be at highest risk because of the depth and length of immunosuppression required (del Castillo et al., 2016; Jacobson et al., 2008; Lanternier et al., 2017; Sivagnanam and Pergam, 2016). These patients are also at increased risk for non-*pneumophila* legionellosis and non-serogroup 1 *L. pneumophila* infections (Ampel et al., 1990; Dowling et al., 1984; Knirsch et al., 2000; Muder and Victor, 2002; Singh et al., 2004). Particular immunosuppressive agents have been linked to legionellosis, chiefly glucocorticoids such as prednisone (Htwe and Khardori, 2017). Patients receiving tumor necrosis factor inhibitors for rheumatologic and inflammatory bowel diseases are also at increased risk for legionellosis (Lanternier et al., 2013). Likewise, patients with renal dysfunction (including those on dialysis), liver disease, lung disease, and known cardiac dysfunction are more susceptible to legionellosis (Chidiac et al., 2012; Ongut et al., 2003; Viasus et al., 2013).namely high body temperature (OR 1.67, $p < 0.0001$ Immunosuppressed patients also have increased severity of disease including intensive care unit (ICU) admission, intubation, and death.

Genetic predisposition may account for enhanced susceptibility to disease from *Legionella* spp. in those with or without other risk factors (Berrington and Hawn, 2013). Legionellosis is linked to genetic polymorphisms in three human Toll-like receptors (i.e., TLR-4, TLR-5, and TLR-6), components of the innate immune system that recognizes pathogen-associated molecular pattern (PAMP) molecules (Hawn et al., 2003, 2005; Misch et al., 2013). Also associated with an increased risk for legionellosis is a common haplotype of the GMP-AMP synthase-stimulator of interferon genes (STING) pathway (HAQ TMEM173/STING), which is central for innate immune sensing of bacterial infections (Ruiz-Moreno et al., 2018).

Clinical Manifestations of Legionellosis

Legionella spp. cause clinically significant disease among susceptible human hosts. The most common manifestations are pneumonia (i.e., classical Legionnaires' disease) and Pontiac fever. Diagnosis can be challenging as many clinical signs and symptoms typical of legionellosis are often found in both infectious and non-infectious diseases (see Figure 2-2) (Cunha, 1998; Phin et al., 2014). More rarely, *Legionella* spp. have been associated with skin and soft-tissue infections, bacteremia, endocarditis, and septic arthritis (Banderet et al., 2017; Heriot et al., 2014; Kilborn et al., 1992; Pearce et al., 2011; Qin et al., 2002).

Worldwide, *Legionella* pneumonia is the most common manifestation of legionellosis. *Legionella* pneumonia is often classified as an "atypical pneumonia" along with those caused by bacterial pathogens such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. When compared with common bacterial pneumonia agents, atypical pneumonias may present common symptoms and radiologic findings and less common presentations (e.g., diffuse interstitial patterns on chest x-ray). Clinical and radiologic findings cannot distinguish between these pathogens and other causes of community-acquired pneumonia. However, they respond to antibiotic classes and agents that primarily target intracellular infections (Sharma et al., 2017). Following exposure, *L. pneumophila* has an incubation period of approximately two to ten days (Bartram, 2007). About 10 percent of cases have an incubation period longer than ten days, such that case information should be collected for a minimum of 14 days prior to onset of symptoms for community cases.[3] Likewise, incubation periods may be longer for hospitalized populations, which of-

[3] See https://legionnaires.ecdc.europa.eu/?pid=107.

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Management of Legionella in Water Systems

FIGURE 2-2 Clinical symptoms of legionellosis: Pontiac fever and *Legionella* pneumonia (Legionnaires' disease). SOURCE: Courtesy of Kyoko Kurosawa.

ten include immunosuppressed hosts (Bargellini et al., 2013). Finally, the incubation period may also be dose-dependent (Prasad et al., 2017).

Initial symptoms of Legionnaires' disease typically include fever, cough, and myalgias. Other commonly reported symptoms include headache, confusion, shortness of breath, sputum production, anorexia, nausea, and diarrhea; patients with community-acquired pneumonia who present with neurologic and gastrointestinal symptoms may be more likely to have legionellosis (CDC, 2017; Cunha, 1998). Some patients with *Legionella* pneumonia present with acute respiratory failure, hypotension, and sepsis-like signs that can mimic other common causes of bacterial pneumonia (e.g., *Streptococcus pneumoniae*). In contrast, patients who are immunosuppressed may present without fever, cough, or other more typical symptoms (del Castillo et al., 2016; Sivagnanam and Pergam, 2016).

Pontiac fever presentation is less specific and therefore less frequently reported. It is often described as a "flu-like" illness, with fever, headaches, and myalgias as the primary symptoms; chills, vertigo, diarrhea, and physical weakness or lack of energy (asthenia) are other symptoms (Tossa et al., 2006). Pontiac fever cases are defined in part by their absence of pneumonia. Since many other illnesses resemble Pontiac fever, the diagnosis usually relies on the recognition of typical clinical features during an outbreak situation; therefore, sporadic cases are likely to be missed (Murdoch, 2003). Pontiac fever in particular may be underdiagnosed in children, whose febrile illnesses are frequent and often self-limited (Qin et al., 2002).

It is unclear why patients develop Pontiac fever rather than pneumonia; consequently, the pathogenesis of the disease remains unclear. Several pathways for Pontiac fever have been hypothesized, including bacterial toxins, allergic responses, and exposure and reaction to *Legionella*-carrying ameobae (Edelstein, 2007). A self-limiting disease, Pontiac fever does not require treatment with antibotic therapy, leading some to hypothesize that the disease is not directly related to infection by these bacteria. At the same time, there have been outbreaks where patients who develop Pontiac fever have positive urinary antigen testing, suggesting that the disease is associated with ingestion or inhalation of either live or dead microorganisms (Burnsed, 2007). Mechanism of exposure may also play a role, as some recreational outbreaks have been linked to both *Legionella* pneumonia and Pontiac fever, whereas others are tied only to Pontiac fever (Euser et al., 2010; Leoni et al., 2018).

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Management of Legionella in Water Systems

Not all *Legionella* spp. are thought to cause Pontiac fever, as the disease is most frequently linked to *L. pneumophila* exposures. Similar to pneumonia, however, non-*pneumophila* species such as *L. feelii, L. micdadei,* and *L. bozemanii* can also cause Pontiac fever (Cramp et al., 2010; Fentersheib et al., 1990; Fields et al., 2001; Herwaldt et al., 1984; Huhn et al., 2002). Only one study has suggested Pontaic fever was associated with exposure to water sources with higher concentrations of *Legionella* spp. (i.e., more than 10^3 colony forming untis per liter [CFU/L]) (Remen et al., 2011). Interestingly, in the same study, younger nursing staff were at higher risk, suggesting immune responses to prolonged or prior exposures may provide protection from this form of disease. Species-specific strains or particular bacterial activities themselves may be critical to disease outcomes. For example, a *L. fellii* serogroup with a monopolar flagellum associated with *Legionella* pneumonia showed a higher cell infection rate, stronger internalization by host cells, and greater cytotoxicity in vitro than a different *L. fellii* serogroup without a flagellum that was associated with Pontiac fever (Wang et al., 2015a). The lower risk associated with Pontiac fever, the limited diagnostic work-up, and the rarity of documented positive cultures linked to the disease make studies of pathogenesis difficult. Regardless of the outstanding questions concerning the pathogenesis of Pontiac fever, it is clear that exposure to water or soil contaminated with *Legionella* spp. is required for the development of the disease.

Diagnosis of Legionellosis

Presenting Laboratory Findings

Beyond clinical symptoms, laboratory findings may point to a diagnosis of *Legionella* pneumonia. Patients can present with either leukocytosis or leukopenia, hyponatremia, elevated liver enzymes, and renal dysfunction. Non-specific blood tests that suggest inflammation (e.g., C-reactive protein) can also be elevated (Fiumefreddo et al., 2009). Clinical prediction tools, such as the Winthrop-University Hospital criteria (Cunha et al., 1998), Community-Based Pneumonia Incidence Study Group score (Fernández-Sabé et al., 2003), Japan Respiratory Society score (Yanagihara et al., 2001) and a six-parameter clinical score developed by Fiumfreddo and colleagues (2009) are thought to have poor sensitivity for legionellosis, but may be useful for their negative predictive value (Miyashita et al., 2017).

Radiology

There are no unique radiologic findings specific for legionellosis. For *Legionella* pneumonia, chest radiographs often demonstrate focal infiltrates or consolidations consistent with pneumonia (Poirier et al., 2017). Computed tomography (CT) findings may show multi-lobar or air-space disease with associated ground-glass opacities; and lymphadenopathy and pleural effusions may be seen as well (Mittal et al., 2017). Among the immunocompromised, *Legionella* can present as pulmonary nodules with or without cavitation (del Castillo et al., 2016; Mittal et al., 2017). Patients with Pontiac fever are defined by their lack of findings on radiologic imaging.

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Management of Legionella in Water Systems

Legionella-Specific Diagnostics

Culture. Cultures can be collected from pulmonary and extra-pulmonary sites (Mercante and Winchell, 2015). *Legionella* requires special culture media, most commonly buffered charcoal yeast extract agar (see Descours et al., 2014, for a recent analysis of different media). Growth usually occurs within three to five days, although two weeks may be required, as antibiotics used to reduce background respiratory microbiota can inhibit *Legionella* growth (Pierre et al., 2017). Growth from clinical samples may be limited or delayed if, prior to specimen collection, patients have been given antibiotics targeting *Legionella* spp. Non-*pneumophila Legionella* spp. tend to be more fastidious, may require longer incubation times (Mercante and Winchell, 2015), may be inhibited by some culture media (Lee et al., 1993), and require considerable technical laboratory expertise to culture (Lucas et al., 2011). Most culture-based systems are optimized for *L. pneumophila* and may limit growth of non-*pneumophila* species. Another complication arises when patients have multiple strains of *Legionella* during an active infection (Coscolla et al., 2014; Zhang et al., 2014). Because of these challenges, most hospital-based laboratories do not routinely test for *Legionella* spp. by culture. Yet, cultures are critically important to epidemiologic investigations, as they allow for analysis of relatedness within clusters and between clinical and environmental samples. In the United States culture diagnosis has declined from more than 60 percent in the early 1990s to 5 percent from 2005 to 2009 (Mercante and Winchell, 2015). In Europe, where cultures are more often utilized, 79 percent of culture-confirmed cases were reported as *L. pneumophila* serogroup 1 (ECDC, 2019).

Urinary Assay. The *Legionella* urinary antigen test (UAT) is the most frequently used method for legionellosis diagnosis in the United States (Mercante and Winchell, 2015). The UAT is routinely available on-site at 25 percent of acute-care hospitals (Garrison et al., 2014) and commercial laboratories. The test is popular because of the rapid turn-around time for on-site laboratories, ease of use, high sensitivity, and the ability to identify *L. pneumophila* serogroup 1, the most prevalent *Legionella* spp. associated with clinical disease, without the need for invasive procedures. However, the UAT can be negative very early in the disease and is of limited value in patients who cannot produce urine (anuric), e.g., due to kidney failure. On the other hand, the UAT can remain positive for months after an infection, particularly in immunosuppressed patient populations (Kashuba and Ballow, 1996; Kohler et al., 1984; Munoz et al., 2009). A major limitation of diagnosis strategies that focus on the UAT alone is their failure to detect important non-serogroup 1 *L. pneumophila* infections and non-*pneumophila* infections.

Serology. Acute and convalescent titers for *Legionella* may be helpful in documenting *Legionella* exposures, but have limited sensitivity for confirmation of Legionnaires' disease (Botelho-Nevers et al., 2016; Plouffe et al., 1995). Indeed, up to 20 to 30 percent of patients with proven *Legionella* may not mount an antibody response sufficient for diagnosis (Benz-Lemoine et al., 1991). For patients with altered immunity, the sensitivity and the specificity of seroconversion to non-*pneumophila Legionella* spp. is unclear (Reller et al., 2003). Even with the presense of high levels of antibody, one cannot differentiate recent versus past exposure, limiting the use of serology in acute infections (Mercante and Winchell, 2015). Serological testing for *Legionella* can also cross-react with *Coxiella burnetti* (the agent of Q fever) and *Mycoplasma pneumoniae*, among others (Boswell et al., 1996; Musso and Raoult, 1997).

Serology can provide important information for epidemiologic investigations. In a large outbreak in Norway, acute-phase *Legionella* tests (i.e., culture, UAT, and PCR) detected about 56 cases, whereas serology detected an additional 47 cases (Simonsen et al., 2015). Thus, serology may identify individuals with less severe disease and symptoms (e.g., Pontiac fever) who might otherwise be missed during large industrial exposures and outbreaks. Nevertheless, the use of serology diagnosis for either sporadic disease or outbreak investigation has declined (Mercante and Winchell, 2015).

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Management of Legionella in Water Systems

Direct Fluorescent Antibody Testing. Direct fluorescent antibody (DFA) testing is infrequently used to diagnose *Legionella*. The sensitivity of DFA can be very low (11 to 40 percent) (Hayden et al., 2001; She et al., 2007), and it often does not detect non-*pneumophila Legionella* spp. (Reller et al., 2003). Although some argue DFA has high specificity when positive, caution is needed as a positive DFA in the absence of other supportive evidence is thought to be insufficient for *Legionella* diagnosis (Haldane et al., 1993; Reller et al., 2003).

Molecular Testing. Polymerase chain reaction (PCR) and other nucleic acid amplification tests are highly sensitive assays for lower respiratory tract specimens but are primarily available in referral or research laboratories. Most published studies utilize PCR testing that targets the gene encoding the macrophage infectivity potentiator (*mip*) surface protein of *L. pneumophila* (Phin et al., 2014). One study found a four-fold increase in *Legionella* case detection with PCR testing of lower-respiratory specimens compared to culture (Murdoch et al., 2013), and another found only 40 percent of PCR-positive specimens were also culture-positive (Rucinski et al., 2018). Compared to UAT, PCR tests may be more sensitive, detecting an additional 18 to 30 percent of cases (Avni et al., 2016). PCR may have the advantage for *Legionella* diagnosis in patients already on empiric therapy with *Legionella* active antibiotics, which limit bacterial growth by culture.

Most PCR methods currently detect serogroup 1 strains but cannot distinguish among *L. pneumophila* serogroups (Benitez and Winchell, 2013), and most probes target *L. pneumophila* specifically. There are newer PCR assays that target common non-*pneumophila* species including *L. longbeachae, L. micdadei,* and others (Cross et al., 2016). Broader *Legionella* spp. PCR tests have been developed (Benitez and Winchell, 2013; Chen et al., 2015), but to date only one test has been approved by the U.S. Food and Drug Administration (FDA) for testing of clinical samples. The BioFire® FilmArray® Pneumonia Panel is a multiplex PCR respiratory panel that detects 33 different respiratory pathogens, including *L. pneumophila*. The assay was approved in November 2018 for sputum, endotracheal aspirates, and bronchoalveolar lavage (or mini-BAL) lower-respiratory tract samples. PCR assays have been licensed in Europe, but most available assays are primarily laboratory-developed assays of variable sensitivity (Ricci et al., 2018). Of note, PCR is less sensitive for non-respiratory samples (e.g., blood; Avni et al., 2016; von Baum et al., 2008).

Pharmaceutical Therapy

Legionella spp. are intracellular pathogens that not only avoid phagosome–lysosome fusion and degradation, but also replicate within alveolar macrophages and epithelial cells (Newton et al., 2010). Therefore, the mainstay of drug therapy for legionellosis are antibiotics that target the intracellular space. Guidelines in the United States and in Europe recommend macrolides and fluoroquinolones as first-line therapy (Mandel et al., 2007; Pea, 2018; Woodhead et al., 2011). Macrolides work primarily by disrupting the 50S subunit of bacterial ribosomes, thereby inhibiting protein synthesis, which is critical for the microbe's survival. Most early studies evaluated the macrolides erythromycin and clarithromycin, but azithromycin is the preferred agent as it is better tolerated (Langley et al., 2004), associated with fewer side effects than other macrolides, and is the most effective macrolide in animal models (Fitzgeorge et al., 1990; Plouffe et al., 2003).

Compared with macrolides, fluoroquinolones, which inhibit bacterial DNA gyrase and topoisomerase IV enzymes, are more potent against *Legionella* spp. in both in vitro and in vivo models of infection (Pedro-Botet and Yu, 2009). Currently, there is no randomized clinical trial comparing macrolides to

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Management of Legionella in Water Systems

fluoroquinolones for antibiotic therapy of legionellosis. However, in non-randomized, observational studies, fluoroquinolones were more effective than macrolides (i.e., erythromycin and clarithromycin) in fever resolution and length of hospitalization (Burdet et al., 2014; Garcia-Vidal et al., 2017; Griffin et al., 2010). Despite therapy, mortality rates for cases treated with both drug classes remain around 10 percent (Burdet et al., 2014).

Beyond macrolides and fluoroquinolones, other agents such as rifampin/rifampicin, tetracyclines, and trimethoprim-sulfa are used, sometimes in combination (Pedro-Botet and Yu, 2009). Although data are limited, some experts recommend that patients with severe clinical illness may benefit from combination therapy (Nakamura et al., 2009; Varner et al., 2011).

Selection for antibiotic-resistant *Legionella* is considered very limited, as humans are a dead end in the life cycle of *Legionella* spp. Indeed, just one case of suspected person-to-person tranmission has been reported in more than 40 years (Correia et al., 2016). Although infrequent, there are data demonstrating both clinical failures and *Legionella* that, under macrolide pressure, have documented macrolide resistance primarily through mutations in the bacterial ribosome (Descours et al., 2017; Dowling et al., 1985; Nielsen et al., 2000). To date, fully resistant strains have not been observed in wild-type isolates (Vandewalle-Capo et al., 2017). There is also concern that widespread use of azithromycin for other conditions among hospitalized patients could lead to increased resistance in *Legionella* (Torre et al., 2018). Similar to macrolides, rare resistance to fluoroquinolones has been identified, primarily through changes in bacterial DNA gryrase genes (Almahmoud et al., 2009; Bruin et al., 2014; Jonas et al., 2003).

LEGIONELLA SPECIES AND STRAINS

The *Legionella* genus is in constant flux, blurring the boundaries between species. Variation is generated by high rates of genetic exchange among species as well as by homologous recombination between exogenous DNA and the bacterial chromosome (Gomez-Valero et al., 2014, 2019; Joseph et al., 2016; Sanchez-Buso, 2014). Within the genus, both genome size and guanine-cytosine (GC) content vary widely (see Figure 2-3). Furthermore, among the pangenome of 80 sequenced *Legionella* strains representing 58 species, only 6 percent of the genes were encoded by each genome examined (Gomez-Valero et al., 2019). For example, although the flagellar regulon contributes to *L. pneumophila* infection of macrophages and amoebae (reviewed by Appelt and Heuner, 2017), flagella genes were absent in 23 of 80 sequenced genomes from 58 *Legionella* spp. (Gomez-Valero et al., 2019).

To further guide diagnosis and identification of the environmental source of the infectious bacteria, *L. pneumophila* strains can be classified by several techniques. Terms commonly used to describe particular isolates of bacteria are explained in Figure 2-4.

L. pneumophila can be divided into serogroups according to the structure of its lipopolysaccharide (LPS), a component of the outer membrane of these Gram-negative bacteria and the predominant antigen recognized by the human immune system (Ciesielski et al., 1986; Conlan and Ashworth, 1986). Although 16 distinct "serogroups" of *L. pneumophila* have been identified, the majority of disease cases are caused by serogroup 1 strains. For example, in Europe from 2011 to 2015, serogroup 1 strains were associated with 83 percent of the cases confirmed by culture (Beauté, 2017), a frequency similar to that reported by a 2002 international prospective study (Yu et al., 2002). More rarely, strains of other serogroups are isolated from Legionnaires' disease patients, and the pattern varies by region. In two international studies, serogroups 3, 4, 5, 6, and 10 were each associated with less than 2 percent of culture-confirmed cases (Beauté, 2017; Yu et al., 2002). In Denmark from 1993 to 2006, serogroup 3 was identified in 23 percent and serogroup 6 in 5 percent of 419 culture-confirmed cases (St. Martin et al., 2013). In contrast,

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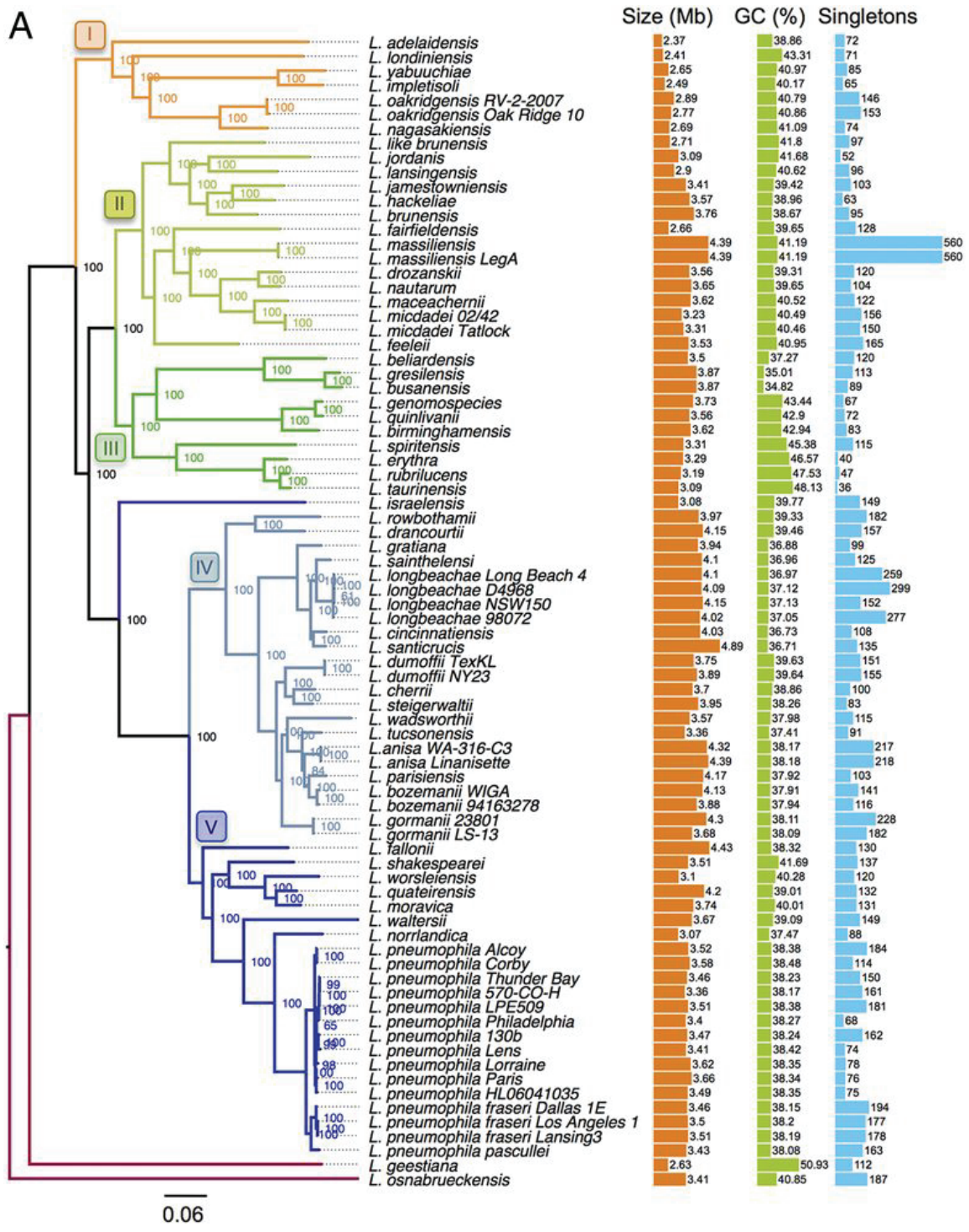

FIGURE 2-3 Diversity of size and gene content of *Legionella* genomes. Phylogeny of the genus based on the core genome, genome size, GC content, and number of singletons (genes identified in only a single species) of each species are depicted. Numbers represent bootstrap values. Branches are colored according to the clade (lineages that share a common ancestor) to which they belong. Genome size and GC content include plasmids if present in the corresponding species. The number of singletons is based on the results of OrthoMCL (takes into account orthologs and paralogs). Each species has been compared with the others without taking into account strains from the same species to avoid bias due to the number of strains sequenced within a species. SOURCE: Gomez-Valero et al. (2019).

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Management of Legionella in Water Systems

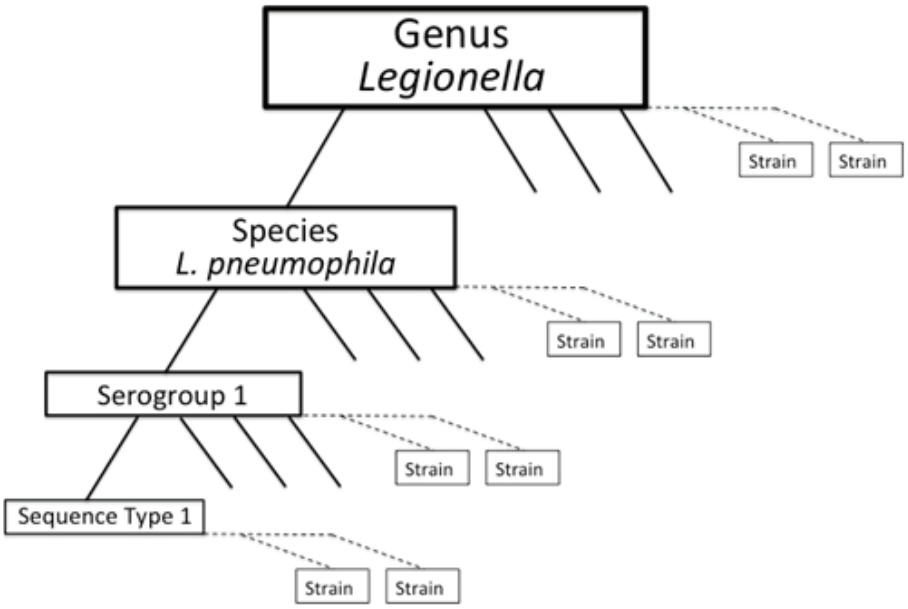

FIGURE 2-4 Nomenclature of *Legionella*. Genus and species are taxonomic categories that denote the degree of similarity among organisms. Serogroup refers to a distinct antigenic profile of the outer membrane lipopolysaccharide. Sequence type is defined by the DNA sequence of seven genomic loci designated by the field. Strain (dashed lines) is a more general term used to distinguish bacterial isolates without reference to their genetic or antigenic identity; for example, *L. pneumophila* cultures isolated independently are initially given different strain names until additional information on species, serogroup, or sequence type is obtained.

in Ontario, Canada, serogroup 6 *L. pneumophila* accounted for 47 percent of the disease cases not caused by serogroup 1 strains (Khan et al., 2013). In Michigan, serogroup 6 *L. pneumophila* also predominated in a surveillance study of premise plumbing one year after the 2014-2015 Legionnaires' disease outbreaks in Flint (Byrne et al., 2018).

L. pneumophila is the most prevalent reported species of *Legionella* in building water systems, whereas non-*pneumophila* strains show more geographic variation. Recent surveillance studies of hundreds of buildings in Germany and Hungary identified 58 to 84 percent of the isolates as *L. pneumophila* (Barna et al., 2016; Dilger et al., 2018; Kruse et al., 2016). Temperature is likely one factor that influences the prevalence of particular species. For example, in a study of more than 13,000 warm-water systems in southern Germany, *L. anisa* composed 18 percent of the total isolates obtained from water at 20°C but only 8 percent at 60°C (Dilger et al., 2018).

The clinical predominance of *L. pneumophila* serogroup 1 does not simply reflect a relative abundance in the environment (Doleans et al., 2004; reviewed by Mercante and Winchell, 2015). It also appears to grow better in humans than other *Legionella* species. For example, compared with seven other serogroups, the composition of serogroup 1 LPS equips *L. pneumophila* to resist killing by the alternate complement pathway (Khan et al., 2013), a key barrier of the human innate immune system. The serogroup 1 LPS O-antigen is also extremely hydrophobic (Zähringer et al., 1995), which may contribute to *L. pneumophila* survival in the human lung via evasion of toxic lysosomes (Fernandez-Moreira et al., 2006) or perhaps within aerosols. Two other observations suggest that the serogroup 1 LPS enhances

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Management of Legionella in Water Systems

L. pneumophila virulence. Unlike environmental strains, the majority of clinical isolates display a distinct LPS epitope encoded by the *lag-1* gene and recognized by particular monoclonal antibodies (MAb2 and MAb3/1), a structural feature that is used for diagnosis and risk-assessment (Kozak et al., 2009). It is also striking that the only genes shared by greater than 200 serogroup 1 strains comprise a locus dedicated to LPS biosynthesis (Cazalet et al., 2008). A cluster of these serogroup 1 LPS genes can spread horizontally among the legionellae (Cazalet et al., 2008; Merault et al., 2011) expanding the genetic diversity of serogroup 1 strains. Moreover, the LPS locus of at least two *L. pneumophila* serogroup 1 lineages exhibits an elevated rate of genetic exchange (David et al., 2017), further expanding their diversity. Whether serogroup 1 strains are better equipped to survive in aerosols or to colonize engineered water systems warrants investigation.

Because the *L. pneumophila* genome is dynamic, related strains of the same serogroup must be distinguished using molecular methods. Since 2005, the international *Legionella* community has applied a multi-locus DNA sequence typing scheme and online tools (Gaia et al., 2005; Ratzow et al., 2007; Underwood et al., 2006). Currently, more than 2,000 *L. pneumophila* sequence types (STs) can be distinguished based on the nucleotide sequence of seven alleles. By combining sequence-based typing with classical epidemiology, investigators can perform trace-back studies to identify outbreak sources, as well as assess regional patterns and persistence in particular environments. For example, Kozak-Muizniek and colleagues (2016) conducted a comprehensive phylogenetic analysis of hundreds of *L. pneumophila* strains collected in the United States from outbreaks, sporadic clinical cases, and environmental surveillance, all of which were submitted to the CDC over a 30-year period.

Worldwide, the most prevalent sequence type is ST1 within serogroup 1. In the United States from 1982 to 2012, this sequence type accounted for 49 percent of the *L. pneumophila* strains obtained from water and 25 percent of the sporadic disease isolates (Kozak-Muizniek et al., 2016). Likewise, in China over a seven-year period, 49 percent of environmental isolates were ST1 *L. pneumophila* (Qin et al., 2014). Multi-year surveillance studies in England, France, and Wales identified ST1 *L. pneumophila* as composing approximately 20 percent of environmental strains (Cassier et al., 2015; Harrison et al., 2009), and a Japanese analysis discovered that 74 percent of *L. pneumophila* isolates from cooling towers were ST1 (Amemura-Maekawa et al., 2012). Nevertheless, even among ST1 serogroup 1 *L. pneumophila* genomes, substantial diversity is generated by genetic recombination, as evident from whole genome sequence analysis of more than 200 ST1 strains (David et al., 2017). Thus sequence-typing alone is not sufficient to establish epidemiological associations of ST1 strains.

Nonetheless, sequence-based typing of large strain collections has identified regional variations in the endemic *L. pneumophila* populations and infection patterns. For example, ST1 strains caused multiple outbreaks in Belgium from 2000 to 2010 (Vekens et al., 2012), but the first outbreak in the United States was not recorded until 2012 (Kozak-Muiznieks et al., 2014). And although ST222 strains of *L. pneumophila* appear to be endemic in the northeastern regions of the United States and Canada, this type has been reported only recently and just once in three other countries (Byrne et al., 2018; Kozak et al., 2009; Kozak-Muiznieks et al., 2016; Tijet et al., 2010). In Western Europe, the *L. pneumophila* strain type most frequently isolated from patients is ST47 (also known as the Lorraine strain), yet no Asian or U.S. case has been attributed to this genotype (reviewed by Kozak-Muizniek et al., 2016). The biological basis for either the geographic distribution or the clinical prevalence of particular strains of legionellae remains to be determined. Knowledge of the genetic attributes that increase *L. pneumophila* fitness in distinct environments could guide detection and remediation strategies for particular geographic regions.

Despite the diversity of legionellae, research on the virulence and resilience mechanisms is focused on *L. pneumophila* serogroup 1 strains. Indeed, a literature search for titles and abstracts that contain "pneumophila" and "serogroup 1" identified more than 450 research articles; in contrast, "pneu-

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Management of Legionella in Water Systems

mophila" and "serogroup 6" identified just 64. Even more striking, a title search for "pneumophila" identified approximately 3,000 articles, whereas "micdadei" returned only 101. With the rapidly expanding opportunities to integrate epidemiological studies, genomics, and laboratory-based tests of virulence and persistence, the field is poised to advance knowledge of how, when, and where these common aquatic and soil microbes threaten human health.

L. pneumophila Life Cycle

As an environmental microbe, *L. pneumophila* adapts to fluctuating conditions by altering its physiology. Multiple distinct cell types have been defined based on a combination of morphological, biochemical, genetic, and molecular features (see Box 2-1; Robertson et al., 2014). Depending on its environment, *L. pneumophila* can differentiate between replicative, transmissive, filamentous, mature infectious forms, and viable-but-not-culturable-like (VBNC-like) cells (see Figure 2-5). *L. pneumophila* cells obtained from solid media are a mix of replicating, transmissive, and filamentous cell types, whereas more homogenous cell populations can be isolated from broth cultures. Each specialized cell type differs in its capacity to infect host cells and tolerate antibiotics, biocides, and other environmental stresses, as discussed below.

Replicative and transmissive forms are two cell types observed when culturing *L. pneumophila* in rich bacteriological media at 37°C with aeration. Replicative cells are isolated during the exponential growth phase, and the transmissive cell type is generated in the stationary phase (Brüggemann et al., 2006; Byrne and Swanson, 1998). To alternate between replicative and transmissive states, *L. pneumophila*

BOX 2-1
Bacterial Cell Terminology

Culturable: Bacteria that can be grown on a suitable culture medium.

Infectious: Bacteria capable of entering, surviving, and replicating within host cells or tissues.

Mature infectious form: A *L. pneumophila* a cell type that develops efficiently within certain host cells, contains abundant energy storage inclusions, and, compared to transmissive cells, has thicker outer membranes and is even more infectious and resistant to a variety of stresses, including certain antibiotics, detergents, and basic pH.

Replicative: A cell type that is actively multiplying or in an exponential growth phase. When in this state, *L. pneumophila* expresses pathways needed to generate progeny cells but not factors that promote infection or its spread from one host cell to another nor resistance to a variety of stresses.

Transmissive: A cell type that is not replicating (post-exponential or stationary phase) but is motile, spreads among host cells, and evades host lysosomes. Compared to replicative cells, transmissive cells are more resistant to a variety of stresses, including heat, osmotic pressure, and acidic pH.

Viable: Bacteria that are metabolically active and retain the capacity to grow when conditions are suitable.

Viable but non-culturable: A reversible dormant state in which bacteria have intact outer membranes and are metabolically active, yet do not grow on suitable media.

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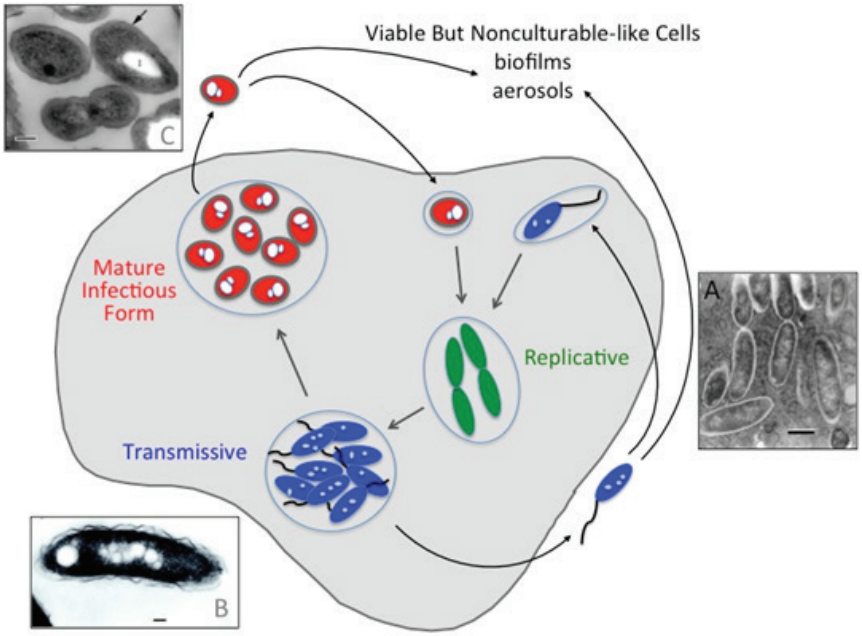

FIGURE 2-5 *L. pneumophila* alternates between multiple cell types within a host protozoan (gray). (A) replicative cells lack cytoplasmic inclusions; scale bar = 0.5 μm. (B) transmissive or stationary phase cells have wavy outer membranes, pseudomembranous inclusions, and polar flagella; scale bar = 0.1 μm. (C) mature infectious form cells have thickened outer membranes (arrow) and large inclusions (I); scale bar = 100 nm or 0.1 μm. Once released from the host, *L. pneumophila* may differentiate to a VBNC-like form, attach to biofilm, or be spread in aerosols.
SOURCES: Faulkner et al. (2008); Faulkner and Garduño (2002); Garduño et al. (2002).

reprograms its gene expression and metabolic profile (Brüggemann et al., 2006; Dalebroux et al., 2009; Faucher et al., 2011, reviewed by Oliva et al., 2018). For example, when nutrients are plentiful in broth, amoebae, or macrophages, *L. pneumophila* rely on the regulatory protein CsrA to repress production of not only flagella but also virulence factors that promote transmission between host cells, while activating pathways that catabolize serine and glucose and generate energy storage granules, or "inclusions" of polyhydroxybutyrate (PHB; Eylert et al., 2010; Gillmaier et al., 2016; Häuslein et al., 2016, 2017; James et al., 1999; Sahr et al., 2017). Once nutrients become limiting, *CsrA* repression is relieved, and *L. pneumophila* begin to catabolize PHB, utilize glycerol as a precursor for biosynthesis, modify their LPS and surface composition, acquire stress resistance, assemble a flagella, produce numerous virulence factors for export by a Type IV secretion system and become competent to evade phagosome-lysosome fusion (Eylert et al., 2010; Fernandez-Moreira et al., 2006; Harada et al., 2010; Häuslein et al., 2016, 2017; Mendis et al., 2018; Nevo et al., 2014; Sahr et al., 2017; Trigui et al., 2015). Thus, replicative phase cells specialize in generating progeny, whereas transmissive cells are primed to escape one host cell, survive and disperse in the environment, and establish a protected replication niche in a new host cell.

In water and in lungs, a filamentous cell type of *L. pneumophila* has been observed (reviewed by Robertson et al., 2014). In general, filamentation is observed after exposure to environmental stress, including scarce nutrients, high temperatures, ultraviolet (UV) light, or antibiotics. Relatively few studies have focused on filamentous forms, and the regulatory controls that govern filamentation are not known. Nevertheless, some fitness advantages have been described. When *L. pneumophila* are cultured without aeration in rich media at 37°C, their elongated morphology likely enhances attachment to biofilm, as thick meshworks of multinucleate, filamentous cells readily adhere to glass (Piao et al., 2006).

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Management of Legionella in Water Systems

When co-cultured with epithelial cells and macrophages, filamentous *L. pneumophila* are internalized within phagolysosomal compartments that fail to seal; thus, these leaky host vacuoles are less toxic to the elongated prey (Prashar et al., 2012, 2013). Filamentous cells can revert to the typical short rod morphology once static cultures are aerated (Piao et al., 2006) or after ingestion by macrophages (Prashar et al., 2013). Additional research is needed to illuminate the molecular mechanisms that govern filamentation and when and where this multinucleate elongated cell type increases *L. pneumophila* fitness.

In amoebae and ciliates, intracellular *L. pneumophila* can further differentiate into hardy mature infectious forms (MIF; Faulkner and Garduño, 2002; reviewed by Robertson et al., 2014). Such MIF cells are characterized by thick cell walls, abundant PHB storage granules, and metabolic dormancy. Compared with cells obtained from either stationary phase broth or macrophage cultures, MIF *L. pneumophila* are more resistant, by orders of magnitude, to basic pH, detergents, chlorine, and antibiotics, and they adhere to macrophages more readily (Abdelhady and Garduño, 2013). MIFs can also be released from amoebae and ciliates within membrane-bounded vesicles, which provide an additional layer of protection. Thus, MIF cells appear to be well equipped for transmission within aerosols to the human lung (Robertson et al., 2014).

Once either transmissive or MIF *L. pneumophila* encounter adequate nutrients within host amoebae or macrophages, they return to a replicative form that generates numerous progeny. For example, transmissive *L. pneumophila* will persist as single cells within macrophages or amoebae vacuoles until adequate threonine is acquired; subsequently, the bacteria switch to the replicative form (Sauer et al., 2005). Within amoebae, robust *L. pneumophila* replication ensues when arginine relieves transcriptional repression by the arginine repressor, ArgR (Hovel-Miner et al., 2009, 2010). Transporter proteins embedded in the host vacuolar and bacterial membranes equip replicative *L. pneumophila* to obtain amino acids needed for bacterial replication (Schunder et al., 2014).

After prolonged environmental stress, *L. pneumophila* is thought to differentiate into a VBNC-like cell type. Described for many bacteria, such a VBNC adaptation increases bacterial resistance but also impedes environmental surveillance strategies that rely on culture (reviewed by Li et al., 2014). *Vibrio vulnificus* is a marine Gram-negative pathogen whose VBNC state has been analyzed in molecular detail. After four days exposure to 5°C artificial seawater, culturability of *V. vulnificus* declines 8 logs. Once the cell suspension is returned to 22°C, within less than 10 hours culturability rapidly increases, by greater than 6 logs (Whitesides and Oliver, 1997). This efficient revival is coordinated by a quorum sensing signal transduction system (Ayrapetyan et al., 2014). Thus, the aquatic pathogen *V. vulnificus* is genetically programmed to respond to shifts in temperature and cell density by efficiently alternating between replication-competent and VBNC states.

Compared to *V. vulnificus,* the capacity of *Legionella* spp. to alternate between replication and a resilient VBNC-like state remains enigmatic. When MIF *L. pneumophila* are held for weeks in hot, nutrient-poor water, the majority acquire features of VBNC cells (Al-Bana et al., 2014). For example, 30 days after exposure to 45°C double-deionized water, the capacity of MIFs to form colonies on rich media steadily declines by more than 6 logs; yet, more than 80 percent of the cells have an intact cell membrane, as judged by cell membrane integrity stains. These MIF-derived, VBNC-like cells are resistant to detergent and remain intact when co-cultured with the ciliate hosts *Tetrahymena tropicalis* and *T. thermophila*, as judged by qualitative electron microscopy studies. However, MIF-derived, VBNC-like bacteria do not readily resume replication when cultured on rich medium or when ingested by a range of host phagocytes known to support robust *L. pneumophila* replication, including *Acanthamoebae castellanii, T. tropicalis, T. thermophila,* and human monocytic mouse fibroblast cell lines (Al-Bana et al., 2014). Therefore, whether MIF-derived, VBNC-like *L. pneumophila* pose a risk to public health remains an open question.

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Management of Legionella in Water Systems

Compared to MIF cells, transmissive *L. pneumophila* exhibit a different profile after prolonged exposure to 45°C tap water (Al-Bana et al., 2014). After 45 days, culturability declines more than 8 logs, but only about 20 percent of the population maintains viability, as judged by either vital staining or qualitative ultrastructure analysis. Although these VBNC-like cells remain intact after treatment with detergent or ingestion by *A. castellani,* only about 1 in 10^5 of this population resumes replication in this permissive amoebae host.

Several investigations have reported that nutrient, chemical, or temperature stress triggers *L. pneumophila* to differentiate into a VBNC-like cell type (Alleron et al., 2008; Dietersdorfer et al., 2018; Ducret et al., 2014; García et al., 2007; Hwang et al., 2006; Kirschner, 2016; Schrammel et al., 2018). In general, after prolonged stress, stationary phase *L. pneumophila* lose culturability, yet bind a vital stain or retain intact ribosomes (Dietersdorfer et al., 2018; Epalle et al., 2015; Ohno et al., 2003; Steinert et al., 1997). Numerous experimental factors alter generation and resuscitation of these VBNC-like *L. pneumophila*, including water composition, bacterial strain, growth phase, cell density, and host cell type. Quantification of VBNC-like populations is also affected by the method used to prepare control dead cells, the medium in which cells are suspended, the density of the cell suspension, and the sensitivity of instruments used to detect fluorescence markers that distinguish between live and dead cells (Braun et al., 2019). In contrast to our mechanistic understanding of VBNC *V. vulnificus* and several other bacteria, neither the environmental conditions nor the regulatory pathways that stimulate *L. pneumophila* to alternate efficiently between VBNC-like and replicative or MIF cell types have been delineated.

A major outstanding question is whether VBNC-like *L. pneumophila* cause infections in humans. In early studies that utilized a guinea pig model to assess virulence of VBNC-like *L. pneumophila*, no viable bacteria were recovered after infection (Steinert et al., 1997). When co-cultured with amoebae, some VBNC-like cells appear to resume replication; however, the quantitative data provided make it difficult to rule out that a minor population of culturable cells survived the initial stress treatment and subsequently initiated the amoebae infection. In a recent comprehensive study, VBNC-like *L. pneumophila* obtained 221 days after starvation were 20- to 100-fold less infectious for human monocyte-derived macrophages than bacteria obtained from broth cultures (Dietersdorfer et al., 2018). Thus, more research is required to determine whether, or under what conditions, VBNC-like *L. pneumophila* can establish infections in humans.

A limitation of current laboratory research practices and disinfection studies is the failure to take into account the distinct cell types of *L. pneumophila*. Environmental surveillance largely relies on culture-based detection (ISO, 1998), which does not detect VBNC-like cells. Genomic DNA tests applied in the clinic or in the field cannot distinguish among dead, live, VBNC, or infectious bacteria. Sensitivity to detergents, biocides, antibiotics and other stressors differs dramatically for replicative, transmissive, and MIF cells (Abdelhady and Garduño, 2013; reviewed by Robertson et al., 2014). The capacity of specialized *L. pneumophila* cell types to survive in aerosols and consequently gain access to the human lung has not been analyzed. The biochemical and environmental conditions that trigger development or resuscitation of VBNC-like *L. pneumophila* are not yet understood. Therefore, development and application of a standardized set of molecular markers specific to each cell type would advance the *L. pneumophila* field and ultimately guide clinical treatment and environmental remediation practices. Markers are currently available for replicative and transmissive forms of *Legionella* (Sauer et al., 2005) and for MIF (Abdelhady and Garduño, 2013), but not for VBNC-like *Legionella* or *Legionella* residing in biofilms. In the meantime, it is imperative that clinical, epidemiological, and research investigators be cognizant of the *L. pneumophila* life cycle and move toward newer approaches that can identify the cell type(s) in their samples.

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MICROBIAL ECOLOGY OF *LEGIONELLA*

The microbial ecology of legionellae has been poorly studied since *L. pneumophila* was first cultivated from the environment. Although the genus *Legionella* contains 61 species and DNA has been identified for several addditional *Legionella* spp. that have not yet been cultivated (Edagawa et al., 2008; Parthuisot et al., 2010; Wery et al., 2008; Wullings and van der Kooij, 2006), what is known about legionellae ecology is almost exclusively based on studies with *L. pneumophila.* The original isolation and identification of *L. pneumophila* from water environments and environmental aerosols led to the biased consideration of this pathogen as a planktonic aquatic bacterium. While it is certainly present in water environments, current understanding points to its growth along with other pathogenic legionellae within various free-living protozoan hosts that feed on bacteria associated with biofilms (i.e., surface-attached microbes and their extracellular matrix) (Hilbi et al., 2011). Indeed, several *Legionella* spp. are thought to have developed various virulence factors as defense against predation by free-living protozoa (i.e., protozoa that grow in the environment on natural organic matter and microbes, not obligate parasites that only grow within another living organism) (Cianciotto, 2015), as have various other genera of so-called amoeba-resisting bacterial pathogens (Kebbi-Beghdaji and Greub, 2014). This section discusses principles of *Legionella* ecology as well as the two growth habitats for pathogenic legionellae—its primary reservoir in nature and its secondary habitat in engineered environments that may generate infectious doses delivered via aerosols to humans.

Principles of *Legionella* Ecology

Biofilms consist of microorganisms that grow attached to moist soil, sediment, decaying organic matter or other solid surfaces. They are largely hydrated gels composed of extracellular polymeric substances, consisting of carbohydrates, fats, protein and nucleic acids excreted by bacteria (Flemming et al., 2016). Gradients of nutrients, pH, and oxygen within the biofilm matrix support the varying needs of different microorganisms in the heterogeneous biofilm community. Various protozoa, and later on microinvertebrates, will naturally develop and feed on biofilms, further influencing the microbial diversity of mature biofilms. In oligotrophic environments such as drinking water, a "mature" biofilm consisting of a relatively stable microbial community composition can take several years to develop (Martiny et al., 2003). In contrast, most published biofilm experiments are typically undertaken after a limited period of development (Storey et al., 2004a, 2011).

L. pneumophila may form a mono-species biofilm in the laboratory and grow necrophilically on other decaying cells (Temmerman et al., 2006). Moreover, free, inactive *Legionella* persist within biofilms (Hindré et al., 2008). However, **the primary growth habitat of *L. pneumophila* is within amoebae** (Kuiper et al., 2004) **or other free-living protozoa that are associated with biofilms** (Buse et al., 2012; Hellinga et al., 2015). Within these protozoan hosts associated with fixed or free-floating biofilms (Hsu et al., 2011), pathogenic legionellae can replicate to problematic levels (Ashbolt, 2015; Declerck et al., 2010; Hamilton et al., 2019).

As illustrated in Figure 2-6 and Figure 2-7, large numbers of *L. pneumophila* can be released from the biofilm environment within fragments of biofilm, within protozoan trophozoites and cysts, or within expelled amoebal vesicles (membrane-bound structures containing undigested food and microorganims). These released *L. pneumophila* cells then disperse in the bulk water phase among other planktonic microorganisms. The dependency of *L. pneumophila* growth on protozoan hosts that graze on biofilms associates the ecology of *L. pneumophila* indirectly to the ecology of its host protozoan and supporting biofilm microorganisms.

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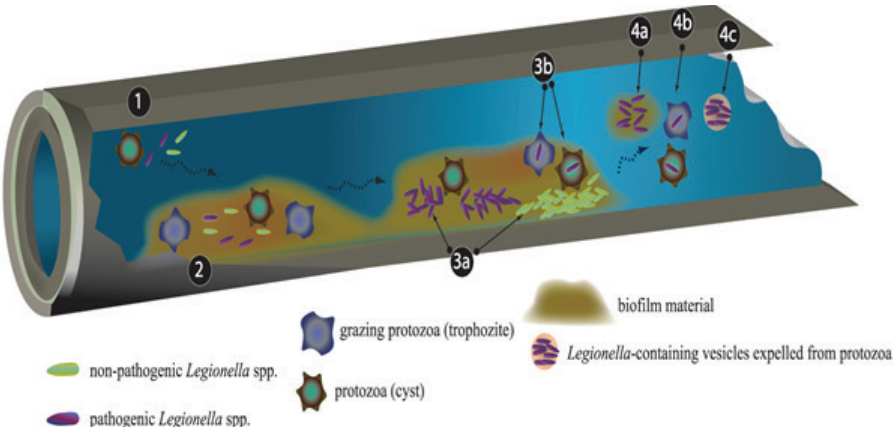

FIGURE 2-6 *Legionella* spp. along with various protozoa species in building water systems (1) and their associated biofilms (2), which contain a variety of microbes including bacteria, fungi, and higher organisms such as amoebae (not all of which are shown). *Legionella* either colonize the biofilm (3a) or are ingested by grazing protozoa (3b). The intracellular fate of *Legionella* after ingestion can vary: they are either digested by the protozoa, they can parasitize and eventually kill the protozoan host, or the protozoa may expel them in vesicles or the *Legionella* may persist within protozoan cysts. *Legionella* are then released from the biofilm in a variety of ways. *Legionella* bacteria that have colonized and proliferated within the biofilm can be released as this material sloughs off (4a), they can be found either within the trophozoite or cyst form of certain protozoa (4b), or they can be released within a vesicle derived from their protozoan host (4c). SOURCE: Lau and Ashbolt (2009).

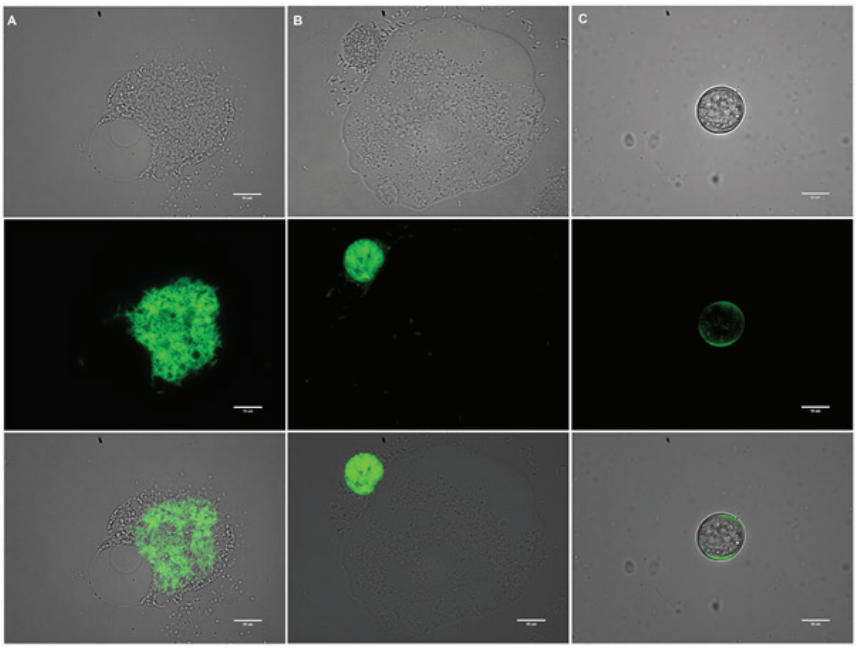

FIGURE 2-7 Micrographs of *Legionella* inside a protozoan host. The top row is light microscopy, the second row is fluorescence to highlight the viable *L. pneumophila* (expressing the green fluorescent protein gene) and the bottom row shows the top two rows combined. Panel A shows intracellular growth of *L. pneumophila* in Willaertia magna (ATCC 50035). Panel B shows the release of a vesicle containing *L. pneumophila* from W. magna (ATCC 50035) during intracellular growth. Panel C shows trapped *L. pneumophila* cells within a W. magna (ATCC 50035) cyst. SOURCE: Courtesy of Mohamed Shaheen.

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Role of Free-Living Protozoa in Growth of Legionellae

Rowbotham (1980) first showed that *L. pneumophila* multiply in different protozoan hosts. Moreover, *L. pneumophila* multipled in sterile water when amoebae were added, but not when amoebae were removed by filtration (Kuiper et al., 2004; Nahapetian et al., 1991; Wadowsky et al., 1988). Subsequently, many free-living protozoa (amoebae and ciliates) have been identified that can serve as hosts for growth of *Legionella* (see Table 2-1). It is likely that other higher animal organisms can also serve as growth and/or transport hosts for *L. pneumophila* (Hellinga et al., 2015). Of note, *L. pneumophila* cells will not grow within the dry, dormant cysts of protozoa, although the bacteria are preserved and show increased resistance to disinfection proceses such as heat, chemicals, sonication, and UV (Cervero-Arago et al., 2014; Declerck et al., 2010; Storey et al., 2004b).

TABLE 2-1 Known Hosts of *Legionella*

Organism	Eukaryote	Reference
Acanthamoeba polyphaga	Amoebae	Rowbotham, 1980
Acanthamoeba castellanii	Amoebae	Rowbotham, 1980
Naegleria gruberi	Amoebae	Rowbotham, 1980
Naegleria jadini	Amoebae	Rowbotham, 1980
Naegleria lovaniensis	Amoebae	Tyndall and Domingue, 1982
Acanthamoeba royreba	Amoebae	Tyndall and Domingue, 1982
Acanthamoeba palestinensis	Amoebae	Anand et al., 1983
Tetrahymena pyriformis	Ciliate	Fields et al., 1984
Naegleria fowleri	Amoebae	Newsome et al., 1985
Vahlkampfia jugosa	Amoebae	Rowbotham, 1986
Echinamoeba exudans	Amoebae	Fields et al., 1989
Hartmanella cantabrigiensis	Amoebae	Fields et al., 1989
Vermamoeba [Hartmanella] vermiformis	Amoebae	Fields et al., 1989
Hartmanella sp.	Amoebae	Fields et al., 1989
Acanthamoeba culbertsoni	Amoebae	Fields et al., 1989
Tetrahymena thermophile	Ciliate	Kikuhara et al., 1994
Dictyostelium disocideum	Amoebae	Hägele et al., 2000
Balamuthia mandrillaris	Amoebae	Shadrach et al., 2005
Caenorhabditis elegans	Nematode	Rasch et al., 2016
Willaertia magna	Amoebae	Dey et al., 2009
Diphylleia rotans[a]	Flagellate	Valster et al., 2010
Echinamoeba thermarum[a]	Amoebae	Valster et al., 2010
Neoparamoeba spp.[a]	Amoebae	Valster et al., 2010
Acanthamoeba griffini, Acanthamoeba jacobsi, Naegleria australiensis, Naegleria philippinensis, Naegleria italica	Amoebae	Hsu et al., 2011
Stylonychia bifaria[a]	Ciliate	Rasch et al., 2016
Stylonychia mytilus[a]	Ciliate	Rasch et al., 2016
Ciliophrya spp.[a]	Ciliate	Rasch et al., 2016

[a] Candidate host; in vitro studies are needed to confirm their role as environmental host.

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Management of Legionella in Water Systems

Not all protozoa will serve as hosts under all conditions or for all strains and species of *Legionella* (e.g., Wadowsky et al., 1991), perhaps due to novel non-coding RNA expressed during predator–prey interactions (Weissenmayer et al., 2011). For example, some protozoa may be resistant to infection with *L. pneumophila* because they digest *L. pneumophila* (Amaro et al., 2015); these eukaryotes could potentially serve as biological control agents (Maita et al., 2018, as suggested by Wang et al., 2013). Some protozoa have a preference for other bacterial prey (Shaheen et al., 2019). Finally, some species of amoeba contain symbionts that do not allow *Legionella* to replicate within the host (Okubo et al., 2018; Maita et al., 2018).

The protozoan hosts for *L. pneumophila* graze on microorganisms present in the biofilm or sediments. By phagocytosis, host cells engulf and internalized prey microbes within cell membranes known as phagosomes (Abu Kwaik et al., 1998). Normally, the phagocytosed prey is delivered to lysosomes where it is digested by the acidic pH and lysosomal enzymes. Nutrients liberated through this process fuel the protozoan cell. However, many bacterial species, including pathogenic *Legionella* spp., have evolved strategies to escape digestion by the protozoan cell and persist in vacuoles within the protozoan host (Vandenesch et al., 1990). Within these vacuoles, these bacteria may multiply, especially at temperatures greater than 30°C (Buse et al., 2017; Caicido et al., 2018). Bacterial proliferation eventually kills or lyses the protozoan cell, releasing the intracellular progeny into the aquatic or soil environment (Kuiper et al., 2004). This strategy likely enables fastidious bacteria such as *L. pneumophila* to persist and compete with other bacteria in otherwise low-nutrient (oligotrophic) and inhospitable environments (King et al., 1988). As a consequence of adaptation to resist amoeba digestion, various bacteria either grow pathogenically, become benign, or form a stable symbiotic relationship with protozoa (Schmitz-Esser et al., 2010; Shu et al., 2018) as discussed further below.

Effects of the Protozoan Host on Virulence and Stress

Over millennia, free-living protozoa have contributed to the development of a repertoire of virulence and stress-response genes in *Legionella* and other amoeba-resisting bacteria (Guimaraes et al., 2015; Koubar et al., 2011; Trigui et al., 2015). Considerable horizontal gene transfer between amoeba and their internalized bacteria (Guimaraes et al., 2015) also contributes to ongoing changes in traits within legionellae. The host and the conditions for culturing legionellae may also affect its infectivity, such as if cells are VBNC-like, in the replicative or the transmissive stage of *Legionella*'s life-cycle (Fonseca and Swanson, 2014), or as short rods versus filamentous morphologies (Garduño et al., 2002; Vandenesch et al., 1990). Adaptation of *L. pneumophila*'s lipid A cell surface is one of a series of factors that affects its ability to infect host amoebae (Albers et al., 2007). As discussed previously, not describing and controlling the cell form(s) used in infection studies could well be contributing to the differing views reported in the literature.

The increase in infectivity following *L. pneumophila* growth in amoebae may depend on the protozoan host and the animal model used, although the mechanism of this increased virulence is unknown. While no difference was seen in the infectivity of guinea pigs via aerosols of *L. pneumophila* cells grown in co-culture with an *Acanthamoeba* spp. compared to pure culture cells from agar plates (Vandenesch et al., 1990), *Acanthamoeba castellanii*- and *Vermamoeba vermiformis*-associated *L. pneumophila* were described as more pathogenic in macrophages and in a mouse model than an equal number of non-amoeba-associated *L. pneumophila* (Brieland et al., 1997; Cirillo et al., 1994). For example, *L. pneumophila* grown in *Acanthamoeba* are some 100-fold more infectious in epithelial cells and ten times more infectious in macrophages or other cell lines than agar-grown *L. pneumophila* (Cirillo et al., 1994, Garduño et al., 2002). Importantly, after intracellular replication in free-living protozoa, higher resistance has been document-

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Management of Legionella in Water Systems

ed for *L. pneumophila* stressed by heat, oxidants, acids, osmotic shock (Kwaik et al., 1997), biocides (Barker et al., 1992, Berk et al., 1998), and antibiotics (Barker et al., 1995, Garduño et al., 2002). Other cellular differences between co-cultured *L. pneumophila* and *L. pneumophila* grown alone on agar include differences in cellular fatty acid composition (Barker et al., 1993; Vandenesch et al., 1990). However, a limitation of each of these comparative studies is that it is unclear whether the agar-grown cell samples contained exponential-phase "replicative" bacteria that are readily degraded in lysosomes, post-exponential-phase "transmissive" bacteria that evade lysosomes, or a mixture of the two.

Role of Temperature

Legionellae have been observed in environments ranging from 0°C to 45°C, indicating that legionellae are psychrophilic to mesophilic (Wullings and van der Kooij, 2006). However, most of the described species of the genus *Legionella* are mesophilic and grow between 25°C and 43°C under laboratory conditions (Garrity et al., 2005). Under environmental conditions, growth of *L. pneumophila* has been observed between 25°C and 45°C (Buse et al., 2017; Tison et al., 1980; van der Kooij et al., 2016; Wadowsky et al., 1985; Yee and Wadowsky, 1982). Since the growth of *L. pneumophila* in these environments largely depends on amoebae, studies have also focused on *L. pneumophila* growth in protozoan hosts at different temperatures. *L. pneumophila* proliferate in *Acanthamoeba palestinensis* and *A. castellanni* at 25°C and 35°C, respectively, but are digested by the amoeba at 15°C and 20°C (Anand et al., 1983; Ohno et al., 2008), which is consistent with generally low levels of *Legionella* observed in natural environments at these lower temperatures.

The optimal temperature range for *L. pneumophila* to express several factors that promote infection and transmission is between 25°C and 30°C, not 37°C or higher. These factors include flagellar-based motility (Ott et al., 1991); PilD, a critical component of Type II secretion and Type IV pili, two machines that equip *L. pneumophila* to move across surfaces by sliding motility (Stewart et al., 2009); and LvhB2, a virulence factor exported by Type II secretion that enhances *L. pneumophila* infection of host cells at 25°C, but not 37°C (Ridenour et al., 2003). A functional Type II secretion system also increases *L. pneumophila* survival in water at temperatures of 17°C and below and bacterial replication in amoebae at 22°C to 25°C (Söderberg et al., 2004).

Studies differ in the maximum temperature observed for *L. pneumophila* growth. Some researchers observed growth up to 45°C (Kusnetsov et al., 1996; Tison et al., 1980), whereas others did not observe growth at 42°C or higher (Ohno et al., 2003; van der Kooij et al., 2016). Van der Kooij and colleagues (2016) observed that *L. pneumophila* serogroup 1 strains of different sequence types had different optimum and maximum growth temperatures when grown under drinking water conditions in a biofilm monitor. In addition, using the same biofilm monitor, *L. pneumophila* was not capable of growth in the naturally formed biofilm with temperatures greater than 41°C. A 2-log lower *V. vermiformis* host count at 42°C compared to 38°C indicated that the absence of a thermotolerant host at 42°C prevents proliferation of *L. pneumophila* in this system (van der Kooij et al., 2016)2016. Indeed, different *L. pneumophila* strains have different optimal temperatures when grown in protozoan hosts (Buse and Ashbolt, 2011), and the protozoan community composition also varies with temperature in drinking water systems (Valster, 2011). Thus, both the strain of *L. pneumophila* and host protozoan diversity affect the temperature range for growth of *L. pneumophila*.

At temperatures greater than 50°C, the number of cultivable *L. pneumophila* declines. The time required to reduce the concentration of viable bacteria by 90 percent is referred to as the decimal reduction time. Decimal reduction times between 100 and 1,000 minutes were observed for *Legionella* at

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Management of Legionella in Water Systems

50°C (van der Kooij, 2014). The lowest reduction time (100 minutes) was observed for *L. pneumophila* precultured with natural microbiota. Moreover, these decimal reduction times decreased to around two minutes at 60°C for *L. pneumophila* pure cultures grown under natural conditions (Dennis et al., 1984; Schulze-Robbecke et al., 1987; van der Kooij, 2014). No cultivable *L. pneumophila* were observed after heat shock treatment for 10 minutes at 70°C with pure cultures of different *L. pneumophila* strains (Allegra et al., 2008). In contrast, metrics of viability (membrane-intact cells and adenosine triphosphate or ATP present) could still be measured for most strains, and, when the suspension was subsequently incubated with a protozoan host, *L. pneumophila* was cultivated. Membrane integrity can be a poor indicator for viability in *L. pneumophila* (Hammes et al., 2011, Wullings et al., 2016), and free ATP can still be present after cell death (Nescerecka et al., 2016). Nevertheless, the capacity to culture bacteria from a protozoan host demonstrates that at least some *L. pneumophila* cells remained viable after heat-shock treatment for 10 minutes. Unfortunately, a decimal reduction time was not calculated. An earlier study of several *L. pneumophila* strains showed that the decimal reduction time at 70°C varied between 1.1 and 2.6 minutes (Stout et al., 1986), meaning that 10 minutes of exposure to 70°C would be expected to result in a 3.8- to 9.1-log reduction. Therefore, the Allegra et al. (2008) report that *L. pneumophila* cells survived 10 minutes of treatment at 70°C is consistent with previous observations.

Inactivation of pure cultures of ten different *Legionella* species, eight different *L. pneumophila* serogroups and one to five different *L. pneumophila* strains showed that the decimal reduction times at 60°C ranged from 2 to 5 minutes (Stout et al., 1986). This difference in decimal reduction time was observed between species, serogroups, and strains, but was only determined by loss of culturability, not by other measures of viability loss (hence, some cells may be VBNC-like). In addition, Allegra and colleagues (2008) also observed that the different *L. pneumophila* strains showed different reduction curves for the membrane-intact cells when treated at 70°C (see Figure 2-8). Thus, the reduction times after temperature disinfection can be strain-, serogroup-, and species-dependent. Interestingly, Allegra et al. (2011) showed that repeated thermal shocks actually selected for heat-resistant *L. pneumophila* strains.

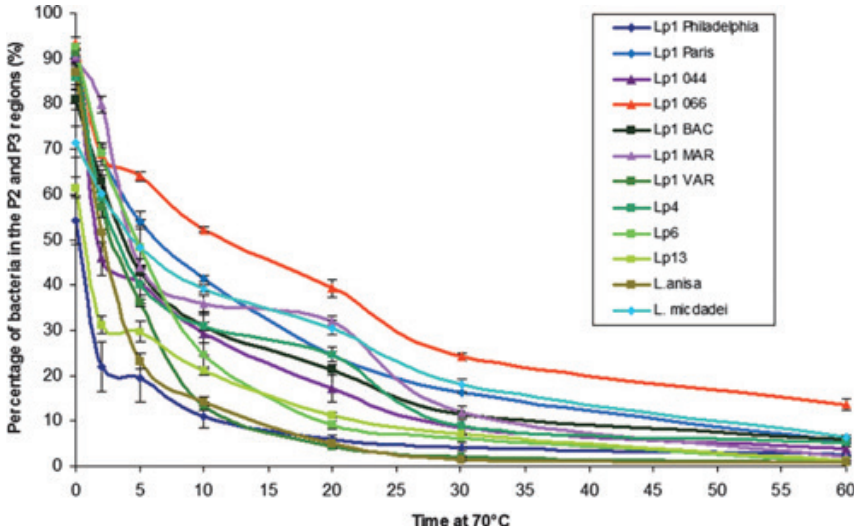

FIGURE 2-8 Inactivation curves for *L. anisa* and *L. micdadei* strains, different *L. pneumophila* (Lp) serogroups (1, 4, 6 or 13), and different strains of *L. pneumophila* serogroup 1 (Philadelphia, Paris, 044, 066, BAC, MAR and VAR) after exposure to 70°C. For each strain, the result at each time point shown is the percentage of bacteria detected in both the P2 (viable, culturable cells) and P3 (VBNC-like cells) regions and is expressed as the mean ± standard error from two to five independent experiments. SOURCE: Allegra et al. (2008).

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Management of Legionella in Water Systems

Most recently, Cervero-Aragó and colleagues (2019) investigated two *L. pneumophila* strains for more than 80 days using a combination of cell-based viability indicators with cells incubated at 55°C, 60°C, and 70°C. Culturability was lost after 3 to 8 hours, 60 minutes, and less than 2 minutes, respectively; whereas, based on viability indicators, a 4-log reduction was achieved only after 150, 8 to 15, and 1 to 4 days, respectively. To investigate cells in a VBNC-like state, Cervero-Aragó et al. (2019) evaluated the infectivity of these heat-shocked *L. pneumophila* in amoebae and a lung macrophage cell line (THP-1). Infectivity lasted for at least 85 days at 55°C and 60°C and for up to 8 days at 70°C, albeit with reduced efficiency. Cervero-Aragó et al. (2019) concluded that a prolonged thermal regime at or above 60°C at the central parts of warm-water building systems is not only effective against culturable *L. pneumophila* but also against VBNC-like cells.

Since *L. pneumophila* seems to multiply mainly in protozoan hosts, the effect of high temperatures on possible protozoan hosts for *L. pneumophila* might also contribute to eradication of *L. pneumophila*. Most protozoan host species of the genus *Acanthamoeba* cannot multiply at temperatures above 37°C (de Jonckheere, 1980). However, another protozoan host for *L. pneumophila* (such as *V. vermiformis*) continues to multiply above 50°C (Kuchta et al., 1993; Rohr et al., 1998). Cervero-Arago et al. (2013) showed that trophozoites of two *Acanthamoeba* strains and two *V. vermiformis* strains, isolated from drinking water, had a decimal reduction time of 7.2 to 11 minutes at 50°C and less than 0.34 to 1.4 minutes at 60°C. In contrast, the decimal reduction time of cysts of these protozoan species varied between 30 and 76 minutes at 50°C and between 4.7 and 10.7 minutes at 60°C, with *Acanthamoeba* strains being the most thermotolerant. These reduction times at 60°C are considerably longer than for *L. pneumophila*, implying that decimal reduction times for *L. pneumophila* inside cysts are likely to be longer than for planktonic *L. pneumophila* cells. Indeed, Storey et al. (2004b) showed persistence of *L. pneumophila* within cysts after 10 minutes at 80°C.

Role of Nutrients

Growth of legionellae in defined media demonstrate that these bacteria require specific nutrients, including certain amino acids and ferric iron (George et al., 1980; Ristroph et al., 1981). Indeed, legionellae are readily recovered in relatively nutrient-rich reclaimed wastewaters (as reviewed by Caicedo et al., 2019). Conversely, free cells of *L. pneumophila* cannot compete successfully with oligotrophic bacteria in nutrient-poor aquatic environments such as drinking water (van der Kooij, 2014). As described above, *L. pneumophila* circumvents this problem by multiplying in protozoan hosts, which provide its required nutrients. Since these protozoan hosts graze on bacteria, the concentration of protozoa depends on the concentration of prey bacteria that are present. A clear correlation between biofilm concentration and numbers of cultivable *L. pneumophila* has been observed in a biofilm monitor fed with unchlorinated drinking water types that differ in assimilable organic carbon (AOC) concentration and inoculated with *L. pneumophila* (Learbuch et al., 2019; van der Kooij et al., 2017). The biofilm concentration also correlates with the AOC concentration in the drinking water (van der Kooij et al., 2017). This implies that the *Legionella* numbers in drinking water are indirectly correlated to the AOC concentration of the water. Based on these data, the authors deduced for drinking waters sourced via riverbank infiltration a threshold biofilm concentration of 50 μg ATP/cm^2 and a threshold AOC concentration of 1 μg C/L to initiate growth of *L. pneumophila* in the product drinking water.

Notably, an AOC concentration of less than 1 μg C/L in drinking water is extremely low and cannot be achieved by drinking water plants in the United States (Volk and LeChevallier, 2000). Even in the Netherlands, where microbial growth in drinking water systems is limited by controlling AOC

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Management of Legionella in Water Systems

concentrations instead of using a disinfectant residual, the majority of treatment plants produce drinking water with AOC concentrations above 1 µg C/L (Paul van der Wielen, personal communication). Others have not observed a relationship between organic carbon and *L. pneumophila* numbers in drinking water supplemented with different fulvic acid concentrations (Williams et al., 2015), indicating that other environmental factors (e.g., host protozoan concentration) contribute to *L. pneumophila* growth as well.

A relationship between several minerals (e.g., iron, zinc, calcium, manganese, magnesium) and *Legionella* numbers in premise plumbing systems has been observed (van der Kooij, 2014, and references therein), although findings are not consistent among studies. For instance, Vickers and colleagues (1987) observed that calcium and magnesium, but not iron and zinc, correlated with *L. pneumophila* in hospital water systems, whereas Bargellini and colleagues (2011) observed that iron and zinc correlated with *L. pneumophila* in hot-water systems of hotels and private homes. The role of ferric iron in growth of *L. pneumophila* has been studied intensively; it is a prerequisite for growth of *L. pneumophila* in chemically defined media (Reeves et al., 1981; States et al., 1985; Warren and Miller, 1979). The addition of the iron chelator lactoferrin reduces viability of *L. pneumophila* (Goldoni et al., 2000). In addition, ferric/ferrous ions also promote *L. pneumophila* virulence (Allard et al., 2009). Iron overload has also been associated with increasing *Legionella* infectivity rates of amoebae and macrophages as indicators of increased virulence (Buracco et al., 2017; James et al., 1999). On the other hand, excessive iron inhibits *Legionella* biofilm formation (Hindré et al., 2008). The effect of other mineral elements on the growth of *L. pneumophila* in premise plumbing is still not well understood (Borella et al., 2005).

Low nutrient availability in artificial media inhibits *L. pneumophila* growth, generating VBNC-like cells. As discussed previously, whether *Legionella* forms VBNC cells is controversial. VBNC-like *L. pneumophila* cells persisting in drinking water for more than 100 days that can be resuscitated by amoeba co-culture have been described (Steinert et al., 1997). It remains difficult, however, to make definitive conclusions because the lack of growth in the absence of a protozoan host was not proven (only that *L. pneumophila* was below a certain detection limit). Still, others have made similar observations in which resuscitation through a protozoan host recovered the culturability of *L. pneumophila* on agar media (Alleron et al., 2008; Ducret et al., 2014; Garcia et al., 2007; Hwang et al., 2006). Furthermore, it was observed that detection of *L. pneumophila* from environmental samples is improved when a co-culture method with a protozoan host is used (Garcia et al., 2007; La Scola et al., 2001; Sanden et al., 1992; Schalk et al., 2012). This is strong evidence that not all viable *L. pneumophila* strains in the environment will be cultivated when using artificial media.

Legionella in the Natural Environment

Aquatic Environment

Soon after *L. pneumophila* was first isolated and described, the organism was observed at low numbers (approximately 1 percent of total bacterial community) in water from different lakes and rivers in the United States using DFA techniques and isolated by infecting guinea pigs (Fliermans et al., 1979, 1981). The frequency of *L. pneumophila* isolation correlated with water temperature, and more strains could be isolated from surface waters in summer (Fliermans et al., 1979). Around the world, legionellae were identified among the natural microbiota in surface waters (e.g., Carvalho et al., 2007, 2008; Ortiz-Roque and Hazen, 1987; Parthuisot et al., 2010) or groundwater (Costa et al., 2005; Riffard et al., 2001). These studies show in general that legionellae numbers are low (less than 10^3 CFU/L). Detected only sporadically, *L. pneumophila* is not among the dominant *Legionella* species in surface waters and groundwater that have

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Management of Legionella in Water Systems

water temperatures below 25°C. In contrast, *L. pneumophila* predominated among the legionellae isolated from natural hydrothermal vents and hot springs where water temperatures were above 27°C, reaching numbers up to 10^6 CFU/L (Marrao et al., 1993; Verissimo et al., 1991). In an acidic hot spring with a temperature of 30°C to 47°C and a pH of 2.7, 16S rRNA gene sequences of *L. pneumophila* were not detected, indicating that the low pH selected for other *Legionella* species (Sheehan et al., 2005). *L. pneumophila* has been identified in natural water from thermal springs used in spas, a suspected source for Legionnaires' disease (van Heijnsbergen et al., 2015). It should be noted that the protozoan hosts for *L. pneumophila* also reside in natural aquatic environments (reviewed in Plutzer and Karanis, 2016).

Soil Environment

Legionellae also inhabit soil. For example, a large number of legionellae isolates (n=114) belonging to 12 different *Legionella* species were obtained from soil samples in Thailand (Travis et al., 2012). Moreover, *L. longbeachae*, another causative agent of Legionnaires' disease, is mostly isolated from potting mixes and gardening soil (Whiley and Bentham, 2011 and references therein), although it resides in aquatic environments as well (Joly et al., 1984; Marrie et al., 1994). In contrast to *L. pneumophila*, *L. longbeachae* contains genes that encode 12 cellulolytic enzymes, which together may fully degrade cellulose. Accordingly, *L. longbeachae* is equipped to metabolically degrade plant material (Cazalet et al., 2010), supporting the notion of its natural habitat being associated with degrading plant matter.

Morris and colleagues (1979) isolated *L. pneumophila* from mud and sand sediments sampled from the bottom of a stream impacted by thermally polluted water. Furthermore, *L. pneumophila* was detected in these soil samples by fluorescent antibody staining, although the microbes could not be cultivated on agar media or after guinea pig inoculation. Others have detected *L. pneumophila* in soil, in one case throughout the year in the same garden soil (Travis et al., 2012; van Heijnsbergen et al., 2016). In Australia, the same unusual *L. pneumophila* strain type was isolated from a Legionnaires' disease patient and from soil in the patient's work area, implying a direct link between soil and disease (Wallis and Robinson, 2005). Likewise, natural soil has been identified as a possible source for various cases of Legionnaires' disease (van Heijnsbergen et al., 2015). Although different *Legionella* species have been isolated from soil, and soil or dust contamination of engineered systems has been associated with outbreaks (van Heijnsbergen et al., 2016), the ecology of legionellae in soil has not been studied intensively. Free-living protozoa known to be hosts for *L. pneumophila* (e.g., *V. vermiformis* and *Acanthamoeba* spp.) are also common in soil samples (Denet et al., 2017; Tyml et al., 2016). Hence, *L. pneumophila* in the soil environment likely replicate within protozoan hosts, although proof for this phenomenon is still lacking.

Legionella in Engineered Environments

The growth of pathogenic legionellae to problematically high densities (Hamilton et al., 2019) seems to be favored in various engineered environments that support free-living protozoa associated with biofilms and that generate aerosols (Buse et al., 2012). The engineered environments that support *Legionella* growth include drinking water treatment plants, plumbing within buildings (i.e., premise plumbing), cooling towers, wastewater treatment plants that receive warm industrial effluents (Loenenbach et al., 2018), and a myriad of devices that operate with warm water including hot tubs. As shown in Figure 2-9, these compartments are a potential source of Legionnaires' disease if contaminated aerosols are generated that can be inhaled or aspirated by people in their vicinity.

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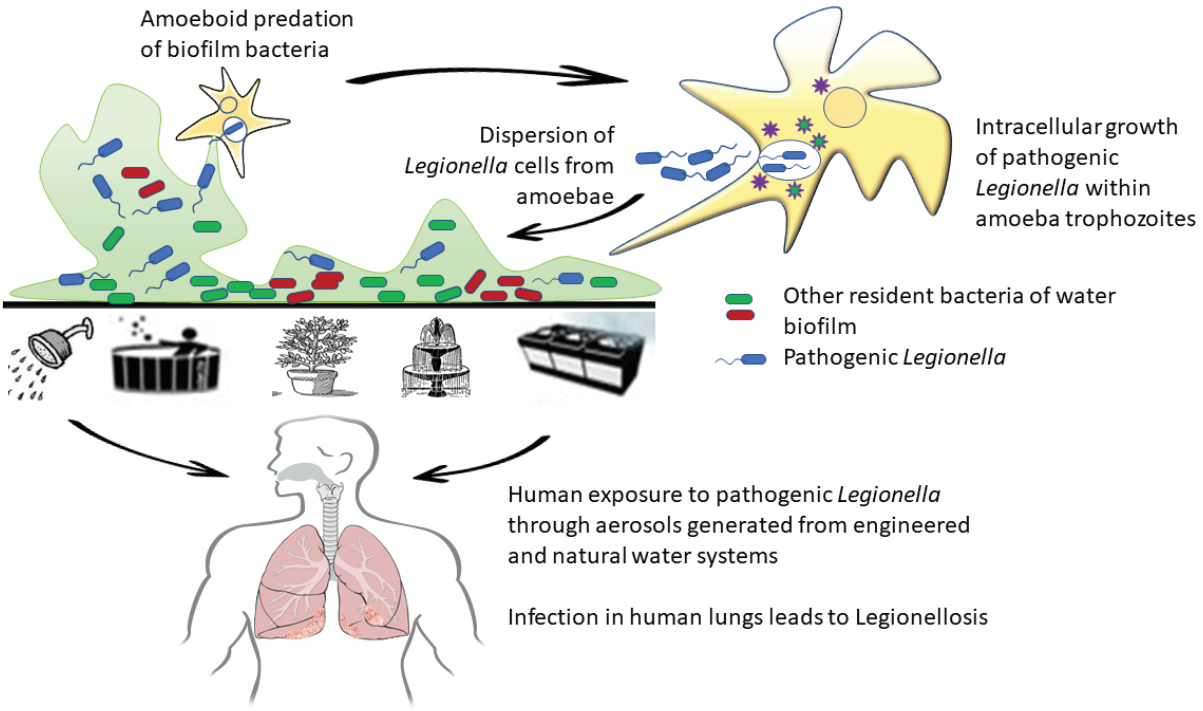

FIGURE 2-9 Major pathways leading to *Legionella* infections in engineered environments.
SOURCE: Courtesy of Mohamed Shaheen.

Drinking Water Distribution Systems and Premise Plumbing

Various species of legionellae have been detected in drinking water (Buse et al., 2012; Donohue et al., 2014; Hull et al., 2017). *Legionella* can enter drinking water systems by many possible routes, starting with source water that is contaminated by industrial, thermally elevated wastewater. For example, *Legionella* can grow within free-living protozoa associated with sand filters used in drinking water treatment and within amoebae that pass through drinking water treatment into distribution (Loret and Greub, 2010; Lu et al., 2016). Lu et al. (2015) provided evidence for atmospheric (soil/dust) ingress of *Legionella* through air vents into drinking water reservoirs and growth within reservoir sediments. *Legionella* may also enter drinking water distribution systems during construction (Francois Watkins et al., 2016; Knox et al., 2016; hypothesized in Mermel et al., 1995; Stout et al., 2000) or main breaks (as suggested in Rhoads et al., 2017a).

Drinking water distribution systems containing free-living protozoa harboring pathogenic legionellae can also "seed" premise plumbing; subsequent growth in dead-ends and other stagnant regions may lead to sporadic cases and outbreaks of Legionnaires' disease (Beer et al., 2015; Hamilton and Haas, 2016; Schoen and Ashbolt, 2011). In particular, the last few distal meters of piped water in premise plumbing are likely zones where problematic concentrations of *L. pneumophila* develop (i.e., 10^5 to 10^6 CFU/L; Hamilton et al., 2019; Schoen and Ashbolt, 2011). *L. pneumophila* has been isolated from hot/cold mixing valves, tap aerators, plastic shower hosing, and shower heads (Collins et al., 2017; Proctor et al., 2018); household "cold"-water storage tanks (Peter and Routledge, 2018); and stagnant hot-water lines within an optimal temperature window for intracellular growth (i.e., 28°C to 45°C) (Proctor et al., 2017). The many reasons for this proliferation are discussed below.

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Management of Legionella in Water Systems

Stagnation. Stagnant areas in premise plumbing support more cultivable legionellae (including *L. pneumophila*) than other parts of premise plumbing (Fisher-Hoch et al., 1982; Tobin et al., 1981). Ciesielski et al. (1984) showed that hot-water tanks with stagnant water support higher *L. pneumophila* numbers (10^5 to 10^6 CFU/L) compared to hot-water tanks in which water was continuously replaced (less than 10^4 CFU/L). Compared to non-stagnant water, stagnant water has lower or no disinfectant residual (Fisher-Hoch et al., 1982; Wang et al., 2012), lower water temperatures (Patterson et al., 1994), higher concentrations of organics (LeChevallier et al., 1996; Wang et al., 2012), lower dissolved oxygen concentrations (Wang et al., 2012), higher biomass concentrations (Lautenschlager et al., 2010), altered microbial community composition (Dai et al., 2018a; Lautenschlager et al., 2010), and higher numbers of protozoan hosts (Wang et al., 2015b)—factors that all influence *L. pneumophila* growth.

Corrosion. The impact of corrosion products on *Legionella* proliferation is multifaceted (Brazeau and Edwards, 2013). By consuming residual disinfectant, these compounds create a more favourable environment for *Legionella* growth. Increased bioavailability of various metal corrosion products, such as iron, may also upregulate virulence in legionellae, stimulate general biofilm growth (Buse et al., 2012), and contribute to *Legionella* growth in hot-water heaters (Dai et al., 2018b; Ji et al., 2017; Proctor et al., 2017). Iron released during the recent massive corrosion event in Flint, Michigan, contributed to loss of chlorine residual and, as a required nutrient (Reeves et al., 1981; States et al., 1985; Warren and Miller, 1979), this metal was also hypothesized to stimulate *Legionella* growth (Rhoads et al., 2017a). Van der Lugt et al. (2017) also recently reported that iron rust in stainless-steel shower heads resulted in increased *Legionella anisa* plate counts. Corrosion products can also promote heterotrophic biofilm growth by producing electron donors, such as hydrogen, and by stimulating autotrophic metabolism and fixation of organic carbon in the system (Rhoads et al., 2017b).

Pipe Materials. Pipe material may influence growth of *L. pneumophila*. For example, rubber material in a model pipe system enhanced growth of *L. pneumophila*, except when a biocide (thiuram) was present in the rubber material (Niedeveld et al., 1986). Plastic pipe materials can also enhance growth of *L. pneumophila*, especially those used in premise plumbing, such as soft PVC (PVC-P), polyethylene, polypropylene, or polybutylene materials (Rogers et al., 1994a,b; van der Kooij et al., 2002). The biofilm concentration on each type of pipe material correlates with *L. pneumophila* load (Learbuch et al., 2019). Therefore, pipe materials most likely affect *L. pneumophila* growth indirectly: higher biofilm concentrations support more protozoan hosts, which generate higher counts of *L. pneumophila* (van der Kooij et al., 2017). European standardized laboratory tests have demonstrated that, compared to an inert material such as glass, rubber (natural and synthetic), soft PVC (i.e., PVC-P), polyethylene, polypropylene, and polybutylene significantly enhance microbial growth (Hambsch et al., 2014) because of the growth-promoting organic compounds that these materials release. In contrast, stainless steel, PVC-C, and PVC-U did not enhance growth of *L. pneumophila* in these laboratory tests. A field study of several buildings demonstrated that the highest cultivable legionellae numbers were present in the biofilm on rubber components of taps (van Hoof et al., 2014), consistent with various laboratory test results.

In premise plumbing, the impact of copper pipes on legionellae is not consistent among studies, possibly due to differences in biofilm microbiota and the physiological status of cells. Several laboratory studies report that copper inhibits growth of *L. pneumophila* (e.g., Learbuch et al., 2019; Rogers et al., 1994b; Schoenen et al., 1988). In addition, Danish buildings with copper premise plumbing showed lower cultivable legionellae counts than buildings with iron pipes (Pringler et al., 2002). In contrast, others observed enhanced growth of *L. pneumophila* on copper compared to PVC-U or PVC-C (Buse et al., 2014a,b; Gião et al., 2015; van der Kooij et al., 2002). Likewise, by comparing bacteria growing in

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Management of Legionella in Water Systems

tubing downstream of biofilm reactors with copper versus PVC-U coupons, Lu et al. (2014) also noted that injected *L. pneumophila* actually survive better downstream of copper. A companion paper by the same group (Buse et al., 2014a) further indicated that the copper coupons were colonized by and released a greater number of *L. pneumophila* when co-inoculated with *Acanthamoebae polyphaga* and measured by qPCR, but *L. pneumophila* were only cultivable from PVC-U coupons.

There are several possible explanations for the apparent enigma of net effects of copper plumbing on *Legionella*. First, van der Kooij and colleagues (2005) observed that new unused copper material initially inhibited growth of *L. pneumophila* due to the release of copper ions, but when the copper material was corroded, release of copper ions was reduced and inhibition of *L. pneumophila* no longer occurred. Interactions of the copper pipe with the local water chemistry is also important to consider. Proctor et al. (2017) noted that benefits of copper pipe for depressing *L. pneumophila* levels were only apparent at or below 41°C. Above 53°C, *L. pneumophila* were no longer detectable, and thus pipe material did not matter. Buse et al. (2017) noted that a higher pH (greater than 8.2), which limits dissolution, can also limit antimicrobial activity of copper pipe. Build-up of corrosion byproducts over time also limits the antimicrobial activity of copper toward *Legionella* (van der Kooij et al., 2005). In addition to having stronger antimicrobial properties than solid Cu, free Cu^{2+} in solution can induce other reactions, such as corrosion and associated hydrogen production, which could indirectly impact *Legionella* (Proctor et al., 2017; Rhoads et al., 2017b).

Copper might also induce a VBNC-like state for *L. pneumophila*, as has been suggested for *Pseudomonas aeruginosa* (Flemming et al., 2014). Induction of a VBNC-like state through copper exposure decreased the number of *L. pneumophila* detected by cultivation (Learbuch et al., 2019; Rogers et al., 1994a; Schoenen et al., 1988; van der Kooij et al., 2002), but not the number quantified by DNA-based methods (Buse et al., 2014a,b; Gião et al., 2015). Consistent with this hypothesis, after batch incubations with copper ions, Proctor et al. (2017) reported sharper decreases in *L. pneumophila* numbers by plate counts versus qPCR. Also, copper (and other) materials influence the microbial composition of premise plumbing biofilms (Buse et al., 2014a; Proctor et al, 2018), with copper resulting in less biofilm growth than various hard and soft plastics (Proctor et al., 2018; van der Kooij et al., 2017). Interestingly, while less biofilm may accumulate on copper materials than on plastics, the types of bacteria and amoeba present could be more supportive of *L. pneumophila* growth than those on plastics (Buse et al., 2014a,b; Gião et al., 2015). In particular, *V. vermiformis* is the *L. pneumophila* host most often associated with warm- and hot-water (largely copper-pipe) systems (Buse et al., 2017; Ji et al., 2017). Hence, along with biofilm concentration, the species composition of the biofilm is important for growth of amoebae that favor *L. pneumophila* replication. Overall, *L. pneumophila* growth appears enhanced in biofilms dominated with α-Proteobacteria, key prey for protozoan hosts (van der Kooij et al., 2018).

Once within the complex plumbing of a large building, *L. pneumophila* may persist given the right combinations of temperature, stagnation, and subsequent loss of residual disinfectant, often exacerbated by the presence of iron oxides/hydroxioxides/humics (Butterfield et al., 2002) and other pipe corrosion products (Rhoads et al., 2017b). *L. pneumophila* strains have remained detectable in simulated building water systems for a long time (i.e., up to 2.4 years) (Paszko-Kolva et al., 1992; Skaliy and McEachern, 1979; Wadowsky and Yee, 1985), with the one apparent clone in buildings causing outbreaks over decades (Garcia-Nunez et al., 2008). This prolonged survival in water has been attributed to the organism's ability to produce and store poly-3-hydrobutyrate, a carbon/energy source when nutrients are scarce (James et al., 1999; Mauchline et al., 1992). Recently, Shaheen and Ashbolt (2019) showed that viable cells of a *L. pneumophila* serogroup 1 strain remained in a dormant-like state associated with amoebae for over two years in drinking water. Such persistence may be associated with the expression of a Type II

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Management of Legionella in Water Systems

secretion system, a transport mechanism that promotes bacterial growth at ambient drinking water temperatures (less than 25 °C) (Söderberg et al., 2004). In cold water, *Legionella* persist within trophozoites and acquire nutrients sufficient for maintenance from the host, but the population does not expand. Cold-water systems are unlikely to result in cases of legionellosis, except in warm climates where the water temperature exceeds 25°C for extended periods.

Cooling Towers and Industry Wastewater Treatment Works

Cooling towers provide a favorable environment for proliferation of *Legionella* due to not only their warm water temperatures but also the large surface area available for biofilm colonization. In addition, cooling towers can broadly disperse aerosols, from hundreds of meters to kilometres away (Nguyen et al., 2006). Cooling towers operate within the temperature window that supports *L. pneumophila* growth within amoebae (Berk et al., 2006; Canals et al., 2015; Critchley and Bentham, 2007; Hammer, 2018; Llewellyn et al., 2017; Nguyen et al., 2006; Scheikl et al., 2016), making control reliant primarily upon the use of biocides. It is also critical to position building air intakes well away from cooling tower-generated aerosols, while accounting for thermal inversion and other atmospheric phenomena (Engelhart et al., 2008).

Extensive outbreaks of legionellosis have also tracked to activated sludge treatment of pulp and paper mill and brewery effluents, which are typically not disinfected and are within 30°C to 40°C (Maisa et al., 2015; Nygård et al., 2008). On the other hand, conventional municipal wastewater treated by the activated sludge process typically has low levels of legionellae, probably in part due to the temperatures being below 30°C (Caicedo et al., 2018).

Hot Tubs

Public and private hot tubs are typically maintained at 38°C to 44°C, a favorable temperature range for *L. pneumophila*. A common feature linked to *Legionella* growth in hot tubs is biofilm build-up on internal plumbing surfaces that periodically contain stagnant warm water for extended periods (hours to days) (Costa et al., 2010). Sudden mobilization with entrained air and/or water circulation can aerosolize *Legionella* cells (likely associated with biofilm and amoebae) and lead to human infections (Fallon and Rowbotham, 1990; Leoni et al., 2018). Because hot tubs are inherently warm, there is a heavy reliance on biocides to suppress microbial growth (e.g., Qin et al., 2013). However, biocides can by no means eradicate all resident microbes, and these chemicals can also shape the microbial communities inhabiting the hot tubs. Hot tubs are *Legionella* infection risks not only for their users but also for attendants and patrons who pass down-wind of aerosols (Costa et al., 2010; Hamilton et al., 2018).

Other Devices

As with any device exposed to air and moisture, humidifiers and nebulizers can support biofilm growth and associated legionellae and deliver aerosols to susceptible individuals, particularly in healthcare settings (Kyritsi et al., 2018; Mastro et al., 1991; Yiallouros et al., 2013). For example, supermarket vegetable misters have been sources of Legionnaires' disease (Barrabeig et al., 2010). Other devices that generate aerosols from stored/stagnating warm water sources and have been associated with cases of

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Management of Legionella in Water Systems

Legionnaires' disease include car windshield wiper fluids and sprayers (Wallensten et al., 2010), car wash facilities (Baldovin et al., 2018), and decorative fountains (Decker and Palmore, 2013).

Plant Growth Media and Bagged Compost

The major non-water medium associated with cases of Legionnaires' disease is garden soil and compost materials, which most often promote the growth and detection of *L. longbeachae* (Currie et al., 2014; Whiley and Bentham, 2011). However, *L. longbeachae* is probably under-reported even more than non-serogroup 1 *L. pneumophila* and may also occur within a range of environments discussed above such as cooling towers (Bacigalupe et al., 2017; Thornley et al., 2017).

EXPOSURE PATHWAYS

As pathogenic legionellae grow to high concentrations in free-living protozoa associated with biofilms, infectious *Legionella* cells may be released in aerosols in various forms: as free cells, cells within biofilm fragments, or cells associated with free-living protozoan trophozoites, cysts, or expelled vesicles (membrane-bound structures containing undigested materials) (see Figure 2-7; Lau and Ashbolt, 2009; Shaheen and Ashbolt, 2017). While *Legionella* infections are the most frequently identified etiologic agents from environmental aerosol exposures, other amoeba-resisting bacterial pathogens may also cause infections but go undetected because of inadequate methodologies used to identify agents (Lamonth and Greub, 2010; Lienard et al., 2017).

Common exposure pathways include breathing in aerosols in the 2- to 10-μm size range generated by showers, hot tubs, humidifiers, spray misters, cooling towers, car washers, windshield wiper spray, aeration basins used in wastewater treatment, and water (decorative) features and fountains. Aspiration of drinking water is another exposure pathway. A particular feature of *L. longbeachae* infections is the association with aerosols generated from wood and bark residuals and poorly matured compost sold as potting media in sealed plastic bags (Steel et al., 1990), since *L. longbeachae* and its supporting free-living protozoa hosts thrive in the biofilm environment associated with warm, partly decaying wood residuals.

Most reports of Legionnaires' disease from building exposures involve hot water mixed with cold water used for showering or held in hot tubs. Cold tap water that has warmed, such as in humidifiers, or aspirated stagnant drinking water can also be problematic. Features that increase the likelihood of significant exposures include the use of hot- or cold-water storage tanks in buildings, aerators on taps, water conserving (finer misting) showerheads, and high-rate aeration of hot tubs.

Notably, most cysts of free-living protozoa are too large to reach the lower respiratory tract (i.e., they are greater than 10 μm). Larger biofilm fragments are also less likely to reach the sites for lung macrophage infection. In contrast, amoebae are known to expel cells and food in membrane-bound vesicles, for which a few hundred infectious *L. pneumophila* cells have been estimated per vesicle (Shaheen and Ashbolt, 2018), making *Legionella*-encapsulated vesicles a likely but rarely studied environmental form of exposure. Also, infected trophozoites may rupture within the airways, releasing several hundred free bacterial cells (Buse and Ashbolt, 2012) within the respiratory size. In support of amoeba-associated infectious *L. pneumophila* cells is the report of *Acanthamoeba* antibodies in people with legionellosis (C. Chappell, personal communication), but this association may be accidental, given the high likelihood for people to have antibodies to this genus of environmental amoebae (Chappell et al., 2001). Unfortunately, neither the biochemical nor genetic attributes that promote *L. pneumophila* survival in aerosols have been

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Management of Legionella in Water Systems

identified, despite the large number of cases and isolates obtained from outbreaks (e.g., Bennett et al., 2014).

Physicochemical conditions of the aerosols may impact domestic, commercial, and industrial human exposures. For example, lung deposition may be more likely for bacteria in an isotonic solution (close to 0.9 percent salinity or 1,100 milliSiemens [mS]/cm^2) (Haddrell et al., 2014). This level is typical of hot-tub aerosols, which are around 1,200 mS/cm^2 compared to 4,000 mS/cm^2 in cooling towers and less than 200 mS/cm^2 in tap water. Hence, aerosols from hot tubs and perhaps cooling towers may be more likely to reach deep into the lungs (Richard Bentham, Flinders University, Adelaide, personal communication, May 14, 2018). The likelihood of aerosol entry into the lungs is further enhanced in hot tubs because people sitting in or near the units breathe in close proximity to the water surface (Moore et al., 2015). If atmospheric conditions such as relative humidity and wind direction are favorable, then *Legionella*-containing aerosols may infect people some tens of kilometers downwind (Nygård et al., 2008).

From epidemiology studies of Legionnaires' disease in the United States (reviewed by Garrison et al., 2016), the common known pathways for exposure appear to be from potable water within buildings and from cooling tower aerosols, followed by hot tubs, fountains, and other devices. Among the building categories, hotels and resorts, long-term care facilities such as nursing homes, and hospitals are the most likely to be associated with an outbreak of Legionnaires' disease. However, given that most cases of Legionnaires' disease are sporadic (see Chapter 3) and the sources of such exposures are not identified, the relative disease burden from cooling towers, from homes and larger buildings, or from other engineered water features has yet to be determined.

CONCLUSIONS AND RECOMMENDATIONS

L. pneumophila is now the leading cause of reportable drinking water-associated disease outbreaks in the United States. To reduce this significant healthcare burden, a deeper understanding of *Legionella* ecology, the genetic traits that equip *Legionella* strains to colonize engineered water systems, and how *Legionella* survive in aerosols and thrive in the human lung is required. These and other important topics for future research are discussed in greater detail below.

There is a need to better understand the mechanistic pathways for the development of Pontiac fever, and what roles the pathogen, endotoxins, *Legionella*-harboring amoebae, or other exposures play in disease pathogenesis. Additional studies aimed at understanding the differences in *Legionella* species characteristics associated with Pontiac fever are also needed. Because Pontiac fever is associated with less mortality, focused studies examining this clinical entity have been limited to date. Pontiac fever reporting occurs primarily through outbreak investigations, which limits assessments of true incidence, population risk, and an understanding of the relationship between certain *Legionella* species and serotypes and disease manifestations. There is a need to develop improved diagnostic tools for Pontiac fever (including molecular methods) that would enhance overall *Legionella* epidemiology and outbreak investigation and detection.

There is a need to better characterize legionellosis among neonates, young children, and adolescents, who may have varied epidemiologic risk factors for exposure to *Legionella* and differing risk for disease manifestations. There have been limited studies of Legionnaires' disease among children. The majority of current guidelines and recommendations focus on adult disease or target high-risk patient populations (e.g., immunocompromised hosts). Studies of community-acquired pneumonia,

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Management of Legionella in Water Systems

fever, and non-respiratory viral influenza-like illness among pediatric populations that assess *Legionella* are needed.

Studies that further assess the contribution of aspiration of potable water as a mechanism for clinical legionellosis both in community outbreaks and among sporadic cases are needed. Inhaled respiratory droplets are thought to be the primary mode of exposure to *Legionella*, but other methods of exposure through water-based contact are poorly characterized. Aspiration, including microaspiration and silent aspiration, is thought to be potentially linked to legionellosis. Links between feeding tubes and among conditions that increase risk for aspiration, together with studies demonstrating potential short-term oral colonization, suggest potential risks from this pathway.

The capacity of *L. pneumophila* to resist detergents, heat, chemical disinfectants, and antibiotics, as well as predatory amoebae and white blood cells, depends on its growth phase. The resilience and infection potential differs by orders of magnitude for replicative, stationary or transmissive phase, and the mature infectious form of *L. pneumophila*. **Therefore, protocols should be developed to generate, identify, enumerate, and report distinct *Legionella* cell types.** These classifications are fundamental to not only experimental reproducibility but also to the development and accurate assessment of strategies to eliminate virulent legionellae from patients and engineered water systems.

Whether *L. pneumophila* persistence within built water systems is promoted by the bacterium's differentiation into an apparent viable-but-non-culturable state that is both resilient and reversible remains an urgent question with implications for public health. To date, studies of VBNC-like *L. pneumophila* are largely descriptive; for example, quantification of resuscitation from the VBNC-like form is lacking. Needed are protocols to generate and isolate pure populations of VBNC-like cells for physiological, biochemical, genetic, molecular, and infection studies. Molecular or biochemical markers that distinguish individual VBNC-like, MIF, replicating, and stationary phase *L. pneumophila* cells would also accelerate this research and enable experimentalists to distinguish true resuscitation of VBNC-like cells from regrowth of a minor population of cells.

Ecological studies have almost exclusively focused on the impact of environmental conditions on growth, survival, and inactivation of *L. pneumophila*. To clarify whether the ecological principles observed for *L. pneumophila* apply to other pathogenic *Legionella* species, research on the ecology of *L. longbeachae*, *L. micdadei*, *L. dumoffi* and other pathogenic *Legionella* species is warranted. In addition, studies on the ecology of *L. pneumophila* have focused primarily on building water systems, leaving the ecological conditions responsible for *L. pneumophila* growth in other environments (e.g., cooling towers, wastewater treatment plants, hot springs, soils) largely unexplored. New research in these two areas could result in improved control measures for other pathogenic *Legionella* species and for *L. pneumophila* in environments other than premise plumbing.

The acceleration of genomics in the clinical, environmental, and laboratory sciences has expanded awareness of the extraordinary diversity within the *Legionella* genus. Yet, most knowledge of *L. pneumophila* pathogenesis comes from a relatively small number of domesticated laboratory strains. **A wealth of genomic data can now inform research to identify specific genetic markers of resilience and virulence among the environmental and clinical *Legionella* and accelerate the rational design of risk assessment tools and environmental remediation methods.**

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Management of Legionella in Water Systems

Clarifying the diversity of free-living protozoa that support or diminish the intracellular growth of legionellae in water and soil environments is fundamental to understanding and controlling legionellosis. Whether legionellae persist within free-living protozoa versus growing to high numbers appears to be influenced by many poorly understood factors, including temperature, species of bacterial prey available, presence of host symbionts, and host cell form. Direct (locational) observations and metagenomic studies of microbial diversity are required to provide a stronger ecological foundation to identify the protozoa that control the growth of pathogenic *Legionella* in various environments. Microcosm studies could investigate how nutrients and biocides affect the life stages of the host protozoa (e.g., by triggering encystation), identify the key host species, and elucidate the role of other free-living protozoa that might feed on the primary hosts of legionellae.

Despite clear evidence that people acquire Legionnaries' disease by inhaling contaminated water or soil, **neither the biochemical nor genetic attributes that equip *Legionella* bacteria to survive in aerosols have been identified.** Knowledge of the antigens or genetic loci that confer resilience of airborne legionellae and other factors like packaging (within biofilm, vesicles, trophozoites) would guide risk assessment of microbes that colonize engineered water systems.

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3
Quantification of Legionnaires' Disease and *Legionella*

This chapter addresses what is known about the incidence of Legionnaires' disease from surveillance systems and the occurrence of *Legionella* bacteria in water systems including the methods used to collect both clinical and environmental data. Both the tracking of disease incidence and monitoring the number of *Legionella* bacteria in various water systems are fraught with difficulties. These difficulties include deciding who to test, where and when to sample the environment, what methods to use, and how to interpret the data. Despite these challenges, advances have been made and are likely to continue as legionellosis becomes a higher public health priority.

Most cases of Legionnaires' disease are never linked to any specific environmental source, for many reasons. Most individuals are never diagnosed, even among those who seek medical care. Those who are diagnosed may have no associated clinical isolate to confirm the results of the urinary antigen test. Sampling for *Legionella* in buildings is routine in the United States for only a subset of acute care hospitals and other potential sources such as hotels. In addition, most states do not have the capacity to investigate environmental sources of Legionnaires' disease, with few environmental microbiologists or engineering experts on staff in public health departments. It is still the case that information on Legionnaires' disease stems mostly from investigations of recognized outbreaks, which account for only 4 percent of cases in the United States (Hicks et al., 2011). Not known is whether the environmental exposures found in outbreak investigations accurately represent the exposures for the majority of cases.

More information is needed about environmental exposures that result in disease in order to estimate their risk. To assess the level of risk of Legionnaires' disease, a quantitative microbial risk assessment (QMRA) framework can be designed using an estimate of the concentration of *Legionella pneumophila* (the pathogen most likely to cause disease) associated with a particular source (e.g., showerhead, hot tub, cooling tower) combined with dose-response information about the bacterium. As quantification of viable *Legionella* in water samples increases, this framework can be used to better understand which environmental exposures are most likely to lead to cases of legionellosis. This chapter ends with a discussion of the role of QMRA in linking clinical and environmental data and informing subsequent actions as well as in determining risk-based numerical values for *Legionella* in water.

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Management of Legionella in Water Systems

INCIDENCE OF LEGIONELLOSIS IN THE UNITED STATES

To quantify Legionnaires' disease incidence, national surveillance is undertaken that builds on local and state surveillance efforts. All states require that public health authorities be notified of those diagnosed with Legionnaires' disease or Pontiac fever. In turn, states voluntarily report their numbers to the U.S. Centers for Disease Control and Prevention (CDC). Separately, states also report *waterborne disease* outbreaks to the CDC, including those caused by *Legionella*. Together this information serves as a basis for quantifying the incidence of Legionnaires' disease and contributes to our knowledge of the epidemiology of the disease. Before describing the nation's *Legionella* surveillance systems, the diagnostic tests used to identify cases of Legionnaires' disease are briefly reviewed (building on the Chapter 2 discussion).

Diagnostic Tests for Legionellosis Used in Surveillance

According to CDC, the preferred diagnostic tests for Legionnaires' disease are culture of lower respiratory secretions on selective media and the urinary antigen test. Serological assays can be nonspecific and are not recommended in most situations, while polymerase chain reaction (PCR) is utilized by some academic and reference laboratories.

Culture of sputum or bronchoalveolar lavage specimens from pneumonia patients is important to determine if *Legionella* is the causative agent, regardless of species and serogroup. *L. pneumophila* forms colonies on buffered charcoal yeast extract agar within three to five days. As discussed in Chapter 2, most non-*pneumophila Legionella* species (spp.) may require longer incubation times and different media, and some culture media do not support growth of certain non-*pneumophila Legionella* spp. Culturing *Legionella* is challenging because of the needs for a lower-respiratory specimen and technical expertise in the laboratory. Furthermore, a history of prior antibiotic use interferes with culture. Most hospitals do not routinely culture sputum for *Legionella,* although some academic health centers routinely culture bronchoscopy specimens in patients with pneumonia of unknown etiology. Culture methods are critically important to epidemiologic investigations because molecular analysis can link clinical isolates to environmental samples to document the source of the exposure.

Most patients with reported Legionnaires' disease are diagnosed as a result of a positive *Legionella* urinary antigen test (UAT), which is available at commercial laboratories. Its advantages include ease of use, relatively high sensitivity, and the ability to noninvasively diagnose *L. pneumophila* serogroup 1. The UAT also has a rapid turn-around time (within hours), but this benefit is only available at the 25 percent of acute-care hospitals that conduct the test on site; otherwise, one to three days or more are required (Garrison et al., 2014; McClean et al., 2010) or sometimes longer, particularly for sites that send samples to outside laboratories. The UAT's selectivity for *L. pneumophila* serogroup 1 means that patients with clinically important non-serogroup 1 *L. pneumophila* infections and non-*pneumophila Legionella* infections will be missed. Finally, as mentioned in Chapter 2, UAT results can be negative early in the disease course and are less likely to be positive with less severe disease (Mercante and Winchell, 2015).

Serology is a valuable tool for epidemiologic studies, but it has little clinical impact because of the delay in receiving results (Reller, 2003). Blood samples taken three to six weeks apart are analyzed for rises in antibody titer to *Legionella*. In most cases of Legionnaires' disease, a four-fold increase in antibody titer is detected within three to four weeks although it may take longer. Thus, both sensitivity and specificity of serologic tests can be problematic.

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Molecular testing for *L. pneumophila* consists of highly sensitive PCR and other nucleic acid amplification tests. Most published studies utilize PCR testing that targets the macrophage infectivity potentiator (*mip*) surface protein of *L. pneumophila* (similar to the PCR tests done for environmental samples). As discussed in Chapter 2, PCR tends to detect more cases than UAT and culture tests, and it has the additional advantage of being useful in patients who are already on antibiotic therapy. PCR methods can currently detect *L. pneumophila* serogroup 1 and a few non-*pneumophila* species (Benitez and Winchell, 2013; Cross et al., 2016; Merault et al., 2011). Importantly, PCR for *Legionella* has been limited primarily to referral laboratories and research laboratories because of its difficulty, limited training, and the need for specialized instrumentation. Recently a multiplex PCR panel that includes *L. pneumophila* was approved by the U.S. Food and Drug Administration (FDA) for clinical use (Biofire® FilmArray® Pneumonia Panel) on sputum, endotracheal aspirates, bronchoalveolar (BAL), and mini-BAL lower-tract samples.

The criteria for diagnosing legionellosis used by the CDC are given in Box 3-1. These are likely to undergo revision in 2019 (Richard Danila, Minnesota Department of Public Health, personal communication, April 25, 2019).

Surveillance Systems for Legionnaires' Disease in the United States

All surveillance data must be interpreted in the context of the "surveillance steps" that lead to diagnosis and reporting (see Figure 3-1). To be counted as a case, a person with legionellosis must seek medical care or be assessed as part of an outbreak. A clinical specimen (e.g., urine, respiratory) must be submitted for testing, and the specimen must be tested for the presence of *Legionella*. This in turn requires that the laboratory be able to identify *Legionella*. All cases must meet the surveillance case definition given in Box 3-1. All 50 states, the District of Columbia, and U.S. territories (referred to collectively as the

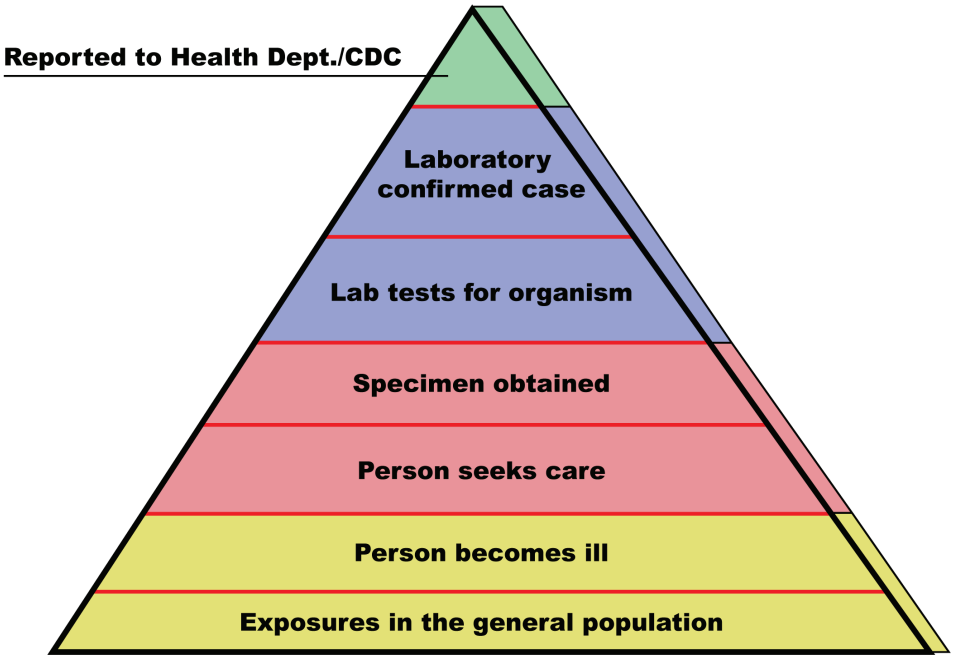

FIGURE 3-1 Disease surveillance steps.
SOURCE: Adapted from https://www.cdc.gov/foodnet/surveillance.html.

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BOX 3-1
CDC Laboratory Criteria for Diagnosis of Legionellosis

Confirmed Cases:

- By culture: isolation of any *Legionella* organism from respiratory secretions, lung tissue, pleural fluid, or other normally sterile site
- By detection of *L. pneumophila* serogroup 1 antigen in urine using validated reagents
- By seroconversion: fourfold or greater rise in specific serum antibody titer to *L. pneumophila* serogroup 1 using validated reagents on specimens collected three to six weeks apart.

Suspected Cases:

- By seroconversion: fourfold or greater rise in antibody titer to specific species or serogroups of *Legionella* other than *L. pneumophila* serogroup 1 (e.g., *L. micdadei*, *L. pneumophila* serogroup 6) using validated reagents on specimens collected three to six weeks apart.
- By seroconversion: fourfold or greater rise in antibody titer to multiple species of *Legionella* using pooled antigen and validated reagents on specimens collected three to six weeks apart.
- By the detection of specific *Legionella* antigen or staining of the organism in respiratory secretions, lung tissue, or pleural fluid by direct fluorescent antibody (DFA) staining.
- By the detection of specific *Legionella* antigen or staining of the organism in respiratory secretions, lung tissue, or pleural fluid by immunohistochemistry (IHC).
- By detection of *Legionella* species by a validated nucleic acid assay (e.g., PCR).

SOURCE: CDC (2010).

states) require that cases diagnosed as Legionnaires' disease or Pontiac fever be reported to local or state public health authorities. These cases are to be reported from the state to the CDC. If any step in this process does not occur, an individual ill with legionellosis will not be counted by the CDC. When cases reported through surveillance are clustered in time and space, an outbreak may be identified.

As suggested in Figure 3-1, there are significant losses in numbers as one proceeds through the surveillance steps, such that the number of cases reported to the CDC is likely to be an underestimate of the true incidence of legionellosis by as much as eight- to ten-fold (Dooling et al., 2015; Mercante and Winchell, 2015; Phin et al., 2014; St-Martin et al., 2013; von Baum et al., 2008).

Two national surveillance systems maintained at the CDC have the capacity to collect information on all diagnosed cases of legionellosis from states. These are the National Notifiable Disease Surveillance System (NNDSS) and the Supplemental Legionnaires' Disease Surveillance System (SLDSS). Separately, CDC has regulatory authority over the cruise ship industry, which must report all cases of Legionnaires' disease to the CDC.

National Notifiable Disease Surveillance System

Since the disease's recognition in 1976, surveillance for legionellosis has been conducted by all states, the District of Columbia, and U.S. territories. Reporting is mandatory for all diagnosed cases of Legionnaires' disease and Pontiac fever by healthcare providers and clinical laboratories to local and state health officials; cases must be reported within a short time period from diagnosis, usually within one to seven days.

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All cases of notifiable diseases are then reported voluntarily to CDC from public health officials in states through the National Notifiable Disease Surveillance System (NNDSS). Historically, notifiable diseases have been reported weekly, and the CDC has published preliminary case counts weekly. However, legionellosis reports are often sent to the CDC at irregular and sometimes lengthy intervals, such that the weekly counts may be low and the preliminary statistics for legionellosis often incomplete. Data shared on cases through this system are primarily demographic (e.g., place of residence) and clinical (e.g., date of onset of illness). Environmental source information, including the setting (e.g., hospital, hotel), type of water system (e.g., hot tub, decorative fountain), and type of water exposure (e.g., potable water, recreational untreated water) are not collected by the NNDSS. The NNDSS does not provide information on whether a case is travel-associated, healthcare-associated, or community-acquired.

Supplemental Legionnaires' Disease Surveillance System

A Supplemental Legionnaires' Disease Surveillance System (SLDSS) is available at the CDC to collect more comprehensive data on Legionnaires' disease cases from all states. The SLDSS includes potential environmental exposures, such as whether a case is travel-associated or whether an individual had exposure to hot tubs, respiratory therapy equipment, or a healthcare or senior-living facility. However, these data are often incomplete and not timely, and they frequently do not identify the potential environmental source of exposure. Therefore, these data have been insufficient to track trends in community-acquired, travel-associated, or healthcare-acquired cases (Cynthia Whitney, CDC, verbal communication, March 21, 2018).

In 2018, the CDC published the first surveillance summary focused on Legionnaires' disease using NNDSS and SLDSS data from 2014 and 2015, analyzing for associations with healthcare facilities, senior- or assisted-living facilities, and travel (CDC, 2018a). Future summaries are planned with the goal of better understanding the burden, impact, and trends of Legionnaires' disease over time.

Critique of National Surveillance and Next Steps

Given the loss of cases associated with each step in Figure 3-1, it is no surprise that the NNDSS and SLDSS do not account for most patients with legionellosis. In contrast to the steps leading to diagnosis, however, the reporting step itself is quite complete. In a 2011–2015 study conducted through the Active Bacterial Core Surveillance System to find all laboratory-confirmed cases of legionellosis, almost all cases found in the study had been previously reported through the NNDSS (Dooling et al., 2015).

Having two separate surveillance systems has been problematic, and the CDC plans to address the issue. The CDC is currently integrating the NNDSS and SLDSS through the NNDSS Modernization Initiative (Sam Posner, CDC, personal communication, September 21, 2018), a CDC-wide initiative designed to enhance the system's capabilities to provide more comprehensive, timely, and higher quality data. Case information that historically was sent through multiple routes will be consolidated into a single data stream.

Surveillance has been frequently referred to as "data for action," yet neither the NNDSS nor the SLDSS is robust for this purpose because states have not routinely investigated single cases for source(s) of exposure. Better understanding the source of environmental exposure could lead to improved prevention and control measures. Acknowledging that environmental investigation of every case is unlikely to occur because such investigations are resource intensive, more in-depth studies will be necessary to

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Management of Legionella in Water Systems

investigate a subset of cases by setting, source of water (e.g., potable water supply, cooling tower), and building water system for potential environmental exposure.

For decades, legionellosis programs both in states and at the CDC have been given low priority compared to other preventable infectious diseases, including communicable respiratory conditions. Furthermore, because the programs were initially focused on outbreak detection and control, the CDC and other public health agencies did not build expertise and capacity in fields that are needed to understand legionellosis prevention and control (e.g., building water systems, environmental engineering, and industrial hygiene). Legionellosis surveillance has not had dedicated resources to ensure timely environmental investigation of cases. Many state public health laboratories do not have the resources to identify, quantify, or subtype *Legionella* in water specimens; only three states have capacity to perform genome sequencing (Richard Danila, Minnesota Department of Health, email communication, September 29, 2018). CDC has recently devoted resources to legionellosis in some states through its Epidemiology and Laboratory Capacity cooperative agreements. These include Arizona, California, Colorado, Georgia, Illinois, Los Angeles County, Maryland, Michigan, Minnesota, Nebraska, Nevada, New York City and State, Ohio, Philadelphia, Tennessee, Utah, Virginia, Washington, DC, and Washington State. Some agreements have focused on getting public health laboratories, environmental health experts, and epidemiologists working together; others emphasize locating, registering, and testing cooling towers, whereas others focus on hotels; still others prioritize better cluster detection (Richard Danila, Minnesota Department of Health, personal communication, July 23, 2018). More efforts like these cooperative agreements are needed to help state and local health departments build their capacity for *Legionella* surveillance and response. New York City provides one of the most comprehensive legionellosis surveillance systems in the United States (see Box 3-2).

With respect to travel-associated cases, the Council of State and Territorial Epidemiologists (CSTE) has stated that surveillance for legionellosis lacks the timeliness and sensitivity necessary to detect outbreaks of these cases (CSTE, 2005). CDC is uniquely positioned to identify connections between cases that occur in residents of different jurisdictions, which is most likely with travel-associated outbreaks. It is particularly important that travel-associated cases be reported by the states to the CDC in almost real time to prevent delays in investigation and control. Following the 2005 CSTE position statement, CDC instituted a dedicated email address to improve reporting of travel-associated cases. Europe has a more extensive reporting system for travel-associated cases, discussed later in this chapter.

Academic centers currently play little, if any, role in either building or assessing prevention and control efforts for legionellosis. If the CDC chose to take a much more comprehensive approach to legionellosis, both the Integrated Food Safety Centers of Excellence and the Regional Centers of Excellence in Vector-Borne Diseases could serve as models. Under the Food Safety Modernization Act of 2011, the CDC designated six Integrated Food Safety Centers of Excellence at state health departments and affiliated university partners not only to identify and implement best practices in foodborne disease surveillance and outbreak response, but also to serve as a resource for other state, regional, and local public health professionals[1]. In 2017, five universities were established as regional Centers of Excellence to help prevent and rapidly respond to emerging vector-borne diseases across the United States. The goals of these centers include building effective collaboration between academic communities and public health organizations at federal, state, and local levels for surveillance, prevention, and response; training public health experts in the knowledge and skills required to address vector-borne disease concerns; and conducting applied research to develop and validate effective prevention and control tools and methods and to anticipate and respond to disease outbreaks.

[1] See https://www.cdc.gov/foodsafety/centers/index.html, accessed March 9, 2019.

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BOX 3-2
Legionellosis Surveillance Data Summary, New York City, 2007–2017

Surveillance Methods

New York City (NYC) legionellosis surveillance data are comprised of reported positive *Legionella* clinical laboratory test results, clinical patient information, and patient exposure information obtained through patient interview. The NYC Health Code mandates that positive *Legionella* clinical laboratory test results be reported to the NYC Department of Health and Mental Hygiene (DOHMH). Electronic laboratory reports are sent to the NYC DOHMH Bureau of Communicable Disease through the Electronic Clinical Laboratory Reporting System. For each reported positive *Legionella* clinical laboratory test (urinary antigen test, culture, PCR, or paired serology) the NYC DOHMH conducts: (1) a medical record review using a standardized data abstraction tool; and (2) a standardized 11-page telephone or in-person interview of the patient or their next-of-kin. The healthcare facility's medical records include chest x-ray and computed tomography (CT) scan results, along with the recorded history of the patient's clinical symptoms and medical treatment. The patient interview collects information on the patient's home, work, and other addresses, presenting symptoms, and health history, along with information on known water exposures, travel, and healthcare visits during the ten days before onset of symptoms (the typical disease incubation period). Information gathered from these sources is used to determine if the patient's illness meets the case definition of a confirmed or possible case of legionellosis, and to assess if there are possible exposure sources or locations that require further investigation, based on the occurrence of legionellosis among other people who shared those possible exposures.

Results of Trends in Reported Legionellosis Cases, NYC, 2007-2017

As shown in Figure 3-2-1, from 2007 to 2017 rates of legionellosis increased for both men and women, and in all age groups. Legionellosis cases occurred more frequently among men (62 percent) than women (38 percent). The majority (69 percent) of patients diagnosed with legionellosis were adults aged 55 years or older. Rates of legionellosis increased for all racial groups, with the highest rate of increase among the non-Hispanic Black/African American population. Thirty nine percent of all cases occurred in people who identified as non-Hispanic Black/African American (approximately 22 percent of New Yorkers are non-Hispanic Black/African American). Rates of legionellosis increased in all five NYC boroughs. The largest number of legionellosis cases (n = 472, 32 percent of all cases) occurred in the Bronx, home to about 17 percent of the NYC population. Rates of legionellosis increased in neighborhoods of all income levels. The highest rates and the greatest rate of increase occurred in very high poverty neighborhoods.

Figure. Trends in Legionnaires' disease rates per 100,000 people, by demographic groups, NYC 2007-2017

Group	2007	2017	AAPC	*p*-value
Total	2.3	5.1	8.1	<0.01
Sex				
Female	1.4	3.8	9.2	<0.01
Male	3.2	6.5	7.4	0.01
Race and Ethnicity				
Black/African American (NH)	2.5	7.6	11.4	<0.01
Latino/Hispanic	1.6	3.3	8.3	<0.01
White (NH)	2.2	5.4	8.3	0.01
Asian (NH)	0.4	2.4	21.1	<0.01
Age Group (years)				
<35 years	0.2	1.6	9.3	0.03
35 to 54 years	1.5	2.5	4.4	0.11
55 to 64 years	4.0	8.6	9.1	<0.01
65 to 74 years	3.2	10.1	11.6	<0.01
75 to 84 years	6.1	11.0	6.2	0.01
≥85 years	5.2	10.2	7.9	0.03

Group	2007	2017	AAPC	*p*-value
Borough of Residence				
Bronx	4.1	7.0	6.6	0.02
Brooklyn	1.8	3.4	4.8	0.02
Manhattan	2.7	6.4	9.4	0.01
Queens	1.5	4.8	11.0	<0.01
Staten Island	1.5	5.7	15.7	<0.01
Neighborhood Poverty Level (% below FPL)				
Low (<10%)	2.0	4.8	7.3	0.02
Medium (10 to <20%)	1.6	4.5	9.2	<0.01
High (20 to <30%)	2.3	4.6	5.7	0.03
Very High (≥ 30%)	3.2	6.4	9.6	<0.01

Abbreviations: AAPC, average annual percent change; FPL, federal poverty level; NH, non-Hispanic.
Data sources: Population and poverty data from NYC DOHMH population estimates, modified from US Census Bureau intercensal population estimates, 2000-2016. Updated September 2017.

FIGURE 3-2-1 Trends in Legionnaires' disease rates per 100,000 people.

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Results from Medical Record and Patient Interview Data, NYC, 2013-2017

Health Conditions and Behaviors. The majority of legionellosis patients (72 percent) reported at least one chronic health condition. The most common conditions reported were diabetes (24 percent) and lung disease (19 percent). About half (45 percent) of patients reported a history of current or past tobacco smoking.

Exposure Settings. About 8 percent of legionellosis cases were definite healthcare-associated,[1] while about 4 percent were possible healthcare-associated.[2] About 9 percent of legionellosis patients reported traveling outside of NYC for at least one day during their ten-day disease incubation period. Among people diagnosed with legionellosis, 23 percent reported working during their incubation period.

Reported Water Exposures or Changes to Water Service. The following possible water exposures were reported by legionellosis patients as occurring during the ten-day disease incubation period: air humidifier, 1 percent; hot tub, 1 percent; swimming pool, 1 percent; decorative fountain, 2 percent; gym, 2 percent; respiratory equipment, 5 percent; shower outside home, 5 percent; grocery store, 10 percent. In 5 percent of cases, patients reported plumbing maintenance at the residence during the ten-day disease incubation period, and in 5 percent of the cases, patients reported a water service disruption.

Clinical Diagnostic Testing

The majority (90 percent) of legionellosis cases were diagnosed by *Legionella* urinary antigen test only. Ten (10) percent of legionellosis cases included an isolate from a clinical culture that could undergo molecular analysis for comparison to isolates from possible environmental sources.

Conclusions

From 2007 to 2017, legionellosis in NYC occurred at the highest rates among those who were aged 55 years and older, in neighborhoods with the highest poverty rates, and among those who identified as non-Hispanic Black/African American. From 2013 to 2017, the majority of people diagnosed with legionellosis in NYC had chronic conditions or health behaviors that are reported risk factors for developing legionellosis, including diabetes, chronic lung disease, and tobacco smoking. Data from patient interviews and medical record reviews point to the challenges involved in using surveillance data to identify a source for individual cases of legionellosis that are not part of a cluster: nearly 90 percent of cases were community-associated, where numerous exposures to aerosols of water may occur during the ten-day disease incubation period. Only a very small proportion of people recall specific water exposures during their ten-day disease incubation periods. Conversely, many people may experience unrecognized aerosol exposures during that time, from cooling towers and other sources. These patient histories offered little guidance for testing possible environmental sources for individual cases of legionellosis.

Only about 10 percent of cases included a clinical isolate that can undergo molecular analysis for comparison to isolates from possible environmental sources. Thus, NYC's experience suggests that even if local and state health departments had budgetary and personnel capacity to test any and all possible environmental exposures for each individual case of legionellosis, source attribution would be possible, at best, for only about 10 percent of cases.

These data indicate that any rigorous effort to better understand the sources of exposure that cause individual legionellosis cases will require well-funded, coordinated studies involving medical centers, laboratories, and health departments in areas with capacity for the consistent collection and cultivation of both clinical and environmental *Legionella* cultures for a substantial proportion of cases. This is resource intensive because most sporadic cases involve multiple possible environmental sources of *Legionella* exposure, and environmental isolates that do not match clinical isolates may still require on-going public health follow-up when they indicate possible disease risk from a potential environmental source.

[1] Patient spent all of the ten-day disease incubation period in an acute-care hospital or nursing home.
[2] Patient spent some portion of the ten-day disease incubation period in an acute-care hospital or nursing home.

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Management of Legionella in Water Systems

U.S. Department of Veterans Affairs Surveillance System

In addition to the national systems, the Veterans Health Administration (VHA) collects information on all cases of legionellosis within its healthcare system. The VHA operates the largest integrated healthcare system in the United States, with more than 1,200 sites of care, serving about 6 million veterans annually. In federal fiscal year (FY) 2016, 91 percent of veterans using VHA benefits were male, with a median age of 64 years and with higher morbidity than in the rest of the United States (Gamage et al., 2018), which as discussed in Chapter 2 are populations with an increased risk of contracting Legionnaires' disease. As discussed in detail in Chapter 5, the VHA has a *Legionella* prevention policy for medical facilities to limit *Legionella* growth in building water systems, requiring the collection of both environmental and clinical data. Concomitant to publication of the policy in 2014, the VHA Central Office implemented a national standardized Legionnaires' disease reporting system. Compared to the CDC's notifiable disease reporting system, the VHA collects more detailed information on each case, partly to assess if a person was exposed while inside a VHA facility. As more environmental data are collected throughout the VHA system, the surveillance system will become critical for evaluating the effectiveness of the VHA's legionellosis prevention policies and also provide useful information for public health agencies and other healthcare facilities.

Waterborne Disease Outbreak Reporting System of the National Outbreak Reporting System

A third U.S. national surveillance system—the National Outbreak Reporting System or NORS—is also maintained by the CDC and collects data on waterborne and foodborne disease outbreaks in the United States. CDC categorizes the sources of waterborne disease outbreaks as follows: (1) drinking water, (2) treated recreational water, (3) untreated recreational water, and (4) another environmental exposure or undetermined source. *Legionella* was added to this system in 2001. Data from this system are currently publicly available on the NORS dashboard;[2] one can sort outbreaks by etiologic agent, year, state, setting (e.g., hotel, trailer park, hospital), water exposure (see above), and type of water system (e.g., hot tub, decorative fountain, cooling tower). NORS does not include detailed information on the setting and type of water system, which would be particularly useful for improving understanding of sources and conditions conducive to transmitting legionellosis.

The waterborne disease outbreak reporting system was initiated in 1971 as a partnership between CDC, CSTE, and the U.S. Environmental Protection Agency (EPA). It is dependent on public health departments in individual states to voluntarily provide complete and accurate data for waterborne disease outbreaks. The waterborne disease outbreak reporting system is important because outbreaks are most likely to be investigated for environmental sources.

A limitation of the NORS program for legionellosis is that the database (and hence the categories of setting, water types, and water exposure) was developed for enteric pathogens, making it less useful for pathogens capable of growth in water systems and transmitted by aerosolized water. Also, NORS data for legionellosis are not updated frequently; until December 2018, only data through 2014 were available.

[2] See www.cdc.gov/norsdashboard.

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Management of Legionella in Water Systems

European Surveillance

In most European countries, laboratory-confirmed Legionnaires' disease cases must be reported to the public health authorities of the country (e.g., in Germany, reporting is mandatory to national authorities within 24 hours of diagnosis). Most countries of the European Union report annually to the European Centers for Disease Control (ECDC) through the European Legionnaires' Disease Surveillance Network (ELDSNet) (Lara Payne, ECDC, personal communication, October 6, 2018). In 2017, 30 countries participated in ELDSNet. Members of this network review relevant technical documents and assist ECDC in organizing an annual meeting. ELDSNet collaborates with partners, such as the World Health Organization (WHO), public health authorities of non-EU countries, and tour operators. The incidence of Legionnaires' disease in Europe ranges widely among countries, which may largely reflect the variability in diagnosis and reporting. The burden of disease and trends are analyzed and reported in a detailed annual surveillance summary dedicated to Legionnaires' disease (e.g., ECDC, 2019).

Considerable focus of ELDSNet has been on travel-associated Legionnaires' disease, which accounts for approximately 20 percent of cases. (The European definition of travel-associated is more restrictive than in the United States and requires a stay in an overnight accommodation in the ten days before symptom onset.) The operating procedures of the surveillance scheme for travel-associated Legionnaires' disease in the EU and European Economic Areas (EEA) were updated in December 2017 (ECDC, 2017a), such that these cases are reported in almost real-time. In 2015, the estimated median delay between onset of illness and report to ELDSNet was only 17 days. When a cluster is identified within an EU/EEA country, all participating countries are notified and the public health authorities where the accommodation site is located are expected to report on the investigations conducted on the accommodation site. If the timeline for reporting is not fulfilled or control measures are deemed unsatisfactory by the ECDC, the name of the accommodation site is published on the ECDC website and the International Federation of Tour Operators is notified.

Trends in Reported Legionellosis in the United States

From 2007 to 2017, the rate of reported legionellosis cases through the NNDSS increased from 0.91 cases to 2.29 cases/100,000 persons, with more than 7,400 cases reported in 2017. Although case reporting is officially for legionellosis, 98 percent of the case reports represent individuals hospitalized with pneumonia (Dooling et al., 2015). Therefore, the trends primarily reflect more severe cases of Legionnaires' disease. It is likely that trends in treatment of outpatients with Legionnaires' disease and Pontiac fever follow trends similar to the hospitalization data.

Reported rates of legionellosis are lower in some areas of the United States (e.g., the West) than other areas. But for all areas of the country, the rates have increased from 2005 to 2015 (see Figure 3-2; Cooley, 2018). Weather patterns likely contribute to geographic differences, with warm, humid weather increasing Legionnaires' disease risk. Population and building density as well as regional differences in water treatment could also be playing a role.

In the United States, seasonal trends are evident, with cases rising in late spring, increasing in the summer, and peaking in late summer and fall. In 2016, 78 percent of cases were reported for the seven months of June through December. The lowest months are generally January through April. As with other variables, for all months from 2007 to 2016, the trend in incidence is generally upward.

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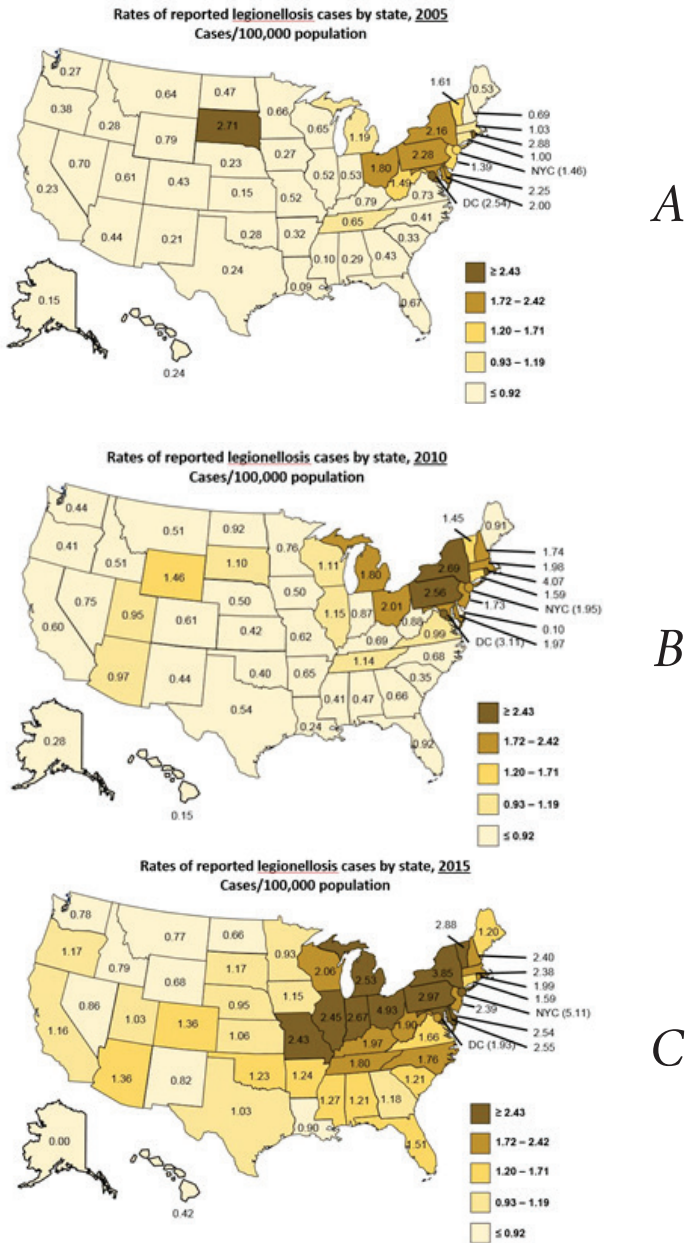

FIGURE 3-2 Rates of reported legionellosis cases by state for 2005 (A), 2010 (B), and 2015 (C). Values are cases per 100,000 population. SOURCE: Cooley (2018).

After leveling off or decreasing from 2007 to 2010, European case rates have increased from 1.0 to 1.8 cases/100,000 persons from 2011 to 2017 (see Figure 3-3), with the majority of cases (69 percent) reported from France, Germany, Italy and Spain. Australia has also noted increases in cases of *L. pneumophila* between 2005 and 2014 but not of *Legionella longbeacheae. L. longbeacheae* disease is rarely reported in the Unites States. Figure 3-3 shows that European rates are slowing relative to those of the Unites States, with the U.S. rate superseding the European rate since 2011.

Legionellosis cases can be subdivided into various categories. For example, cases may be recognized as part of an outbreak, a term used to describe two or more people with Legionnaires' disease exposed to *Legionella* at the same place at about the same time. Cases not recognized as part of an outbreak

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Management of Legionella in Water Systems

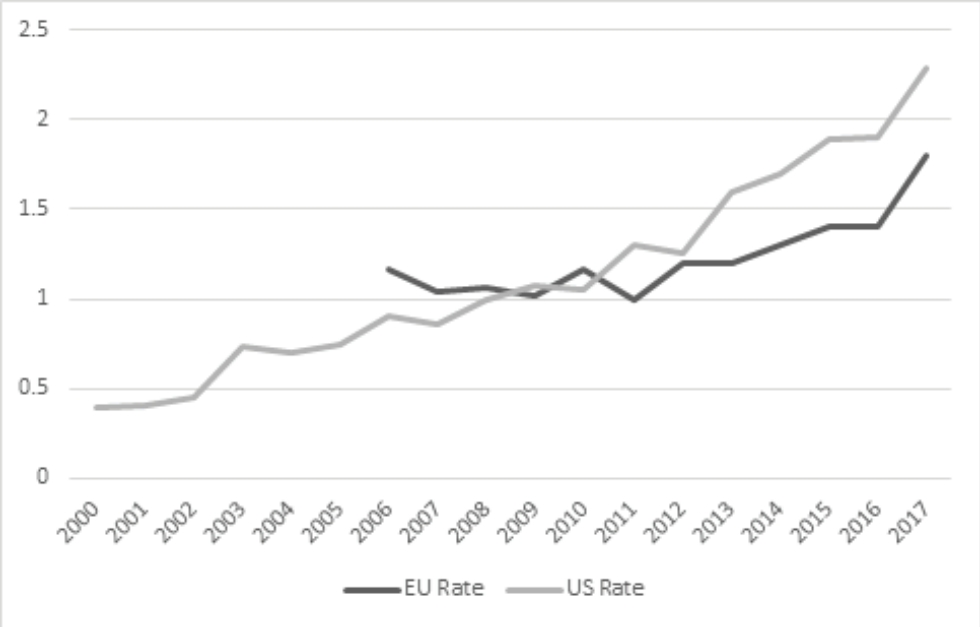

FIGURE 3-3 U.S. and European trends in Legionnaires' disease rate (number per 100,000 people).
SOURCES: 2013–2017 European data from ECDC (2019); 2012 European data from ECDC (2018); 2011 European data from ECDC (2017b); 2008–2010 European data from ECDC (2016); 2006–2007 European data from ECDC (2014); 2000–2009 U.S. data from Hicks et al. (2011); 2010–2015 U.S. data estimated by the Committee from https://www.cdc.gov/legionella/qa-media.html; 2016 U.S. data from CDC (2017b); 2017 U.S. data from CDC (2018b).

are considered sporadic. In the United States, waterborne disease outbreaks in the NORS system are subdivided into whether the outbreak source was identified as potable water, recreational water (treated or untreated), or another water source.

Frequently, cases are also categorized as either "healthcare-associated," "travel-associated," or "community-acquired." "Definite" healthcare-associated cases are defined as patients that stayed overnight in a healthcare facility (e.g., a hospital or long-term care facility) for the entire ten days before symptom onset, while "possible" cases are defined as patients with exposure to a healthcare facility for a portion of the ten days preceding symptom onset (CDC, 2018a). Travel-associated cases must have a history of spending at least one night away from home, either domestically or abroad, in the ten days before symptom onset (CSTE, 2005). Cases are designated as community acquired when the patient did not spend at least one night away from home in the ten days before onset of illness or was not exposed to a healthcare facility in the ten days before onset of symptoms. Various categorizations are used below to parse occurrence data in the Unites States.

Healthcare-Associated Cases

Healthcare-associated cases of Legionnaires' disease make up approximately 20 percent of all legionellosis cases reported in the United States. In 2015, among 21 jurisdictions that reported exposure information on more than 90 percent of cases through the SLDSS, 3 percent of cases were considered "definite" and 17 percent had "possible" exposure to a healthcare facility in the ten days before symptom onset (Soda et al., 2017). Of the definite cases, 80 percent were associated with long-term care facilities,

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Management of Legionella in Water Systems

18 percent with hospitals, and 2 percent with both. In addition, 3 percent were associated with assisted- or senior-living facilities (CDC, 2018a). An analysis of case reports to the ECDC between 2011 and 2015 reported 7.3 percent as healthcare-related, 4.9 percent of cases as nosocomial (i.e., from a hospital specifically) and 2.4 percent as "other" healthcare-related cases (Beauté, 2017).

Data from the VHA between 2014 and 2016 show that the rate of Legionnaires' disease significantly increased among veterans receiving VHA healthcare services but with no exposure to a VHA healthcare facility during the disease incubation period (from 0.9 to 1.47/100,000 enrollees). The rate of Legionnaires' disease among those with an overnight stay at a VHA facility during the disease incubation period significantly decreased (from 5.0 to 2.3/100,000 enrollees with an overnight stay). Most "definite" cases of healthcare-associated Legionnaires' disease (11 of 13) were in long-term care VHA facilities (Gamage et al., 2018).

Travel-Associated Cases

The CDC has reported data on travel-associated Legionnaires' disease from a limited number of jurisdictions. Benin (2002) found that 20 percent of Legionnaires' disease cases were reported as possibly travel-associated between 1980 and 1998. From 2005 to 2006, 24 percent of cases reported through the SLDSS were possibly travel-associated (Smith et al., 2007).

In Europe, 20 percent of Legionnaires' disease cases reported between 2011 and 2015 were travel-associated (Beauté, 2017). ECDC's case definition for travel-associated cases includes only lodging in a commercial establishment (e.g., hotel, resort), which is a more restrictive definition than the U.S. definition, in which any night away from home during the incubation period was reported as travel-associated. Nonetheless, data on travel-associated cases in the United States are similar to European data.

Box 3-3 discusses Legionnaires' disease rates for cruise ships, which have plateaued. Hotels and other commercial accommodation sites have been clearly documented to be an important source of environmental exposure to *Legionella.*

BOX 3-3
Cruise Ship Industry: Legionnaires' Disease Prevention and Control Efforts, 2007–2017

Despite a 21 percent increase in passengers and a marked increase in Legionnaires' disease outbreaks in the United States in the past decade, there was no significant increase in cruise ship associated outbreaks reported to the CDC in the five-year period from 2007 to 2011 (11 outbreaks) compared to 2012 to 2016 (12 outbreaks). In 2017, there were two cruise ship outbreaks (Sam Posner, CDC, email communication, April 17, 2019). These data suggest that prevention measures taken by the cruise ship industry appear to have been at least partially effective in addressing the threat of Legionnaires' disease outbreaks associated with cruise travel. Many in the cruise ship industry have engaged *Legionella* consultants to assure safety of their water supply and have conducted routine environmental sampling for *Legionella*, including quantitative culturing. Of particular note, CDC has regulatory authority over vessel sanitation and has provided guidance to cruise ships for Legionnaires' disease prevention for more than 20 years. The guidance and inspections of hot tubs and other potential environmental sources by the CDC's Vessel Sanitation Program (VSP) and the adverse publicity and liability associated with outbreaks investigated by CDC using its regulatory authority may have contributed to the attentiveness of cruise lines to maintenance of their water operations. The VSP 2011 Operations Manual and updates are available at http://www.cdc.gov/nceh/vsp.

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Management of Legionella in Water Systems

Community-Acquired Cases

Most Legionnaires' disease cases in the United States are considered to be community-acquired (either sporadic or as part of an outbreak). This is consistent with what is found in Europe, where 70 percent of Legionnaires' disease cases reported to ELDSNet between 2011 and 2015 were community-acquired (Beauté, 2017). Similarly, the Robert Koch Institute (2013, 2015) estimated that about 70 percent of reported legionellosis cases are neither related to an outbreak nor nosocomial, but rather acquired in private or professional surroundings.

Unfortunately, most of the information on community-acquired cases in the United States comes from outbreak investigations or from the many publications on individual outbreaks. The most comprehensive review of sporadic, community-acquired cases (Orkis, 2018) included 47 articles on sporadic cases (excluding healthcare- and outbreak-associated cases) in which a total of 28 environmental sources were identified. Potable water from single family homes, large building water systems, and car travel appeared to contribute to a substantial proportion of the sporadic Legionnaires' disease cases. Cooling towers were also noted to be a potentially significant source. The difficulty in source attribution was noted, with definitive links using molecular typing between environmental sources and clinical isolates being made in only eight cases. The authors noted that understanding the risk magnitude of potential sources would make future public health investigations more efficient and enhance prevention efforts.

den Boer (2015) performed source investigations on more than 75 percent of 1,991 patients with Legionnaires' disease between 2002 and 2012 (source investigations were only done for clusters of disease after 2006). The paper noted the difficulty and the resource intensity of investigations to locate with certainty the source of an infection, and it reported outcomes of investigations of sporadic cases together with outcomes of cluster investigations. Of the 1,484 source investigations performed, only 367 (24.7 percent) of the sources were positive for *Legionella* spp., and only 41 patients (2.3 percent) were found to have a clinical strain that matched the environmental source. The sources that matched included a healthcare setting (40 percent), residence (18 percent), industrial complex (8 percent), swimming pool (5 percent), wellness center (8 percent), hotel (5 percent), spa (5 percent), and car wash (3 percent). The study also examined 105 clusters associated with 266 patients based on location and geography: 26 percent of the clusters were associated with garden centers, 16 percent with healthcare facilities, 10 percent with a residence, 9 percent with wellness centers (e.g., spas, saunas), 7 percent with hotels, 5 percent with cooling towers, and 5 percent with holiday parks.

Che and colleagues (2003) reported an increased risk of sporadic cases of community-acquired Legionnaires' disease in industrial areas of France. They evaluated 880 cases from 1998 to 2000 that were not associated with an outbreak and in which individuals did not report an overnight hospital stay or traveling within ten days of disease onset. Seventy-nine percent of the cases were caused by *L. pneumophila* serogroup 1. A higher risk was reported in areas with exposure to aerosols and plumes of smoke, with the greatest risk being in areas with more than one industrial exposure. However, the results are inconclusive and the findings deserve further study.

A study by the New York City (NYC) Department of Health and Mental Hygiene looked at the potential role of occupation among 335 community-acquired cases. Compared with the general population, legionellosis case-patients who were working in the two weeks before diagnosis were significantly more likely to work in transportation, repair, protective services; cleaning services; or construction (Farnham et al., 2014).

Community-acquired cases are commonly attributed to private water systems, under the assumption that the small number of people exposed would not draw the attention of epidemiologists to investigate. For example, Bonilla Escobar et al. (2014) demonstrated that a healthy, immunocompetent

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young person with no other risk factors contracted Legionnaires' disease from an improperly maintained household humidifier, but no conclusions were drawn about the frequency of humidifiers being sources of *Legionella* infections. In another case study, two unrelated individuals appeared to contract Legionnaires' disease in their homes and both had solar water heaters with inadequately heated water (Erdogan and Arslan, 2016). Currently, it is largely unknown how often private water sources, particularly in individual homes, are the environmental exposure source for sporadic cases.

Outbreak Data That Reveal Environmental Sources

Most legionellosis outbreaks are detected through analysis of surveillance data compiled through the mandatory reporting systems described above. As discussed previously, and unlike the surveillance data reported through NNDSS or SSLDS, NORS data (now available from 2009 to 2017) are examined by water type, i.e., whether the outbreak is associated with drinking water, treated or untreated recreational water, or another water system. During 2013 to 2014, 19 states reported 42 outbreaks associated with **drinking water;** *Legionella* was implicated in 57 percent of the outbreaks (see Figure 3-4), 13 percent of the cases, 88 percent of the hospitalizations, and all 13 deaths[3]. From 2000 to 2014, NORS reported 363 outbreaks associated with **treated recreational water** that had a confirmed infectious etiology; 16 percent were caused by *Legionella* and legionellosis was confirmed or suspected to be responsible for all eight deaths (Hlavsa, 2018). During 2013 to 2014, 15 outbreaks were associated with "**another" environmental exposure to water**; *Legionella* was responsible for 63 percent of the outbreaks, 94 percent of hospitalizations, and all 17 deaths (McClung et al., 2017). Finally, 11 of 12 outbreaks associated with an **undetermined exposure to water** were caused by *Legionella* (McClung et al., 2017).

[3] See www.cdc.gov/healthywater/surveillance/drinking-water-tables-figures/html.

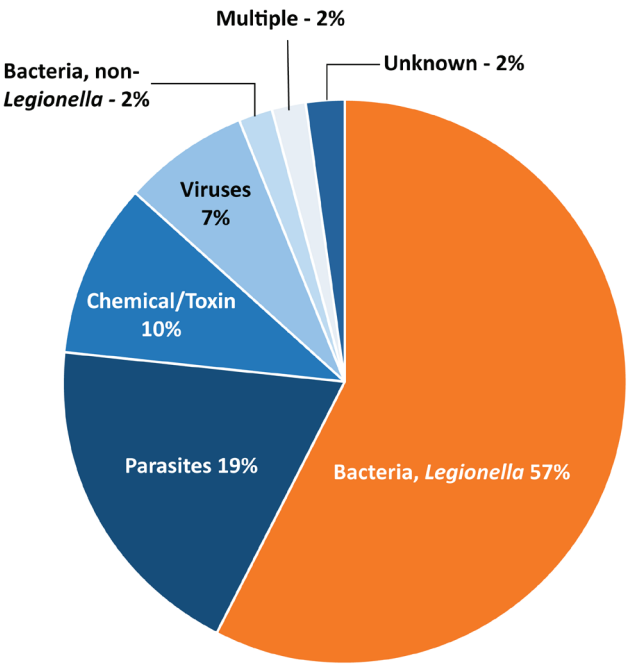

FIGURE 3-4 NORS reported drinking water-associated disease outbreaks, 2013–2014 (n=42).

SOURCE: CDC (2017).

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Management of Legionella in Water Systems

Unfortunately, published analyses of NORS data generally do not reveal the setting (e.g., hotel, hospital) or water exposure (e.g., spa, decorative fountain), although some of the data are available and could be stratified for further analysis. The Committee analyzed NORS data between 2009 and 2017, during which 290 legionellosis outbreaks were reported. A substantial percentage of cases were associated with hotels and healthcare facilities. Other implicated locales included long-term care facilities, assisted-living or rehabilitation facilities, apartment buildings, indoor workplaces, factories or industrial settings, and prisons. Within those settings, cooling towers, hot tubs, and ornamental fountains were implicated. The goal of this cursory analysis is to raise awareness of the data available via the NORS dashboard that could be analyzed to determine environmental exposures associated with legionellosis cases.

Garrison and colleagues (2016) analyzed data from 27 building-associated Legionnaires' disease outbreaks (2000–2014) that were investigated by the CDC between 2000 and 2014. Common exposure settings were hotels (44 percent), long-term care facilities (19 percent), and hospitals (15 percent). Common sources (within the settings) were found to be showers and faucets (56 percent), cooling towers (22 percent), hot tubs (7 percent), decorative fountains (4 percent), and industrial equipment (4 percent).

By reviewing the peer-reviewed literature and government documents published between 2006 and 2017, Hamilton and colleagues (2018a) identified 119 legionellosis outbreaks globally for which an environmental source was associated with the event. Potable water was identified as the source in 42 outbreaks (30 percent), although this was not subdivided to better understand whether a specific water system or fixture deficiency was the culprit. Cooling towers, air conditioning, or evaporative condensers were identified in 41 outbreaks (30 percent). Cooling towers were associated with 50 percent of the confirmed cases of legionellosis and the greatest number of fatalities. Fifteen (15) percent of outbreaks occurred at hotels.

One of the world's largest outbreaks of Legionnaires' disease was linked to a hot tub exhibited at a Dutch flower show (den Boer et al., 2002). Simply pausing at the hot tub was deemed the most important risk factor for infection, confirming that a contaminated hot tub, even if not used directly, can cause illness in susceptible people. Of particular importance is the potential role of municipal water systems. In Flint, Michigan the governor's task force concluded that the management of the Flint River-sourced water supply may have contributed to the outbreaks of legionellosis in 2014 and 2015 in Genesee County (Flint Water Advisory Task Force, 2016), and scientific studies identified aspects of the water that were conducive to *Legionella* proliferation (Rhoads et al., 2017; Zahran et al., 2018). Outbreaks have also been attributed to wastewater treatment plants (Kusnetsov, 2010; Loenenbach et al., 2018).

The investigation of a large outbreak of Legionnaires' disease in NYC in 2015 illustrates how a multi-disciplinary approach to outbreak detection and subsequent investigation can lead to successful control (Box 3-4, Chamberlain, 2017). This investigation is unique in its scope, timeliness, and the extent to which clinical and environmental data were paired to determine the source of the *Legionella.* It also illustrates the resource intensity and difficulty of investigations of Legionnaires' disease outbreaks.

Why Are Rates of Legionnaires' Disease Increasing?

Although often put forward as potential explanations for the increase in Legionnaires' disease incidence, neither improved reporting nor improved diagnosis are supported by available data as a major contributor to the rapid increase since 2000. Indeed, reporting of diagnosed cases was documented to be extremely high for the period 2011 to 2013 (Dooling et al., 2015). Currently there are very limited data available to assess the role of diagnostic testing in increased incidence.

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BOX 3-4
2015 Legionnaires' Disease Outbreak Investigation, Bronx, New York

In July 2015, the New York City Department of Health and Mental Hygiene (DOHMH) detected an increase in cases of Legionnaires' disease in the South Bronx, using the surveillance system described in Box 3-2. The purpose of the investigation was to describe patient demographic characteristics and comorbidities, identify environmental exposures, and implement control measures.

Reporting and Case Follow-up

Physicians and clinical laboratories are required to report positive *Legionella* test results to DOHMH. For each case reported, epidemiologists review patient medical records, interview the patient (or the patient's proxy) to determine if the report meets the CSTE/CDC national case definition for legionellosis, and identify risk factors and potential exposures.

Cluster Identification Analyses

Two methods are used to identify clusters that could be community outbreaks of reportable diseases. Each week, the historical limits method compares case volume in the most recent four-week period with comparable data from the previous five years at the city, borough, and neighborhood levels. A separate daily spatiotemporal cluster detection method is based on the space-time permutation scan statistic, and computes a ''recurrence interval,'' which is the number of days of surveillance required for the expected number of clusters at least as unusual as the observed cluster to be equal to 1 by chance. Additionally, an automated daily algorithm compares the building identification number (i.e., a unique code for every structure in New York City) assigned to the patient's address with a list of health care and congregate living facilities to identify concerning events not already detected by epidemiologists.

To guide environmental sampling, a multi-focused cluster test with the space-time permutation scan statistic was used to assess clustering of cases of Legionnaires' disease around cooling towers.

Case Definitions

An outbreak-associated case of Legionnaires' disease was defined as clinically compatible illness meeting the national case definition for Legionnaires' disease (Box 3-1), modified to include *L. pneumophila* serogroup 1 (Lp1) DNA detected by quantitative PCR (qPCR) in postmortem specimens, in either a resident of one of seven South Bronx ZIP codes (i.e., the outbreak zone) or in a person who worked in or visited the outbreak zone during the ten days before his or her symptom onset date (or collection date of the earliest confirmatory test if onset date was unknown) between July 2, 2015, and August 3, 2015. *Legionella* subtyping, as described hereinafter, was used to refine the case definition.

Deaths from Legionnaires' disease were defined as (1) patients meeting the case definition whose death was attributed to Legionnaires' disease within 30 days of the diagnosis date, or (2) patients meeting the outbreak definition in which the Office of Chief Medical Examiner listed *Legionella pneumonia* as the immediate cause of death.

Analyses of Patient Characteristics

The patient demographic and clinical characteristics were summarized and adjusted odds ratios (aORs) and 95 percent confidence intervals (CIs) were calculated using multivariable logistic regression and the mid-P exact method to assess the relationship between fatality and comorbidities, smoking status, and number of days from onset to diagnosis. Odds ratios were adjusted for age and sex.

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Environmental Monitoring

Cooling tower sampling in the outbreak zone was prioritized per the location of patients with Legionnaires' disease and the multi-focused cluster test. Although the city had no complete official registry of cooling towers at the time, cooling towers in the area were identified by examining city records of water credit and construction permit applications, in addition to publicly available satellite imagery. The sampled locations in cooling towers were thought to be most representative of the water aerosol generated. If the cooling tower basin was safe to access, a swab of biofilm was collected.

Methods. The New York State Department of Health Wadsworth Center and the New York City Public Health Laboratory tested cooling tower water samples for the presence of *Legionella* using PCR and culture methods. Use of PCR allowed for the rapid screening of samples to prioritize culture and cooling tower remediation. Samples in which *L. pneumophila* DNA was detected were processed and cultured at the Public Health Laboratory with standard microbiological methods. Isolates were identified as Lp1 through direct fluorescent antibody staining. Pulsed-field gel electrophoresis subtyping was performed at the Public Health Laboratory and Wadsworth Center with identical methods.

Epidemiologic Results

In total, 138 patients met the outbreak case definition of outbreak-associated Legionnaires' disease, and 128 (93 percent) were hospitalized. Illness onset peaked on July 26, 2015, and the last patient linked to the outbreak became ill on August 3, 2015. Sixteen (12 percent) patients died, five in their homes. A total of 108 patients (78 percent) resided in the outbreak zone. Of the remaining 30 patients, 16 resided in other Bronx ZIP codes, nine in other New York City counties, two in other New York State counties, and three in other states.

Several events led the investigation to one potential cooling tower source. On July 28, 2015, DOHMH received a physician inquiry about a cluster of respiratory illnesses among residents of a supportive housing residence for people with medical needs, including HIV infection, and the building identification number analysis identified two reports of Legionnaires' disease from this building. On July 29, 2015, the CDC notified DOHMH of a traveler who had been diagnosed with Legionnaires' disease and had spent part of the incubation period at a hotel in the South Bronx (Building A). Building A was located less than a block away from the supportive housing residence, and the cooling tower, which was not previously known to city agencies, was detected through satellite imagery. The multi-focused cluster test identified unusual case clustering of Legionnaires' disease cases around Building A, with a recurrence interval of 1.36 million years.

Environmental Results

The environmental investigation began on July 28, 2015. During the next three weeks, 55 cooling towers from 46 buildings in the outbreak zone were identified, inspected, and sampled. PCR results were available within 24 to 36 hours. Lp1 DNA was detected by qPCR in water samples from 21 cooling towers and successfully cultured from 14. An order to immediately remediate was issued to owners of cooling towers that tested positive for Lp1 by qPCR.

Whole-genome sequencing of the 14 Lp1 cooling tower isolates revealed the Building A strain to be indistinguishable from the 26 outbreak-associated clinical isolates. No strain from any other cooling tower matched to the Lp1 culture obtained from any patient during the investigation, as judged by whole-genome sequencing.

An order to disinfect all cooling towers within 14 days was issued to all NYC building owners on August 6, 2015. Tracking compliance with the citywide order presented its own difficulties, including the need to review more than 10,000 documents submitted to the city to demonstrate compliance.

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Conclusions

A large outbreak of Legionnaires' disease resulted in severe illness and death in a NYC neighborhood. Epidemiologic, environmental, and laboratory investigations implicated a hotel cooling tower as the likely source of the outbreak. The outbreak response was expedited by a screening of water samples collected from cooling towers using a qPCR-based assay for Lp1 DNA followed by culture of PCR-positive cooling towers. Previous outbreak investigations relied on culture, which, if successful, can take several weeks to identify and subtype. Using qPCR allowed rapid screening, prioritization, and focusing of control efforts on potential outbreak sources.

Both host factors and environmental factors are likely to contribute to the increased number of cases of legionellosis since 2000. As discussed in Chapter 2, increasing numbers of persons are at higher risk of acquiring Legionnaires' disease because of aging of the population, increased use of immunosuppressant drugs, and higher prevalence of comorbid conditions, including diabetes and chronic obstructive pulmonary disease. There is a growing dependence on heating, ventilation, and cooling systems, as well as increased complexity of indoor plumbing systems in large buildings, which have a labyrinth of water lines and features ranging from hundreds of showerheads along lengthy hospital corridors to hot tubs and indoor decorative fountains. Changes in plumbing materials could play a factor. In addition, increased efforts to conserve water with attendant slower flow in plumbing systems likely enhances biofilm formation and therefore increases risk of *Legionella* growth in premise plumbing (see Chapter 4). Inadequate maintenance of public water supplies (e.g., water main breaks, corrosion of pipes) may increase risk for contamination of building water systems and other water devices or equipment. Contaminated environmental sources, from dental hygiene equipment to street cleaning machines, continue to be newly identified (Ricci et al., 2012; Schönning et al., 2017; Valero et al., 2017).

Changing environmental conditions are also facilitating human exposure to aerosolized water containing *Legionella*. Multiple hydrologic factors including humidity and rainfall may influence legionellosis risk, and climate change, including global warming, is likely contributing to the increase in cases (see Chapter 2).

Despite the increase in reported rates, most cases of legionellosis are not diagnosed, even among those who seek medical care, and there is little evidence that diagnostic testing has improved for legionellosis between 2007 and 2016. Diagnostic testing for pneumonia in the Unites States has been generally discouraged for many reasons. Reimbursement practices deter use of microbiologic diagnostic tests for pneumonia. Professional guidelines of the American Thoracic Society and the Infectious Disease Society of America have also discouraged routine testing of hospitalized patients for community-acquired pneumonia (Bartlett, 2011; Mandell et al., 2007). Although these guidelines are currently being updated, it is not expected that the guidelines' approach to legionellosis will change. At one academic medical center, adherence to these guidelines for testing of patients for *Legionella* would have resulted in an underestimate of the burden of Legionnaires' disease of at least 41 percent (Hollenbeck and Mermel, 2011). In this study, even with more robust testing than recommended by the guidelines, only 35 percent of patients discharged with a diagnosis of pneumonia had been tested.

Microbiologic analysis standards in most laboratories have declined. The belief that a deep respiratory secretion is needed for *Legionella* culture has discouraged testing, although this assumption is incorrect; sputum specimens that may be inadequate for culture of other pathogens may be sufficient for culture of *Legionella* (Bartlett, 2011; Ingram and Plouffe, 1994). In 2011, Bartlett reviewed reasons why testing has declined for diagnosis of community-acquired pneumonia. In particular, the Clinical

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Management of Legionella in Water Systems

Laboratory Improvement Amendments regulations led to the demise of the "house staff laboratory" and the distancing of microbiological analysis from the site of care, which may delay diagnoses. Obviously, there are fewer options at most community and rural hospitals, many of which have only basic laboratories. Legionnaires' disease diagnostics, particularly use of culture, may have declined as a result of many of these factors. It is not known whether the use of PCR has had any impact on legionellosis diagnoses, although this may change as more molecular assays gain FDA approval.

There has been little, if any, federal research funding for applied research on legionellosis, which, in turn, may depress training on legionellosis in academic healthcare centers. As a result, academic healthcare centers in the Unites States have limited expertise on Legionnaires' disease. The National Institute of Allergy and Infectious Diseases has focused its *Legionella* funding on basic science related to *Legionella* and the pathogenesis of the organism (Heilman, 2015).

True Incidence of Legionellosis

It is difficult to determine from available data the true incidence of legionellosis in the United States, although reported cases are certainly an underestimate. Some studies have attempted to determine the incidence of Legionnaires' disease in hospitalized patients with pneumonia. A population-based study in two counties in Ohio in 1991 estimated 8,000 to 18,000 individuals were hospitalized with community-acquired Legionnaires' disease per year in the Unites States (Marston et al., 1997). From 2013 to 2015, 98 percent of patients with pneumonia in a Pittsburgh VHA hospital were tested for Legionnaires' disease with at least one diagnostic test, documenting that at least 1.7 percent of community-acquired pneumonia and 0.6 percent of healthcare-acquired pneumonia was caused by *Legionella* (Decker et al., 2016). The incidence of Legionnaires' disease among hospitalized patients was reported as 8/100,000 veterans, with an incidence of 6/100,000 for community-acquired Legionnaires' disease. More recently, Gamage et al. (2018) reported an incidence of Legionnaires' disease in the nationwide VHA system of 1.9/100,000 for the years 2014 to 2016. Since both VHA studies lacked data on veterans admitted to hospitals outside the VHA system, the incidence of pneumonia among veterans was underestimated. The CDC is currently working on better estimates of morbidity and mortality related to waterborne pathogens, including Legionnaires' disease, but these reports will not be available until late 2019.

To develop its own estimate of the incidence of Legionnaires' disease, the Committee relied on the estimate from the population-based Etiology of Pneumonia in the Community (EPIC) study of community-acquired pneumonia that required hospitalization (Jain et al., 2015). This CDC-led study is the more recent of only two such studies conducted in the United States that determined the incidence of Legionnaires' disease (the other being Marston et al., 1997). The EPIC study was conducted from 2010 to 2012 in Nashville, Tennessee, and Chicago, Illinois, and considered 2,488 patients. Using mainly UAT, Jain et al. estimated an incidence of community-acquired pneumonia caused by *L. pneumophila* of 4/100,000. Starting with this value, the Committee increased this rate to 4.44/100,000 after assuming a 90 percent sensitivity of the UAT for detection of *L. pneumophila* serogroup 1. This estimate is conservative; other have found that the UAT only detects of 80 percent of *L. pneumophila* serogroup 1 cases (Mercante and Winchell, 2015; Yzerman, 2001).

Another adjustment to the estimated incidence was made to account for the fact that the EPIC study was not designed to estimate Legionnaires' disease, and methods of enrollment and exclusion criteria (e.g., excluding immunosuppressed patients) as well as limited testing likely resulted in significant underestimates of the burden of community-acquired Legionnaires' disease. The Committee assumed that the enrollment and exclusion criteria removed at least 10 percent of actual cases, leading to a rate of 4.88/100,000 people. This adjustment is conservative given other, higher estimates of hospitalized

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Management of Legionella in Water Systems

patients with community-acquired pneumonia. For example, Rameriz and colleagues (2017) studied adults hospitalized with pneumonia in Kentucky and reported rates of community-acquired pneumonia more than double those in the EPIC study and similar to rates found by Griffin et al. (2013), a study based on national Agency for Healthcare Research and Quality hospitalization data. Ramirez et al. (2017) attributed the higher rates in their study compared to those in EPIC to the stringent exclusion criteria used by EPIC.

Next, the Committee incorporated evidence (supported by Mercante and Winchell, 2015) that at least 20 percent of patients hospitalized with Legionnaires' disease have non-*L. pneumophila* serogroup1 disease, which was not captured in the EPIC study.[4] This consideration increased the rate to 6.17/100,000. The Committee then assumed that 10 percent of all legionellosis cases are healthcare-associated (see previous sections of this chapter), numbers which also would not have been captured in the EPIC study, leading to an adjusted rate of 6.85/100,000.

The EPIC study gathered and analyzed data from 2010 to 2012, such that the incidence cited in that study would reflect those years. According to Figure 3-3, there has been a doubling of the number of reported cases from 2011 to 2018, and this increase should be reflected in any current rate. There is little information available on the frequency of testing or whether diagnostic testing has improved (which could account for the observed doubling), has remained stable, or declined since 2011. The Committee assumed a range from as little as 50 percent of the doubling of reported cases being real (such that the other 50 percent is attributable to improved testing) to 100 percent of the doubling being real, which leads to a rate of 10.25 to 13.7/100,000. Although plausible, the Committee did not consider the possibility that diagnostic testing had decreased, a situation that would further increase its estimate of disease cases.

The U.S. Census Bureau on July 1, 2018, estimated there are 327.2 million people in the United States, of which 253.2 million are 18 years of age and older (children are excluded because there are limited data on estimates of Legionnaires' disease rates in children).[5] Thus, the Committee arrived at an estimate of 26,000 to 35,000 hospitalized cases of Legionnaires' disease per year.

The EPIC study considered only cases of community-acquired pneumonia that required hospitalization. To determine the incidence of outpatient Legionnaires' disease, the Committee consulted von Baum et al. (2008) who analyzed data from CAPNETZ, which is a medical competence network for community-acquired pneumonia funded by the German Ministry for Education and Research. von Baum et al. (2008) documented that the fraction of individuals with community-acquired pneumonia who were treated as outpatients was similar to that of persons with community-acquired pneumonia who were hospitalized. To be conservative, the Committee made a similar assumption, although there is evidence that, in the United States, the number of outpatients diagnosed with community-acquired pneumonia substantially exceeds the number of inpatients diagnosed with community acquired pneumonia.[6] Thus, **the Committee arrived at an estimate of 52,000 to 70,000 cases of Legionnaires' disease per year in the United States (or a rate of 20.5 to 27.4/100,000).** This estimate of the rate is approximately ten times higher than the reported rate for 2017 and is felt to be very conservative, as it considers only those cases of Legionnaires' disease for which treatment was sought (either inpatient or outpatient). It is a coarse analysis that does not reflect all of the uncertainties.

An analysis using different methods to estimate Legionnaires' disease in hospitalized patients with pneumonia provides further evidence that Legionnaires' disease may be substantially underdiagnosed in the United States. Cassell et al. (2019) reviewed hospitalization data for all non-federal hospitals in Connecticut from 2000 to 2014; using the International Classification of Diseases, they compiled time series for pneumonia and influenza, and estimated (with a mixed-effects model) the percentage of cases due to

[4] 31 of 32 EPIC cases were detected by UAT, with a single case detected by PCR. Cultures were not performed.

[5] See https://www.census.gov/quickfacts/fact/table/US/PST045218.

[6] See https://www.ahrq.gov/professionals/quality-patient-safety/hais/tools/ambulatory-care/cap-toolkit.html, accessed June 22, 2019.

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Management of Legionella in Water Systems

Legionella, influenza, and respiratory syncytial virus. The annual incidence rate of Legionnaires' disease among hospitalized patients was predicted to be 11.7/100,000; this rate was also approximately ten times higher than the average reported rate during the 14-year study period. The estimates of the burden of Legionnaires' disease put forward by both the Committee and by Cassell et al. (2019) suggest that the U.S. rate of Legionnaires' disease may be far higher than that indicated by notifiable disease statistics.

ENVIRONMENTAL MONITORING

Monitoring of *Legionella* bacteria in water systems has been done for several reasons. Water sampling has often been undertaken to locate the source of the bacteria after an outbreak of Legionnaires' disease was documented or after cases began to accumulate. Routine monitoring is done to verify that a water management plan is working and to determine background levels of *Legionella*. For example, monitoring of cooling towers or hospitals, in the absence of cases of disease, has largely focused on whether or not to implement water treatment. Presence/absence approaches, where positive results initiate action, have frequently been used rather than quantitative measures. Assessment monitoring has often been done in conjunction with water treatment to determine treatment efficacy. Monitoring is also often carried out for research purposes, which is a valuable means of providing generalizable information to the scientific and practitioner communities about conditions in water systems that are conductive to *Legionella* growth and the means to control it. Table 3-1 provides a general overview of various methods currently available for environmental monitoring and how each may be applied toward these four goals. Of note, there is presently a great deal of variability in how the methods are actually applied to various systems and scenarios. This is likely because choosing the most appropriate methods, which systems and locations to target for testing and how often, and what medium to sample, are dependent on specific aspects of the water system and building being sampled. These are important considerations for a building's water management plan (discussed in Chapter 5). This section describes the individual methods and compares their strengths and weaknesses for various purposes. Finally, it summarizes what decades of data collection have revealed about *Legionella* presence and concentrations in various engineered, environmental niches.

Methods

Many of the methods used to analyze environmental samples for *Legionella* are the same as those discussed previously for clinical studies of Legionnaires' disease. Historically, culture-based methods have been applied as the standard method for monitoring and to obtain isolates for further characterization. However, new methods have been developed that shorten the delay inherent to culture methods and allow for more real-time information gathering.

The methods for environmental monitoring still do not fully account for *Legionella*'s complex ecology (see Chapter 2). For example, swabbing has been used as a sampling method because *Legionella* are known to be associated with biofilms that form in pipes and fixtures, yet quantitative data (e.g., area swabbed, method, other measures of total biomass obtained) have not been consistently reported. Few studies address the relationship of *Legionella* with amoeba and instead measure mostly planktonic bacteria. Recent knowledge of the ecology of *Legionella* spp. has been slow to impact the development of new methods, even in the research arena.

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TABLE 3-1 Sampling for *Legionella* in Water Systems: Purpose, Methods, and Other Considerations

Purpose of Testing	Which Method(s)?		Which Water Systems?	Spatial/Temporal Considerations?	Which Medium/ Volume[a] to Sample?
Outbreak Investigation *Culture needed for comparison to patient isolates*	• qPCR/PCR- Rapidly identify suspect sites for further testing • Culture- Confirm viable *Legionella* • Serogroup, sequence typing, whole-genome sequencing- Compare to patient isolates		Suspect sources? Cooling towers, hot and cold taps, showerheads, hot tubs, decorative fountains, etc.	As soon as possible when an outbreak is suspected.	Water Numbers would be expected to be high in case of outbreak
Routine Monitoring *Select one, apply consistently*	• qPCR- Monitor baseline (viable + non-viable + VBNC) • Culture- Monitor baseline (viable and culturable)	• qPCR positives should be followed up by culture • Culture negatives- Be aware of VBNC • Either can be used to flag concerns and changes in system	Where there is patient risk, e.g., point-of-use devices in intensive care units, neonatal care units Where there is system vulnerability, e.g., stagnant zones, distal taps, substandard plumbing material	Continuous- Develop feasible plan and frequency (May be stipulated for some entities, locales, guidance, standards).	First draw water samples Biofilms are sampled routinely, but the value of these data over sampling of the water column unclear.
Mitigation Assessment *Select one or more, apply consistently*	• qPCR- Do numbers increase or decrease following mitigation? Note DNA from dead *Legionella* could still be detectable after disinfection. • Culture- Provides information on viability. • Amoebae co-culture- Evidence for VBNC forms? Changes in virulence?		The system subject to mitigation. Check upstream and downstream of target system and a comparable control.	Before and after mitigation, ideally long-term. Assess the overall effect or changes in baseline. Sample relevant inlets and outlets to point of mitigation.	Water Biofilm- Can assess if mitigation is reaching sources in biofilms
Research *Varies according to research question*	In addition to all of the methods above, consider: • Amplicon sequencing to address the responses of broader microbial community • Metagenomics—broader context of functional genes, viruses, other factors • Viability qPCR or flow cytometry—indicator of the viable fraction of *Legionella*		Water systems in place in the field. These are more real-world, but where there is a weaker understanding of factors at play. Simulated water systems. This allows for controlled variables and statistical replication, but less real-world significance.	Depends on research question. Longer-term studies are valuable but lacking. Water chemistry fluctuates with time. Three or more years may be required to achieve stable biofilm, which short-term studies overlook	Water Biofilm Aerosols- Need to understand transfer of *Legionella* from biofilms to respirable, infectious aerosols

[a] Volume to be determined based on application and desired detection limit. Larger volumes provide lower detection limits, but also may dilute the *Legionella* present in first-flush samples

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Management of Legionella in Water Systems

Table 3-2 compares several methods in use for detection, isolation, characterization and quantification of *Legionella* from building water systems. The table includes whether the method (1) elicits a presence/absence or quantitative result; (2) allows the bacteria to be isolated; (3) can be used routinely; (4) identifies species, serogroups or genotypes; and (5) detects bacteria that are potentially viable, culturable, or those which are inactivated (killed). Each method has advantages and disadvantages. While culture methods have remained the gold standard, they may need to be adapted or supplemented with other methods to assist in developing risk estimates and informing outbreak investigations. Depending on the application, it is likely that combinations of methods will be used in the future.

Culture Methods

Culture methods capture cells that grow and produce colonies on solid agar, generating quantitative data in the form of colony forming units (CFU), or in some cases in liquid media. In many early studies using these methods, no quantification was undertaken because the goal was to isolate colonies and identify serogroups using antibodies. Thus, the methods initially focused on cultivation and isolation of the bacteria only. One major shortcoming that still exists today is the length of time it takes to culture *Legionella*, as results may not be available for eight or more days. This can result in precious time lost for outbreak investigation, but this delay is not typically problematic for routine monitoring.

By the late 1970s and early 1980s, media formulations were focused on growth of *L. pneumophila*, which led to the predominance of buffered charcoal yeast extract (BCYE) agar and the use of antibiotics as well as acid or heat pretreatment. The BCYE media used for culture tests is insufficient to recover all *Legionella* spp., although it does not exclusively detect *L. pneumophila* (Lee et al., 1993). Protocols that used filtration to sample larger volumes of water as well as swab samples became more prevalent (Cordes et al., 1981; Witherell et al., 1988). By 1990, improvements had been made, yet full assessment of a standard method was not forthcoming. There was concern regarding the standardization of the methods towards improved recovery and identification. After examining methods recommended by the VHA, CDC, and a group in Germany, Ta et al. (1995) made recommendations to enhance recovery of culturable species and identification of strains. Finally, in 1998 International Organization of Standardization (ISO) culture methods were updated and published (ISO, 1998). A variety of standardized and consensus-based methods are now available including *Standard Methods for the Examination of Water and Wastewater* (APHA, 2007); *Procedures for the Recovery of Legionella from the Environment* (CDC, 2005); and ISO methods ISO 11731-2 (100-ml membrane filtration) (ISO, 2004, 2017). Procedures were directed toward the isolation of culturable colonies, in part to facilitate comparison of environmental and clinical isolates during outbreak investigations.

A new, easier culture method specifically for *L. pneumophila* has been developed that uses a liquid-based most-probable-number (MPN) approach (Legiolert™/Quanti-Tray™, IDEXX). The comparative data from four studies (see Box 3-5) suggest that the method is equivalent to other methods but generally trends higher in concentration estimations, which could elicit more violations and trigger remediation more often. One limitation of the reported evaluations of the MPN method was the lack of confirmation tests on positive wells in the tray. None of the studies mentioned in Box 3-5 evaluated the positives with genetic confirmation, but tested only via culture. The method also does not differentiate among serogroups of *L. pneumophila* nor is its specificity for all 61 species of *Legionella* available, making further testing necessary if this information is needed. Another drawback of this MPN method is that cultures are not readily available for molecular discrimination assays. As new methods develop, there is a need for greater systematic study and reporting of information, including a full description of the types

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TABLE 3-2 Comparison of Methods for Environmental *Legionella* Monitoring

Method	Potential for Quantification	Potential for Isolation	Level of Use*	Discerns Serogroups/ Sequence Types?	Form of Bacteria Measured	Pros	Cons
Culture Methods							
ISO	Yes	Yes	Routine	Yes	Culturable	Standardized Historical data	Time to results; may underestimate VBNC, other serogroups and species, risks
CDC	Yes	Yes	Routine	Yes	Culturable	Standardized Historical data	Time to results; may underestimate VBNC, other serogroups and species, risks
AHPA	Yes	Yes	Routine	Yes	Culturable	Standardized Historical data	Time to results; may underestimate VBNC, other serogroups and species, risks
*Molecular Methods^*							
PCR	No	No	Research, used with cultivation	No	Inactivated, VBNC+, Culturable	Can support sequencing	Need to process gels
qPCR	Yes	No	Research, potential for diagnostics and surveillance	No	Inactivated VBNC+ Culturable	Rapid results Greater sensitivity and specificity	Measures inactivated cells, less historical use
ddPCR	Yes	No	Research, potential for diagnostics and surveillance	No	Inactivated VBNC+ Cculturable	Rapid results Greater sensitivity and specificity	Measures inactivated cells; few studies using and comparing the method
Emerging Methods							
Next Generation Sequencing	No	No	Research	No	Inactivated VBNC+ Culturable	Provides info on how bacteria relate to microbial community	Takes special expertise, instrumentation. More cost and time to obtain results
Amoeba Co-culture	No	Yes	Research	Yes	Culturable	Improves isolation of difficult-to-culture strains	Adds at least 3 days to cultivation
Liquid-based MPN	Yes	Yes	Research, potential for routine use	No	Culturable	Simple set up, may be specific to Lp	8 days for results More difficult to confirm
EMA-PCR	Yes	No	Research	No	Viable	Can be used with molecular tools	Not proven to work with disinfection
PMA-PCR	Yes	No	Research	No	Viable	Can be used with molecular tools	Not proven to work with disinfection
Flow Cytometry	Yes	Yes	Research, potential for routine use	Yes	Inactivated VBNC+ Culturable	Simple set up, specific to Lp serogroups based on antibodies	Early commercial release, limited validation, higher detection limit

*Categories include Routine, Research, Potential for Routine, or Potential for Diagnostics and Surveillance; ^Molecular tools require special instruments, training, and expertise; VBNC+: Viable-but-Non-Culturable.

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Management of Legionella in Water Systems

of samples compared, characterization of the genera and species eliciting false positives, and genetic characterization of the *Legionella* spp. and serogroups that are detected.

Although culture methods have been standardized, inter-laboratory precision and accuracy are still uncertain. In a methods comparison (Ta et al., 1995), filtration, use of BCYE agar, and acid buffer treatment gave the highest recoveries. One inter-laboratory study using seeded samples for proficiency testing examined how well various laboratories performed in detecting and quantifying *Legionella* (Lucas et al., 2011). Ten in-house protocols (which were not described in the paper) were used, based on American Society of Microbiology, ISO, or CDC methods. CDC and nine other laboratories including county, state, hospital, and private entities participated, with CDC as the reference laboratory. The key findings included the following:

- The detection limit of the methods and laboratories were similar; samples were negative 93.1 percent of the time with less than 10 CFU/mL and positive 85.3 percent of the time with samples with greater than 10 CFU/mL.
- Quantification errors averaged about 1 log and underestimated the expected concentrations. However, this conclusion was tenuous, as formal assessment of the quantification results were not clearly articulated in the publication.
- Statistics on accuracy and precision with only ten laboratories was similar to European studies. While the details were not provided, the study concluded that sampling protocol, treatment regimen, culture procedure, and laboratory experience did not significantly affect the accuracy of reported concentrations.

The advantages of culture include (1) its ability to compare with historical samples, (2) it is an accepted measure of viability, and (3) it can be used to isolate bacteria for epidemiologic investigations. The disadvantages are that final results are not available for eight to 14 days depending on the chosen laboratory, making rapid decisions impossible, and the cost and expertise needed to run the method limits its widespread use. Furthermore, the method cannot capture *Legionella* cells in the VBNC-like state, and it favors *L. pneumophila* and a few other *Legionella* spp., such that not all *Legionella* spp. associated with disease are identified (Lee et al., 1993). Approaches to recover the bacteria from the VBNC-like state have been reported (Oliver, 2005), including co-culture with *Acanthamoeba polyphaga* (Dusserre et al., 2008) as discussed below. Newer MPN methods may be easier to implement and, once fully vetted, could facilitate more widespread use by utilities, building owners, and public health laboratories.

Use of Amoeba

Amoeba co-culture for the recovery of legionellae from clinical and environmental samples was first described by Rowbottom (1980, 1983). While there are many bacterial pathogens that resist the digestive processes of predatory amoeba (so-called amoeba-resisting bacterial pathogens, Thomas et al., 2010), *L. pneumophila* is the most recognized in water systems (Corsaro et al., 2010; Tosetti et al., 2014). Amoeba of the genus *Acanthamoeba* are generally used for co-culture (Pagnier et al., 2008) because of the ease with which they are grown in cell culture, but different amoebal hosts and incubation temperatures may influence which specific *L. pneumophila* strains are recovered (Buse and Ashbolt, 2011). Use of amoeba from the local environment has also recovered *L. pneumophila* when other American Type Culture Collection (ATCC) *Acanthamoeba polyphaga* failed to recover any isolate (Dey et al., 2019).

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BOX 3-5
Comparative Studies on Legiolert™

Four studies have evaluated *Legionella* occurrence and concentrations in side-by-side comparisons of Legiolert™, an MPN method in which the sample is distributed in a tray to generate a colorometric result after eight days of incubation, to other methods used more routinely. The first comparison (Satory et al., 2017) was against the ISO 11731-2 membrane filtration method with 290 paired samples. The second comparison (Petrisek and Hall, 2018) was against the standard culture method of APHA (2007) with 491 potable water samples and 846 nonpotable water samples. A third study (Rech et al., 2018) compared Legiolert™ to the CDC method (CDC, 2005) and examined 288 non-potable water samples. The fourth study (Spies et al., 2018) involved six laboratories comparing Legiolert™ (using 448 samples of 100 ml volumes) to ISO 11731-2 (100-ml membrane filtration) and ISO 11731 (1 ml direct plating). Table 3-5-1 provides the results. Confirmation is not a part of the MPN test as described, although cultured cells could be recovered for further testing/isolation.

TABLE 3-5-1 Comparative Studies on Legiolert™

Comparison Method	Sample Numbers	Sample Types	Results
ISO 11731-2 Membrane Filtration	290	Cold and hot taps showers circulation lines, boiler outlets	Overall, Legiolert™ provided a greater mean concentration. There were 3.3 percent false positives.
Standard Culture Methods (APHA, 2007)	491 846	Potable Water Non-potable water	There was no statistical difference between the methods; Legiolert™ < 0.5 percent and <0.9 percent false positivity rate for potable and non-potable samples, respectively. Did not mention a confirmation to *L. pneumophila* specifically**
CDC Method (CDC, 2005)	288	Non-potable water, mostly cooling towers	No differences were found between the methods. Non-pneumophila found in ten samples but only by the CDC method
ISO 11731-2 (100-mL membrane filtration) ISO 11731 (1 mL plating)	448	Cold and hot taps, showers, building circulation systems	For the 100-mL method, four of six laboratories had higher *Legionella* counts with the MPN method and the other two showed no difference. With the 1-mL method, five of six labs showed no difference. The specificity was found to be 97.9 percent.

** They confirmed 25 percent of the positive cells by recovering the liquid from the cells in the tray and re-isolating the bacteria on standard agar media.

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Management of Legionella in Water Systems

Methods to recover amoebae from environmental samples are based on those developed over the past several decades. An environmental sample is applied to a lawn of viable *E. coli* prey on non-nutrient agar plates (e.g., 2% Neff's saline) and incubated at 25°C for up to two weeks, identifying any clearing zones with observable trophozoites moving away from the originally applied zone, and then re-streaking onto fresh plates (e.g., Amaro and Shuman, 2019; Lorenzo-Morales et al., 2005). The use of different prey and temperatures can recover a greater diversity of isolates, but is generally not undertaken.

To isolate legionellae using the amoeba co-culture method, an environmental water sample is incubated with amoeba obtained from a fresh, exponential culture using several dilutions to optimize the prey-to-host ratio, and then incubating the co-culture at 30°C for 12 hours. Co-cultures are observed by phase microscopy to identify trophozoites exhibiting lysis or growth of intracellular bacteria. Finally, the *Legionella* is isolated on BCYE agar.

Amoebae co-culture methods have not been standardized and have primarily been used in the research arena and in reference laboratories in Europe for water and clinical samples. This culture technique takes at least an additional three days, whereby the sample is first co-cultured, then the resulting amoebae-resisting bacteria are grown as usual on BCYE agar or are rapidly identified by qPCR/sequencing (e.g., Corsaro et al., 2009; Lienard et al., 2011). Advantages of co-culture are improved isolation and detection of viable microbes and recovery of isolates to compare to clinical isolates. Amoebae co-culture is also presumably biased toward *Legionella* that readily infect amoebae, thus serving as a proxy for virulence within human macrophages. The disadvantages of co-culture are lack of quantification, the time to obtain results, lack of standardization, and minimal information on its utility in routine monitoring.

PCR, qPCR, and dPCR

There has been significant growth in the use of molecular techniques either in combination or independently for detection and characterization of *Legionella* in environmental samples (Borges et al., 2012). PCR was first introduced in 1985 and initially provided presence/absence data. Today PCR kits that include appropriate standards and quality controls and instruments to run the test are widely available. PCR can be much less expensive than culturing *Legionella* and entails less time per sample, producing results in hours instead of days. Because it relies on DNA sequence recognition, PCR can provide very high specificity and confidence in detecting the intended target.

PCR works by cycling between high and low temperatures to separate and then anneal the DNA in a water sample. Specific, small pieces of DNA called primers direct the polymerase enzyme to copy a specific gene sequence. Finally, the genetic sequence of the DNA fragment that has been amplified is determined. The amount of target DNA produced each cycle increases exponentially, enabling easy visualization of the final PCR product by staining and verifying the correct molecular weight by size separation methods, such as electrophoresis. In practice, the water sample is initially filtered, the captured bacteria are removed from the filter and lysed, and their DNA is extracted for use as the template in the PCR amplification reaction. The method detects all cells in the sample, including culturable, inactivated, and VBNC-like cells, and potentially any DNA from dead organisms. PCR approaches are available for all species in the genus of *Legionella* (by analyzing the 16S or 23S rRNA gene), for *L. pneumophilia* (*mip* gene), and for *L. pneumophila* serogroup 1 (a region of the *wzm* gene, spanning nucleotides 99 to 392). Primer sets have also been published for *L. anisa, L. bozemanii, L. longbeachae* (Saint and Ho, 1999), and *L. micdadei* (Cross et al., 2016). The use of *L. pneumophila* serogroup 1-specific primers is relatively new, but appears to be gaining momentum since it was first introduced (Mérault et al., 2011).

More recently, quantitative PCR (qPCR) and droplet digital PCR (ddPCR) methods have been developed, which are a great improvement over traditional PCR in that they provide quantitative information. The quantitative units of qPCR and ddPCR are gene copies (GC) per unit volume (e.g., GC/L). qPCR works the same as traditional PCR, but it incorporates a dye or probe in the reaction and uses a

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Management of Legionella in Water Systems

specialized instrument that can detect and quantify the signal as product is formed. Comparison of the exponential product amplification curves of samples to those generated by a standard curve of positive control DNA templates of known concentration allows quantification of gene copies per reaction. Units can then be converted to gene copies per volume of sample collected and subject to DNA extraction. ddPCR is a newer alternative to qPCR that provides rapid absolute quantification, without need for a standard curve, and is less sensitive to PCR inhibitors. Consequently, ddPCR can be applied to more than one genetic marker at a time, a procedure called multiplexing. The method works by dividing the sample into about 60,000 droplets wherein the PCR reaction occurs; the numbers of positive and negative droplets then provide a most probable number of the concentration.

Figure 3-5 provides the results from a seeded water sample using the primers and gene sequence for the genus *Legionella* (23S rRNA gene) and the *L. pneumophila*-specific *mip* gene.

Because qPCR and ddPCR capture all DNA, even from dead cells, more evaluation is needed before one could apply these methods during routine monitoring, particularly in environments containing high levels of disinfectants (e.g., cooling towers, hot tubs) where there is likely to be more DNA derived from dead cells. Culture and qPCR have been compared and contrasted for drinking water and cooling towers for detection of *L. pneumophila* and *L. pneumophila* serogroup 1 (Toplitsch et al., 2018). Twenty (20) drinking-water samples were examined, and the agreement was very good for *L. pneumophila* (90 percent positive by qPCR, 95 percent positive by culture, and 85 percent positive for both). In contrast, samples from cooling towers (n = 52) were scored as 60 percent positive using qPCR, 23 percent positive by culture methods, and 19 percent positive by both methods. For *L. pneumophila* serogroup 1, the agreement was poor for drinking water (10 percent, 5 percent, and 0 percent positive by qPCR, culture, or both, respectively), although slightly better for cooling towers (21 percent, 13 percent, and 4 percent positive by qPCR, culture, or both, respectively). When both tests were positive, generally qPCR reported 10- to 100-fold higher concentrations, although there was a positive correlation between the two tests. Another

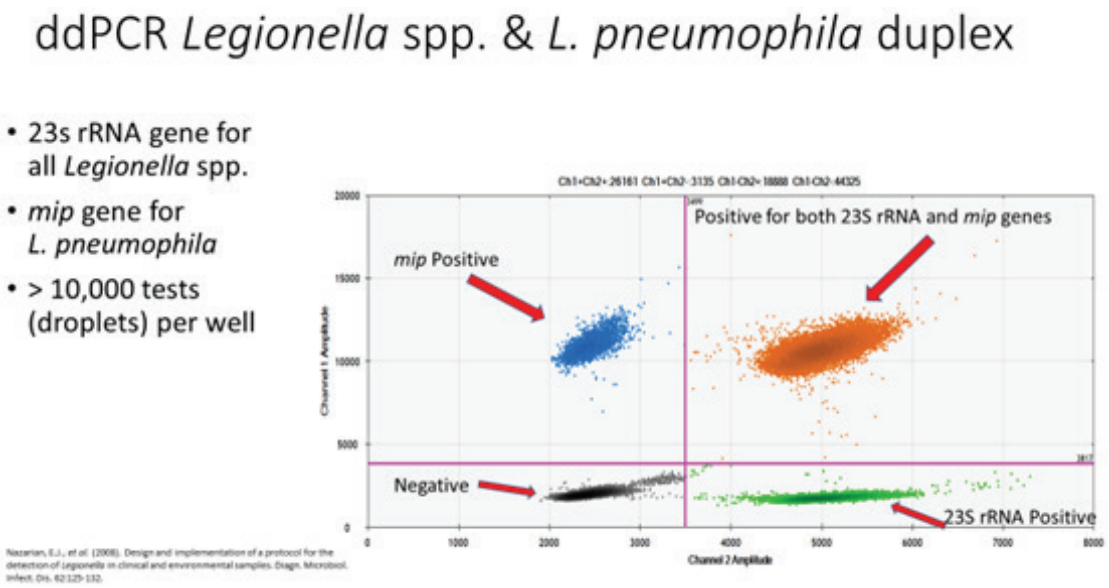

FIGURE 3-5 Results of a seeded water sample tested for two targets measured by ddPCR. The four quadrants show the number of droplets positive for the mip gene and the 23S gene (top right quadrant) or only the mip or 23S gene (left top and bottom right quadrants, respectively). The left bottom quadrant shows the number of droplets negative for both genes. Taken together, these results produce a most probable number for gene copies for both genes.
SOURCE: Courtesy of Joan Rose.

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Management of Legionella in Water Systems

study similarly found that quantification of *L. pneumophila* by qPCR trends with that by culture in both hot water and cooling tower samples, but with consistently higher estimates (Yaradou et al., 2007). Lee et al. (2011) attempted to translate CFU/L into gene copies/L by comparing international results for both metrics from 232 cooling tower samples and 506 hot- and cold-water samples. There was a 2-log difference between qPCR (gene copies/L being higher) and culture (CFU/L) in cooling towers for *Legionella* species, but only a 0.71-log difference for *L. pneumophila*. For drinking water taps, there was a 1.05-log and 0.62-log difference between gene copies/L and CFU/L, respectively, for *Legionella* and *L. pneumophila*. PCR and culture-based tests can produce distinct results for several reasons. In addition to the capture of both VBNC-like and dead cells by PCR, variability in the distribution of the bacteria in any given water sample (e.g., one sample may have a clump of cells), differences in detection limits, efficiencies of the methods, and multiple gene or genome copies within a cell can result in different outcomes.

The advantages of qPCR and ddPCR include rapid results, the ability to design primers that have high specificity, and low cost, which allows for large numbers of samples to be tested. The disadvantages are that qPCR detects cells regardless of their viability. The use of PCR methods is becoming more widespread for clinical surveillance and outbreak detection and, if applied appropriately, could also be used for routine monitoring of water systems. Cooling towers are rarely monitored routinely by qPCR, in part because of the high concentrations of disinfectant and corresponding high levels of DNA from dead cells. However, even an increase in total *Legionella* DNA means that growth conditions are not being controlled somewhere in the system and is worthy of further investigation. When applied consistently, qPCR can be very useful for estimating baseline numbers of *Legionella*, even in disinfected systems, with increases and decreases indicative of growth and death in the system. Yaradou et al. (2007) noted good correspondence between qPCR and culture-based methods targeting *L. pneumophila* in cooling towers and suggested that qPCR could be adapted for more wide-scale cooling-tower monitoring in the future. It is not unprecedented to move from a culture-based method to qPCR, as was done for recreational waters (i.e., beaches) for *E.coli* and enterococci monitoring (Gonzalez and Noble, 2014). Now that there is an ISO method for qPCR detection of *Legionella* (ISO, 2019), it would be appropriate to compare the two methods (qPCR and a culture method) for a variety of buildings and water systems in order to help interpret qPCR-generated data. It is likely that greater application of qPCR will occur in the future given the speed with which qPCR can provide information.

Viability Analyses. To alleviate concerns that qPCR also detects non-viable bacteria, several methods have been developed that favor DNA (or RNA) detection and quantification of viable *Legionella*. One such method uses ethidium monoazide (EMA) or propodium monoazide (PMA) in combination with qPCR (Nocker et al., 2006; Nogva et al., 2003), referred to as viability qPCR. The first working principle is that on light exposure, both PMA and EMA bind to DNA and, as a result, this bound DNA can no longer be amplified by qPCR because the qPCR primers cannot bind to EMA/PMA-bound DNA (see Figure 3-6). Second, theoretically EMA and PMA cannot enter a cell when the cell membrane is intact, which is one of the viability parameters of a microbial cell (Hammes et al., 2011). As a result, free DNA and DNA from cells with a compromised membrane are bound with EMA or PMA, and that DNA will not be amplified during qPCR. In a similar way, cell integrity vital staining can be used in combination with flow cytometry.[7]

Viability qPCR has been used to quantify membrane-intact legionellae cells (e.g., Chen and Chang, 2010; Lizana et al., 2017). In general, these studies showed that when disinfected water samples were exposed to PMA or EMA, the gene copy numbers of *Legionella* calculated were between the number of *Legionella* colony forming units obtained by culture and the number of gene copies obtained with qPCR

[7] E.g., https://www.rqmicro.com/products/l-pneumophila-kit.

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Management of Legionella in Water Systems

without PMA or EMA exposure. Accordingly, PMA or EMA seem to bind some of the *Legionella* DNA from membrane-intact cells that might still be viable after disinfection. However, serious precautions have been raised about the use of EMA and PMA to quantify viable *Legionella*, especially for environmental samples (Kirschner, 2016). These methods are not appropriate for studies involving a disinfectant whose mode of action does not affect membrane integrity, such as UV. Furthermore, there has been a lack of consistency among viability qPCR studies. For instance, the optimal EMA or PMA concentration for the viability assay reported in one study was shown to be cytotoxic to *Legionella* in another (Chang et al., 2010; Reyneke et al., 2017; Scaturro et al., 2016). In addition, the PMA method can overestimate viable *Legionella* cells (Scaturro et al., 2016). Moreover, Taylor et al. (2014) concluded that PMA is not an appropriate method for discriminating between live and dead *Legionella* cultivated under environmental conditions. Similar results have been obtained with EMA and PMA treatment of *Legionella* cells directly harvested from drinking water biofilms or cooling tower water, although the assay worked well with laboratory grown *Legionella* cells (Ditommaso et al., 2014; Wullings et al., 2016).

When compared to live/dead stain flow cytometry, viability qPCR for *L. pneumophila* overestimated membrane-intact cells when a large portion of the cells were membrane-compromised but underestimated membrane-intact cells when a large portion of the cells were membrane-intact. Thus, viability qPCR appears to be qualitative rather than quantitative. Furthermore, the performance of EMA and PMA treatment is much lower with shorter amplicon lengths (less than 200 base pairs or bp) than with larger amplicon lengths (greater than 400 bp) (Ditommaso et al., 2015; Wullings et al., 2016). Accordingly, larger qPCR gene targets of *Legionella* may be optimal. However, most companies providing molecular tools for qPCR recommend that amplicon lengths not exceed 200 bp for optimal qPCR. Kontchou and Nocker (2019) have recently optimized the PMA assay for *L. pneumophila*, which includes a longer amplicon (633 bp), higher incubation temperature, and addition of EDTA and deoxycholate. They determined

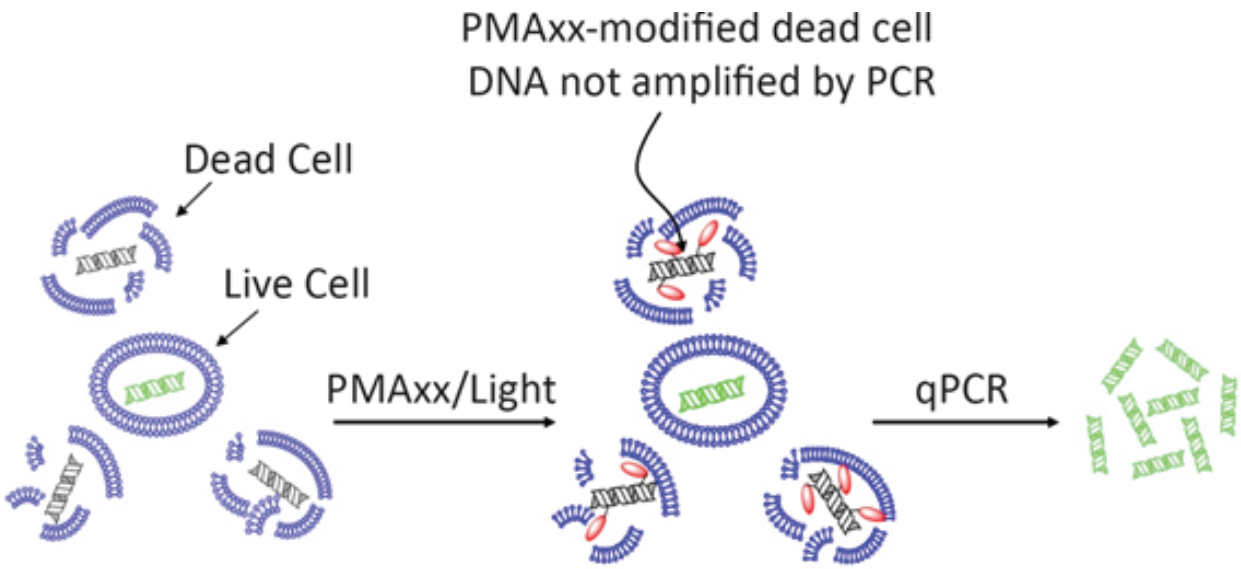

FIGURE 3-6 Principles of live/dead quantification with PMA and qPCR.
SOURCE: https://biotium.com/product/viability-pcr-starter-kits. Image by Biotium® Inc.

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Management of Legionella in Water Systems

that the membrane-intact *L. pneumophila* cell numbers obtained with PMA-qPCR were in agreement with membrane-intact cell numbers obtained with flow cytometry, demonstrating potential for this optimized assay, with the caveat that *L. pneumophila* strains were cultivated under optimal conditions. Overall it can be concluded that, although PMA or EMA treatment in combination with qPCR might have merit to distinguish between membrane-intact and membrane-compromised *Legionella*, additional studies on the reliability of the method, standardization of the method, and its application to environmental samples need to be performed before qPCR assays can be applied routinely to detect viable *Legionella*.

Another promising molecular method that distinguishes between viable and nonviable *Legionella* detects precursor RNA, which is only produced by viable cells on exposure to fresh nutrients (Cangelosi and Meschke, 2014). To detect *L. pneumophila* by assaying for precursor RNA, samples are exposed to fresh nutrients for three hours, RNA is extracted, and then RNA from the precursor region of the 16S rRNA gene of *L. pneumophila* is specifically amplified with reverse transcriptase (such that the method is called RT-qPCR) (Boss et al., 2018). In one study, *L. pneumophila* in drinking water samples taken from public sport facilities was analyzed by RT-qPCR, cultivation, and qPCR. For 86 percent of the samples, the results with RT-qPCR and cultivation were consistent. In 7 percent of the samples the culture method was positive but RT-qPCR was negative, whereas in the other 7 percent of the samples RT-qPCR was positive but culture was negative. In addition, 17 percent of the samples that were negative with RT-qPCR were positive with qPCR, indicating the presence of DNA from dead *L. pneumophila*. Others have also used RT-qPCR to detect RNA of specific genes (including virulence genes) of *L. pneumophila* after exposure to synthetic grey water (Buse et al., 2015) or copper (Lu et al., 2013). The specific analysis of virulence genes in these assays might not only provide information on viable *L. pneumophila* cells but also on their virulence potential. Although RT-qPCR seems promising, additional studies are needed in which RT-qPCR results are compared with cultivation, qPCR, and viability qPCR for detection and quantification of *Legionella* in different environmental samples.

Next Generation DNA Sequencing

A handful of studies have used next-generation DNA sequencing approaches to examine *Legionella* or other relevant members of the microbial community in drinking water systems. Amplicon sequencing is one application that is applied to amplified PCR products obtained from DNA extracted from mixed microbial communities. Most often amplicon sequencing uses universal primers for bacterial 16S rRNA genes to profile which organisms are in a particular drinking water or biofilm sample. Organisms are identified based on the similarity of the 16S rRNA gene sequence to entries in online databases, and the term operational taxonomic unit (OTU) defines the bacteria identified. Because at best the resolution is at the genus level, the presence of pathogens cannot be ascertained.

Nevertheless, amplicon sequencing has proved to be a powerful tool to reveal the surprising diversity of microorganisms inhabiting drinking water (Pinto et al., 2012) as well as estimate their relative abundance. In one laboratory study of domestic hot water, qPCR and amplicon-sequencing-based methods estimated *Legionella* spp. to be around 3 percent of the total community (Ji et al., 2018). Next-generation DNA sequencing can be applied directly to the DNA extract, without first PCR-amplifying a gene of interest, an approach referred to as shotgun metagenomic sequencing. The advantage of shotgun metagenomic sequencing is its potential to sequence *all* genes in a sample, including markers of function (e.g., nitrification, iron oxidation, virulence), and thus provide much richer functional information and taxonomic resolution (Gomez-Alvarez et al., 2012). However, currently metagenomic sequencing is very costly; consequently, researchers tend to employ less thorough sequencing, which results in false nega-

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Management of Legionella in Water Systems

tives because of high detection limits and lack of coverage. Both amplicon sequencing and metagenomic sequencing also provide rich information about non-*Legionella* species in water systems and could potentially provide new insight into the role of microbial ecology in *Legionella* propagation (Dai et al., 2018). However, for potential application to *Legionella* monitoring, these tools are still in their infancy (Borthong et al., 2018). In the future, next-generation sequencing of both environmental and human isolates could potentially provide insight into the relationship between environmentally abundant *Legionella* and disease and perhaps help to identify previously unidentified clusters of disease.

The third application of next-generation sequencing is whole genome sequencing of individual *Legionella* isolates (Reuter et al., 2013). Whole genome sequencing makes possible high-resolution phylogenetic comparisons of isolates associated with outbreaks, and it can also be adapted to determine the sequence type (Raphael et al., 2016). Raphael et al. (2019) have used whole genome sequencing on cultures of clinical specimens to reveal a highly diverse population of strains causing legionellosis in Arizona.

Sampling Strategy

A *Legionella* monitoring plan for water systems should include (1) the purpose of the monitoring, (2) what medium to sample, (3) the method to be used, and (4) where and when to sample. As discussed in Chapter 5, the precise sampling strategy should be developed and adapted to the system of interest as part of a comprehensive water management plan (see the example in Box 3-6). Monitoring for *Legionella* in building water systems can have many purposes including to investigate outbreaks, to support remediation or mitigation, to demonstrate compliance with a guideline or regulation, as part of diagnostic surveys, and for research (see Table 3-1). Once the purpose is determined, the methods should be linked to the desired information. The priority may be confirmation or quantification, determining viability, or distinguishing serogroups or sequence type. For example, culture and viability are of interest when disinfection is being used for remediation. For compliance monitoring, the methods are usually prescribed. Surveys generally attempt to use standardized methods to facilitate comparison. Nonetheless, newer methods such as qPCR have great potential to quantitatively examine more samples at a lower cost and much more rapidly. Legiolert™ may enable greater ease in sampling at a lower cost than current culture methods, although the time to receive results remains a week.

First, the water system to be sampled must be identified, such as cooling towers, residences, public buildings like hotels, resorts, hospitals, drinking water, and wastewater. In particular, points thought to be most vulnerable to *Legionella* growth and where potential for human exposure is high should be prioritized. For example, within buildings, premise plumbing monitoring should include distal sites that have potential both for *Legionella* growth and human exposure; these include showers and taps, decorative fountains, and storage tanks. Although *Legionella* growth is less likely in the hotter water of recirculation lines and water heaters, sampling these locations is also important for confirmation and to provide a baseline.

The various media that can be targeted for sampling include the bulk water, biofilm, or the aerosols generated. Most sampling strategies and methods have focused on the bulk water because it is easy to collect, various volumes can be readily targeted, and it can be concentrated via filtration. In addition, first-flush samples are thought to capture water that has been stagnating (thus more likely allowing for bacterial growth), potentially better representing what has sloughed or diffused off of the biofilm. (It should be noted that most studies lack any quantitative assessment of stagnation. For example, a study of 807 drinking water samples from nine buildings found occurrences to be significantly correlated with stagnation, but this was described only qualitatively as "low withdrawals" [Völker et al., 2016)]).

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Management of Legionella in Water Systems

Legionella bacteria are known to associate with biofilms and their amoeba. However, swab samples have had limited value in decision making for remediation of premise plumbing. Swabs are not analyzed routinely because it is impossible to collect a representative biofilm sample from the miles of premise plumbing in a building, there is no standard method available, and there is no consistent way to report the concentrations found. Developing better methods for sampling premise plumbing biofilms is clearly a research need.

Because aerosol sampling is much more complicated than sampling the bulk water and still under development, aerosols are generally not included in a sampling strategy. Nonetheless, aerosols can be collected as they are generated using various types of impingers or impactors. A research program to understand the difference between measured *Legionella* concentrations in bulk water and in aerosols would be useful (Prussin et al., 2017).

The detection methods applied should include more than one technology (likely a culture method and a molecular method, e.g., qPCR) and be quantitative. Laboratories will continue to use culture but may use more than one medium; this may be unnecessary if, for example, qPCR or dPCR was used first to examine more rapidly the concentrations of specific species or *L. pneumophila* serogroup 1. The detection limit should be carefully documented, addressing both the volume collected and concentrated. More experience is needed where both types of results (culture and molecular methods) are available, thus providing knowledge on their comparability. Sivaganesan et al. (2019) has compared qPCR methods to culture for fecal indicator bacteria on beaches over many years during the swim season. These data are now being analyzed in several states to address the comparable level of gene copies per 100 ml that would lead to beach closure on the same day rather than waiting 24 hours to obtain culture data. A similar approach could be used for *Legionella*.

The frequency of environmental sampling for *Legionella* is highly variable and ranges from once per week to once per year, depending on many factors such as the size and use of the building. Box 3-6 describes the *Legionella* sampling strategy applicable to large buildings with complex premise plumbing systems such as hospitals, while Box 3-7 describes the sampling strategy for cooling towers; both boxes prescribe sampling frequencies. In general, however, the numbers of samples taken and how often they are collected have been based on resources and logistics rather than on an understanding of the ecological niche of the bacteria. Temporal studies with recommendations on how often to monitor and over what time frame have yet to be undertaken. Nor has there been a clear statistical assessment of the frequency of sampling needed to capture *Legionella* growth, blooming, and sloughing events. To evaluate temporal changes such as seasonality, several years of monitoring would be needed.

More widespread and improved national laboratory certification is needed for current approaches and for new methods, which includes standardized protocols, quantitative assessment, training and proficiency testing. The Environmental *Legionella* Isolation Techniques Evaluation (ELITE) Program has oversight from the CDC, but since November 2016, the Wisconsin State Laboratory of Hygiene has managed the production and distribution of testing samples as well as analysis of laboratory results. Twice per year, participating laboratories receive cultures for verification tests.[8] The program issues certificates to laboratories that successfully isolate legionellae from simulated environmental samples by culture, but it is not a laboratory certification process. New York State certifies laboratories[9] as do the Quebec and Alberta provincial governments in Canada.

[8] See https://wwwn.cdc.gov/elite/Public/FAQ.aspx.
[9] See https://www.wadsworth.org/regulatory/elap.

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BOX 3-6
***Legionella* Sampling Strategy in Large Buildings**

Large buildings, including hospitals, which house vulnerable populations, tend to formalize their management of *Legionella* in building water management plans (see Chapter 5 for more description of these plans). Although not universal, these plans often require some form of *Legionella* sampling to gauge the effectiveness of the building's water treatment system and to determine if the treatment needs to be modified to maintain plan effectiveness. Sampling strategies are unique to any given building, and both the water management plan and the sampling strategy are subject to change as surrounding and contributing environmental conditions change.

A frequently used guidance for developing a water management plan is the American Society of Heating, Refrigeration and Air-Conditioning Engineers (ASHRAE) standard 188 (ASHRAE, 2015). This standard does not provide a sampling strategy nor address biological testing for *Legionella*, but it does reference a companion document ASHRAE 12-2000 (ASHRAE, 2000) which states that "culturing for *Legionella* may be appropriate if carried out for a specific purpose, such as verifying the effectiveness of a water treatment protocol." The CDC toolkit (CDC, 2017a), which aims to make ASHRAE 188 more practical, also makes reference to environmental testing for *Legionella* to validate the effectiveness of control measures.

Once water temperature, disinfectant residual, and distal point flushing programs have been considered to aid in identifying sampling locations and potential *Legionella* growth risks, *Legionella* sampling should be the basis for validating any water management plan, regardless of building size, configuration, or even building population composition, which are risk factors secondary to plan development. Initial samples will define the extent or even if *Legionella* is present and the extent to which the plan should be developed. In very general terms, the initial sampling would include bulk water samples from the water source entering the building, from storage tanks if used, and from both hot and cold water distal sites at multiple points in the building. Initial sample draws should be evaluated by competent third party entities rather than contractors or vendors who are responsible for mitigation modalities. Samples should be tested by culture (e.g., ISO, 2017) or by qPCR (e.g., ISO, 2019). When sampling, it is highly recommended to record specific sample location, temperature, disinfectant residual, pH, and plumbing zone flushing and usage. These additional data points will minimize resampling time and define the conditions contributing to any given water management issue. Both culture-based and qPCR-based monitoring must be taken into context and compared to a baseline, not interpreted in isolation.

Following initial testing, water management plan development will move forward based on the test results and other associated risk factors unique to the building. At this point, *Legionella* sampling will evaluate changes to the plan and any required mitigation to maintain water safety for water uses within the building.

For large buildings, the building manager will need to identify the potential locations where *Legionella* may be present and propagate, based on the number of potable water systems and the number of distribution components. Examples are as follows:

- Potable sources: Some building configurations have multiple water mains. A sample should be taken from each source.
- Potable tanks: If used, potable tanks should be tested. Water tanks will extend the age of water.
- Potable zones: Larger buildings, particularly high-rise buildings, may have multiple building zones as a result of building height and pressures. A sample should be taken from each zone.
- Distribution risers: Samples should be drawn from enough risers to provide a good evaluation of all risers. If sampling and testing is done frequently enough, i.e., monthly, a random selection of risers would be possible. Selection should always include risers in which water use is minimal.
- Horizontal distribution: Samples should be taken from enough of the horizontal distribution to be representative of the entire length. At a minimum, the end point of the horizontal distribution should be sampled to determine whether mitigation is reaching the farthest point of the system.

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- Potable hot-water: All system points listed above should be tested for both hot- and cold-water systems. *Legionella* is more likely to exist and propagate in hot-water systems where temperatures range from 29.4°C to 40.6°C (85°F to 105°F). More hot-water points should be sampled than cold.
- Potable hot-water heat exchangers: Where used, they should be evaluated and sampled.
- Potable hot-water return piping: Where used, it should be sampled, as conditions are often suitable for *Legionella* growth.

Once the locations that will provide a good indication of system performance are identified, the interval for sampling can be determined. In cases where initial testing indicated there was no presence of *Legionella* anywhere in a facility, and the building use composition indicated no risk of exposure to building occupants, sampling may be once every six months or even once per year. The sampling interval is also driven by the building's risk tolerance. A hospital with a large immunocompromised patient population and zero tolerance for *Legionella* may opt for more frequent sampling. In either case, the sampling strategy is dictated by risk and water management plan parameters.

BOX 3-7
***Legionella* Sampling Strategy for Cooling Towers**

For routine maintenance of cooling towers, a *Legionella* sampling program is key in ensuring that the operation and maintenance activities, as well as the water treatment, are effective. In the event of a Legionnaires' disease outbreak associated with a cooling tower, a well-planned sampling strategy can help to isolate specific components of the cooling tower system that are responsible. This sampling strategy should identify or rule out suspected sources and their transmission pathways.

A thorough visual assessment of the cooling tower should be conducted prior to any sampling, to determine the condition of the various components of the cooling tower and their potential to amplify and transmit bacteria. Table 1.3 in HSG274 Part 1 (HSE, 2013) denotes the various parts of a cooling tower and Figures 1.5 and 1.6 are photographs of the cooling tower fill conditions (see www.hse.gov.uk/pubns/priced/hsg274part1.pdf). Operation and maintenance records, as well as water treatment records and any past sampling data, should also be examined for gaps or unusual results as well as follow-up actions and validation results.

Once the equipment and its components have been visually inspected, a sampling plan should be devised to take into account any potential problems. Sampling locations for cooling towers should include the locations listed below, either in routine sampling or during an outbreak. However, these locations will vary depending on the cooling tower's components. The CDC (2015) sampling procedure for outbreaks of disease, shown in Table 3-7-1 below, indicates the number and type of samples, and the targeted process for each location.

Table 3-7-1 *Legionella* Sampling for Cooling Towers SOURCE: CDC (2015)

Cooling towers[a]			
Make-up water (water added to replace water loss because of evaporation, drift, or leakage)	1	1L bulk water	Direct
Collection basin (an area below the tower where cooled water is collected and directed to the sump)	2	1L bulk water and a biofilm swab at the water line	Direct
Sump (a depressed chamber contiguous to the basin, where water flows to facilitate pump suction; may also be used as collection point for silt and sludge)	2	1L bulk water and a biofilm swab at the water line	Direct
Storage tank or reservoir in the system	1	1L bulk water	Direct
Drift eliminators or other surfaces that remain moist	1	1 biofilm swab	Direct
Heat sources (e.g., chillers)	1	1L bulk water	Direct

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Management of Legionella in Water Systems

Various documents such as AIHA (2015) and PWGSC (2013) provide additional guidance regarding the type of samples to be collected, the sampling locations, the frequency, and the proper handling and analytical methods for both routine and outbreak monitoring of cooling towers. The recommended frequency for routine *Legionella* monitoring may vary from weekly (PWGSC, 2013) to quarterly (HSG274, 2013) depending on the outcomes of the visual inspection, past issues, and targeted outcomes. Other physical parameters to monitor include temperature, pH, residual (free) chlorine, other disinfectant levels, and water flow rates.

When preparing a routine sampling strategy for cooling towers, it should be noted that:

1. Cooling towers tend to operate fully only during the summer months, although some will be operated sporadically throughout the winter depending on cooling needs.
2. Cooling towers do not continuously circulate water even when they are in operation, which provides conditions ideal for *Legionella* growth.
3. Cooling towers are frequently not accessible for inspection or sampling.
4. The plumbing configuration for a group of cooling towers can be very confusing. Therefore, it is necessary to properly trace the piping for each tower to pinpoint the sampling locations that will reflect the conditions for any given cooling tower and its associated equipment.
5. Because cooling towers are essential to the operation of modern buildings, it is difficult to take a cooling tower offline to allow for inspection, sampling, disinfection, or repair. A heat transfer plan should be part of the sampling strategy.
6. Surveillance monitoring is completed on a regularly scheduled basis. However, it is recommended to vary the testing time for comparison purposes (e.g., after a long weekend, mornings, afternoons). The same applies to locations within a system when possible, for example, by sampling different heights of fill of the cooling tower.
7. Personal protection equipment including eye and respiratory protection and anti-slip footwear should always be used when working around cooling towers.

Occurrence of *Legionella* in Water Systems

Much of the emphasis for environmental sampling of *Legionella* has been to understand its occurrence and (in some cases) concentrations in different locations. Sampling has focused on sites where aerosols that might contain the bacteria are formed, including cooling towers, showers, hot tubs, fountains, and buildings with vulnerable populations (e.g., hospitals). Over the years, better methods and lower detection limits have increased the percentage of samples that test positive for *Legionella*, yet concentrations have remained variable. Despite this variability, a general picture regarding the occurrence of the genus, its various species, and serogroups is emerging.

The sections below present occurrence and (when available) concentration data on cooling towers, residences, hotels and resorts, recreational venues, hospitals, cruise ships, and drinking water and wastewater treatment plants. The data were generated using either culture methods that quantify colony forming units (CFU) and include cells that grow and produce colonies on solid agar, or qPCR for which the data are referred to as gene copies (GC) and that include live, VBNC-like, and dead cells with intact DNA. Data presented below represent both outbreak investigations as well as routine sampling.

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Management of Legionella in Water Systems

Cooling Towers

Legionella data from cooling towers were collected from general surveys conducted in the absence of outbreaks as well as from outbreak investigations. One of the first studies to collect environmental data on *Legionella* in cooling towers was conducted in 1983 (Howland and Pope, 1983). Nine cooling towers were routinely sampled over an 18-month period (162 samples). The culture methods used only identified presumptive *L. pneumophila,* which was found in all samples and all systems (100 percent positive). The levels were noted to be higher in systems that were used seasonally (i.e., shutdown in the winter and drained); however, the data were not presented in detail.

In 1983, a 12-city study took place to investigate *Legionella* in potable water and cooling towers in Canada (Tobin et al., 1986). Calgary, Edmonton, Fredericton, Halifax, Mississauga, Montreal, Ottawa, Poplar River, Quebec City, Regina, Winnipeg, and Vancouver were part of the survey. Sampling occurred from July to September, using a 1- to 2-liter sample that was filtered and plated on BYCE agar. Of the cooling towers that were specifically examined, 28.9 percent of the samples were positive. *Legionella* concentrations in cooling towers were a maximum of 3.3×10^4 CFU/L with a geometric mean of 4×10^3 CFU/L. Almost all isolates were *L. pneumophila* species including serogroups 1, 3, 4, and 6. One isolate was *L. dumoffii*.

A 2016 study collected 196 cooling tower samples across various regions of the United States (Llewellyn et al., 2017). In this study, 62 percent were positive by qPCR for *Legionella* spp., 32 percent were positive for *L. pneumophila,* and 20 percent were positive for *L. pneumophila* serogroup 1. The authors cultured only PCR-positive samples and found that 47 percent were positive for *Legionella* spp., 32 percent were positive for *L. pneumophila,* and 24 percent were positive for *L. pneumophila* serogroup 1. No concentrations were reported and no geographic differences were found.

A study of cooling towers in Singapore was one of the few conducted in a tropical environment (Lam et al., 2011). Over an eight-year period (2000–2008), 18,164 samples were analyzed by culture methods and 15.6 percent were positive for *Legionella*. However, a greater prevalence of positivity was found in the first three years, ranging from 48 to 68 percent, which then dropped to between 12 and 15 percent from 2004 to 2008. Although it was speculated that this decline was because of the switch to chloramines, the drop occurred prior to implementing the change in disinfectants (which was in 2005). Again, concentrations were not reported.

Investigations into 255 industrial cooling towers in China revealed a positivity rate of 37 percent using culture techniques (Li et al., 2015). 121 isolates were characterized and all were *L. pneumophila*, mostly serogroup 1 (56.2 percent), although serogroups 6, 5, 8, 3, and 9 (at 20.7, 9.9, 6.6, 5.0, and 1.6 percent, respectively) were also identified. Concentrations between 100 CFU/L and 88,000 CFU/L were reported, with an average of 9,100 CFU/L.

Widespread monitoring of cooling towers in New York City was undertaken during an outbreak of Legionnaires' disease from November 2014 to January 2015. This included power plant cooling towers, in which 29 of 30 samples were positive by PCR (although primers or genes examined were not mentioned), as well as shopping mall cooling towers, in which eight of ten were positive by PCR for *L. pneumophila*. Those that were positive were cultured, and 90 percent (27/30) and 12 percent (1/8) from the power plants and shopping mall cooling towers, respectively, were positive for *L. pneumophila* serogroup1 using serology (Benowitz et al., 2018). Concentrations were not reported in these studies. The methods used are poorly described, with no indication of the detection limit for the sampling.

Walser et al. (2014) summarized 19 outbreaks associated with cooling towers from around the world, nine of which had environmental sampling data. Interestingly, the *Legionella* concentrations were greater than 5×10^5 CFU/L and as high as 1×10^8 CFU/L with an average 1.4×10^7 CFU/L, with the exception of one outbreak from Norway (2×10^3 CFU/L). These concentrations are above the average found in the Chinese studies of 9.1×10^3 CFU/L. Attack rates were not calculated because it was unknown how

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Management of Legionella in Water Systems

many people were exposed to the cooling towers. The concentrations were not related to the number of cases or cases/day, although there was a positive relationship between duration of the outbreak and concentrations.

Residences and Public Buildings

Surveillance of *Legionella* in residential premise plumbing taps and showers has been undertaken in many parts of the world because of the concerns associated with sporadic cases of Legionnaires' disease in a community that cannot be linked to hospitals, hotels, or cooling towers. Some studies have linked an individual with Legionnaires' disease to a source within their residence, such as Chen et al. (2002). *L. pneumophila* serogroup 6 was isolated from both the patient and his home potable water system as confirmed by pulsed-field gel electrophoresis (a method used to fingerprint DNA from bacteria). Other studies implemented over the past 30 years have tried to broadly survey environmental data from residences in China, Germany, Italy, Spain, the United Kingdom (UK), and the United States. In some cases, there was an attempt to examine levels of *Legionella* in taps in homes or areas of a city where Legionnaires' disease cases had occurred (Stout et al., 1992).

The data from 11 studies are shown in Figure 3-7. Taken together, these data show that the percentages of samples positive for *L. pneumophila* (using culture methods for *Legionella* followed by colony confirmation test specific to *L. pneumophila*) ranged from 5 percent to as high as 33 percent. When culture methods for *Legionella* (without colony confirmation testing) were used, positives ranged from 8 percent to 23 percent. As expected, qPCR reported higher numbers of positive samples for *Legionella* spp. (28 percent to 100 percent) but not notably higher for *L. pneumophila* (3 percent to 64 percent). Average concentrations for *L. pneumophila* reported in the various studies were 1.1 x 10^3 CFU/L (in the UK), 3-5 x 10^3 CFU/L (Spain) and 1 x 10^4 to 6 x10^5 CFU /L (Pittsburgh). Using qPCR approaches, concentrations were reported at 4.0 x 10^3 GC/L for *L. pneumophila* (UK) and 10^4 GC/L (China). For other *Legionella* species, the concentrations were 1.2 x 10^4 GC/L (UK) and 7.7 x 10^4 to 8.4 x 10^6 GC/L (China). Levels were found at 10^5 GC/L for *Legionella* spp. in rain barrels (where no *L. pneumophila* was detected).

Insights are provided by the studies in Figure 3-7. Stout et al. (1992) found *L. pneumophila* was associated with lower water temperatures in water heaters (at or below 41°C), with no prevalence in any particular kind of tap. While many suggest warm-water taps should be sampled, the data suggest that all taps can be positive. In China, *L. pneumophila* was more frequently found in public buildings than in residential buildings, perhaps because of higher water age (Liet al., 2018). In public buildings in China, negative correlations were noted between *Legionella* numbers and total chlorine residuals and between total 16S rRNA gene copy numbers and total chlorine in both the first draw and post flushing (Li et al., 2018). Storage appeared to increase *Legionella* numbers, which were slightly higher in underground systems (average 1.95 x 10^6 ± 2.49 10^6 GC /L) compared to rooftop storage (7.8 x 10^5 ± 1.40x 10^6 GC/L, $P < 0.05$).

A German study (Dilger et al., 2018) involved 76,200 samples taken from 13,397 warm-water systems. Ninety-four (94) percent were private homes, with the rest being schools, town halls, sports facilities, hotels, hospitals, and retirement homes. While the average *Legionella* concentration was not reported, 14 percent had less than 10^3 CFU/L (reported per 100 mL in the paper, i.e., 100 CFU/100mL) and 0.19 percent had 10^4 to 10^5CFU/L (which according to German standards is a level at which showering would be restricted). 20.7 percent of samples were positive for *Legionella* spp., of which *L. pneumophila* was the prominent species (83.9 percent) followed by *L. anisa*, and 12 other species. The differences in abundance of the various species detected was partly explained by temperatures, as *L. pneumophila* was present at all temperatures from 10°C to 60°C, while *L. anisa* was more abundant at low temperatures and other species were limited to narrower temperature ranges.

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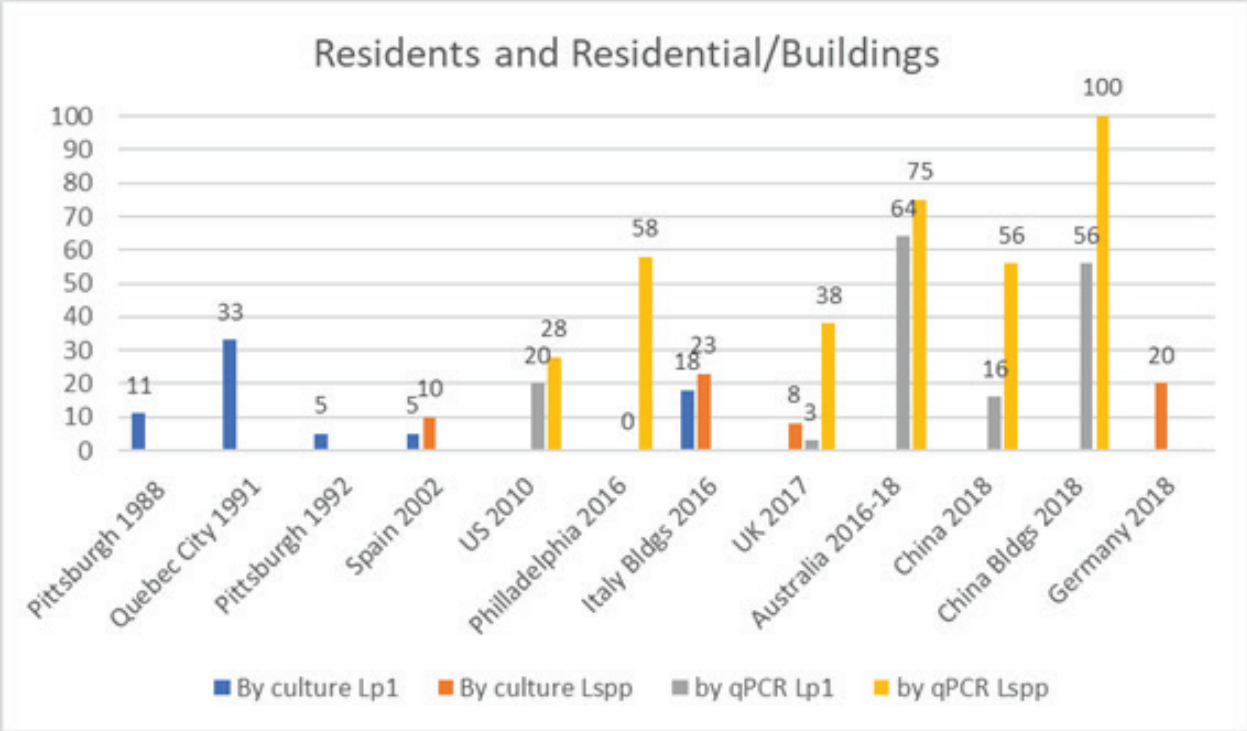

FIGURE 3-7 Percentage of samples positive for *L. pneumophila* and other species using culture and PCR from publication dates of 1988 to 2018 in large surveillance studies of households. SOURCES: Pittsburgh 1988 (Lee et al., 1988); Quebec City (Alary and Joly, 1991); Pittsburgh 1992 (Stout et al., 1992); Spain (Codony et al., 2002); U.S. 2010 (Donohue et al., 2014); Philadelphia (Hamilton et al., 2018b); Italy (Totaro et al., 2017); UK (Collins et al., 2017); both China columns (Li et al., 2018); Germany (Dilger et al., 2018).

Higher *Acanthamoeba* concentrations in taps fed by tanks compared to those fed by mains were reported in the studies in Hong Kong, Korea, and the UK (Boost et al., 2008; Jeong and Yu, 2005; Seal et al., 1992). *L. pneumophila*, *Acanthamoeba*, and *V. vermiformis* were also detected in tank and tap water in the Chinese study (Li et al., 2018).

Donohue et al. (2014) surveyed 68 public and private cold-water taps from 2009 to 2010. Low concentrations of *L. pneumophila* serogroup 1 were found, between 40 and 620 GC/L, in around 50 percent of the positive samples; yet on occasion, a high level was found up to 10^5 GC/L, creating an average of 1.97 x10^3 GC/L with a median of 62 GC/L. This study found that 47 percent of sampled drinking fountains were contaminated with *L. pneumophila* serogroup 1, with 18 percent of the fountains (3/17) consistently positive.

The prevalence of *Legionella* in hot and cold water was investigated in 141 homes equipped with various types of domestic water heaters (38 percent gas, 38 percent electric, 18 percent oil, and 7 percent solar) in four regions of France (Wallet et al., 2016). Samples by culture exceeded 1,000 CFU/L in 5 percent of hot water and 5.6 percent of cold water from mixing valves and taps. Results using solid phase cytometry for *Legionella* were strikingly higher, with a prevalence of 41 percent in hot water, 52 percent for cold water, and 53 percent for mixed water.

Verhoef et al. (2004) showed that *Legionella* was present more often in homes that had not been inhabited for ten days than those that had been occupied. Although the results were not significant, the study suggested that some Legionnaires' disease attributed to temporary accommodation sites (e.g., hotels) might be due to domestic exposure.

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A study in Australia examined the occurrence and concentrations of *Legionella* in home showers using qPCR (Hayes-Phillips et al., 2019). *Legionella* spp. and *L. pneumophila* were positive in 74.6 percent (50/68) and 64.2 percent (43/68) of the showers, respectively. The researchers also demonstrated that qPCR had the potential to demonstrate increased growth potential of the bacteria and exposures at temperatures between 40°C and 60°C.

Hotels and Resorts

Legionella is frequently found in hotels and resorts. Papadakis et al. (2018) collected 518 samples from 119 hotels in Crete and assayed them by culture; of these, 36 percent (n = 43/119) of the hotels and 13 percent of the samples (n = 67/518) tested positive. The majority of positive samples were from swimming pool showers (see Figure 3-8). Like many studies, few samples (n = 5) tested positive for *L. pneumophila* serogroup 1. Figure 3-9 and Table 3-3 show the distribution of species, serogroups, and concentrations, respectively. The concentrations of *L. pneumophila* serogroup 1 ranged from 3.5×10^2 to 1.15×10^3 CFU/L. This study is similar to many surveys where a range of isolates is found, with concentrations similar to those previously reported.

In Flint, Michigan, 16 samples from hotels and schools were collected from 2015 (during the Legionnaires' disease outbreak) to 2016 (after the outbreak). No *L. pneumophila* was detected, but about 50 percent of the samples were positive for *Legionella* spp. by qPCR at 2.3×10^3 GC/L (Rhoads et al., 2017).

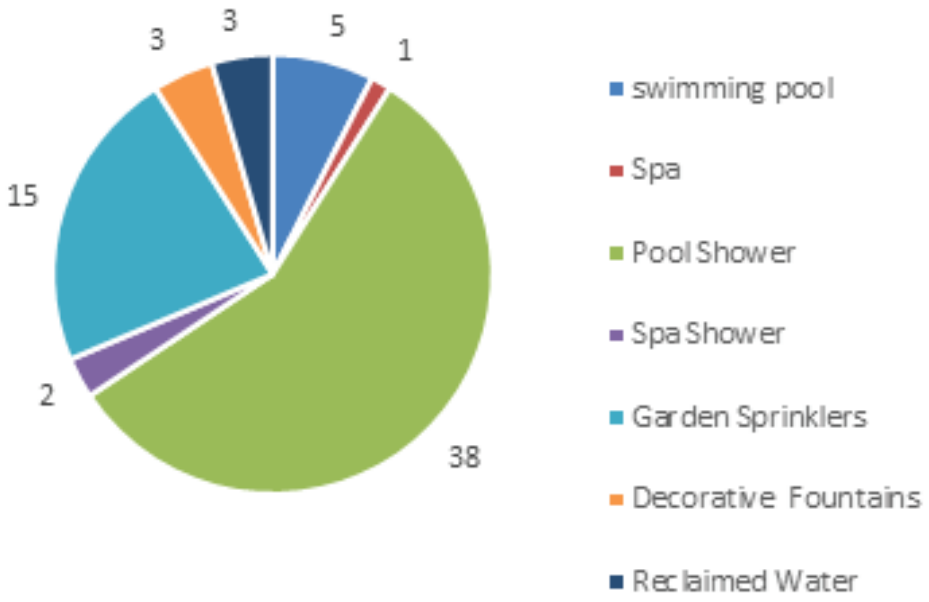

FIGURE 3-8 Note no detection in hotel showers, Jacuzzis, or soil; however, only 2, 15, and 2 samples were collected from these locations, respectively. SOURCE: Papadakis et al. (2018).

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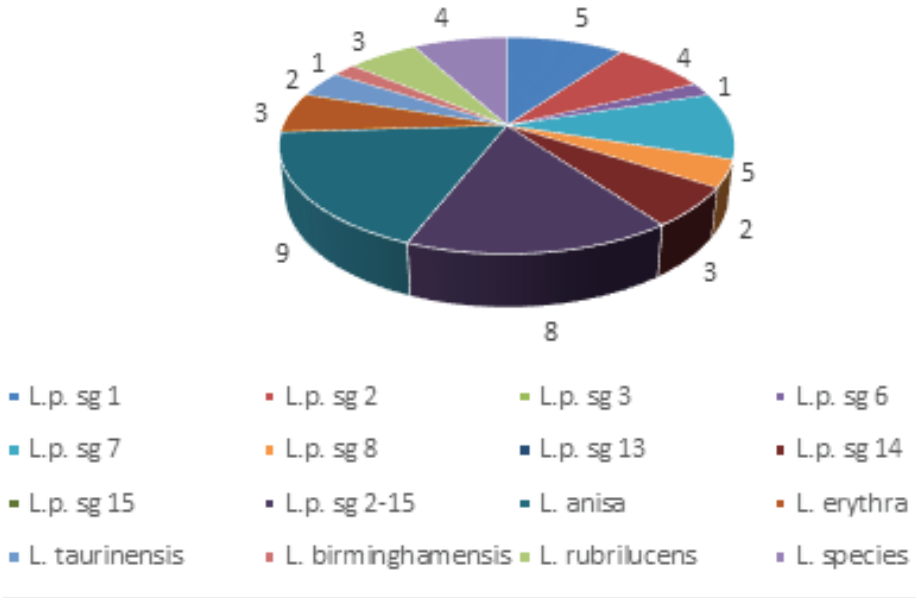

FIGURE 3-9 Distribution of *Legionella* species and serogroups detected in hotel swimming pool showers by culture. SOURCE: Papadakis et al. (2018).

TABLE 3-3 Concentration Ranges of *Legionella* Species and Serogroups Detected in Hotel Swimming Pool Showers by Culture

Species/Serogroup	# of Positive Samples	Pool Shower Low CFU/L	Pool Shower High CG
L.p. sg 1	5	350	1150
L.p. sg 2	4	100	2050
L.p. sg 3	0		
L.p. sg 6	1		150
L.p. sg 7	5	200	3350
L.p. sg 8	1		50
L.p. sg 13	0		
L.p. sg 14	3	150	100,000
L.p. sg 15	0		
L.p. sg 2-15	8	50	100,000
L. anisa	9	250	300,000
L. erythra	3	400	13,000
L. taurinensis	2	650	8,250
L. birminghamensis	1		50
L. rubrilucens	3	50	6,500
L. species	4	50	1,000

SOURCE: Papadakis et al. (2018)

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Management of Legionella in Water Systems

In a study of 51 hotels in Greece and Corfu that had been linked to travel-associated Legionnaires' disease (via epidemiological methods although no outbreaks were identified), Kyritsi et al. (2018) reported that 74.5 percent of the hotels were colonized with *Legionella* spp. The study took place between October 2011 and December 2012, and hygienic inspections and physiochemical data were also collected. Samples were primarily collected from showers (n = 496), with a few others from swimming pools (n = 36), taps (n = 8), coolers (n = 2), boilers (n = 3), cold-water tanks (n = 3), hot tubs (n = 4), cooling towers (n = 3) and one fountain, for a total of 556 samples. For each sample, 500 mL were filtered and assayed by culture methods with a detection limit of 100 CFU/L. In hot- and cold-water taps, *L. pneumophila* was found in 76.8 percent of the samples (with *L. pneumophila* serogroup 1 and *L. pneumophila* serogroups 2-15 at positive rates of 35.8 percent and 41.4 percent, respectively). Non-*pneumophila Legionella* was detected in 10.9 percent of the samples. Detection was greater in hot water (41 percent positive) and hot tubs (75 percent) compared to cold-water samples (21.4 percent). Those systems with copper piping had samples that were 12.1 percent positive versus 30.4 percent positive in systems without copper. Free chlorine levels of greater than 0.375 mg/L were negatively associated with *Legionella*. The following parameters were positively associated with *Legionella* in the cold-water systems (pH > 7.45, heterotrophic bacteria $\geq 2.5 \times 10^4$ CFU/mL, conductivity $\geq$ 1,775 uS/cm (at 25°C), hardness $\geq$ 321 mg $CaCO_3$/L, and calcium concentrations $\geq$ 150 mg $CaCO_3$/L) (Kyritsi et al., 2018). The regulations in Greece set a limit of 10^3 CFU/L for *Legionella.* Some of the hotels in this study that were deemed unsatisfactory using parameters such as hygiene and chlorine were also above this limit for *Legionella*.

Recreational Venues. Recreational sources such as hot tubs and hot-spring baths have long been associated with outbreaks of Legionnaires' disease and Pontiac fever, primarily caused by *L. pneumophila* serogroup 1. Table 3-4 shows the concentration data collected from recreational waters by Leoni et al. (2018) during outbreak investigations that included environmental monitoring using culture techniques. The *Legionella* concentrations were generally greater than 10^5 CFU/L in these outbreaks, with little association among cases, attack rates, and concentrations. Pontiac fever outbreaks showed much higher attack rates than Legionnaires' disease.

TABLE 3-4 Attack Rates, Case Numbers, and Legionella Concentrations of Selected Outbreaks of Recreational Waters

Venue	Attack Rate (%)	Cases	Concentrations (CFU/L)
Pontiac Fever			
indoor whirlpool	38	13	1.00E+06
hotel whirl spa	66-72	45	9.00E+04
resort spa	86	6	100
Legionnaires' Disease			
public bathhouse	0.13	23	8.80E+05
public bathhouse	0.2	34	8.42E+04
hot-spring bath	1.5	295	1.60E+06
public bathhouse	0.13	9	1.30E+06
public whirlpool spa	?	3	1.50E+05

SOURCE: Leoni et al. (2018).

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Hospitals

There is great concern about *Legionella* infections in hospitals because of their susceptible populations. As mentioned in Box 3-6, in many large hospitals *Legionella* monitoring has been undertaken to confirm that water treatment is suppressing bacterial growth in the premise plumbing. The goal for most hospitals is to detect no *Legionella*. Monitoring is undertaken to provide assurance to patients and managers of the building that controls are working. Culture methods are used most frequently, and any positive results tend to instigate investigation and remediation.

Stout et al. (2007) examined *Legionella* culture data from 20 hospitals in 14 U.S. states between 2000 to 2002 (see Table 3-5). As few as ten and as many as 80 samples were collected per hospital. *Legionella* (specifically *L. pneumophila* serogroup 1, *L. pneumophila* serogroups 2-14, and *L. anisa*) was detected in 70 percent of the hospitals. These investigators characterized "high level colonization" as when 30 percent or more of the distal outlets were positive for *L. pneumophila*. A total of 668 samples were collected and 21.4 percent were positive for *L. pneumophila* serogroup 1, 9.4 percent for *L. pneumophila* serogroups 2-14, and 9.9 percent for *L. anisa.* At hospitals that were positive, the percentages ranged from 5 to 83 percent, 5 to 67 percent, and 4 to 28 percent for *L. pneumophila* serogroup 1, *L. pneumophila* serogroups 2-14, and *L. anisa,* respectively. Eleven (11) hospitals had *L. pneumophila* serogroup 1 but only four of these had known cases of Legionnaires' disease.

TABLE 3-5 *Legionella* Detection in Premise Plumbing of 20 Hospitals

Hospital Location	Cases of Legionellosis Identified	>30% of distal water outlets positive for *L. pneumophila*	*L. pneumophila* sg 1 %+ (#+/total)	*L. pneumophila* sg 2-14 %+ (#+/total)	*L. anisa* %+ (#+/total)
CA	Yes	Yes	47 (7/15)	0 (0/15)	13 (2/15)
PA	Yes	Yes	30 (12/40)	25 (10/40)	0 (0/40)
NY	Yes	Yes	36 (8/22)	0 (0/22)	0 (0/22)
IA	Yes	Yes	35 (19/55)	0 (0/55))	0 (0/55)
NE	No	Yes	83 (58/70)	0 (0/70)	24 (17/70)
OH	No	No	25 (11/44)	0 (0/44)	0 (0/44)
AZ	No	No	20 (10/49)	12 (6/49)	16 (8/49)
MI	No	No	5 (2/44)	14 (6/44)	7 (3/44)
FL	No	No	17 (2/12)	0 (0/12)	8 (1/2)
WV	No	No	12 (7/58)	0 (0/58)	12 (7/58)
CA	No	No	7 (3/42)	0 (0/42)	0 (0/42)
OH	No	No	0 (0/57)	67 (38/57)	28 (16/57)
TN	No	No	0 (0/28)	7 (2/28)	4 (1/28)
MA	No	No	0 (0/20)	5 (1/20)	0 (0/20)
KY	No	No	0 (0/10)	0 (0/10)	0 (0/10)
MI	No	No	0 (0/44)	0 (0/44)	0 (0/44)
DE	No	No	0 (0/23)	0 (0/23)	9 (2/23)
NY	No	No	0 (0/12)	0 (0/12)	0 (0/12)
NY	No	No	0 (0/13)	0 (0/13)	0 (0/13)
MI	No	No	0 (0/10)	0 (0/10)	0 (0/10)

SOURCE: Stout et al. (2007)

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Management of Legionella in Water Systems

Two hospitals in Flint, Michigan, were tested after an outbreak of Legionnaires' disease in 2014 and 2015. The prevalence and concentrations of *Legionella* from October 2015 and March 2016 were measured using qPCR (see Table 3-6 and Rhoads et al., 2017). These two time points corresponded to before and after the Flint drinking water was switched from the Flint River back to Lake Huron; October 2015 was also identified as near the end of the outbreak. The percent positives ranged from 3 to 74 percent for *L. pneumophila* and from 29 to 94 percent for *Legionella* spp. Concentrations in the positive samples were similar (10^3 GC/L), regardless of the percent positive. Nonetheless, both percent positives and concentrations were considerably higher in October 2015 compared to March 2016.

Although dozens of hospitals are monitoring for *Legionella*, long-term monitoring data are not readily available. Box 3-8 describes the *Legionella* monitoring program and its results, as well as the engineering approaches used, in one hospital after a decade of testing the water in the hospital's premise plumbing. This extensive database suggests that non-detects can be achieved and that improvements in water treatment of hospital plumbing systems assist in achieving this outcome.

Monitoring has also been used to prove that remediation efforts in hospitals are successful after an outbreak. A nosocomial outbreak of Legionnaires' disease in 2013 in Australia was followed by extensive cleaning of the water system using heat, flushing, and chlorination (Bartley et al., 2016). The environmental monitoring used culture methods, which attempted to match the clinical isolates to water isolates from the patients' rooms (showers and taps were cultured). Overall 18 percent of the water samples were positive for *L. pneumophila* serogroup 1 ranging from 6.3 percent to 71.4 percent positive in one of the wings of the hospital. The premise plumbing was treated with 60°C water for ten minutes, yet positive samples were still detected (5/89, 5.6 percent). Disinfection was then carried out by flushing the system with a chlorinated alkaline detergent (pH = 10.0) and then superchlorinating with 10 mg/L free chlorine. Three cycles of treatment were needed to rid the hospital of *Legionella*.

TABLE 3-6 Percentage of Samples Positive and Average Concentrations for *Legionella* spp. and *L. pneumophila* at Hospitals in Flint, Michigan, October 2015 and March 2016, by qPCR

Locations	Total # of samples	Lp # +	% Positive	Average Concentration GC/L	L spp. # +	% Positive	Average Concentration GC/L
October 2015							
Total	98	51	52	3,000	80	82	3,300
Hospital A	46	34	74	3,000	43	94	3,400
Hospital B	52	17	33	3,000	36	69	3,100
March 2016							
Total	44	1	2	Below quantification	16	36	2,300
Hospital A	35	1	3	Below quantification	10	29	2,500
Healthcare facility	9	0	0	Below quantification	6	67	1,900
Grand total	142	52	36.5		96	67.7	

SOURCE: Rhoads et al. (2017).
Note: GC=gene copy detected by qPCR.

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BOX 3-8
Hospital Monitoring: Reviewing an 11-year Data Set

A hospital on the east side of NYC has maintained records of *Legionella* testing of its potable water for more than a decade. From 2007 to 2017 there were only three positive cultures. Interestingly, the positive cultures were all found in bulk water samples of distal sites, while swab samples from the same sites gathered at the same time tested negative. This analysis describes the testing methodology and system configuration, and it reviews potential conclusions that may be drawn from the results.

History. The hospital includes a high-rise tower with less than 500 registered inpatient beds. The hospital sees approximately 23,500 inpatients per year in this facility. The patient population is primarily immunocompromised and is highly susceptible to waterborne pathogens, including *Legionella*. In 1999, the hospital experienced what potentially was the first nosocomial case of *Legionella*. The patient was diagnosed with *Legionella jordanis* and *Legionella bozemanii* serogroup 2. Both *Legionella* types were also detected in environmental samples of potable water in the hospital.

Potable Water System. The primary water source to the hospital is the NYC water supply. Hospital floors at basement, ground, first, second and third levels are supplied from street pressure; all other floors (4 to 21) are supplied from two gravity roof tanks. Inpatient beds are on floors 4 to 19. Two wooden water tanks are located on the roof, each with a total capacity of 10,000 gallons, of which 4,750 gallons are held as fire reserve and 5,000 gallons are available for domestic use.

The hospital's water heaters are the instantaneous type with minimal storage capacity. Temperature is set at 60°C (140°F) and mixed locally at faucets and shower bodies. Circulating pumps on the hot-water returns operate in a continuous mode.

Inpatient bathrooms, sinks and showers, nurse server sinks and all other potable distal sites from the fourth to the 19th floor are fed from 18 pairs of hot and cold risers. Water distribution begins in the ceiling of the 19th floor and ends in the ceiling of the third floor. Hot-water returns with balancing valves are at the base of each hot-water riser and return back to the heaters on the 20th floor.

Secondary Water Treatment. Following the first diagnosed Legionnaires' disease patient in 1999, the hospital installed secondary water treatment to prevent *Legionella* growth and propagation in the building plumbing in March 2000. Research and discussions with the hospital's infection control group indicated that long-term mitigation should primarily address the potable hot-water system. To ensure effective treatment levels were maintained, quarterly water testing for *Legionella* was performed after secondary treatment was installed; these longitudinal records provided the basis and the data for this review.

Water Testing Protocol. During the analysis period, potable water testing was performed quarterly. The bulk of the samples were taken twice at each distal site, once by swab and once a first draw of bulk water. All samples were drawn and sent to a third-party lab, overnight delivery, in lab-provided containers. The swabs were taken from inside the faucet/shower with the screen/head removed.

Water Testing Dataset. The review of sampling data began in March 2007 and continued through December 2017. Both water column and swab samples were collected quarterly from approximately 40 to 46 locations that were either showers or faucets. Showers represented 85 percent of the samples collected (1,445 total samples, half were swabs) and faucets represented the other 15 percent (253 samples, half were swabs). Of the 1,698 samples collected over the 11 years, only three were positive. One sample from a shower was positive for *L. pneumophila* serogroup 1 (140 CFU/mL) and the other two positive samples were *Legionella anisa* (8 CFU/mL and 10 CFU/mL from a faucet and shower, respectively). The faucet sample positive for *L. anisa* was taken at a sink in a newly renovated ICU prior to occupancy. It should be noted that while

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the shower water tested positive, the swab samples taken at the same time from the same location tested negative. All tests were performed by culture; the detection limits were 10 CFU/swab sample and 1 CFU/mL for the water sample. It is unclear if seasonality was involved, although the positives were found in spring and fall (March and September). Engineering data such as disinfectant residual, pH, temperature, and estimated water age were not measured or recorded at the time of sampling.

Conclusions. Ten years of quarterly testing were performed from 2007 to 2017. During this period, 1,698 tests were performed, resulting in three positive cultures. The three positives were all obtained from the bulk water samples while the corresponding duplicate swab samples were negative. Over the 11-year period of testing, and after the implementation of secondary water treatment, the level of positivity was reduced to two-tenths of one percent, substantially below the 28 percent positivity rate at system implementation measured in the year 2000.

Cruise Ships and Ferries

Goutziana et al. (2008) studied *Legionella* on cruise ships and ferries in Greece. No *Legionella* was found in the ten cruise ships' water systems. However, 14 of the 21 ferries were positive when 276 samples of hot and cold water were analyzed, and remediation commenced. There was greater contamination in the ferries' hot-water systems, with 38, 34, 19, 15, and 7 percent of the samples positive for *Legionella* spp., *L. pneumophila*, *L. pneumophila* serogroup 1, *L. pneumophila* serogroups 2-14, and *L. pneumophila* serogroup 1 concurrent with other serogroups, respectively. In cold water, 18, 15, 11, 4, and 2 percent of the samples were positive for *Legionella* spp., *L. pneumophila*, *L. pneumophila* serogroup 1, *L. pneumophila* serogroups 2-14, and *L. pneumophila* serogroup 1 concurrent with other serogroups, respectively. In another similar study, 12 cruise ships were found to be negative for *Legionella*, while 28 ferries were sampled and found to be positive 81 percent of the time (Mouchtouri and Rudge, 2015).

Drinking Water and Wastewater

Many fewer monitoring studies have focused on drinking water or wastewater systems compared to the other categories, with most studies undertaken as investigative special surveillance studies. A national study found *Legionella* spp. in 12 of 18 samples (67 percent positive by qPCR) from the sediments of drinking water storage tanks of ten states (i.e., Alabama, Arizona, California, Illinois, New Jersey, North Carolina, Ohio, Pennsylvania, Tennessee) at average concentrations of 5.2 x 10^3 cell equivalents(CE)/gram of wet weight of sediment (Lu et al., 2015). *L. pneumophila* was found in 33 percent of the samples and *L. pneumophila* serogroup 1 was found in 28 percent. (To facilitate comparison with other studies, dry weight rather than wet weight should have been recorded.) Developing consensus on methods and data reporting is needed for these types of investigations in order to begin to build national databases and to understand the role of drinking water in seeding of premise plumbing.

Drinking water and reclaimed water were examined for *Legionella* species by Garner et al. (2018) using qPCR (see Table 3-7). Prevalence was higher in reclaimed water compared to potable water (89 percent versus 55 percent), and concentrations of gene copies were 10- to 100-fold higher in reclaimed water. There was no quantification of *L. pneumophila*, although it was annotated in samples using metagenomic approaches.

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TABLE 3-7 *Legionella* spp. by qPCR in Potable and Reclaimed Waters and Biofilms

Sample	% Positive (n=)	Gene Copy/L
Potable water POE	67 (15)	5.6×10^5
Potable water POU	56 (102)	4.7×10^5
Reclaimed water POE	91 (22)	3.8×10^7
Reclaimed water POU	87 (96)	9.6×10^7
Swabs from potable water POU	52 (60)	1.9×10^5
Swabs from reclaimed water POU	92 (51)	5.6×10^6

Note: averages in the final column were determined from positive samples only. POE refers to the point of entry to the distribution system while POU refers to the point of use from the distribution system. SOURCE: Garner et al. (2018).

The best known example of a drinking water source playing a major role in an outbreak of Legionnaires' disease occurred in Flint, Michigan, in 2014–2015. The outbreak coincided with a change in the source and treatment of drinking water for the City of Flint. In the absence of proper chemical corrosion control, this change in source water led to drastic increases in iron levels in the water and also risked disrupting biofilms coating the surfaces of pipes, releasing *Legionella* into the potable water supply of many buildings. Box 3-9 discusses this case in greater detail.

Wastewater treatment plants have been identified as sources for Legionnaires' disease or Pontiac fever in different countries. In 2013, a large outbreak of legionellosis (159 cases) occurred in Warstein, Germany. The source for the outbreak was a cooling tower that received river water into which a biological wastewater treatment plant discharged (Maisa et al., 2015). The effluent of this wastewater treatment plant contained high numbers of *L. pneumophila* (approximately 10^7 CFU/L), and genotyping showed identical patterns in patient strains and strains from the wastewater treatment plant (Maisa et al., 2015). Investigations at the treatment plant showed that the aerobically pre-treated wastewater contained high numbers of cultivable legionellae (10^8 to 10^{10} CFU/L) (Noguiera et al., 2016), demonstrating that legionellae were capable of multiplying in this treatment process.

BOX 3-9
2014- 2015 Legionnaires' Disease Outbreaks in Flint, Michigan

Flint is an industrial city in Genesee County, Michigan, whose economy boomed in the 1960s. Subsequent changes in the auto industry decreased factory jobs, with unemployment peaking around 17 percent in 2009 and reaching about 5 percent in 2018 (Bureau of Labor Statistics). By 2018 the Flint population had decreased by about 50 percent. Since 1954, the municipal water source was Flint River water treated at the Flint Water plant. In 1967, the city began purchasing water from Detroit Water and Sewerage Department (DWSD), which treats Lake Huron water at the Fort Gratiot plant. To reduce costs, in April 2014, the city switched back to Flint River water treated at the Flint Water plant. However, corrosion control measures were inadequate. Within a few weeks of the switch, residents complained of not only red and smelly water, but also skin rashes, respiratory irritation, and gastrointestinal problems. By the end of 2014, the Genesee County Health Department also recognized an increase in legionellosis cases, a pattern that repeated in the summer of 2015. In October 2015, the municipal water was switched back to DWSD, with appropriate corrosion control. A massive flushing program was also in place through spring of 2016. At that point, 79 Legionnaires' disease cases and 12 deaths had been reported. By the following summer, legionellosis cases had declined to historic baseline rates (Rhoads et al., 2017; Zahran et al., 2018). Table 3-9-1 gives a timeline of the Flint water crisis events.

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TABLE 3-9-1 Timeline of the 2014 - 2015 Flint Water Crisis

April 2014	Michigan Department of Environmental Quality (DEQ) approves source water switch and a Flint River changeover ceremony is held. On April 25th, the community begins receiving treated Flint River water.
May 2014	Complaints begin of poor water quality (smell, taste, discoloration).
J**une 2014**	**6 cases of legionellosis occur.**
August 2014	Flint water tests positive for E. coli. Two boil water advisories are issued.
September 2014	**32 total cases of legionellosis have occurred.**
November 2014	City increases hydrant flushing to address red water concerns.
December 2014	City receives official violation notice from DEQ for violations of the Safe Drinking Water Act (SDWA) for total trihalomethanes (TTHMs).
End of 2014	**42 total cases of Legionellosis have occurred in 2014.**
February 2015	High levels of lead are found at a residence (up to 397 ppb).
May 2015	**3 cases of legionellosis occur.**
June 2015	**9 cases of Legionellosis occur.**
June 2015	City receives second violation notice from DEQ for violations of the SDWA for TTHMs.
July 2015	Flint installs a granular activated carbon filter to control TTHMs by removing organic matter.
September 2015	**44 total cases of Legionellosis have occurred in 2015.**
October 2015	Flint switches back to DWSD-treated water from Lake Huron.
October 2015	Governor Snyder appoints the Flint Water Advisory Task Force to investigate.
December 2015	For corrosion control, Flint increases phosphate concentration from 1 to 2.5 mg/L.
January 2016	Federal emergency declared by President Obama.
March 2016	Flint Water Advisory Task Force Report issued.
May 2016	Massive "Flush for Flint" campaign to ensure corrosion control is delivered throughout.
Summer 2016	Legionnaires' disease cases return to pre-2014 levels.

SOURCE: Adapted from Masten et al., 2016.

Epidemiology. During the period that Flint residents received treated Flint River water, their risk of Legionnaires' disease was elevated 6.3-fold (Figure 3-9-1A). That the switch in source and treatment of the municipal water system accounted for this increased disease risk was supported by additional independent epidemiological analyses. When purported hospital-associated cases were disregarded, the risk remained elevated by a factor of 5.7. After boil-water advisories were announced, the odds of Legionnaires' disease cases among Flint residents declined, most likely due to reduced water use among Flint residents after the boil-water advisory (Zahran et al., 2018). And, in communities bordering Flint, the probability of legionellosis cases in each census tract correlated to their number of residents who commuted into Flint (Zahran et al., 2018).

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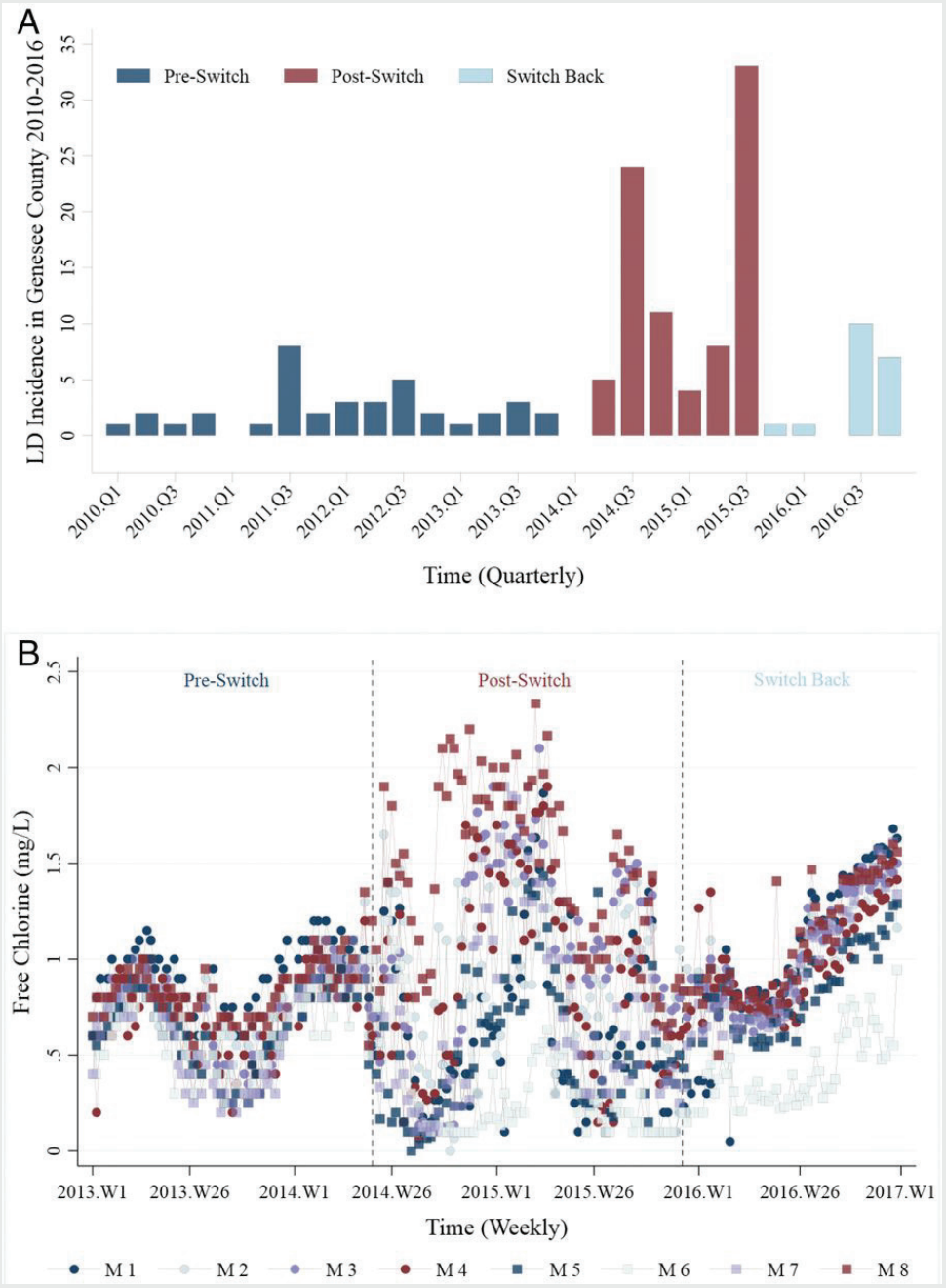

FIGURE 3-9-1 Spike in Legionnaire's disease cases coincident with switch in water supply and increased variation observed in the Flint water distribution system. A. Quarterly Legionnaires' disease incidence in Genesee County, MI, 2010 through 2016. The count of Legionnaire's disease cases in Genesee County as compiled in the Michigan Disease and Surveillance System at the quarterly time step. B. Free chlorine at eight monitoring locations in Flint's water distribution system, 2013-2016. Free chlorine (mg/L as Cl2) was reported weekly during the three water regime phases defined above (vertical lines) and the periods and dates (year/week) shown at eight locations in Flint. SOURCE: Zahran et al. (2018).

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Water Quality Monitoring. In addition to inadequate corrosion control of Flint River water, multiple water parameters conducive to *L. pneumophila* persistence or growth were reported. These included slightly elevated distribution water temperature, elevated organic matter, high iron concentrations, and elevated or depleted chlorine residual (Figure 3-9-1B; Masten et al., 2016; Rhoads et al., 2017; Zahran et al., 2018). Iron, an essential nutrient for *L. pneumophila* (Mengaud and Horwitz, 1993), also inactivates chlorine. Indeed, during the period Flint received corrosive river water, as the concentration of free chlorine in water in a census track declined, the probability of Legionnaires' disease cases in that sector increased (Zahran et al., 2018).

Microbiological Monitoring. Water samples collected in October 2015 from the cold-water taps of public restrooms in two Flint hospitals (Schwake et al., 2016) contained *Legionella* and *L. pneumophila* gene copy numbers considerably higher than those reported previously for U.S. drinking water systems in the absence of a legionellosis outbreak (Donohue et al., 2014) (mean concentration range of 1,170 and 2,480 versus 2 gene copies/mL).

In fall of 2016, after Flint had switched back to Lake Huron water, a surveillance study of 130 residences cultured *L. pneumophila* from 13 Flint homes. Of the 16 *L. pneumophila* strains isolated from premise plumbing, one was serogroup 1, and the rest were serogroup 6 (Byrne et al., 2018). In contrast, all 33 clinical isolates submitted from 2013 to 2016 to the Michigan Department of Health and Human Services Bureau of Laboratories by hospitals in southeast Michigan were *L. pneumophila* serogroup 1 (Byrne et al., 2018), consistent with widespread diagnosis by the urinary antigen test.

Conclusions. During the time that Flint River water was used as the city's primary source, corrosion within the Flint municipal water system created conditions favorable for *Legionella* persistence and proliferation. *L. pneumophila* strains naturally present at low levels within the Flint distribution system and building premise plumbing would likely thrive with the influx of organic carbon and iron and the concomitant drop in free chlorine characteristic of the corrosive treated Flint River water. Unfortunately, the small number of clinical and environmental *L. pneumophila* isolates collected during the 2014-2015 outbreak limited the molecular epidemiology attempts to identify the source(s) and parameters that accounted for this outbreak. Only 11 patient isolates were collected in Genesee County between 2014 and 2015 and available for whole genome sequencing, and only eight of these were associated with any exposure in Genesee County during the outbreak. This emphasizes the importance of collecting clinical isolates for tracking potential sources of disease. It should be noted that if the Flint hospitals where patients were likely exposed to *Legionella* had had effective water management plans including on-site controls of *Legionella*, there likely would have been very different outcomes in terms of patients contracting Legionnaires' disease. Indeed, disease cases stemming from one hospital in Flint decreased dramatically after a biocide system was installed in the hospital. Nonetheless, while the Flint outbreak is an example of the failure of an important barrier—treatment of the building water system—it is also unique in highlighting the role of drinking water utilities in creating conditions conducive to *Legionella* proliferation in premise plumbing.

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Wastewater treatment plants that service wood-, plant- or food-processing industries in Denmark, Finland, Sweden, and the United States have also been identified as a source of *L. pneumophila* (Castor et al., 2005; Gregersen et al., 1999; Kusnetsov et al., 2010). At these locations, only workers at the treatment plants became ill with Legionnaires' disease or Pontiac fever. *L. pneumophila* at relatively high concentrations (10^7 to 10^9 CFU/L) was mainly observed in sludge and effluent at these plants.

Two recent separate outbreaks of Legionnaires' disease in The Netherlands were traced to biological wastewater treatment plants that treat animal waste (Loenenbach et al., 2018; Alvin Bartels, Dutch National Institute for Public Health and the Environment, personal communication, July 2018). *L. pneumophila* was observed in high numbers (10^6 to 10^8 CFU/L) in their aeration ponds, which contain nutrient-rich water and operate at 35°C. Genotyping of the *L. pneumophila* strains demonstrated that the same sequence type (ST 1646) was observed in patients and in the treatment plant aeration ponds (Loenenbach et al., 2018). Box 3-10 describes the investigation of a Norwegian outbreak of Legionnaires' disease attributed to a wastewater treatment plant.

BOX 3-10
Wastewater Treatment Plant Identified as a Source for Legionnaires' Disease

A wastewater treatment plant in Norway was identified as a source for Legionnaires' disease, leading to 56 cases and ten deaths in 2005, and five cases and two deaths in 2008 (Borgen et al., 2008; Nygård et al., 2008). This plant treated wastewater from a wood refinement factory using both an air-treatment process (air scrubber) and a biological treatment process (aeration ponds). In the air-treatment process, process air was mixed with fresh air before it entered the air scrubbers, where it was sprayed with water. In the biological treatment process, microbial degradation of organic substances from the wastewater was achieved in two large aeration ponds (30,000 m^3 of liquid), and the effluent of the plant was discharged to a river (Olsen et al., 2010).

In 2005, the same genotype of *L. pneumophila* serogroup 1 was observed in patients and in water sampled from the air scrubbers and from a river sample downstream of the wastewater treatment plant (Nygård et al., 2008). Since the water temperature in the air scrubbers was approximately 40°C and it expelled greater than 4 m^3 of water per hour as aerosol and was never disinfected, initially the air scrubbers were the suspected source for the outbreak in 2005 (Nygård et al., 2008). However, despite the control measures taken for the air scrubbers, a second outbreak linked to the same plant occurred in 2008 (Borgen et al., 2008). Additional research showed that *L. pneumophila* serogroup 1 was present in high numbers in the aeration ponds (10^8 to 10^{10} CFU/L) and in the effluent of the plant (up to 10^6 CFU/L) that was discharged in the river (Olsen et al., 2010). In river water downstream of the treatment plant (up to 1.6 km downstream), *L. pneumophila* serogroup 1 was detected at 10^4 to 10^6 CFU/L. The *L. pneumophila* strains were genotyped, and the same sequence type isolated from the patients in 2005 and in 2008 was also observed in the aeration ponds and the river. Moreover, air samples taken above the aeration ponds were consistently positive for *L. pneumophila* by PCR, and cultivation detected up to 3,300 *L. pneumophila* CFU/m^3 air (Blatny et al., 2008). Air samples taken upwind of the aeration ponds were generally negative for *L. pneumophila*, but downwind samples were regularly positive. Therefore, the aeration ponds (and not the air scrubbers) were identified as the primary source of the 2005 and 2008 outbreaks (Olsen et al., 2010).

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Management of Legionella in Water Systems

Occurrence Summary

The vast majority of studies reviewed for this chapter reported presence/absence data but not quantitative concentration data, making it difficult to draw meaningful conclusions about the extent of *Legionella* risk from built water systems. Nonetheless, the preceding section makes it clear that over the 30 years that *Legionella* data have been gathered, the percent positives and concentrations found have not changed significantly over time or with building or device type. Thus, whether large-scale surveys examine cooling towers, residences, hotels, or hospitals, between 30 and 80 percent of the samples are positive for *Legionella* species and 3 to 20 percent are positive for *L. pneumophila*.

The more limited set of studies for which concentrations were reported demonstrates that higher concentrations of *Legionella* are associated with higher disease risk. For example, the studies of *Legionella* outbreaks associated with cooling towers suggest that duration of the outbreak, but not the total number of cases, is related to *Legionella* concentrations averaging greater than 10^6 CFU/L (Walser et al., 2014). One small study in Flint, Michigan, showed positivity levels in hospital taps dropping from 55 percent to 2 percent for *L. pneumophila* along with concentrations dropping from 10^6 CFU/L to below detection limits once the outbreak subsided. Similarly, in two Flint hospitals there was a drop from 80 percent to 40 percent positivity for *Legionella* spp. (with no drop in concentrations) after the outbreak (Rhoads et al., 2017). Non-detectable CFU/L is possible in hospital taps as shown by data obtained from a major hospital's 11-year monitoring program (see Box 3-8).

A number of the studies cited in this chapter included environmental monitoring that recorded concentrations of culturable *Legionella*. The Walser et al. (2014) review of cooling tower outbreaks from France, Germany, Italy, New Zealand, The Netherlands, Norway, Spain, and the UK reported *Legionella* concentrations (for nine outbreaks) ranging from 2.0×10^3 to 1.0×10^8 CFU/L with an average of 1.39×10^7 CFU/L. Leoni et al. (2018) evaluated nine recreational outbreaks of Pontiac fever and Legionnaires' disease associated with hot tubs and bathhouses. Their work reported *Legionella* concentrations ranging from 8.4×10^4 to 1.6×10^6 CFU/L with an average of 8.0×10^5 CFU/L. An outbreak associated with a wastewater treatment plant showed that *Legionella* concentrations from the aerators ranged from 2.0×10^6 to 2.2×10^9 CFU/L with an average of 1.1×10^9 CFU/L (Loenenbach et al., 2018). Finally, Orkis et al. (2018) reviewed data from sporadic cases of disease from several environments (e.g., apartments, homes, high rises, and associated showers and storage tanks) and reported a range of 1.0×10^4 to 2.0×10^5 CFU/L with an average of 1.0×10^5 CFU/L. These data were contrasted to routine sampling concentrations of *Legionella* from reclaimed water, residential properties, hotel showers, and industrial cooling towers (Codony et al., 2002; Johnson et al., 2018; Li et al., 2015; Papadakis et al., 2018). The results are graphed in Figure 3-10. The goal of this exercise was to see if there was an obvious break in the data between sporadic cases and outbreaks, similar to an analysis done for *Cryptosporidium* (Haas and Rose, 1995). The Committee identified the concentration of 5×10^4 CFU/L as such a break. Hence, **a *Legionella* concentration of 5×10^4 CFU/L should be considered an "action level"—that is, a concentration high enough to warrant serious concern and to move remediation forward immediately. A lower action level may be necessary to protect those at higher risk for legionellosis such as hospital patients, particularly those in intensive care, cancer, and solid-organ transplant units.**

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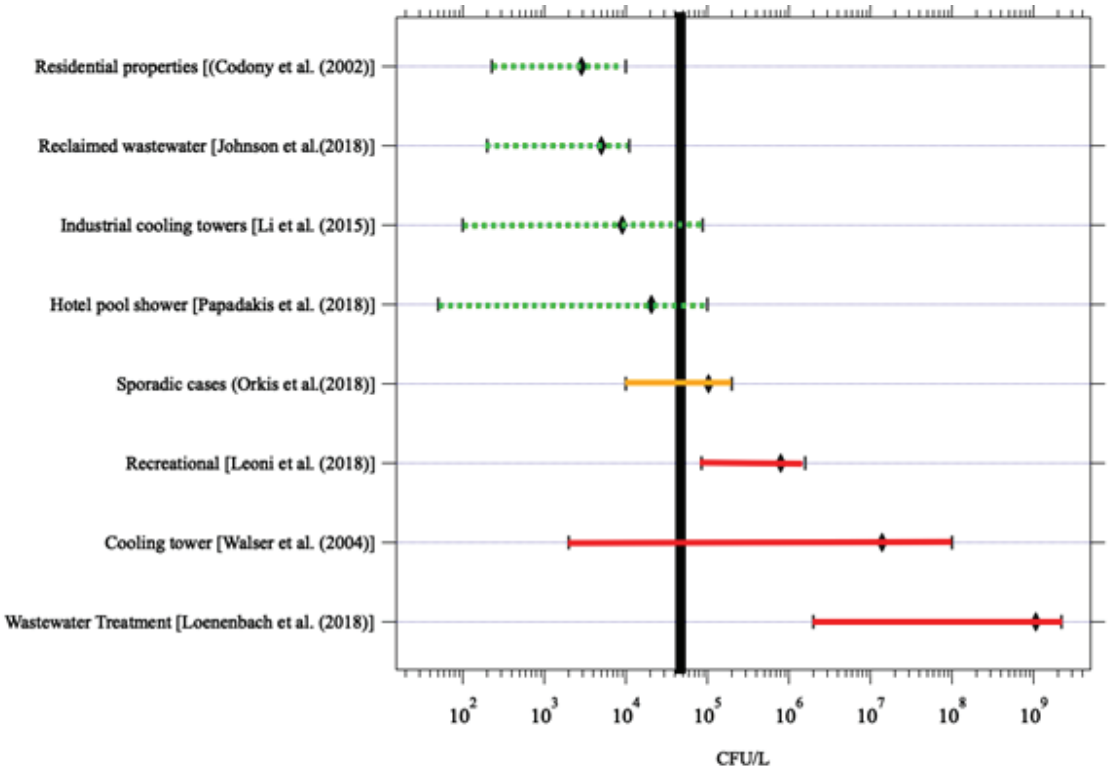

FIGURE 3-10 Concentrations of culturable *Legionella* during outbreaks and routine monitoring from various environments (ranges shown as bars, averages shown as diamonds). Red solid lines are outbreaks. Green dashed lines are routine sampling. The orange solid line is from sporadic cases. The solid black line is the 5 x 104 CFU/L action level identified by the Committee as a break between sporadic cases and outbreaks.
SOURCES: Cooling towers outbreaks (Walser et al., 2014), recreational water outbreaks (Leoni et al., 2018), wastewater treatment plant outbreaks (Loenenbach et al., 2018), sporadic cases from buildings (Orkis et al., 2018), reclaimed wastewater (Johnson et al., 2018), residences (Codony et al. 2002), showers at hotel pools (Papadakis et al., 2018), and industrial cooling towers (Li et al., 2015).

QUANTITATIVE MICROBIAL RISK ASSESSMENT FRAMEWORK FOR *LEGIONELLA*

Quantitative microbial risk assessment (QMRA) is the process whereby the risk associated with exposure to pathogens is assessed (Haas et al., 2014). It evolved from the National Academies of Sciences, Engineering, and Medicine's framework on risk assessment (see Box 3-11), which focused on chemical and physical environmental hazards. QMRA can also be used to assess the Legionnaires' disease risk from exposure to waters containing *L. pneumophila* under various scenarios (e.g., aerosols from toilets, showers, or cooling tower drift).

Risk assessment has multiple applications in understanding and controlling problems from *Legionella*. For example, given an acceptable level of risk in a particular venue or application (e.g., hospital showers, cooling towers), one can use QMRA to estimate the concentration of *L. pneumophila* in the breathing zone (or ultimately, in the water being aerosolized) that would result in that risk. This concentration could be used as a standard, criterion, or operational target to which one would compare the results of routine environmental sampling for *Legionella* to determine whether it is necessary to remediate a building water system and to what extent (i.e., the "how clean is clean" problem). This does not imply

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BOX 3-11
Risk Terminology and Definitions

Kaplan and Garrick (1981) set forth the concept of risk as the likelihood of a consequence from a hazard, with attendant uncertainty and variability. As delineated in a framework set forth by the National Academies of Sciences, Engineering, and Medicine (NAS, 1983), human health risk assessment involves the delineation of a hazard, assessment of exposure, determination of the dose-response relationship and aggregation in a risk characterization. These terms are formally defined as:

Risk: The potential for realization of unwanted, negative consequences of an event (Committee on Foundations of Risk Analysis, 2015).

Hazard identification: The process of determining whether exposure to an agent can cause an increase in the incidence of a health condition (NAS, 1983).

Dose-response assessment: The process of characterizing the relation between the dose of an agent administered or received and the incidence of an adverse health effect in exposed populations and estimating the incidence of the effect as a function of human exposure to the agent (NAS, 1983).

Exposure assessment: The process of measuring or estimating the intensity, frequency, and duration of human exposures to an agent currently present in the environment or of estimating hypothetical exposures that might arise from the release of new [agents] into the environment. In its most complete form, it describes the magnitude, duration, schedule, and route of exposure; the size, nature, and classes of the human populations exposed; and the uncertainties in all estimates (NAS, 1983).

Risk characterization: The process of estimating the incidence of a health effect under the various conditions of human exposure described in the exposure assessment. It is performed by combining the exposure and dose-response assessments. The summary effects of the uncertainties in the preceding steps are described in this step (NAS, 1983).

Risk management: Risk management is the process of weighing policy alternatives and selecting the most appropriate regulatory action by integrating the results of risk assessment with engineering data and with social, economic, and political concerns to reach a decision (NAS, 1983).

conducting QMRA for each situation, but rather developing a generic QMRA for types of buildings or exposures to develop actionable cleanup targets (e.g., cleanup such that the average of ten air samples does not exceed a certain value).

Another application of QMRA is outbreak investigations. In this situation the plausibility of a particular source being the cause of an outbreak can be determined by back-calculating the *Legionella* concentrations that would have been there if in fact that site was the cause. There are many other applications of QMRA in the design or remodeling stage of a building. QMRA can inform design decisions and determine, for example: (1) the length of a shower hose that should not be exceeded to avoid unacceptable amplification of pathogens; (2) the setback distances from populations for large industrial cooling towers; or (3) the adequacy of building-level hydraulic design to maintain acceptable microbial quality. In all the above cases, even in the absence of precise data for all inputs, risk can be calculated by estimating the uncertainties for each input and propagating them through the calculations.

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From a mechanistic standpoint, a *Legionella* QMRA can be conducted by going through the series of steps shown in Figure 3-11. Given a recovery-corrected concentration of infectious and viable *Legionella* in water, the aerosol generation rate can be computed. Some enrichment of *Legionella* in the aerosol may occur, since bacteria selectively accumulate at air-water interfaces (Schäfer et al., 1998). The size distribution of bacterial-laden aerosols is important with respect to transport, survival, and passage to the lungs.

Once aerosols of the appropriate size are inhaled, the inhaled dose can be used to determine the risk from the exposure via application of a dose-response model. There are dose-response models for L. pneumophila that have been derived from animal experiments and validated against outbreaks (Armstrong and Haas, 2007a, 2008). These are consistent with the beta-Poisson and exponential models (Haas, 2015), such that there is no "threshold" dose below which zero risk occurs. In other words, for any dose, no matter how small, there is a finite non-zero risk of infection thence illness, since even a single organism can, in some fraction of hosts, multiply to a biologically significant level in vivo.

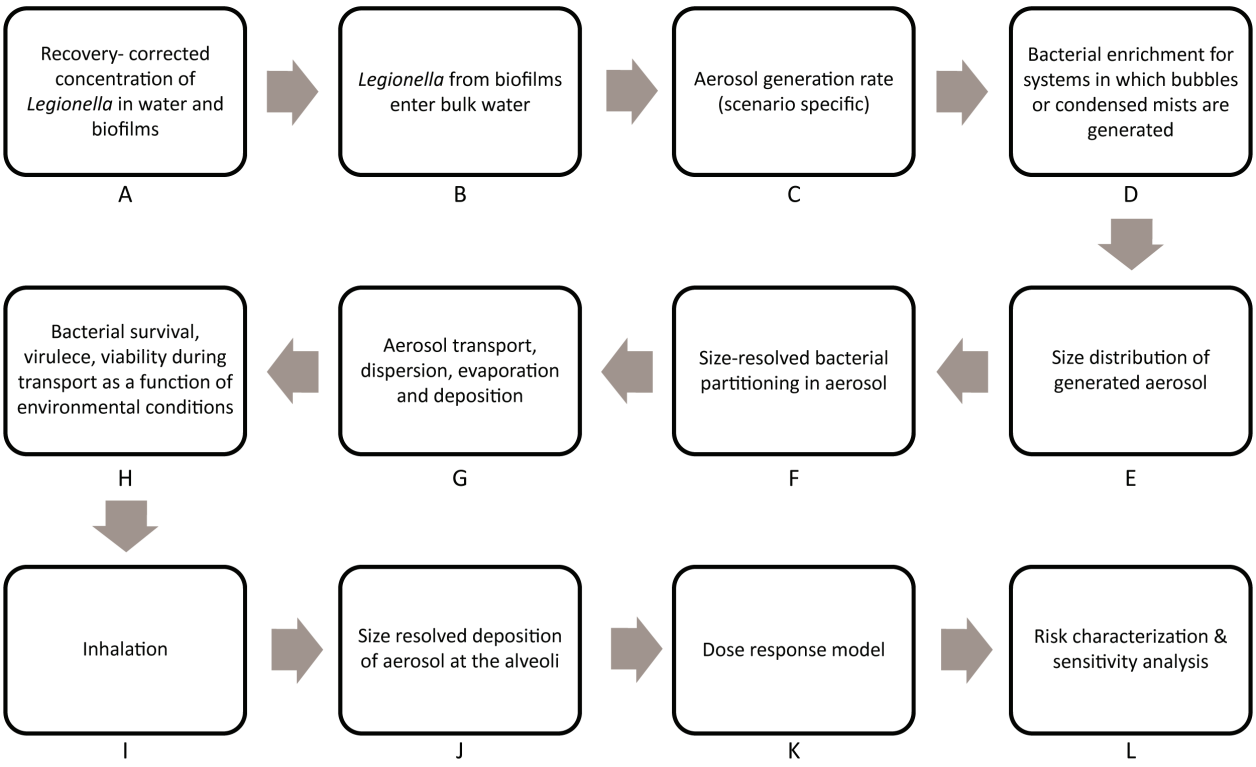

FIGURE 3-11 Framework for *Legionella* QMRA. SOURCE: Revised from Hamilton and Haas (2016). Reproduced with permission of R S C Publications in the format Book via Copyright Clearance Center.

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Management of Legionella in Water Systems

Because the QMRA approach relies on dose-response models from only a few selected strains for which animal testing has been performed, one uncertainty is the incorporation of any strain variability, or variability associated with prior history of bacterial exposure, such as the acquisition or expression of virulence factors (Buse et al., 2015). Also, the current dose-response models are only for L. pneumophila serogroup 1; the relative potency of other serogroups is unknown. The dose-response models do not account for any differences in host characteristics, such as age, gender, or immune status.

If actual data are available for microorganisms at one of the intermediate points in the flow chart, it is possible to start the QMRA at that point. For example, size-resolved microbial concentrations in aerosols might exist which could be used as a starting point (Step F). There have been over 18 exposure assessments and more than ten full risk assessments conducted on *L. pneumophila* (Hamilton and Haas, 2016).

In some cases, concentrations may only be reported as presence/absence. In this situation, concentrations can be estimated using an MPN approach. This is discussed and illustrated in Box 3-12, which indicates that non-detects can be informative *if* the volume examined is known. Non-detects, as well as samples that are "too numerous to count" (TNTC), can also be informative for exposure assessment as long as the volumes examined and the cut-offs for TNTC are known (Haas and Heller, 1988).

Environmental measurements of *Legionella* are frequently made using molecular methods, with qPCR being the most prevalent technique. However, direct sequencing approaches (Timms et al., 2017) may become more common. (A discussion of these and putative viability assays is found earlier in this chapter.) Exposure estimates are necessary to produce good risk estimates, and the number of samples collected in a monitoring program and their detection limits should be sufficient to determine exceedance or compliance with an acceptable risk value. The number of samples can be determined using standard quality control statistics.

As was made obvious earlier in this chapter, the chosen *Legionella* sampling method may influence the measurements of occurrence and concentration. For example, a recent study comparing the concentrations of *Legionella spp.* in wastewater treated for non-potable reuse found dramatic differences between the results from culture, qPCR, and EMA-qPCR methods (Johnson et al., 2018), as shown in Figure 3-12. Culture-based methods generally reported the lowest occurrence and concentrations.

Regardless of the sampling method used for exposure assessment, quantification of any microorganism carries with it many sources of variability. Some variability may be inherent in the time-to-time and place-to-place differences in actual microbial levels, which is irreducible by more sampling. This variability was exemplified by a detailed investigation of hot- and cold-water outlets in nine residential homes and hotels in Cologne, Germany (Völker et al., 2016). The 807 samples taken showed significant variability (up to 4 logs) in *Legionella* spp. concentrations in flushed samples between sampling points within a single building and, for a given point, between hours in a day or between weeks. Other variability may be due to the experimental techniques themselves, including sample collection, concentration, decontamination, processing, and detection. Only a true end-to-end comparison can assess the extent of this intrinsic variability. Such a study requires that a sample be spiked with a known number of organisms and then processed through the entire protocol (i.e., concentration, decontamination, detection) to assess the recovery and its variability. An example of such a study is Bonilla et al. (2015). Sufficient numbers of samples should be taken to make the effect of this intrinsic variability small with respect to the irreducible variability.

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BOX 3-12
Using Presence/Absence Data to Estimate Concentrations

Consider that a number (N) of samples, each of volume (V) have been collected. Of these, P samples are found to be positive. The fraction positive is then $f = \frac{P}{N}$. What is the estimate for the concentration (μ) of microorganisms in the system from which the samples were drawn? This is analogous to the single dilution MPN analysis, which has long been discussed (e.g., Cochran, 1950). Under the assumption that the microorganisms in the system from which the samples are drawn are randomly distributed, i.e., Poisson, the following is the best (maximum likelihood) estimate:

$$\mu V = -ln(1 - f) \qquad (1)$$

For many other organisms (although not for *Legionella*), the distribution of microorganisms in water is not random but more heterogeneous than the Poisson distribution (El-Shaarawi et al., 1981; Gale et al., 1997; Pipes et al., 1977). This may be because of intrinsic variability in the environment, or variability in the enumeration, or both. An alternative to the Poisson is the negative binomial distribution with an overdispersion parameter "k"; small k values indicate greater overdispersion, and the limit of k→∞ is the Poisson distribution.

$$\mu V = k\left[(1 - f)^{-1/k} - 1\right] \qquad (2)$$

Figure 3-12-1 is a plot of the estimate for μV given the fraction of samples positive in the case of the Poisson as well as negative binomial distributions with different "k" values. Below a fraction positive of approximately 10 percent, the impact of heterogeneity is negligible. The utility of this approach can be illustrated with a simple example. Suppose 50 mL samples are used and less than 5 percent of them are found to be positive for *Legionella*.

From equation (1), $\mu V = -ln(1 - 0.1) = 0.105$ and therefore $\mu < 0.21/100mL$.

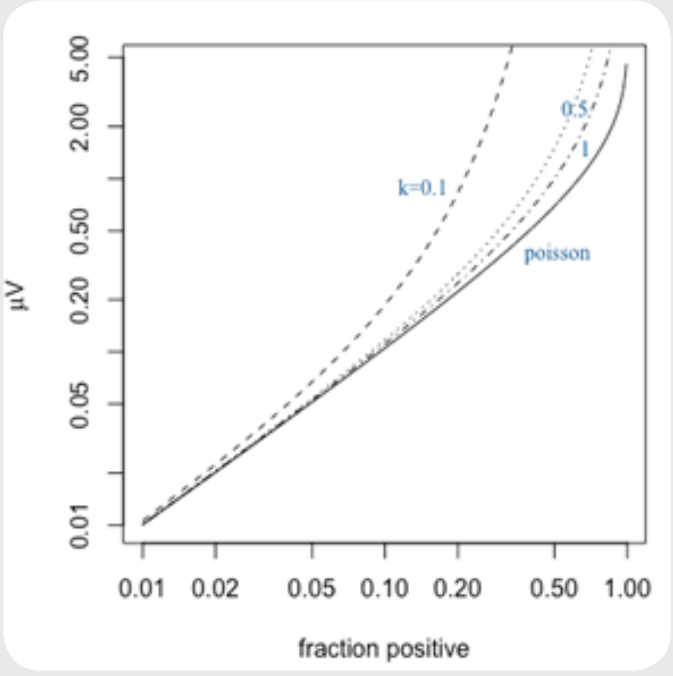

FIGURE 3-12-1 Estimation of Mean Density Given Fraction of Positive Samples of Volume vs. Poisson compared to Negative Binomial Distributions.

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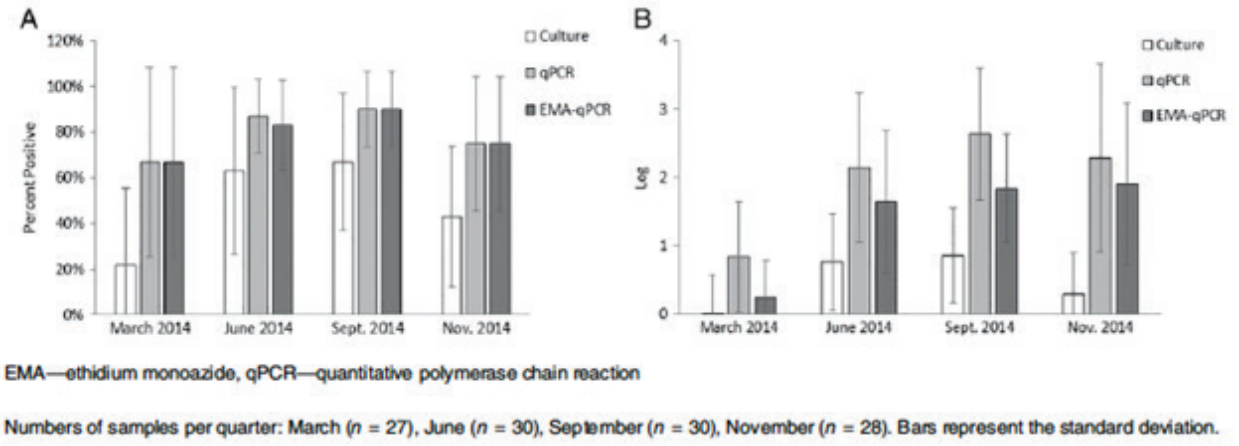

FIGURE 3-12 Seasonal occurrence (A) and concentration (B) of *Legionella* (in CFU/mL for culture, and genomic units per mL for qPCR and EMA-qPCR).
SOURCE: Johnson et al. (2018).

For *L. pneumophila*, there are no good published studies to assess the intrinsic variability of different sampling methods, including culture techniques, molecular techniques, or various proprietary test kits. However, one known factor (albeit with coliforms) is that the variability associated with methods that result in actual concentrations tends to be less than variability associated with MPN-type techniques, although this does depend on how many actual counts are enumerated, and the protocol (number of dilutions and replicates per dilution) of an MPN. As an example, early work by Thomas and Woodward (1955) showed that the MPN enumeration of coliform tended to have about 2.5 times the coefficient of variation for replicates than the membrane filter colony count methods.

QMRA Case Studies for *Legionella*

As an example of a forward QMRA, the risks associated with *Legionella* exposure in aerosols generated from toilet flushing using reclaimed wastewater were examined by Hamilton et al. (2018c). The key inputs required were:[10]

- The concentration of *L. pneumophila*; in this analysis, the monitoring results from several water reuse facilities were used (Johnson et al., 2018) in which *Legionella* spp. were measured using culture techniques, qPCR, and EMA-qPCR, the latter of which is thought to be more closely related to viability (Mansi et al., 2014).
- Measurements of aerosol concentrations in a respirable size range in the vicinity of the toilet after flushing; the size-resolved concentrations from Johnson et al. (2013) were used and aerosols in the range of 1 to 10 μm were considered respirable.
- Respiration rate for light activity of 0.013 to 0.017 m^3/min from the Exposure Factors Handbook (EPA, 2011) was used.

[10] This is designated as "Model 2" in the paper. Three different models, yielding a span of results, were compared.

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Management of Legionella in Water Systems

- Number of flushes per day; a value of 5/d was used (DeOreo et al., 2016).
- Time of exposure to aerosol per occurrence; a range of 1 to 5 minutes exposure per flush was used based on Lim et al. (2015).
- Dose-response relationship for *L. pneumophila* developed by Armstrong and Haas (2007a) from the underlying data of Muller et al. (1983) and Fitzgeorge et al. (1983) were used.

In particular, the first bullet (concentration) has uncertainty because of the issues associated with environmental measurements of viable infectious *L. pneumophila* discussed above. The final bullet (dose-response) has uncertainty because of the use of animal models on a particular strain of *Legionella,* although this has been shown to be consistent with human outbreaks (Armstrong and Haas, 2007b).

Several factors not considered could be of importance. These include the difference between *Legionella* spp. and *L. pneumophila*, the possibility of accumulation of microorganisms at air–water interfaces and thus selective enrichment in the aerosols (Blanchard, 1989), and any inactivation of microorganisms in the period between aerosol formation and inhalation. Based on this analysis, using the three different means of enumerating bacteria in the water (i.e., culture techniques, qPCR, and EMA-qPCR), the annual risks (median) were estimated to be:

- 3.2×10^{-9} (using culture)
- 1.02×10^{-7} (using qPCR)
- 2.56×10^{-8} (using EMA-qPCR)

When compared to a common benchmark of 1/10,000 annual risk, these estimates were substantially lower.

It is also possible to perform a reverse QMRA (Soller et al., 2010), in which the starting point is the desired risk of a scenario (Step L in Figure 3-11); then, the calculations are run "backwards" to ascertain the water quality (Step A in Figure 3-11), aerosol concentration, etc. corresponding to that desired risk. An example of a reverse QMRA is the work of Schoen and Ashbolt (2011), of which a portion is summarized here. They considered the risk of *Legionella* exposure during a single showering event. Starting from a maximum inhaled *L. pneumophila* dose of 1-100 CFU,[11] they considered what the water concentration in the shower might be to attain that level. Key inputs required for their reverse QMRA were:

- Aerosol production rate and microbial partition coefficient (from bulk water to aerosol); values used were based on the experiments of Perkins et al. (2009).
- A respiration rate of 0.012 – 0.025 m^3/min was used (EPA, 2004).
- Size-specific aerosol deposition fractions in the lungs from Schlesinger (1989) were used.
- Duration of exposure in the shower was assumed to be 15 minutes (Perkins et al., 2009).

With this analysis, they computed that a bulk air concentration of 35 to 3,500 CFU/m^3, and a bulk water concentration of 3.5×10^6 – 3.5×10^8 CFU/L would be required to attain the delivered dose.

In all cases, the performance of a QMRA (either in the forward or reverse directions), requires a substantial number of input parameters, each of which may have uncertainty. The resultant risk estimate (or in the case of a reverse QMRA, the exposure estimate) will also not be known with certainty. The calculation of these uncertainties is possible using a variety of techniques, with Monte Carlo methods being the most common.

[11] This would produce a risk unacceptably high in the general population, but was used as an extreme example.

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Management of Legionella in Water Systems

Acceptable Risk

A key question for any QMRA is what level of risk should be regarded as acceptable. This is not (solely) a scientific question, but must be informed by policy, economic, and other social factors. In developing U.S. drinking water regulations for virus and protozoa, the EPA was informed by an annual risk level of 10^{-4} infections/year (Regli et al., 1991). For regulation of carcinogens, a range of 10^{-4} to 10^{-6} cases/lifetime has been used as a range of acceptability (Travis and Hattmer-Frey, 1988). The World Health Organization has widely promoted the use of 10^{-6} DALY/person-year as being acceptable for microorganisms in drinking water (Havelaar and Melse, 2003; WHO, 2008).

The broad community of stakeholders in the *Legionella* arena need to be engaged in a deliberative process to develop acceptability levels in different venues (Renn, 1999). It may be that different venues with different types of exposure and different exposed populations should have different acceptability levels—for example, hospitals with acute susceptible populations and relatively short stays, versus cooling towers with broad, potentially frequent exposure to the general population.

The level of risk that may be regarded as acceptable is associated with the type of hazard (how well it is understood, natural versus human-derived), the consequences (e.g., death) and the ability to control the exposure. For drinking waterborne pathogens, The Netherlands has codified an annual risk of 10^{-4} (1 infection in 10,000 over a one-year time frame). In the United States, for drinking water standards primarily aimed at controlling mild to moderate gastroenteritis, a value of 10^{-4} infections per year is also considered acceptable. However, it is important to examine the daily risk versus an annual risk, as both are incurred every day in the context of drinking water. Annual risk is translated to a daily risk via the relationship below (Haas, 1996):

$$P_{annual} = 1 - (1 - P_{daily})^{365}$$

If daily risk varies day to day, then the annual risk can be computed as follows:

$$P_{annual} = 1 - \prod_{i=1}^{365} (1 - P_i)$$

For an exposure that is relatively continuous to a large population, an annual risk level may be an appropriate approach to control. This could be pertinent to exposures such as large industrial cooling towers. For exposures that may only be short-term, especially to susceptible subpopulations, the control of daily risk could be appropriate. This could be pertinent to situations such as hospitals and nursing homes.

Use of a daily risk level could lead to a different monitoring and control scheme. This is illustrated by the hypothetical Figure 3-13 below. The red line indicates the uniform daily risk that would correspond to 1/10,000 infections per year. The black plot illustrates a random set of daily risks that over the course of the year would result in the same annual risks, despite a high degree of day-to-day variability. For shorter-term exposures, therefore, a population would be exposed to higher risks from time to time rather than to a uniform risk. In the case of *Legionella*, there is a lack of data to know how variable day-to-day exposures, and hence the resultant risks, might be.

In addition to the choice of annual or daily (or some other time period) averaging for assessing acceptability of risk in particular venues, the choice of the endpoint metric needs to be addressed by risk managers. As noted above, both 10^{-4} annual risk of infection and 10^{-6} DALY per person per year have been put forth as useful endpoint metrics in the context of drinking water. These were developed with regard to the risks of gastroenteric pathogens such as enteric bacteria, viruses, and protozoans (e.g., *Giardia* and *Cryptosporidium*). Such organisms have mild to moderate health consequences, such that the 10^{-4} annual risk of infection and 10^{-6} DALY endpoints produce similar results with respect to acceptable microbial quality of water (i.e., the concentration of *Cryptosporidium* in water).

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Management of Legionella in Water Systems

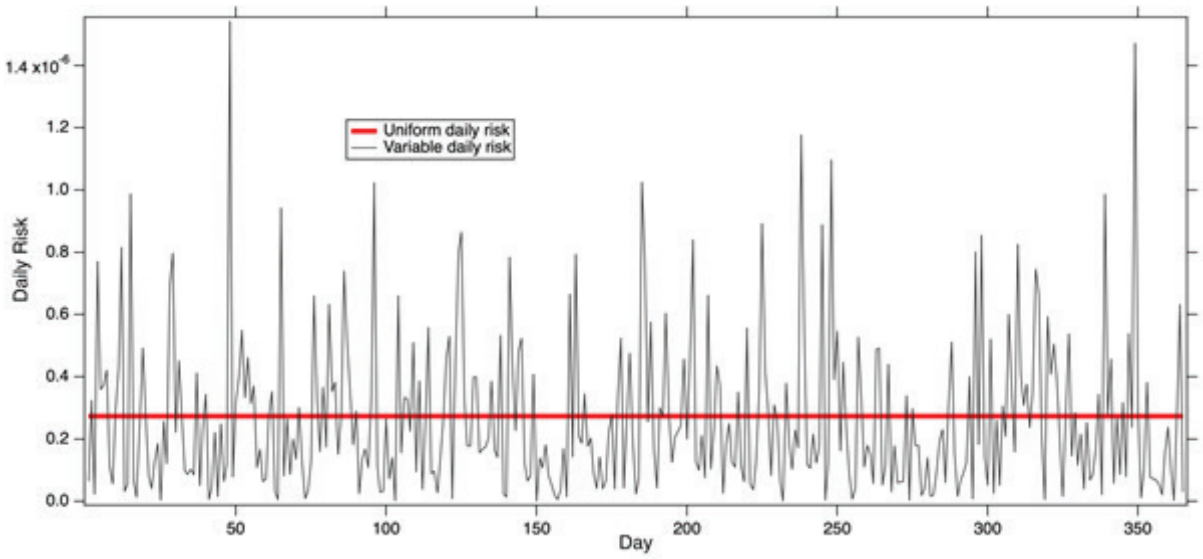

FIGURE 3-13 Sketch of uniform daily risk vs. variable daily risk.

However, the severity of legionellosis leads to a much higher ratio of DALYs per infection as noted in Table 3-9. Compared to cryptosporidiosis, legionellosis is more than 300-fold more consequential. Hence, endpoints of 10^{-4} annual risk of infection and 10^{-6} DALY are not equivalent in this case.

TABLE 3-9 Ratio of DALYs to Infections for Various Pathogens Conveyed Via Water

Illness	DALYs/100 infections
Cryptosporidiosis	0.3
Norovirus	0.3
Salmonellosis	0.3
Hepatitis	17
Legionellosis	97

SOURCE: Abstracted from van Lier et al. (2016).

This is also illustrated in Figure 3-14, in which the water concentrations corresponding to acceptable risk based on per exposure or annually (using either infections or DALYs as the endpoint) are graphed for different types of exposures. In this case, faucet, shower, and toilet exposures using both conventional and water-efficient fixtures are tabulated. Once a risk manager has decided what endpoint metric and acceptability level and what averaging period (if any) are appropriate, then the corresponding water concentration can be determined. For example, if an acceptable annual risk of 10^{-4} has been chosen, then the concentration of *L. pneumophila* measured at a conventional faucet, toilet, or showerhead should be no more than 10^5, 8.6×10^5, and 1.4×10^3 CFU/L, respectively (see Table 3-10). On the other hand, if acceptable risk is based on the 10^{-6} DALY, then the concentration of *L. pneumophila* measured at a conventional faucet, toilet, or showerhead should be no more than 10^3, 8.8×10^3, and 14 CFU/L, respectively. (These numbers are revisited in Chapter 5 as thresholds to help interpret monitoring data.)

Risk management decisions need to be developed for target levels of acceptability to *Legionella* in various settings. While U.S. practice has been to use a 1/10,000 annual infection endpoint as a measure of

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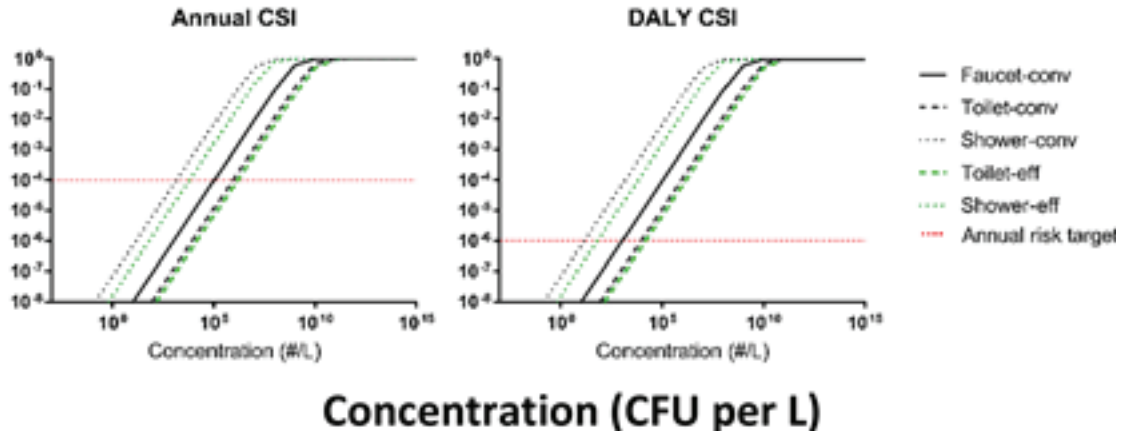

FIGURE 3-14 Curves of *L. pneumophila* concentration versus risk from conventional (conv) and water efficient (eff) fixtures. CSI = clinically symptomatic infection (i.e., disease). SOURCE: Hamilton et al. (2019). https://pubs.acs.org/doi/10.1021/acs.est.8b03000>, and include a notice to readers that further permissions related to the material excerpted should be directed to the ACS.

acceptability in drinking water (Rose et al., 1991), WHO has promoted use of a 10^{-6} DALY annual risk as an endpoint because of the increased severity of Legionnaires' disease. Which risk target is more appropriate, and whether an annual or a daily (or some other time period) average is more appropriate, are specific questions that need to be addressed by risk managers.

The examples above focused on exposure to aerosols in the indoor environment from plumbing fixtures. It is also possible to conduct a QMRA for exposure to cooling towers and other aerosols in the outdoor environment (see Hamilton et al., 2018c), but these circumstances require much more site-specific information. This includes (1) characteristics of the cooling tower, including aerosol generation rate and height, (2) the concentration of *L. pneumophila* within the water producing the aerosol, and (3) wind direction (relative to exposed population), velocity, and meteorological conditions (atmospheric stability).

TABLE 3-10 *L. pneumophila* Concentrations in Various Plumbing Fixtures that Correspond to Target Risk Levels.

Devices/Fixtures	Critical Average Concentration (CFU/L)
Target Risk Value: 10^{-4} infections per person per year	
Conventional faucet	104,000
Conventional toilet	857,000
Conventional shower	1,410
Target Risk Value: 10^{-6} DALY per person per year	
Conventional faucet	1,060
Conventional toilet	8,830
Conventional shower	14.4

NOTE: Median estimates from a Monte Carlo simulation.

SOURCE: Hamilton et al. (2019).

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Management of Legionella in Water Systems

How to Respond to Data and Information Generated from Sampling

The role of liability in the control and prevention of Legionnaires' disease has been mixed in the United States. Multi-million-dollar lawsuits are not uncommon for Legionnaires' disease when the environmental source is tracked to a large building or other entity where the owner and/or other persons are responsible for the safety of those served by an implicated water system. Manslaughter charges have been filed on rare occasions. To protect their clients, some lawyers have advocated that the water facilities considered at-risk (e.g., hotels, hospitals) test their water for *Legionella* as part of a water management plan, while others have advocated that it is better not to test since results could potentially be used against their client. This latter argument will probably not become entrenched as testing becomes more common, and "not knowing" may hurt rather than help the defense. The growing number of litigants and large size of settlements may result in the insurance industry pushing many clients with water systems serving the public into improving their prevention program for legionellosis.

A challenge inherent in implementation of *Legionella* control programs by healthcare centers, assisted-living facilities, hotels, and other commercial buildings, as well as public water supplies, is balancing professional or commercial responsibility with notification of the public when disease cases or water system contaminations occur. No guidelines currently exist, for hospitals or other building management or municipalities, on how to release information when *Legionella* and Legionnaires' disease are detected. Such guidelines are critically important, given the need to provide accurate, actionable information to the public, while protecting patient confidentiality, and taking resource limitations for the entities involved in releasing information into account. CSTE's Legionnaires Disease Surveillance Working Group plans to focus on risk communication, including notification and disclosure, with regards to Legionnaires' disease outbreak investigations and will be coordinating with other relevant national organizations, including the CDC, in the coming months (Monica Schroeder, CSTE, personal communication, April 26, 2019). A policy framework for risk communication should be developed by a coalition of stakeholders, with representatives from infectious disease, epidemiology, microbiology, and public health; healthcare and assisted-living management; hotel and resort management; cooling tower and municipal water management; insurance; liability and privacy law; and ethics. The work of this coalition could be informed by the European Legionnaires' Disease Surveillance Network (ELDSNet); the Public Services and Procurement Canada's *Legionella* Management Communications and Actions Protocol; the federal Sunshine Act to increase transparency in government; and the CDC Foodborne Diseases Active Surveillance Network (FoodNet), a national food safety policy and prevention effort that monitors trends, attributes illness to source, and disseminates information about current foodborne illnesses to the public.

CONCLUSIONS AND RECOMMENDATIONS

This chapter has demonstrated that Legionnaire's disease rates have been rising in the United States and Europe for the past 20 years, and current reported incidence is likely a substantial underestimate of the actual disease burden. **The Committee estimates 52,000 to 70,000 cases of Legionnaires' disease in the United States each year.** There are many sources of *Legionella* risk in engineered water systems, from cooling towers to premise plumbing to hot tubs. Most of the occurrence data gathered from these sources has not been reported as concentrations, making it difficult to discern trends over time and conduct microbial risk assessment. In only a few outbreak investigations have clinical and environmental data been linked to definitively show that a particular water system was the etiological source of disease cluster. The following conclusions and recommendations are made to improve surveillance and diagno-

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sis of legionellosis, monitoring of water systems for *Legionella*, and identification of sources of exposure for both sporadic and outbreak-associated Legionnaires' disease.

There is an urgent need to develop better clinical tools that will capture more Legionnaires' disease cases and identify pathogenic *Legionella* beyond *L. pneumophila* serogroup 1. The increasing rates of legionellosis, combined with its associated morbidity and mortality, demand improved diagnostics. First, hospitals in both rural and urban areas should have access to on-site urinary antigen testing to facilitate more targeted antimicrobial therapy and to increase disease recognition. Second, efforts to develop standardized molecular methods for *Legionella* diagnoses (including non-*pneumophila* species and *pneumophila* serogroups other than serogroup 1) should be prioritized by research laboratories and federal agencies. Such methods could increase understanding of the extent of the underestimate of reported disease rates and should be accessible outside of research and academic institutions. Finally, the U.S. Department of Health and Human Services should fund multi-center prospective studies of clinical respiratory samples using these new assays to better understand prevalence and diversity of the *Legionella* species and serogroups causing clinical disease. Once the "true" diversity of human-infectious legionellae is identified, a range of environmental niches could then be explored to identify isolates representing genotypes by niche and preferred methods for their identification from environmental samples. There is also a need for education and a cultural shift from empiric treatment to use of available and future diagnostic tools for *Legionella* to better characterize the true incidence of legionellosis in the community.

The CDC should strengthen the (soon-to-be-merged) NNDSS and SLDSS to include environmental exposures as feasible, including both the potential exposure setting and the type of related building water systems. Although all cases will not receive thorough environmental investigations, at a minimum it should be discerned whether a case may be associated with a healthcare facility, accommodation site, hot tub or other well-recognized potential source, as well as some information about the building water system and any known deficiencies (e.g., water main breaks) during the incubation period. Similarly, within NORS, the CDC should consider housing *Legionella* outbreak data in a separate database from enteric pathogens to make NORS more useful for legionellosis prevention and control. In addition, timely analyses by setting and type of water system, with more frequent updating of publicly available data, would improve the usefulness of NORS for assessment of *Legionella* prevention efforts.

An improved understanding of sporadic, community-acquired cases of Legionnaires' disease is critical to reducing the rising rates observed over the last 20 years. **Determining the most common sources of sporadic disease will require well-funded, population-based studies in multiple jurisdictions (e.g., cities, counties, states).** Such studies would require the recruitment of multiple medical centers with an adequate number of *Legionella* cases each year, willingness and capacity to collect clinical samples for *Legionella* culture, environmental personnel with knowledge of how to sample the most likely sources of exposure for legionellosis patients, and laboratory capacity to reliably grow *Legionella* from clinical and environmental samples. In the United States, clinical cultures are currently available for less than 10 percent of cases; thus, an effective study would have to dramatically improve on the current capacity to obtain cultures from patients. Enhanced clinical culture capacity is also essential to accurately assess the contribution to disease from non-*pneumophila Legionella,* and *L. pneumophila* that is not serogroup 1 (recommended above).

The CDC should work with states to gain closer to real-time reporting and investigation of travel-associated cases. Many outbreaks of travel-associated disease can be best detected at the national

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Management of Legionella in Water Systems

level, since many of the patients who report staying in a hotel or other accommodation during the incubation period have crossed state lines. Currently, reporting of travel-associated cases from many states is neither timely nor complete. Better understanding travel-associated cases is an easy target for intervention, as these data are often readily available from patient interviews, can help to link individual cases to larger clusters, and may help to identify opportunities to limit further exposures.

Although additional *Legionella* program efforts are underway in some states, these efforts are not comprehensive, and most state health departments are severely lacking (both in resources and expertise) in their programs of surveillance, prevention, and control for Legionnaires' disease. **Regional Centers of Excellence for prevention and control of legionellosis could serve as a backbone to strengthen the capacity of state health departments to detect and investigate cases of Legionnaires' disease.** These centers could be modeled on the Integrated Food Safety Centers of Excellence and the Centers of Excellence for Vector Borne Diseases, with modifications to include the relevant disciplines needed for *Legionella* applied research and control. The Centers could undertake critical applied research (e.g., optimizing culture methods and comparing them to new methods and coordinating the in-depth, multiple-jurisdiction studies of environmental exposures recommended above). By building a cadre of experts in *Legionella* prevention and control that includes industrial hygienists and engineers, these centers could promulgate best practices for prevention and control measures (see Chapter 4). Finally, these Centers could train and assist building managers as they create water management plans, and they could initiate certification programs for those responsible for the safety of water systems in built environments (see Chapter 5).

A systematic study to compare culture methods for *L. pneumophila* (and other pathogenic legionellae) with qPCR, viability-qPCR and RT-qPCR is needed to determine comparability. qPCR and its variants offer a more rapid method to quantify *Legionella* in the environment and could be used consistently to inform decisions on decontamination and restoration of affected systems, to investigate the bacteria's ecology and exposure pathways, and as a quality control method. Yet, there are few comparisons of methods, and a better sense of real world performance under "normal" and "bloom" conditions is needed. There are reasons why culture techniques may underestimate the true *Legionella* risk (e.g., VBNC cells) whereas qPCR might overestimate risk (due to response to nucleic acid in nonviable organisms). Whether use of viability qPCR or RT-qPCR could balance these issues in unknown. With side-by-side comparisons of methods in a broad range of settings, it may be that PCR-based or other simplified methods or test kits could be shown to be useful predictors of human health risk and adequacy of remediation.

By reviewing dozens of *Legionella* studies on various building types from around the world, the Committee found the ***Legionella* occurrence data to be highly variable and sparse, making comparisons among studies difficult and detection of spatial and temporal trends almost impossible.** The available data suggest that cooling towers, hot tubs, showers, and wastewater treatment plants can be hot spots for growth of *Legionella* and exposures. This data set could be improved by adopting standardized molecular methods that allow for greater quantitation and more rapid results. Improved environmental monitoring methods could facilitate a temporal and spatial assessment of changes in *Legionella* levels within buildings in several special studies to better understand background levels, potential exposure, and ultimately risk. Finally, a collaborative, widespread national survey of *Legionella* that included distribution systems, premise plumbing in various types of buildings, and cooling towers would be useful for further understanding the concentrations of concern and the risks of sporadic Legionnaires' disease.

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The Committee's analysis of studies on *Legionella* occurrence that collected concentration data suggests that a ***Legionella* concentration of 5 x 10^4 CFU/L should be considered an "action level," that is, a concentration high enough to warrant serious concern and trigger remediation.** This concentration could be used for many purposes, including to set an acceptable risk level for Legionnaires' disease and for regulations and guidelines on *Legionella* management in building water systems (see Chapter 5).

There is a good framework to perform QMRA for various *L. pneumophila* exposures. To strengthen these tools, additional knowledge is needed about the impact of virulence and strain differences, phenotypic alterations in potency and aerosol survival, and generation rate of aerosols from various devices. Data on exposures, especially for cooling towers, are lacking. Also, validation of models for predictive growth of *L. pneumophila* in water systems is required. QMRA has many applications from setting action levels for the occurrence of *L. pneumophila* in different venues or targets for remediation to informing design and permitting decisions about pipe length, setback distances for large industrial cooling towers, and building-level hydraulic design to maintain acceptable microbial quality. QMRA can be used to determine *Legionella* concentrations in building water systems that correspond to certain Legionnaires' disease risk levels.

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4

Strategies for *Legionella* Control and Their Application in Building Water Systems

This chapter focuses on strategies for *Legionella* control in building water systems. Such controls should ideally begin as early as the design and commissioning phases and subsequently be applied routinely as preventative measures and, when necessary, for remedial purposes, i.e., in response to outbreak or flags raised by monitoring data. A summary of the key strategies for controlling *Legionella* by affecting their growth and survival (or that of their free-living amoebae hosts) is presented first. The real-world application of these strategies for *Legionella* control in building water systems and devices is then described. Table 4-1 summarizes which specific controls are applicable to which building water systems and devices. The chapter also discusses emerging issues, such as potential conflicts among strategies for green building design, water and energy conservation, and more prospective *Legionella* control strategies.

As detailed in the following sections, factors known to influence *Legionella* growth in water systems include temperature, disinfectant type and levels, hydraulic conditions (particularly avoiding stagnation), presence of nutrients, pipe materials, presence of distal devices, and extent of aerosol formation. Many of these factors come into play during the initial building design and commissioning stages, while others can more readily be adjusted in existing buildings. For example, in a building, the pipe sizing, the materials and devices used, and the flow conditions are determined prior to the building's construction and harder to adjust once a building is operating. Factors such as temperature, disinfectants, and distal devices can be more easily adjusted after building construction and during operation. Control of *Legionella* can be based not only on limiting its growth, but also on limiting the opportunities for humans to be exposed, for example by avoiding the formation of aerosols, particularly those of ideal size (less than 10 mm) for inhalation and deep deposition into the lungs. Aerosols can also be diverted, as in the case of drift eliminators on cooling towers, to reduce potential for human exposure. Additional barriers, such as point-of-use size-exclusion filters, can also be considered for immunocompromised or other sensitive populations.

In addition to drinking, potable water is used for other critical services in buildings, especially hot tubs, spas, and Jacuzzis (collectively referred to as hot tubs), cooling towers, humidifiers, decorative features such as fountains, medical equipment, dental units, and ice machines. Although any of these water systems has the potential to grow and transmit *Legionella*, this discussion is limited to the premise plumbing of buildings, cooling towers, humidifiers, hot tubs, and corresponding water supplies, though some of the basic principles apply to other systems as well.

The precise target for *Legionella* control can be quite complex in terms of species, serotypes, strains, and corresponding virulence factors. Notably, some treatments may shift the composition of types and

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TABLE 4-1 Overview of *Legionella* Control Strategies and Relevance of Their Application to Building and Water System Types.

Strategy	Building Water Systems			Large Engineered Systems			Other Devices		
	Large Institutional Buildings (page 205)	Green Buildings (page 227)	Households (page 209)	Potable Water Supply (page 200)	Wastewater Treatment (page 204)	Reclaimed Water Systems (page 203)	Cooling Towers (page 211)	Humidifiers (page 214)	Hot Tubs (page 215)
Temperature Control (page 177)	√	X (incentive is to reduce temperature)	√	? (limited options)			? (future possibility)	√	
Disinfection (page 185)	√	√	? (only POU UV devices)	√	? (somewhat limited)	√	√		√
Manage Hydraulics (page 192)	√	X (prone to low flow/stagnation)	√	√		√	√	√	
Nutrient Limitation (page 194)				? (Dutch example)		√		√	
Plumbing Materials (page 195)	√	√	√	? (limited for DS mains)		√	√		
Distal Portion of Plumbing (page 196)	√	X (low-flow faucets used)	√						
Aerosol Control (page 199)	√	√	√		√		√		

NOTES: √ = a strategy has been successfully used in a particular system; ? = a strategy could be partially used in a particular system, but there are noted limitations/considerations; X = a strategy is actually being worked against in a particular type of system; blank boxes are where there is no indication that a strategy can be used in a particular system.

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Management of Legionella in Water Systems

virulence of *Legionella*, which is difficult to assess and not typically measured. This chapter provides information based on the targets that are described in the available literature. Still, it is important to note that the type of *Legionella* detection method will also influence the perception of efficacy of various controls. The majority of well-documented case studies base their evaluation on measurements of *Legionella* or *Legionella pneumophila* using culture-based methods, which cannot detect viable but non-culturable (VBNC-like) forms. Certain control strategies like heat treatment, chlorine-based disinfectants, and copper-silver ionization are known to trigger *L. pneumophila* to enter a VBNC-like state (see Chapter 2, Allegra et al., 2008, 2011).

It is clear from research and practice that, in most situations, "zero" is not an achievable target for evaluating whether *Legionella* has effectively been controlled, for several reasons. First, some level of *Legionella* is common in drinking water systems in the absence of an outbreak. For example, *L. pneumophila* serogroup 1 was detected in nearly half of public and private cold-water taps tested in a national survey, with the mean and median concentrations being 1.97×10^3 gene copes per liter (GC/L) and 62 GC/L, respectively (Chapter 3; Donohue et al., 2014). Second, current human-health risk models indicate that a bulk water concentration much higher than "zero" (see Chapter 3; Perinez et al., 2018; Pourchez et al., 2017) is actionable and associated with transmission of *Legionella* into the lungs. Third, monitoring methods are limited in their ability to assess live cells and are subject to detection limits; none can confirm "zero."

In evaluating any building water system, it is important to recognize that *Legionella* does not exist in isolation, but is part of a complex microbial ecosystem spanning biofilms, bulk water, and aerosols. Thousands of other species of bacteria and other microbes reside in these environments (Chapter 2; Pinto et al., 2014) and can potentially enhance or inhibit the growth of *Legionella* (Paranjape et al., 2019; Wang et al., 2013a). Most notoriously, free-living amoebae play a key role in amplifying *Legionella* and enhancing its virulence; thus, it has been suggested that effective control strategies should also target amoebae (Thomas and Ashbolt, 2011). However, such approaches that potentially tap into more precise control of the microbial ecology of premise plumbing to manage *Legionella* are still in their infancy. Here we seek to provide information about how various controls influence *Legionella* and, where possible, their free-living amoebal hosts.

FUNDAMENTAL FACTORS FOR *LEGIONELLA* CONTROL

Temperature

A fundamental control strategy for *Legionella* in buildings is to keep the hot- and cold-water systems at temperatures outside the organism's growth range of 25°C to 43°C (see Chapter 2). Warm water leaves a water system especially vulnerable to *Legionella* colonization and growth. Several studies summarized in this section, across multiple scales, countries, and building settings, demonstrate the overarching benefit of elevated temperature for *Legionella* control. In particular, water heater settings of greater than 60°C are a key threshold for reducing positive detection of *Legionella* as well as for reducing Legionnaires' disease cases and outbreaks. Adjusting the temperature at the water heater outlet to ensure temperatures greater than 55°C to distal points[1] can be highly effective in reducing the proportion of *Legionella*-positive swabs or water samples (Arvand et al., 2011; Blanc et al., 2005).

Temperature control strategies fall into two broad categories: *preventive* and *curative*. Preventive refers to maintenance of (1) elevated temperatures (greater than 55°C) to limit colonization and growth of *Legionella* across hot-water systems and (2) sufficiently cool temperatures (less than 25°C) across cold-water systems. Curative approaches, on the other hand, are somewhat varied in their application,

[1] "Distal point" refers to the point of connection to a fixture such as a faucet, showerhead, thermal mixing valve, etc. Hence, the distal point is just upstream of the point of use. Temperature measurements at the tap are representative of conditions at distal points unless there is a thermostatic mixing valve.

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Management of Legionella in Water Systems

generally involving elevating the temperature temporarily as a "heat-shock" approach. Heat shocks may be applied one time or many times, for various durations, and over a range of temperatures (60°C to 70°C). It should be noted that eradication of *Legionella* species (spp.) and *L. pneumophila* reservoirs can only be achieved at very high temperatures. Work by Epalle et al. (2015a) shows that only strict thermal treatment (i.e., 70°C for 60 minutes) kills more cells and renders non-infectious all *L. pneumophila* strains, both environmental and clinical, but milder heat treatment shocks (60°C to 70°C for 30 minutes) do not. Recent investigations by Cervero-Arago et al. (2019) suggest that prolonged exposure to high temperature (greater than 60°C) can be efficient against both culturable and VBNC-like cells of *L. pneumophila*, and most importantly, that the loss of culturability after heat exposure is associated with decreased virulence and host infection.

The temperature set at the water heater is not equivalent to the temperature experienced at the tap. One controlled study demonstrated that hot water received in taps can cool to room temperature within 30 minutes (Rhoads et al., 2015a). To counteract this, large institutional buildings, such as hospitals, are required by plumbing codes to have hot-water circulation lines leading from the water heater, throughout the building, and back to the heater. This helps provide hot water on demand in distal reaches of the building and also keeps the water lines sufficiently hot to deter *Legionella* growth. Recirculation lines cannot reach each point of use, such that the volume of water between the recirculating pipe and the faucet or showerhead will remain stagnant between uses. Even with recirculation, temperature losses are expected throughout the piping as a function of water circulation and piping isolation. This can result in large variations of water temperatures at distal points, including temperatures that increase risk for *Legionella* growth (Bédard et al., 2015; Boppe et al., 2016).

None of the control strategies discussed in this chapter occur in isolation, and they all have interactive effects. In the case of temperature, the associated water-use frequency is an important factor in determining the temperature regime experienced at the tap (Rhoads et al., 2015a). Thus, efficacy of temperature control is intimately related to the hydraulics of the system. Figure 4-1 illustrates a standard hot-water system as commonly applied in large institutional buildings, including recirculating options and points where temperature control may be applied. This section focuses on the basic evidence of temperature control efficacy, while later parts of the chapter discuss specific applications in buildings and devices.

Impact of Temperature on Legionella in Building Water Systems

Groothuis et al. (1985) observed that when the temperature of a hot-water return line in buildings is maintained at 60°C, cultivable *L. pneumophila* was not observed, but when the temperature was lowered to 54°C, *L. pneumophila* was culturable. Similar observations have been made by others. *L. pneumophila* could be cultivated from a hot-water system at a hospital that maintained hot water at 43°C to 45°C, but not at a hospital where hot water was maintained at 58°C to 60°C (Plouffe et al., 1983). Apartments in the Chicago area (n = 95) that had water temperatures below 60°C in the premise plumbing were more often colonized with cultivable *L. pneumophila* (42 percent) than were systems with water temperatures above 60°C (7 percent) (Arnow et al., 1985). In a survey of 40 Italian hotels, hot water above 60°C in the drinking water system and above 55°C in the outlet water was protective from legionellae (Borella et al., 2005). Finally, cultivable legionellae were only isolated from drinking water in hotels (n = 385) in Greece when water temperatures were between 23.7°C and 60.3°C (Mouchtouri et al., 2007).

Table 4-2 summarizes several examples of the efficacy of thermal controls in healthcare facilities. The Hungarian study (Barna et al., 2016) in Table 4-2 is particularly illustrative of the overarching importance of thermal control of *Legionella* in hot-water plumbing. Over seven years, 1,809 samples were collected from healthcare facilities (n = 22), accommodation sites (n = 21), educational institutions (n = 26),

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Management of Legionella in Water Systems

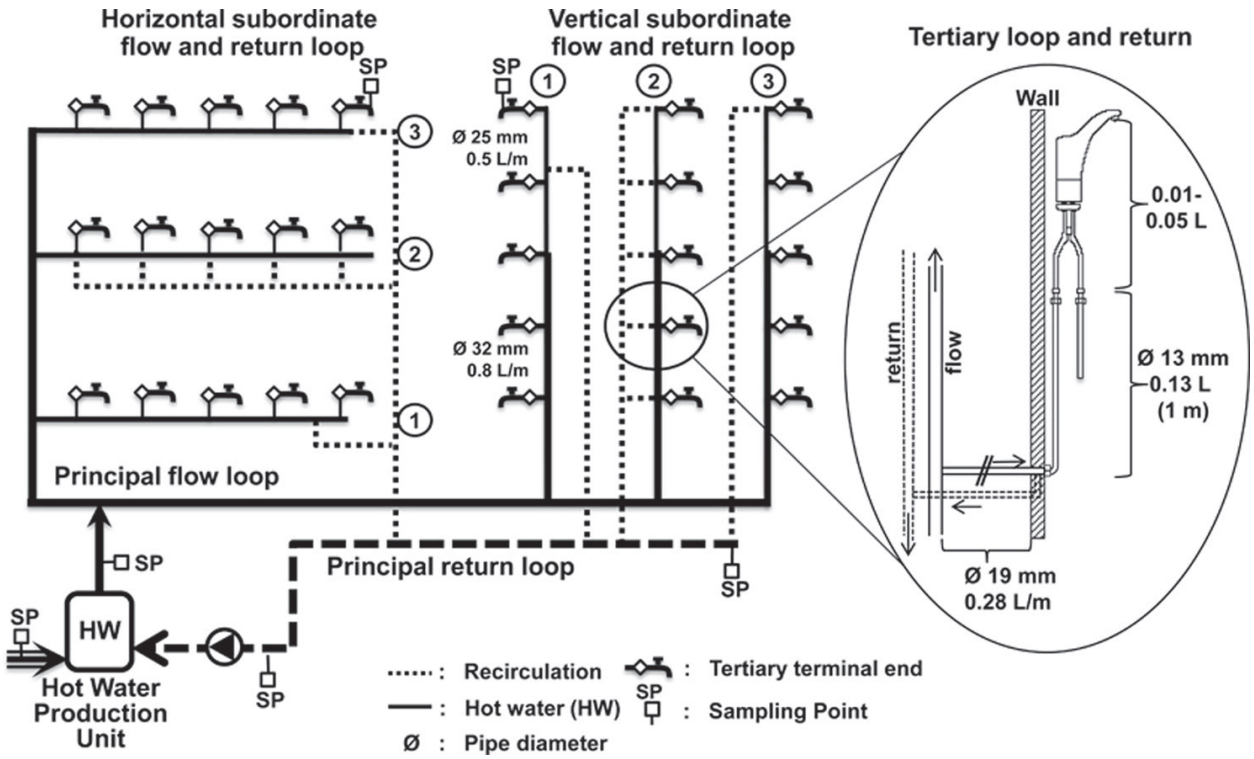

FIGURE 4-1 General schematic of a hot-water system including temperature control points. Three different types of vertical and horizontal hot-water systems are represented: (1) recirculation before the last tap; (2) recirculation connected after each device; and (3) recirculation connected after the last device.
SOURCE: Bédard et al. (2015).

office buildings (n = 10), industrial buildings (n = 35), and private residences with central (n = 26) and individual hot-water supplies (n = 26). Water temperature was found to be the most important factor in a multiple linear regression analysis of 11 system and water characteristics associated with *Legionella*. In general, Table 4-2 and other reports on the efficacy of the implementation of temperature control in healthcare facilities (Bargellini et al., 2011; Lee et al., 2011; Serrano-Suarez et al., 2013) reveal moderate success. Differences among these reports most probably reflect whether the temperature set points were actually reached across the whole system, including at the outlets (e.g., faucets and showers). In most case studies, the actual application of temperature control is poorly documented, with only partial information on temperatures available for the water heater and the return line.

Indeed, thermal control is greatly improved if hydraulic deficiencies are addressed, ensuring that water temperatures greater than 55°C reach distal points, resulting in lower positivity and concentrations of *L. pneumophila* using both culture and quantitative polymerase chain reaction (qPCR) methods (Boppe et al., 2016; Blanc et al., 2005; Lecointe et al., 2018). Bédard et al. (2015) showed that local deficiencies in the hydraulics of hot-water recirculation resulted in lower temperatures and elevated levels of *L. pneumophila*; they correlated these issues to the location where clinical cases of Legionnaires' disease occurred. Heat-shock treatment at 70°C to remove *L. pneumophila* reservoirs and then maintaining temperatures above 55°C at the distal points of a large 1,000-bed hospital were highly efficient at reducing *L. pneumophila* to undetectable levels (using either culture methods or qPCR).

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TABLE 4-2 Long-term Healthcare Facility Experience Showing the Importance of Maintaining an Adequate Preventive Thermal Regime to Control *Legionella*

Size of Building(s) Number of Samples Study Length	Key Findings	Reference
Hospital with 870 beds in Switzerland Number of samples unknown 7-year study	• On-site disinfection introduced after regulations lowered the hot-water temperature to 50°C for energy conservation. • Study showed that chemical treatment is not efficient without adequate thermal regime. They operated parallel hot-water systems with (1) copper-silver (Cu-Ag) ionization using 0.6 mg Cu/L and a temperature of 50°C, and (2) ozonation using 0.3 mgO_3/L residual and a temperature of 50°C. • After 3 years, the positivity for *Legionella* spp. remained high in both the ozone-treated networks (65% to 56%) and in Cu-Ag-treated systems (90% to 93%). • After increasing the temperature to 65°C, *Legionella* prevalence decreased to 29% (O_3) and 39% (Cu-Ag). • Increasing temperature was effective in reducing the prevalence and the concentration of *Legionella* spp. in the biofilm swabs. The remaining positive points were associated with temperatures < 50°C because of poor water circulation.	Blanc et al. (2005)
450-bed Swedish hospital with history of *L. pneumophila* nosocomial cases and 1991 outbreak (31 cases)	• Over a ten-year period, *L. pneumophila* prevalence and nosocomial cases of legionellosis were monitored. • Period 1: temperature of hot water at 45°C; outbreak occurrence. Period 2: temperature of hot water set to 65°C with regular flushing (18 months). Period 3: temperature of hot water set to 65°C and > 55°C in the return loop without weekly flushing. • During Periods 2 and 3, positivity decreased from nearly 100% (during Period 1) to 5-23% with remaining low incidence of nosocomial cases (1/year).	Darelid et al. (2002)
18 facilities in the Czech Republic 805 samples	• Highest levels of colonization by *L. pneumophila,* as shown by concentrations in 1-min flush, measured at distal sites where the temperature was 40-45°C. • When temperature was raised to greater than 50°C, positivity decreased. Only non-detects at temperatures over 60°C. • Treatment by shock chlorination (50 mg/L for 2 hours) was less efficient at temperatures of 45-49.9°C.	Hruba (2009)
4 healthcare facilities in Germany 625 samples (316 cold and 309 hot)	• Field studies support the importance of maintaining elevated temperatures at distal locations (estimated by the temperature after 1 minute of flushing), with 4 to 11% of samples positive at temperatures greater than 55°C vs. 14 to 82% positive at temperatures less than 55°C.	Arvand et al. (2011)

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TABLE 4-2 Continued

Various building types in Hungary 1,809 samples 7-year study	• Surveyed healthcare facilities (22), accommodation sites (21), educational institutions (26), office buildings (10), industrial buildings (35), and private residences with central (26) or individual hot water supply (26). • Monitoring for *Legionella* over 7 years shows that when hot-water temperature was greater than 55°C, 16% of samples exceeded 10 CFU/L, as compared to 54% for systems with temperatures below 55°C. • For all systems combined, a temperature decrease of more than 10°C within the system led to 62% of samples with concentrations greater than 1,000 CFU/L, compared to 46% for a 5-10°C decrease and 40% for less than 5°C decrease.	Barna et al. (2016)
Pediatric hospital with 450 beds in Quebec 46 samples	• Old hospital with copper piping had very high positivity for *L. pneumophila*. Positivity (%) and concentrations of *L. pneumophila* varied with temperature at the outlets, ranging from no detection at temps greater than 60°C, to 56% positive at temps greater than 55°C, to 100% positive at taps with temps between 40 and 45°C. • Using continuous temperature and flow measurements, areas at risk for lower temperatures were identified. Hydraulic distribution of hot water was improved by balancing return loops and removing dead ends and faulty mixing valves. • Corrective action reduced positivity much more drastically than it did the range of concentration at positive sites.	Boppe et al. (2016)
Tertiary care hospital with 400 beds in Quebec 2 hot water systems 64 samples from hot water system	• Following nosocomial cases of legionellosis, a large hot-water system already using Cu-Ag treatment but with high positivity for *L. pneumophila* (81.5%) was disinfected using heat shock at 70°C. • Temperatures were adjusted from previous set points of 55°C at the water heater and 50°C in the main recirculation pipes (to meet energy conservation goals) to 60°C at the heater with a minimum of 55°C in the return loop. • Extensive temperature and *L. pneumophila* monitoring conducted in the hot-water system and at taps for 2 years. • *L. pneumophila* levels decreased rapidly by culture and more slowly by qPCR, but a significant portion of taps remained positive (20%). The remaining low concentration, positive samples were in areas with hydraulic deficiencies.	Bédard et al. (2016a)
Primary and tertiary hospital with 1,000 beds in France 127 sampling locations 726 samples	• New hospital colonized by *Legionella* spp. (21.3% culture) and *L. pneumophila* (28% qPCR and 1.1% culture) during commissioning, even with a preventive flushing program in place. • Curative and corrective measures over 4 years included (1) thermal shock treatment at 70°C for 30 minutes at each point, and (2) increasing mean distal temperatures from 31°C during start up to 49.1°C. This decreased positivity by 24.1% for *Legionella* spp. by culture with no detectable *L. pneumophila*. • First efforts of hydraulic balancing to ensure greater than 50°C at all distal points decreased positivity further to 2.5%, with remaining positive points where temperature was below 38°C. Improved balancing further increased distal temperatures to 56.3°C, resulting in no positive detection of *L. pneumophila* by both culture and by qPCR for the following 4 years. Low levels of *Legionella* spp. persisted by culture and qPCR, *L. anisa* being the only strain identified.	Lecointe et al. (2018)

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Management of Legionella in Water Systems

The effects of temperature on legionellosis risk are dynamic and intimately connected to the plumbing configuration and hydraulic conditions. Rhoads et al. (2015a) observed that setting the water heaters at a temperature that technically is within the inhibitory range for *Legionella*, in this case 51°C, can actually enrich for *Legionella* in distal pipes. Further, a seemingly simple matter of whether a hot-water pipe is oriented with upward or downward flow can directly affect *Legionell*a levels close to the point of use. Indeed, since cooler water is denser, upward plumbed pipes experience convective mixing, which delivers more nutrients and pushes distal pipes back into the warm-water range conducive to *Legionella* growth (Rhoads et al., 2016b).

Thermal Control in Residential Hot-Water Systems

Residential water systems vary depending on the type of building, with centralized hot water generation being more common in large buildings, often with recirculation. In residences, electric or fuel-heated tanks and on-demand water heaters are commonly used, with a possibility of in-tank recirculation. Balancing the thermal and sanitary performance of domestic hot-water storage is a growing concern as energy stored in sanitary hot-water systems represents about 14.8 percent of total residential energy consumption in the United States[2] and 19 percent of residential energy consumption in Canada.[3]

The type of water heater and the presence of storage and recirculation are critical features in determining the risk of *Legionella* spp. and *L. pneumophila* in residential hot-water systems. Electric water heaters are by design thermally stratified, with lower temperatures found in the bottom section; in contrast, oil and gas water heaters are not stratified because the heating element is located under the bottom of the tank. On-demand water heaters are discontinuous and will deliver water at a set temperature without any storage if properly sized. Many extensive field studies in American, Canadian, Danish, and German residential water systems have demonstrated the prevalence of *Legionella* in hot-water heaters that are thermally stratified (Alary and Joly, 1991; Dewailly and Joly, 1991; Marrie et al., 1994; Mathys et al., 2008; Stout et al., 1992; Wallet et al., 2016). In particular, Dewailly and Joly (1991) investigated 205 electric water heaters using high-volume samples (500 mL) and reported more than 45 percent positivity for *L. pneumophila* serogroups 4 and 2 in the water heater sediments, while no positives were detected in 50 oil or gas water heaters sampled. They identify the major factors for positivity to be the type of water heater (electric versus gas) and the temperature at the bottom of the water heater (less than 40°C). Alary and Joly (1991) observed that 39 percent of the 178 electric water heaters sampled in the Quebec City area were positive for *L. pneumophila* by culture with a wide variety of serogroups present. Despite a relatively high water heater outlet temperature (56.6°C ± 0.4°C) in electric water heaters, 12 percent of faucets and 16 percent of showers were positive. Noteworthy is the fact that no gas- or oil-fired water heaters operated at a higher temperature (61.5°C ± 1.1°C) had distal sites (showers and taps) that were positive for *L. pneumophila*. In a survey of 343 German residential water heaters with a water tank and, in some cases, recirculation, 94 percent of sites were positive for *Legionella* spp. in flushed samples by culture, most (93.7 percent) being *L. pneumophila* (Mathys et al., 2008). No positive sites were detected by culture if a temperature greater than 60°C in the main piping was maintained or if on-demand water heaters producing water with higher temperatures were used. Borella et al. (2004) found that tank size and the distance between the heater and the tap were significant factors in positivity and that different species and serotypes of *Legionella* were associated with different heater types.

Studies have also shown the importance of maintaining high temperatures at the distal ends of hot-water systems. In Germany, an analysis of over 30,000 water samples collected over a period of

2 See https://www.eia.gov/consumption/residential/data/2015.

3 See https://www.nrcan.gc.ca/energy/products/categories/water-heaters/13735.

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seven years (2003 to 2009) from 4,600 public buildings for compliance purposes was completed to establish the prevalence of *Legionella* and the conformity of hot-water systems to regulated minimum temperature requirements (Kistemann and Wasser, 2018). Overall, 15.8 percent of all samples were positive for *Legionella*, with positivity highest at distal sites (18.8 percent), lower in the recirculation loop (10.2 percent), and lowest in flushed samples (4.7 percent). More importantly, concentrations were higher by more than an order of magnitude at distal sites, corresponding to lower mean temperatures (47.2°C) versus temperatures found in the recirculation (54.8°C) and in the flushed samples (58.8°C). Figure 4-2 summarizes the impact of water temperature on the percentage of exceedances of the German standard of 100 colony forming units (CFU)/100 mL at distal sites, in the main piping, and in the recirculation loop. In the two lowest temperature classes (up to 45°C), approximately 22 percent of the samples were above the standard in the flushed samples (Vorlauf), 20 percent in the samples from the recirculation loop (Rucklauf), and about 15 percent at distal sites (Peripherie). The situation reverses when temperatures exceed 45°C, with increased prevalence at the distal sites. Even with temperatures at the outlet of 55°C to 60°C after a one minute flush, 5 to 7 percent of the samples remain positive, while fewer positives are found in the flushed and return loop (1 to 3 percent).

Heat Shock

Temporarily elevating the temperature, or heat shock, is applied in a variety of forms and generally is intended as a temporary remedial or emergency measure, not as a preventive measure. An example would be maintaining a water temperature of at least 70°C for at least 30 minutes at each point of use for decontamination of an entire building water system. The efficacy of heat shock is controversial. For example, Temmerman et al. (2006) observed that *Legionella* numbers increased following system recovery from heat shock, presumably because of bacterial growth on nutrients liberated from killed cells (necrotrophic growth).

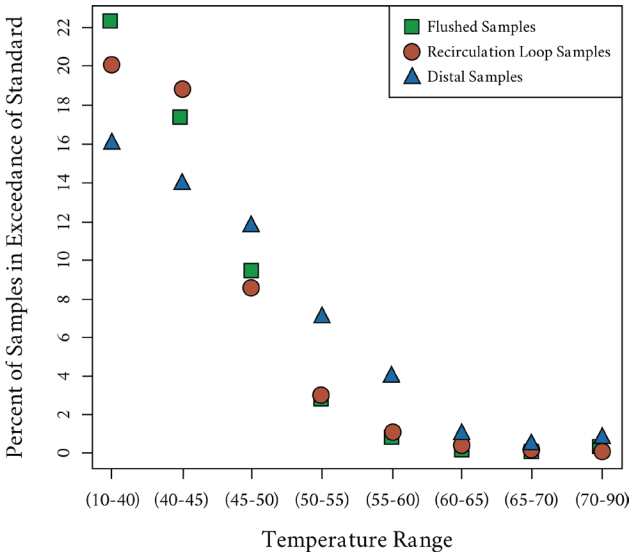

FIGURE 4-2 Relationship between temperature (x-axis) and the percentage of samples exceeding the German standard of 100 CFU/100mL (y-axis) for *Legionella* spp. from public buildings in Germany over a seven-year period. The green squares are for flushed samples, the blue triangles are distal samples, and the red circles are samples from the recirculation loop.

SOURCE: Kistemann and Wasser (2018).

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Management of Legionella in Water Systems

Temperature, duration, and frequency of heat shock application are certainly important factors. The efficacy of a stringent thermal shock (70°C for 30 minutes) on culturable *Legionella* is high in water but limited in biofilms, and most importantly, of short duration (Saby et al., 2005). Moreover, frequent heat shocks can promote the emergence of heat-resistant *L. pneumophila* strains, as observed in hospital water systems submitted to periodic extreme temperature (24 hours at 65°C a few times a year), while no such resistance was observed for strains isolated from the system where heat shock treatments (70°C for 30 minutes) were sparingly applied (Allegra et al., 2011).

Periodic heat shocks at 60°C were compared to a well-managed system continuously maintained at 60°C by analyzing *L. pneumophila* and microbiota in the water plumbing (Ji et al., 2018). Results suggest that maintaining the water system at a set point of 60°C and water use frequency are more promising for the long-term control of both the microbial community and *L. pneumophila*.

Heat shock should be considered as an extreme remediation measure because of such potential problems as (1) the dislodging of particles from piping walls due to thermal shock, which can subsequently cause clogging in balancing valves; (2) damage to equipment from sustained high temperatures; and (3) requirement for close supervision during the process to protect patients, staff, and visitors from scalding. Compatibility of system materials for heat shock is a key consideration. For example, faucets should be designed and constructed with materials that can withstand a superheating treatment. Each component of the system should be evaluated to determine the effect of high water temperatures on materials and equipment (e.g., thermostatic mixing valves). Mitigation measures, such as bypass, should only be considered to protect equipment that cannot withstand the specified temperature and time, since they can themselves become a reservoir for *Legionella*.

Scalding

The higher water temperatures (greater than 140°F/60°C) that prevent *Legionella* growth are associated with an increased risk of scalding and burns. Those at increased risk include young children, elderly patients (older than 65 years of age), and those with substance-abuse disorders, physical disabilities, neurologic illness/disabilities or altered mental status. The U.S. Centers for Disease Control and Prevention (CDC) found that between 2001 and 2006, adults older than 65 years made an estimated 51,700 initial visits to emergency rooms for nonfatal scald burns (CDC, 2009). Over this time period, the average was 8,620 visits per year with an estimated average annual rate of 23.8 visits per 100,000 population. Although most scalding and burn injuries in the homes are related to exposures other than hot water, such as food, cookware, and microwaved items, the risk of scalding from home premise plumbing remains important. It is difficult to tell from CDC (2009) which cases were, in fact, plumbing related. Bathtubs and showers are associated with prolonged exposure to larger body-surface areas, and therefore are particularly concerning for scalding of at-risk populations.

As shown in Table 4-3, scalding and burns are linked to water temperature and time of exposure (Armstrong, 1978; Moritz and Henriques, 1947), as is the growth potential of *Legionella* (Klein, 2018). The CDC, the American Academy of Pediatrics, the American Society of Sanitary Engineering Scald Awareness Task Group, and other safety-promotion organizations recommend that home hot-water heater thermostats be set at 49°C to 53°C (120°F to 130°F) to reduce scalding risks (Lukefar and Ezekial, 1994)[4]. CDC (2009) recommends that hot-water heaters be kept below 49°C (120°F) to minimize the risk for scalding in the home. Most municipalities and state regulations recommend that home hot-water heater temperatures remain below 49°C (120°F), since most burns occur in the home and not at hospitals

[4] See http://www.asse-plumbing.org/WaterHeaterScaldHazards.pdf.

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Management of Legionella in Water Systems

or rehabilitation facilities where there are more at-risk patients (CDC, 2009; Haik, 2007; Tung et al., 2005). Maximum allowable temperatures in hospitals and healthcare organizations are often regulated by states. Data from 39 states reported regulating maximum allowable hospital water temperature from as low as 43°C (110°F) to as high as 53°C (130°F) (Mandel et al., 1993).

Table 4-3 shows the trade-off between scald risk and the risk of *Legionella* growth. This table was submitted for inclusion in the 2020 Uniform Plumbing Code pending a member vote. In buildings with sensitive populations, the production and storage of hot water at greater than 60°C (140°F) will likely require the use of thermostatic mixing valves to blend cold and hot water to appropriate temperatures at the tap. It is important for these devices to be routinely serviced and for temperature to be monitored closely (Bédard et al., 2015; Johansson et al., 2006).

TABLE 4-3 Water Temperature, Risk of Scalding/Burning, and *Legionella* Growth Potential

°F	°C	Time to First-degree Burn	Time to Second-degree Burn	*Legionella* Growth Potential
<77	<25			No
80	27			Low
90	32			Moderate
100	38			Very high
110	43			Very high
116	47	35 min	45 min	Moderate
122	50	1 min	5 min	Very low
131	55	5 sec	25 sec	No
140	60	2 sec	5 sec	No
149	65	1 sec	2 sec	No
154	68	instantaneous	1 sec	No

SOURCE: Adapted from Armstrong (1978) and Klein (2018).

Disinfection

Maintenance of a disinfectant residual can be an integral part of a building's water management plan for control of *Legionella*. Disinfection methods should be paired with scheduled water testing to ensure that the system maintains a residual. Many of the disinfectants reviewed below have demonstrated at least some degree of efficacy towards management of *Legionella* in drinking water distribution systems and building water systems. Hence, the choice, and success, of disinfection technology will depend on additional considerations such as cost, operator training, materials (corrosion), water chemistry, system configuration, and water use patterns.

Chemical Disinfection

Chemical disinfectants, particularly oxidizing agents such as chlorine, chlorine dioxide, chloramine, and ozone, are widely used to control *Legionella* spp. and protozoa—both as disinfectants in

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Management of Legionella in Water Systems

drinking water distribution systems and as secondary disinfectants within buildings. The disinfectant should ideally inactivate microorganisms in the bulk water, but also penetrate and inactivate microorganisms associated with biofilms. Overall, the efficacy of disinfectants depends on the culture condition of *Legionella* spp. and their host protozoa and the physicochemical characteristics of the water (e.g., temperature, pH, organic carbon, hardness).

Disinfection strategies are sometimes evaluated in terms of "CT" or disinfectant concentration (measured in mg/L) multiplied by time of exposure (measured in minutes). Very high disinfectant levels (4 mg/L or more) applied for many hours might be recommended when responding to an outbreak in a hospital or nursing home but would be impractical and excessive for routine water treatment in premise plumbing. Choice of a disinfectant also needs to consider corrosion impacts on pipe materials, reliability, and safety. Because *Legionella* spp. can use protozoa and their cysts as a protective shield against disinfectants, it is imperative to consider the efficacy of each disinfectant for both organisms. In some systems, multiple points of application are necessary to maintain chemical residuals throughout the entire network.

Chlorine. Chlorine is the most commonly used disinfectant by water utilities in the United States. Chlorine adversely affects the cell membrane, nucleic acids, respiration, and enzymatic activity of microbes, leading to their inactivation (Kim et al., 2002). During treatment, chlorine can be added to water as elemental chlorine (chlorine gas), sodium hypochlorite solution, or dry calcium hypochlorite. In water, chlorine exists as hypochlorous acid and hypochlorite ion, where the hypochlorous acid predominates when pH is below 7.5 and is a more effective biocide.

Generally, maintenance of a free chlorine residual in potable water systems is effective for control of *Legionella* spp. (Kim et al., 2002). For example, planktonic *Legionella* spp. resuspended in water were eliminated within three minutes by 2 mg/L free chlorine derived from sodium hypochlorite (Miyamoto et al., 2000). Mouchtouri at al. (2010) disinfected *Legionella*-positive cooling towers by circulating water with 5 mg free chlorine/L for five hours. Systems with pH greater than 8.0 received higher free chlorine dosages of 15 to 20 mg/L to achieve the required disinfection level; disinfection was considered successful when samples showed concentrations less than 1 CFU/mL (10^3 CFU/L). Hyperchlorination with 4 to 6 mg/L decreased *L. pneumophila* in plumbing systems by 5 to 6 logs over six hours (Muraca et al., 1987). The decline in *L. pneumophila* was more rapid at 43°C than at 25°C. However, a higher dose of chlorine was required at 43°C to overcome thermal decomposition and maintain a chlorine residual of 4 to 6 mg/L. The high temperatures likely accelerated chlorine reactions with demand-causing compounds, including natural organic matter and reduced metals like iron or manganese.

The ecology of *Legionella* plays an important role in disinfection efficacy; whether the bacteria is shielded from the disinfectant depends on whether it is planktonic or within a protozoan trophozoite or cyst. Amoebae cysts are much more resistant to disinfection than the free-living trophozoite (De Jonckheere and Van de Voorde, 1976). *Legionella* spp. in protozoa cysts survived 25-fold more chlorine disinfectant than planktonic cells after 18 hours (Kilvington and Price, 1990). Dupuy et al. (2011) showed that co-culture significantly increased survival of *L. pneumophila* at 30°C, but not at 50°C.

Guidelines for the maintenance of continuous chlorine residuals in building premise plumbing to prevent amplification of *Legionella* tend to recommend residual concentrations similar to those required in drinking water distribution systems. The Allegheny County (Pennsylvania) Health Department specifies that potable water, from entering a building through to all outlets (e.g., faucets, showerheads), should maintain at least 0.3 mg/L free residual chlorine (Moore and Shelton, 2014). The California Code of Regulations, Title 22, Section 60306, requires that industrial or commercial cooling towers maintain a 0.3 to 0.7 mg/L free chlorine residual (State of California Energy Commission Staff, 2004).

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Management of Legionella in Water Systems

Chlorination can have adverse effects on the plumbing system by making the water acidic, which in turn can make the water more corrosive to pipes, joints, fittings, and fixtures. If chemical flushing is used with hyperchlorination, these adverse effects can be more pronounced.

Chlorine Dioxide. Unlike free chlorine, chlorine dioxide does not hydrolyze when it enters water; it remains a dissolved gas in solution. As a neutral compound, it can easily diffuse through cell membranes of microorganisms where it disrupts protein synthesis. It is typically generated on site for immediate use by slowly adding a strong acid (e.g., hypochlorous or sulfuric acid) to a sodium chloride solution.

Chlorine dioxide has been found to be more effective in penetrating biofilms than chlorine (Kim et al., 2002; Lin et al., 2011; Walker et al., 1995), and it is effective over a wider pH range (Lin et al., 2011). Loret et al. (2005) evaluated 0.5 mg/L chlorine dioxide for control of *Legionella* grown in biofilms in a pilot-scale premise plumbing system incubated at 30°C. *Legionella* populations decreased to undetected levels (less than 500 CFU/L) within six days of treatment. As with chlorine, the presence of amoebae reduces the efficacy of chlorine dioxide disinfection of *Legionella* (Dupuy et al., 2011). Despite the effectiveness of chlorine dioxide, it is not commonly used as a disinfectant in the distribution system due to the toxicity of the disinfectant and some of its byproducts (EPA, 1998) and the potential for objectionable odors (Dietrich et al., 1991).

There have been a handful of real-world applications of chlorine dioxide treatment of premise plumbing. Walker et al. (1995) reported elimination of *Legionella* spp. to below detection in a hospital water system after treatment with 50 to 80 mg/L chlorine dioxide. Srinivasan et al. (2003) evaluated the use of chlorine dioxide (0.3 to 0.5 mg/L residual) for 17 months in a hospital and found *Legionella* occurrence decreased from 41 percent to 4 percent in distal sites. Only *L. anisa* was recovered during the chlorine dioxide treatment and it was cultured from both the hot- and the cold-water systems. No cases of nosocomial *Legionella* infection were detected in the building with the chlorine dioxide system during the 17-month evaluation. Marchesi et al. (2013) reported reduction in *L. pneumophila* contamination in three hospital hot-water (60°C) systems over a three-year period using a chlorine dioxide dose of 0.50 to 0.70 mg/L and a targeted residual of 0.3 mg/L at distal sites. Cristino et al. (2012) described use of chlorine dioxide after shock treatment to maintain 0.3 mg/L residual at the tap after 5 minute of flushing in a hospital. *Legionella* counts remained acceptable (less than 10^3 CFU/L), and no cases of hospital-acquired legionellosis occurred during the study period. Zhang et al. (2009) reported that after installation of a chlorine dioxide system it took months to achieve a 0.11 mg/L chlorine dioxide residual within two hospital systems, but the occurrence of *Legionella* at hot-water taps decreased from 60 percent to less than 10 percent of sampling sites, and no cases of hospital-acquired Legionnaires' disease were detected.

Monochloramine. Monochloramine is formed by adding free chlorine in a solution of ammonium chloride at a chlorine-to-nitrogen molar ratio of 0.5 (pH 8.5). Disinfection with monochloramine has gained traction in the United States because the disinfectant is more stable in the distribution system, it minimizes the formation of disinfection byproducts, and it can penetrate biofilms better than free chlorine (LeChevallier et al., 1988; Lee et al., 2011; Pressman et al., 2012). Monochloramine has a lower chlorinous odor threshold than free chlorine (EPA, 1994), but it has a much lower disinfection efficacy than free chlorine (Symons, 1978) and requires a much longer contact time or higher dose if used as a primary disinfectant.

One of the challenges with using monochloramine, particularly within a building system, is properly managing the chlorine-to-ammonia ratio (4.5:1) at an optimum pH (8.3) in order to form monochloramine without stimulating nitrification within biofilms. Nitrification is a microbial growth process by which ammonia is sequentially oxidized to nitrite and nitrate. Nitrite catalyzes the decay of chloramines

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Management of Legionella in Water Systems

and can leave a system without disinfectant residual and hence even more vulnerable to bacterial regrowth. Nitrifying bacteria fare better at warmer temperatures, making nitrification a summer problem for water utilities, which often implement flushing campaigns and even temporarily convert to free chlorine. Nitrification can be even more problematic in buildings because some premise plumbing is consistently maintained at a warm temperature, there is a high surface area-to-volume ratio for biofilm formation, and stagnant conditions can be especially conducive to slow-growing autotrophic organisms like nitrifiers and stimulate further decay of chloramines (Zhang and Edwards, 2009)—all of which could potentially undermine chloramine disinfection systems in premise plumbing.

As a disinfectant in the water supply distribution system, chloramines appear to be more effective than free chlorine in reducing the overall risks from *Legionella*. Kool et al. (1999) examined 32 hospital-acquired (nosocomial) outbreaks of Legionnaires' disease from 1979 to 1997 where drinking water was implicated. They found that the odds of a nosocomial *Legionella* outbreak were 10.2 times higher in hospitals supplied by a water system that maintained free chlorine than in those supplied by a water system using a chloramine residual. Similar results were obtained by Heffelfinger et al. (2003), who surveyed 152 hospitals with reported cases of hospital-acquired Legionnaires' disease. Flannery et al. (2006) showed significant reductions in the occurrence of both amoeba and *Legionella* spp. in building plumbing systems in San Francisco after the utility converted from free chlorine to chloramines. The prevalence of amoebae decreased from 169 of 1,405 (12 percent) samples when chlorine was used to 78 of 944 (8 percent) samples collected after conversion to monochloramine. Prior to the conversion, *Legionella* spp. were cultured from 61 of 169 (36 percent) samples in which amoebae were present versus 291 of 1,236 (24 percent) samples without amoebae. After conversion to monochloramine, *Legionella* were found in 1 of 78 (1 percent) samples containing amoebae and 8 of 866 (1 percent) samples without amoebae. *Legionella* occurrence was also reduced in 96 buildings in Pinellas County, Florida, when the drinking water distribution system converted from chlorine to monochloramine disinfection (Moore et al., 2006). When free chlorine was used, 20 percent of the buildings were colonized with *Legionella* in at least one sampling site. Within a month after chloramination, *Legionella* colonization was reduced by 69 percent. Monochloramine appeared to be more effective in reducing *Legionella* in hotels and single-family homes than in county government buildings, perhaps because of more consistent water usage.

Chloramines also appear to be more effective than chlorine when used as a treatment in buildings. Coniglio et al. (2015) studied the addition of monochloramine after two hospital hot-water systems failed to control *Legionella* with thermal treatment (65°C to 70°C), shock chlorination (50 mg/L free chlorine for one hour at distal sites), point-of-use filters (0.2 micron), and hydrogen peroxide (17 mg/L). Prior to chloramine treatment, 100 percent of samples were positive with *L. pneumophila* serogroups 3 and 6. Monochloramine treatment began at 3.0 mg/L and was then reduced to 2.0 to 2.5 mg/L after one month. *Legionella* was not detected during the following year except for one month when the monochloramine generator failed for 15 days. In a three-year study of monochloramine addition to a hospital in Italy, Marchesi et al. (2012, 2013) reported that a residual between 1.5 and 3.0 mg/L effectively controlled *Legionella* occurrence, with seven of the eight positive samples occurring within the first eight months and the eighth positive sample occurring at 15 months, when the monochloramine dose decreased below 1 mg/L.

Not all studies have been as straightforward, however. Duda et al. (2014) showed that although monochloramine concentrations of 1 to 4 mg/L significantly reduced the occurrence of *Legionella* in a hospital hot-water system (with the average number of positive sites declining from 53 percent to 9 percent), during certain months when nitrate, total ammonia, and pH levels were elevated, the percentage of positive samples increased, suggesting inadequate control of the chloramination process and nitrification. *Legionella* speciation changed from 90 percent of samples testing for *L. pneumophila* serogroup 1 to only 49 percent post-disinfection, while *L. bozemanii* occurrence increased.

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Management of Legionella in Water Systems

The effectiveness of monochloramine is generally thought to be due to its ability to penetrate biofilms and inactivate the bacteria (Donlan et al., 2002; LeChevallier et al., 1988). Lee et al. (2011) and Pressman et al. (2012) both used microelectrodes to demonstrate that monochloramine had greater penetration into biofilms than chlorine, but this penetration did not necessarily translate to immediate loss of viability. Johnson et al. (2018) found that amoebae in five free chlorinated reclaimed water systems were mostly (50 percent to 95 percent) in the active trophozoite phase; however, in the chloraminated system, 87 percent of the mesophilic amoebae and 66 percent of the thermophilic amoebae were in the cyst phase. They hypothesized that the penetration of chloramines into the biofilm might trigger the amoebae to form cysts rather than outright kill the protozoa. Since *L. pneumophila* only amplifies in the trophozoite stage, it may be possible to manage *Legionella* risk by limiting the free-living trophozoite population. Additional research is needed to examine the precise action of monochloramine on *Legionella* persistence and growth within pipeline biofilms.

Ozone. Ozone attacks unsaturated bonds of aldehydes, ketones, and carbonyl compounds (Langlais et al., 1991) and can participate in electrophilic reactions with aromatic compounds and neutrophilic reactions with many cellular components (i.e., fatty acids, carbohydrates, amino acids, proteins, nucleic acids). These reactions collectively affect the cytoplasmic membrane of bacterial cells and their protein structure as well as DNA. However, because ozone does not form a stable residual and decomposes rapidly in water, it is not typically used for building plumbing systems, but primarily to disinfect water supplies.

Several laboratory studies have evaluated ozone for inactivating *Legionella* (Domingue et al., 1988; Muraca et al. 1987) and amoebae cysts (Langlais and Perrine, 1986; Wickramanayake et al., 1984). There are few studies of using ozone to treat a building water system. Edelstein et al. (1982) applied continuous ozonation to the water of one wing of an unoccupied hospital building while the other wing used chlorinated tap water. The results were inconclusive, with both the ozonated and chlorinated sections having some positive results for *Legionella* (three of 12 samples positive for the ozone treatment, eight of 12 samples positive for the chlorine treated wings). Moreover, when the ozone was discontinued *L. pneumophila* regrew and reached levels similar to the pre-treatment densities. The authors noted that residual ozone at a faucet or shower would be released as a gas and could create a health hazard if inhaled.

Ultraviolet Irradiation

Ultraviolet (UV) light may not directly kill microorganisms but rather damages their DNA and proteins, which prevents them from replicating and becoming infectious. UV intensity times the duration of exposure is commonly referred to as fluence (mJ/cm^2) and describes UV disinfection capability. Fluence represents the energy per unit area falling onto a surface. Maximum efficacy with UV is attained at 254 nm (Kim et al., 2002) but turbidity, natural organic matter content, and particulate matter can affect UV disinfection capability. Medium-pressure UV light sources may also generate higher wavelength UV light (268 and 286 nm) that impacts proteins more than nucleic acids (Beck et al., 2017). Because UV does not provide a residual, it is only effective at the point of treatment and is typically combined with a chemical disinfectant for distributed water to effectively control *Legionella* spp.

All *Legionella* isolates tested by Cervero-Aragó et al. (2014) required 5 to 6 mJ/cm^2 UV fluence to inactivate 4 logs. However, a higher fluence was required when *Legionella* was co-cultured with amoeba. Muraca et al. (1987) found that UV irradiation at 30 mJ/cm^2 reduced *L. pneumophila* by 5 log units in 20 minutes although the very high concentrations of the bacteria could have affected the UV adsorption of the suspension. *Legionella* inactivation requires slightly higher doses when the bacteria are exposed

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Management of Legionella in Water Systems

to light repair (i.e., DNA repair mediated by enzymes activated by visible light), but has a similar level of inactivation when either low-pressure or medium-pressure lamps are used (see Table 4-4). Notably, when amoeba co-culture was used on samples below detection using buffered charcoal yeast extract (BCYE) agar plates, VBNC-like cells were resuscitated (Grossi et al., 2018). Hence, previous reports only using plate culture to assay inactivation may overestimate actual UV inactivation, particularly for higher wavelength UV light.

Hijnen et al. (2006) reported a log reduction of *Acanthamoeba* spp. with 40 mJ/cm^2. A 3-log inactivation of various *Acanthamoeba* species and *Vermamoeba vermiformis* was achieved with fluences of 23 to 100 mJ/cm^2; the higher levels were required for cyst inactivation. Overall, inactivation of *Acanthamoeba* spp. and *V. vermiformis* required higher levels of UV compared to *Giardia* or *Cryptosporidium* (EPA, 2006).

TABLE 4-4 UV Doses (mJ/cm^2) for Inactivation of *L. pneumophila*

L. pneumophila Strain	Lamp Type	1-log	2-log	3-log	4-log
Philadelphia Type 2	LP	0.92	1.84	2.76	No data
Philadelphia 1 (no light repair)	LP	0.5	1	1.6	No data
Philadelphia 1 (with light repair)	LP	2.3	3.5	4.6	No data
Philadelphia 1 ATCC33152	LP	1.6	3.2	4.8	6.5
Philadelphia 1 ATCC33152	MP	1.9	3.8	5.8	7.7

NOTES: LP = low-pressure lamps, which have a single output around 254 nm. MP = medium-pressure lamps, which have polychromatic output at multiple wavelengths. SOURCES: EPA (2016); Knudson (1985); Oguma et al. (2004).

Copper-Silver Ionization

The use of copper-silver (Cu-Ag) ionization to control *Legionella* in building water systems is widespread, partly because it is relatively low cost and low maintenance compared to other controls. Copper (Cu) and silver (Ag) both have biocidal activity, especially when used in combination. In ionization chambers, both metals can be ionized through electrolysis to form positively charged ions. The copper ions interact with negatively charged cell walls of *Legionella* spp. (and other bacteria), disrupting cell wall permeability and subsequent nutrient uptake. The copper ions penetrate the cell wall and create an entrance for silver ions, which bond with DNA, RNA, cellular proteins and respiratory enzymes, immobilizing the cell and curtailing cell division.

Field studies constitute the majority of the published reports on the efficacy of copper-silver ionization for controlling *Legionella* in building plumbing systems (Blanc et al., 2005; Chen et al., 2008; Demirjian et al., 2015; Dziewulski et al., 2015; Kusnetsov et al., 2001; Liu et al., 1994, 1998; Mòdol et al., 2007; Rohr et al., 1999; States et al., 1998; Stout and Yu, 2003). These reports typically describe applying copper-silver ionization to remediate situations where *Legionella* have already colonized the system. Most studies have looked at the disinfection effects of these ions used together, but Lin et al. (1996) examined the effects of each ion individually. They reported 6-log reduction of *L. pneumophila* serogroup 1 in 2.5 hours with 0.1 mg/L copper. Similarly, a 6-log reduction *L. pneumophila* was obtained within six hours on exposure to a solution of 50 µg/L silver ions (Miyamoto et al., 2000). Cloutman-Green et al. (2019) reported effective *Legionella* management in a healthcare building hot-water system operated at 42°C (range 37°C to 44°C) supplemented with copper-silver ionization operated at 0.37/0.034 mg/L,

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Management of Legionella in Water Systems

respectively. The authors reported a reduction in energy and carbon emissions of 33 percent and 24 percent, respectively, compared to an equivalent temperature-controlled system.

June and Dziewulski (2018) provide an excellent review of copper-silver ionization for the inactivation of *Legionella.* The review suggests that there have been mixed results when considering the efficacy and reliability of copper-silver ionization for controlling *Legionella*. Copper-silver ionization is slower acting compared to other disinfectants and more dependent on water chemistry (e.g., pH, total dissolved solids or TDS), as the silver can precipitate in the presence of high dissolved solid concentrations, becoming unavailable for disinfection. *Legionella* can be protected from copper and silver ions when associated with biofilms or amoebae, and the potential for *Legionella* to develop resistance to copper and silver ions has been suggested (EPA, 2016a). Indeed, dominant sequence types of *L. pneumophila* isolated from two hospitals' hot-water systems with and without copper-silver ionization have been shown to be highly resistant to copper (Prévost et al., 2017). The development of resistance to copper and silver may be a concern in ensuring the long-term efficacy of copper-silver ionization. Longitudinal case studies report that copper-silver ionization can become ineffective for the control of *Legionella* in biofilms and water in large existing healthcare facilities (Blanc et al., 2005; Rohr et al., 1999). A further concern is that bacteria that develop resistance to heavy metals may also develop antibiotic resistance (Chen et al., 2015), although additional research is needed to determine if there is an increase in antibiotic resistance in water treated with copper-silver ionization. June and Dziewulski (2018) suggest approaches for improving copper-silver ionization efficacy and reliability, including increasing the dissolved oxygen and sodium content of the treated water, applying copper and silver ions in combination with other disinfectants, and using copper and silver ions at higher temperatures.

Other Disinfecting Agents

Bromine behaves similarly to chlorine, existing in water as hypobromous acid to form HOBr and OBr^- depending on the pH (Kim et al., 2002). Bromine has generally less efficacy against *Legionella* spp. compared to chlorine. Bromine, iodine, and iodophore are variously effective against *Acanthamoeba culbertsoni* and *Naegleria fowleri* cysts (De Jonckheere and Van de Voorde, 1976). Although used for potable water disinfection in some emergency instances, use of bromine, iodine, or hydrogen peroxide in water supply distribution systems and building water systems is not widely practiced.

Peracetic acid is thought to disinfect by impacting lipoproteins in the cell membrane (Rossoni and Gaylarde, 2000). Unlike chlorine and hydrogen peroxide, its potency is not greatly compromised by organic matter or enzymes (Baldry et al., 1991), and it has acceptable potency at neutral pH and can be effective for biofilms (Rossoni and Gaylarde, 2000). However, peracetic acid has had limited use within building plumbing systems.

Non-oxidizing biocides such as BNPD (2-bromo-2-nitropropane-1, 3-diol), glutaraldehyde, guanidines, dithiocarbamates, isothiazolin, halogenated amides such as DBNPA (di-bromo-nitrilo-propionamide), halogenated glycols such as bronopol (2-bromo-2-nitroproprionamide), and some quaternary ammonium compounds are commonly used in cooling towers (Kim et al., 2002). Among non-oxidizing biocides, glutaraldehyde, DBNPA, isothialozin and bromopol were found to be effective against to varying degrees (Kim et al., 2002). The biocides MBC-115 [a quaternary ammonium comprised of poly(oxyethylene (dimethyliminio) ethylene (dimethyliminio) ethylene dichloride)] and MBC-215 (an isothiazine derivative of a mixture of 5-chloro-2-methyl-4-isothiazolon-3-one and 2-methyl-4-isothiazolin) have been widely used in cooling towers to control *Legionella* spp. Berk et al. (1998) found the efficacy of both

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Management of Legionella in Water Systems

compounds on *Legionella* spp. to be poor, although this may have been due to the presence of amoebae. Barker et al. (1993) found that the antiseptics polyhexamethylene bioguanide and benzisothiazolone were ineffective against *L. pneumophila* grown with *A. polyphaga* compared to *L. pneumophila* pure cultures. Both biocides attack the bacteria cell membrane; amoebae proteins coating *Legionella* may have conferred biocide resistance. Miller and Simpson (1999) reaffirmed the resistant nature of protozoa cysts to disinfection with some of these alternative compounds.

Manage Hydraulics

Appropriate hydraulic system design and maintenance are essential for effective *Legionella* control. In particular, hydraulics are essential to maintaining and delivering water at an inhibitory temperature as well as distributing disinfectants throughout the building. Recent guidelines following years of mandatory *Legionella* control in Europe stress the need to properly manage hydraulics to ensure homogeneous temperature and biocidal control in all areas of the hot-water system, including balancing under varying demand (Centre Scientifique et Technique du Bâtiment, 2012; Health and Safety Executive, 2013). Construction and operational standards for buildings often specify minimizing stagnation (e.g., via recirculation loops, elimination of hydraulic and physical dead ends).

In many cases, differences among reports on the efficacy of thermal control on *Legionella* probably reflect whether the temperature set points were hydraulically achieved across the whole system, including at the outlets (faucets and showers). For example, a single piece of deficient equipment such as backflow preventers on a single mixing valve can influence the hot-water temperature distribution within an entire building wing, causing hot-water temperature to decrease in those sectors (Boppe et al., 2016). The presence of stagnation caused by dead legs, inadequate system hydraulic balancing, or lack of occupancy also reduces the disinfectant efficiency in these areas. As a global recommendation, extended periods of stagnation and the presence of dead legs should be avoided. To reach this goal, minimum water velocity should be maintained at all times within the recirculation pipes. The Centre Scientifique et Technique du Bâtiment (CSTB, 2012) proposes maintaining the highest value between 0.2 m/s and the velocity required to maintain heat loss below 5°C.

Flushing to Control Distal Growth

Flushing of water can have significant benefits in terms of water quality and more specifically *Legionella* levels. Flushing can reduce total cell counts in premise plumbing by dislodging loose deposits and biofilm, which tend to harbor higher levels of heavy metals, *Aeromonas*, ATP (indicator of biological activity), and *Legionella* as judged by operational taxonomic units quantified by amplicon sequencing (Liu et al., 2017). Flushing systematically reduces total and viable bacterial cells and heterotrophic plate counts in large buildings (Bédard et al., 2018; Lautenschlager et al., 2010), and in most instances will lower the concentrations of *L. pneumophila* concentrations in household and hospital taps (Bédard et al., 2019; Cristina et al., 2014). Lipphaus et al. (2014) found that flushing reduced total cell counts by flow cytometry in infrequently used cold-water hospital taps, but had a less pronounced effect on hot-water taps. Periodical flushing of water is particularly useful to prevent colonization and limit the growth of *Legionella* at the distal sites of cold- and hot-water systems. Manual flushing is recommended in guidance and is widely used during building commissioning or after periods of vacancy (e.g., weekends, vacations).

There is no consensus on the optimal flushing frequency to prevent *Legionella*. Several guidance documents recommend weekly flushing of low-use faucets and showers (e.g., ECDC, 2017; HSE, 2013). A

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Management of Legionella in Water Systems

much higher flushing frequency was suggested by Totaro et al. (2018)—a study done in an Italian hospital that was experiencing elevated *L. pneumophila* positivity and concentrations, despite optimal temperature control and on-site addition of chlorine dioxide. Five dead-end locations and the main return loop were all positive for *L. pneumophila* serogroups 3 and 10–14 (concentrations ranging from 8 x 10^3 to 1.3 x 10^5 CFU/L) before the installation of time-flow taps. Operating the five time-flow taps for one minute every six hours (64 L per day) slightly decreased the *Legionella* concentrations. After further increasing the flushing frequency to one minute every two hours (192 L per day), no positives were observed. These findings suggest that implementing automated periodic flushing may be necessary if hydraulic corrective actions such as the elimination of dead legs and the balancing of flows cannot be implemented.

Storage facilities and dead-end pipes where water velocities and turnover can be very low are locations that are more susceptible to biofilm development. Sediments can accumulate in areas of low flow, increasing disinfection demand and promoting bacterial growth. Stratification caused by warm water temperatures can prevent adequate mixing. Inlet–outlet configurations can result in "last in, first out" flow patterns in which older water never leaves the storage tank, causing stagnation, dissipation of disinfectant residuals, and microbial growth. Increasing the frequency of storage tank cleaning will minimize sediment accumulation and help control biofilms.

Relationship Between Flow Rates and Biofilm Formation in Pipes

Higher flow rates and turbulence can reduce biofilm formation (Donlan et al., 1994; Kirisits et al., 2007). At lower residence time, the erosion of cells on the surface due to higher shear force and enhanced diffusion of disinfectant within a thinner boundary layer are factors suggested to explain the effect of flow dynamics on biofilm formation (Donlan et al., 1994). A study in which biofilms were first established under laminar or turbulent flow looked at the effect of unsteady hydraulic conditions on the biological quality of the drinking water (Manuel et al., 2010). Once the biofilm was established, periods of stagnation promoted bacterial accumulation for both the planktonic and biofilm bacteria. These cells were carried away once the flow was resumed, increasing the bacterial concentration in drinking water. Similarly, the ratio of *L. pneumophila* cell detachment from biofilm following exposure to 0.1, 0.3, and 0.7 m/s was found to increase with flow velocity (Shen et al., 2015). Initial adherence of *L. pneumophila* strains to an existing biofilm was conducted in quasi-stagnant conditions (0.007 m/s) prior to exposure to water flow. The same trends were observed both in smooth and rough biofilm, although *L. pneumophila* adhesion was enhanced by biofilm roughness. This enrichment was attributed to increased interception of the suspended *L. pneumophila* in flowing water on biofilm surface (Shen et al., 2015).

Dissimilar results have been found by others. The impact of turbulent, transition and laminar flow on existing and newly formed biofilm was investigated by Tsagkari and Sloan (2018). They found that turbulent flow did not reduce biofilms; instead, biofilm thickness and density increased under turbulent flow conditions equivalent to 0.25 m/s in a 30.3-mm diameter pipe. Another key parameter is the surface-to-volume (S/V) ratio, which fundamentally drives the relative amount of surface area available to colonize and overall biomass production potential for pipes (Tsvetanova and Hoekstra, 2012). The authors observed a significant effect of S/V ratio on the planktonic biomass, with concentrations 4 to 14 times higher with higher S/V ratios. Premise plumbing piping usually has a small diameter and thus a larger S/V ratio than the distribution system.

There are few methodologies available to assess, in detail, hydraulically deficient areas within an existing water system. CSTB (2012) suggests investigating common causes such as valve obstructions

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Management of Legionella in Water Systems

(leading to stagnation or reduced water velocity within the return loop), type of control elements installed, re-circulation pump design and operation, and the lack of balance between the different secondary flow and return loops. Given the intimate relationship between temperature and hydraulics, temperature is not only a very effective proxy for residence time, but also relatively easy and inexpensive to monitor (Bédard et al., 2015). Systems that fail to maintain control temperatures at the point of use despite adequate water heater temperatures are considered at risk and hydraulically deficient.

Nutrient Control

An indirect strategy for management of *Legionella* in building water systems could be controlling biofilms, which are the food source for free-living protozoa (Characklis and Marshall, 1990; LeChevallier et al., 2011; NRC, 2006). One of the most common ways to control biofilms is to limit nutrients in the water—a strategy used by some western European countries that also tend to distribute potable water with little or no disinfectant residual (Bartels, 2018; Exner, 2018). Hence, much of the work investigating the effect of limiting organic carbon on biofilm growth, and hence on *Legionella,* has been conducted in The Netherlands.

A substantial portion of the organic carbon present in drinking water is derived from complex natural organic matter (for example, from decaying leaves), a form that cannot be directly utilized by microorganisms. Thus, a direct measurement of total organic carbon does not indicate the fraction that is actually bioavailable to drinking water microbes. Instead, bioassays have been developed to directly measure the biodegradable fraction of organic carbon in the water, specifically the assimilable organic carbon (AOC) and biodegradable dissolved organic carbon (BDOC) assays. Organic carbon levels in U.S. drinking water supplies typically average 100 μg/L for AOC (ranging from 50 to 250 μg/L) and 0.3 mg/L for BDOC (ranging from 0 to 1.0 mg/L); surface water supplies have higher levels of biodegradable organic matter than groundwater supplies (LeChevallier et al., 1996; Volk and LeChevallier, 2000).

In terms of setting nutrient limits for water exiting a drinking water treatment plant, only extremely low levels of AOC (less than 50 μg/L) have been observed to have a measurable effect on downstream numbers of total bacteria as judged by heterotrophic plate counts (HPCs) or ATP (LeChevallier et al., 1991). Much lower AOC levels of 5 to 10 μg/L were associated with lower *L. pneumophila* levels in Dutch drinking water distribution systems (van der Kooij and van der Wielen, 2014). The same research group also observed a strong correlation among AOC, biofilm concentration, and *L. pneumophila* growth, with no growth observed at AOC levels below 1 μg/L (van der Kooij et al., 2017). Similarly, Learbuch et al. (2019) treated water with a pilot reverse-osmosis system and subsequent remineralisation to obtain very low AOC levels and showed that the water did not support growth of *L. pneumophia*. On the other hand, Williams et al. (2015) performed extensive bench-scale tests in simulated glass water heaters with spiked AOC levels ranging from 0 to 15,000 μg/L over 17 months and could find no correlation with *Legionella* concentration, although total bacterial numbers by HPCs did correlate.

It is important to recognize that such low AOC levels can be very difficult to achieve and maintain in drinking water because AOC can be generated in water mains and by the bacteria native to the plumbing. Dai et al. (2018) conducted a bench-scale study of controlled, replicated simulated glass water heaters representing a range of premise plumbing conditions that were fed biofiltered water (to simulate the AOC removal process used at water treatment plants or in whole-house filters). Although biofiltering the water substantially reduced the TOC and 16S rRNA gene copy numbers, there was no measurable effect on *Legionella* gene copy numbers. Instead, the individual plumbing conditions, such as the presence of iron corrosion sediments, nitrification, or cross-linked polyethylene (PEX) pipe material leaching organic carbon, dominated the effects on the microbial community composition and, in some cases, *Legionella*.

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Management of Legionella in Water Systems

Iron Corrosion and Inorganic Nutrients

Much of U.S. water distribution systems consist of century-old unlined iron mains, which are beyond their designed lifespan and subject to substantial corrosion as well as intrusion during water main breaks. Corrosion of pipe surfaces provides not only a habitat for bacterial proliferation and protection from chlorine disinfectant residuals but also a source of nutrients. Aerobic microbial respiration consumes oxygen, resulting in a reduced redox environment that can accelerate corrosion and produce a disinfectant demand. Corrosion of pipe surfaces and deposition of corrosion products can also create tubercles and surface roughness that protect biofilm organisms from hydraulic shear (Characklis and Marshall, 1990). The resulting turbulent flow can help transport nutrients and detritus, further enhancing the biofilm environment.

Growth of certain microbes is also promoted by other inorganic substances can also serve as electron donors or acceptors including methane, ferrous iron, reduced sulfur compounds, hydrogen gas, manganese, ammonia, and nitrite. These substances can stimulate autotrophs to fix organic carbon into the system, leading to more bacterial cells and associated organic matter. The accumulation of organic carbon and reduced inorganic compounds (e.g., iron, nitrite, sulfides) in biofilms can create a disinfectant demand that protects the attached microbes from being inactivated. In particular, iron-oxidizing bacteria oxidize ferrous iron to produce ferric iron oxides. Not only is iron a known nutrient for *Legionella*, it also reacts with chlorine, thereby increasing microbial risk by removing the disinfectant residual.

Plumbing Materials

Plumbing materials are an important factor to consider in *Legionella* control. Common plumbing materials in buildings include copper, iron, and numerous plastics, with cross-linked polyethylene (PEX) and cross-linked polyvinyl chloride (PVC) being particularly suitable for hot-water plumbing because of their tolerance of higher temperatures. Each pipe material will influence the building-level water chemistry and shape the biofilms that colonize premise plumbing in a unique manner (Ji et al., 2015). Being able to identify a pipe material that most effectively limits proliferation of *Legionella* for a given water chemistry and building type would be valuable as a passive barrier. It is important to recognize that water chemistry varies regionally, seasonally, and as dictated by various upstream water treatment processes (Dai et al., 2018), making it difficult to predict how incoming water will react with different pipe materials.

Although copper pipe has well-known antimicrobial properties, it does not universally control *Legionella.* Indeed, copper has been associated with decreased, increased, and comparable numbers of *Legionella* relative to other pipe materials (Rhoads et al., 2017b). As described in Chapter 2, the age of copper pipe, temperature, pH, and general water chemistry influence the dissolution chemistry and overall antimicrobial action of copper towards *Legionella*. The composition of the biofilm community also matters, e.g., interactive effects of amoebae and copper appear to favor survival of *Legionella* (Buse et al., 2017; Ji et al., 2017). Thus, it is clear that copper pipe cannot be the sole agent to control *Legionella*; other microbiological, chemical, and site-specific factors needs to be considered.

PEX and other heat-tolerant flexible polymeric plastic materials have gained popularity for their ease of use for hot-water plumbing. These materials, however, are well known to leach organic carbon and can stimulate bacterial growth (Proctor et al., 2018). In particular, flexible pipe materials commonly employed to plumb showerheads are especially vulnerable to biofilm formation and microbial growth, producing total bacterial cell counts ranging from 10^6 (PE-Xc—applied as a rigid control plastic) to 10^8

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Management of Legionella in Water Systems

(PVC-P) cells/cm^2 of hose (Proctor et al., 2016). A comprehensive comparison of six different shower pipe materials indicated that these materials had a profound influence on the microbial community composition, including the occurrence of genera containing *Legionella* and other pathogens (Proctor et al., 2016). However, interestingly, *Legionella* operational taxonomic unit were lower when total bacterial cell counts were higher, suggesting *Legionella* were out-competed. An eradication strategy based on this probiotic concept is discussed later in this chapter.

Iron pipe is extremely vulnerable to biofilm formation, partly because of its susceptibility to corrosion. Even without corrosion and with depleted AOC and sufficient chlorine residual, iron is highly prone to biofilm build-up compared to other materials, such as PVC (Camper, 1996). Iron pipes also support a more diverse microbial population than do PVC pipes (Dai et al., 2018; Norton and LeChevallier, 2000). While no longer used in modern buildings, legacy iron pipe remains common in older buildings, water mains, and service lines. One major survey found that cast iron pipes comprise an estimated 38 percent of water distribution system pipes in the United States (McNeill and Edwards, 2001). Even in modern systems built without iron, other sources, such as steel components in water heaters, can elevate iron levels in water. When iron components corrode, they not only release iron into the water, but in the process accelerate the decay of disinfectants (Zhang and Edwards, 2009; Zhang et al., 2010). Depletion of disinfectant residuals by iron will leave downstream components vulnerable to microbial regrowth. Depletion of chlorine in general (Zahran et al., 2018) and by iron corrosion specifically (Rhoads et al., 2017a) has been hypothesized to account for the Legionnaires' disease outbreak that occurred when corrosive water was distributed in Flint, Michigan. Thus, addressing the problem of legacy iron pipe is a critical engineering control to consider for *Legionella*. In 2012, the American Water Works Association estimated that it would cost $455 million to replace just the cast iron pipe in U.S. distribution systems (AWWA, 2012). In the meantime, awareness of the presence of iron pipes and other components and practicing appropriate corrosion control, e.g., through orthophosphate addition federally mandated by the Lead and Copper Rule, are key to reducing this potential risk factor for *Legionella* growth in premise plumbing.

Finally, other plumbing materials besides the pipes themselves can potentially influence *Legionella*. For example, certain pipe gaskets and elastic sealants (containing polyamide and silicone) can be a source of nutrients for bacterial proliferation (Colbourne et al., 1984).

Managing the Distal Portion of the Plumbing

Managing the distal portion of premise plumbing is the last opportunity to control *Legionella* risk in building water systems. The distal section between the main piping of a building and the point of use has a number of unique features that are favorable to biofilm and *Legionella* growth. Unlike the main and secondary piping, the distal section immediately upflow of the point of use may include numerous components such as faucets, showerheads, thermostatic valves, backflow valves, interconnection piping, and aerators. Because of all these components, the materials found at distal sites vary extensively compared to the main premise plumbing system. In addition, the smaller diameter piping and correspondingly larger surface-to-volume ratios at distal sites provide niches for biofilm growth. These sites are also subject to recurring stagnation, which hinders the maintenance of control measures such as temperature or residual disinfectants. Together, these factors create opportunities for *Legionella* to thrive at distal sites.

There is strong evidence that concentrations of *Legionella* in the distal sites of premise plumbing can be significantly higher than in the more centralized sections of the premise plumbing of a building. Using monitoring data required by German regulations, a large investigation in Cologne focusing mostly on residential buildings revealed that 32.7 percent (223 of 712) of samples were positive for *Legionella* spp. (Kruse et al., 2016), with most positive detections (63.9 percent) found only at distal sites, rather than in

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Management of Legionella in Water Systems

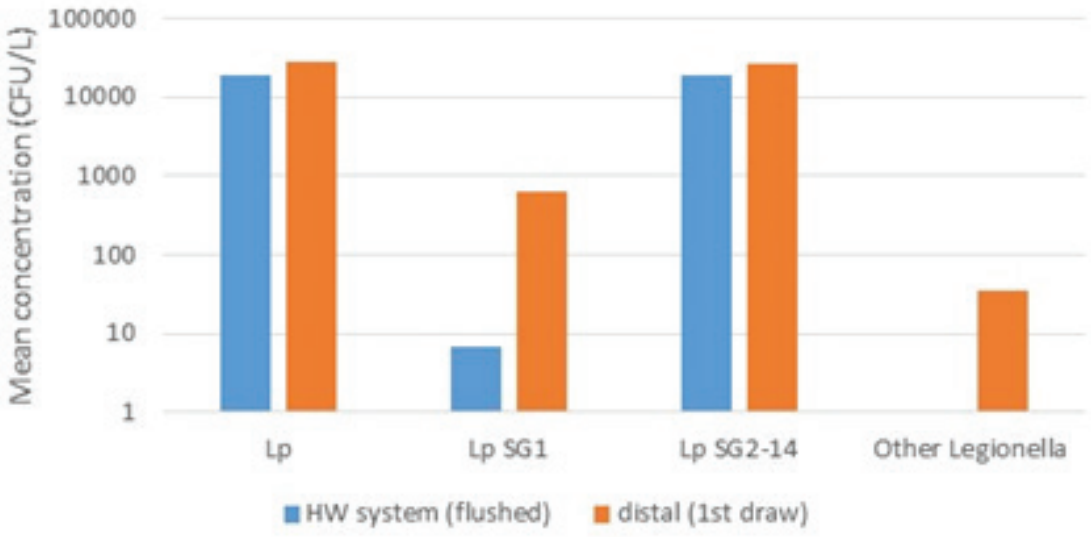

FIGURE 4-3 Concentrations of various *Legionella* species and strains in Italian hospital water systems. First draw samples reflect conditions at the distal ends, while flushed samples represent conditions in the main hot-water system. SOURCE: Cristina et al. (2014).

the central recirculation system. Similarly, a large Italian database of regulatory sampling results for the monitoring of *Legionella* spp. and *L. pneumophila* in hospitals in first-draw and flushed samples was analyzed by Cristina et al. (2014), who found high average concentrations of various *Legionella* strains and species both in the main hot-water plumbing and in first draw samples at taps. As shown in Figure 4-3, significant amplification was noted for *L. pneumophila* serogroup 1 and other *Legionella* in first-draw samples, which specifically measure concentrations in the distal sites.

Biofilm growth and *Legionella* proliferation at distal sites can be prevented through various actions. Small diameter piping in the distal portion of premise plumbing can minimize water volumes and their age. Water circulation can be maximized by a combination of improved design (e.g., limiting the number of outlets) and preventive flushing procedures. The use of biostable materials (see previous section on plumbing materials) and minimization of the surface area available for biofilm growth should also be considered when selecting any distal devices, including faucets and flow-reduction aerators. Finally the use of thermostatic valves, which provide surfaces for biofilm growth at temperatures optimal for *Legionella*, should be carefully weighed against the risk of scalding and only used when justified on a risk basis. In cases where the premise plumbing is compromised, corrective action can be taken by installing point-of-use filtration barriers or flash disinfection devices.

Challenges of Thermostatic Mixing Valves and Electronic Faucets

Electronically activated faucets and thermostatic mixing valves increase *Legionella* risk because they provide surfaces for biofilm growth and water at ideal temperatures (42°C to 49°C) for *Legionella*. Thermostatic mixing valves, mixing manual faucets, and electronic faucets are complex devices composed of various combinations of synthetic, organic, and metal-based materials, often with multiple nooks and crevices where biofilm and *Legionella* can proliferate.

Used mainly in showers and faucets to prevent scalding, thermostatic mixing valves combine hot and cold water to achieve a set temperature that can be adjusted to protect users. There is limited

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Management of Legionella in Water Systems

information available on the impact of thermostatic mixing valves on the prevalence of *Legionella* at the point of use. In The Netherlands, thermostatic mixing valves in hotels and hospitals previously found positive for *Legionella* spp. were investigated in detail (van Hoof et al., 2014). Biofilm swabs and water samples (cold, hot, and mixed) were collected from two types of thermostatic mixing valves, and *Legionella* was quantified both by culture and qPCR. In seven instances, *Legionella* spp. were detected in at least one sample, with swab samples taken from rubber components of the valves showing the highest concentrations, which is in agreement with the high potential of rubbers to support growth of *L. pneumophila* (Niedeveld et al., 1986).

The interplay among materials, water quality, and temperature was investigated at the pilot scale by testing the impact of shower-faucet materials and iron-rust deposits on the growth of *L. anisa* in the absence of any chlorine residual (van der Lugt, 2017). Three types of shower faucets were tested: a faucet with a stainless-steel 304 housing and a ceramic mixer, a brass housing with a ceramic mixer, and a brass thermostatic mixing valve faucet. Increasing levels of positivity were observed for the stainless-steel faucets (14.3 percent), the brass (32.1 percent), and the faucet with the thermostatic mixing valve (85.7 percent), and adding iron rust deposits collected from a building water tank increased the maximum *L. anisa* concentrations observed. These results suggest that thermostatic valves are the faucet type most vulnerable to *Legionella* contamination and that iron corrosion byproducts can enhance the potential for *Legionella* spp. proliferation in faucets.

Several approaches can minimize the impact of thermostatic mixing valves including changing their configuration, placing them as close as possible to the point of use, avoiding all dead volumes such as bypasses, providing ready access for maintenance and cleaning, and selecting valves made of materials that do not support biofilm growth and that can withstand elevated temperatures and oxidants for disinfection. Within thermal mixing valves, integrated check valves prevent backflow into cold- or hot-water feed piping. Unfortunately, some of these check valves are susceptible to breakage and fouling. Their failure results in the mixing of cold and hot water in the piping, which leads to poor service and temperature conditions favorable to the growth of *Legionella* (Boppe et al., 2016). Several guidance documents specify the maintenance and even the installation of backflow valves (Castex and Houssein, 2005). Many guidelines and regulations require the use of thermostatic mixing valves only if needed based on a scalding risk assessment (e.g., Government of South Australia, 2013; HSE, 2013a).[5]

Electronically activated faucets have been linked to greater risk of contamination by premise plumbing pathogens, including *Legionella*, and have been shown to be the cause of several nosocomial outbreaks (Charron et al., 2014; Leprat et al., 2003; Moore and Walker, 2014; Yapicioglu et al., 2011). Sydnor et al. (2012) showed that nearly all electronic-eye faucets were colonized by *Legionella* spp. compared to only 45 percent of manual faucets. More importantly, the electronic-eye faucets were more resistant to disinfection by chlorine dioxide (Sydnor et al. 2012). Importantly, electronically activated faucets typical contain thermostatic mixing valves and flow-reducing devices such as complex aerators. Bacterial colonization of such faucets results from the tepid water temperature, type of materials used, and the lower flows typical of these devices (Charron et al., 2015).

Terminal Tap Water Filters

Different types of terminal filters, often referred to as point-of-use (POU) filters, are available commercially and can be installed either at faucets or retrofitted to showerheads to prevent exposure in high-risk patient care areas. Such filters, typically of 0.2-μm porosity, provide a physical barrier to *Legionella*, are disposable, and are sometimes impregnated with biocides.

[5] See https://www.cdc.gov/legionella/wmp/ monitor-water-guidance.html.

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Management of Legionella in Water Systems

Many studies mention the high cost of these filters, driven by the large number of devices that may need to be installed and their relatively short life (eight to 30 days) before clogging or breakthrough (Marchesi et al., 2011; Sheffer et al., 2005; Zhou et al., 2014). In the same hospital complex in France, three POU shower filter devices showed wide ranges of use before clogging, ranging from three days to more than six months (Lecointe et al., 2010). Some reports show either low-level breakthrough or a return of contamination after one week of use (Vonberg et al., 2005) or 12 weeks (Baron et al., 2014). The time before clogging is dependent on the type of POU device and on the nature of the feed water.

In a cancer center in Pennsylvania, a new extended-life faucet filter ensured total removal of *Legionella* spp. for 12 weeks, exceeding the recommended period of use of 62 days, while mean concentrations at control faucets ranged from non-detect to more than 600 CFU/mL (Baron et al., 2014). A multi-layer design including two pre-filters of 30- and 1-mm porosity resulted in minimal flow restrictions and extended the life of the devices, halving the number of change-outs and associated costs. Recently, an electrically heated carbon nanotube and polymer membrane POU filter were proposed to inactivate any captured bacteria by increasing temperature on the membrane to 71°C to 83°C (Oh et al., 2019). Although this new membrane-interface POU removed 99.99 percent of *L. pneumophila*, further validation is warranted. Extreme care must be taken to ensure that water pressures at POU filters do not exceed manufacturer's recommendations. Pressures in excess of ratings can cause filter media to break away and release contaminated water at the distal device.

Showers and taps have been designed and fitted with UV lamps located immediately before the outlet for microbial control and have been installed in a number of hospitals in the UK (Moore and Walker, 2014), but their efficacy remains to be seen. Using on-site UV treatment on the incoming water main was credited for avoiding any positive detects of *Legionella* in a new hospital and for the lack on any documented Legionnaires' disease in the subsequent 13 years (Hall et al., 2003), although critical information about system hydraulics and other treatment was not provided.

Aerosol Formation Prevention

Aerosol formation is a critical risk factor in the transmission of legionellosis (Hamilton et al., 2018a). Therefore, preventing or reducing their formation can be an effective strategy for managing *Legionella* risk. Laminar flow of water is preferred, as devices that intentionally break the water stream (e.g., shower nozzles, faucet aerators, spray nozzles) can create respirable droplets less than 5 μm (see Figure 4-4; ASHRAE, 2000). Therefore, aerators should be removed from faucets to create a laminar flow (enHealth, 2015). Falkinham (2013) recommends the following to reduce aerosol exposures in the bathroom: (1) replace a showerhead with one that produces water streams (holes larger than 1-mm diameter) rather than a fine mist, (2) replace a showerhead with one that contains a microbiological filter (i.e., pore size less than 0.45-μm diameter) to reduce the proportion of aerosol droplets containing bacteria that can enter the lung, (3) open a window in the bathroom (if possible), (4) replace an inefficient fan with one that exhausts bathroom air rapidly, and (5) minimize the time that bathroom aerosols are created, for example, by shortening showers.

Cooling towers and evaporative condensers incorporate drift eliminators to remove water droplets generated within the units (e.g., CoolClean, 2019; VisTech, 2019). The main purpose of these devices is to collect water droplets on a surface, which then directs the water back to the cooling tower. Newer design standards can reduce the drift to a maximum of 0.0005 percent of the cooling tower flow (Stodlka and Vitkovi, 2016). The humidity of the air, however, can cause larger droplets to be reduced by evaporation to 5 μm or less. At wastewater treatment plants, changes in aeration technology (e.g., use of fine bubble diffusers) or covering the aeration basins can reduce aerosol formation and transport (Prussin et al., 2017).

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Management of Legionella in Water Systems

Standard Aerator
Draws up to 50%
Produces Aerosols
Bacterial growth on screen

Spray Aerator
Produces a small shower
Produces Aerosols
Bacterial growth on screen

Non-Aerated Laminar Flow
Does not mix air and water
Reduced aerosols
No surfaces for growth

FIGURE 4-4 Examples of faucet aerators and impact on aerosol Formation.
SOURCE: https://www.plumbingsupply.com/water-saving-low-flow-aerators.html.

HOW THESE CONTROLS ARE APPLIED TO SPECIFIC SYSTEMS

The strategies discussed above can be applied in various ways to all of the major building water system types for the purpose of *Legionella* control. Table 4-1 provides an overview of the type of controls relevant to particular systems, categorizing them as (1) large engineered systems (potable water supply, wastewater treatment facilities, water reuse systems); (2) building water systems (large buildings, households, green buildings); and (3) other devices (cooling towers, humidifiers, hot tubs). The following sections provide an overview of how the various control strategies are or are not applied to each system in theory and in practice. Legal frameworks and guidance documents addressing these various systems will be covered in Chapter 5. In general, whether a water system presents a potential risk as a *Legionella* source and requires control depends on the following criteria (HSE, 2013b):

- Presence of *Legionella* in the system water;
- Water temperature between 20°C to 45°C;
- The system has the means to create and/or spread aerosols;
- The system stores and/or re-circulates water;
- The system is likely to contain a source of nutrients for *Legionella*, such as contaminants from the surroundings or from the process, including the presence of sludge, rust, scale, organic matter, or biofilm.

Public Water Supplies

Public water supply is an important consideration in *Legionella* management, as the characteristics of the water chemistry will vary seasonally and regionally, depending on drinking water source. The local water supply will be characterized by varying degrees of hardness, corrosivity, and nutrient content, which in turn impacts disinfectants and plumbing materials. Correspondingly, distinct microbiomes

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Management of Legionella in Water Systems

have been noted in controlled premise plumbing pipe rigs as a function of the local water chemistry (Ji et al., 2015).

In theory, public water supplies that already comply with local, state, and federal safe water regulations and implement standard practices, including maintaining a disinfectant residual, hydraulic control via routine flushing, and cleaning of storage tanks, have a strong foundation for controlling *Legionella* risk. The underlying statutes of these regulations and practices were developed to provide protection from a wide range of chemical and microbiological hazards. Because of cold water temperatures and the presence of a disinfectant residual, public water distribution systems are generally thought to harbor low levels of *Legionella*, although there are few data to support this assumption. Continued emphasis on the following elements is essential for reducing exposure to *Legionella* from public water supplies.

Control Options

Disinfection. Most water utilities in the United States strive to maintain a minimum of 0.2 mg/L disinfectant residual in all parts of the pipeline system (AWWA, 2018). The voluntary Partnership for Safe Water program, for example, requires that all member systems use secondary disinfection and that "optimized" systems meet these residual disinfectant goals throughout the distribution system:

- ≥ 0.20 mg/L and ≤ 4.0 mg/L for free chlorine,
- ≥ 0.50 mg/L and ≤ 4.0 mg/L for total chlorine (chloramines),
- ≥ 0.20 mg/L and ≤ 0.80 mg/L for chlorine dioxide.

The goals are to be achieved for 95 percent of the routine readings each month, and individual routine sample sites should not have consecutive residual readings less than the residual disinfectant goal. Additionally, well-run systems specifically target areas known to experience low disinfectant residuals due to the pipe materials (e.g., unlined cast iron mains), long retention times, or water quality characteristics (e.g., organic matter, inorganic chemicals, pH, temperature). In these cases, the stability of the disinfectant residual can be increased by replacing old mains, improving the circulation within the distribution system, or improving treatment processes.

To improve control of *Legionella*, EPA has proposed to review the Surface Water Treatment Rule residual disinfectant requirement for "at least 0.2 mg/L at the point of entry and detectable in at least 95 percent of samples collected within the distribution system."[6] Several papers suggest that disinfectant residuals are lost once water starts to stagnate in premise plumbing (Bédard et al., 2018; Charron et al., 2015; Prévost et al., 1997). Additional research is needed to understand the persistence of distribution system disinfectant residuals within building plumbing. This is important not only for large buildings where it is often assumed that residuals are insufficient to affect *Legionella*, but also for single-family homes and small buildings, where there is little solid information on the persistence of residuals.

Hydraulic Management. Public water systems should have a routine program for systematically flushing and cleaning the distribution system, as over time bacterial growth can be promoted by precipitation of treatment chemicals, settling of fine silt, and corrosion products that form sediments within the pipelines. Implementation of a "uni-directional" flushing program is recommended, during which hydrants are opened near the treatment plant, and water is flushed systematically away from the plant toward the ends of the system; this approach avoids recirculating water from unflushed pipes into the cleaned sections of the system. Application of a hydraulic model is useful to ensure that adequate water pressure is maintained while achieving the targeted velocity (greater than 5 ft/s) (Friedman et al., 2002).

[6] See https://www.epa.gov/dwsixyearreview/six-year-review-3-drinking-water-standards.

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Management of Legionella in Water Systems

Hydraulic management of the distribution system is also important to avoid areas of water stagnation that can result in the loss of a disinfectant residual and the potential for regrowth. Areas of greatest concern are dead-end or dead-leg sections of pipes (e.g., at the ends of a pipeline where there is no circulation), inadequate mixing in storage reservoirs and tanks, and areas of the distribution system with poor circulation. Distribution system hydraulic models can identify these stagnant areas to evaluate options to mitigate. Water circulation is often improved by creating loops in the pipe system, avoiding closed valves, and installation of automatic flushing valves (NAS, 2006).

Like distribution system pipelines, sediments and corrosion products can accumulate in storage tanks, which require periodic inspection and cleaning. *Legionella* spp. have been detected by qPCR in 66.7 percent of municipal drinking water storage tank sediments from 18 sites (Lu et al., 2015). The AWWA Manual M42 (AWWA, 2013) recommends that tanks be drained and inspected at least once every three years or as required by state regulatory agencies. Periodic inspections by operators are recommended more frequently (monthly or weekly) and can be aided by drone technology to alleviate the need for a person to climb the tank. Water quality in the tank can be improved by installation of devices to ensure water circulation and to prevent stratification, stagnation, and loss of the disinfectant residual (EPA, 2002a).

Nutrient Limitation. Nutrient limitation in public water supplies includes reducing nutrients during water treatment, corrosion control, and preventing nitrification in the distribution system. Biological filtration treatment processes (e.g., rapid sand filtration for groundwater treatment and biological active carbon filtration and slow sand filtration for surface water treatment) are pivotal for nutrient removal during drinking water treatment. Controlling corrosion of cast iron pipes in the distribution system prevents iron from leaching into the environment, which can limit growth of *L. pneumophila* because iron is an essential nutrient. Finally, when the chlorine-to-ammonia ratio (4.5:1) is not properly managed in chloraminated drinking water, nitrification can occur, enhancing biofilm biomass and increasing the number of protozoan hosts for *L. pneumophila*.

Plumbing Materials. Most public water supply distribution systems consist of hundreds of miles of cast-iron mains, which will never be replaced in a time frame that would allow for better *Legionella* control. Even where plastic pipes have been installed, metal hydrants, valves, and other appurtenances remain. Pipes, valves, gaskets, coatings, and other materials that contact public drinking water supplies must be approved for use according to NSF/ANSI 61: Drinking Water System Components–Health Effects.[7] Unfortunately, the NSF/ANSI 61 standard does not address the microbial growth potential of materials in contact with water, unlike similar standards in Europe (van der Kooij et al., 2003; Prest et al., 2016 a,b). Further, it is not simple for water utilities to change the materials already present in their distribution systems. However, NSF/ANSI 61 could implement standards to reduce microbial growth on water-contact materials so that utilities have better information in the future.

For many utilities, corrosion control is implemented in compliance with the Lead and Copper Rule (EPA, 1991). However, these procedures may not be sufficient to address corrosion of other metallic materials.

Temperature Control. It is impractical for most public water systems to effect major changes in water temperature in their distribution systems, but there are practices that can be used by some utilities to impact water temperature. For example, intakes can be positioned below the thermocline in some raw water supplies, so that the cooler source water can be withdrawn. In some systems, warm surface waters can be blended with cooler groundwater supplies. Management of water mixing and turnover in elevated storage tanks can prevent water stratification during warm weather and help to control water temperature and disinfectant residual loss (Peter and Routledge, 2018).

[7] See http://www.nsf.org/services/by-industry/water-wastewater/municipal-water-treatment/nsf-ansi-standard-61.

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Management of Legionella in Water Systems

Reclaimed Water Systems

Reclaimed water is municipal wastewater treated to high standards for beneficial use such as drinking water or irrigation water (EPA, 2012). This is a growing practice that presents many advantages, especially reducing water demand in arid and drought-prone regions as well as avoiding negative consequences of unintended, *de facto* reuse (NRC, 2012). A challenge with reclaimed water is that the level of treatment is dictated by the particular application. For direct or indirect potable reuse, the level of treatment often surpasses that for conventional drinking water treatment. In these instances, the control measures for *Legionella* would be similar to those outlined above for public water systems.

Reclaimed water treated for unrestricted reuse refers to non-potable water used where public access is not restricted. Water classified for unrestricted urban reuse is commonly applied for spray irrigation on parks, playgrounds, schoolyards, and residences, and for other applications such as toilet flushing, air conditioning, fire protection, construction, ornamental fountains, and other water features. *Legionella* has been routinely detected in many unrestricted reuse systems (Ajibode et al., 2013; Birks et al., 2004; Buse et al., 2015; Garner et al., 2018; Jjemba et al., 2010; Johnson et al., 2018). These systems typically do not maintain a disinfectant residual nor are they routinely flushed or cleaned. Jjemba et al. (2010) described the characteristics that contribute to the growth of microbes in reclaimed water distribution systems, including warm temperatures, elevated levels of biodegradable organic carbon and other nutrients, loss of disinfectant residuals, and variable use patterns that lead to stagnation and depressurization, among others. A recent survey of four reclaimed water distribution systems indicated elevated *Legionella* gene markers at the point of use, compared to paired potable water systems monitored in the same study (Garner et al., 2018). Brunkard et al. (2011) reported one outbreak of Legionnaires' disease associated with use of reclaimed water at a mass-transit vehicle washing station. Hamilton et al. (2018a) reported that risks of *Legionella* exposure from reclaimed water used for irrigation or cooling towers could exceed 10^{-4} annual risk of infection for various scenarios. A review by Garner et al. (2016) highlighted that reclaimed waters are very different from traditional potable waters in terms of water quality, conveyance practices, exposure routes, and health risk. Because distinct water chemistries could place reclaimed water plumbing in uncharted territory for *Legionella* control, the authors call for water quality management guidelines and regulations more specifically tailored to recycled water. Jjemba et al. (2015) reported on best management practices (BMPs) for maintaining water quality in reclaimed water systems (see Box 4-1). Many of these BMPs are similar to those mentioned for public water systems (e.g., optimizing water age, managing storage, corrosion control, biofilm control, etc.), but managing risk of inhalation, rather than ingestion, needs to be emphasized.

Treating recycled water for purposes of direct potable reuse is gaining momentum. For example, a 2 million gallon per day direct potable reuse plant in Big Spring, Texas, treats wastewater to drinking water standards via microfiltration, reverse osmosis, and UV disinfection before blending with raw drinking water sources and routing to a conventional drinking water treatment plant (Trussell et al., 2015). Given that such an approach meets current drinking water standards, there should not be any special concerns related to *Legionella* beyond that of a typical municipal water supply. Nonetheless, out of an abundance of caution, efforts are underway to understand how blending of direct potable reuse water with conventional water supplies and treatments may adversely affect distribution systems via corrosion and other processes (Water Research Foundation, 2018). A pilot-scale survey following incubation of a range of direct potable reuse blends from different utilities in PVC pipe over eight weeks indicated only rare detection of *Legionella* spp. gene markers by qPCR (Garner et al., 2019). While this result is encouraging, longer-term studies and monitoring are recommended as municipalities begin blending direct potable reuse water.

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BOX 4-1
Best Management Practices for Reclaimed Water Systems

1. Optimizing reclaimed water storage
2. Minimizing the impact of reclaimed water corrosivity
3. Improving customer perception
4. Managing reclaimed water total dissolved solids (TDS)
5. Controlling algae in reclaimed water reservoirs and distribution systems
6. Managing snails and other macroorganisms in reclaimed water
7. Minimizing regrowth, odor and biofilms in reclaimed water systems
8. Monitoring of cross-connection control
9. Managing reclaimed water age to enhance quality and operational bottlenecks
10. Ensuring pressure sustaining reclaimed water systems
11. Staying within reclaimed water turbidity targets
12. Operational management of reclaimed water supply and demand challenges
13. Monitoring the distribution system
14. Considering emerging contaminants in reclaimed water

SOURCE: Adapted from Jjemba et al. (2015)

Wastewater Treatment Plants

Wastewater treatment plants, especially those with biological treatment processes, can be a source for *L. pneumophila* (Caicedo et al., 2019). What measures can be taken to control legionellae depends on the treatment process in the wastewater treatment plant. For example, certain aerosol-producing installations at treatment plants (e.g., air scrubbers) can be controlled by disinfection using hot steam or hypochlorite treatment (Olsen et al., 2010). Norway is one of the few countries where control measures for aerosol-producing devices in wastewater treatment are regulated.

In most outbreaks involving wastewater treatment plants, the biological treatment process is identified as the main cause for *L. pneumophila* growth (Caicedo et al., 2019). Control measures that are normally taken against legionellae (e.g., thermal control, chemical disinfection) are difficult to implement in biological treatment processes because these control measures will also eradicate the microorganisms that treat the wastewater. In addition, laboratory experiments have shown that disinfection of wastewater effluent with chlorine dioxide, hydrogen peroxide, silver ions, ozone, and alkalinization did not result in reduction of cultivable legionellae (Noguiera et al., 2016). As a result, alternative control measures have been implemented at plants that have been identified as the source for an outbreak of Legionnaires' disease or Pontiac fever. At locations where only workers became infected with *L. pneumophila*, workers were required to wear respirators that prevent inhaling of aerosols and/or prevent use of *L. pneumophila*-contaminated waters for cleaning purposes (Castor et al., 2005; Gregersen et al., 1999; Kusnetsov et al., 2010).

Different control measures have been taken at wastewater treatment plants where the biological treatment process (e.g., an aeration pond) was identified as the source for *Legionella* infection among residents who live in the vicinity of the plant. One example is a plant in Norway that treated wood refinement waste. As the ultimate infection control measure, this plant was shut down, but its organic content was then released into the river (Borgen et al., 2008). During a large Legionnaires' disease outbreak in Warstein, Germany, several control measures were implemented at the biological wastewater treatment

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Management of Legionella in Water Systems

plant that was the primary source of the outbreak (Noguiera et al., 2016). UV was installed to treat the effluent before it was discharged into the river, which resulted in a 1.6- to 3.4-log reduction of legionellae in the effluent (from about 10^6 CFU/L to about 10^4 CFU/L). Second, the aerobic pre-treatment process was stopped, which resulted in a significant decrease of *L. pneumophila* in the wastewater (to 10^2 CFU/L) and in the effluent (below the detection limit). Finally, measures were taken to reduce aerosol emission from the wastewater treatment plant, although these measures were not specified. In the Netherlands, control measures at two biological treatment plants that were involved in small outbreaks of *L. pneumophila* focused on preventing aerosolization from the aeration ponds to the open air. This was done by successively erecting tents to cover the aerated ponds in combination with ventilation to prevent overpressure in the covering tents (Loenenbach et al., 2018).

Large Buildings

Large buildings include most hospitals and many long-term care facilities, as well as apartment complexes, hotels, offices, high rises, schools, prisons, and industrial complexes. *Legionella* is inherently more difficult to manage in larger building water systems because the plumbing networks are correspondingly larger and subject to more variability, making it more challenging to ensure that controls are adequately supplied throughout the building. The extended stagnation periods experienced by water in large building premise plumbing place these systems at further risk. Thus, *Legionella* management in large buildings tends to focus on thermal control (Bédard et al., 2015; Boppe et al., 2016) or on-site disinfection. Any controls that have been emplaced on the municipal water supply up to the property line, e.g., a minimum chlorine residual of 0.2 mg/L, are unlikely to provide reliable protection throughout a large building plumbing network.

Another challenge is that large buildings often require substantial water storage for water security purposes. However, during storage the water quality can degrade substantially, posing problems in times of need. Large buildings also often employ potable or recycled water for other purposes, including humidifiers, landscape irrigation, decorative fountains, hot tubs, swimming pools, and cooling towers to manage extensive HVAC needs. In this section the emphasis is on piped potable water used for drinking and bathing, though general principles apply to other piped water systems. Cooling towers, humidifiers, and hot tubs are discussed in separate sections.

Design and commissioning of a large building is a key opportunity to ensure that *Legionella* control is prioritized, including appropriate design and implementation of hot- and cold-water systems and HVAC features. Further, large building water systems should be configured to facilitate collection of water for *Legionella* monitoring as well as implementation of maintenance and remediation (e.g., sampling and injection ports on hot-water lines). Hospitals or other buildings where sensitive populations are housed should be designed to facilitate remediation in the case of contamination by *Legionella* or other pathogens. Unfortunately, in reality the majority of existing large buildings were not designed in this manner and present numerous complex challenges for *Legionella* control.

Much of what has been learned to date about management of *Legionella* in large buildings comes from hospitals. Table 4-5 summarizes long-term hospital experience with various combinations of disinfection and thermal regimes, including long-term studies (up to ten years) with extensive monitoring to support findings. From these data, the two controls that emerge as being most broadly effective are (1) temperature set points of greater than 60°C at the water heater and greater than 55°C in the recirculation loop and (2) chloramine as an on-site disinfectant. Combining elevated temperature with addition of disinfectants yielded the best results in some cases.

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TABLE 4-5 Long-term Hospital Experience Using Multiple Strategies for the Control of *Legionella*

Type of facility	Permanent regime	Shock disinfection	Targets	Findings	References
Hospital with 1,077 beds 9 years	ClO_2 for greater than 9 years Chloramines – 26 weeks	None	*Legionella* spp. and Mycobacterium avium complex (MAC)	ClO_2 for greater than 9 years reduced *Legionella* positivity to 51% but with high concentrations (greater than 10^5 CFU/L) remaining at some sites. Chloramines at 2 mg/L for 26 weeks reduced all sites from greater than 10^3 CFU/L to non-detect but increased positivity for MAC.	Casini et al. (2014)
Hospital with four circuits (A-D) 5-18 years with *Legionella* contamination	A: >55°C -60°C B: >65°C one day per quarter C : A&B + chlorine D: chlorine	A. 30-min 70°C heat shock twice per year B. three 30-min 70°C heat shocks, then none C. none D. chlorine	*Legionella* spp. and *L. pneumophila*	Frequent heat-shock treatment (65°C) develops temperature resistance in some *Legionella* strains. The combination of maintaining 65°C one day per quarter combined with chlorine was more efficient than repeated heat shocks at 70°C.	Allegra et al. (2011)
Hospital with three wings	ClO_2 two types reactors– 1 year Chloramines – 1 year	ClO_2: 0.6 to 0.9 mg/L Chloramines: 2 mg/L and 3 mg/L	*L. pneumophila* and *Pseudomonas aeruginosa*	ClO_2: positivity went from 100% to 57-61% ClO_2 less effective for *L. pneumophila* sg1 With chloramines, quick (<1 month) and large reduction in # positive sites and concentrations of *L. pneumophila*. 2 mg/L chloramines: < 100 CFU/L for *L. pneumophila*; 3 mg/L chloramines: below detection limit for *L. pneumophila*. Both disinfectants reduced *P. aeruginosa*.	Marchesi et al. (2012)
Two hospitals A: 255 beds B: 450 beds	A: sub-optimal thermal regimes and Cu-Ag ionization B: suboptimal thermal regime	None	*Legionella* spp. *L. pneumophila*	Need for online temperature monitoring for system characterization Large differences between sectors Poor thermal regime results in greater *Legionella* and *L. pneumophila* prevalence Framework for risk analysis using temperature profiling	Bédard et al. (2015)

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TABLE 4-5 Continued

16 hospitals 5 years	Cu-Ag ionization	50% used superheat/ flush and 31% used hyperchlorination	*Legionella* spp. *L. pneumophila* sg1 *L. pneumophila* sg2-14	50% of sites reported zero positive samples in the years after implementation 5% hospitals reported cases of nosocomial legionellosis (from 100% before)	Stout and Yu (2003)
Hospital with 450 beds 11 years	Increasing temperature from 45°C to 65°C with distal temperature of 56°C - 61°C for 5 minutes after outbreak	Weekly flushing of all taps and showers at 65°C for 5 minutes over 18 months	*Legionella* spp. *L. pneumophila* sg1 *L. pneumophila* sg2-14	Striking decrease from ~100% to less than 20% samples positive with lower concentrations of *L. pneumophila* sg1 (<500 CFU/100mL) Increasing temperature arrested Legionnaires' disease outbreak, but four cases occurred during 10 years even with only 5% positivity.	Darelid et al. (2002)
Two hospitals A: 364 beds B: 672 beds 2 years	ClO_2 dosages of 0.5-0.7 mg/L in cold water	Not specified	*Legionella* spp. Heterotrophic plate counts	Reduced positivity from 60% to less than 10% Increased again after 2 years Decreased heterotrophic plate counts	Zhang et al. (2009)
Hospital with 1,266 beds	Target dosages of Cu/Ag 0.2/0.02 mg/L Cu/Ag concentrations at distal sites mean 0.16/0.014 mg/L	2 superheat/flush treatments	*Legionella* spp.	Positivity in intensive care units of 14% and 66% after two superheat/flush treatments Low Cu-Ag dosages were not effective Increased Cu-Ag dosages lowered positivity to 0-5% No nosocomial cases after implementation	Chen et al. (2008)
Hospital with 765 beds	ClO_2 dose of 0.3 mg/L distal concentration for 9 years Monochloramine at 3 mg/L for one year	Superheat (>60°C) for 2 days, 8 times in 4 years Hyperchlorination (20-50 mg/L) for 1-2 hours, 12 times in 8 years	*Legionella* spp. *L. pneumophila*	Superheat treatment led to an insignificant temporary reduction Hyperchlorination effective for 2 months ClO_2 reduced positivity from 97% to 54% *Legionella* spp. but less for *L. pneumophila*	Marchesi et al. (2011)
57 buildings	Conversion from free chlorine (0.6 mg/L) to monochloramine (1.9 mg/L) in the distribution system Only 13% of water heaters >60°C	None	*L. anisa*, *L. bozemanii*, *Legionella* spp., *L. pneumophila* sg1 and 2-14	Increased *Legionella* colonization was observed in buildings with temperature less than 50°C Chloramines strikingly (60% to 4%) and rapidly (<3 months) reduced the percentage of sites positive for *L. anisa*, *L. bozemanii*, *Legionella* spp., *L. pneumophila* sg1 and 2-14	Flannery et al. (2006)

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Management of Legionella in Water Systems

Control Options

Temperature Control. Maintaining a high water temperature (ideally greater than 60°C) in hot-water lines is the primary line of defense against *Legionella* in large buildings. This can be accomplished in part by installing multiple water tank heaters. Recirculating lines are also commonly employed to ensure delivery of hot water throughout the building. Recirculating lines are susceptible to heat loss and can readily fall into the ideal temperature range for *Legionella* growth if not maintained at a sufficiently high temperature (Brazeau and Edwards, 2013a,b,c). This can be avoided by insulating recirculating pipes (as required in Canadian building codes for large buildings) and making sure the recirculating velocities are sufficiently high. Recently, the California Exchange Commission has mandated insulation of hot-water lines (CEC, 2019). Despite the challenges mentioned above, maintaining water above 55°C across the whole system in large buildings with multiple recirculation loops can be done at relatively low cost (Bédard et al., 2015, 2016). Successful and low-cost hospital interventions have shown that poor temperature maintenance can be corrected by removing dead-end pipes, inadequate heat exchangers, and faulty thermostatic valves that can cause flow inversions and mixing with cold water (Bédard et al., 2016; Boppe et al., 2016; Lecointe et al., 2018).

Likewise, temperatures of cold-water lines can also increase into the *Legionella* growth range, particularly in warm climates and as water makes its way through extensive distal plumbing within the warmer building envelope. In such cases, cold-water line flushing and pipe insulation to minimize heat transfer to the cold-water piping can help. In a study of a major hospital in Germany, the cold-water lines were as contaminated with *Legionella* as the hot-water lines, and 35 percent were positive, even at sites where the measured temperature was less than 20°C (Arvand et al., 2011).

Disinfection. As mentioned previously, disinfectant residuals from the distribution system may not persist in the premise plumbing of large buildings. Hence, many hospitals and long-term care facilities in particular have found on-site disinfection to be highly beneficial. Disinfectant can be added at a constant level to manage *Legionella* risk, or it can be increased in response to elevated *Legionella* numbers or an outbreak. Low doses of disinfectant are often an effective preventative measure, but much higher doses are required for remediation purposes (see Table 4-5). Disinfection systems are typically added to hot-water lines to avoid any concerns with human consumption, as hot-water lines are not intended to produce water for ingestion, but they can be added to cold-water lines as well. Popular disinfectants for this purpose include chloramine, chlorine, copper-silver ionization, and chlorine dioxide. However, it is important to be aware of the local water chemistry, pipe materials, and other constraints of relying on such disinfectants (Rhoads et al., 2014). For example, iron plumbing components can reduce the chlorine residual by stimulating its decay. During a major Legionnaires' disease outbreak at an Illinois veteran's home in Quincy, reaction of on-site chlorine addition with old iron pipes delivering water throughout the campus significantly depleted chlorine residual (Rhoads et al., 2018). Copper-silver can also lose its efficacy and fail to be delivered appropriately, for example, by plating onto pipe surfaces instead of maintaining dissolved form, if installed incorrectly, or if the water chemistry is incompatible (Triantafyllidou et al., 2016; Walrayen et al., 2016). Chloramine is probably the most popular on-site disinfectant, but its decay can be accelerated by nitrifying microorganisms, which happen to thrive in a similar warm temperature range as *Legionella*. UV can also be applied, but it may be most effective at the point of use since it does not leave a disinfectant residual.

Hydraulic Management. Fundamental to reducing *Legionella* risk is managing the hydraulics of the plumbing system to ensure delivery of both hot water and disinfectant. As discussed previously,

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Management of Legionella in Water Systems

recirculating lines are commonly employed to achieve this purpose. Aside from temperature and disinfectant delivery, maintaining a low water age itself is a key aspect of hydraulic design. Installing flushing devices can help alleviate other water age issues, such as taste, odor, microbial growth, and nitrification (Nguyen et al., 2012). Dead legs and other flow anomalies must be avoided at all cost. For extremely large buildings or other situations where it is difficult to control water age, automatic flushing devices and programs may be beneficial as a routine maintenance or remedial measure. There is no consensus on the optimal frequency and duration of flushing for efficient *Legionella* control, but evidence clearly demonstrates that the use of frequent (one minute every two hours) automated flushing of hot-water taps with low use or poor recirculation (dead-ends) can eliminate *Legionella* positivity (Darelid et al., 2002; Totaro et al., 2018).

Distal Devices and Aerosol Control. Even with maintaining water temperature and disinfectant levels in hot-water lines, it is critical to consider the mode of delivery at the fixture. Benefits and susceptibilities of various faucets and means of delivery were discussed in a previous section. Low-flow fixtures have been promoted to both conserve water and in some cases energy. However, as a consequence of their lower flow, these fixtures, primarily faucets but also showers, increase water age and restrict disinfectant levels, including the disinfection provided by elevated water temperatures. As such, low-flow fixtures present a greater risk for *Legionella* development in the distribution systems that feed them. Low-flow fixtures should be restricted from use in hospitals and long-term care facilities due to their high-risk occupant populations.

As previously discussed, faucets with a "hands-free" designs, including automatic sensors and foot pumps, do not reduce microbial risk (Sydnor et al., 2012). Compared to traditional fixtures, these designs tend to have higher surface area for biofilm formation and are more conducive to *Legionella* growth. The same is true of the thermostatic mixing valves that produce warm water to enhance the comfort of the hand-washer. Faucet and fixture selection is a key decision, as these are typically installed as a building-wide standard.

In extreme cases where *Legionella* growth is uncontrolled and patient populations are extremely sensitive, size exclusion point-of-use ultrafilters can be installed. These will effectively remove *Legionella* from the water at the tap. However, such filters are quite costly and not a sustainable long-term solution. Selecting a device that can function with the incoming water quality, as well as proper installation and maintenance, are key to ensuring cost-effective use and efficacy (Baron et al., 2014).

Households

Households are a poorly understood source of *Legionella* that may contribute to the large percentage of legionellosis cases known to be sporadic (see Chapter 3; Adams et al., 2015; McClung et al., 2017; Shah et al., 2018). While water use in the home is generally more consistent than in public buildings, old piping (e.g., galvanized steel), dead legs, and low-use locations can all provide the opportunity for *Legionella* growth. Additionally, most home hot-water heaters are set at temperatures to limit the risk of scalding but are within the range for *Legionella* growth (see Table 4-3). Travel, hospitalization, home construction and remodeling, and other events that restrict water use can lead to potential opportunities for *Legionella* to proliferate in household water systems. Finally, there is the potential for *Legionella* growth in devices found in homes that are in contact with water, including humidifiers, nebulizers, and hot tubs. Given all of these potential sources of contamination, a key risk prevention strategy at the household level is communicating the risks of *Legionella* to immunocompromised individuals and to those who purchase devices for in-home use that could create aerosols containing *Legionella*.

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Management of Legionella in Water Systems

Households may be served by a public water supply or by private wells. An estimated 13 million households rely on private wells for drinking water in the United States (U.S. Census American Housing Survey, 2017 data[8]), but EPA regulations do not apply to these private systems. Little information is available about occurrence of *Legionella* in private well water (Stojek and Dutkiewicz, 2011). Well water is not routinely disinfected, which could potentially leave well owners more susceptible to *Legionella*. For example, in a large field study of 255 domestic water heaters, those fed by a groundwater source distributed without any treatment were more often positive (46.3 percent) than water heaters supplied by surface water sources with residual chlorine (26.2 to 27.5 percent) (Dewailly and Joly, 1991). Most groundwater supplies in the United States would be considered low risk because of their cold temperature, but there are areas of the country where groundwater may be warm enough to support *Legionella* growth (Riffard et al., 2001). However, for most private systems, management of *Legionella* risk is mainly associated with managing the hot-water system and the devices in the home that come into contact with water and produce aerosols, as described below for typical households. Intrusion of soil and other contamination that could contain *Legionella*, particularly as a result of major weather events, also require attention. Well owners are given general guidance on how to remediate such intrusion events, typically by addition of bleach (i.e., chlorination) as a shock treatment. Specific guidance on *Legionella* control is needed for well owners, especially for immunocompromised individuals.

Control Options

Most of the strategies summarized in Table 4-1 could play a role in managing *Legionella* in households, though homeowners seldom implement them formally.

Hydraulic Management. To prevent biofilm growth and exposure to *Legionella*, homeowners are recommended to perform several maintenance activities, including the regular flushing of sediments from hot-water tanks and cleaning of faucet aerators, showerheads, hot tubs, nebulizers, evaporative cooling fans, and humidifiers (Leoni et al., 2018). Guidance is also provided in a recent Water Research Foundation report (#4664—Customer Messaging on Plumbing System Issues) that developed materials for water utility websites.[9]

Because smaller-diameter pipes are found in buildings and homes, premise plumbing is particularly prone to growth of biofilm bacteria and resulting water quality problems. Although there are no ways to reduce the nutrient content of water entering premise plumbing, other strategies can be employed to control biofilm growth, including flushing pipes to reduce water age and deliver disinfectant residuals throughout the home. Indeed, one hypothesis for traveler's associated Legionnaires' disease is that the individual is exposed to stagnant plumbing upon returning home (Verhoef et al., 2004). After prolonged absence, flushing should be considered as a preventive measure since stagnant water may have high concentrations of bacteria including *Legionella*, bad taste and odor, no disinfectant residual, and elevated concentrations of metals such as copper and lead.

Temperature Control. Elevating water heater temperatures is an obvious household intervention, though this can be restricted by building codes, which vary from state to state. For highly elevated water temperatures, the scalding risk may also not be worth the trade-off for certain elderly or less mobile individuals. Also, for many reasons delivery of hot-enough water temperatures to the point of use can be a problem in households just as it is for hospitals and hotels. Water in households typically sits

[8] See https://www.census.gov/programs-surveys/ahs/data/interactive/ahstablecreator.html.
[9] See http://amwater.com/corp/legionella-homeowners.

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Management of Legionella in Water Systems

stagnant during the day, and homes can be vacant for long periods during vacations. As discussed previously, the choice of hot-water heater design is also important to minimizing the risk of legionellosis.

Distal Devices. *Legionella* can be amplified at distal sites such as faucets and showers in the household. Selecting faucets to minimize the potential for *Legionella* growth can be achieved by selecting simple designs without electronic activation and only with mixing valves if needed. If thermostatic mixing valves are justified for scald prevention, then models with the valve integrated to the body of the faucet with minimal volumes of tepid water would offer a lower risk (Charron et al., 2015).

Reverse osmosis units are not uncommon at the household level and can be installed as whole-house POU filters. Based on size exclusion, *Legionella* should be eliminated after passing through reverse osmosis. However, household filters, including reverse osmosis units and carbon black filters, can also remove disinfectants. Thus, if applied at the whole-house level, they could potentially leave downstream plumbing at risk of colonization. Carbon black filters, which are typically applied as faucet mounts or used in filters for water directly intended for drinking or cooking, provide surface area for microbial growth and result in elevated HPCs. A study by the World Health Organization indicated that there was no measureable human health risk associated with increased HPCs from POU filters (Hunter, 2003).

Disinfection. On-site disinfection is likely unrealistic for most homeowners although chlorination is commonly recommended to well owners for remedial purposes. Point-of-use UV units are gaining in popularity, for example, under sinks where drinking water is drawn and as part of refrigerator-dispensed drinking water. Such units need to be evaluated in terms of efficacy for *Legionella* control and most effective placement.

No national recommendations have been developed to help protect individual households from legionellosis. However, some studies have recommended steps to limit potential exposures to *Legionella* (e.g., Pedro-Botet et al., 2002). Much of the effort for homeowners focuses on water temperature and water flow during periods of decreased use. Increasing the water temperature in households to 60°C (140°F) can help limit *Legionella* growth in home hot-water systems, but must be weighed individually against the risk of scalding and burns. Tankless, on-demand hot-water heaters may provide an opportunity to limit the amount of water that is at risk and may have higher disinfectant residuals (Brazeau and Edwards, 2013b). Prevention of water stagnation while residents are not at home, such as flushing the taps at least weekly, may help to prevent *Legionella* growth. Alternatively, homeowners can decrease water-heater temperatures to levels that do not promote *Legionella* growth when they expect to be away from home for prolonged periods; this may be less effective in areas where normal ambient summer temperatures are high. For immunocompromised or high-risk individuals, additional measures such as POU filters for sinks and showerheads can be considered (Baron et al., 2014). Use of humidifiers, particularly those using water misting, should be discouraged among higher-risk patients (Hines et al., 2014; Yiallouros et al., 2013).

Cooling Towers

Heating, ventilation, and air conditioning (HVAC) systems are designed to condition and to distribute air to provide a comfortable indoor environment. HVAC systems can be a source of *Legionella* infections because they have abundant water and can disseminate *Legionella*-contaminated aerosols (Aaron, 2017). Within HVAC systems the two most likely sites to harbor *Legionella* are the humidification

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Management of Legionella in Water Systems

and the cooling equipment. This section deals exclusively with cooling equipment, while the following section deals with humidifiers.

Evaporative heat transfer devices such as cooling towers and evaporative condensers are used to dissipate waste heat from the condenser of chillers providing air conditioning to a building. There are two basic types of evaporative heat transfer devices—a direct-contact device that exposes water directly to the cooling atmosphere, and a closed-circuit device that involves indirect contact between the heated fluid and the atmosphere. Their construction and operation are extensively detailed in documents by various organizations (such as the Cooling Technology Institute; ASHRAE, 2016).

Open and closed recirculating wet and wet/dry cooling towers may show some emissions because of drift and volatilization. Plume formation can be important in open and closed wet cooling towers when air with a high moisture content leaves the cooling tower, mixes with the atmosphere and begins to cool down. Both wet and wet/dry device types can be sources of *Legionella* infections due to their large use of water, their operating temperature, and their capacity to generate aerosols.

The single most important component of a cooling tower is the fill or heat-transfer surface, as different geometries and fill materials affect the heat rejection rate. Fills are susceptible to fouling, scaling, and microbiological growth (DOE, 2011). Within the water distribution and mechanical components of cooling towers, polypropylene, acrylonitrile butadiene styrene, and fiberglass-filled nylon have largely supplanted the bronze nozzles of earlier cooling towers, and PVC and fiberglass piping have replaced most iron and steel piping. Therefore, the materials typically used now are resistant to corrosion, erosion, and microbial growth (SPX, 2009).

Cooling towers are usually situated outdoors and open to the elements. This location makes them popular for birds and bugs to live in or around and susceptible to dirt and debris carried by the wind, providing nutrient sources for microorganisms in the system (DOE, 2011). A variety of microorganisms can grow in cooling towers during the course of normal operation, which involves water temperatures ranging from 29°C to 35°C (ASHRAE, 2000). Bacteria can grow in condensers and in the cooling tower fill, while algae can grow on wet cooling tower components exposed to sunlight. Biofilms are frequently found in chiller bundles, on the surfaces of heat exchangers, and in the system's piping (DOE, 2011).

By design, cooling towers use a significant amount of water, as they dissipate heat by evaporation. Geographic and climate concerns such as water availability or sewer usage restrictions may dictate unusually elevated water recirculation needs for the heat rejection equipment. However, the increased cycles can increase the concentrations of metals, minerals and contaminants (SPX, 2009).

Control Options

Control options in cooling towers are somewhat limited and based primarily on the use of disinfectants to prevent microbial growth. Materials selection during cooling tower design and construction can also affect whether the tower becomes a site of *Legionella* amplification. A major preventive strategy when cooling towers are not in use is to recirculate the water. Finally, though not traditionally considered as a control for cooling towers, future cooling tower designs using elevated temperatures could aid *Legionella* prevention.

Disinfection. Chlorination and hyperchlorination are commonly used chemical treatments to limit microbial growth in cooling towers, although numerous chemical disinfection methods have been used (Kim et al., 2002). However, these treatments generally do not completely eliminate the *Legionella*. If the treatments are discontinued, recolonization can occur after a lag period sometimes as short as two weeks. For example, Iervolino et al. (2017) showed the recolonization by *Legionella* of hyperchlorinated

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Management of Legionella in Water Systems

cooling towers can take place within weeks or months of the initial treatment. Paranjape et al. (2019) found that continuous chlorine application in a cooling tower reduced microbial diversity and promoted the presence of *Pseudomonas,* creating a non-permissive environment for *Legionella* spp.

Silver and copper ions have also been used in cooling towers to control bacterial growth (Lin et al., 2002). In a study by Martinez et al. (2004), a chlorine concentration of 0.3 parts per million (ppm or mg/L) was combined with 200 parts per billion (ppb) of silver (Ag) and 1.2 ppm of copper (Cu). This method had an appreciable impact on levels of coliform bacteria, iron-related bacteria, sulfate-reducing bacteria and slime-forming bacteria in a cooling tower.

Constant use of a single biocide can promote the establishment of a treatment-resistant microbial community in the cooling system. The typical solution for this problem is to routinely alternate between two or more biocides. However, the use and handling of toxic biocides should be evaluated to prevent overexposure of the maintenance workers and the building occupants.

Chemical-free water sterilization methods such as ozone and UV light have also been used sporadically in cooling towers. Ozone is considered to be effective against microbial contamination at a concentration of 0.2 to 1.0 mg/L. However, ozone gas is harmful to humans and must be handled carefully to avoid human overexposure. Furthermore, incorrect implementation can hamper the smooth operation of the cooling system. Of the half million or more cooling towers in the United States, it is estimated that only 300 to 1,000 use ozone. Likewise, UV has not been widely accepted for cooling tower use because of scaling of the UV system and issues arising from improper application of the technology (Rossman, 2003). The efficiency of these technologies either by themselves or in combination with other water treatments remains to be proven.

Cooling Tower Materials. An important element in controlling biofilm growth within cooling towers are the materials selected for the construction of the heat rejection equipment. In reality, the equipment purchase specifications are mostly concerned with the performance and economics of the cooling tower operation. A study by Türetgen and Cotuk (2007) found that heterotrophic plate counts and *L. pneumophila* concentrations on galvanized steel were significantly higher than on six other construction materials used in a cooling tower (i.e., copper, stainless steel, polyvinyl chloride, polyethylene, polypropylene, glass). Corrosion-proof and anti-microbial resins are now being used for cooling towers (Sullivan, 2018). In selecting materials for cooling towers, not only is the bacterial growth potential of materials important, but also the performance and longevity of the materials in terms of how they are affected by the selected chemical and non-chemical treatments.

Temperature Control. Temperature control in cooling towers is not generally considered to be an option because the temperature rise in a condenser or heat exchanger will increase the potential for calcium carbonate scaling, which can damage the fill materials. Indeed, most fill materials cannot be utilized in temperature applications above 49.9°C to 51.7°C (120°F to 125°F). However, given the proven efficacy of raising potable hot-water temperatures to 60°C (140°F) to control *Legionella*, the Committee suggests that refrigeration, HVAC, and cooling tower manufacturers collectively design and develop new systems that can operate at condenser water temperatures whereby the temperature going to the cooling tower will be greater than 60°C. In this proposed conceptual system, the condenser water temperature coming from the refrigeration equipment or chiller would be 65°C to 70°C and travel first to a reheat heat exchanger. By heating the reheat water in the heat exchanger, the water temperature would drop to 60°C before transport to the cooling tower, dropping the temperature to 55°C and then back to the refrigeration equipment or chiller. At such operating temperatures *Legionella* would be unlikely to survive.

Such designs would require additional energy consumption to increase the corresponding refrigerant gas pressures and temperatures to heat the condenser water to such levels. However, additional heat,

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Management of Legionella in Water Systems

in excess of the temperatures required, could be removed by a heat exchanger and used for the building's reheat water system, increasing the overall efficiency. Finally, the creation of cooling towers that could withstand such temperature increases could potentially reduce the need for chemical biocides.

Humidification Equipment

In both residential and commercial buildings, humidification equipment uses water to cool and humidify the air. These units come in two basic types. Isothermal units such as steam humidifiers use energy to produce a steam vapor and are considered non-aerosol-generating. On the other hand, adiabatic units allow direct contact between the water and the airstream, producing aerosols. Certain adiabatic units, such as atomizers or spray humidifiers, introduce water droplets directly into the airstream. Other adiabatic units, such as evaporative units and air washers, are considered non-aerosol-generating because the process only involves air absorbing the moisture as it passes over a pan or wetted device (ASHRAE, 2016).

Different designs of humidifiers have different levels of risk for *Legionella* growth (BMEC, 2009). Steam releasing-type humidifiers convert water to vapor that is then discharged into the selected space. Because of the high temperatures involved, and the fact that water droplets are not generated, this design is not considered a high risk for *Legionella* growth. Vaporization devices or direct evaporative coolers use a porous substrate to provide an extended surface area for water evaporation. The water is either circulated over the media or the media are rotated through a water bath. Thus, no water droplets are produced that could be contaminated with *Legionella* bacteria. The water used tends to be maintained at temperatures below the *Legionella* growth temperature range of 25°C to 43°C.

On the other hand, water spray devices such as misters, air washers and spray humidifiers can produce aerosols through the use of ultrasonic vibrators, spinning disks, or spray nozzles. When their source water comes directly from the building's cold-water supply or if the source water has been sent through reverse osmosis, these humidifiers can be used safely. However, when the source water is in holding tanks or in the pipes exposed to heat, the temperature of the water can reach 25°C to 43°C, a range that supports *Legionella* growth. Ultrasonic humidifiers and centrifugal sprays are thought to be most susceptible to *Legionella* contamination (BMEC, 2009). To limit the risk of legionellosis, these devices should be avoided for use in new buildings. Existing units of these types are recommended to be replaced during building renovation projects (PWGSC, 2013).

Regarding portable humidifiers, a review of the literature indicates that most of the disease transmission associated with these units is due to aerosol producing humidifiers, i.e., ultrasonic and impeller units. Generally, the disease transmission is because the humidifiers were not properly cleaned or disinfected (Public Health Ontario, 2017). The appropriateness of allowing bedside humidifiers in institutions housing patients and residents who are more vulnerable to respiratory disease has been a topic of considerable debate.

Control Options

Disinfection. There are limited chemical treatment options to reduce or eliminate *Legionella* bacteria from humidification systems. This is because the chemicals have the potential to be discharged into

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Management of Legionella in Water Systems

HVAC air distribution systems and ultimately be inhaled by the building's occupants. Water treatments such as softening and demineralization address the quality of the supply water necessary for the operation of the equipment but not the potential for microbial growth. Several Korean studies found that the use of disinfectant chemicals directly in the water of personal humidifiers has caused interstitial lung disease in children (Park et al., 2014, 2017; Pickering, 2014). Other water treatments, such as the use of UV or photochemical ozone generators instead of chemicals, have been considered (ASHRAE, 2000). Regular monitoring is needed to determine whether these treatments remain effective (HSE HSG 274, 2013c).

Temperature Control. Water storage temperatures for all HVAC equipment are recommended to be either above, or below, the 25° to 43°C range where *Legionella* thrives.

Hydraulic Management. Rigorous maintenance of humidification equipment is critical including regularly scheduled maintenance of the system, avoidance of water stagnation in the water tanks, pans, and basins, and use of water treatment where necessary. If these precautions are not feasible, the equipment must be taken out of service. Similarly, for smaller humidifier units (portable or home size), rigorous maintenance and drainage are recommended as well as appropriate cleaning and disinfection offline with suitable agents as per the manufacturer's instructions (Public Health Ontario, 2017).

Hot Tubs and Swimming Pools

Legionella outbreaks have been caused by contaminated hot tubs (Benkel et al., 2000; Campese et al., 2010; Moore et al., 2015). Indeed, hot tubs were the third leading cause of legionellosis outbreaks among 27 investigations reported between 2000 and 2014, following potable water and cooling towers (Garrison et al., 2016). The warm water in these devices is often at the optimal growth temperature for *Legionella* growth (30°C to 40°C). Aerosols created by the water jets in some hot tubs can transmit the bacteria to people sitting in the units who are breathing very close to the water surface (Moore et al., 2015). Moreover, aerosols released from the water can be dispersed by air currents or ventilation systems, placing people outside the hot tub at risk for *Legionella* infection.

Hot-tub water is typically filtered and treated with chlorine, bromine, or ozone (Leoni et al., 2018). Although disinfection is the primary management option, the warm temperatures in hot tubs make it hard to maintain disinfectants at the levels needed to kill bacteria including *Legionella*. Therefore, hot tubs should be periodically inspected by health officials to ensure they are operating properly and adequately cleaned. Facility managers should check the amount of disinfectant in the water and the pH and have a regular schedule for cleaning that includes removing any films or algae from the sides of the hot tub. Filters in these units should be replaced in accordance with the manufacturer's specifications. If *Legionella* is detected in a hot tub, the facility manager should follow CDC[10] or American Society for Heating, Refrigerating, and Air-Conditioning Engineers guidelines for cleaning and disinfection (ASHRAE, 2015).

Although most recreational water *Legionella* outbreaks are linked to the warm water of hot tubs, the CDC also outlines guidance for pool operators. These include a 12-step program for prevention of recreational water illnesses, training, procedures for pool operations, and videos and guidance for the safe handling of pool chemicals.[11] Facility operators should know and obey all applicable laws and regulations. If there are shower facilities associated with pools, facility managers should be cleaning and disinfecting the showerheads and faucets on a regular basis.

[10] See http://www.cdc.gov/Legionella/downloads/hot-tub-disinfection.pdf.
[11] See https://www.cdc.gov/healthywater/ swimming/aquatics-professionals/index.htm.

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Management of Legionella in Water Systems

EMERGING OPPORTUNITIES AND UNINTENDED CONSEQUENCES

There is much still to be learned about *Legionella* ecology and its response to engineering controls. Currently, knowledge of built environment microbiomes is rapidly expanding (NASEM, 2017), largely driven by next-generation DNA sequencing, which promises to provide new insights. At the same time, U.S. infrastructure is aging beyond its intended lifespan and experiencing shifts in water demand, along with changes in behaviors and expectations of water consumers. Thus, the current situation presents both opportunities and challenges.

Presently there is a major push towards advancing "green" building features in the United States, with the important goals of conserving energy, water, and materials. Water conservation features are driven by the need to reduce unsustainable water extraction, particularly as supplies experience greater pressure as a result of drought and other consequences of climate change. The need to reduce dependency on fossil fuels and limit production of greenhouse gases drives incorporation of energy-saving features, but these measures often have consequences for water systems as well. The U.S. Green Building Council (USGBC) reported that green building construction expenditures currently outpace those of general construction, with projected outlays of $224.4 billion in 2018 (USGBC, 2015). Developed by the USGBC, the Leadership in Environmental Engineering Design (LEED) certification system ascribes points for various building attributes, with "platinum" being the highest level of certification. Particularly relevant to this report are features by which such buildings can earn points for "potable water savings" and "energy savings" (USGBC 2016a,b). The following examples illustrate some of the complex and untested scenarios that can have unintended consequences and increase risk of *Legionella* growth in building water systems (Rhoads et al., 2015b) and highlight emerging opportunities to advance science and better understand and address such challenges.

Prebiotic and Probiotic Control of *Legionella*

Given that it is impossible to eradicate microbes or biofilms from engineered water systems, the possibility of intentionally shaping the *kinds* of microbes that colonize piped water systems to suppress pathogen growth niches has been proposed (Wang et al., 2013a). By definition, a *probiotic* approach would be to intentionally add such beneficial microorganisms, whereas a *prebiotic* approach controls the environment (e.g., water chemistry, pipe material, temperature) to favor desirable microorganisms. This exploratory concept remains to be tested and demonstrated in practice. Nonetheless, this is an interesting area for future research. As described in Chapter 2, there are several unique aspects of *Legionella*'s microbial ecology that lend support to the possibility of prebiotic or probiotic control.

One prebiotic approach extends from the examples of general biofilm control via nutrient reduction previously described in this chapter. Biological treatment that reduces the levels of biodegradable organic matter can help reduce the density of biofilm bacteria, and thus decrease the number of protozoan hosts available for *Legionell*a replication. In particular, the composition of organic matter could be tailored to select for a biofilm community that is a poor food source for amoebae (Amaro et al., 2015) or for protozoa that digest *Legionella* (Amaro et al., 2015; Anderson et al., 2011; Maita et al., 2018). This possibility is supported by the fact that certain free-living amoebae are known to preferentially prey on certain bacteria rather than *Legionella* (Shaheen and Ashbolt, 2019).

Alternatively, the thermal and disinfection controls described above may indirectly control *Legionella* by decreasing the population of free-living protozoa. Likewise, by manipulating other environmental factors such as oxygen levels, metals, organic carbon, stagnation, pipe materials, and other physicochemical and biological parameters, the ecology and life stage of free-living amoebae in water

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Management of Legionella in Water Systems

systems (and hence *Legionella*) could be managed. Another possibility would be to impose conditions (e.g., through nutrient deprivation, disinfection, or temperature shock) that shift free-living amoebae populations to the cyst stage, hence reducing *Legionella* growth potential because it is only capable of growing in trophozoites, not cysts.

One probiotic approach entails adding microbes that are a more preferred food-source for amoebae than *Legionella* but are non-digestible. Since the amoebae would derive little nutritional benefit from grazing on such a biofilm, their populations would decline or encyst. In particular, water systems would be supplemented with microbes that compete with α-Proteobacteria, key prey for protozoan hosts of *L. pneumophila* (van der Kooij et al., 2018). Further, manipulating the types of free-living protozoa inhabiting the system presents several possibilities. For example, some amoebae are capable of digesting *L. pneumophila* (Amaro et al., 2015; Maita et al., 2018) or contain symbionts that do not allow ingested *Legionella* to replicate within the host (Maita et al., 2018; Okubo et al., 2018).

Prebiotic and probiotic approaches may be particularly attractive in the future given inherent limitations in existing engineered controls. In fact, relative resistance to both disinfectants and heat treatment are common features among *Legionella* and other pathogens that plague premise plumbing (Falkinham, 2015). As noted in Chapter 2, after intracellular replication in free-living protozoa, *L. pneumophila* can actually become more resilient to heat, oxidants, acids, osmotic pressure (Kwaik et al., 1997), biocides (Barker et al., 1992, Berk et al., 1998), and antibiotics (Barker et al., 1995, Garduño et al., 2002). Moreover, resistance to chlorine can spread among *L. pneumophila* on the ICE-box mobile genetic element, providing a mechanism for emergence of strains that persist in treated water (Flynn and Swanson, 2014). Thus, traditional use of disinfectants, depending on how effectively they are applied, may beneficially or detrimentally tip the microbial community balance towards one that favors *Legionella*. Better understanding the life stages and the ecology of free-living protozoa and *Legionella* in water systems could be critically important to advancing the possibility of prebiotic and probiotic control, as well as informing optimization of other more traditional engineered controls.

Unintended Consequences of Water Conservation

LEED-certified green buildings typically conserve 20 to 50 percent of potable water, although that value will rise as "off-grid" operations are adopted. To achieve water conservation goals, alternative sources of water are used for various purposes, including toilet flushing, landscaping, or even potable applications. Alternative sources include reclaimed water, greywater, and rainwater, which may present unique risks compared to traditional potable water. The other main approach to water conservation is incorporation of fixtures and appliances that use less water, such as low-flush toilets and low-flow and metered faucets. While current LEED certification does take into consideration "indoor environmental quality," the focus is on criteria such as ventilation, thermal comfort, daylight, tobacco smoke, and avoiding volatile organic compound-emitting materials, rather than water quality or *Legionella*. The need for these additional criteria is beginning to be recognized and would enhance the benefits of the green building movement (Cedeno-Laurent et al., 2018).

High Water Age

Deteriorating water quality due to high water age is a fundamental challenge of water storage, which many hospitals and other buildings require to ensure water security in emergency situations. For

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Management of Legionella in Water Systems

example, the Centers for Medicare & Medicaid Services (CMS) has mandated that hospitals be self-sufficient for 96 hours without essential utilities and deliverable items, including potable water. Many hospitals elected to maintain large stocks of potable water to meet the required 96-hour reserve. Any efforts to conserve water inherently increase stagnation and overall water age, both at the municipal level (i.e., main distribution system water age) and at the building-level (i.e., premise plumbing water age) (Rhoads et al., 2016a). One survey found the premise plumbing water age in a typical LEED-certified healthcare suite to be eight days; it was more than six months in an off-grid office suite (Rhoads et al., 2016a). High water age has long been known to be detrimental to main distribution systems due to enhanced corrosion, development of taste and odor issues, loss of disinfectant residual, and regrowth of microorganisms (EPA, 2002b). Increased distribution system water age can also increase water corrosivity for premise plumbing (Masters et al., 2015). A national survey indicated that there is excessive "overdesign" of water mains based on actual fixtures and flow rates (Buchberger et al., 2015), which further exacerbates water age problems at the community scale.

Once water enters the complex, high surface area and warm premise plumbing environment, such problems are only magnified. Meanwhile, the ability to compensate for lower flows is constrained by current building codes, such as mandating larger pipe sizes (Klein, 2018). A study of a newly constructed residences with green plumbing features occupied by college students noted a clear pattern of diminished water quality at the least frequently used taps (Salehi et al., 2018). In the LEED-certified healthcare suite noted above, disinfectant residual was entirely absent at all sampling points; more than 80 minutes of flushing was required before the municipal chloramine residual could be detected (Rhoads et al., 2016a). Further, the plumbing materials themselves enhanced disinfectant decay, with chloramine decay rates being 20 to 144 times faster when the well-flushed water sat in the plumbing compared to in a clean glass container. As water stagnates, it is also more often within an optimal temperature range for *Legionella* growth. In the LEED-certified healthcare suite, *Legionella* spp. gene copies were nondetectable in the incoming water supply, but were in the range of 10,000 to 100,000 GC/mL in three of the five premise plumbing sampling locations (Rhoads et al., 2016a).

Low-Flow and Metered Faucets

Lower-flow fixtures, including toilets, dishwashers, washing machines, showerheads, and faucets are required by the EPA WaterSense program to reduce flows by at least 20 percent (EPA, 2016b). Lower flows reduce the rate at which consumers can draw water, but this can backfire because more flushing time is needed to obtain the target hot or cold temperature, depending on the application. Lower flow also pushes hydraulics into the laminar flow range, which is less effective for scouring biofilms, and can increase numbers of biofilm-associated *Legionella* (Liu et al., 2006). Metered faucets are very common in green buildings, only delivering a pre-determined aliquot and aiming to conserve water by incorporating electronic sensors to ensure that they are only opened when in use. Additionally, although such "hands-free" devices are intended to reduce spread of germs, ironically several studies have now confirmed that they have a propensity to grow *Legionella* and other pathogens, such as *P. aeruginosa* (Yapicioglu et al., 2011). Notably, Sydnor et al. (2012) cultured *Legionella* from 19 of 20 electronic faucets and only nine of 20 manual faucets co-located across three hospital units; this trend was even stronger when repeated sampling was taken into account. Further, *Legionella* colonizing electronic faucets were less responsive to chlorine dioxide disinfection than were *Legionella* in traditional faucets. Although it is not fully known why, the internal plastic components and the mixing of water create an ideal temperature for *Legionella* growth, which likely contributes to this problem.

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Management of Legionella in Water Systems

Rainwater Harvesting

Collection of rainwater in cisterns is common throughout many parts of the world, particularly the rural tropics and sub-tropics, but this practice is also becoming a more intentional aspect of modern green building design elsewhere. The EPA does not regulate the water quality of residential rainwater harvesting systems, but some state and local agencies do issue voluntary water quality guidelines for residential rainwater harvesting systems. Yet, natural rainwater is not as "clean" as one might assume, as it is highly susceptible to atmospheric and rooftop sources of contamination, including bird droppings, heavy metals (Förster, 1999; Lee et al., 2010), herbicides (Bucheli et al., 1998), and pesticides (Zorbrist, 2000). The type of roof material also affects microbial water quality (Clark et al., 2019). A recent qPCR survey of *Legionella* in harvested rainwater tanks in Queensland, Australia encountered *Legionella* spp. in nearly 100 percent of tanks and *L. pneumophila* in 17 percent of tanks (Hamilton et al., 2017). A follow-up study in Philadelphia similarly noted qPCR detection of *Legionella* spp. in more than 50 percent of rooftop rainwater harvesting barrels (Hamilton et al., 2018b). Similar to findings from sediments in drinking water reservoirs (Lu et al., 2015), soil and dust are likely sources of these legionellae and associated protozoa.

Various factors associated with rainwater storage, collection, and use are likely to exacerbate potential problems with *Legionella*. Rainwater is characteristically low in pH and alkalinity, resulting in corrosive water whose problems were noted previously. Metal tanks are among the most frequently encountered materials (Hamilton et al. 2017) and will be directly affected by corrosion. Further, rainwater harvesting inherently entails storage, during which time typical water age problems are incurred and can be exacerbated by poor maintenance. Hamilton et al. (2017) noted in their survey of Australian tanks that 50 percent were never cleaned or desludged in their lifetime. Finally, the water savings incurred by rainwater harvesting can indirectly increase the water age within potable water plumbing. One study found that using rainwater to flush toilets resulted in a 58 percent to 80 percent reduction in potable water use, with premise plumbing water age at some taps exceeding three weeks (Nguyen et al., 2012).

Off-Grid Systems

At the extreme end of "green infrastructure" are off-grid or "net zero" buildings, which do not rely on an external water network for potable water or wastewater services (EPA, 2013). Such independence from water utilities is a primary goal of certifications such as the Living Building Challenge. The characteristics of these buildings include use of water-saving devices to reduce water consumption,[12] rain-water harvesting, cisterns, on-site grey water or black water reuse, constructed wetlands, composting toilets, xeriscaping, and local aquifer recharge among other practices (Rhoads et al., 2015b). Such design configurations, however, raise a unique set of challenges and corresponding public health concerns. It is critical that these water systems be managed to control risks from *Legionella* and other water-related pathogens.

A recent survey estimated the premise plumbing water age of an off-grid "net zero" building to be between two to almost seven months, far exceeding that of a conventional building (Rhoads et al., 2016a). A 3,000-gallon tank for storing roof-top-harvested rainwater plus supplemented groundwater was primarily responsible for such a high water age. Disinfectant was not added to the water; rather, the water was subjected to serial filtration to 5 μm followed by a granular activated carbon (GAC) filter and UV disinfection. *Legionella* spp. gene markers measured by qPCR were detected throughout the system, including immediately post-treatment, in the storage tank, and in hot and cold flushed and stagnant water at 10^3 to 3 x 10^4 GC/mL (Rhoads et al., 2016a).

[12] See https://living-future.org/lbc.

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Management of Legionella in Water Systems

Because of the unique designs for off-grid buildings, each should have its own water management plan following the principles outlined in Chapter 5. Source water should be properly filtered and disinfected, considering that even in rainwater samples Rhoads et al. (2015) reported *Legionella*, as measured by qPCR. The potential for extended water age means that the water management plans should address recirculation of water within the building plumbing system.

As part of the water management plan, off-grid buildings should pay close attention to keeping the hot water hot (55°C to 60°C) and the cold water cold (less than 25°C). Use of heat pumps or solar hot-water heating may result in water temperatures that are insufficient to prevent *Legionella* growth (Rhoads et al., 2016). Temperatures will fluctuate on a diurnal basis and be influenced by seasonal and weather patterns if a solar heating system is not also paired with a non-solar water heater (van Amerongen et al., 2013). A review of the literature by van Amerongen et al. (2013) did not find, however, that solar heaters were more prone to *Legionella* detection than conventional heating systems, but they did point out that design and maintenance were important.

Flushing water lines and cleaning and inspecting storage tanks are important activities for off-grid systems, just as they are for public water systems; both should be included as part of the overall water management plan. Corrosivity of rainwater could put system components at risk and enhance conditions for *Legionella*.

Biowalls

Biowalls are an example of a green building feature that is gaining popularity. These walls of plants maintained in the indoor environment are advertised as a natural "botanical filter" that improves indoor air quality, helps "reduce sick building syndrome," and saves energy by recycling internal air.[13] However, a scientific literature review did not indicate that such claims have been tested. The perpetually moist environment of the biowall, along with a rich soil inoculum, maintained within a warm building envelope, could create an ideal habitat for *Legionella* proliferation. Further, the intentional "filtering" of air through the biowall clearly creates the potential for aerosol formation and occupant exposure. Thus, biowalls meet several criteria of a building system of concern worthy of scrutiny for its potential to be a source of *Legionella* exposure. Accordingly, appropriate engineered controls should be considered.

Unintended Consequences of Energy Conservation

As noted above, elevated water temperature is a master variable for *Legionella* control in buildings. Incentives in green buildings that encourage lowering this temperature to achieve energy savings can create conditions conducive to *Legionella* growth (Brazeau and Edwards, 2013b). Water heating is the second largest consumer of energy in the home and, accordingly, the EPA ENERGY STAR® program recommends a lower water-heater setting of 48.8°C (120°F) (EPA, 2019). This and other similar policies are in need of critical evaluation. For example, at one point the California Energy Commission (CEC) required recirculation for hot-water lines longer than ten feet, under the assumption that this would reduce water usage by lowering the time needed to achieve target shower temperature (Brazeau and Edwards, 2011); however, head-to-head studies revealed substantial heat loss and failure to achieve target temperatures with recirculation (Brazeau and Edwards, 2013a). Current California plumbing code now requires insulation of hot-water lines to conserve heat, and recovery of heat from drains is also encouraged (CEC,

[13] See https://www.purdue.edu/biowall/.

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Management of Legionella in Water Systems

2019). Thus, there is a need for comprehensive cost-benefit analyses of actual energy savings achieved with various types of heaters, temperature settings, and corresponding plumbing configurations versus their impacts on water quality known to present risk factors for *Legionella* proliferation (Brazeau and Edwards, 2011). Analysis is needed to ensure that energy savings goals are actually met, while factoring in important public health considerations.

One comprehensive hospital case study clearly illustrates the unintended consequences of implementing reduced water heater temperatures (Blanc et al., 2005). Following the implementation of energy conservation regulations, hospitals in Switzerland were required to lower their hot-water temperature from 65°C to 50°C. To minimize bacterial contamination of their hot-water plumbing, the Lausanne University Hospital first upgraded its hot-water plumbing by eliminating dead ends and improving flow patterns. A thermal-shock treatment was then conducted before implementing on-site disinfection in 1995. Two separate premise plumbing systems were treated with: (1) ozone with a residual of 0.3 mg/L and (2) copper-silver at 0.3 mg/L. After three years, the positivity for *Legionella* spp. remained high in ozone-treated networks (66 percent to 56 percent) and in copper-silver-treated systems (90 percent to 93 percent). Increasing the temperature to 65°C at the water heater decreased the bacterial occurrence back to acceptable levels, although some areas remained persistently positive and were associated with poor hot-water recirculation leading to temperature losses (Blanc et al., 2005).

The experience at the Lausanne University Hospital demonstrates the importance both of elevated tank temperatures and maintaining sufficiently hot delivery lines. Nonetheless, reducing the temperature at the water heater outlet and shutting down the recirculation during low-usage periods (e.g., night, weekends) remain two major targets of energy conservation. Well-documented case studies in real systems show clearly that a reduction in temperature at the water heater outlet can lead to a significant increase in the likelihood of *Legionella* detection and the level of contamination at the tap. Further, shutting down the recirculation during the night will create stagnant conditions for periods of eight hours or more. Even in insulated systems, water will reach the ideal temperature for *Legionella* growth during such long stagnation periods (Bédard et al., 2016a).

Energy conservation projects that add a heat exchanger to pre-heat the water prior to the water heater have also been increasing in popularity in healthcare facilities. The installation of these devices should be carefully studied to evaluate operating conditions. The very large surface present in heat exchangers, coupled with temperatures ranging between 25°C and 43°C, provide ideal conditions for *Legionella* growth. Recent field investigation revealed contamination of such a heat exchanger by a *L. pneumophila* strain that matched clinical isolates from cases occurring a few weeks after the installation of the device (Bédard et al., 2016b). Disinfecting the device on a weekly basis and determining operating conditions to minimize *L. pneumophila* should be mandatory in healthcare facilities.

Other options for reducing energy demand of water heating include solar heaters and on-demand heaters. Solar heaters come in various configurations, typically employing a pre-heat tank and taking advantage of water stratification to draw water from the top before either being used directly, feeding a traditional tank heater or on-demand water heater. This subsequently incurs less energy input to heat to the target temperature. A typical feature of solar water heaters is some level of added water storage, which takes advantage of the high heat capacity of water. Rhoads et al. (2016a) observed that the added storage incurred by a solar water heater in a net zero energy home increased the hot-water age from less than one day to between two to three days. Further, due to cloudy days, the solar pre-heat tank may essentially end up in the optimal temperature range for *Legionella* growth. *Legionella* spp. copy numbers measured by qPCR in the hot-water manifold that received the heated water and delivered it to taps were markedly high, upward of 10^6 GC/mL (Rhoads et al., 2016a). On the surface, on-demand heaters could be an effective alternative, only delivering hot water where and when needed, and these devices

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Management of Legionella in Water Systems

are currently recommended by CEC (2019). However, there are many logistical constraints to their installation and use, and their benefits for *Legionella* control need to be more critically evaluated (Brazeau and Edwards, 2013c).

Potential Trade-Offs with Other Microbial Risks

Finally, it is important to consider whether recommendations herein intended for *Legionella* control could potentially have unintended consequences by favoring survival of other pathogens that are problematic in premise plumbing. A report sponsored by the Water Research Foundation (Project 4813) summarized common challenges encountered in premise plumbing that favor the proliferation of multiple pathogens, in particular *P. aeruginosa*, nontuberculous mycobacteria, *Acanthamoeba* spp. and *N. fowleri* (Pruden et al., 2013), though other examples include *Acinetobacter baumanii* and *Aeromonas* spp. Falkinham (2015) described several key commonalities among such organisms, including preference for biofilm environments, capacity to resist predation by protozoans, tolerance to disinfectants, and antibiotic resistance. Ideally, such commonalities could be capitalized upon to identify "silver bullet" approaches that offer protection against all pathogens that, like *Legionella*, are prone to proliferation in premise pluming. Indeed, efforts to reduce biofilms and amoebae hosts described in this chapter should in theory also address amoebal pathogens occurring in the plumbing. However, given that some of these organisms are markedly tolerant of disinfectants (e.g., mycobacteria), the higher doses required could pose other concerns, including generation of disinfection byproducts and selection of strains that are more tolerant of disinfectants. Also, whereas chloramines appear to be particularly effective against *Legionella* spp., *Mycobacterium avium* levels can increase when water systems are switched from chlorine to chloramine (Pryor et al., 2004; Wang et al., 2013b). Concerns have also been raised that drinking water disinfectants might inadvertently select for antibiotic-resistant bacteria, due to multifunctional or co-located antibiotic resistance genes, as was evidenced by a metagenomic-based DNA sequencing study (Shi et al., 2013). In particular, metal and antibiotic resistance traits are commonly co- or cross-selected among bacteria, begging the question of whether copper-silver ionization exerts similar effects when applied to drinking water (Chen et al., 2015). Khan et al. (2016) observed that chlorine resistance and minimum inhibitory concentration of various antibiotics positively correlated among several tap water bacterial isolates. Long-term exposure to low levels of chlorine was also recently associated with selection of antibiotic-resistant *P. aeruginosa* (Mao et al., 2018; Shrivastava et al., 2004) and upregulation of antibiotic resistance genes in *A. baumannii* (Karumathil et al., 2014).

Elevated water temperatures appear to also reduce growth of most pathogens in premise plumbing, but slightly hotter water temperatures may be necessary for mycobacteria. For example, viable mycobacteria have been observed in household water heaters, but numbers of positive heaters were substantially lower when the temperature was higher than 55°C (Falkinham, 2011). In the lab, 90 percent survival of mycobacteria was observed following exposure to 50°C for 60 minutes (Schulze-Röbbecke and Buchholtz, 1992).

Thus, there is need for research that harmonizes engineered control efforts to minimize the risk of other microbial problems, including growth, virulence, and antibiotic resistance of multiple pathogens. Ideally, selected controls for *Legionella* should have comprehensive benefits for control of other pathogens in water systems.

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Management of Legionella in Water Systems

CONCLUSIONS AND RECOMMENDATIONS

For any given building water system, there are multiple strategies that can be successfully employed and should be used. Figure 4-5 provides an overview of the controls discussed in this chapter and the importance of considering their integration and applicability to various water systems. The different strategies available for controlling *Legionella* in water systems are feasible at different stages of a building's life cycle, with some being feasible mainly during initial construction (such as the choice of plumbing materials) while others are implemented during ongoing operation and maintenance (such as disinfection and flushing). Table 4-6 summarizes how the various control strategies should be considered at different stages of a building's life: design, commissioning, operations (including routine monitoring), and corrective action when necessary. It is critical to recognize that no single control strategy should be relied upon to control *Legionella* in building water systems, and multiple barriers are encouraged to the extent possible (Figure 4-5). Also, the effectiveness of many of the controls are interdependent, for example, optimal hydraulics are required for effective delivery of thermal and chemical disinfectant while reactivity of the plumbing materials and the water source chemistry could lead to disinfectant decay. Furthermore, as summarized in Table 4-1, not all controls are relevant to all water systems. For example, while thermal control is a primary barrier against *Legionella* in building systems, it cannot be applied to large engineered

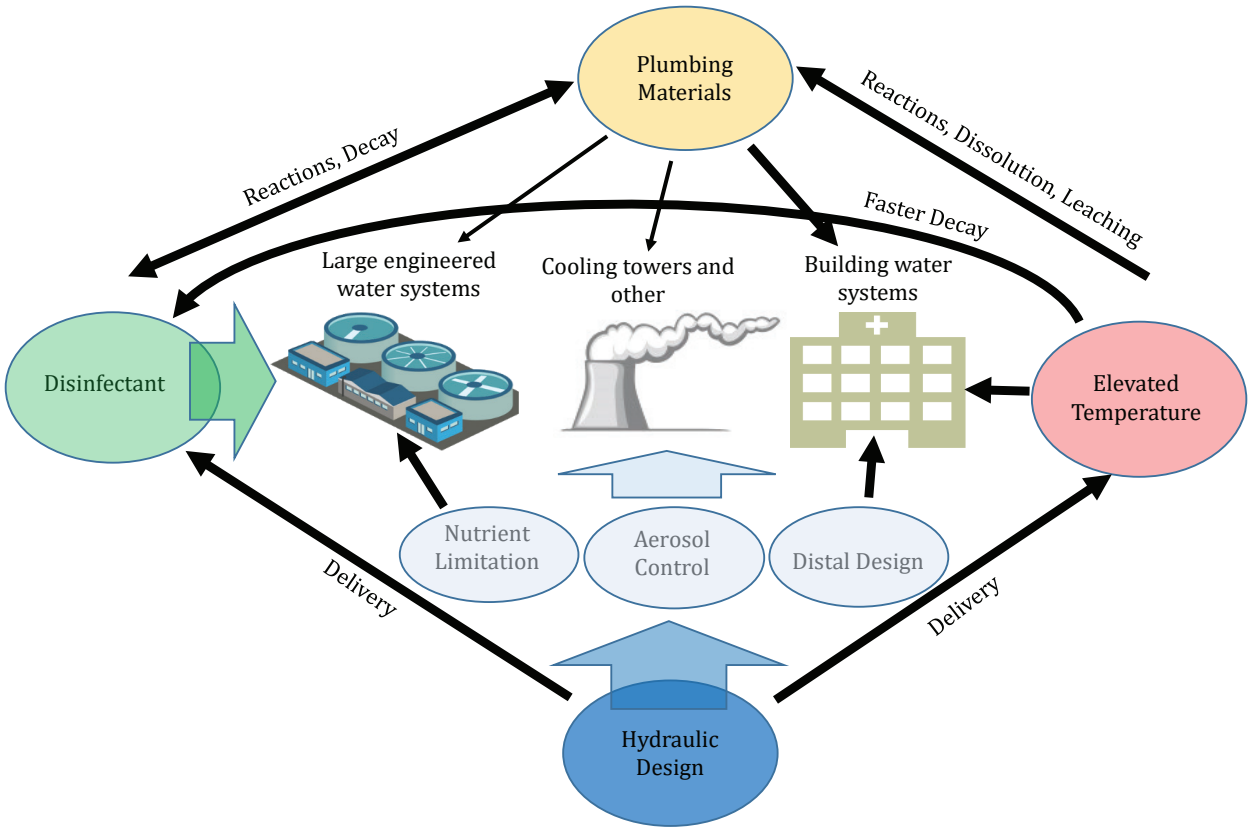

FIGURE 4-5 Interactions between *Legionella* controls in different water system types. Disinfection and hydraulic design apply to all systems. Only key examples are provided; not all systems or scenarios are represented.

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TABLE 4-6 Summary of Implementation of Various Engineering Controls and Corrective Actions at Various Stages of Building Design, Commissioning, and Operations

Control	Design	Commissioning	Operations	Corrective Action
Hydraulic Control	pipe sizing and flow distribution to minimize water age and avoid stagnation	minimize periods of no use, preventive flushing during periods of no use	verify hydraulic balancing	modify hydraulics, correct deficient circulation
Materials Issues	select biostable materials and ensure corrosion control	cleaning, preventive flushing, disinfection	verify corrosion control	replace failing materials, eliminate corrosion byproducts
Source Water Quality	consider the quality of the source water: corrosivity, nutrient content, and ability to maintain disinfectant residual	delay filling of system during commissioning to avoid long periods without use	verify corrosion control, disinfectant residuals, and general microbiological water quality indicators	flush, adjust pH, hardness, corrosivity, etc. or switch to improved water supply
Temperature	minimize distance between hot-water heater and distal points, select hot-water heater, heat trace	delay start-up of hot-water system during commissioning to avoid long periods without use	maintain target temperatures across the system	adjust operational temperature
Disinfection	include chemical disinfection in design	apply shock disinfection	set disinfectant residual targets and monitor for compliance across the system	apply shock disinfection
Aerosol Transmission Prevention	select devices to minimize aerosol formation	verify absence of *Legionella* in premise plumbing before occupancy		replace devices to minimize aerosol formation
Water Management Plan	include from beginning of design	determine and apply specific commissioning plan for *Legionella* control	apply management plan	modify management plan

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Management of Legionella in Water Systems

systems, such as wastewater treatment plants, because of the nature and scale of these systems. Other competing goals, such as commitment to water and energy savings for green building certification, must also be taken into consideration. Water management plans (discussed in detail in Chapter 5) are essential to *Legionella* control for any water system, as they provide the opportunity to adapt and tailor the strategy to the specific system of concern and employ and integrate all applicable barriers (see Table 4-6).

Two rows in Table 4-6 do not correspond precisely to controls discussed in this chapter. First, source water quality is listed (rather than the narrower nutrient limitation), as there are important water quality considerations at each stage of a building's life cycle and multiple control strategies will affect water quality. Second, there is a final row on water management plans for protecting a building from a *Legionella* outbreak because having a plan itself is a critical control. (Such plans are discussed in detail in Chapter 5.)

The conclusions and recommendations below highlight key lessons regarding *Legionella* control strategies for the building and device types discussed in this chapter.

For all types of buildings, hot-water heater temperature should be maintained above 60°C (140°F) and the hot-water temperature to distal points should exceed 55°C (131°F). Maintaining temperature outside *Legionella's* preferred growth range is the paramount *Legionella* control strategy for all buildings that provide hot water and has been proven successful by numerous longitudinal field studies. Temperature control is most effective in large, complex hot-water systems that are hydraulically balanced, with dead-end pipes removed and faulty devices that compromise the distribution of hot water identified and replaced.

There is growing evidence that, compared to free chlorine, a monochloramine residual better controls *Legionella* risk from building water systems, although the reasons for the improved performance are not yet clear. It is possible that amoebae trophozoites are more sensitive to monochloramine, causing the amoebae to encyst and thus preventing the proliferation of *Legionella* within their host. Additional research is needed to examine the precise action of monochloramine on *Legionella* persistence and growth within pipeline biofilms. Better understanding of the potential for nitrification in building plumbing is also required, as this reaction could negatively impact the effectiveness of a chloramine residual for *Legionella* management.

Additional research is needed to evaluate the potential for nutrient limitation (concentration and composition) to control *Legionella* growth in distribution and building water systems. These studies should examine, in full-scale drinking water systems, the impact of nutrient reduction on the concentration and composition of the microbiome in biofilms and water including amoebae growth and life stages and the subsequent effect on occurrence and decrease of pathogenic *Legionella* species.

New NSF/ANSI standards regarding microbial growth potential of materials are needed so that water utilities, plumbers, and building contractors can include *Legionella* control when making decisions about pipe material usage. Certain plastic components (e.g., PEX) tend to lead to bacterial proliferation. Iron components in distribution systems and premise plumbing should be replaced or otherwise managed with appropriate corrosion control to avoid disinfectant decay and release of iron as a nutrient for *Legionella*. Because of conflicting accounts in the literature about their role in *Legionella* growth, copper pipes cannot be relied on as a barrier to *Legionella* colonization and growth. More research is needed to identify circumstances when copper's antimicrobial properties are enhanced.

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Management of Legionella in Water Systems

There is clear evidence of *Legionella* amplification in the distal parts of some hot-water systems, likely due to a combination of water stagnation and loss of temperature control and disinfectant residual. Some features of distal devices such as aerators, thermostatic mixing valves, complex designs, and shower hose materials have been linked to increased prevalence of *Legionella*. Additional research is needed to understand the conditions in distal reaches of premise plumbing that promote the amplification of *Legionella* so that improved distal devices can be designed.

Research is needed on new control technologies that limit the capacity of devices and building water systems to generate aerosols, particularly those smaller than 10 microns. The formation of aerosols is an important risk factor in the transmission of *Legionella*. Faucets and showerheads that limit the formation of fine mists should be used in locations where high-risk individuals could be exposed (e.g., hospitals). Technologies to minimize aerosols from cooling towers should strive for the highest efficiencies, and older cooling towers should be retrofitted with newer drift eliminators that meet higher standards.

Research is needed to better understand the persistence of distribution system disinfectant residuals within building plumbing. Public water supplies that maintain a disinfectant residual and manage hydraulics to prevent stagnation (such as through routine flushing and cleaning of storage tanks) are helping to reduce *Legionella* exposure from the distribution system. Nonetheless, it is unclear to what extent the disinfection residual can achieve *Legionella* control within premise plumbing, for both single-family homes and small buildings as well as larger buildings.

Guidance about *Legionella* is needed for homeowners, especially consumers from at-risk segments of the population. In particular, there is a need to identify plumbing configurations and devices that inadvertently increase risk of *Legionella* proliferation as well as accessible, practical control options such as flushing taps after periods of disuse. Residential water systems can benefit from most of the control strategies discussed in this chapter, yet they are almost never formally implemented because of a lack of understanding or awareness on the part of homeowners and occupants.

Low-flow fixtures should not be allowed in hospitals and long-term care facilities because of their high-risk occupant populations. Low-flow fixtures have been promoted to conserve water and in some cases energy. However, because of their lower flow, these fixtures, primarily low-flow faucets but also showers, increase water age and restrict disinfectant levels, including the disinfection provided by elevated water temperatures. As such, low-flow fixtures present a greater risk for *Legionella* development in the plumbing systems that feed them.

New designs are needed to help advance control of *Legionella* in cooling towers and humidifiers. Humidifier designs that produce water droplets within the temperature range conducive to *Legionella* spp. growth (such as evaporative pan, drum-type, water spray-type, sprayed coil-type humidifiers or air washers) should be avoided for use in new buildings, and existing units of these types should be replaced during building renovations. When designing and locating HVAC systems, it is important to prevent *Legionella* contamination and growth by considering equipment and material selection, proper drainage, and access for maintenance. Strategies relying on disinfectants should consider using alternate types of biocides at regular intervals, since bacteria can regrow in cooling towers when biocide use is infrequent and irregular. Finally, cooling tower manufacturers should collectively design new systems that can operate at condenser water temperatures whereby the temperature going to the cooling tower will be greater than 60°C.

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Management of Legionella in Water Systems

Green buildings have exacerbated many of the problems with *Legionella* by lengthening water residence times (which leads to loss of disinfectant residual) and lowering hot-water temperatures in premise plumbing. Criteria for certifying green buildings, energy-conserving features, and water-conserving features should be modified to take into account risk factors for growth of *Legionella* and other water-based pathogens in building water systems. Substantial water conservation can still be potentially achieved while protecting public health with more overt management of water age, e.g., through routine flushing of a target fraction of the water use. Given the strong evidence that water heater settings below 60°C place a system at risk for *Legionella* growth, appropriate plumbing designs to conserve heat in the system may be the only reasonable path forward.

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5
Regulations and Guidelines on *Legionella* Control in Water Systems

In the United States, management of *Legionella* in water systems occurs on an ad hoc basis, spanning from regulations that require some buildings to have water management plans that include monitoring of water samples for *Legionella* along with treatment, to no requirements at all. In between exists a range of codes, standards, and guidance documents that have been sporadically adopted and typically target some of the high-risk zones for *Legionella* growth. Contributing to this widespread inconsistency in approaches to managing *Legionella* is the lack of any federal law that targets *Legionella* contamination of water supplies and building water systems as sources to be controlled.

This chapter begins by describing why the Safe Drinking Water Act does not provide any substantial control of *Legionella* in water systems. It then describes the many regulations, directives, codes, and guidance documents that can affect whether *Legionella* management occurs in the United States and the resulting significant lack of coverage. The chapter also describes the approach Europe and other countries have taken to manage *Legionella,* where stricter regulations have been imposed, and discusses how effective the regulations have been to date. For both the national and international regulations or guidance, this chapter describes the regulation, the control methods advocated, whether there is a *Legionella* monitoring requirement (and if so, whether it is based on percentage positive or concentration), and demonstrated effects of the guidance or regulations on Legionnaires' disease rates or results of environmental sampling for *Legionella*. Finally, the chapter's conclusions and recommendations suggest how the universe of approaches in the United States can be improved upon to better protect the public from exposure to *Legionella*.

LACK OF FEDERAL LAWS AND REGULATIONS PERTINENT TO *LEGIONELLA*

The Safe Drinking Water Act (SDWA) was originally passed by the U.S. Congress in 1974 to protect public health by regulating the nation's public drinking water supplies. The law was amended in 1986 and 1996 and requires actions by the U.S. Environmental Protection Agency (EPA) to protect drinking water and its sources—rivers, lakes, reservoirs, springs, and groundwater. (The SDWA does not regulate private wells or systems that serve fewer than 25 individuals.) Congress directed the EPA to address *Legionella* through the development of a treatment technique requirement, which is used when monitoring for the contaminant is deemed infeasible or unreliable. In 1989, EPA enacted the Surface Water Treatment Rule (SWTR), which requires public water systems using a surface water supply, or a groundwater

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Management of Legionella in Water Systems

supply under the direct influence of surface water, to filter and disinfect the water (the latter of which is meant to control microbial contamination including *Legionella*). The SWTR requires disinfectant residual to be monitored in the distribution system and at the entry point to the distribution system. The disinfectant level must be at least 0.2 milligrams per liter (mg/L) at the point of entry and detectable in at least 95 percent of samples collected within the distribution system. Public water systems must maintain a residual disinfectant level of less than 4.0 mg/L as a running annual average within the distribution system, as outlined in the Stage 1 Disinfectant/Disinfection By-Product Rule. The SWTR established a Maximum Contaminant Level Goal (MCLG, a non-enforceable guideline) of zero *Legionella* organisms in drinking water. This scenario of having no *Legionella* present in a drinking water system is consistent with the Centers for Disease Control and Prevention's (CDC) position that there is no known safe level of *Legionella*.[1] However, potable water supplies are not sterile, and *Legionella* exists in distributed water at some non-zero frequency of detection (LeChevallier 2019a,b).

The SWTR has been effective for controlling enteric organisms, such as norovirus, *Giardia* and *Cryptosporidium,* using a multiple-barrier approach at the treatment plant. These pathogens are reduced via filtration and can be inactivated via disinfection given the correct disinfectant and contact time (e.g., *Cryptosporidium* is resistant to chlorination but can be inactivated with ozone or ultraviolet [UV] light). These enteric viruses and protozoa do not multiply in the distribution system or in premise plumbing. Unfortunately, these principles do no extend to *Legionella* and some other environmental pathogens, which can grow in the pipe network after treatment. Hence, even a few cells that enter the distribution system can seed plumbing downstream. As discussed in Chapter 4, municipal water systems are not thought to be a major source of *Legionella* because tap water suitable for potable consumption is disinfected and is usually below the optimum temperature for growth of *Legionella*. However, low levels of *Legionella* may break through treatment barriers when the microbes are entrapped in the cysts of free-living amoebae or inside protozoa hosts where they are protected from disinfection (Dupuy et al., 2011). *Legionella* can also grow in oligotrophic environments where the disinfectant residual has declined and biofilms have developed (LeChevallier, 2019b).

Although there are many reports of *Legionella* proliferation in building water systems (see Chapter 3), there are relatively few monitoring studies of the organism in the distribution systems of U.S. public water supplies. Wang et al. (2012) detected *Legionella* species (spp.) using quantitative polymerase chain reaction (qPCR) in two chloraminated drinking water distribution systems: *Legionella pneumophila* was detected in 5.6 percent of samples and *Legionella* spp. concentrations were reduced 45-fold after tap samples were flushed for three minutes (suggesting that the microbes were primarily in the distal lines of the sampling taps). Lu et al. (2016) examined large volume (90 L) ultrafiltration concentrates from six sites within a distribution system in Georgia and frequently (57 percent) detected *Legionella* spp. by qPCR at an average concentration of 85 cell equivalents per liter. *L. pneumophila* was detected at similar frequency (6 percent) as the previous study. Concentrations of *Legionella* spp. were 0.4- to 78-fold higher in the distal sections of the distribution system compared to the entry point, suggesting growth within the distribution system.

Some municipal drinking water systems have summertime water temperatures that are favorable for the growth of *Legionella*, especially in southern climates where water temperatures may be greater than 30°C. LeChevallier (2019a,b) detected culturable *L. pneumophila* using the Legiolert™ assay in 15 of 1,087 (1.4 percent) distribution system samples (after flushing the taps for three to five minutes), and all positives occurred when water temperatures were greater than 18°C. Concentrations of *L. pneumophila* were less than 100 MPN/L except when chlorine residuals were less than 0.1 mg/L. The studies concluded that it was important that water utilities maintain at least a 0.1 mg/L chlorine residual, particularly

[1] See https://www.cdc.gov/washington /testimony/2013/t20130205.htm.

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Management of Legionella in Water Systems

when water temperatures are greater than 18°C. Riffard et al. (2001) detected *Legionella* by both culture and molecular methods in warm and cold groundwater, which under the EPA Groundwater Rule (Federal Register Volume 71, Number 216, 2006) may not be required to be disinfected. Many water supplies have storage tanks that may be prone to high water temperatures where water stratification can prevent mixing and cause subsequent loss of a disinfectant residual. Lu et al. (2015) detected *Legionella* spp. including *L. pneumophila*, *L. pneumophila* serogroup1 and *L. anisa* by qPCR in 66.7 percent of municipal drinking water storage tank sediments from 18 sites across the United States. At least one outbreak of Legionnaires' disease has been associated with a community water system storage tank whose chlorine residuals were low (Cohn et al., 2015).

Despite the water utilities' maintenance of a distribution system residual, the responsibility for most public water systems ends at the meter or property line; utilities have little control over how building owners maintain their premise plumbing systems. Thus, even the best water quality delivered by a public water supply can degrade once it enters a large building. Large building complexes may contain miles of internal plumbing with features much more favorable for bacterial growth than the main distribution system (NRC, 2006); thus, it is not reasonable to expect that minimal disinfectant residuals in the distribution system persist throughout the premise-plumbing network. Flushing specific devices (e.g., showerheads or faucets) may be practical (albeit time consuming) in such large buildings, but may be impractical for the entire building system and could negate water conservation practices. For small buildings and single-family residences, the plumbing network is much simpler. Although stagnation occurs, intervals of high water use (e.g., showering, bathing, washing clothes) will periodically bring a disinfectant residual into the building. Building owners and homeowners should be made aware of the practices that can reduce disinfectant levels and increase the risk of bacterial growth (such as whole-house filters and water softeners). Thus, a partnership between the building owners (or those maintaining the plumbing system) and the public water utility is vital. Such shared responsibility requires communication, coordination, and close consultation, which is lacking in most cases.

Ironically, the SDWA itself can be a barrier to improving water quality in some building systems. As an added measure to manage *Legionella* risk, hospitals and long-term care facilities are increasingly using on-site disinfectants. However, the addition of disinfectant to a water system serving 25 or more people deems the building a "consecutive water system" under the SDWA. This means that the building owner can be required to comply with all the requirements that apply to a public water system, including bacteriological monitoring, control of disinfection byproducts, corrosion, and water quality reports to consumers, among others—a substantial burden and cost to building owners. Some have claimed that such an interpretation of the SDWA would make implementation of building water treatment systems untenable, as there would be hundreds of thousands of water systems to regulate. For many systems, the disinfectant boost would be only on the hot-water system (where *Legionella* tends to proliferate), which some do not consider a potable supply. EPA, however, defines water "intended for human consumption" as water used for drinking, bathing, showering, hand washing, food preparation, dishwashing and maintaining oral hygiene (40 Code of Federal Regulations [CFR] §141.801 and 63 FR 41940, Aug. 5, 1998), which clearly encompasses hot-water systems.

A provision in the SWDA (40 CFR §141.29) allows states to combine consecutive systems for monitoring and compliance purposes. This provision could substantially reduce the transactional complexity of implementing treatment in building water systems. Yet EPA has provided no guidance on this provision, and there are no examples of any state using it. At the current time, buildings that have installed some type of secondary control for *Legionella* protection can technically be regulated as public water supplies; in practice, whether they are depends on the intensity of enforcement by state environmental agencies.

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Management of Legionella in Water Systems

Given the lack of concrete requirements stemming from the SDWA and the limited jurisdiction of water utilities responsibility, it can be concluded that the SDWA is not protective of the end user with respect to *Legionella* contamination. Water leaving drinking water distribution systems is not intended to be nor is it sterile, and *Legionella* spp. are going to be found in building water systems if looked for (e.g., Donohue et al., 2019).

STATE AND LOCAL REGULATIONS AND OTHER ENFORCEABLE POLICIES

Despite the absence of federal regulations or laws that could broadly control the presence of *Legionella* in water systems, there are local and state regulations that attempt to do just that. Likewise, agencies of the federal government have certain enforceable policies that affect buildings under their control. This section discusses the policies of the U.S. Department of Veterans Affairs and the Centers for Medicare & Medicaid Services, as well as New York City and State regulations for *Legionella* control in cooling towers and in certain healthcare facilities. Plumbing and building codes can also significantly impact control of *Legionella* amplification and transmission in buildings and can be widely enforced, but only at certain times during the life of a building.

Department of Veterans Affairs Directive 1061

Veterans Health Administration (VHA) Department of Veterans Affairs Directive 1061 establishes policy for the prevention and control of healthcare-associated Legionnaires' disease in VHA-owned buildings in which patients, residents, or visitors stay overnight (DVA, 2014a). Included are 170 medical centers that provide acute care, 134 community living centers, and 48 domiciliaries. The 2014 policy is premised on the notion that healthcare-associated Legionnaires' disease is most likely caused by the building's water systems, particularly the hot-water system. VHA follows the CDC definitions for "definite" and "possible" healthcare-associated Legionnaires' disease described previously (see page 106). The 2014 Directive replaces VHA policies that took effect in 2008, 2009, and 2012.

The Directive outlines a comprehensive approach to *Legionella* management, similar to some of the U.S. guidance documents and standards discussed later in this chapter, as well as several European regulations. The VHA approach consists of assessing risks, monitoring water quality, and implementing commensurate engineering controls to limit the growth of *Legionella*. Also included is monitoring of implemented controls, validating that the control measures are effective at inhibiting *Legionella* growth, and modifying measures as necessary. The Directive relies primarily on temperature control and biocides to control *Legionella* amplification in building water systems.

The preamble to the Directive sets up the tradeoff between temperature control of *Legionella* and scalding. *Legionella* are killed above 50°C (124°F), but above 110°F people are at risk of scalding. Hence, the directive does not require 50°C to be maintained in the distal parts of the hot-water system. Although this tradeoff complicates *Legionella* control in the VHA system, it was thought necessary because of their elderly and vulnerable patient population. The cold-water system is not thought to support *Legionella* growth, but it could if piped water temperatures remain greater than 25°C for several weeks.

The VHA Directive is structured around the various responsibilities of many people within VHA who will implement the Directive. In particular, the director of every medical facility is to establish a multi-disciplinary Facility Water Safety Committee to be chaired by the medical facility associate director and to include representatives from engineering and facilities management, infectious diseases, infection prevention and control, pathology and laboratory medicine, hemodialysis (if performed on

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Management of Legionella in Water Systems

site), safety and industrial hygiene, and occupational health. The facility directors must ensure that each building subject to the Directive has a written Legionnaires' disease prevention plan in compliance with the Directive. This plan must include:

a. Schematics of the building water systems (hot and cold) that show how water is distributed, circulated, stored, heated and cooled, treated, and monitored.
b. A risk assessment of the building for healthcare-associated Legionnaires' disease. This is an annual evaluation of factors that may indicate increased risk, such as patient population risk factors, presence of building units associated with increased risk (e.g., transplant units), past cases of healthcare-associated Legionnaires' disease, and past positive environmental test results.
c. Identification of water system management points for the building's potable water system(s), where monitoring and controls can be implemented to prevent the growth of *Legionella* and prevent scald injury.
d. Establishment of engineering control strategies including control limits, a monitoring schedule, and a dead-leg elimination and prevention plan.
e. Documentation of the water quality monitoring and monitoring of control measures, including process flow diagrams of the different control strategies and monitoring for each building's hot- and cold-water plumbing systems.
f. Validation that the control measures are effectively inhibiting *Legionella* growth, which involves monitoring for both *Legionella* and Legionnaires' disease.

The engineering controls discussed in the Directive are more expansive than in the 2009 VHA directive and rely primarily on temperature control supported by biocide use. The particular temperature requirements are that hot-water storage tanks must be maintained at a minimum of 140°F (60°C), instantaneous and semi-instantaneous heat exchangers must be at 130°F (54.4°C), and water in the potable hot-water system piping must be no lower than 124°F (51.1°C). To avoid scalding, the water at outlets must not exceed 110°F (43.3°C), so thermal mixing valves must be used (as discussed in Appendix B of the Directive). Biocide use is considered optional, but if used, monitoring of the residual is required in various locations. Their accompanying Plumbing Design Manual (DVA, 2014b) better explains all the engineering controls. When a case of Legionnaires' disease is found at a facility, then emergency remediation is needed, which may include thermal eradication or shock chlorination.

Validation of the control measures requires both monitoring for Legionnaires' disease and environmental monitoring of *Legionella*. The environmental monitoring consists of quarterly testing of *Legionella* in the hot- and cold-water systems (at least ten outlets each per building). The facility can choose to test additional areas and to take swab samples. If samples are positive, then additional testing of that outlet and nearby outlets and remediation are required. Depending on where positive hits occur, the entire building water system may require remediation. Notably, any amount of *Legionella* detected is considered positive and requires action (although *Legionella* concentrations are recorded).

Clinical testing of pneumonia patients at VHA facilities for Legionnaires' disease uses both the urine antigen test and culture methods, especially if there are environmental samples that test positive for *Legionella*. When a definite healthcare-associated case of Legionnaires' disease is found at a VHA facility, remediation of potentially implicated water systems is required followed by environmental testing to confirm remediation success. Possible healthcare-associated cases of Legionnaires' disease trigger a slightly less heightened response that may involve environmental testing and remediation. Investigation of environmental sources of definite or possible healthcare-associated cases can go beyond the building premise plumbing to other systems.

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Management of Legionella in Water Systems

After publication of the Directive in 2014, to oversee the program implementation VHA staff began collecting clinical and environmental data and performed site visits as needed (Ambrose et al., 2019). Among many of the challenges observed was how difficult it is to maintain hot-water temperatures and biocide residuals at end points, particularly in large water storage tanks. It also became apparent that diagnosis of Legionnaires' disease relied primarily on use of only the urine antigen test instead of both the urine antigen test and clinical culture. They also noted a lack of habitual follow-up on optimizing implementation of engineering controls.

Despite these challenges and others, an analysis of the clinical data from the first three years of Directive 1061 implementation was recently published (Gamage et al., 2018). Almost 50,000 urine antigen tests were performed for VHA patients during this time period. The highest percentage of positives for the urine antigen tests were in the summer months and in the Northeast. Of the total of 491 Legionnaires' disease cases diagnosed in VHA facilities from 2014 to 2016, 67 percent were patients who had no VHA exposure, 3 percent had definite VHA exposure, and 31 percent had "possible" VA exposure (most of these cases were outpatient, making exposure difficult to attribute to a particular source). Most of the "definite" VHA exposure patients were in long-term care, which is a high-risk healthcare setting. According to Gamage et al. (2018), the total and the non-VHA associated Legionnaires' disease rates increased from 2014 to 2016. This was true both when calculating the number of cases either per total number of VHA enrollees or per number of VA enrollees who *used the system*. These cases were thought to be community-acquired Legionnaires' disease. In contrast, the rate of *VHA-associated* cases of Legionnaires' disease with overnight exposure decreased from 2014 to 2016. While it cannot be proven that implementation of the 1061 Directive was the cause for this decrease, it did occur over the time period of implementation of the Directive.

The environmental data collected from 2014 to 2016 are not yet published but were made available on a preliminary basis during a presentation to the Committee on October 22, 2018, and at a subsequent conference (Gamage and Roselle, 2018, 2019). Included are *Legionella*, biocide, temperature, and pH data collected quarterly from at least ten hot- and ten cold-water samples. In fiscal years 2015 to 2017, almost 150,000 samples were recorded from routine quarterly testing representing data from 790 buildings. Forty-four (44) percent of the 361 buildings with three full years of data had no detection of *Legionella*. In fiscal year 2015, *Legionella* was detected in less than 8 percent of the samples, and the percentage of positive *Legionella* samples decreased significantly over the three-year period (fiscal years 2015 to 2017).

These clinical and environmental data sets being collected by the VHA are unique in their number of sites and their broad scope. Their comprehensive analysis offers enormous potential for understanding the effectiveness of measures required by the Directive to control *Legionella* contamination of water systems and to monitor risk of Legionnaires' disease for individuals.

Centers for Medicare & Medicaid Services Memorandum

The Centers for Medicare & Medicaid Services (CMS) have regulatory authority over hospitals, critical access hospitals, and long-term care facilities that receive Medicare or Medicaid funds. The pertinent regulations include 42 CFR §482.42 for hospitals, which states: "The hospital must provide a sanitary environment to avoid sources and transmission of infections and communicable diseases. There must be an active program for the prevention, control, and investigation of infections and communicable diseases." Similarly, 42 CFR §483.80 for skilled nursing facilities and nursing facilities states: "The facility must establish and maintain an infection prevention and control program designed to provide a safe, sanitary, and comfortable environment and to help prevent the development and transmission of

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Management of Legionella in Water Systems

communicable diseases and infections." And finally, 42 CFR §485.635(a)(3)(vi) for critical access hospitals states that policies must include: "a system for identifying, reporting, investigating, and controlling infections and communicable diseases of patients and personnel."

On June 2, 2017, CMS wrote a directive that requires Medicare-certified healthcare facilities to have water management policies and procedures to reduce the risk in building water systems of growth and spread of *Legionella* and other pathogens (e.g., *Pseudomonas*, *Acinetobacter*, *Burkholderia*, *Stenotrophomonas*, nontuberculous mycobacteria, fungi) (CMS, 2017). The directive endorsed the American Society of Heating, Refrigerating and Air-Conditioning Engineers' (ASHRAE) 188 standard and mentioned the CDC (2017) toolkit to aid hospitals and other facilities in implementing the ASHRAE standard. Quoting from the memo: "Healthcare facilities are expected to comply with CMS requirements to protect the health and safety of its patients. Those facilities unable to demonstrate measures to minimize the risk of Legionnaires' disease are at risk of citation for non-compliance with the CMS Conditions of Participation. Accrediting organizations will be surveying healthcare facilities deemed to participate in Medicare for compliance with the requirements listed in this memorandum, as well, and will cite non-compliance accordingly." In accordance with ASHRAE 188, the CMS memo does not explicitly require hospitals and nursing homes to conduct monitoring of *Legionella* within facilities.

In the United States there are more than 15,000 nursing homes and 4,784 hospitals registered with Medicare.[2] These numbers do not represent individual buildings because one hospital can have multiple buildings associated with it. These numbers, however, are similar to those cited in Circle of Blue (2018), which says that the CMS memo applies to 15,688 nursing homes and 6,862 hospitals, which includes children's care, psychiatric, and rehabilitation centers. According to the Circle of Blue report from December 9, 2018, it is too early to know whether hospitals are complying with the CMS memo. Many of the larger hospitals that receive Medicare and Medicaid reimbursements independently instituted *Legionella* management in their buildings years ago. Given that nursing homes are surveyed for compliance annually and hospitals are surveyed only every three years, it may take time for CMS to obtain enough data to establish the level of compliance. CMS has yet to announce how many of the compliance surveys completed since the memo's publication in 2017 found inadequate *Legionella* management plans.

Given its brevity and reliance on ASHRAE 188, the CMS memo does not provide any specifics; for example, it does not indicate the required temperatures for building hot-water systems (unlike the VHA Directive 1061, which is very prescriptive, as detailed above). However, CMS defines "immediate jeopardy" with respect to scalding as "access to hot water of sufficient temperature to cause tissue injury" (CMS, 2014). This vague definition has been interpreted differently by states, from South Dakota allowing an operating hot-water temperature of 125°F (52°C) to other states that have defined immediate jeopardy as 105°F (40.5°C). CMS could have a rapid, profound impact on *Legionella* management in facilities that receive Medicare and Medicaid reimbursements if it specified that immediate jeopardy is not reached until hot-water temperatures are greater than 125°F (52°C) (see Table 4-3).

New York City and New York State Cooling Tower Regulations

The first regulation in the United States to require registering and monitoring cooling towers for *Legionella* was enacted in 2005 in Garland, Texas, for cooling towers associated with multifamily housing; it was later revised to include hotels and places of accommodation (Whitney et al., 2017). The ordinance was simple and implemented at low cost to the health department, resulting in a decrease in the number of contaminated cooling towers over time. All testing was required to be independent of those responsible for maintenance.

[2] See data.medicare.gov.

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Management of Legionella in Water Systems

Ten years later, New York City passed similar legislation following recent outbreaks of Legionnaires' disease caused by cooling towers in the city. Local Law 77 when into effect in 2015, with the New York City Department of Health and Mental Hygiene implementing the law. New York State followed by creating Title 10 Part 4 of the New York Codes of Rules and Regulations (10 NYCRR Part 4 "Protection against *Legionella*"). Final adoption of the New York State regulations occurred in July 2016. The state's regulations apply statewide, including in New York City, such that there is overlap between the city and state regulations.

The New York City and New York State regulations require cooling tower owners to take the following actions:

1. Register existing and new cooling towers with the city and state.
2. Sample each cooling tower for *Legionella* every 90 days.[3] Notify the city within 24 hours if *Legionella* culture results are greater than 10^6 CFU/L; the state every 90 days while the cooling tower is in operation; and the local health department within 24 hours for any result greater than 10^6 CFU/L.
3. Perform daily chemical treatment of system water.
4. Monitor temperature, pH, conductivity, and biocides at least three times per week. Microbial monitoring (heterotrophic plate counts) must be performed weekly, wetted surfaces are visually inspected weekly, and chemical treatment equipment is also checked.
5. Inspect the cooling towers every 90 days and obtain annual certification, by a qualified person.
6. Develop and follow maintenance program and plan in line with the ASHRAE 188 standard.
7. There are various other requirements for drift eliminators, materials, cleaning, and documentation.
8. If an owner does not register, have a maintenance program and plan, obtain certification, disinfect, perform or obtain culture sampling and analysis, or inspect a cooling tower within the required time and manner, New York State or the local health department may determine that the situation constitutes a nuisance and may take action, as authorized by law. New York State or the local health department may also take any other action authorized by law, including imposing any and all applicable civil and criminal penalties.

More details on reporting, enforcement, penalties, and updates can be found in the official documentation (NYC, 2016a,b).

As of April 2019, there were approximately 6,100 cooling towers registered in New York City and about 11,000 in New York State (including New York City). Currently, results from the New York City *Legionella* sampling are not publicly available, but this will change in October 2019. Cooling tower data for New York State are publicly available.[4] Both the city and state programs have seen progress in implementation and adherence to the existing regulations. For New York State, rates of cooling tower compliance with current regulations increased from 30 percent in 2017 to 67 percent in 2018. In New York City, the cooling tower registry has been invaluable in providing real-time information for Legionnaires' disease cluster response. Promptly locating cooling towers and having a history of operations and

[3] All monitoring thresholds in this chapter are expressed in CFU/L for consistency. However, this is not meant to imply that all samples are 1 L in volume. Sampling protocols differ between jurisdictions.

[4] See https://health.data.ny.gov/Health/Registered-Cooling-Towers-Beginning-August-2015/24a4-muw7.

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Management of Legionella in Water Systems

maintenance records has provided valuable information for identifying potential sources and evaluating risk. Additional benefits of the regulations include:

- An increase in the proportion of cooling tower systems that have a maintenance program and plan;
- An increase in the proportion of cooling tower systems that have water treatment including biocide, anti-corrosion, and anti-scaling treatment;
- An increase in the proportion of cooling tower systems that document and maintain operational records; and
- An increase in *Legionella* and bacterial monitoring during cooling tower operation.

The proportion of cooling towers testing positive for *Legionella* in samples collected by the department is typically below 30 percent and has remained relatively stable in the first two years of implementation of the regulations.

New York State Healthcare Facility Requirements for *Legionella*

As of July 2016, all general hospitals and residential healthcare facilities in New York State are required to perform an environmental assessment, prepare and implement a sampling and management plan to sample their potable water systems for *Legionella*, and institute control measures in the event of a *Legionella* exceedance. The New York State regulations apply to buildings of general hospitals that provide in-patient services or buildings of residential healthcare facilities that provide a "health-related service," such as lodging, board, and physical care. The regulation does not apply to administrative buildings of such facilities, general hospital buildings that only provide outpatient services, or to diagnostic and treatment centers providing only outpatient services.

All covered facilities must perform an environmental assessment of the facility using a specified environmental assessment form prior to providing services, and when specified by the New York State Department of Health (NYS DOH), such as when there are suspected or actual cases of legionellosis, after certain construction and repairs, and after expansion and relocation of certain medical units. Furthermore, all covered facilities must adopt and implement a *Legionella* culture-based sampling and management plan for their potable water systems. New covered facilities must adopt this plan prior to providing services. *Legionella* culture sampling and analysis must occur at 90-day intervals during the first year of sampling and management plan implementation, and annually thereafter. Portions of any potable water system that serve hematopoietic stem cell transplant or solid organ transplant patients must continue to be sampled and analyzed at intervals not to exceed 90 days. *Legionella* culture sampling and analysis must also occur in a timeframe determined by the state health department.

All *Legionella* culture analyses must be performed by a laboratory that is approved to perform such analysis by the New York State Environmental Laboratory Approval Program (ELAP). When 30 percent or more of *Legionella* culture samples contain *Legionella,* regardless of species, facilities are required to institute control measures, resample their water system, and notify the NYS DOH. (This 30 percent threshold stems from the Allegheny County guidance mentioned in a subsequent section.) The covered facility must maintain the required environmental assessment and any associated sampling results on the facility premises for at least three years. These records must be made available to the NYS DOH immediately on request. The department may conduct an assessment and/or *Legionella* culture sampling and analysis of the potable water system at any time. A violation of any provision of the regulation is subject to civil and criminal penalties. Each day that an owner remains in violation of any provision of this Subpart

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Management of Legionella in Water Systems

constitutes a separate and distinct violation of each such provision.[5] Citations during routine facility inspections are issued by healthcare facility surveyors, who are tasked with implementing the 2017 CMS memo on *Legionella* prevention in healthcare facilities. NYS DOH reports that letters of non-compliance sent to healthcare facilities have had positive effects (mostly immediate responses and compliance).

Legionella data stemming from this regulation are not currently available on a public platform, nor is direct reporting of culture data to the NYS DOH a requirement of the regulations. NYS DOH is developing measures to evaluate the effectiveness of the regulations, while recognizing that several more years of data will be needed to identify meaningful trends.

Plumbing Codes

Plumbing codes dictate almost every facet of building plumbing design and installation, including insulation, materials used, allowable pipe size and length, allowable volume from a hot-water source to a tap, control of heated water systems including storage and circulation, drain water heat recovery, and commissioning. Building owners have to be in compliance with plumbing codes when a building is being built or renovated; hence, codes are mainly enforceable prior to a certificate of occupancy being signed. Some plumbing codes can be used to partially manage *Legionella* in building water systems, and those codes are the focus of this section. Plumbing codes can provide a backstop for buildings, such as residences, that would otherwise not fall under any guidance documents or other enforceable policy for *Legionella* management.

The three main plumbing codes are the International Plumbing Code (ICC, 2017), the Uniform Plumbing Code (IAPMO, 2018a), and the National Standard Plumbing Code (IAPMO, 2018b). Plumbing codes are adopted at the state level but are generally enforced at the county or municipal level by the relevant inspection entity. The International Plumbing Code is revised every three years by the International Code Council (ICC). It has been adopted at the state or local level in 35 states. The Uniform Plumbing Code was developed by the International Association of Plumbing and Mechanical Officials (IAPMO), also on a three-year cycle, and has been adopted in 13 states, mainly in the west and northwest United States including California. The National Standard Plumbing Code was developed by the Plumbing Heating and Cooling Contractors of North America (which was recently purchased by IAPMO) and has been adopted in New Jersey and parts of Maryland and is not discussed further here. It should be noted that in states with state-wide codes, these codes may be modified by local ordinances. For example, California adopts a statewide plumbing code, but in Colorado each jurisdiction (individual cities and counties) can adopt different codes. For all three codes, product manufacturers tend to drive the code change proposals.

Historically, plumbing codes were not written with the goal of managing building water systems for *Legionella*. In fact, some codes (unintentionally) work against the control of *Legionella*. For example, pipe-sizing requirements that were set more than 50 years ago remain unchanged, even though plumbing fixture flow rates, flush volumes, and appliance volumes have been reduced every decade since the 1950s. Because there have been significant reductions in average residential water use since the 1980s without concomitant reductions in pipe sizes, household flow rates have been drastically reduced. There are many unintended consequences of having lowered water use in conjunction with oversized pipes. Foremost among them is that hot water takes much longer to arrive at taps. As discussed in Chapter 4, increased water residence times in premise plumbing systems can lead to conditions highly conducive to *Legionella* growth. A related issue is that plumbing codes were created under the assumption of fixed-orifice de-

[5] See https://www.health.ny.gov/environmental/water/drinking/ legionella/hospitals_health_care.htm, https://regs.health.ny.gov/content/subpart-4-2-health-care-facilities.

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Management of Legionella in Water Systems

vices. Today, however, many devices have pressure-compensating aerators, which provide a constant flow rate to the consumer above 20 psi pressure. The use of such aerators should allow builders to more correctly size pipes, but these corrections have not yet found their way into plumbing codes.

A second plumbing code feature that affects *Legionella* management is the temperature requirement, particularly in public bathrooms. Since 2006, the International Plumbing Code has stipulated that, for public bathrooms, the temperature of hot water at handwashing stations must be between 85°F (29.4°C) and 110°F (43.3°C)—the definition of tempered water. Hence, the codes require delivery of water in the temperature range optimal for *Legionella* growth. The 2018 International Plumbing Code defines "hot water" as greater than 110°F (43.3°C), while the Uniform Plumbing Code defines it as 120°F (48.9°C).

To meet the temperature requirements, plumbing codes mandate the use of certain devices, such as thermal mixing valves, to deliver water of various temperatures to various locations in premise plumbing, particularly near end-use points and at emergency stations. The International Plumbing Code also requires thermal mixing valves for every public handwashing sink. As discussed in Chapter 4, these devices tend to fail without warning in a few years, especially when substandard devices are used. The plumbing codes do not require periodic testing of thermal mixing valves. Another device requirement found in plumbing codes is for combination tub and shower valves that deliver cold, warm, or hot water. Often, the highest flow rate than can be achieved with these devices is for the mixed temperature water, not the hot water, leading to oversized pipes.

Material requirements in plumbing codes can affect *Legionella* management. Both the International Plumbing Code and the Uniform Plumbing Code dictate materials to be used for piping, devices, and joints, among others, with the list of acceptable materials being determined mainly by the manufacturers. To avoid future liability, manufacturers tend to avoid promoting materials that leach compounds. Nevertheless, it would be preferable if the requirements in the plumbing codes were based on robust studies of what materials are more or less favorable to growth of *Legionella*.

Indeed, to have the greatest positive effect on *Legionella* management, plumbing code changes would suggest new ways to design plumbing systems before a building is constructed. The main tenet of an ideal code would be to correctly size pipes to reflect lowered water use and measured pressure drops in systems with modern pipe materials and fittings. In addition, builders should be incentivized, perhaps with energy credits, to build compact plumbing cores with no more than ten feet between the hot-water source and fixtures. Another practice to incentivize would be the use of electric tankless water heaters that would require no mixing valves, or the use of heat trace to maintain adequately high temperatures in pipe branches. Finally, the plumbing codes could define tempered water to be between 120°F and 130°F (43.3°C to 48.9°C), such that water delivered to taps would not be in the range of optimum *Legionella* growth.

GUIDANCE DOCUMENTS

Many guidance documents that outline steps to manage *Legionella* in building water systems have appeared over the past five years. The most prominent of these are discussed below, including the ASHRAE 188 standard, guidance from the American Industrial Hygiene Association (AIHA, 2015), National Sanitation Foundation International (NSFI) standard 453, and the guidelines from the Allegheny County Health Department in Pennsylvania.

In general, like the VHA Directive, the major guidance documents take a risk-based approach to managing *Legionella* in building water systems. To a greater or lesser extent, they each follow the

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Management of Legionella in Water Systems

general principles of risk management and require development of a plan or program to mitigate the risk (variously called water safety plans, water management programs, and other terms). Each plan or program typically follows the basic steps shown below (which are similar to those within the VHA Directive):

- Establish a program team.
- Describe each water system.
- Analyze where potential hazards may exist, develop, or propagate.
- Identify control measures and where they should be applied to stay within limits.
- Monitor certain parameters (not necessarily *Legionella*) to determine if control measures are working.
- Confirm that the program is being implemented as designed (verification) and that the program effectively controls the hazardous conditions (validation).
- Document everything.

Depending on the guidance document and its developers, certain specifics for managing *Legionella* in water systems are enhanced or expanded to meet the needs of their organizations. Interestingly, each guidance document is sufficiently vague to permit individual users the flexibility and latitude to address those program aspects either unique or specific to their own buildings or uses. On the other hand, the lack of strong commonality among these documents on the details and specifics of managing *Legionella* in water systems collectively creates confusion. In fact, one of the primary drivers for the creation of the CDC's tool kit (CDC, 2017) was to specify how to actually apply the ASHRAE 188 standard. Highlights of each major guidance document and their particular differences are identified below.

Allegheny County Health Department *Legionella* Guidelines

Guidance documents produced by the Allegheny County Health Department (1993, 1997, 2014) were some of the first to address *Legionella* in building water systems. These guidance documents say that all facilities should take a risk management approach regarding *Legionella* in their water systems. A key recommendation is development of a water safety plan, the elements of which are described above. However, there is no requirement in the water safety plan for a program team or for documentation in the Allegheny County Health Department guidance. The guidance specifically outlines different types of control measures, from thermal disinfection to point-of-use filters. Finally, unlike the other guidance documents, this guidance includes a section on managing Legionnaires' disease in patients.

The Allegheny County Health Department guidance documents are the basis for the 30 percent positivity rule that has permeated many other guidance documents as well as the previously described New York State regulations for healthcare facilities. Best et al. (1983) found that whenever monthly site positivity of environmental testing for *Legionella* in a large building exceeded 30 percent, cases of Legionnaires' disease appeared in those months. Furthermore, when positivity fell to 20 percent or less, no cases of disease were observed. The 30 percent value is very controversial, as is noted in the 2014 guidance from Allegheny County. The Committee notes substantial difficulties with using this guidance, including the fact that the analysis has not been repeated and validated elsewhere and it has frequently been applied in situations that lack an adequate number of samples. While it was useful in the 1990s, comprehensive guidance based on *Legionella* concentration along with the frequency of detection would be more consistent with the available science.

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Management of Legionella in Water Systems

ASHRAE Standard 188 on *Legionella* in Building Water Systems

The ASHRAE 188 standard (ASHRAE, 2015) is a guidance document for all types of buildings and their water systems, with the exception of residential single-family homes. The core of the standard is for each building to have a water management program that has seven elements, as described in the bulleted list above. For ASHRAE 188, the most important element is the creation of a program team to make decisions about other aspects of the water management program. Notably, ASHRAE 188 does not specify that monitoring of *Legionella* in the building water system is necessary unless the program team decides that it is. Instead, to manage *Legionella* occurrence, the focus is on controlling and monitoring certain physicochemical factors (e.g., temperature, disinfectant residual, and maintenance).

ASHRAE 188 considers individual types of water systems, from the potable water system to cooling towers and evaporative condensers, spas, fountains, and aerosol-generating misters. There are some peculiarities for each type of water system, and the standard states that details are given in ASHRAE Guideline 12 (ASHRAE, 2000). The standard also covers requirements for *designing* building water systems, such as documenting potential hazards in all major water systems, as well as documentation of all the water systems themselves upon installation, including what was built and where, what materials were used, and corresponding manuals. Detailed instructions for commissioning, including flushing and disinfection, have to be provided.

Annexes treat specific issues or building types, such as Annex A for healthcare facilities. This Annex calls for a yearly evaluation of the likelihood of legionellosis in healthcare facilities, which is not mentioned in the main part of the standard. Annex C states that any *Legionella* testing must be done by accredited laboratories.

CDC Tool Kit

The CDC tool kit (CDC, 2017) was created to help building owners and managers develop and implement a water management program to reduce a building's risk for growing and spreading *Legionella*. The toolkit both simplifies and explains ASHRAE 188, and it applies the principles to healthcare facilities. For example, there are a series of questions to be answered to determine if a particular building is at risk of *Legionella* contamination, as well as sections that specify how to assemble the program team. There is a useful flow diagram of a building's water system, which is then used repeatedly throughout the water management program to identify areas that may be susceptible to *Legionella* growth and to show where control measures will be applied. Examples are given of when a control limit is exceeded and corrective actions are necessary, and what to do if *Legionella* is found in a building. The toolkit provides further details for healthcare facilities, which are more likely to suffer adverse effects from *Legionella* contamination.

AIHA Guidance on *Legionella* in Building Water Systems

AIHA (2015) is a guidance document intended to help building managers anticipate, recognize, evaluate, and control *Legionella* in buildings. It covers premise plumbing; cooling towers and evaporative condensers; hot tubs, whirlpools, and spas; decorative fountains and water features; humidifiers; the water supply system; and sprinklers, eyewash stations, and safety showers. The guidance differentiates its approach to *Legionella* management (which comes from the industrial hygiene field) from what is labeled

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Management of Legionella in Water Systems

"current health practice" that goes into action only after a case of Legionnaires' disease has occurred. The guidance describes such "current health practice" as appropriate for diseases transmitted between persons, but ineffective when the environment is the source of the etiologic agent. Hence, AIHA (2015) focuses on identifying sites of *Legionella* amplification and exposure pathways using measurements of viable *Legionella* bacteria; it does not endorse sampling surrogates such as disinfectant residual.

Similar to other guidance documents, AIHA (2015) is based on risk assessment, but it tends to be more descriptive. It specifically calls for *Legionella* samples to be collected (to be assayed via the culture method) from selected water systems on an ongoing basis to determine the effectiveness of control strategies and identify potential hazards. AIHA (2015) recommends that, although PCR techniques can be used as a complementary analysis, they should not replace culture-based methods. Table 5-1, taken from the guidance document, provides levels of *Legionella* that can be thought of as action levels to compare to routine sampling results. For all water system types (except cooling towers), a measured concentration below 1 CFU/mL (1,000 CFU/L) is considered to be at the detection limit. Between 1 and 10 CFU/mL (1,000 to 10,000 CFU/L), *Legionella* amplification could be possible. A sample above 10 CFU/mL (10,000 CFU/L) indicates that amplification has occurred, and action needs to be taken (for cooling towers, the document suggests that 100 to 1,000 CFU/mL [10^5 to 10^6 CFU/L] is indicative of possible amplification). These values mirror those of the Occupational Safety and Health Administration (OSHA), which used to suggest guidelines for *Legionella* to assess the effectiveness for water system maintenance but no longer does.[6]

TABLE 5-1 AIHA Data Interpretation Guidelines

Sample Source	Non Detectable	Acceptably Low*	Action	Possible Amplification	Action	Indicates Amplification	Action
Humidifiers & Misters	<1 CFU/mL	<1 CFU/mL	1	1–10 CFU/mL	2	>10 CFU/mL	3
Decorative Fountains and Water Features	<1 CFU/mL	<1 CFU/mL	1	1–10 CFU/mL	2	>10 CFU/mL	3
Hot Tubs, Whirlpools and Spas	<1 CFU/mL	<1 CFU/mL	1	1–10 CFU/mL	2	>10 CFU/mL	3
Potable Water	<1 CFU/mL	<10 CFU/mL	1	10–100 CFU/mL	2	>100 CFU/mL	3
Industrial Working Fluids	<1 CFU/mL	<10 CFU/mL	1	10–100 CFU/mL	2	>100 CFU/mL	3
Cooling Towers & Evaporative Condensers	<10 CFU/mL	<100 CFU/mL	1A	100–1,000 CFU/mL	2A	>1,000 CFU/mL	3A

*May be limited by *Legionella* levels in the building source water supply (e.g., municipal water). Action levels (see AIHA 2015 for complete details): (1) Continue to monitor as per the plan. (2) If no cases of legionellosis, reassess maintenance and treatment plans; make adjustments as necessary. If cases of legionellosis occur, take immediate steps to clean and disinfect the system. Notify appropriate health authorities. (3) Take immediate steps to clean and disinfect the system. Adjust control plan as needed. SOURCE: AIHA (2015).

Unlike the other guidance documents, AIHA (2015) discusses side effects of various treatment techniques that need to be taken into account. The guidance also provides considerable detail about how to protect workers and building occupants (such as with point-of-use devices) during remediation activities.

[6] See https://www.osha.gov/dts/osta/otm/otm_iii/otm_iii_7.html#app_iii:7_3.

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Management of Legionella in Water Systems

NSFI Standard 453 for Cooling Towers

NSFI standard 453 (NSFI, 2017) provides minimum practices for treating, operating, and maintaining cooling towers to avoid *Legionella* growth. The standard uses the terms *program* (all the conducted activities) and *plan* (the documentation of the program) and adheres to the bulleted list of risk management elements discussed previously.

Standard 453 requires treatment of cooling towers with an oxidizing biocide as well as maintenance of pH, corrosion control, scale and deposit control, and conductivity. Startup procedures for cooling towers are outlined, including initial startup and after a system shut-down. Routine inspection, service, and maintenance are outlined, including weekly, quarterly, and when there is an issue. Cycles of concentration are a key operating parameter for cooling towers that need to be monitored, managed, and documented.

Monitoring of biocides is required as part of standard 453, as is testing for heterotrophic plate counts and *Legionella*. If concentrations of *Legionella* are less than 10 CFU/mL (10,000 CFU/L), no action is needed. If concentrations are between 10 and 100 CFU/mL (10,000-100,000 CFU/L), then the entire program needs to be reviewed and on-line remedial treatment is needed. Between 100 and 1,000 CFU/mL (10^5 to 10^6 CFU/L), a visual inspection is also required (in addition to the above) to determine if full draining and repair are required. Greater than 1,000 CFU/mL (10^6 CFU/L) requires off-line remedial treatment, and the standard describes the conditions for completely shutting down the cooling tower. This standard will be superseded by NSFI standard 444, which, when released, will cover all building water systems, not just cooling towers.

REGULATIONS AND POLICIES FROM OTHER COUNTRIES

Although there are no nationwide regulations for *Legionella* management in the United States, several other countries, notably those in Europe, have enacted regulations meant to manage *Legionella* in various types of water systems. Some of these mirror the document produced by the World Health Organization (WHO) in 2007, which advocated that buildings have a water safety plan and monitor temperature, pH, and (for validation purposes only) *Legionella*. This section summarizes information gathered by the Committee from representatives of six countries about their *Legionella* laws, regulations, guidance documents, and codes. Their presentations described the regulations, noted what water systems they apply to, and discussed the extent of compliance with the regulations. Each presenter described the environmental monitoring that must accompany the regulations, including threshold levels above which remedial or preventive action is taken. Finally, they talked about whether the regulations have had an impact on reducing rates of Legionnaires' disease or environmental concentrations of *Legionella*. The six countries are Australia, Canada, France, Germany, the Netherlands, and the United Kingdom.

The European Working Group for *Legionella* Infections (EWGLI) published guidelines for the prevention, control, and investigation of infections caused by *Legionella* spp. (EWGLI, 2017), but their recommendations have no legal standing. A new European Drinking Water Directive was developed in 2018 (EU, 2018), which makes risk assessment in domestic building water systems obligatory. This risk assessment includes risks linked to products and materials in contact with drinking water and monitoring for lead and *Legionella*. *Legionella* was included in the directive because (1) it has been found by the WHO to cause the highest health burden of all waterborne pathogens in the European Union (EU) and (2) the European Centre for Disease Prevention and Control recommended regular checks and appropriate control measures to human-made water systems to prevent cases of Legionnaires' disease at

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Management of Legionella in Water Systems

tourist accommodation sites, hospitals, long-term healthcare facilities, or other settings where sizeable populations at higher risk may be exposed (ECDC, 2017). How *Legionella* sampling and analysis should be performed is also defined in the new EU drinking water directive. One-liter samples must be taken at the consumer's tap without prior flushing and analyzed for culturable *Legionella* according to ISO 11731 (ISO, 2017). When the culturable *Legionella* number in a drinking water sample does not comply with 1,000 CFU/L, resampling has to be performed, and new samples have to be screened for *L. pneumophila*. When *L. pneumophila* is detected, action has to be taken. If *L. pneumophila* is not detected during resampling and cultivable *Legionella* is less than 10,000 CFU/L, no action has to be taken. Each EU member state determines what action their country will be take when these action levels are exceeded. After the first vote in the EU parliament, several amendments were suggested, but the expectation is that the new directive will be adopted soon by the EU parliament. EU countries without *Legionella* regulations will have to comply with the new action levels. Those countries that already have *Legionella* regulations in place (discussed below) tend to be more strict than the new European directive; as a result, they will not have to modify their regulations.

The Netherlands

Four laws in the Netherlands were revised to include *Legionella* spp., in each case following an outbreak. For the first *Legionella* outbreak, in 1999, a hot tub on display in Bovenkarspel was found to be the source of the bacteria, resulting in more than 200 cases of Legionnaires' disease with 32 fatalities (den Boer et al., 2002). This outbreak led to the addition of regulations to the Drinking Water Act, the Hygiene and Safety Act, and the Safety at Work Act. In 2006, a second outbreak caused by a contaminated cooling tower in Amsterdam led to the creation of new regulations in the Environmental Protection Act. *Legionella* is the only pathogen in premise plumbing to be a target of Dutch regulations.

The Drinking Water Act regulations apply only to buildings labeled "priority premises" such as hospitals and other healthcare facilities with overnight stays, hotels and other accommodations that house more than five people, truck stops with showers, harbors and marinas with showers, asylum centers, and prisons. The Act requires that a risk management plan for the building be created, and include such risks as water stagnation, tepid temperature, formation of aerosols, presence of high-risk individuals, past cases of Legionnaires' disease, whether the building accommodates travelers, whether it is used for temporary events, and lack of proper maintenance. The owner of the building must periodically update the risk management plan. Management plans are generally created by certified consultants and must conform to technical guidelines (e.g., about how, when, and where to sample).

The highest priority control methods discussed in the Act are temperature control, flushing, UV treatment, and filtration. Secondary methods include electrochemical treatment such as copper-silver ionization. Chlorination is a tertiary treatment, although it conflicts with the long-standing Dutch paradigm of not carrying a disinfectant residual in finished water. In terms of temperature control, cold water must be maintained at less than 25°C, while hot water must be higher than 60°C throughout the hot-water system. The Act requires that buildings be sampled every six months for *Legionella* spp. using culture methods. If the concentrations are less than 100 CFU/L, no further action is taken. Above 100 CFU/L and especially above 1,000 CFU/L, certain response actions are required such as informing the users of the building, taking appropriate measures to prevent a public health threat, and notifying the Inspectorate. It is noteworthy that these numbers were chosen for practical reasons and are not health-based. The detection limit for the laboratories is 100 CFU/L, and 1,000 CFU/L was a practical number larger than 100 CFU/L.

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Management of Legionella in Water Systems

The Hygiene and Safety Act is similar to the Drinking Water Act, but it applies to swimming and bathing facilities above a certain size and where aerosols are dispersed. It does not apply to hot tubs. As above, a risk management plan is required, and the monitoring requirements are the same as in the Drinking Water Act. Major differences are that certification of consultants is not required, there are no technical guidelines available, and any disinfection method can be used.

The Environmental Protection Act applies to wet cooling towers only. Like the previous two Acts, it requires a risk assessment and management plan that includes treatment and monitoring. Technical guidelines are also available to help guide the creation of such plans. However, no specific treatment is required as long as an effective method is used. Similarly, the monitoring requirements are loose, with no specific threshold above which action must be taken and no recommended frequency of monitoring. This Act does not require that the consultant creating the risk management plan be certified, but the plan must be updated when cooling tower operations change or the surroundings change. The Act requires all cooling towers built after 2010 to be registered; currently, about one-third of all towers are registered.

The Safety at Work Act aims to protect workers from *Legionella* exposure. As with the other Acts, a risk assessment and management plan is needed. The Act does not require particular treatment methods or monitoring frequency, although it does specify a threshold of 100 CFU/L as measured by culture.

Implementation of the Drinking Water Act regulations has been tracked since 2009 via facilities inspections. The trends suggest that more and more of the facilities are becoming "no risk." For cooling towers, data from 2011 and 2015 suggest that municipalities are identifying their cooling towers (88 percent) and that a substantial portion of towers are being registered (30 percent). On the other hand, inspections lag behind, with two-thirds of inspectorates not visually inspecting their cooling towers. Less information is available on implementation of the Hygiene and Safety Act and the Safety at Work Act. All of the regulations, except the Safety at Work Act, are supposed to be enforced via inspections, which could then lead to warnings, fines, and facility closure.

There is no information on whether these regulations have affected either rates of Legionnaires' disease or environmental sampling of *Legionella*. In the Netherlands in general, Legionnaires' disease rates are still going up (they were 3.3/100,000 in 2017—ECDC, 2019), although travel-associated cases seem to have leveled off. Many believe the national data are insufficient to evaluate the impact of the regulations, particularly given the lack of data on both Legionnaires' disease rates and *Legionella* concentrations collected at the same location.

Germany

German regulations for *Legionella* spp. extend drinking water regulations into premise plumbing. In 1987, the German Federal Health Department said that drastic reduction in *Legionella* concentrations was necessary to reduce infections, further emphasizing that the goal should be "as low as reasonably achievable." The country's federal Protection Against Infection Act regulates water for consumption as well as swimming pools and bathing water and all wastewater treatment plants. For drinking water in particular, there is not only the Protection Against Infection Act, but also the EU Drinking Water Directive (discussed previously), a German ordinance on the quality of water for human consumption, and proposals of the German federal Environmental Protection Agency. The Protection Against Infection Act requires a *Legionella* risk management plan for every large building that has more than 400 liters of hot water or more than three liters of hot water between the water heater and the last tap at the end of the pipe. Healthcare facilities are required to maintain a temperature of 60°C at hot-water heaters and 50°C at distal points of hot-water systems. To facilitate compliance with the regulations, there are at least six technical standards that stem from the Act.

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Management of Legionella in Water Systems

The federal German Emissions Control Act and technical guidance cover every open cooling tower. They have similar requirements for a management plan, monitoring, and concentration thresholds above which action must be taken.

The Protection Against Infection Act also targets *Legionella* that may stem from the disposal of wastewater, both industrial and municipal. The impetus for its implementation was a 2013 outbreak caused by outflow from a wastewater treatment plant. Specifically, a brewery was disposing of warm (38°C) wastewater, which was found to have high levels of *Legionella* (10^7 CFU/L), and the receiving river was contaminated for 12 kilometers downstream of the outfall with some 200,000 CFU/L of *Legionella* (Maisa et al., 2015). Therefore, it was decreed that wastewater treatment plants must be monitored for *Legionella* by culture methods. It has now become evident that warm wastewaters from breweries, paper mills, and sugar processing plants can have very high *Legionella* concentrations.

These regulations require monitoring of environmental samples for *Legionella* spp. at various locations in a building; measured concentrations must be less than 100 CFU/100mL (1,000 CFU/L). This concentration is called a technical action level and, as in the Netherlands, it is not a health-based number, but rather a value above which certain additional precautions must be taken, including checking the sanitary and technical condition of the drinking water installation in the form of a risk analysis and informing public health agencies.

The regulations are accompanied by many technical guidance documents and rules for planning and construction, much like plumbing and building codes in the United States. Code of Practice W551 (DVGW, 2004) addresses measures to reduce *Legionella* growth in buildings and is particularly relevant, as it recommends that one keep the volume of stored hot water small, keep the hot water hot and the cold water cold, avoid stagnation, maintain and inspect, rehabilitate, and perform more microbiological examinations. There is also a code for remedying microbial irregularities in drinking water installations (W556, 2015), and one for cleaning and disinfecting drinking water installations (W557, 2012). Guideline 6023 deals with qualifications and staff training. Cooling towers are subject to a Cooling Tower Code of Practice, which has threshold concentrations above which remedial actions are required.

All of Germany has to comply with the regulations, and compliance is high because building owners can be punished by law for not complying. Implementation of the regulations in large cooling towers and most building water systems is now broad, although the implementation is not as widespread for small cooling towers. The sewage regulations are only being enforced in North Rhine Westphalia. In general, the government tries to educate water consumers about *Legionella* by posting information on every public health department's website. If monitoring data are above the action level for a large apartment building, the building owner has to inform the occupants. As a result, people have become much more aware of *Legionella*. There are also guidelines for the homes of immunosuppressed people.

Germany has been trying to determine the impact of their regulations with the LeTriWa (Legionellen in der Trinkwasser) Project conducted in Berlin from 2017 to 2019, which is reviewing outbreak reports and follow up surveillance. There is no indication that cases of Legionnaires' disease have gone down since the regulations came into effect. In 2017, the case rate in Germany was 1.6 per 100,000 people (ECDC, 2019). However, the LeTriWa study has shown that since the regulations went into effect, the percentage of buildings that have culturable *Legionella* has declined from 70 percent to just 10 percent (Exner, 2018). There is also anecdotal evidence that a hospital that had 11 cases of Legionnaires' disease in 1990 has had no cases since the implementation of controls (Exner, 2018).

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Management of Legionella in Water Systems

England

England's regulations for *Legionella* management have evolved from two pages of guidance in 1980 to hundreds of pages today. The primary impetus for creating regulations was the 1985 outbreak of Legionnaires' disease at Stafford Hospital. Engineering guidance was then developed for cooling towers and evaporative condensers. In 1991, the Health and Safety Commission published the Approved Code and Practice for the Prevention of Legionellosis. In 1998, there was specific guidance for hot- and cold-water systems. In 2000, everything was combined into one guidance called L8, in which there are various levels of documents: laws, regulations, approved codes of practice, and technical guidance.

Much of the guidance stems from the 1974 Health and Safety at Work Act, which aims "to ensure the health and safety of employees and non-employees so far as reasonably practicable." Although the term "reasonably practicable" is ambiguous, it has held up over the years because the risks of Legionnaires' disease are significant and the consequences may be deadly, so high cost is justified. The various UK laws and regulations have many facets in common. The Control of Substances Hazardous to Health regulations have a series of requirements, including a risk assessment and control measures. The Management of Health and Safety at Work regulations also require risk assessment, more planning control, monitoring, and review of preventive measures. The Notification of Cooling Towers and Evaporative Condensers Regulations of 1992 are the only regulations that specifically address *Legionella.* Cooling towers must also be registered, and more than 90 percent are.

The main L8 regulations have four accompanying guidance documents that cover evaporative cooling systems, hot- and cold-water systems, spas and pools, and other systems. The regulations apply to all systems containing water likely to exceed 20°C for which there is a means of creating and transmitting water droplets that may be inhaled. The building types covered include shops, offices, factories, hospitals, industrial plants, entertainment facilities, and rented properties, among others, but private residences are excluded. Healthcare facilities have a slightly different set of regulations stemming from the Health and Social Care Act of 2008, a new set of regulations, a new Code of Practice, and new technical memos. To maintain their registration, all healthcare facilities must follow the Code of Practice. The latest version of the technical memo uses the terms water safety groups or water safety plans and highlights the role of climate change. It applies not just to *Legionella* but also to *Pseudomonas aeruginosa* and mycobacteria, among other pathogens.

The maintenance of an adequate temperature control regimen is presented as the preferred approach for *Legionella* control (Department of Health and Estates and Facilities Division, 2006a,b; HSE, 2013). Hot-water temperature leaving the water heater should be maintained at more than 60°C, temperatures in the return loop should be above 50°C, and temperature at determined sentinel points (including the farthest draw-off point) should exceed 50°C for all types of buildings and, for healthcare facilities, above 55°C after draw-off of one minute (HSE, 2013).

The monitoring requirements for cooling towers are quarterly sampling for *Legionella* spp. with a target of less than 100 CFU/L. Heterotrophic plate counts have to be less than 10,000/mL. For hot- and cold-water systems, *Legionella* tests are not required, although it is recommended if biocide failure has occurred, if there are high-risk individuals in the building, where biocides are used as the primary control and not high temperature, or if a case of Legionnaires' disease has been associated with the premises. At concentrations above 100 CFU/L and 1,000 CFU/L, certain actions have to be taken. More stringent requirements for monitoring of healthcare facilities and for spas and pools exist as well.

Health and safety executive inspectors enforce the Health and Safety at Work Act for hospitals, heavy industry, and manufacturing premises. Unfortunately, due to a shortage of funding, no preventive inspections are conducted. England has not had the resources to determine what percentage of buildings

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Management of Legionella in Water Systems

are colonized with *Legionella*, although there is no reason to believe that the proportion of buildings with *Legionella* has changed. To make the regulations more enforceable, fines have been raised and are now in the millions of pounds. England has not measured the effectiveness of its *Legionella* regulations. In 2017, the case rate for Legionnaires' disease in the United Kingdom was 0.8 per 100,000 people (ECDC, 2019).

In England, specific *Legionella* regulations exist for dentistry, managed by the Care Quality Commission (CQC). To comply with these requirements of the CQC, the Department of Health's Health Technical Memorandum 05-01 (Department of Health and Estates and Facilities Division, 2013) requires all dental practices to perform a comprehensive *Legionella* risk assessment to identify potential hazards relating to exposure to *Legionella* bacteria from their water systems. In part, this involves decontaminating reusable instruments and daily flushing of dental unit water lines in primary care dental practices.

France

Regulations for *Legionella* surveillance and control in France were first introduced in 1997 for hot-water systems in healthcare facilities and more recently strengthened and extended to all public buildings (République Française 2005a,b, 2010a,b,c). The revised regulations set mandatory minimum temperatures and require *L. pneumophila* monitoring at defined points within hot-water systems, including outlets serving vulnerable persons.

In healthcare facilities, temperature is to be monitored daily or continuously at the hot-water heater outlet and at each return loop and weekly at service points. Temperatures must be greater than 55°C at hot-water heaters and greater than 50°C at distal points in the system. Furthermore, *L. pneumophila* concentrations by culture should be below the detection limit for all samples in hospitals with immunocompromised populations, otherwise immediate corrective measures must be taken. For non-immunocompromised patients, the threshold for immediate corrective measures is 1,000 CFU/L.

Environmental monitoring is also required in other public buildings with collective warm-water systems (e.g., hotels, nursing homes, senior residences, campsites, and tourist accommodation sites) and in some specific types of equipment such as cooling towers, atomizers used in public places, and thermal equipment. In public buildings with collective warm-water systems, the regulations state that the *L. pneumophila* concentration should not be greater than 1,000 CFU/L in hot water. If monitoring results are above the threshold, remedial actions should be taken immediately by the facility manager to protect the public and restore water quality. In spas, *L. pneumophila* should not be detected. In cooling towers, *L. pneumophila* concentration should not be greater than 1,000 CFU/L. When results come back higher than 100,000 CFU/L, the cooling tower should be stopped immediately, remedial actions should be taken by the facility manager, and the environmental authority must be informed. In thermal equipment supplied with natural mineral water, *L. pneumophila* and *Legionella* spp. should not be detected. In collective water-misting systems, *L. pneumophila* should not be detected. If the concentration is between 10 and 1,000 CFU/L, remedial actions should be started; when the concentration exceeds 1,000 CFU/L, the system must be stopped immediately.

Unlike other European countries, the French regulations are mainly based on environmental monitoring and specify what should be done by the facility manager in case of *Legionella* contamination or legionellosis cases, with less emphasis on a water management plan. Regional health and environmental agencies are the enforcement agencies for these regulations.

There has been no consolidation or analysis by the health ministry of environmental monitoring of *Legionella* for the many types of building hot-water systems and devices discussed above. Hence, it is not known whether the regulations have reduced the detection of *Legionella* in the environment. Nonetheless,

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Management of Legionella in Water Systems

the number of legionellosis cases has stabilized (2.4 cases per 100,000 in 2017) and there have been no recent outbreaks (ECDC, 2019).

Australia

Regulations for management of *Legionella* in Australia are enforced by states or territories. As such, they vary in some details between jurisdictions, but they are all based on joint Australia and New Zealand standards (AS/NZS). These regulations are generally administered by state health agencies. Renewed interest in *Legionella* arose after a large outbreak at the Melbourne aquarium in 2000, attributed to a badly managed cooling tower. A hospital outbreak in 2013 led to increased testing at healthcare facilities. The regulations now focus on cooling towers and hot-water systems in buildings such as hospitals and other healthcare facilities. Spas are regulated under recreational water legislation (which is not discussed further).

Three national standards are enforced by the states and territories. The enHealth (2015) guidelines are for *Legionella* control during operation and maintenance of premise plumbing in healthcare and aged-care facilities. First published in 1991, the AS/NZS 3896 standard specifies sampling for *Legionella* spp. in water, while AS/NZS 3666 focuses on air handling and water systems of buildings, with an emphasis on cooling towers. These standards all have a general requirement for a risk management plan, as well as monitoring requirements for *Legionella* and other variables.

As per AS/NZS 3666, most jurisdictions in Australia require cooling towers to be registered, and they require dosing with a biocide, fitting of drift eliminators, regular servicing (monthly), and cleaning (every six months)—all of which are documented in a risk management plan. Some jurisdictions require monitoring of *Legionella*, with a range of required frequencies, and all testing is undertaken by standard culture methods. According to the regulations, a concentration of less than 10 CFU/mL (10,000 CFU/L) is considered to be non-detect. If samples exceed 10 CFU/mL twice consecutively, the building must be investigated, disinfected, and retested. If the concentration is greater than 1,000 CFU/mL (10^6 CFU/L) then decontamination is required. This concentration is not a science-based number; rather, it is based on what a well-maintained cooling tower can stay below. AS/NZS 3666 also specifies testing of heterotrophic plate counts (HPC), with thresholds of (1) less than 100,000 CFU/mL, (2) between 100,000 and 5 million CFU/mL, and (3) greater than 5 million CFU/mL. Some jurisdictions require notification of the public health regulator at lower *Legionella* or HPC levels, such as 10 CFU/mL.

The Australian regulations applicable to premise plumbing have taken two approaches. The first is to regulate only hot-water systems, allowing water delivered to bathrooms to be no more than 45°C (although they operate the hot-water system at 55°C to 60°C and have thermostatic mixing valves). The second is a risk assessment approach for all water systems, which is similar to ASHRAE 188 and other countries' regulations. The second approach is becoming more popular and stems from the enHealth guidelines for *Legionella* control in healthcare and aged-care facilities. There are no prioritized treatments of contaminated systems, but some hospitals do booster chlorination. As in the United States, this process can make the hospital a drinking water provider, but there is little oversight or regulatory burden involved. If a hospital has such a treatment system, it must hire professionals to manage the system. In general, the frequency of *Legionella* monitoring in premise plumbing is lower than in cooling towers.

There have not been any documented, quantitative impacts of the regulations on rates of Legionnaires' disease or environmental detection of *Legionella.* Australia has approximately 340 Legionnaires' disease cases reported each year, equally divided between *L. pneumophila* and *L. longbeachae* (see Figure 5-1 for cases in Queensland). *L. longbeachae* is more common in the south of Australia and generally associated

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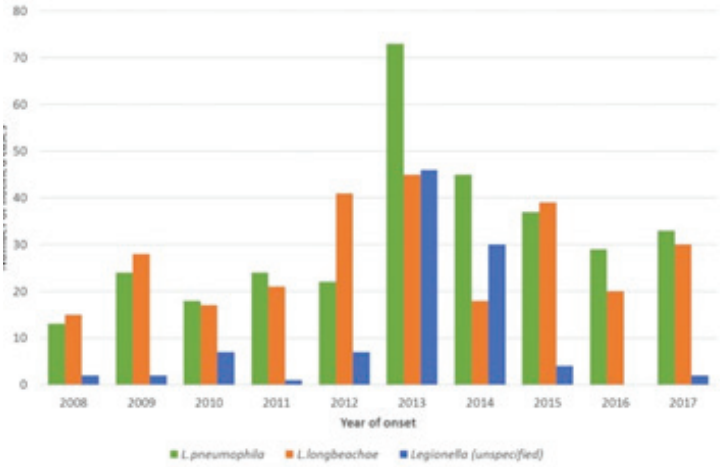

FIGURE 5-1 Number of notified cases of legionellosis by species, Queensland, 2008 to 2017.

SOURCE: Queensland Health (2018).

with soil and compost exposures. Cases have been relatively constant from 1997 to 2017, and the 2018 rate was 1.6 per 100,000 people. In Victoria, there was an increasing trend in Legionnaires' disease rates that peaked with the Melbourne aquarium outbreak. Program administrators state the regulations have helped to improve understanding of locations of higher risk and have led to better communication between building owners and operators (Cunliffe, 2018). In the next one to two years, *Legionella*-related regulations will be undergoing review in several jurisdictions and may be updated to include refinements in monitoring *Legionella*. In many ways, the Australian regulations are less strict than the Dutch regulations: their implementation varies by jurisdiction, some have not yet fully embraced the risk management paradigm, the suite of buildings covered is more limited (hotels are not covered unless they have a cooling tower), and the concentration thresholds for action are higher.

Canada

Compared with Europe, Canada has more limited and provincial regulations for *Legionella* management in buildings. After a Legionnaires' disease outbreak in Quebec City, the Public Services and Procurement Canada (PSPC) standard MD-15161 for control of *Legionella* in mechanical systems was created in 2013, covering the 360 buildings that are federally owned and managed by PSPC.· The PSPC portfolio is comprised mostly of office buildings across Canada. MD-15161 mandates minimum design, installation, operation, maintenance, and validation testing requirements to reduce the risks associated with *Legionella*. There are specific requirements for cooling towers; open water systems (e.g., ornamental water features); other heating, ventilation, and air conditioning (HVAC) components (e.g., humidifiers, drain pans); and domestic hot- and cold-water systems. Like other industry standards, MD-15161 requires the development of a site-specific plan (*Legionella* Bacteria Control Management Program) to identify susceptible systems, their risks and hazards, and site-specific considerations, and to ensure that appropriate mitigation measures and maintenance procedures are put in place. The plan must be reviewed and updated every five years, when there is a major change in procedures or replacement of equipment, or when *Legionella* testing has triggered an unscheduled disinfection of a system.

Temperature requirements are similar to many other countries, with greater than 60°C for hot-water heaters and greater than 50°C for distal points in hot-water systems (PWGSC, 2016). The monitoring required is specific to total *L. pneumophila*. The methods for cooling towers include monthly

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Management of Legionella in Water Systems

culture testing for total *L. pneumophila*, with action levels of less than 10 CFU/mL (10^4 CFU/L); 10 to 1000 CFU/mL (10^5 to 10^6 CFU/L), which triggers cleaning and disinfection of the system; and more than 1,000 CFU/mL (10^6 CFU/L), which additionally requires the immediate cessation of any aerosol dispersal. qPCR for total *L. pneumophila* is conducted at system start-up, with action levels of less than 10 GE/mL; 10 to 100 GE/mL, which triggers a review of operations and treatment; and more than 100 GE/mL, which triggers cleaning and disinfection of the system. A residual oxidant test on a building's incoming water service is also required. To support implementation of the MD-15161 standard, a separate communications protocol has been developed that ensures timely, consistent, and appropriate communication to required stakeholders based on the maintenance action level triggered by the *Legionella* testing result.

Although MD-15161 is required of all the Crown-owned buildings managed by PSPC, the standard is starting to be adopted and applied by other federal departments that manage federal property. There is periodic reporting of compliance to MD-15161 to PSPC senior management and periodic auditing of facilities to ensure compliance to MD-15161. Nonconformities are identified through reporting and auditing and, when identified, a plan is put in place to rectify the problem.

PSPC started implementing MD-15161 in its portfolio in 2013 and started monitoring compliance in 2014, which has led to increased awareness of *Legionella* control from project inception to building operation and maintenance. There has also been a concomitant reduction in the number of positive results in cooling towers, as shown in Table 5-2, which provides data on the number of times unscheduled cleaning and disinfection of a cooling tower system was triggered by the *Legionella* testing required by MD-15161. There are approximately 200 cooling towers in the PSPC inventory.

TABLE 5-2 Effects of MD15161 on Cooling Tower Performance

Year	Number of times a cooling tower system required unscheduled cleaning and disinfection as per MD15161
2014	48
2015	27
2016	10
2017	11
2018	10

SOURCE: Data courtesy of Public Services and Procurement Canada.

Quebec Cooling Tower Regulations

Following the 2012 Quebec City Legionnaires' disease outbreak of 181 cases and 16 fatalities, the Régie du Bâtiment du Quebec (RBQ) introduced cooling tower regulations in 2013. Since then, all cooling towers in the Province of Quebec must be registered with provincial authorities. Cooling towers are defined as all open recirculating cooling systems, including cooling towers, fluid coolers, and evaporative condensers. The regulation requires a documented mechanical maintenance program and a documented water treatment program, including mandatory decontamination procedures. Mandatory monthly culture-based sampling for *L. pneumophila* was added in 2014 (RBQ, 2014). At levels less than 10^4 CFU/L, no action is required. At levels between 10^4 and 10^6 CFU/L, the cause of these high levels must be identified, and the owner must apply and confirm the efficacy of corrective measures. The health-based emergency

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Management of Legionella in Water Systems

threshold is set at levels greater than 10^6 CFU/L, at which all equipment producing aerosols must be stopped and the owner must apply the emergency decontamination procedure and verify the efficacy of the corrective treatment. Compared to similar regulations in Europe, higher numbers were chosen as thresholds so as to not alarm people and to avoid the ambiguous implications of violating lower numbers.

Racine et al. (2019) collected and analyzed cooling tower treatment results from more than 323 evaporative cooling systems, along with corresponding *L. pneumophila* regulatory sampling results (n = 8,936) from July 2014 to June 2017. Water quality (i.e., hardness, alkalinity, chlorides, free and total chlorine, pH, conductivity) and treatment (corrosion and scale inhibitor, dispersant dosages) were determined. The analysis suggests that the introduction of the Quebec regulations raised the level of awareness and accountability in the management of cooling tower treatment programs, which led to a reduction in levels and incidences of *Legionella* positivity over the three-year period (see Figure 5-2). Interestingly, *L. pneumophila* control was most effective in systems using halogen-based biocides and on-line control of dosage. The study suggests that a regular review of the cooling tower treatment program and monitoring results, including *L. pneumophila* sampling, leads to a willingness to continue implementing control measures.

The Société Québécoise des Infrastructures (SQI) manages all cooling towers for provincial government buildings, which totals 39 buildings and 58 cooling towers. The buildings are located in different cities throughout the province and are fed by different water sources. Although all cooling towers are managed by SQI, each has a separate maintenance contract and, therefore, various disinfectants and frequencies of application. In total, 24 different biocides, both oxidants and non-oxidants, are used at various concentrations. Among cooling towers, 43 of 58 have two different disinfectants with continuous, daily, or weekly application. Only 13 of 58 cooling towers are operated year-round; the others are not operated during the winter months.

Monitoring results by culture and qPCR obtained between January 2014 and June 2017 were analyzed for temporal trends. Overall, a larger number of samples was positive by qPCR than by culture, as expected. As seen in Figure 5-3, the regulations were followed by a rapid decrease of positivity in cooling towers as measured by qPCR and culture. The small number of positive samples reveals significant progress in establishing efficient treatment regimes.

In 2016, case rates for Legionnaires' disease in Canada were reported at 0.87 per 100,000 people (Public Health Agency of Canada, 2016).

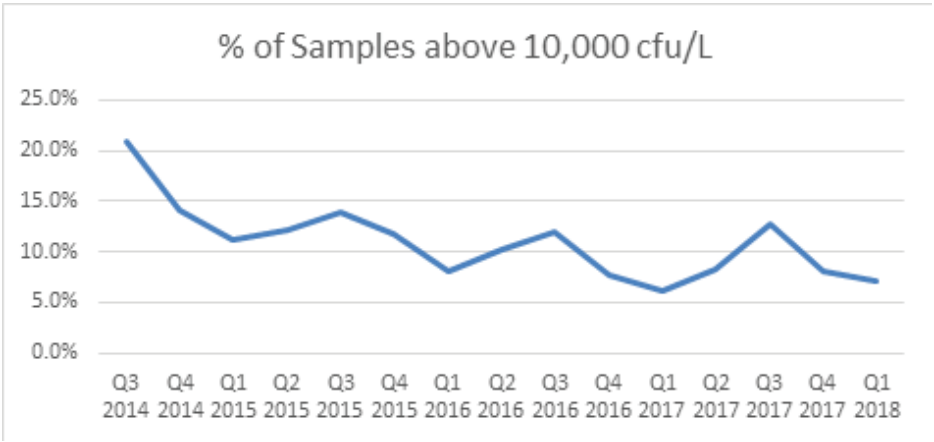

FIGURE 5-2 Percentage of Quebec cooling towers with *L. pneumophila* serogroups 1-14 concentrations exceeding 104 CFU/L over time.
SOURCE: Adapted from Racine et al. (2019).

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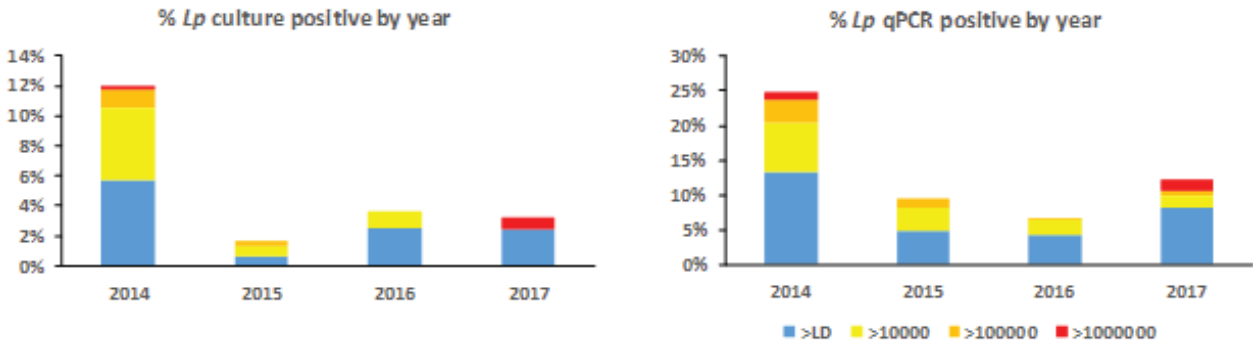

FIGURE 5-3 Percentage of cooling towers testing positive for *Legionella* by culture or qPCR, 2014-2017. Colors indicate samples above certain concentration thresholds.
SOURCE: Created using data from SQI.

Table 5-3 summarizes the above information on international laws and regulations governing *Legionella* management in water systems. The table illustrates the ubiquitous presence of temperature control as a control strategy for *Legionella* in buildings, as well as a requirement for monitoring of *Legionella* in building water systems—with the threshold for taking action between 10^3 and 10^4 CFU/L. This is consistent with Van Kenhove et al. (2018) who analyzed regulations in a much larger suite of countries and found that maintaining temperatures above 60°C and below 25°C, as well as monitoring of critical points, were common principles among the regulations.

For most of the countries, it is too early to make conclusions about the impact of regulations on rates of legionellosis, although there is evidence that the regulations are leading to declines in environmental detection of *Legionella*. Both the German building water system and Canadian government and Quebec cooling tower regulations have coincided with declines in the frequency of detection of *Legionella*. Lam et al. (2011) suggest that enactment of Environmental Public Health Regulations for cooling towers and water fountains in 2001 may have contributed to the decline of Legionnaires' disease cases in Singapore. The percentage of cooling towers testing positive for *Legionella* decreased from 58 percent during 2000–2002 to 13.7 percent during 2004–2008. While these examples do not provide direct evidence that regulations can decrease disease rates, they suggest that making *Legionella* control a priority is useful public policy.

In almost all cases, regulations for *Legionella* monitoring and control in Europe and elsewhere stemmed from a large outbreak. Prior to the existence of the regulations, there were few if any monitoring data, making the background level of *Legionella* in building water systems impossible to determine. The regulations have led to increased recognition of Legionnaires' disease, which may be contributing to increasing rates observed in the past few years. As more monitoring data are collected and analyzed, it is anticipated that the role of these regulations in preventing disease will become clearer.

STEPS FORWARD FOR U.S. *LEGIONELLA* MANAGEMENT

In the United States, there are no national regulations or guidance documents similar to those described in Table 5-3 for other countries, despite the 8,453 reported cases of Legionnaires' disease in the United States in 2018 (or 2.29 cases per 100,000, which is likely a gross underestimation of the actual burden—see Chapter 3). Furthermore, even among the directives, regulations, and guidance documents

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TABLE 5-3 International Laws and Regulations regarding *Legionella* Management in Building Water Systems

Country	*Regulation/Standard/ Guideline*	*Buildings/Devices Covered*	*Risk Management Plan Required?*	*Preferred Treatment*	*Monitoring Thresholds (All Converted To CFU/L)*	*Enforcement/ Implementation*
Netherlands	1. Drinking Water Act (2011) 2. Hygiene and Safety Act (2000) 3. Safety at Work Act (2007) 4. Environmental Protection Act (2010)	1. Priority premises, which are basically large buildings 2. Swimming and bathing facilities 4. Wet cooling towers	Yes	Temperature control, flushing, UV, filtration	< 100 CFU/L, no action > 1,000 CFU/L, take response actions	National. Implementation of the Acts is increasing, but not yet 100%. Enforcement is via inspections, fines, possible facility closure
Germany	1. Protection against Infection Act 2. Emissions Control Act (2017)	1. Large building premise plumbing, swimming pools, bathing water, WWTPs 2. Cooling towers	Yes	None, though temperature control and avoiding stagnation evident in codes	> 1,000 CFU/L, take response action	National. Very high compliance. Small cooling towers slowly coming under regulation.
England	1. Health and Safety at Work Act, L8 regulations (2013 4th edition) 2. Health and Social Care Act (2008) 3. Notification of Cooling Towers and Evaporative Condensers Regulations (1992)	1. Evaporative cooling systems, hot- and cold-water systems, spa/ pool systems 2. Healthcare facilities 3. Cooling tower registration	Yes	Temperature control, biocides	< 100 CFU/L, no action 100-1000 CFU/L, take response actions > 1,000 CFU/L, alarm bell	England only. Enforced by inspectors, but they can do no preventative work.

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TABLE 5-3 Continued

France	Regulations began in 2002 (République Française 2005a,b, 2010a,b,c)	Buildings except private residences, cooling towers	Only for cooling towers at this time	None apparent	< 1,000 CFU/L target for public facilities < 100 CFU/L target for prevention of nosocomial infections < 50 CFU/L target for hospitalized at-risk patients	Regional health and environmental agencies enforce the regulations
Australia	1. enHealth guidelines (2015) 2. Standards AS/NZS 3666 (2002, 2011) AS/NZS 3896 (2008, 2017)	1. Premise plumbing in healthcare and aged-care facilities 2. Cooling towers	Yes for cooling towers; becoming more risk-based for buildings	1. Temperature control, but broadening. 2. Biocides	< 10^4 CFU/L, no action > 10^6 CFU/L, take response actions	Varies by state and province
Canada	Standard MD-15161 (2013)	Cooling towers, open water systems, HVAC components, and hot- and cold-water systems in 360 buildings	Yes	None	< 10^4 CFU/L, no action > 10^6 CFU/L, take response actions	Oversight from Public Services and Procurement Canada, who does reporting and auditing
Quebec Cooling Tower Regulations	Régie du Bâtiment RBQ (2014)	Cooling towers	Yes	Biocides	< 10^4 CFU/L, no action ≥ 10^4 to < 10^6 CFU/L, take response actions ≥ 10^6 CFU/L, alarm bell	Oversight from Société Québécoise des Infrastructures

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Management of Legionella in Water Systems

that extend to U.S. buildings, guidelines for interpreting *Legionella* monitoring data are lacking because of uncertainties over how to respond to certain values. These uncertainties have effectively hindered water utilities and building managers from testing for *Legionella*. Guidelines on routine environmental testing for *Legionella* vary among different documents:

- AIHA (2015) recommends that *Legionella* testing be conducted for validation of the water management plan or as part of an outbreak investigation. The goal is to have no positive samples, but corrective actions are required if samples have more than 10^3 CFU/L (see Table 5-1).
- ASHRAE 188 recommends that the team responsible for developing and implementing the building's risk management plan for *Legionella* control decide whether *Legionella* testing should be conducted. CMS (2017) requires that all healthcare facilities be consistent with ASHRAE 188.
- DVA (2014a) recommends routine environmental testing for *Legionella* in VHA facilities with prescribed actions required for any positive *Legionella* sample, regardless of the concentration.
- NSFI 453 requires monitoring for *Legionella* in cooling towers. *Legionella* is to be maintained at less than 10^4 CFU/L and investigations and corrective actions taken if levels are higher.
- The New York State regulations require hospitals and healthcare facilities to monitor their potable water systems for culturable *Legionella* and institute control measures and notify authorities when 30 percent or more of the samples contain *Legionella* spp.

Only the New York State regulations are enforced by law and impose civil and criminal penalties. The VHA guidelines are internally mandated, and the policy outlines specific responsibilities for various individuals. The CMS memo (2017) requires that all hospitals and healthcare facilities receiving Medicare or Medicaid funds have a water management plan or potentially lose funding (e.g., be "at risk of citation for non-compliance with the CMS Conditions of Participation"). Thus, all VHA facilities along with cooling towers and healthcare facilities in New York State are currently required to implement water management plans and monitor for *Legionella*. The CMS requirements, which cover hospitals and nursing homes nationwide, do not require monitoring for *Legionella* because ASHRAE 188 leaves the decision to the water management team. All other buildings and private residences are formally protected from *Legionella* only through the application of building and plumbing codes, and then only at discrete points in time when the codes are enforced. **There is a need for more uniform protection of public health from *Legionella* in hospitals and healthcare facilities, cooling towers, and building water systems across the country.** The following recommendations are made to develop a more comprehensive policy for *Legionella* management in the United States.

Recommendation 1. Expand the CMS Memorandum to Require Monitoring for *Legionella* in Environmental Water Samples

The CMS memo, which has high enforceability, requires that hospitals and long-term care facilities develop and implement water management plans. This memorandum has appropriately targeted buildings in which the mortality rates of Legionnaires' disease are high because of vulnerable patient populations, and it has increased awareness within healthcare organizations and provided needed focus on waterborne pathogens (e.g., *Legionella*). Routine quantitative *Legionella* monitoring programs would enable these institutions to assess the effectiveness of their water management programs. All healthcare organizations should have the capacity and expertise to use these data proactively to help limit nosocomial legionellosis. Such enhanced data collection from within hospital systems structures could help

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Management of Legionella in Water Systems

to refine the data thresholds needed for prevention. This emphasis on monitoring is supported by the international regulations discussed above, by the VHA Directive and the New York State regulations, by AIHA (2015), and by the recent position paper from the America Water Technologies (AWT, 2019). The latter states that "*Legionella* testing is the only direct or 'active' way (currently) to validate program effectiveness, short of proving there is no Legionnaires' disease associated with the water management plan systems." Such an effort would also require strengthening of environmental laboratory capacity to process, evaluate, and interpret results from water samples, and it would necessitate documentation of laboratory proficiency. See below for a discussion of how to respond to the *Legionella* monitoring data that would stem from enforcement of an updated memo.

Recommendation 2. Register and Monitor Cooling Towers

Regulations and guidelines requiring the registration of cooling towers provide a demonstrable public health benefit with minimal regulatory burden to building owners and managers. Cooling tower registries enable a rapid public health response to community clusters of legionellosis cases, including timely remediation of possible sources of infection, and they can also be used to assess the contribution of cooling towers to overall disease incidence. In addition, regulations requiring ongoing *Legionella* monitoring of cooling towers have been shown to reduce cooling tower colonization rates in several jurisdictions where they have been implemented (e.g., Quebec Cooling Tower Regulations, Lam et al., 2011; Garland, Texas, Whitney et al., 2017). Unless the location of cooling towers is known, it is impossible to react quickly to identify the source of an outbreak or to assess the overall contribution of cooling towers to the occurrence of Legionnaires' disease.

Recommendation 3. Require Water Management Plans for All Public Buildings

The standard of care specified for water management plans (see the seven bullets on page 256) should be considered best management practice for all public buildings, including hotels, businesses, schools, apartments, and government buildings. This would extend the spirit of the Safe Drinking Water Act (particularly when building water treatment is used) into building water systems not covered by the CMS memo. The recommendation here is to make water management plans a requirement for all public buildings. This requirement would target the buildings likely to be sources of sporadic legionellosis, which constitutes 96 percent of all cases (see Chapter 3). ASHRAE 188, AIHA (2015), and other guidance documents are available to help create a water management plan that can meet this requirement. Derivative products that provide details for specific building types and devices, much like the CDC Toolkit has done for healthcare facilities, would be useful to help implement this recommendation.

The team developing and implementing the water management plan would outline the operation, monitoring, and maintenance of building water treatment systems using licensed and trained individuals to collect and retain appropriate records and monitoring data. (The required training of professionals is discussed in a subsequent section.) Similar to other public health certifications, application records and monitoring results could be required only on inspection, which would minimize unnecessary compliance reporting activities. Should inspections reveal serious defects in the execution of the building water management plans, penalties, including loss of certification and public notices on building entrances, could be used.

Ideally, this requirement would be codified by either local jurisdictions with authority (e.g., build-

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Management of Legionella in Water Systems

ing inspectors) or state authorities (e.g., departments of environmental protection or health). Once codified, the requirements could be supported by insurance companies—that is, without a water management plan, a building would not qualify for insurance.

Recommendation 4. Require a Temperature of 60°C (140°F) at Hot-Water Heaters and 55°C (131°F) to Distal Points

Optimal operating temperatures at critical points in the hot-water system are based on an international consensus that maintaining minimum temperatures across the different parts of a hot-water system is the first barrier to implement to restrict *Legionella* growth, even if continuous disinfection is present. Typically, the requirements include maintaining temperatures of greater than 60°C at the water heater and in reservoirs, greater than 55°C in the return loop, and ensuring that distal points reach a minimum temperature of 55°C within one minute of use. Monitoring temperature at the distal point of hot-water systems would be necessary to verify that this requirement is being met. As discussed in Chapter 4 and shown in Table 4-3, 55°C carries a scalding risk that can be reduced with the use of thermal mixing values in buildings with sensitive populations.

The countries previously discussed in this chapter all include objectives for optimal operating temperatures in the hot-water system; design and operational specifications for water heaters, storage, and recirculation systems; and recommendations for maximum temperature at distal points. In England, France, Germany, and the Netherlands, periodic monitoring of *Legionella* and temperature is mandatory, with a frequency varying from continuous to weekly or annually depending on the parameters, the risk classification, and the location of the point of use. The change recommended here would align the United States with these countries.

These temperature requirements could be codified by changing building and plumbing codes. However, to impact healthcare facilities more immediately, this requirement could be instituted by modifying the CMS memo. It is also possible to incorporate these requirements into ASHRAE or other guidance; ASHRAE 12-2000 section 4.1.6 already states: "In a high-risk system, cold water should be below 20°C, hot water should be stored above 60°C and returned and circulated at above 51°C." A required temperature at distal points could be inserted into ASHRAE 12-2000 as it undergoes revision in the near future.

Recommendation 5. Require a Minimum Disinfectant Residual Throughout Public Water Systems and Concomitant Monitoring for *Legionella*

It is important that water entering domestic and public buildings be of the highest quality possible. Currently, federal regulations allow for no disinfectant residual in 5 percent of the measurements in distribution systems that use surface water as a source (EPA, 1989). Federal law does not require groundwater systems to maintain any disinfectant residual within their distribution systems. *L. pneumophila* has been shown to grow in public water systems in which chlorine residuals were less than 0.1 mg/L (LeChevallier, 2019b). EPA should require a minimum disinfectant residual throughout public water systems and validate treatment performance by routine monitoring for *L. pneumophila* from sampling sites representative of the distribution system. Monitoring could focus on warm-water conditions and be triggered once water temperatures consistently exceed 20°C although some detection may occur above 15°C (LeChevallier, 2019b). Corrective actions should be taken once the concentration of *L. pneumophila,* or the frequency of occurrence, exceeds specific trigger levels consistent with science-based and develop-

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Management of Legionella in Water Systems

ing guidelines and risk assessments.

Legionella has been on the EPA Candidate Contaminant List for the past ten years, which means that the agency should be evaluating methods to determine the occurrence of the organism in public water systems. However, no action has been taken because the agency is unsure how to interpret or communicate positive *Legionella* results in treated water supplies. The development of guidelines for interpreting monitoring data, outlined below, could provide the framework for including *Legionella* in the next round of unregulated contaminant monitoring (UCMR 5) scheduled to begin in 2022.[7] However, utilities need not wait until EPA conducts the UCMR monitoring; they could start collecting this information now and set internal targets for distribution system optimization.

Develop Guidelines for Interpretation of *Legionella* Monitoring Data Using a Risk-Based Framework

The lack of clear guidelines from the EPA or the CDC has hampered collection by building owners and water utilities of *Legionella* occurrence data over fears that a single detection could trigger onerous remediation requirements by public health and environmental regulators. In fact, monitoring for *Legionella* in the absence of any cases of Legionnaires' disease has not been recommended by the CDC.[8] ASHRAE 188 does not require *Legionella* monitoring as part of the building water management plan. Yet, three of the five recommendations above incorporate monitoring of *Legionella* in building water systems, which will require a framework in order to interpret the data.

There are at least two contexts in which monitoring results might be used to make decisions. The first is to detect the imminent threat of an outbreak of legionellosis based on monitoring and quantifying *Legionella* at points close to end uses. The Committee's review of available data, presented in Chapter 3, indicates that when a series of measurements show *Legionella* levels in excess of 5×10^4 CFU/L, there is an imminent risk of an outbreak occurring. At this point, urgent action to discontinue exposure and implement a remediation plan is appropriate. For individuals who are highly susceptible (e.g., immunocompromised patients in hospital and healthcare settings), or where a greater safety factor is desired, it would be appropriate to reduce this action level multifold. The 5×10^4 CFU/L action level, which would be relevant to all building water systems, falls between the lower thresholds found in the European countries and the higher thresholds found in Australia and Canada, as discussed above. This action level is also consistent with the AIHA (2015) guidelines for all building water systems (except cooling towers). Notably, none of the numeric thresholds from these other regulations or guidances stem from any risk-based assessment but rather from practicality and expert judgement.

The second context for data-based decisions is when there is a routine program of quantifying *L. pneumophila*[9] to determine that the risk of legionellosis is acceptably low. In this case, quantitative microbial risk assessment (QMRA) can be used to develop routine operational targets for different types of building water systems. For example, based on an analysis of acceptable risk levels, and using a 10^{-6} DALY/person-year as a target (Hamilton et al., 2019; see Chapter 3) single sample water concentrations of *L. pneumophila* of less than 1,060 CFU/L, 8,840 CFU/L, and 14.4 CFU/L in faucets, toilets, and showers, respectively, could be regarded as acceptable. In practice, one would use the most stringent number, which would be the 10^3 CFU/L for buildings with just toilets and sinks and 10 CFU/L for buildings with showers. For buildings with showers, the number 10 CFU/L equates to 1 CFU/100 mL, which is the detection limit of current monitoring approaches for many laboratories (ISO, 2017). From a risk

[7] See https://www.epa.gov/dwucmr.

[8] See https://www.cdc.gov/legionella/health-depts/ashrae-faqs.html.

[9] *L. pneumophila* is indicated here, rather than *Legionella* spp., only because the current dose-response relationship is for *L. pneumophila*.

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Management of Legionella in Water Systems

protection standpoint, this value substantiates the very reasonable goal of having only non-detects in a hospital environment (see Box 3-8).

Cooling towers have been more difficult to model with QMRA because the exposure pathway from the water column via aerosols to individuals is much more complex and poorly described. Further research using dispersion models will be necessary to further refine *L. pneumophila* concentrations that correspond to specific risk values from cooling towers.

Train and Educate Those in Relevant Disciplines and Occupations Who Are Responsible For the Safety of Water Systems

The five recommendations above will require training and education on legionellosis and on the prevention and control of *Legionella* amplification in water systems for a variety of professionals, including building owners and operators, engineering consultants, clinicians and epidemiologists, laboratory technicians, inspectors, and architects, among others. The medical community curriculum should be expanded to include all aspects of diagnosing and treating legionellosis in the most effective manner. This education should also include sufficient aspects of water management to effectively educate patients on inherent risks within their homes that may require attention when they are released from the hospital. Education and training are also needed for those designing water systems, for those overseeing municipal water supplies, for those developing and implementing plumbing codes, and for those in government responsible for the safety of buildings, cooling towers, and the potable water supply. Building operators and their staff require a basic understanding of *Legionella*, their ecology and growth conditions, as well as sampling collection techniques for *Legionella*. Initial training, as well as continuing education, should be required for individuals responsible for maintenance of water operations and premise plumbing. Box 5-1 discusses two recent training programs specific to *Legionella*.

In addition to being trained, those managing building water systems should be part of the water management program team and they should be certified to operate any water treatment system. This way, the operator's certification can be held responsible, and possibly lost, if the building water systems are not properly maintained (in addition to any possible criminal liabilities for failure to act upon their training and certification). The certification should also require on-going educational training. Multiple entities could, and in some cases have, developed certification programs.

Disconnect Between Experts in Design, Construction, Operations, and Materials

Building water system design is often compromised because water management plans and their successful implementation are currently not understood across the building professional landscape. Even in cases where the building owner is very specific on a plan or a design to prevent waterborne pathogens, the building industry has multiple fragmented or siloed participants who preclude successful *Legionella* prevention. Without continuous, almost daily, interaction with all participants in the building and construction process, the likelihood of achieving the desired result can be marginal.

One challenge to progress is that the largest portion of tacit knowledge resides with the building owner and building operations professionals. In many instances, barriers to success can be associated with a general lack of understanding about water management plans by other professionals represented across the paradigm of building construction—engineers and architects who design the building, construction managers and general contractors who hire and manage the trades, and the trade groups that build the building. Although building commissioning professionals add to oversight on behalf of the own-

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BOX 5-1
Recent Training Modules Relevant to Control of *Legionella*

The CDC in conjunction with the Western Region Public Health Training Center at the University of Arizona recently launched a free on-line training program titled Preventing Legionnaires' Disease: A Training on *Legionella* Water Management Programs (see https://www.cdc.gov/nceh/ehs/elearn/ prevent-LD-training.html). The training provides an opportunity to gain knowledge on how to reduce *Legionella* risk via water management programs, similar to the approach in the CDC's tool kit (CDC, 2017) developed following the release of ASHRAE 188. Training helps build common language among professionals utilizing water management programs through case study templates and other practical resources. The program is designed for professionals involved in water management programs including public health professionals, infection preventionists, building managers, maintenance and engineering staff, safety officers, and equipment and water treatment suppliers, as well as consultants. The training is relevant to building water systems in hospitals, retirement homes and long-term care facilities, hotels, apartments, and other buildings, as well as other devices that may need a water management program even if the building does not, such as cooling towers, decorative water features, hot tubs, and misters.

The American Society of Sanitary Engineering (ASSE) offers training and certification on infection control and water quality. Unlike the CDC training, the ASSE training is trade specific and requires prerequisite training and experience to take the certification coursework. The ASSE/IAPMO/ANSI Series 12000-2018, Professional Qualifications Standard for Infection Control Risk Assessment for All Building Systems, defines general knowledge requirements for developing and implementing water systems risk management programs and sets minimum criteria for training and certifying employers, plumbers, pipefitters, HVAC technicians, and sprinkler fitters. Different aspects of the series 12000 certification are currently provided through certified instructors and 18 union-based trade schools. The certification program provides general knowledge of pathogens, biohazards, and infectious diseases for plumbing, piping, and mechanical systems workers, or any individual who has the potential for exposure to pathogens, biohazards, or other potentially infectious material. Additional parts of the series provide general knowledge about contamination and infection prevention procedures to protect facility occupants and operations. The higher level (12060 to 12063) certifications build on the lower series designations as prerequisites and provide additional general knowledge on developing and implementing water systems risk management programs for plumbing, mechanical, and water-based fire protection systems (see http://www.assewebstore.com/asse-iapmo-ansi-series-12000-2018-download/). As more and more facilities, particularly healthcare facilities, begin requiring training and certification in infection control, ASSE 12000 series certifications will prove to be valuable credentials. The certifications address the need for construction and maintenance personnel to become proficient in identifying and managing potential situations where they may be exposed to bloodborne, waterborne, and airborne pathogens. These certifications also cover the responsibility of personnel to protect building occupants and operations from pathogens and hazards, especially in healthcare facilities. These certifications allow recipients to comply with standards and all piped systems that currently reside in all occupied buildings (see http://www.asse-plumbing.org/asse/personnel-certification/12000).

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Management of Legionella in Water Systems

er and the operators, unless these individuals are specifically educated and understand the relevance of water safety, their value in preventing waterborne pathogens via effective design and plans is negligible. In most cases, construction design and plans to specifically reduce the incidence of waterborne pathogens come at a higher cost than standard construction methods.

Building design and construction professionals are further segregated by building type, with commercial building construction being highly specialized. Each of the major categories of building type (e.g., commercial offices, factories, warehouses, schools, retail, entertainment, data facilities, healthcare) has specific subgroups with special needs and requirements. Requirements regarding aesthetics and specific use are developed by architects and design professionals while infrastructure systems are developed by mechanical and design engineers. The design professionals may be highly specialized and segregated, whereas the building trades (e.g., carpenters, plumbers, electricians) are common to all. Training and certification are mechanisms for overcoming this inherent segregation, such that all professionals involved in building design, construction, and operation have an equivalent *Legionella* knowledge base.

Implementation and Cost Considerations

Although ordered 1 to 5, the five recommendations discussed above are not prioritized. In fact, accomplishing any one of them would lead to important legionellosis risk reduction, with the effect being cumulative as more recommendations are instituted. The five goals differ substantially in the necessary implementation schedule, what entities would provide oversight, their cost, and what other capacities need to be in place to support them.

Adding a requirement for monitoring within the CMS memo (Recommendation #1) could be expanded relatively quickly. Meeting this goal would entail an initial assessment of the current laboratory capacity for testing and an estimate of the number of samples that might be added to the annual work load. Most labs that are ELITE certified (see Chapter 3) can accurately identify *Legionella* bacteria, but quantification needs to be improved and should be made part of every proficiency testing program before *Legionella* monitoring can occur on a large scale. Once capacity is adequate, the implementation of monitoring could be accomplished in phases over the next three years, based on populations at risk, with oversight from the U.S. Department of Health and Human Services. Examples of hospitals already conducting such monitoring (e.g., see Box 3-8) will provide case studies and protocols.

Registering cooling towers (Recommendation #2) could follow New York's lead, and is most appropriately coordinated at the state level, including state and city departments of health or departments of environmental protection. Any state with an outbreak or some threshold number of legionellosis cases could be prioritized, with the objective of all states meeting the requirement over a five-year time frame.

The requirement to develop water management plans in public buildings (Recommendation #3) may be the most complex and costly recommendation by the Committee, as it would require that building owners become trained and incentivized to conform via governance structures. Hopefully, with oversight from the states and assistance from OSHA, this recommendation would be implemented over the next decade by those with expertise in engineering and building water quality. Key business chains, such as hotels, could take national leadership roles, and insurance companies could require water management plans before insuring buildings.

Increasing temperature requirements (Recommendation #4) will require education and oversight via local jurisdictions and plumbing codes. Given the three-year cycles inherent to changing most plumbing codes, this requirement could not be expected to happen quickly, nor would the requirements reach a broad swath of at-risk buildings, given the limited time frames of code enforcement. However, if the

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Management of Legionella in Water Systems

temperature requirement was codified in the CMS memo, then much more rapid risk reduction, based on elevating building water temperatures, could occur.

And finally, water utilities will be responsible for managing, monitoring, and addressing disinfectant residuals and new requirements for *Legionella* monitoring in drinking water distribution systems (Recommendation #5). EPA should be involved, and ultimately a few of the larger utilities will likely provide guidance on best practices to implement the strategy. It is anticipated that implementation of the recommendation would take five to ten years.

Clearly, capacity building will be needed, including training programs (discussed previously), accreditation and certification of laboratory programs, and education of qualified and proficient consultants. In addition, the many work streams that will be created must be devoid of conflicts of interest, which is challenging given that many professionals are linked to a specific mitigation strategy or promote a specific product or service. For example, any individual, vendor, or contractor who develops a water management plan or provides a mitigation modality should not be responsible for monitoring the effectiveness of the plan.

None of the five recommendations for *Legionella* risk reduction are without implementation costs, although these are currently unknown. For this reason, cost-benefit analyses conducted by the appropriate responsible entities (such as water utilities for Recommendation #5) would be worthwhile to better understand the costs involved in carrying out the individual recommendations. Some costs will likely be passed from building and cooling tower owners onto building occupants. It may be possible, however, to meet some of the financial needs imposed by the five recommendations by adding a fee onto user water bills. Such a fee is similar in nature to the fees charged or collected by other utilities and subsequently used to subsidize improvements, conduct research, or to enhance existing utility processes. The fees could also support education and training for individuals to become competent professionals in waterborne pathogens and disease mitigation and prevention.

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Acronyms

AIHA	American Industrial Hygiene Association
ANSI	American National Standards Institute
AOC	assimilable organic carbon
APHA	American Public Health Association
ASHRAE	American Society of Heating, Refrigerating and Air-Conditioning Engineers
ASTM	American Society for Testing and Materials
ATCC	American Type Culture Collection
ATP	adenosine triphosphate
AWWA	American Water Works Association
BAL	bronchoalveolar
BCYE	buffered charcoal yeast extract
BDOC	biodegradable dissolved organic carbon
BMP	best management practice
CAPNETZ	Competence Network for Community-Acquired Pneumonia
CCL	Candidate Contaminant List
CCR	consumer confidence reports
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CFU	Colony forming units
CMS	Centers for Medicare & Medicaid Services
CSTE	Council of State and Territorial Epidemiologists
CT	computed tomography
DALY	Disability-adjusted life years
DFA	direct fluorescent antibody testing
DNA	deoxyribonucleic acid
DOHMH	Department of Health and Mental Hygiene
DVA	Department of Veterans Affairs
DWSD	Detroit Water and Sewerage Department
ECDC	European Centers for Disease Control
EEA	European Economic Area

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Management of Legionella in Water Systems

ELAP	NYS Environmental Laboratory Approval Program
ELITE	Environmental *Legionella* Isolation Techniques Evaluation
EMA	ethidium monoazide
EPA	Environmental Protection Agency
EU	European Union
EWGLI	European Working Group for *Legionella* Infections
FDA	Food and Drug Administration
FY	fiscal year
GAC	granular activated carbon
GC	gene copy
GCHD	Genesee County Health Department
HHS	Department of Health and Human Services
HIV	human immunodeficiency virus
HPC	heterotrophic plate count
HVAC	heating, ventilation, and air conditioning
IAPMO	International Association of Plumbing and Mechanical Officials
ICU	intensive care unit
IHC	immunohistochemistry
ISO	International Organization for Standardization
LD	Legionnaires' disease
LEED	Leadership in Energy and Environmental Design
Lp	*Legionella pneumophila*
LPS	lipopolysaccharide
MCLG	maximum contaminant level goal
MIF	mature infectious form
MIP	macrophage infectivity potentiator
MPN	most-probable-number
NIAID	National Institute of Allergy and Infectious Diseases
NNDSS	National Notifiable Disease Surveillance System
NOM	natural organic matter
NORS	National Outbreak Reporting System
NSF	National Science Foundation
NSFI	National Sanitation Foundation International
NYC	New York City
NYS	New York State
PCR	polymerase chain reaction
PEX	cross-linked polyethylene
PFGE	pulsed field gel electrophoresis
PHB	polyhydroxybutyrate
PMA	propodium monoazide
POE	point of entry
POU	point of use
PSPC	Public Service and Procurement Canada
PVC	polyvinyl chloride
PWGSC	Public Works and Government Services Canada
QMRA	quantitative microbial risk assessment

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qPCR	quantitative PCR
RNA	ribonucleic acid
RO	reverse osmosis
SLDSS	Supplemental Legionnaires' Disease Surveillance System
SQI	Société Québécoise des Infrastructures
ST	sequence type
S/V	surface-to-volume
SDWA	Safe Drinking Water Act
SWTR	Surface Water Treatment Rule
TDS	total dissolved solids
TLR	toll-like receptors
TNTC	too numerous to count
TOC	total organic carbon
UAT	urinary antigen test
UCMR	Unregulated Contaminant Monitoring Rule
USGBC	U.S. Green Building Council
UV	ultraviolet
VBNC	viable-but-not-culturable
VHA	Veterans Health Administration
VSP	Vessel Sanitation Program
WHO	World Health Organization

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Appendix
Biographical Sketches of Committee Members and Staff

JOAN B. ROSE, (NAE), Chair, is a professor at Michigan State University and holds the Homer Nowlin Chair in Water Research. She serves as the co-director of the Center for Advancing Microbial Risk Assessment, which addresses evidence-based risk assessments for management of waterborne pathogens. Dr. Rose is an international expert in water microbiology, water quality, and public health safety, and has published more than 300 manuscripts. For more than 20 years, she has been involved in drinking-water investigations of waterborne outbreaks and is well known for her work on the waterborne outbreak of Cryptosporidium in Milwaukee. She is a pioneer in the emerging science of viral metagenomics—sequencing virus DNA in water sources, discharges, and shipping ballast using next generation high-throughput technology. Her global activity includes investigation of waterborne disease outbreaks and the study of water supplies, treatment, and reclamation. Her applied research interests include study of microbial pathogens in recreational waters and climatic factors impacting water quality. Dr. Rose recently won the Stockholm Water Prize and is a member of the National Academy of Engineering. She is a member of the International Joint Commission, Health Professionals Advisory Board. She has served on numerous boards and committees of the National Academies of Sciences, Engineering, and Medicine and is currently a member of the Board on Environmental Studies and Toxicology. Dr. Rose earned her B.Sc. from the University of Arizona, her M.S. from the University of Wyoming, and her Ph.D. from the University of Arizona, all in microbiology.

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Management of Legionella in Water Systems

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Dr. Haas has specialized in the assessment of risk from and control of human exposure to pathogenic microorganisms and, in particular, the treatment of water and wastewater to minimize microbial risk to human health. Dr. Haas has served on numerous committees of the National Academies of Sciences, Engineering, and Medicine and is a past member of the Water Science and Technology Board and the EPA Board of Scientific Counselors. He has worked on developing risk assessment models for *Legionella*, occurrence in engineered water systems, and disinfection in water systems. He received his B.S. in biology and his M.S. in environmental engineering from the Illinois Institute of Technology, and his Ph.D. in environmental engineering from the University of Illinois at Urbana-Champaign.

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Management of Legionella in Water Systems

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Management of Legionella in Water Systems

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Selecting, Evaluating, and Using Sharps Disposal Containers

U.S. Department of Health and Human Services
Public Health Service
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health
Atlanta, Georgia

January 1998

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DHHS (NIOSH) Publication No. 97-111

FOREWORD

The Occupational Safety and Health Act of 1970 created the National Institute for Occupational Safety and Health (NIOSH). NIOSH is charged with identifying the causes of work-related diseases and injuries, evaluating the hazards of new technologies and work practices, creating ways to control hazards, and recommending occupational safety and health standards.

Occupational exposure to bloodborne pathogens (including the hepatitis B and C viruses [HBV and HCV] and the human immunodeficiency virus [HIV]) poses a significant risk to workers in the health care industry and related occupations. The primary route of exposure to bloodborne pathogens is accidental percutaneous injury caused by needlesticks (puncturing of the skin by a needle or similar sharp object). In the United States, approximately 800,000 needlestick injuries occur in hospitals annually—an average of one injury every 10 seconds. Studies have shown that many of these injuries occur after a sharp (needle or other sharp object) is used; as many as one-third of all sharps injuries have been reported to have occurred during disposal activities.

This document presents a comprehensive framework for selecting sharps disposal containers and evaluating their efficacy as part of an overall needlestick injury prevention plan. The correct and consistent use of rigid sharps disposal containers in the health care environment has been demonstrated to reduce needlestick injuries. This document reviews the Occupational Safety and Health Administration (OSHA) bloodborne pathogens standard and recommends containers on the basis of a site-specific hazard analysis. The document also establishes criteria and provides tools for evaluating the performance of sharps disposal containers.

No single container type meets the disposal containment needs for every facility, but this document establishes a basis for selecting sharps disposal containers that will decrease the risk of percutaneous sharps injury. Each day, thousands of dedicated men and women in health care and related industries risk their well-being to protect and improve the health of others. We must work together to ensure that their jobs are performed in a safe and healthful environment. This document is a valuable tool and an important part of a comprehensive strategy to reduce injury and illness in health care workers.

Linda Rosenstock, M.D., M.P.H.
Director, National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention

ABSTRACT

Occupational transmission of human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) has been well documented. The risk of infection with HIV following one needlestick exposure is approximately 0.3% and ranges from 6% to 30% for HBV and from 5% to 10% for HCV. The passage of the Occupational Safety and Health Administration's (OSHA's) bloodborne pathogens standard (29 CFR* 1910.1030) has increased compliance and awareness of prevention strategies. No single sharps disposal container design meets all the disposal containment needs for all health care settings or for an entire hospital. Container selection should be based on a comprehensive site-specific hazard analysis.

The safety performance criteria for sharps disposal containers are divided into four areas. First, containers should remain **functional** during their entire use. They should be durable, leak resistant, and puncture resistant under all normal environmental conditions. Second, containers must be **accessible** to workers who use, maintain, or dispose of sharp devices. This criterion includes sufficient number, sufficient container volume, and safe access to the disposal opening on individual containers. Other important factors include convenient placement and (if necessary) portability of containers within the workplace. Third, containers should be **visible** to the workers who must use them. Container fill status and warning labels are also important visibility criteria. Fourth, container designs should **accommodate** the user, the facility, and the environment. Although engineering controls such as needleless IV systems and "safety" needles will reduce injuries, proper selection and use of sharps disposal containers are still important. Prevention strategies include implementing engineering controls, using personal protective equipment, training employees, and involving occupational health professionals and workers.

* Code of Federal Regulations

CONTENTS

Foreword iii

Abstract iv

Acknowledgments vi

Public Health Summary vii

I. Introduction 1

II. Sharps Disposal Containers 2

A. Performance Criteria 2
1. Functional criteria 2
2. Accessibility criteria 3
3. Visibility criteria 4
4. Accommodation criteria 4

B. Existing Standards 5

C. Recommended Strategy for Selecting and Using Sharps Disposal Containers 6

III. Concluding Remarks 7

References 8

Appendices

A. Focus group input 10
B. Determining sharps disposal container installation height using standard ergonomics measurements 11
C. Decision logic for selecting sharps disposal containers 13
D. Questionnaire for evaluating sharps disposal container performance 14
E. Recommended reading 19
F. OSHA Hazard Information Bulletin: sharps disposal containers with needle removal features 20

ACKNOWLEDGMENTS

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Drafts of this document have been reviewed by representatives of Federal agencies and labor and industrial groups. NIOSH thanks these individuals for their thoughtful comments, suggestions, and assistance.

PUBLIC HEALTH SUMMARY

What are the hazards?

Workers in the health care industry and related occupations are at risk of occupational exposure to bloodborne pathogens, including human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and other potentially infectious agents.

How do these hazards occur?

The primary route of occupational exposure to bloodborne pathogens is accidental percutaneous (through the skin) injury. Health care workers handle sharp devices and equipment such as hypodermic and suture needles, intravenous blood collection devices, phlebotomy devices, and scalpels. Of the 800,000 needlestick injuries (NSIs) estimated to occur in the hospital setting annually, the greatest number occur to health care workers with the most involvement in direct patient care. Nursing staff and phlebotomists sustain the highest percentage of reported NSIs.

Hospital NSI studies have shown that many of these injuries occur after the device is used and during disposal activities. As many as one-third of all sharps injuries have been reported to be related to the disposal process. The factors most often related to sharps injuries include the following:

- Inadequate design or inappropriate placement of the sharps disposal container
- Overfilling of sharps disposal containers
- Inappropriate sharps disposal practices by the user during patient care

How can these hazards be avoided?

The use of safer needle-bearing products, worker education and training, other measures for preventing sharps injuries, and compliance with standard precautions for preventing exposure to bloodborne pathogens should be part of an overall strategy for preventing NSIs.

Important elements of an overall prevention strategy include the following:

- Engineering controls (an example is the use of safer needle-bearing products)
- Organizational controls (examples are the elimination of unnecessary sharps and training in the use of sharps disposal containers)
- Surveillance of NSIs to assess their frequency and circumstances

The routine use of rigid sharps disposal containers in the health care environment has been demonstrated to reduce NSIs. This document presents a framework for selecting disposable and reusable sharps disposal containers and evaluating their efficacy as part of an NSI prevention plan.

Section I (A) of this document addresses four major criteria for evaluating the performance of sharps disposal containers.

1. Functionality: Containers should remain functional during their entire usage (i.e., they should be durable, closable, leak resistant on their sides and bottom, and puncture resistant until final disposal).

2. Accessibility: Containers should be accessible to workers who use, maintain, or dispose of sharp devices. Convenient placement should also be considered, along with portability of containers within the workplace, if necessary.

3. Visibility: The following should be plainly visible to the workers who use the containers: the container, the degree to which it is full, the proper warning labels, and the color coding of the container.

4. Accommodation: Containers should be accommodating or convenient for the user and the facility and should be environmentally sound (e.g., free of heavy metals and composed of recycled materials). Accommodation also includes ease of storage, assembly, and operation.

Appendix D contains a questionnaire designed to

evaluate container performance based on these four performance criteria. This questionnaire should help product evaluation committees, facility management, and health care workers select and evaluate sharps disposal containers.

Section II (B) of this document presents requirements of the Occupational Safety and Health Administration (OSHA) and recommendations of the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC), concerning sharps disposal container selection and implementation. OSHA's bloodborne pathogens standard is reviewed to establish minimum design performance elements. Recommendations are made for reprocessing reusable sharps disposal containers.

NIOSH recommends selecting a container or combination of containers that are based on a site-specific hazard analysis and have the following components:

- Assessment of workplace hazards (biological, physical, chemical, and radiological containment needs)
- Assessment of size and types of sharps to be disposed of
- Assessment of the volume of sharps to be disposed of at each point of use
- Assessment of frequency of sharps disposal container emptying and mounting bracket servicing by maintenance staff
- Compliance with Federal, State, and local regulations
- Security requirements
- Container transport or mobility needs
- Clinician and procedural variability and movement
- Laboratory equipment variability and movement
- Environmental and disposal constraints
- Cost considerations
- Continued evaluation of medical device technology, including ongoing changes in equipment design and barrier materials

Appendix C presents a decision logic outlining appropriate criteria and priorities for selecting a sharps disposal container. This decision logic can be used alone or in conjunction with the performance evaluation questionnaire (Appendix D) to frame the selection process.

Sharps disposal containers that are functional, accessible, secure from patient and visitor tampering (if necessary), visible, and convenient to use will decrease the risk of percutaneous sharps injury. There is no single container type that meets the disposal containment needs for an entire facility. The diversity of health care settings and procedures makes selecting a single container impossible.

Where can I get more information?

The references and related reading list at the end of this document provide a useful inventory of published reports and literature. If you have any questions about obtaining equipment described here, contact your local biohazard safety/waste equipment supplier or call NIOSH.

1-800-35-NIOSH
(800-356-4674)

SELECTING, EVALUATING, AND USING SHARPS DISPOSAL CONTAINERS

I—INTRODUCTION

The Occupational Safety and Health Administration (OSHA) estimates that more than 5.6 million workers in health care and related occupations are at risk of occupational exposure to bloodborne pathogens, including human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and other potentially infectious agents.[1] Occupational transmission of bloodborne pathogens (including HBV, HCV, and HIV) has been well documented.[2–11] Ongoing surveillance of needlestick injuries (NSIs) and other sharps-related injuries indicate that occupational bloodborne pathogen exposure remains an important public health concern.

The primary route of occupational exposure to bloodborne pathogens is percutaneous injury (i.e., NSI). Health care workers (HCWs) handle sharp devices and equipment such as hypodermic and suture needles, intravenous blood collection devices, phlebotomy devices, and scalpels.

As many as 800,000 NSIs are estimated to occur in the hospital setting annually.[12,13] However, the true incidence of sharps injuries is unknown because many injuries go unreported in both health care and public safety settings. Centers for Disease Control and Prevention (CDC) studies have estimated that the rate of seroconversion following occupational parenteral exposure to infected blood is approximately 6% to 30% for HBV exposures, 5% to 10% for HCV exposures,[3–5] and 0.3% for HIV exposures.[9,14] Other CDC surveillance data on NSIs indicate that 86% of reported occupational HIV exposures result from hollow-bore needles.[14]

NSIs occur most often to HCWs with the greatest involvement in direct patient care. Nursing staff and phlebotomists sustain the highest percentage of reported injuries.[15–20] Other HCWs are at risk of injury from specific types of sharps—for example, surgeons (scalpels and suture needles), dental workers (dental burs), and housekeepers and laundry workers (discarded or lost needles in waste and laundry). The use of safer needle-bearing products and other measures for preventing sharps injuries should be part of an overall strategy to prevent NSIs.[21,22] Compliance with standard precautions for prevention of exposure to bloodborne pathogens should be part of this overall strategy.[23] Moreover, surveillance of NSIs is an integral part of sharps injury prevention and control. Accurate assessment of the frequency and circumstances of these injuries is necessary to direct prevention efforts.

Hospital NSI studies have shown that many of these injuries occur after the device is used and during disposal activities.[15,16,24] As many as one-third of all sharps injuries have been estimated to be related to the disposal process. These injuries have most often been related to a number of factors, including inappropriate sharps disposal practices by the user, inadequate sharps disposal container design, inappropriate sharps disposal container placement,* and overfilling of sharps disposal containers.

The correct and consistent use of rigid sharps disposal containers in the health care environment has been demonstrated to reduce the number of NSIs.[25] Studies indicate that placement of disposal boxes in all patient and treatment rooms decreases the frequency of sharps injury.[15,16,18,25] Investigators have concluded that appropriately placed sharps disposal containers reduce NSIs related to recapping of sharps by as much as 80%.[18] Cost-benefit studies show that when the increased costs of materials management are compared with the decrease in injury compensation costs, sharps disposal containers are cost effective—even when both direct and indirect costs (medical evaluation and followup, treatment costs, and lost workdays) of injury reduction are considered.[24]

In addition to engineering controls such as the use of rigid sharps disposal containers, organizational controls are a vital part of an overall prevention strategy. These include the elimination of unnecessary sharps, changes in device-handling procedures, worker education and training, and placement of sharps disposal containers where sharps are used.

* See Appendix F for an OSHA hazard information bulletin regarding sharps disposal containers with needle removal features.

The purpose of this document is to provide a framework for selecting sharps disposal containers and evaluating their efficacy as part of an overall NSI prevention plan. Both disposable and reusable sharps disposal containers are included. The plan is intended for use by infection control practitioners, purchasers, and others who are responsible for the selection process.

II—SHARPS DISPOSAL CONTAINERS

A. Performance Criteria

Focus group studies (Appendix A) suggest that there are four major criteria for sharps disposal container safety performance: functionality, accessibility, visibility, and accommodation. More detailed descriptions of these criteria follow:

- Functionality: Containers should remain **functional** during their entire usage. They should be durable, closable, leak resistant on their sides and bottoms, and puncture resistant until final disposal. A sufficient number of sharps disposal containers should be provided. Individual containers should have adequate volume and safe access to the disposal opening (inlet).

- Accessibility: Containers should be **accessible** to workers who use, maintain, or dispose of sharp devices. Containers should be conveniently placed and (if necessary) portable within the workplace.

- Visibility: Containers should be plainly **visible** to the workers who use them. Workers should be able to see the degree to which the container is full, proper warning labels, and color coding.

- Accommodation: Container designs should be **accommodating** or convenient for the user and the facility, and they should be environmentally sound (e.g., free of heavy metals and composed of recycled materials). **Accommodation** also includes ease of storage and assembly and simplicity of operation.

1. Functional criteria

Sharps disposal containers should be of sufficient thickness or construction design to be durable, leak resistant, and puncture resistant under normal use and stresses imposed during storage, handling, installation, use, closure, and transport within the user facility before final disposal.* Durability and puncture resistance should remain unaffected by moderate variation in temperatures during storage and use.† Brackets and locking mechanisms used for installation should also be durable.

Barrier material performance. Sharps disposal container material should be resistant to chemical or liquid permeation or degradation, punctures, tearing, abrasion, and laceration.

Closure mechanisms. Closure mechanisms should be designed to minimize exposure to contents and injury to the hand during engagement of the closure mechanism or during transport within the user facility before final disposal. Once activated, the final closure mechanism of a sharps disposal container should be resistant to manual opening.

Stability. Containers (including those designed to be kicked or wheeled) should be stable when placed on a horizontal surface and when used as described in the product labeling. Some manufacturers provide trays, holders, or enclosures to stabilize their containers in certain applications. The use of these items should also be detailed in the labeling.

Size and shape. Where workers handle sharp devices, a sufficient quantity of sharps disposal containers should be available in the appropriate size and shape. Sharps disposal containers should be of sufficient size to accommodate the largest sharp used at the workstation it serves. Containers should also be shaped to accommodate the partic-

* No requirements exist for sharps disposal containers to meet Department of Transportation (DOT) certification for shipping containers. Sharps disposal containers are generally placed within DOT-certified containers before shipping to a final disposal site.

† Caution must be exercised when handling sharps disposal containers at extremes of temperature—such as those encountered by home health care providers when transporting sharps disposal containers in their cars. Sharps disposal containers are not typically designed for high- and low-temperature conditions.

ular type of sharp that requires disposal. At a minimum, one sharps disposal container should be provided at each worksite where sharps are predictably generated or located.

Sharps disposal containers should also be of sufficient size to accommodate the volume of sharps typically generated at the site between maintenance operations. Providing sharps disposal containers of sufficient size will minimize the possibility of overfilling the container, which would compromise its safe operation.

Mounting brackets. Mounting brackets for sharps disposal containers should be rugged and provide for ease of servicing and decontamination.

2. Accessibility criteria

Disposal opening or access mechanism. Sharps disposal containers should be designed to permit safe disposal of sharps. They should be simple and easy to operate. The disposal opening should prevent spills of the contents (objects or liquid) while in use in the intended upright position, during the closure and sealing process, and during transportation within the user facility before final disposal. The design should also minimize any catching or snagging of sharps during insertion into the sharps disposal container. The disposal opening should be identifiable and accessible by the user and should facilitate one-handed disposal.

Security may be a concern in some areas of facilities using sharps disposal containers. For instance, to prevent children and others from putting their hands into the containers, the facility should consider selecting containers with guards that prevent hands or fingers from entering the containers. Where safety features are added to restrict child access, these features should not interfere with the worker's vision of the inlet opening. Injury to visitors may also be a problem.[26] Sharps disposal container options that accommodate these concerns should be available within the facility.

Handles. For some designs, handles may facilitate safe handling of the sharps disposal container. If present, they should be sufficiently sturdy to avoid breaking when the sharps disposal container is in use or during transportation before final disposal. If handles are present, they should be placed so that the user's hands are not close to the disposal opening when the handles are used, and they should be positioned above the full-fill level.

General location and placement. Proper sharps disposal container location and placement should ensure that containers are readily visible and within easy horizontal reach of the user. Placement of containers should be in compliance with any existing State or local regulations or site-specific certification or accreditation licensing requirements. Where containers are fixed to walls or other permanent sites, the vertical height should allow the worker to view the opening or access of the container.

Sharps disposal containers should be placed with no furniture or other obstacles between the site of use and the container. Injuries may result if sharps disposal containers are located in awkward, unsafe locations. These unsafe locations may force workers to make unnecessary movements while holding a sharp and accessing the container. Placement of the sharps disposal container outside the patient room also increases the possibility of injury. Examples of inappropriate installation include placement in the corners of rooms; on the backs of room doors; under cabinets; on the insides of cabinet doors; under sinks; in areas where people might sit or lie beneath the container; near light switches, room environmental controls, or utility system access ways; near mail boxes; or where the container is subject to impact and dislodgement by pedestrian traffic, moving equipment, gurneys, wheelchairs, or swinging doors. Standard operating procedures and practices should be developed to allow the worker to dispose of the device as soon as possible after use—preferably without needing to put the device down and pick it up again.

Special situations may require innovative sharps disposal container placement and security approaches. Examples of these special situations

include pediatric and geriatric wards and mental health or correctional facilities. If necessary, in areas with high patient or visitor traffic, sharps disposal containers should be mounted in a lockable fixture. In the emergency room, sharps disposal containers may need to be mounted on wheels to facilitate the movement of gurneys and monitoring equipment. In some situations, it may be appropriate to mount sharps disposal containers directly on gurneys to facilitate their use. Although some pediatric facilities mount sharps disposal containers high on walls to prevent access by children, such placement should not be so high that it impairs safe access by workers.

Installation height. Installation of a container at an appropriate height for the user may reduce sharps-related injuries. Sharps disposal containers should be placed within arm's reach and below eye level at their point of use. For certain types of permanently fixed, wall-mounted containers, an ergonomically acceptable range of installation height can be calculated (Appendix B). Standard anthropometric tables should be used to determine the normal range of human physical variation. Fixture heights are commonly designed to accommodate 95% of the adult population. The following criteria should be used to determine the optimal range for fixed installation height: (1) users should have a clear, unobstructed view of the container inlet opening, (2) the container should be located within arm's reach, and (3) the fixture height should be below the eye level of 95% of adult female workers. These requirements yield an optimal installation range of 56 to 52 inches at a standing workstation, and 42 to 38 inches for a seated workstation. The upper and lower ranges for the installation height are calculated by allowing for the reach behavior of workers. For a complete explanation of calculating optimal installation height, see Appendix B.

Other ergonomic alternatives include (1) using an extension arm on a fixed-height installation at a seated workstation to bring the sharps disposal container closer to the work surface, (2) providing height-adjustable chairs that allow the worker to view the entire top surface of a container at a seated workstation, and (3) using bracketing and mounting systems designed to allow user adjustment of the container (Appendix B).

3. Visibility criteria

To reduce the chance of percutaneous injury, sharps disposal containers should be visible and recognizable. Safe disposal of sharps requires clear vision of both the sharp device and the container. The disposal opening or access mechanism and current fill status should be visible to the user before sharps are placed in the container.

Sharps disposal containers should carry a hazard warning labeling. Such labels and device colors should imply danger. Either the device color or a warning label should be visible to the user to warn of a potential hazard before sharps are placed in the container. The current fill status of the container should be easily observable by the user before sharps are placed in the container. Sufficient illumination is needed at the container to determine whether any sharp object is protruding from the container or whether the container is grossly soiled at holding points or on opening mechanisms. Container fill status should be obvious under lighting conditions at the installation location. Safety features, security measures, and aesthetics should not distort recognition of the container, fill status, warning labels, or the disposal opening or access.

OSHA's bloodborne pathogens standard [29 CFR 1910.1030, section (g)(1)(I)(C)] contains very specific requirements about the labeling of containers for contaminated sharps: "These labels shall be fluorescent orange or orange-red or predominantly so, with lettering or symbols in a contrasting color." The standard also requires that the biohazard symbol and the word *Biohazard* be displayed; note, however, that "[R]ed bags or red containers may be substituted for labels" in section (g)(1)(I)(E).

4. Accommodation criteria

Sharps disposal container designs should be accommodating to the user, the facility, and the

environment. Accommodation is a measurement of ease of storage and assembly, minimal worker training requirements, ease of operation, and flexibility in design. Container design should promote one-handed disposal. Design and product finish should minimize sharp surfaces or cross-infection hazards. Special aesthetic, operational, or safety features should not hide or impede free access to the device, the inlet, or the closure process. Users should be able to assemble containers easily, if required. Mounting systems should be safe, durable, stable, cleanable, and (where appropriate) lockable. Placement in and removal from mounting systems should be simple and uncomplicated and should not compromise safety and security. To ensure proper fit and functioning of the container mounting system, mounting systems should be used only for the sharps disposal containers for which they were designed. Modifying mounting systems to accommodate containers for which they were not designed is not a safe or effective practice.

Containers should be designed so that they are simple to use. Manufacturers of sharps disposal containers should provide recommended user training information, which could include the following:

1. Assembly instructions
2. Safety considerations
3. Maintenance criteria for reusable containers
4. Optimum storage conditions
5. Warranty information
6. Decontamination recommendations (for re-usable containers and their holders)
7. Container retirement considerations (for re-usable containers and their holders)
8. Bilingual or multilingual material, where needed
9. Sharps disposal container disposal considerations
10. Information for periodic in-service retraining, if required

B. Existing Standards

Existing Federal standards for sharps disposal containers are outlined here. Published sources for other standards are listed in Appendix E.

Sharps disposal containers are regulated as class II medical devices by the Food and Drug Administration (FDA) [21 CFR 860.3].* OSHA's bloodborne pathogens standard establishes minimum design performance elements for sharps disposal containers [29 CFR 1910.1030(d)(4)(iii)(A)]. The standard requires that contaminated sharps "be discarded immediately or as soon as feasible in containers that are:

(i) Closable;
(*ii*) Puncture resistant;
(*iii*) Leakproof on sides and bottom; and
(*iv*) Labeled or color-coded in accordance with paragraph (g)(1)(i) of the standard."

Paragraph (g)(1)(i)(A) of the standard requires that warning labels "be affixed to containers of regulated waste, refrigerators and freezers containing blood or other potentially infectious material; and other containers used to store, transport, or ship blood or other potentially infectious materials. . . ."

Paragraph (d)(4)(iii)(A)(2) further states that "during use, containers for contaminated sharps shall be:

(*i*) Easily accessible to personnel and located as close as is feasible to the immediate area where sharps are used or can be reasonably anticipated to be found (e.g., laundries);

(*ii*) Maintained upright throughout use; and

(*iii*) Replaced routinely and not be allowed to overfill."

When containers of contaminated sharps are being

* FDA identifies three classes of medical devices. Class I devices (e.g., tongue depressors) are subject only to general regulatory controls and receive little Agency oversight. Class II devices (e.g., infant incubators) are subject to special controls, such as performance standards, to ensure their safe and effective use. Class III devices (e.g., implantable pacemakers) are generally life-sustaining or life-supporting and are implanted in the body; they present an unreasonable risk of illness or injury.

moved from the area of use, paragraph (d)(4)(iii)(A) (*3*) requires that they be:

> "(*i*) Closed immediately prior to removal or replacement to prevent spillage or protrusion of contents during handling, storage, transport, or shipping;
>
> (*ii*) Placed in a secondary container if leakage is possible. The second container shall be:
>
> (*A*) Closable;
>
> (*B*) Constructed to contain all contents and prevent leakage during handling, storage, transport, or shipping. . . ."

Finally, the standard states in paragraph (d)(4)(iii)(A) (*4*) that "[R]eusable containers shall not be opened, emptied, or cleaned manually or in any other manner which would expose employees to the risk of percutaneous injury."

Since most sharps disposal containers are designed to be autoclavable, steam ports and air spaces between nestable parts are located on the upper portion of containers. Steam ports allow steam to penetrate to the contents of the container during sterilization procedures. These openings may allow fluid leakage or needle-tip protrusion to occur if the container is placed on its side or overturned. The OSHA standard addresses this concern by further requiring that during handling, storage, and shipment, containers be maintained upright throughout their use, routinely replaced, and not overfilled [29 CFR 1910.1030 (d)-(4)(iii)(A)(*2*)].

C. Recommended Strategy for Selecting and Using Sharps Disposal Containers

The following strategy for selecting and using sharps disposal containers should be implemented as part of an overall NSI prevention plan.

Selection of a container or combination of containers should be based on a site-specific hazard analysis. Components of a site-specific hazard analysis should include the following:

- Assessment of workplace hazards (biological, physical, chemical, and radiological hazard containment needs)
- Assessment of size and type of sharps to be disposed of
- Assessment of the volume of sharps to be disposed of at each point of use
- Assessment of the frequency of sharps disposal container emptying and mounting bracket servicing by maintenance staff
- Compliance with Federal, State, and local regulations
- Security requirements
- Container transport or mobility needs
- Clinician and procedural variability and movement
- Laboratory equipment variability and movement
- Environmental and disposal constraints
- Economic considerations
- Continued evaluation of medical device technology, including ongoing changes in equipment design and barrier materials

An individual or a group should be assigned the responsibility for regular monitoring and maintenance of sharps disposal containers. The designee(s) should frequently and routinely monitor fill levels of containers and be responsible for changing containers before they are overfilled.

Each time a reusable sharps disposal container is returned to service after reprocessing, the user facility should confirm that it meets its original performance elements. In addition, reusable sharps disposal containers should be rendered free of infectious organisms and infectious material each time they are reprocessed and before they are returned to service.

A flow chart describing a decision logic for selecting a sharps disposal container is presented in Appendix C (Figure 2).

This decision logic can be used alone or in conjunction with the performance evaluation questionnaire in Appendix D. Based on the four performance criteria, the questionnaire is designed to assign appropriate criteria and priorities to each step and can be used to frame the selection process. The questionnaire should assist product evaluation committees, facility management, and individual

HCWs with proactive sharps disposal container selection and evaluation. Although it is not possible to provide precise guidelines for evaluating questionnaire scores, the lower the score, the better the sharps disposal container (i.e., the highest score would be 44 points and the lowest would be 220 points). A priority or value must be assigned to a criterion on a case-by-case basis. It may be useful to compare the model of sharps disposal container currently in use with the replacement models under consideration by using the questionnaire scoring system.

Before a new sharps disposal container is introduced, worker training should be conducted to address the proper use of sharps disposal containers. All workers who might come into contact with sharps should be included in this training (e.g., maintenance and laundry service staff). Where appropriate, multilingual educational materials should be developed.

For optimal protective value, the sharps disposal container must be readily available, of sufficient size and capacity, replaced when full, and used by workers. No single container type meets the disposal containment needs for an entire facility. The diversity of health care settings and procedures makes selecting a single container impossible.

III—CONCLUDING REMARKS

Sharps disposal containers that are functional, accessible, secure from patient or visitor tampering (if necessary), visible, and convenient to use will decrease the risk of percutaneous sharps injury. For optimal protective value, the container must be readily available and of sufficient size and capacity. Sharps disposal container use should be part of an institutional process that

- supports surveillance of sharps injury,
- eliminates unnecessary sharps,
- promotes worker education and training in the proper use of sharps disposal containers and safety devices,
- immunizes HCWs at risk of exposure to HBV, and
- advocates compliance with standard precautions.

Products that meet all of the performance criteria identified in this document may not exist. To develop and disseminate products that meet these criteria, manufacturers and end users should work together to design and modify containers.

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APPENDIX A—FOCUS GROUP INPUT

NIOSH initiated several cooperative agreements to conduct research on sharps disposal containers with the Educational Resource Centers (ERCs) during fiscal years 1992–94. These research agreements provided the environments necessary to study interrelated ergonomic, behavioral, and selection/evaluation variables associated with sharps disposal containers in a variety of health care settings.

Input from focus groups was used to develop this document. Experts or users were recruited to supply information to estimate the likelihood of a situation or event based on their experience. Focus groups were used to obtain user input about sharps disposal container design, safety, and management. Studies conducted by NIOSH ERCs selected health care workers considered at risk of exposure to HIV in a variety of health care settings. The evaluation criteria (identified in the performance evaluation questionnaire of this document) were developed, in part, using focus groups. The use of focus groups provided a rapid and relatively inexpensive measurement tool to identify worker perceptions, beliefs, and attitudes regarding the performance of sharps disposal containers.

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APPENDIX B—DETERMINING SHARPS DISPOSAL CONTAINER INSTALLATION HEIGHT USING STANDARD ERGONOMICS MEASUREMENTS

Architects, ergonomists, and interior designers use standard anthropometric tables to determine the normal range of human physical variation. Fixture heights (i.e., the distance from the floor to the opening of the sharps disposal container) are commonly designed to accommodate 95% of the adult population. An ergonomically acceptable range for fixed installations (i.e., containers located in permanent, wall-mounted holding brackets) can be calculated to facilitate the reduction of sharps-related injuries and standardize the container height location within the health care facility. HCWs should be able to comfortably view the entire inlet opening of the disposal container, and containers should be located within arm's reach. Neck and eye fatigue is most effectively reduced when objects to be viewed are slightly below eye level (i.e., 0 to 15 degrees below eye level).

Installation heights vary, depending on whether the installation is designed to be a standing workstation or seated workstation. Maximum and minimum heights for both design situations can be calculated by establishing the eye-level height for each design (standing or sitting), the maximum thumb tip reach (MTTR)* of the target adult female population and the drop in inches based on an angle of 15 degrees. The basic formula is as follows:

$$\text{fixture height} = (\text{eye-level height}) - (\text{tangent } 15^\circ)(\text{MTTR})$$

However, in observations of workers using fixed, wall-mounted containers, nearly all workers bent their elbows and wrists when approaching sharps disposal containers to dispose of used sharps and actually stood closer to the container rather than extending their arms to their maximum reach. On the basis of these data, the calculation can be enhanced to accommodate actual behavior. The upper and lower ranges for the installation height can be modified by allowing for the reach behavior of workers. Thus the middle 50% distance of the MTTR was used to adjust for human behavior and provide for a more functional installation height range.

If eye level equals 57 inches and the modified MTTR is used,

$$\text{fixture height} = 57 \text{ inches} - (.2679)(18.7 \text{ inches})$$
and
$$\text{fixture height} = 57 \text{ inches} - (.2679)(3.7 \text{ inches})$$

Therefore,

$$\text{fixture height} = 57 \text{ inches} - 5 \text{ inches} = 52 \text{ inches}$$
and
$$\text{fixture height} = 57 \text{ inches} - 1 \text{ inch} = 56 \text{ inches}$$

The optimal installation heights for fixed, wall-mounted sharps disposal containers are

Standing workstation:[†,‡]
52 to 56 inches above the standing surface of the user (Figure 1)

Seated workstation:[§]
38 to 42 inches above the floor on which the chair rests

---

* MTTR, the distance from the tip of the thumb to the shoulder.

† All standard measurements were taken from tables contained in J. Panero and M. Zelnick's *Human Dimension and Interior Space*, 1979, pages 98 and 102.

‡ Standing eye level includes a 1-inch shoe heel thickness and a 56.3-inch eye height.

§ Seated eye level includes a 0.25-inch clothing thickness, 1-inch chair seat thickness, 14.9-inch popliteal height, and 27.4-inch erect sitting eye height.

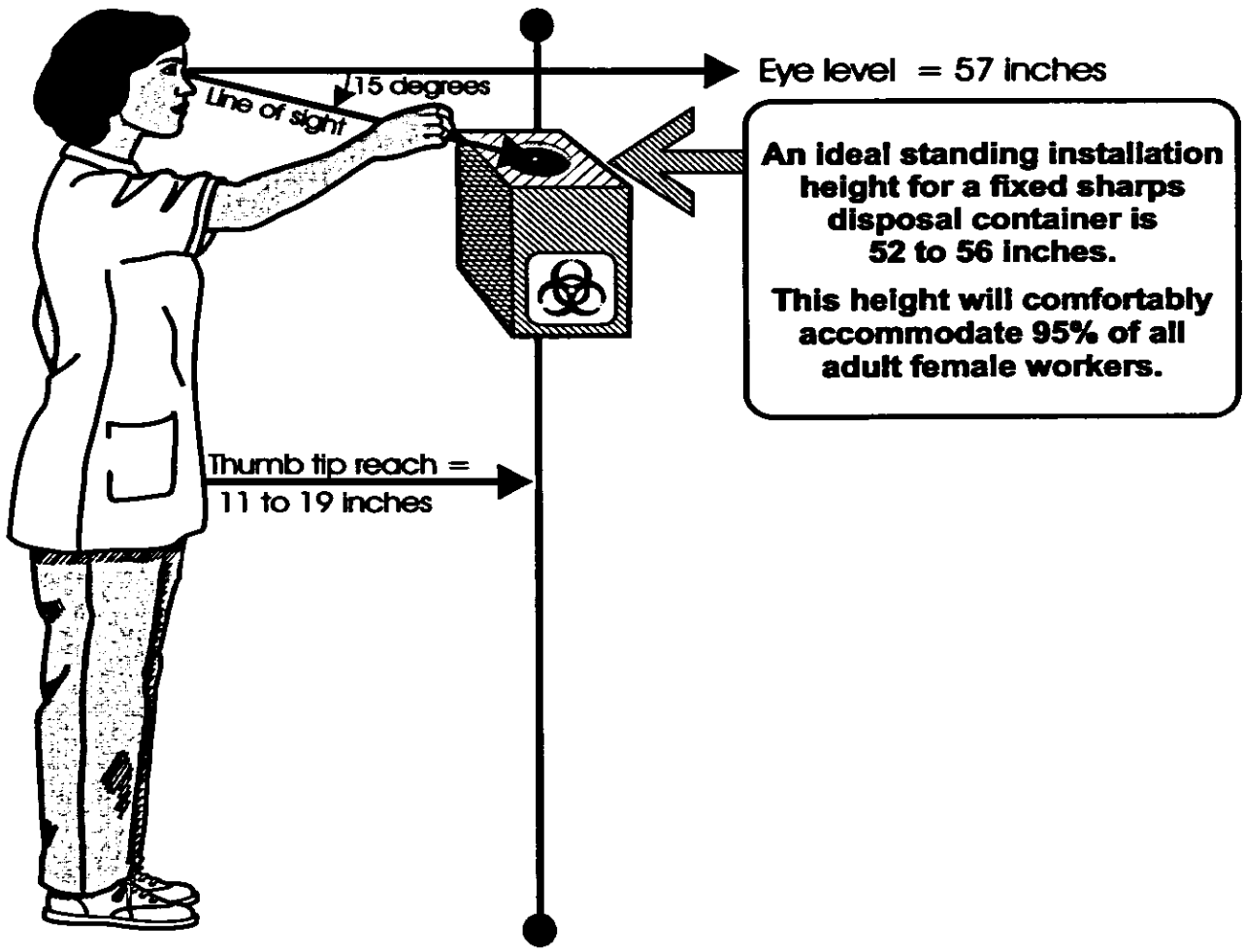

Figure 1. Ergonomic installation height for a wall-mounted work station.

APPENDIX C—DECISION LOGIC FOR SELECTING SHARPS DISPOSAL CONTAINERS

NIOSH has developed a decision logic to present appropriate criteria and priorities for selecting a sharps disposal container (Figure 2). This decision logic can be used to frame the selection process.

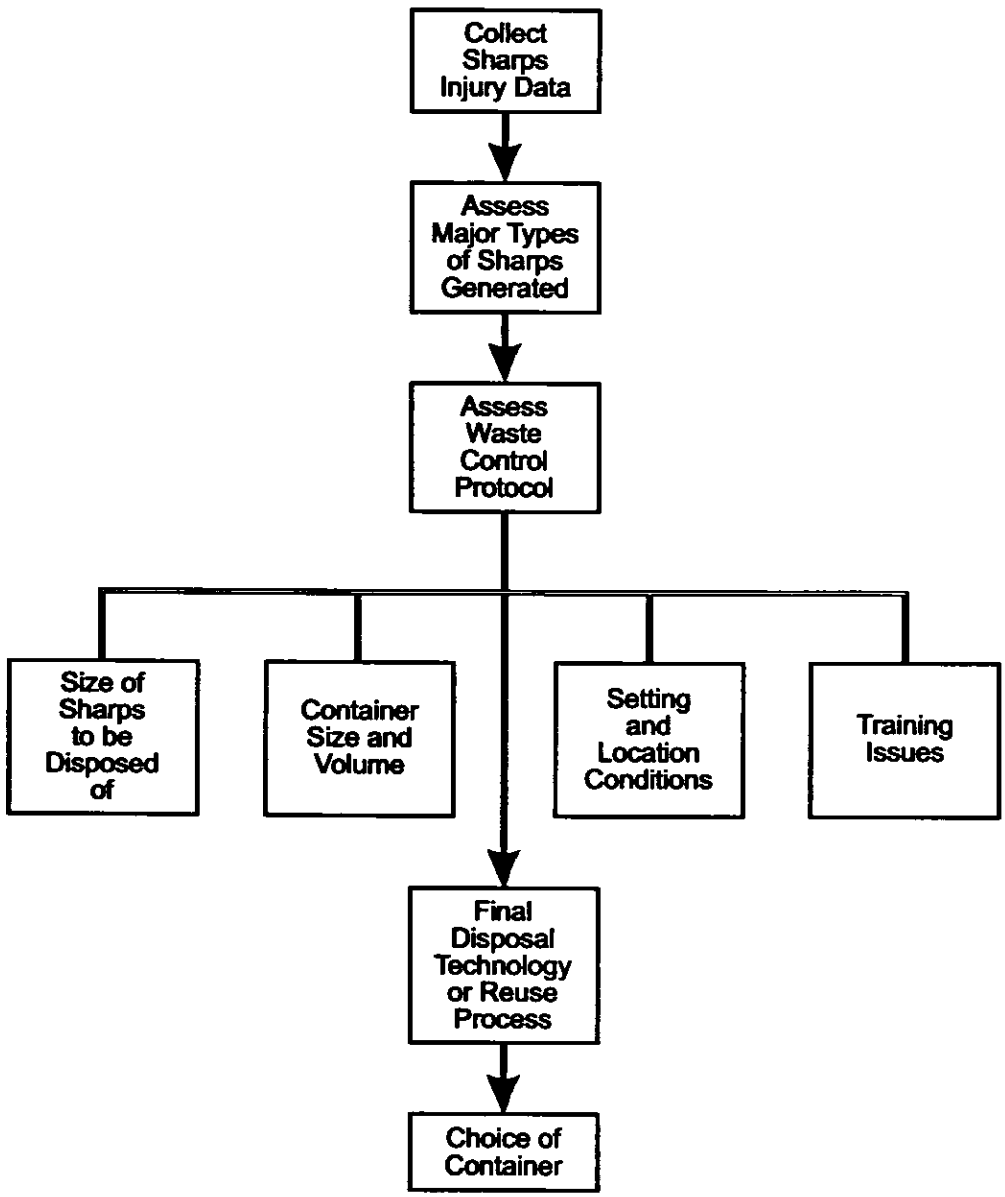

Figure 2. Decision logic for sharps disposal container selection.

APPENDIX D—QUESTIONNAIRE FOR EVALUATING SHARPS DISPOSAL CONTAINER PERFORMANCE

The decision logic may be followed by a questionnaire designed to evaluate container performance based on each of the four performance criteria (functionality, accessibility, visibility, and accommodation). The questionnaire should assist product evaluation committees, facility management, and individual HCWs in proactive sharps disposal container selection and evaluation. Users of this questionnaire should be aware that the ideal product may not exist and that this evaluation tool was constructed on the basis of common product designs available at the time.

Product evaluators should inspect and operate sharps disposal container mechanisms in side-by-side comparisons. Representative sharps (syringes, IV sets, blades, pipettes, etc.) should be on hand in sufficient numbers to test the ease of use and the intended function of candidate products. Actual use conditions should be simulated, if possible. Before inserting test sharps, attempt to reopen sealed containers and attempt to spill or remove contents from unsealed containers if this is a functional requirement of the location of intended use. Evaluation facilitators should provide product manufacturer literature and visual instructions; they should also demonstrate proper operation of each container.

The waste management system represents a considerable investment for health care operations. Sharps disposal containers should be economical to acquire, store, assemble, use, and dispose of. Low unit prices do not always result in lowest overall costs. Total cost for the employer is best measured as a function of wear life, unit cost, capacity utilization, labor cost, capital investment, employee training, installation cost, disposal cost, savings in employee injury costs, employee task confidence, and compliance with standard precautions and 29 CFR 1910.1030 (OSHA's bloodborne pathogens standard). Moreover, evaluation of cost is an ongoing process that may be a driving force in deciding when new sharps disposal containers are required or relocation of existing sharps disposal containers is more appropriate.

At this time, there is no quantitative score that indicates a container is sufficient for a particular purpose. Although it is not possible to provide precise guidelines for evaluating a particular score from the questionnaire, the lower the score from the questionnaire, the better the sharps disposal container (the highest score would be 44 points and the lowest score would be 220 points). The application of priority or value to a criterion must be done on a case-by-case basis. It may be useful to submit the currently used sharps disposal container to the questionnaire scoring system to compare it with the replacement models under consideration.

QUESTIONNAIRE FOR EVALUATING SHARPS DISPOSAL CONTAINER PERFORMANCE

The following product selection questionnaire was developed by the Centers for Disease Control and Prevention's National Institute for Occupational Safety and Health in conjunction with NIOSH Educational Resource Centers; The Johns Hopkins University, Baltimore; the University of Texas, Houston; the University of California, Berkeley; and the Mount Sinai School of Medicine, New York City.

INSTRUCTIONS:

Product evaluators should inspect and operate containers to be evaluated in side-by-side comparisons. Representative sharps (syringes, IV sets, blades, biopsy needles, pipettes, etc.) should be used to test candidate products. Actual use conditions should be simulated, if possible. Prior to inserting test sharps, attempt to reopen sealed containers and attempt to spill or remove contents from unsealed containers if this is a functional requirement. Evaluation facilitators should provide product manufacturer literature and visual instructions and should demonstrate proper operation of each of the containers. Use of this guideline requires knowledge that the ideal product may not exist and that this evaluation tool was based on common product designs available at the time.

FUNCTIONALITY

PLEASE CIRCLE YOUR RESPONSE

	agree				**disagree**
Container is stable when placed on horizontal surface and when used as described in the product labeling for use in trays, holders, or enclosures . . .	1	2	3	4	5
Container provides for puncture, leak, and impact resistance	1	2	3	4	5
Container, labels, warning devices, and brackets are durable	1	2	3	4	5
Container is autoclavable, if necessary	1	2	3	4	5
Container is available in various sizes and capacities	1	2	3	4	5
Container is available with auxiliary safety features (e.g., restricted access to sharps in the container), if required	1	2	3	4	5
Closure mechanism will not allow needlestick injury	1	2	3	4	5
Closure mechanism provides secure seal	1	2	3	4	5
Design minimizes needle-tip flipback	1	2	3	4	5
Design promotes clinical performance (e.g., will not compromise sterile field or increase injury or infection control hazards)	1	2	3	4	5

	agree				disagree
Design resists easy reopening after sealing for final disposal or autoclaving	1	2	3	4	5
Inlet design defeats waste removal when open	1	2	3	4	5
Inlet design prevents spillage of contents (physical or liquid) while sharps disposal container is in use in the intended upright position	1	2	3	4	5
Containers designed to be reopenable have removable lids design with tight closure that facilitates ease of removal with grip safety and comfort	1	2	3	4	5
Mounting brackets are rugged and designed for ease of service and decontamination	1	2	3	4	5

ACCESSIBILITY

	agree				disagree
Container available in various opening sizes and shapes	1	2	3	4	5
Containers are supplied in sufficient quantity	1	2	3	4	5
Container has an entanglement-free opening/access way	1	2	3	4	5
Container opening/access way and current fill status visible to user prior to placing sharps into container	1	2	3	4	5
Internal design/molding of container does not impede ease of use	1	2	3	4	5
Handles, if present, located above full-fill level	1	2	3	4	5
Handles, if present, facilitate safe vertical transport and are located away from opening/access way and potentially soiled surfaces	1	2	3	4	5
Fixed locations place container within arm's reach of point of waste generation	1	2	3	4	5
Fixed locations allow for installation of the container below horizontal vision level	1	2	3	4	5
If necessary, in high patient or visitor traffic areas, container should provide for security against tampering	1	2	3	4	5

VISIBILITY

	agree				disagree
Color or warning label implies danger	1	2	3	4	5
A warning indicator (i.e., color or warning label) is readily visible to the user prior to user placing sharps into container	1	2	3	4	5
Overfill level provided and current fill status is readily visible to the user prior to use placing sharps into container	1	2	3	4	5
Sharps disposal container complies with OSHA requirements	1	2	3	4	5
Disposal opening/access way is visible prior to user placing sharps into container	1	2	3	4	5
Security, mounting, aesthetic, and safety features do not distort visibility of the opening/access way or fill status indicator	1	2	3	4	5

ACCOMMODATION

	agree				disagree
No sharp edges in construction or materials	1	2	3	4	5
Safety features do not impede free access	1	2	3	4	5
Promotes patient and user satisfaction (i.e., aesthetic to extent possible)	1	2	3	4	5
Is simple to operate	1	2	3	4	5
Any emissions from final disposal comply with pollution regulations	1	2	3	4	5
Easy to assemble, if required	1	2	3	4	5
Components of containers that require assembly are easy to store prior to use	1	2	3	4	5
Use allows one-handed disposal	1	2	3	4	5
Product available in special designs for environments with specific needs (e.g., laboratories, emergency rooms, emergency medical services, pediatrics, correctional facilities)	1	2	3	4	5
Mounting system durable, secure, safe, cleanable, and, where appropriate, lockable	1	2	3	4	5
Mounting systems allow height adjustments	1	2	3	4	5
Design promotes task confidence	1	2	3	4	5
Cost effectiveness	1	2	3	4	5

OTHER COMMENTS

What design or performance requirements are missing from the product you evaluated that are really needed to safely or more comfortably conduct your job or sharps-related task?

Additional Evaluator Concerns and Comments:

APPENDIX E—RECOMMENDED READING

Regulation and Standards

1. OSHA. Occupational exposure to bloodborne pathogens: final rule (OSHA 29 CFR 1910.1030). Federal Register 1991;56:64175–82.

2. American Society for Testing and Materials (ASTM). Performance standard specification for puncture resistance of containers for discarded medical needles and other sharps. ASTM Task Force F04.65.01 (in preparation).

3. Canadian Standards Association (CSA). Evaluation of single use medical waste sharps containers for biohazardous and cytotoxic waste. CSA; CAN/CSA-Z316.6 (in preparation).

4. British Standards Institution (BSI). BS 7320:1990: Specifications for sharps containers. London: BSI, 1990.

5. Standards Australia (SA). Australian standard: non-reusable containers for the collection of sharps medical items used in health care areas. New South Wales, Australia: SA, 1992; AS 4031–1992.

Performance Evaluation

1. ECRI. Health devices: sharps disposal containers. ECRI, Plymouth Meeting, PA 1993;22:359–413.

2. American Hospital Association Needlestick Workgroup. Implementing safer needle devices. American Hospital Association, Division of Quality Resources Infection Control. Chicago, IL: December 1992.

Focus Group/End User Assessment Methods

1. Krueger RA. Focus groups: a practical guide for applied research. Newbury Park, CA: Sage Publications, 1988.

2. Milholland AV, Wheeler SG, Hejeck JJ. Medical assessment: the Delphi group opinion technique. N Engl J Med 1973;288:1272–1275.

3. Stewart D, Shadasani PN. Focus groups: theory and practice. Newbury Park, CA: Sage Publications, 1990.

NIOSH ERC Research Publications

1. Decker JA, Deitchman S, Buchta T. Health Hazard Evaluation Report No. 91-342-2271.

APPENDIX F—OSHA HAZARD INFORMATION BULLETIN: SHARPS DISPOSAL CONTAINERS WITH NEEDLE REMOVAL FEATURES

MEMORANDUM FOR: LEO CAREY
Director
Office of Field Programs

FROM: PATRICIA K. CLARK
Director
Directorate of Technical Support

SUBJECT: Hazard Information Bulletin*—Sharps Disposal Containers with Needle Removal Features

The purpose of this bulletin is to alert field personnel to the possible safety and health risks that may arise with the use of some sharps disposal containers that incorporate an "unwinder" mechanism to accomplish needle removal. Unwinders are used to separate needles from syringes or phlebotomy needles from blood collection (e.g., Vacutainer®) apparatus.

In general, sharps containers used for discarding contaminated needles must be closable, puncture-resistant, leakproof on the sides and bottom, and appropriately labeled or color coded (1910.1030 (d)(4)(A)(1)). Additionally, the Occupational Exposure to Bloodborne Pathogens Standard (1910.1030) prohibits needle removal unless the employer can demonstrate that no alternative is feasible or that such action is required by a specific medical procedure. Needle removal must be accomplished through the use of a mechanical device or a properly performed one-handed technique (1910.1030 (d)(2)(vii)(D)). Sharps containers which have well designed unwinders may be used.

However, it has recently come to our attention that some sharps containers do not have well designed unwinders and, therefore, do not meet the intent of the engineering and work practice controls provision of the standard. The design of some of these needle unwinders can cause needlestick injuries when the container becomes overfilled, or when the unwinder fails to properly secure the needle during the removal process.

As stated in OSHA Instruction CPL 2-2.44C, "Enforcement Procedures for the Occupational Exposure to Bloodborne Pathogens Standard," needle removal devices should not create additional hazards. The design of the sharps container and the location of the unwinder must allow the needle removal to be accomplished in a safe one-handed manner. In addition to the above mentioned safety characteristics, evaluation of such sharps containers should also consider the following safety features:

1. The sharps container should be designed so that it is easily and safely determined when the container needs to be emptied; this avoids overfilling and reduces the risk of injury.

2. The sharps container with an unwinder should be stabilized (secured to a wall, table, or tray) to prevent slipping during use.

* The Directorate of Technical Support issues *Hazard Information Bulletins* (*HIBs*) in accordance with OSHA Instruction CPL 2.65 to provide relevant information regarding unrecognized or misunderstood health hazards and inadequacies of materials, devices, techniques, and safety engineering controls. *HIBs* are initiated on the basis of information provided by the field staff, studies, reports and concerns expressed by safety and health professionals, employers, and the public. Information is compiled on the basis of a thorough evaluation of available facts and literature and in coordination with appropriate parties.

3. The design of the unwinder must allow the employee to use the unwinder with a one-handed technique; that is, the employee must not be required to secure the needle with one hand while it is being unwound by the other hand.

4. The unwinder should be designed so that the needles do not slip or slide within the unwinder during the needle removal process; the unwinder should provide a secure capture that prevents movement of the needle while it is removed.

OSHA recommends that procedures requiring needle removal be carefully evaluated to determine the feasibility of equipment redesign or changes in work practices.

Please distribute this bulletin to all Area Offices, State Plan States, Consultation Projects, and appropriate local labor and industry associations.

The Role of the Physical Environment in the Hospital of the 21st Century: A Once-in-a-Lifetime Opportunity

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Report to The Center for Health Design for the *Designing the 21st Century Hospital Project.* This project is funded by the Robert Wood Johnson Foundation.

September 2004

The Role of the Physical Environment in the Hospital of the 21st Century: A Once-in-a-Lifetime Opportunity

A visit to a U.S. hospital is dangerous and stressful for patients, families and staff members. Medical errors and hospital-acquired infections are among the leading causes of death in the United States, each killing more Americans than AIDS, breast cancer, or automobile accidents (Institute of Medicine, 2000; 2001). According to the Institute of Medicine in its landmark *Quality Chasm* report: "*The frustration levels of both patients and clinicians have probably never been higher. Yet the problems remain. Health care today harms too frequently and routinely fails to deliver its potential benefits*" (IOM, 2001). Problems with U.S. health care not only influence patients; they impact staff. Registered nurses have a turnover rate averaging 20 percent (Joint Commission on Accreditation of Healthcare Organizations, 2002).

At the same time, the United States is facing one of the largest hospital building booms in US history. As a result of a confluence of the need to replace aging 1970s hospitals, population shifts in the United States, the graying of the baby boom generation, and the introduction of new technologies, the United States will spend more than $16 billion for hospital construction in 2004, and this will rise to more than $20 billion per year by the end of the decade (Babwin, 2002). These hospitals will remain in place for decades.

This once-in-lifetime construction program provides an opportunity to rethink hospital design, and especially to consider how improved hospital design can help reduce staff stress and fatigue and increase effectiveness in delivering care, improve patient safety, reduce patient and family stress and improve outcomes and improve overall healthcare quality.

Just as medicine has increasingly moved toward "evidence-based medicine," where clinical choices are informed by research, healthcare design is increasingly guided by rigorous research linking the physical environment of hospitals to patients and staff outcomes and is moving toward "evidence-based design" (Hamilton, 2003). This report assesses the state of the science that links characteristics of the physical setting to patient and staff outcomes:

- What can research tell us about "good" and "bad" hospital design?
- Is there compelling scientifically credible evidence that design genuinely impacts staff and clinical outcomes?
- Can improved design make hospitals less risky and stressful for patients, their families, and for staff?

In this project, research teams from Texas A&M University and Georgia Tech combed through several thousand scientific articles and identified more than 600 studies—most in top peer-reviewed journals—that establish how hospital design can impact clinical

outcomes. The team found scientific studies that document the impact of a range of design characteristics, such as single-rooms versus multi-bed rooms, reduced noise, improved lighting, better ventilation, better ergonomic designs, supportive workplaces and improved layout that can help reduce errors, reduce stress, improve sleep, reduce pain and drugs, and improve other outcomes. The team discovered that, not only is there a very large body of evidence to guide hospital design, but a very strong one. A growing scientific literature is confirming that the conventional ways that hospitals are designed contributes to stress and danger, or more positively, that this level of risk and stress is unnecessary: improved physical settings can be an important tool in making hospitals safer, more healing, and better places to work.

RESEARCH PROCESS

The research teams searched through scores of databases and in libraries at Texas A&M, Georgia Institute of Technology, University of Michigan, and elsewhere. The team was looking for studies that are:

- Rigorous, in that they use appropriate research methods that allow reasonable comparisons, and discarding of alternative hypotheses. The research studies were assessed on their rigor, quality of research design, sample sizes, and degree of control.

- High impact, in that the outcomes they explore are of importance to healthcare decision-makers, patients, clinicians, and society.

In 1998, Haya Rubin and her colleagues Amanda Owens and Greta Golden found 84 studies produced since 1968 that met similar criteria (Rubin, Owens, & Golden, 1998). Reviewing the research literature six years later, the team estimated that they would find around 125 rigorous studies. We found more than 600.

RESULTS

The research team found rigorous studies that link the physical environment to patient and staff outcomes in four areas:

1. Reduce staff stress and fatigue and increase effectiveness in delivering care
2. Improve patient safety
3. Reduce stress and improve outcomes
4. Improve overall healthcare quality

I. Reduce Staff Stress and Fatigue and Increase Effectiveness in Delivering Care

There is a growing nurse shortage, and this directly threatens patient safety. And the existing hospital-based nursing force is aging. Registered nurses in the United States average more than 43 years old and will average 50 by 2010 and have a turnover rate

averaging 20 percent per year (JCAHO, 2002). The Joint Commission on Accreditation of Healthcare Organizations (JCAHO), in their 2002 report, *Health Care at the Crossroads: Strategies for Addressing the Evolving Nursing Crisis*, noted that a shortage of nurses in America's hospitals is putting patient lives in danger. JCAHO examined 1,609 hospital reports of patient deaths and injuries since 1996 and found that low nursing staff levels were a contributing factor in 24 percent of the cases. The JCAHO report and surveys of nursing found that physical working conditions, along with support and compensation, are key contributors to turnover and burnout. Environmental support for work has become more critical as the typical patient is more seriously ill, patient loads increase, technology changes, and documentation requirements increase.

While reducing staff stress and fatigue through a healing and supportive environment seems like an obvious goal, there are relatively few studies that have dealt with this issue in any detail. More attention has been given to patient outcomes. However, the following sections review several studies that do document (a) effects of healthcare environments on staff health and safety and (b) improving workplaces to increase staff effectiveness, reduce errors, and increase staff satisfaction. Each section also suggests directions for further research.

Improve Staff Health and Safety through Environmental Measures

Nurses, physicians, and other healthcare employees work under extremely stressful physical conditions. Several studies deal with healthcare employees' risk of contracting infectious diseases from patients due to airborne and surface contamination (Jiang et al., 2003; Kromhout et al., 2000; Kumari et al., 1998; Smedbold et al., 2002). A recent study conducted in the wake of the SARS epidemic in China found that isolating SARS cases in wards with good ventilation could reduce the viral load of the ward and might be the key to preventing outbreaks of SARS among healthcare workers, along with strict personal protection measures in isolation units (Jiang et al., 2003). Another study in Norway found correlations between environmental factors and nasal symptoms of 115 females who worked at 36 geriatric nursing departments. They found significant decrease in nasal inflammation in relation to presence of *Aspergillus fumigatus* in ventilation supply and elevated room temperatures (Smedbold et al., 2002). An evaluation of 17 acute-care or university hospitals in Canada shows that tuberculosis (TB) infection among healthcare workers was associated with ventilation of general or nonisolation patient rooms of less than two air exchanges per hour. The evaluation included all personnel who worked at least two days per week in the respiratory and physiotherapy departments (Menzies, Fanning, Yuan, & Fitzgerald, 2000). This study, like the others, supports the importance of adequate ventilation with good maintenance for ensuring both staff and patient safety in hospitals. Several good studies demonstrating the risk of the sick building syndrome in hospitals also have been compiled within the 2003 *Guidelines for Environmental Infection Control in Healthcare Facilities* by the US Centers for Disease Control and Prevention (CDC) and the Healthcare Infection Control Practices Advisory Committee (HICPAC) (Sehulster & Chinn, 2003).

Nursing staff members are also open to risk of injury from medical equipment such as high-intensity surgical-light sources. One study found that a light source used during surgery could potentially cause retinal damage in surgical staff (Fox & Henson, 1996). Much research has examined the effects of noise on patients, but comparatively few studies are available for healthcare staff. There is evidence that staff perceive higher sound levels as stressful (Bayo, Garcia, & Garcia, 1995; Norbeck, 1985). Importantly, noise-induced stress in nurses correlates with reported emotional exhaustion or burnout (Topf & Dillon, 1988). A recent study by Blomkvist et al. (in press, 2004) examined the effects of higher versus lower noise levels on the same group of coronary intensive-care nurses over a period of months. Lower noise levels were linked with a number of positive effects on staff, including reduced perceived work demands, increased workplace social support, improved quality of care for patients, and better speech intelligibility.

Poor ergonomic design of patient beds and nurses' stations leads to back stress, fatigue, and other injuries among nursing staff. In one nursing home study, Garg and Owen evaluated manual tasks deemed stressful by nursing staff and used the information to select patient-transferring devices and to modify toilets and shower rooms. This nursing intervention resulted in a reduction of back injuries of almost 50 percent, from 83 per 200,000 work hours to 47 per 200,000 work hours. Also, in the four months after the intervention, there were no injuries resulting in lost or restricted workdays (Garg & Owen, 1992).

Thus, reducing staff stress by ergonomic interventions, as well as careful consideration of other issues such as air quality, noise, and light, can have significant impact on staff health. In addition, it is also likely to send a message that maintaining health and safety of staff members is an important goal for the organization.

Increase Staff Effectiveness, Reduce Errors, and Increase Staff Satisfaction by Designing Better Workplaces

Jobs by nurses, physicians, and others often require a complex choreography of direct patient care, critical communications, charting, filling meds, access to technology and information, and other tasks. Many hospital settings have not been rethought as jobs have changed, and, as a result, the design of hospitals often increases staff stress and reduces their effectiveness in delivering care. While much research in the hospital setting has been aimed at patients, there is a growing and convincing body of evidence suggesting that improved designs can make the jobs of staff much easier.

Nurses spend a lot of time walking. According to one study, almost 28.9 percent of nursing staff time was spent walking (Burgio, Engel, Hawkins, McCorick, & Scheve, 1990). This came second only to patient-care activities, which accounted for 56.9 percent of observed behavior. At least four studies have shown that the type of unit layout (e.g. radial, single corridor, double corridor) influences amount of walking among nursing staff (Shepley, 2002; Shepley & Davies, 2003; Sturdavant, 1960; Trites, Galbraith, Sturdavant, & Leckwart, 1970), and two studies showed that time saved walking was translated into more time spent on patient-care activities and interaction with family

members. Sturdavant (1960) found that fewer trips were made to patient rooms in radial units as nurses were able to better supervise patients visually from the nursing station, though the average time spent with patients was the same in radial as well as single-corridor designs. Shepley and colleagues (2003) found that nursing staff in the radial unit walked significantly less than staff in the rectangular unit (4.7 steps per minute versus 7.9 steps per minute). However, Shepley and her colleagues noted that radial designs might provide less flexibility in managing patient loads. Trites and colleagues (1970) found that a decrease in the percentage of time spent walking by staff in radial units was correlated to an increase in the percentage of time spent in patient-care activities. Also, the majority of the staff surveyed preferred to work in the radial units. Hendrich's research showed that decentralized nurses stations reduced staff walking and increased patient-care time, especially when supplies also were decentralized and placed near the nurses' station (Hendrich, 2003; IOM, 2004). Centralized location of supplies, however, could double staff walking and substantially reduce care time irrespective of whether nurses stations were decentralized (Hendrich, 2003)

Workplace design that reflects a closer alignment of work patterns and the physical setting, such as redesign of a pharmacy layout, has been shown to improve work flow and reduce waiting times, as well as increase patient satisfaction with the service (Pierce, Rogers, Sharp, & Musulin, 1990). Other studies that compared delivery times in decentralized and centralized pharmacy systems found medication delivery times are reduced by more than 50 percent by using decentralized drug-dose distribution systems (Hibbard, Bosso, Sward, & Baum, 1981; Reynolds, Johnson, & Longe, 1978).

Other aspects of the environment, such as lighting levels and auditory or visual distractions, can also affect staff effectiveness while performing critical tasks such as dispensing medical prescriptions. There are relatively few studies that have examined the effect of environmental factors on medication errors, though this is clearly an area of great interest and future research potential. This is discussed in greater detail in the following section.

II. Improve Patient Safety

Hospital-Acquired Infections

One critically important way that evidence-based design improves safety is by reducing risk from hospital-acquired infections. The research team identified more than 120 studies linking infection to the built environment of the hospital. Transmission of infection to patients occurs through two general routes: airborne and contact. The research literature shows that the design of the physical environment strongly impacts hospital-acquired infection rates by affecting both airborne and contact transmission routes. The literature suggests a clear pattern wherein infection rates are lower when there is very good air quality and patients are in single-bed rather than multi-bed rooms. Also, there is some evidence that providing numerous, easily accessible alcohol-based hand-rub

dispensers or hand washing sinks can increase hand washing compliance and thereby reduce contact contamination.

Reducing Infections Caused by Airborne Pathogens

Evidence from many studies leaves no doubt that hospital air quality and ventilation play decisive roles in affecting air concentrations of pathogens such as fungal spores (*Aspergillus*) and, in this way, have major effects on infection rates.

Source of airborne infections: Well-conducted research has linked all of the following to air quality and infection rates: type of air filter, direction of airflow and air pressure, air changes per hour in room, humidity, and ventilation system cleaning and maintenance (Lutz, 2003; McDonald et al., 1998). For example, in one study where six patients and one nurse were involved with an outbreak of epidemic methicillin-resistant *Staphylococcus aureus* (EMRSA-15), an environmental source was suspected, and the ventilation grilles in two patient bays were found to be harboring EMRSA-15 (Kumari et al., 1998). The ventilation system, at that time, was working on an intermittent cycle from 4:00 p.m. to 8:00 p.m. Daily shutdown of the system created negative pressure, sucking air in from the ward environment into the ventilation system and contaminating the outlet grilles. The contaminated air blew back into the ward when the ventilation system was started. In another case, the source of infection was the exhaust ducting of the adjacent isolation room ventilation system that allowed the contaminants to enter the unit via a partially open window positioned above a particular bed.

Several studies have identified hospital construction and renovation activities as the sources of airborne infection outbreaks due to dust or particulate generation (Humphreys et al., 1991; Iwen, Davis, Reed, Winfield, & Hinrichs, 1994; Loo et al., 1996; Opal et al., 1986; Oren, Haddad, Finkelstein, & Rowe, 2001). In one study, high spore counts were found within and outside construction sites in a hospital. After control measures were instituted, no further cases of disseminated aspergillosis were identified (Opal et al., 1986). In another study, a nosocomial (hospital-induced) outbreak of invasive pulmonary aspergillosis (IPA) occurred in acute leukemia patients treated in a regular ward with natural ventilation during extensive hospital construction and renovation. The observed infection rate was 50 percent. At this point, some of the patients were moved to a new hematology ward with high-efficiency particulate air (HEPA) filters. During the following three years, none of the patients hospitalized exclusively in the hematology ward developed IPA, although 29% of leukemia patients still housed in the regular ward contracted IPA (Oren et al., 2001).

Controlling and preventing airborne infection: There is convincing evidence that immunocompromised and other high-acuity patient groups have lower incidence of infection when housed in a HEPA-filtered isolation room (Passweg et al., 1998; Sherertz, et al., 1987; Sherertz & Sullivan, 1985). In one study, bone-marrow transplant recipients were found to have a tenfold greater incidence of nosocomial *Aspergillus* infection, compared to other immunocompromised patient populations, when assigned beds outside of a HEPA-filtered environment (Sherertz, et al., 1987). Air contamination is least in

laminar airflow rooms with HEPA filters, and this approach is recommended for operating-room suites and areas with ultraclean room requirements such as those housing immunocompromised patient populations (Alberti et al., 2001; Arlet, Gluckman, Gerber, Perol, & Hirsch, 1989; Dharan & Pittet, 2002; Friberg, Ardnor, & Lundholm, 2003; Hahn et al., 2002; Sherertz, et al., 1987). (Laminar flows are very even, smooth, low velocity airflows that are used in cleanrooms and other settings where high quality ventilation is critical. But laminar flows are relatively expensive and difficult to achieve because furnishings, vents and other features can create turbulence.) HEPA filters are suggested for healthcare facilities by the CDC and HICPAC, but are either required or strongly recommended in all construction and renovation areas (Sehulster & Chinn, 2003).

Effective prevention or control measures during construction and renovation activities include, for example, portable HEPA filters, installing barriers between the patient care and construction areas, negative air pressure in construction/renovation areas relative to patient-care spaces, and sealing patient windows. There is strong evidence of the impact of using HEPA filters for air intakes near construction and renovation sites (Loo et al., 1996; Mahieu, De Dooy, Van Laer, Jansens, & Ieven, 2000; Opal et al., 1986; Oren et al., 2001). A strong study by Humphreys (1991) demonstrates that HEPA filters are not *by themselves* an adequate control measure, and must be employed in conjunction with other measures such as enhanced cleaning, the sealing of windows, and barriers. Cornet et al. (1999) concludes that carefully directed airflow (e.g. laminar airflow) is important, however, we were unable to find and document cost-benefit analysis in the literature to justify the expense versus effectiveness of laminar airflow for patient-care areas near construction and renovation sites

Reducing Infections by Increasing Hand Washing

Although infection caused by airborne transmission poses a major safety problem, most infections are now acquired in the hospital via the contact pathway (Bauer, Ofner, Just, Just, & Daschner, 1990; IOM, 2004). It is well-established that the hands of healthcare staff are the principal cause of contact transmission from patient to patient (Larson, 1988). The importance of assiduous hand washing by healthcare workers, accordingly, cannot be overemphasized for reducing hospital-acquired infections. In this context, the fact that rates of hand washing by healthcare staff are low represents a very serious patient safety challenge. Several studies of hand washing in high-acuity units with vulnerable patients have found that as few as one in seven staff members wash their hands between patients: compliance rates in the range of 15 percent to 35 percent are typical; rates above 40 percent to 50 percent are the exception (Albert & Condie, 1981; Graham, 1990). Hand washing compliance tends to be consistently lower in units that are understaffed and have a high patient census or bed-occupancy rate (Archibald, Manning, Bell, Banerjee, & Jarvis, 1997).

Education programs to increase hand washing adherence have yielded disappointing or, at best, mixed results. Some investigations have found that education interventions generate no increase at all in hand washing. Even intensive education or training

programs (classes, group feedback, for example) produce only transient increases in hand washing (Conly, Hill, Ross, Lertzman, & Louie, 1989; Dorsey, Cydulka, & Emerman, 1996; Dubbert, Dolce, Richter, Miller, & Chapman, 1990). Given the tremendous morbidity and mortality associated with high rates of hospital-acquired infections, there is an urgent need to identify more effective ways for producing sustained increases in hand washing. Is there evidence suggesting improved hospital design can be effective in elevating hand washing?

Effect of number and location of sinks/dispensers on hand washing: The research team identified six studies that examined whether hand washing is improved by increasing the ratio of the number of sinks or hand-cleaner dispensers to beds and/or by placing sinks or hand-cleaner dispensers in more accessible locations (Cohen, Saiman, Cimiotti, & Larson, 2003; Graham, 1990; Kaplan & McGuckin, 1986; Muto, Sistrom, & Farr, 2000; Pittet et al., 2000; Vernon, Trick, Welbel, Peterson, & Weinstein, 2003). These studies, on balance, offer support, though limited, for the notion that providing numerous, conveniently located alcohol-rub dispensers or washing sinks can increase compliance. In particular, the evidence suggests that installing alcohol-based hand-cleaner dispensers at bedside usually improves adherence. As an example, a study by Pittet et al. (2000) found that a combination of bedside antiseptic hand-rub dispensers and posters to remind staff to clean their hands substantially increased compliance. Cohen et al. (2003) likewise reported improved adherence in association with the installation of numerous alcohol-gel dispensers. By contrast, Muto et al. (2000) reported that placing alcohol-gel dispensers next to the doors of patient rooms did not increase adherence. Two other investigations focusing on sinks (water/soap) identified a positive relationship between observed frequency of hand washing and a higher ratio of sinks to beds (Kaplan & McGuckin, 1986; Vernon et al., 2003). Providing automated water/soap sinks, however, appears not to increase hand washing rates compared to traditional non-automated sinks (Larson, et al., 1991; Larson, Bryan, Adler, & Blane, 1997).

Further, three studies offer convincing and important evidence that providing single-patient rooms with a conveniently located sink in each room reduces nosocomial infection rates in intensive care units, such as neonatal intensive care (NICU) or burn units, compared to when the same staff and comparable patients are in multibed open units with few sinks (Goldmann, Durbin, & Freeman, 1981; McManus, A. T., Mason, McManus, & Pruitt, 1994; McManus, A. T., McManus, Mason, Aitcheson, & Pruitt, 1985; Mulin et al., 1997). Although hand washing frequency was not measured in these studies, the investigators posited that increased hand washing was an important factor in reducing infections in the units with single rooms and more sinks. A comparison of an ICU converted from an open unit with few sinks to single rooms with one sink per room found a nonsignificant tendency for hand washing to increase (from 16 percent to 30 percent) but no decline in infection incidence (Preston, Larson, & Stamm, 1981). These results are perhaps explainable by the fact that several sinks in the single-bed unit were placed in comparatively inaccessible or inconvenient locations, such as behind doors or away from staff work paths.

Despite the encouraging overall pattern of findings in these studies, it is not clear how much of the effectiveness in terms of increased hand washing or reduced infection rates can be attributed to the installation of more numerous and/or accessible sinks and alcohol-gel dispensers. Future research should include controlled experiments that systematically vary the number and location of hand-cleaning stations or dispensers. There is also a conspicuous need for studies that define *accessible* locations for hand-cleaning stations in an evidence-based manner—that is, on the basis of empirical analysis of staff movement paths, visual fields, interactions with patients and families, and work processes. In this regard, the neglect of *human factors* knowledge and research methods is a major weakness of the hand washing research and, more generally, of the infection control literature. Research teams should include a human factors specialist and often an environmental psychologist. The urgent need to increase hand washing frequency underscores the high priority that should be accorded this research direction.

Reducing Infections with Single-Bed Rooms

The research team identified at least 16 studies relevant to the question of whether nosocomial infection rates differ between single-bed and multi-bed rooms. The findings collectively provide a strong pattern of evidence indicating that infection rates are usually lower in single-bed rooms. Different mechanisms or factors have been identified or implicated as contributing to lower infection incidence in single rooms. One clear set of advantages relates to reducing airborne transmission through air quality and ventilation measures such as HEPA filters, negative room pressure to prevent a patient with an aerial-spread infection from infecting others, or maintaining positive pressure to protect an immunocompromised patient from airborne pathogens in nearby rooms. A strong study by Passweg et al. (1998) found that the combination of room isolation and HEPA filtration reduced infection and mortality in bone marrow transplant patients and significantly increased their one-year survival rates. Research studying burn patients also has shown that single rooms and good air quality substantially reduce infection incidence and reduce mortality (McManus, A. T. et al., 1994; McManus, A.T., Mason, McManus, & Pruitt, 1992; Shirani et al., 1986; Thompson, Meredith, & Molnar, 2002). Studies of cross-infection for contagious airborne diseases (influenza, measles, TB, for example) have found, as would be expected, that placing patients in single rooms is safer than housing them in multibed spaces (Gardner, Court, Brocklebank, Downham, & Weightman, 1973; McKendrick & Emond, 1976).

Severe Acute Respiratory Syndrome (SARS) outbreaks in Asia and Canada dramatically highlighted the shortcomings of multibed rooms for controlling or preventing infections both for patients and healthcare workers. SARS is transmitted by droplets that can be airborne over limited areas. Approximately 75 percent of SARS cases in Toronto resulted from exposure in hospital settings (Farquharson & Baguley, 2003). The pervasiveness in Canadian and Asian hospitals of multibed spaces in emergency departments and ICUs, together with the scarcity of isolation rooms with negative pressure, severely hindered treatment and control measures. Toronto hospitals were forced to create additional negative-pressure isolation rooms by quickly constructing wall barriers to replace bed curtains and making airflow and pressure adaptations (Farquharson & Baguley, 2003).

In addition to clear advantages in reducing airborne transmission, several studies show that single-bed rooms also lessen risk of infections acquired by contact. As background for understanding how single rooms can lessen contact spread, it should first be mentioned that many environmental surfaces and features become contaminated near infected patients. Examples of surfaces found to be contaminated frequently via contact with patients and staff include: overbed tables, bed privacy curtains, computer keyboards, infusion pump buttons, door handles, bedside rails, blood pressure cuffs, chairs and other furniture, and countertops (Aygun et al., 2002; Boyce, Potter-Bynoe, Chenevert, & King, 1997; Bures, Fishbain, Uyehara, Parker, & Berg, 2000; Devine, Cooke, & Wright, 2001; Neely & Maley, 2001; Noskin, Bednarz, Suriano, Reiner, & Peterson, 2000; Palmer, 1999; Roberts, Findlay, & Lang, 2001; Rountree, Beard, Loewenthal, May, & Renwick, 1967; Sanderson & Weissler, 1992; Williams, Singh, & Romberg, 2003). These and other contaminated surfaces and features act as pathogen reservoirs that increase cross-infection risk. Boyce et al. (1997) found that in the rooms of patients infected with methicillin-resistant *Staphylococcus aureus* (MRSA), 27 percent of all environmental surfaces sampled were contaminated with MRSA

Compared to single-bed rooms, multi-bed rooms are far more difficult to decontaminate thoroughly after a patient is discharged, and therefore worsen the problem of multiple surfaces acting as pathogen reservoirs. Because different staff members who enter a room can touch the same contaminated surfaces, the risk of a nurse unknowingly becoming contaminated should be greater in multioccupancy rooms. Circumstantial support for this point is provided by research on contamination of nurses in units having patients infected by MRSA. Boyce et al. (1997) found that 42 percent of nurses who had no direct contact with an MRSA patient but had touched contaminated surfaces contaminated their gloves with MRSA.

In a study of MRSA infections in NICUs, Jernigan et al. (1996) reported that risk was lowered by isolation in single-bed rooms; high risk was associated with spatial proximity to an infected patient and shared exposure to caregivers. Ben-Abraham et al. (2002) found that nosocomial infection frequency was much lower in a single-bed pediatric intensive care unit than a unit with multi-bed rooms. The investigators tentatively concluded that single-bed rooms helped to limit person-to-person spread of pathogens between pediatric patients. Having a roommate has been identified as a risk factor for nosocomial diarrhea and gastroenteritis (Chang, V. T. & Nelson, 2000; Pegues & Woernle, 1993).

To summarize briefly, there is a convincing pattern of evidence across many studies indicating that single-bed rooms lower nosocomial infection rates. Singles appear to limit person-to-person and person-surface-person spread of infection in part because they are far easier to decontaminate thoroughly than multibed rooms after patients are discharged. Also, single rooms with a conveniently located sink or alcohol-gel dispenser in each room may heighten hand washing compliance compared to multibed rooms with few sinks. Finally, single rooms are clearly superior to multi-bed rooms with respect to reducing airborne transmission of pathogens.

Reducing Medication Errors

The research team identified three rigorous studies that link environmental factors, such as lighting, distractions, and interruptions, with errors in prescribing or dispensing medications (Booker & Roseman, 1995; Buchanan, Barker, Gibson, Jiang, & Pearson, 1991; Flynn et al., 1999). Although there are relatively few studies in this area, the findings suggest a promising research direction that merits further exploration, considering the vital importance of preventing medical errors in hospitals. Results from a large-scale study of the effects of different illumination levels on pharmacists' prescription-dispensing error rates strongly suggested that such errors are reduced when work-surface light levels are relatively high (Buchanan et al., 1991). In this study, three different illumination levels were evaluated (450 lux, 1,100 lux, 1,500 lux). Medication-dispensing error rates were significantly lower (2.6 percent) at an illumination level of 1,500 lux (highest level), compared to an error rate of 3.8 percent at 450 lux. Two investigations of medication dispensing errors by hospital pharmacists found that error rates increased sharply for prescriptions when an interruption or distraction occurred, such as a telephone call (Flynn et al., 1999; Kistner, Keith, Sergeant, & Hokanson, 1994). Thus, lighting levels, frequent interruptions or distractions during work, and inadequate private space for performing work can be expected to worsen medication errors. The process of improving systems and processes to reduce medication errors in hospitals should include an assessment of the environment in which staff members perform their activities. Additional research is required to confirm the findings from studies as well as to identify ways to design better working environments that may reduce or prevent the likelihood of such errors occurring.

There is mounting evidence that the transfer of patients between rooms or different units is a source of medication errors (Cook, Render, & Woods, 2000). Reasons why errors plague room transfers include delays, communication discontinuities among staff, loss of information, and changes in computers or systems. The solution implied is to create an acuity-adaptable care process and patient rooms that substantially reduce transfers. When Methodist Hospital in Indianapolis, Indiana, changed from two-bed rooms in coronary intensive care to acuity-adaptable single-bed rooms, transfers declined 90 percent and medication errors were lowered by 67 percent (Hendrich, Fay, & Sorrells, 2002; 2004). Reducing transfers also saves much staff time, shortens patient stays, and reduces costs (IOM, 2004). Further studies and demonstration projects are needed to ascertain the safety advantages of acuity-adaptable rooms for other types of units and patient categories.

Reduce Patient Falls

There is a very large literature that looks at the causes and risk factors involved in patient falls in hospitals. This is an area of great importance because patients who fall incur physical injuries, psychological effects, and have greater lengths of stay in the hospital (Brandis, 1999). It is estimated that the total cost of fall injuries for older people was

around $20.2 billion per year in the United States in 1994, and is projected to reach $32.4 billion (in 1994 U.S. dollars) in 2020 (Chang, 2004). While the role of the environment in causing or preventing patient falls is widely accepted, there is not yet evidence conclusively tying environmental interventions with reduced falls. Available studies usually examine the location of fall incidents retrospectively or discuss environmental-modification programs such as improving lighting, securing carpeting, and so on. However, a meta-analysis and systematic review of randomized controlled trials of fall-prevention interventions found that there was no clear evidence for the independent effectiveness of environmental-modification programs (Chang, 2004).

Nonetheless, several studies have shown that most patient falls occur in the bedroom, followed by the bathroom, and that comprehensive fall-prevention programs can have an effect. Brandis (1999) reported transfers to and from bed as the cause of 42.2 percent of inpatient falls. Design faults identified in the bathroom and bedroom areas included slippery floors, inappropriate door openings, poor placement of rails and accessories, and incorrect toilet and furniture heights. After the fall-prevention program (which included identifying high-risk patients, management strategies, environmental and equipment modification, and standardization) was implemented, there was an overall decrease of 17.3 percent in falls. Thus, fall-prevention strategies that have included environmental modification have worked in the past. However, it is not clear how much of the effectiveness of such strategies can be attributed to environmental factors alone.

An innovative and promising environmental strategy for reducing falls has its origins in evidence suggesting that many falls occur when patients attempt to get out of bed unassisted or unobserved (Uden, 1985; Vassallo, Azeem, Pirwani, Sharma, & Allen, 2000). It should be mentioned that considerable evidence has shown that bedrails are ineffective for reducing the incidence of falls and may increase the severity of fall injuries from beds (Capezuti, Maislin, Strumpf, & Evans, 2002; Hanger, Ball, & Wood, 1999; van Leeuwen, Bennett, West, Wiles, & Grasso, 2001). To increase observation and improve assistance for patients and thereby reduce falls, Methodist Hospital in Indianapolis, Indiana, changed from a coronary critical care unit with centralized nurses stations and two-bed rooms to one having decentralized nurses stations and large single-bed rooms designed to support family presence (Hendrich, et al., 2002). Comparison of data from two years prior and three years after the new unit design showed that falls were cut by 2/3—from six-per-thousand patients to two-per-thousand. Given that falls are a critical safety problem, additional research is needed to understand the effectiveness of this approach for designing patient-care units.

Improve Patient Confidentiality and Privacy

Confidentiality has emerged as a priority issue in light of research showing that physicians and nurses very frequently breach patient confidentiality and privacy by talking in spaces where they are overhead by other patients or persons (Ubel, Zell, & Miller, 1995). The seriousness of the problem is underscored, for example, by a study of an emergency department at a university hospital that showed that 100 percent of physicians and other clinical personnel committed confidentiality and privacy breaches

(Mlinek & Pierce, 1997). HIPAA, the Health Insurance Portability and Accountability Act of 1998, has further elevated the importance of providing reasonable safeguards to protect the confidentiality of staff conversations with and about patients.

Although the importance of the built environment for patient confidentiality may seem self-evident, only a few studies have directly examined the role of unit design or architecture. A study by Barlas et al. (2001) compared auditory and visual privacy for emergency department patients assigned to either multibed spaces with curtain partitions or rooms with solid walls. Those with curtains reported having far less auditory and visual privacy than patients with walls. An important finding was that 5 percent of the patients in curtained spaces reported they withheld portions of their medical history and refused parts of their physical examination because of lack of privacy (Barlas et al., 2001). None of the patients in rooms with walls reported withholding information. The fact that some emergency department patients with curtains withheld information suggests that lack of privacy can reduce patient safety. Additional convincing evidence of the importance of the emergency department physical environment comes from a study that documented frequent breaches of auditory and visual privacy and confidentiality in areas with curtains compared to rooms with solid walls (Mlinek & Pierce, 1997). A recent questionnaire study of staff in four West Coast hospitals found that nurses overwhelmingly judged single rooms to be superior to double rooms for examining a patient (85 percent) and for collecting a patient's history (82 percent) (Chaudhury, Mahmood, & Valente, 2003).

There is a clear need for additional studies that examine privacy and confidentiality breaches associated with the physical environment in single versus double rooms, multibed spaces in ICUs and other types of units, and in spaces such as waiting rooms and nurses' stations. As well, priority should be accorded to generating more research that investigates how the quality of communication and information *from* patients *to* physicians and nurses is affected by the unit architecture.

Analysis of patient satisfaction data made available by Press Ganey (2003) for this report leaves no doubt that patients in single-bed rooms, compared to those with a roommate, are consistently much more satisfied with "concern for your privacy." The satisfaction data were obtained from 2,122,439 patients who received care during 2003 in 1,462 healthcare facilities (Press Ganey, 2003). Fifty-six percent of the patients were in single rooms; 44 percent had a roommate. Greater satisfaction with privacy in single rooms was evident across all major patient categories and types of unit and across different age and gender groups. Satisfaction with privacy was 4.5 percent higher on average nationally in single rooms than doubles—a substantial difference considering that it can be difficult for hospitals to increase satisfaction scores by even 1 percent to 2 percent.

III. Reduce Stress and Improve Outcomes

Reduce Noise

The research team identified more than 130 references focusing on noise in hospitals in the research literature. Studies tend to fall into three broad categories: those that measure noise levels in hospital spaces but do not assess outcomes, studies of the effectiveness of environmental and/or organizational interventions in reducing noise, and investigations of the effects of noise on outcomes.

World Health Organization guideline values for continuous background noise in hospital patient rooms are 35 dB, with nighttime peaks in wards not to exceed 40 dB (Berglund, Lindvall, & Schwela, 1999). These guidelines notwithstanding, many studies have shown that hospital background noise levels fall in far higher ranges. Background noise levels typically are 45 dB to 68 dB, with peaks frequently exceeding 85 dB to 90 dB (Aaron et al., 1996; Allaouchiche, Duflo, Debon, Bergeret, & Chassard, 2002; Blomkvist et al., in press, 2004; Falk & Woods, 1973; Hilton, 1985; McLaughlin, McLaughlin, Elliott, & Campalani, 1996; Robertson, Cooper-Peel, & Vos, 1998). In judging these noise levels, it is worth noting that the decibel scale is logarithmic; each 10 dB increase represents approximately a doubling in the perceived sound level. A 60 dB sound, accordingly, is perceived as roughly four times as loud as a 40 dB sound. Medical equipment and staff voices often produce 70 dB to 75 dB levels measured at the patient's head, which approach the noise level in a busy restaurant (Blomkvist et al., in press, 2004). Noises from alarms and certain equipment exceed 90 dB (for example, portable X-ray machine), which is comparable to walking next to a busy highway when a motorcycle or large truck passes. A study in a NICU measured peak levels once per minute and found that 31 percent of peaks exceed 90 dB (Robertson et al., 1998). Noise peaks in hospitals can be extraordinarily loud. A recent study recorded 113 dB during shift changes at a large hospital (Cmiel, Karr, Gasser, Oliphant, & Neveau, 2004). Operating room noises from drills, saws, and other equipment are in the range of 100 dB to 110 dB, presenting a significant risk for noise-induced hearing loss (Hodge & Thompson, 1990; Love, 2003; Nott & West, 2003).

The research reviewed suggests that hospitals are excessively noisy for two general reasons (Ulrich, Lawson, & Martinez, 2003). First, noise sources are numerous, often unnecessarily so, and many are loud. Well-documented examples include paging systems, alarms, bedrails moved up/down, telephones, staff voices, ice machines, pneumatic tubes, trolleys, and noises generated by roommates. Second, environmental surfaces—floors, walls, ceilings—usually are hard and sound-reflecting, not sound-absorbing, creating poor acoustic conditions. Sound-reflecting surfaces cause noise to propagate considerable distances, traveling down corridors and into patient rooms, and adversely affecting patients and staff over larger areas. Sound-reflecting surfaces typical of hospitals cause sounds to echo, overlap, and linger or have long reverberation times (Blomkvist et al., in press, 2004; Ulrich et al., 2003).

Environmental interventions that have proven especially effective for reducing noise and improving acoustics in hospital settings include: installing high-performance sound-absorbing ceiling tiles, eliminating or reducing noise sources (for example, adopting a noiseless paging system), and providing single-bed rather than multibed rooms. In general, studies of the effectiveness of noise-reduction measures suggest that environmental or design interventions are more successful than organizational interventions such as staff education or establishing quiet hours (Gast & Baker, 1989; Moore, 1998; Walder, Francioli, Meyer, Lancon, & Romand, 2000).

A clear-cut finding in the literature is that noise levels are much lower in single-bed than multi-bed rooms. Studies of multi-bed rooms in acute care and intensive care units have shown that most noises stem from the presence of another patient (staff talking, staff caring for other patients, equipment, visitors, patient sounds such as coughing, crying out, rattling bed rails) (Baker, 1984; Southwell & Wistow, 1995; Yinnon, Ilan, Tadmor, Altarescu, & Hershko, 1992). A study of multi-bed bays in a children's hospital concluded that noise levels were so high that consideration should be given to abolishing open bay rooms (Couper et al., 1994). Further, patient satisfaction data provided for this report by Press Ganey (2003) unequivocally show that patients in single-bed rooms, compared to those with a roommate, are vastly more satisfied with the "noise levels in and around your room." The satisfaction data, as noted in an earlier section, were obtained from 2,122,439 patients who received care during 2003 in 1,462 healthcare facilities (Press Ganey, 2003). Far higher satisfaction with noise levels in single rooms was evident across all major patient categories and types of unit and across different age and gender groups. Satisfaction with noise level was 11.2 percent higher on average nationally in single rooms than doubles—a huge difference. As was noted above, it can be difficult for hospitals to achieve even 1 percent to 2 percent increases in patient satisfaction scores. The combination of findings from noise-level measurement studies and patient-satisfaction surveys highlight the great advantage of providing single rooms, compared to two-bed rooms, with respect to reducing noise.

A considerable body of research has documented negative effects of noise on patient outcomes. Several studies have focused on infants in NICUs, finding that higher noise levels, for example, decrease oxygen saturation (increasing need for oxygen support therapy), elevate blood pressure, increase heart and respiration rate, and worsen sleep (Johnson, 2001; Slevin, Farrington, Duffy, Daly, & Murphy, 2000; Zahr & de Traversay, 1995). Much research on adults and children has unequivocally shown, as might be expected, that noise is a major cause of awakenings and sleep loss (Blomkvist et al., in press, 2004; Gabor et al., 2003; Meyer et al., 1994; Parthasarathy & Tobin, 2004; Schnelle, Ouslander, Simmons, Alessi, & Gravel, 1993; Topf, 1985; Topf & Davis, 1993; Topf & Thompson, 2001; Yinnon et al., 1992). In multi-bed rooms, noises stemming from the presence of other patients often are the major cause of sleep loss. Berg (2001) found, by monitoring brain activity, that even relatively low decibel levels—38 dB to 40 dB—when coupled with longer reverberation times (sound-reflecting ceiling) significantly fragmented and worsened sleep of volunteers in patient rooms. Berg's (2001) findings have disturbing implications because most hospitals have nighttime sound peaks exceeding those of the patient rooms in his study.

Apart from worsening sleep, there is strong evidence that noise increases stress in adult patients, for example, heightening blood pressure and heart rate (Baker, 1992; Morrison, Haas, Shaffner, Garrett, & Fackler, 2003; Novaes, Aronovich, Ferraz, & Knobel, 1997; Topf & Thompson, 2001). A recent study by Blomkvist et al. (in press, 2004) examined the effects of poor versus good sound levels and acoustics on coronary intensive-care patients by periodically changing the ceiling tiles from sound-reflecting to sound-absorbing tiles. When the sound-absorbing ceiling tiles were in place, patients slept better, were less stressed (lower sympathetic arousal), and reported that nurses gave them better care. There were also indications in this study that the incidence of re-hospitalization was lower if patients had experienced the sound-absorbing rather than sound-reflecting ceiling during their hospital stay (Hagerman et al., in press, 2004). More studies are needed such as that by Blomkvist et al. (in press, 2004), which use experimental research designs and systematically vary noise conditions. Future research should also investigate the effects of noise on re-hospitalization rates and other outcomes. In sum, the main message from the research review is clear: new hospitals should be much quieter, and effective design strategies for quieting hospitals are available.

Improve Sleep

The above section reviewed many studies showing that noise levels are high in hospitals and that noise is a major cause of poorer sleep in patients. Interventions that reduce hospital noise have been found to improve sleep and reduce patient stress. As noted earlier, environmental interventions found to be most effective for reducing noise in hospital settings include: providing single-bed rather than multi-bed rooms, installing high-performance, sound-absorbing ceiling tiles, using sound-absorbing flooring where possible, and eliminating or reducing noise sources (for example, use noiseless paging, locate alarms outside patient rooms).

Reduce Spatial Disorientation

Wayfinding problems in hospitals are costly and stressful and have particular impacts on outpatients and visitors, who are often unfamiliar with the hospital and are otherwise stressed and disoriented. In a study conducted at a major regional 604-bed tertiary-care hospital, the annual cost of the wayfinding system was calculated to be more than $220,000 per year in the main hospital or $448 per bed per year in 1990. Much of this cost was the hidden costs of direction giving by people other than information staff, which occupied more than 4,500 staff hours, the equivalent of more than two full-time positions (Zimring, 1990). While almost all hospitals strongly feel the problems associated with a complicated building and poor wayfinding system, it is usually difficult to tackle this problem with a piecemeal approach. A wayfinding system, as the name implies, is not just about better signage or colored lines on floors. Rather, hospitals are seeking to provide integrated systems that include coordinated elements such as visible and easy-to-understand signs and numbers, clear and consistent verbal directions, consistent and clear paper, mail-out and electronic information and a legible physical

setting (Carpman, 1993). A wayfinding system includes four main components that work at different levels: administrative and procedural levels, external building cues, local information and global structure

Administrative and procedural information: Mail-out maps, electronic information available on the Web and at kiosks and verbal directions are organizational strategies aimed at providing key information to patients to prepare them for their hospital visit. This is not dealt with in this review.

***External building cues*:** Signs and cues that lead to the hospital, especially the parking lot, need to be considered carefully, as they are the first point of contact of the patient with the hospital (Carpman, Grant, & Simmons, 1985). For example, Carpman, Grant and Simmons conducted a video simulation study to assess the relative role of signs and seeing a destination. The hospital wanted to direct most traffic to a parking structure rather than a drop-off lane. When the researchers showed prospective visitors a simulated video showing a design alternative that allow arriving drivers to see the main pavilion with the drop-off lane, 37 percent of the respondents said that they would turn into the drop circle when they could see the entry to the garage, ignoring the signs. As a consequence, the hospital chose to redesign the entry.

***Local information*:** Once patients find their way to the building from the parking lot, they are faced with the prospect of identifying the destination. Informational handouts, information desks, you-are here maps, directories, and signage along the way are critical wayfinding aids (Carpman, Grant, & Simmons, 1983-84; Levine, Marchon, & Hanley, 1984; Nelson-Shulman, 1983-84; Wright, Hull, & Lickorish, 1993). In an experimental study, researchers found that patients who had the benefit of an information system (welcome sign, hospital information booklet, patient letter, orientation aids) upon reaching the admitting area were more self-reliant and made fewer demands on staff. In contrast, uninformed patients rated the hospital less favorably and were found to have elevated heart rates (Nelson-Shulman, 1983-84).

Information provided in you-are-here maps can be useful. However, you-are-here maps should be oriented so that the top signifies the direction of movement for ease of use. When the maps were aligned in directions other than the forward position, people not only took much longer to find their destination, but were significantly less accurate (Levine et al., 1984). Another study found that people who used signs found their destination faster than those who only used maps (Butler, Acquino, Hissong, & Scott, 1993). However, people who were given a combination of handheld maps and wall signs reached their destination more often than those who just used wall signs (Wright et al., 1993).

It is critical to design signage systems with logical room numbering and comprehensible nomenclature for departments (Carpman & Grant, 1993; Carpman, Grant, & Simmons, 1984). For example, inpatients, outpatients, and visitors to a hospital preferred simple terms such as *walkway* or *general hospital* over more complex or less-familiar terms such as *overhead link, medical pavilion* or *health-sciences complex*.

Contrary to the belief that fewer signs in hospital hallways means less clutter and hence less confusion, an experimental study in a hospital found that patients who had access to more number of signs along the way to the destination were faster, less hesitant, asked for directions a fewer number of times, and reported lower levels of stress (Carpman et al., 1984). Based on this study, the authors suggest that directional signs should be placed at or before every major intersection, at major destinations, and where a single environmental cue or a series of such cues (e.g. change in flooring material) convey the message that the individual is moving from one area into another. If there are no key decision points along a route, signs should be placed approximately every 150 feet to 250 feet.

***Global structure*:** In addition to local properties of the spaces that people move through, there are specific characteristics of the overall structure of the system of rooms and corridors that impact the paths people take (Haq & Zimring, 2003; Peponis, Zimring, & Choi, 1990). People tend to move toward spaces and through corridors that are more accessible from a greater number of spaces. Based on observations of search patterns of study participants in a hospital and use of objective measures that quantify spatial characteristics, researchers found that participants tended to move along more "integrated" routes—routes that are, on average, more accessible because they are fewer turns from all other routes in the hospital. This research suggests that it may be important to identify such integrated routes in the plan while placing important facilities and key points such as the entrance (Peponis et al., 1990).

The research supports the value of a systems approach to wayfinding. Wayfinding continues to be a pervasive problem in hospitals because it is not sufficient to consider one or two components separately. Well-designed signs are likely to be quite ineffective in a building that is highly complicated and does not provide simple cues that enable natural movement. While there are more than 17 studies that look at wayfinding in hospitals and other buildings (Brown, Wright, & Brown, 1997; Carpman & Grant, 1993; Carpman et al., 1983-84, 1984; Carpman et al., 1985; Christensen, 1979; Grover, 1971; Haq & Zimring, 2003; Levine et al., 1984; Moeser, 1988; Nelson-Shulman, 1983-84; Ortega-Andeane & Urbina-Soria, 1988; Passini, Rainville, Marchand, & Joanette, 1995; Peponis et al., 1990; Schneider, L. F. & Taylor, 1999; Weisman, 1981; Wright et al., 1993; Zimring & Templer, 1983-84), it is quite difficult to isolate single influences of design on wayfinding performance or of wayfinding on outpatient or visitor stress. The problem is exacerbated by the fact that most hospitals have existing complex buildings upon which they try to superimpose a signage system to make things work. This strategy is ineffective in most cases.

There are some very good studies that deal with designing better signage, optimal spacing and location of signage, types of information that are most effective in way finding, and so on. Similarly, other studies at the global scale have looked at the properties of the building layout that facilitate or impede movement. It is essential that these different pieces of information come together while designing new hospitals where there is opportunity to develop an effective wayfinding system at multiple levels. Additional

studies are needed to ascertain the magnitude of stress that wayfinding problems have on outpatients and family.

Reduce Depression

Several studies strongly support that bright light—both natural and artificial—can improve health outcomes such as depression, agitation, sleep, circadian rest-activity rhythms, as well as length of stay in demented patients and persons with seasonal affective disorders (SAD). At least eleven strong studies suggest that bright light is effective in reducing depression among patients with bipolar disorder or SAD. Further, seven studies show that exposure to morning light is more effective than exposure to evening light in reducing depression (Beauchemin & Hays, 1996; Benedetti, F., Colombo, C., Barbini, B., Campori, E., & Smeraldi, E., 2001; Lewy et al., 1998; Lovell, Ancoli-Israel, & Gevirtz, 1995; Terman, Terman, Lo, & Cooper, 2001; Van Someren, Kessler, Mirmiran, & Swaab, 1997; Wallace-Guy et al., 2002). An experimental study that compared the effect of morning and evening light on patients with winter depression found that morning light was *twice* as effective as evening light in treating SAD (Lewy et al., 1998). Exposure to bright morning light has been shown to reduce agitation among elderly patients with dementia. When elderly patients with dementia were exposed to 2,500 lux for two hours in the morning for two ten-day periods, their agitation reduced. Patients were significantly more agitated on non-treatment days (Lovell et al., 1995).

There is also strong evidence that exposure to bright light improves sleep and circadian rhythms. When the daytime environmental illumination level was increased in different living spaces of a dementia unit, it was found that, during increased illumination periods, the stability of the rest-activity rhythm increased in patients with intact vision, but not in visually impaired patients (Van Someren et al., 1997).

It has also been shown that patients in brightly lit rooms have a shorter length of stay compared to patients in dull rooms. Beauchemin and Hays (1996) found that patients hospitalized for severe depression reduced their stays by an average of 3.67 days if assigned to a sunny rather than a dull room overlooking spaces in shadow.

A recent randomized prospective study assessed whether the amount of sunlight in a hospital room modifies a patient's psychosocial health, quantity of analgesic medication used, and pain medication cost (Walch et al., 2004, in press). Patients undergoing elective cervical and lumbar spinal surgeries were admitted to the bright or the dim side of the inpatient surgical ward postoperatively. The outcomes measured included the standard morphine equivalent of all opioid medication used postoperatively by patients and their subsequent pharmacy cost. This strong study found that patients exposed to an increased intensity of sunlight experienced less perceived stress, less pain, took 22 percent less analgesic medication per hour and had 20 percent less pain medication costs.

Using light as an intervention to reduce depression in clinically depressed as well as non-depressed patients is a relatively inexpensive intervention that has been shown to yield consistently positive results. While many studies deal with the effects of artificial light,

natural daylight in patient rooms has also been found effective in reducing depression, reducing length of stay, and reducing intake of pain medication. Thus, an important consideration while designing hospital layouts may be to optimize exposure to morning light in patient rooms by using an east-facing orientation. This research further implies the possibility that depression might be worsened by architectural designs that block or sharply reduce natural daylight in patient rooms. A hypothetical example would be a hospital having patient-room windows looking out into a roofed atrium with few skylights and little natural daylight. In this example, deprivation of natural daylight could be extreme if patient windows were tinted to prevent users of the atrium from looking into patient rooms and violating privacy.

Provide Nature and Positive Distraction

Positive distractions refer to a small set of environmental features or conditions that have been found by research to effectively reduce stress. Distractions can include certain types of music, companion animals such as dogs or cats, laughter or comedy, certain art, and especially nature (Ulrich, 1991). The focus here is on the last, nature. (There is an additional large research literature on music, but this is not covered in this review.)

As background relevant to assessing the credibility of nature findings in healthcare environments, it should be mentioned that many studies of populations other than hospital patients have produced strong evidence that even fairly brief encounters with real or simulated nature settings can elicit significant recovery from stress within three minutes to five minutes at most (Parsons & Hartig, 2000; Ulrich, 1999). Investigators have consistently reported that stress-reducing or restorative benefits of simply viewing nature are manifested as a constellation of positive emotional and physiological changes. Stressful or negative emotions such as fear or anger diminish while levels of pleasant feelings increase. Laboratory and clinical studies have shown that viewing nature produces stress recovery quickly evident in physiological changes, for instance, in blood pressure and heart activity (Ulrich, 1991). By comparison, considerable research has demonstrated that looking at built scenes lacking nature (rooms, buildings, parking lots) is significantly less effective in fostering restoration and may worsen stress.

Questionnaire studies have found that bedridden patients assign especially high preference to having a hospital window view of nature (Verderber, 1986). Mounting research is providing convincing evidence that visual exposure to nature improves outcomes such as stress and pain. For example, a study in a Swedish hospital found that heart-surgery patients in ICUs who were assigned a picture with a landscape scene with trees and water reported less anxiety/stress and needed fewer strong doses of pain drugs than a control group assigned no pictures (Ulrich, 1991). Another group of patients assigned an abstract picture, however, had worsened outcomes compared to the control group. Ulrich (1984) found that patients recovering from abdominal surgery recovered faster, had better emotional well-being, and required fewer strong pain medications if they had bedside windows with a nature view (looking out onto trees) than if their windows looked out onto a brick wall.

Recently, strong studies using experimental designs have produced additional convincing evidence that viewing nature reduces patient pain as well as stress. These investigations also support the interpretation that nature serves as a positive distraction (Ulrich, 1991) that reduces stress and diverts patients from focusing on their pain or distress. A randomized prospective investigation found that adult patients undergoing a painful bronchosopy procedure reported less pain if they were assigned to look at a ceiling-mounted nature scene rather than a control condition consisting of a blank ceiling (Diette, Lechtzin, Haponik, Devrotes, & Rubin, 2003). Another controlled experiment that used volunteers in a hospital assessed the effect on pain of viewing a soundless nature videotape in contrast to a static blank screen (Tse, Ng, Chung, & Wong, 2002). Subjects who watched the nature scenes evidenced a higher threshold for detecting pain and had substantially greater pain tolerance. Two studies of female cancer patients have shown that taking a virtual reality nature walk while in bed or a hospital room (through a forest with bird sounds) reduced anxiety and symptomatic distress (Schneider, S. M., Prince-Paul, Allen, Silverman, & Talaba, 2004). Research on patients suffering intense pain because of severe burns found that exposing patients to a videotape of scenic nature (forest, flowers, ocean, waterfalls) during burn dressing changes significantly reduced both anxiety and pain intensity (Miller, Hickman, & Lemasters, 1992).

The possibility that nature can improve outcomes even in patients with late-stage dementia, including Alzheimer's disease, has received some support from a quasi-experimental study that found reduced levels of agitated aggressive behavior associated with a shower bath when recorded nature sounds (birds, babbling brook) and color pictures were present (Whall et al., 1997). A well-controlled study of blood donors in a waiting room found that blood pressure and pulse were lower on days when a wall-mounted television displayed a nature videotape, compared to days with continuous daytime television programs (Ulrich, Simons, & Miles, 2003). More research is needed to identify conditions under which television can either be a stress-reducing positive distraction or a stressor in hospitals.

Gardens in healthcare environments*:* Hospital gardens not only provide restorative or calming nature views, but can also reduce stress and improve outcomes through other mechanisms, for instance, fostering access to social support and providing opportunities for positive escape and sense of control with respect to stressful clinical settings (Cooper Marcus & Barnes, 1995; Ulrich, 1999). Based on postoccupancy evaluations of four hospital gardens in California, Cooper-Marcus and Barnes (1995) concluded that many nurses and other healthcare workers used the gardens for achieving pleasant escape and recuperation from stress. Other postoccupancy studies indicate that patients and family who use hospital gardens report positive mood change and reduced stress (Whitehouse et al., 2001). These reports also suggest that gardens and nature in hospitals can heighten patient and family satisfaction with overall quality of care.

Art in healthcare environments: A small number of studies on art in hospitals has yielded findings parallel to those from nature research. Results suggest a consistent pattern wherein the great majority of patients respond positively to representational

nature art, but many react negatively to chaotic abstract art (Ulrich & Gilpin, 2003). For example, Carpman & Grant (1993) studied the preferences of 300 randomly selected inpatients and concluded that the patients consistently preferred nature images but disliked abstract art. Although nature pictures and other emotionally appropriate art elicit positive reactions, there is also evidence that inappropriate art styles or image subject matter can increase stress and worsen other outcomes (Ulrich, 1991). It should not be expected that all art is suitable for high-stress healthcare spaces, as art varies enormously in subject matter and style, and much art is emotionally challenging or provocative.

The pitfalls of displaying emotionally challenging art in healthcare environments are revealed by a study of psychiatric patients (Ulrich, 1991). The unit was extensively furnished with a diverse collection of wall-mounted paintings and prints. Interviews with patients indicated strongly negative reactions to artworks that were ambiguous, surreal, or could be interpreted in multiple ways. The same patients, however, reported having positive feelings and associations with respect to nature paintings and prints.

Provide Social Support

Many studies of several different categories of patients have indicated that social support reduces stress and improves, for example, recovery outcomes in myocardial infarction patients. Considering the well-established importance of social support, it is unfortunate that there is only a moderate amount of research concerning how hospital design can facilitate or hinder access to social support. Most studies have focused on psychiatric units and nursing homes. There is strong evidence that levels of social interaction can be increased—and presumably beneficial social support as well—by providing lounges, day rooms, and waiting rooms with comfortable movable furniture arranged in small flexible groupings. A few well-designed studies in psychiatric wards and nursing homes have found that appropriate arrangement of movable seating in dining areas enhances social interaction and also improves eating behaviors, such as increasing the amount of food consumed by geriatric patients (Melin & Gotestam, 1981; Peterson, Knapp, Rosen, & al., 1977). Much research on day rooms and waiting areas has shown that the widespread practice of arranging seating side-by-side along room walls inhibits social interaction (Holahan, 1972; Sommer & Ross, 1958). A novel study by Harris (2000) found that family and friends stayed substantially longer during visits to rehabilitation patients when patient rooms were carpeted rather than covered with vinyl flooring.

Much evidence indicates that single rooms are markedly better than multi-bed rooms for supporting or accommodating the presence of family and friends. Some research suggests that open-plan multibed rooms deter family presence and accordingly reduce social support (Sallstrom, Sandman, & Norberg, 1987). Multibed rooms greatly reduce privacy for patient-family interactions compared to single rooms and are much more likely to have restricted visiting hours. A clear advantage of single rooms in fostering social support stems from the fact they provide more space and furniture than double rooms to accommodate family presence (Chaudhury et al., 2003). A survey of staff in four hospitals that each had a mix of single and double rooms found that nurses gave high

ratings to single rooms for accommodating family members but accorded double rooms low scores (Chaudhury et al., 2003). Further, patient-satisfaction data obtained from 2,122,439 patients who received care during 2003 provide overwhelming evidence that patients in single-bed rooms, compared to those with a roommate, are much more satisfied with "accommodations and comfort for family and visitors" (Press Ganey, 2003).

Do patients sharing the same room provide each other with stress-reducing social support? While some patients find roommates provide comforting social support, findings from several studies indicate that the presence of a roommate usually is a source of stress rather than social support. In most cases, roommates are linked to stressors, for example, loss of privacy or having a roommate who is unfriendly, has too many visitors, or is seriously ill (Van der Ploeg, 1988; Volicer, Isenberg, & Burns, 1977). An earlier section emphasized that noise is a much greater problem in double rooms than singles, and that noises stemming from the presence of other patients are a major cause of sleep loss.

Improve Communication to Patients

Good staff communication helps reduce patient and family anxiety, promotes better care at home after discharge, and in other ways can improve outcomes. Good communication also tends to be the single most important factor affecting overall satisfaction with care across different patient categories (Press Ganey, 2003). Data obtained from 2,122,439 patients nationally in 2003 show that patients consistently report significantly higher satisfaction with communication from nurses and physicians when they are in single rooms compared to when they have one or more roommates (Press Ganey, 2003). To explain this clear and important advantage of single rooms, Kaldenburg (1999) has proposed that staff in multibed rooms are reluctant to discuss patient issues or give information within hearing of a roommate, out of respect for privacy. Growing concern for patient confidentiality and HIPAA are certain to increase the already major advantages of single rooms with respect to communication.

IV. Improve Overall Healthcare Quality

Provide Single-Bed Patient Rooms

Based on an extremely large and varied body of research reviewed in earlier sections, there can be no question that single-bed rooms have several major advantages over double rooms and open bays. To summarize briefly, these advantages include: lower nosocomial infection rates, fewer patient transfers and associated medical errors, far less noise, much better patient privacy and confidentiality, better communication from staff to patients and from patients to staff, superior accommodation of family and consistently higher satisfaction with overall quality of care.

Reduce Length of Stay

Climate and sunlight influences length of hospital stay as well as sleep-wake patterns among hospitalized patients (Beauchemin & Hays, 1996; Benedetti, Francesco, Colombo, Cristina, Barbini, Barbara, Campori, Euridice, & Smeraldi, Enrico, 2001; Federman, Drebing, Boisvert, Penk, 2000; Hebert, Dumont, & Paquet, 1998; Kecskes et al., 2003; Kinnunen, Saynajakangs, Tuuponen, & Keistinen, 2002). One research group studied the impact of the amount of natural light on the length of hospitalization of patients with unipolar and bipolar disorder. The researchers found that bipolar patients randomly assigned to the brighter, eastern rooms (exposed to direct sunlight in the morning) had a mean 3.67-day shorter hospital stay than patients in west-facing rooms (Benedetti, Francesco et al., 2001). Patients recovering from abdominal surgery had shorter stays if they had a bedside window view of nature rather than if their windows looked out onto a brick wall (Ulrich, 1984).

The large research literature on infection reviewed in an earlier section indicated that the design of the physical environment strongly impacts hospital-acquired infection rates by affecting both airborne and contact transmission routes. Evidence-based design measures, by reducing nosocomial infection rates, play a key role in shortening hospital stays.

Increase Patient Satisfaction with Quality of Care

There is strong evidence that design changes that make the environment more comfortable, aesthetically pleasing, and informative relieve stress among patients and increases satisfaction with the quality of care provided. Renovating a traditional waiting area in a neurology clinic by making small changes to the general layout, color scheme, furniture, floor covering, curtains, and providing informational material and information displays resulted in more positive environmental appraisals, improved mood, altered physiological state, and greater reported satisfaction among waiting patients (Leather, Beale, Santos, Watts, & Lee, 2003).

Patients in well-decorated and well-appointed hotel-like rooms rated their attending physicians, housekeeping, and food-service staff, the food, and the hospital better than patients in standard rooms (typical hospital beds, inexpensive family sitting chairs, and no artwork) in the same hospital. Also, they had stronger intentions to use the hospital again and would recommend the hospital to others (Swan, Richardson, & Hutton, 2003). In another study, it was found that environmental satisfaction was a significant predictor of overall satisfaction, ranking only below perceived quality of nursing and clinical care (Harris, P. B., McBride, Ross, & Curtis, 2002). Several post-occupancy evaluation studies have examined patient and staff satisfaction with the different elements of the healthcare environment such as gardens, individual wards, and patient rooms (Brown, Wright, & Brown, 1997; Heath & Gifford, 2001; Shepley, 1995, 2002; Shepley & Davies, 2003; Shepley & Wilson, 1999; Whitehouse et al., 2001). These studies yield rich context-specific data that describe which aspects of the environment were effective. Some studies show quite clearly that tacit, as well implicit, staff and organizational practices and policies influence how an environment actually functions and is perceived

by patients and staff members. The qualitative and quantitative data provided by such studies are very important in understanding the nature of the problem (e.g. why are the gardens not being used as intended?) as well in developing solutions to tackle the problem. Future research that looks at satisfaction among hospital patients should consider using these multi-method post-occupancy evaluations that use different methods to obtain objective and subjective evaluations of use and satisfaction.

CONCLUSIONS

The research team found more than 600 rigorous studies linking a range of aspects of the built environment of hospitals to staff stress and effectiveness, patient safety, patient and family stress and healing, and improved overall healthcare quality and cost. This deep and wide base of evidence suggests that, parallel to evidence-based medicine, we can move to evidence-based design (EBD). EBD refers to a process for creating healthcare buildings, informed by the best available evidence, with the goal of improving outcomes and of continuing to monitor the success of designs for subsequent decision-making. While it is difficult to conduct rigorous research on the impacts of the healthcare environment—hospitals are complex systems where it is difficult to isolate the impact of single factors and the building industry conducts little impact-based research—The Center for Health Design and other groups have made considerable progress in developing a knowledge base of evidence.

EBD is not about hospitals that are simply nicer or fancier than traditional hospitals. Rather, the focus of evidence-based design is to create hospitals that actually help patients recover and be safer, and help staff do their jobs better. EBD is a process for creating health care buildings informed by the best available evidence concerning how the physical environment can interfere with or support activities by patients, families, and staff, and how the setting provides experiences that provide a caring, effective, safe, patient-centered environment. Many of the improvements suggested by EBD are only slightly more expensive than traditional solutions, if they are more expensive at all.

The large research literature surveyed in this report point to several actions we can take immediately:

- Provide single-bed rooms in almost all situations. Adaptable-acuity single-bed rooms should be widely adopted. Single rooms have been shown to lower hospital-induced nosocomial infections, reduce room transfers and associated medical errors, greatly lessen noise, improve patient confidentiality and privacy, facilitate social support by families, improve staff communication to patients, and increase patients' overall satisfaction with health care.
- New hospitals should be much quieter to reduce stress and improve sleep and other outcomes. Noise levels will be substantially lowered by the following combination of environmental interventions: providing single-bed rooms, installing high-performance sound-absorbing ceilings, and eliminating noise sources (for example, using noiseless paging).

- Provide patients stress reducing views of nature and other positive distractions.
- Develop wayfinding systems that allow users, and particularly outpatients and visitors, to find their way efficiently and with little stress.
- Improve ventilation through the use of improved filters, attention to appropriate pressurization, and special vigilance during construction.
- Improve lighting, especially access to natural lighting and full-spectrum lighting.
- Design ward layouts and nurses stations to reduce staff walking and fatigue, increase patient care time, and support staff activities such as medication supply, communication, charting, and respite from stress.

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APPENDIX: Bibliography

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Improve Patient Safety

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Reduce Stress and Improve Outcomes

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Improve Overall Health-Care Quality

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