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10 Questions

Ten questions concerning the aerosolization and transmission of *Legionella* in the built environment

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ABSTRACT

Legionella is a genus of pathogenic Gram-negative bacteria responsible for a serious disease known as legionellosis, which is transmitted via inhalation of this pathogen in aerosol form. There are two forms of legionellosis: Legionnaires' disease, which causes pneumonia-like symptoms, and Pontiac fever, which causes influenza-like symptoms. *Legionella* can be aerosolized from various water sources in the built environment including showers, faucets, hot tubs/swimming pools, cooling towers, and fountains. Incidence of the disease is higher in the summertime, possibly because of increased use of cooling towers for air conditioning systems and differences in water chemistry when outdoor temperatures are higher. Although there have been decades of research related to *Legionella* transmission, many knowledge gaps remain. While conventional wisdom suggests that showering is an important source of exposure in buildings, existing measurements do not provide strong support for this idea. There has been limited research on the potential for *Legionella* transmission through heating, ventilation, and air conditioning (HVAC) systems. Epidemiological data suggest a large proportion of legionellosis cases go unreported, as most people who are infected do not seek medical attention. Additionally, controlled laboratory studies examining water-to-air transfer and source tracking are still needed. Herein, we discuss ten questions that spotlight current knowledge about *Legionella* transmission in the built environment, engineering controls that might prevent future disease outbreaks, and future research that is needed to advance understanding of transmission and control of legionellosis.

1. Introduction

Legionella is a pathogenic Gram-negative bacterium and the causative agent of a disease known as legionellosis [1–4]. Legionnaires' disease and the less severe form, Pontiac fever, are the two most frequent presentations of legionellosis. The common clinical symptoms of legionellosis include high fever, cough, chills, difficulty breathing, neurological problems, muscle weakness, diarrhea, chest pain, headache, nausea, and vomiting [5]. Case-fatality rates of legionellosis, primarily Legionnaires' disease, fall in the range of ~10–50% depending on the specific outbreak [6]. Information regarding Pontiac fever is limited since many people who contract it do not seek medical attention, possibly due to the similarity in symptoms between this condition and other mild upper respiratory tract infections [7].

Legionella is a unique pathogen due to its water-to-air transmission route. Typically, the bacterium resides and grows in water systems (including as a biofilm on pipes), but it must be aerosolized and inhaled or aspirated to cause disease. Recently, partly motivated by increased incidence, many questions have arisen regarding *Legionella* transmission in the built environment and interventions that may be able to reduce the number of legionellosis cases in the future. We present ten questions and answers about *Legionella*, legionellosis etiology, and engineering controls with the potential to thwart disease transmission. Additionally, we discuss some of the major knowledge gaps that merit further research.

Q1) What is legionellosis, and how is it transmitted?

Legionellosis is an infection caused by gram-negative bacteria of the *Legionella* genus, named after an outbreak occurring at an American Legion convention in Philadelphia in 1976 [3]. Twenty-four of 58 [8] known *Legionella* species have been implicated in human disease. These highly diverse [9] and pleomorphic [10]

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bacteria can be found in a variety of environments and are naturally occurring in freshwater [9] and soil [11]. As their life cycle typically involves endoparasitization and replication within host eukaryotes such as amoebae [12], *Legionella* possess mechanisms to infect human cells, notably macrophages [8].

Legionellosis is a relatively common water-based disease, responsible for more drinking-water-related outbreaks in the United States than all other sources combined [13], although under-reporting, particularly outside of outbreaks, is presumed to be common [14]. Estimates of legionellosis incidence in the United States range from 8,000 [15] to 50,000 cases per year [16], although reported case rates vary greatly by region [17]. The vast majority of cases are caused by one strain of the species *L. pneumophila*, serogroup 1 [6]. Strains responsible for outbreaks appear to be even more specific, with 85% being linked to a subset of serogroup 1 *L. pneumophila*, those belonging to the monoclonal antibody group 2 [18]. The physiological and ecological reasons for the increased virulence of these strains are complex, although specific virulence-related proteins have been identified, such as the O-antigen for serogroup 1[19] and the *mip* gene in *L. pneumophila* [20]. Despite the attention generated by clusters of legionellosis, outbreaks are responsible for a small portion of total cases, approximately 4% in the United States [21]; thus, sporadic cases are much more common. Incidence worldwide is presumably vastly under-reported [22] due to a combination of factors, including heavy reliance on a serogroup 1 *L. pneumophila*-specific urine antigen test for medical diagnosis [23]. Incidence has been rising consistently since the discovery of the disease [24], with a nearly 3.5-fold increase between 2000 and 2011 in the United States [23], leading to legionellosis being considered an increasingly important disease from a public health standpoint.

Legionnaires' disease is an atypical pneumonia with a 2–14 day incubation period [17] during which *Legionella* infect lung tissue, primarily alveolar macrophages [8]. Between 2009 and 2013, a mortality rate of 9% was reported in the United States, although this rate can be highly variable [23]. Conversely, Pontiac fever presents as a febrile, self-limiting disease with a 24–48 h incubation period [17]. Representing 0.5% of total legionellosis cases in the United States [21], Pontiac fever is less commonly associated with reported outbreaks than is Legionnaires' disease. Because its symptoms are similar to those of influenza infections and due to poor consensus on a clinical definition for the disease [7], Pontiac fever is rarely reported and poorly understood [25], although evidence suggests it to be relatively common [7]. At least some cases may be caused by an allergic reaction to a toxin produced by *Legionella* rather than infection [26], but data supporting this notion are limited. Extrapulmonary forms of legionellosis occur, such as endocarditis [27], osteomyelitis [28], and skin infections [29], although these are typically seen in patients who are immunocompromised, a major risk factor for the disease [23]. While more common species and strains of *Legionella* are capable of causing these atypical forms of legionellosis [30], less pathogenic strains are often implicated [31,32] due to lowered immune response often seen in patients with these infections. Old age [23], smoking [33], diabetes [34], and COPD [23] are also among the most common comorbidities positively associated with legionellosis. Despite these risk factors, relatively healthy individuals are also commonly infected [35], making the term “opportunistic pathogen” somewhat of a misnomer for *Legionella*.

As humans are an incidental host for *Legionella*, legionellosis is not typically considered transmissible from person-to-person [17]; however, a single presumptive case has shown evidence of lateral transmission [36]. With an ideal growth range between 28 and 40 °C [37], heated water systems are thought to serve as the primary source for *Legionella* occurrence and transmission, although a wide variety of sources have been linked to legionellosis [38]. Many engineered water systems tend to have physical conditions conducive to *Legionella* [39], biofilms they associate with [40], and eukaryotic hosts they replicate within [41], all factors commonly found and amplified in premise plumbing (i.e., that found in buildings such as homes, schools, and hospitals) [42].

Transmission from contaminated environmental sources occurs via inhalation of aerosols [43] or aspiration of fluid [44]. Inhalation occurs when *Legionella* cells or particles containing them enter the respiratory tract, with aerosol sizes of <10 μm needed for alveolar deposition [45]. Aspiration occurs when physiological barriers, such as the gag reflex, fail to prevent fluid from the mouth or stomach entering the lungs and is most commonly seen in recumbent patients or those with throat obstructions [46]. While commonly seen in typical pneumonias [47], this form of transmission is poorly documented for legionellosis. Transmission of rare forms of legionellosis, most commonly occurring in immunocompromised patients, can occur via direct skin contact [48] or exposure during medical operations [49], along with systemic infection transmission.

Q2) Are there any climatic, socioeconomic, or regional trends associated with legionellosis?

Legionellosis follows a distinct seasonal pattern differing from that of other forms of pneumonia [50], but mirroring that of many water-borne diseases with a peak incidence in the summer [17]. There is also an increase in incidence of cases caused by one species, *L. longbeachae,* in the spring in certain regions [51]. While warmer weather has been shown to be associated with increased presence of *Legionella* in natural water systems [52], legionellosis incidence does not appear to follow climate zone trends in the United States [23]. This is likely due to capability for engineered water systems to provide ideal conditions for the growth of *Legionella* year-round [53]. Despite this, evidence has suggested specific meteorological conditions influence legionellosis transmission rates. Rain events [54], high humidity [55], and low pressure [56] have been repeatedly shown to be positively associated with the number of reported cases, although there have been some dissenting results, potentially due to regional climate differences. Results demonstrating a larger impact from local watershed hydrology than from weather on legionellosis risk suggest that geographic influence on legionellosis extends beyond supporting increased aerosol transmission, at least in certain circumstances [57]; the concentration of *Legionella* in the source is also important when considering these factors.

There may be links between demographic or socioeconomic factors and legionellosis, but there is a paucity of data on this topic. Multiple state public health agencies in the United States have shown people of African descent to represent a disproportionately high number of legionellosis cases [58,59]. In a nationwide examination of public health data by the Centers for Disease Control (CDC), incidence among this group was substantially higher than for whites [23]. Additionally, residents of low-income neighborhoods in the state of New York have also been shown to have increased odds of contracting legionellosis [59]. Further studies will be necessary to determine if these two risk groups are due to medical (comorbidities, limited health care), environmental (low-quality drinking water, premise plumbing deficiencies), or social (smoking rates, high-risk jobs) reasons.

Cases of legionellosis in occupational settings have been documented [60], and workers in certain professions with exposure to aerosols may be at higher risk for legionellosis. For example, workers at wastewater treatment plants may be exposed to exceptionally high levels of *Legionella* aerosols [61–63]. Studies