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INFECTIOUS DISEASE EPIDEMIOLOGY (A REINGOLD, SECTION EDITOR)

Legionella Epidemiologic and Environmental Risks

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Abstract

Purpose of Review *Legionella* bacteria cause Legionnaires' disease (LD), a severe and potentially fatal pneumonia. Legionellosis has been increasing in the USA and in Europe. We reviewed the literature to describe host factors predisposing to LD, environmental factors facilitating *Legionella* proliferation, and transmission modes leading to legionellosis cases and outbreaks.

Findings Men, smokers, and persons 50 years and older, or with chronic pulmonary or immunocompromising conditions, are at risk for LD. Stagnated water and warm water temperature promote *Legionella* growth. Most legionellosis cases result from exposure to aerosolized contaminated water from man-made water systems, including hot tubs and whirlpool spas; hot water systems in large buildings, hotels, and hospitals; and cooling towers.

Summary Water management plans for hot water systems at hospitals, long-term care facilities, and large buildings are important to help prevent LD, and careful epidemiologic investigations remain essential in controlling and preventing legionellosis outbreaks.

Keywords Legionellosis · Legionnaires' disease · *Legionella* · Pontiac fever · Cooling towers

Introduction

Legionellosis is an infectious disease that presents either as Legionnaires' disease (LD) or Pontiac fever. While Pontiac fever is a mild, self-limiting, influenza-like illness, LD is a severe pneumonia with a case-fatality rate of approximately 9% [1•, 2, 3, 4•]. In the USA, 98% of reported cases of legionellosis are LD [4•]. Legionellosis is caused by *Legionella* spp., aerobic Gram-negative bacteria found ubiquitously in natural freshwater bodies, including rivers and lakes. Most human infections result from inhalation of contaminated aerosolized water droplets generated from colonized man-made water environments. Of over 50 *Legionella* spp. identified to date, several are well-documented human pathogens including *L. pneumophila*, *L. longbeachae*, *L. micdadei*, *L. dumoffii*, and *L. bozemanii* [1•, 3]. *Legionella pneumophila* serogroup 1 is the most common cause of LD.

The annual incidence of legionellosis in the USA as reported to the Centers for Disease Control and Prevention (CDC) has increased from 0.42 per 100,000 population, in 2000, to 1.89 per 100,000 population, in 2015 [4•]. By region, incidence is higher in the Northeastern and North Central states than in other parts of the country; however, the increasing burden has been observed in most states [4•]. Of reported cases, approximately 4% are outbreak related, 14% travel associated, 19–20% with healthcare exposure, and the remaining majority considered sporadic [4•]. In Europe, reported LD cases have also increased from 2011 through 2015 [5•]. Reasons for this increase both in the USA and in Europe may be due to several factors, including increased diagnosis and reporting, an increasing susceptible population, aging plumbing infrastructure, and climate change [4•, 5•].

Following the discovery of *Legionella* after the first recognized LD outbreak affecting participants at the American Legion convention in 1976 [6, 7], clinical, epidemiologic, and laboratory studies have led to a greater understanding of LD pathogenesis, diagnosis and treatment, epidemiology, populations at risk for infection, and environmental sources. We reviewed the literature to describe the host factors predisposing certain populations to LD, environmental factors necessary for survival and proliferation of *Legionella* spp., and

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many environmental modes of transmission that have been associated with legionellosis cases and outbreaks.

Legionellosis Host Risk Factors and Susceptible Populations

Host risk factors predisposing individuals to legionellosis are well described and include men, smokers, persons 50 years and older, or with co-morbid chronic pulmonary conditions, diabetes, or immunocompromising conditions, including malignancy, transplantation, or medications [3, 8–12]. It is important to note that the extremes of age, smoking, and co-morbidities can increase risk for all-cause pneumonia and its associated morbidity and mortality [13]. Though rare in children, LD has been documented in neonates with various water exposures, including cases due to water births and a nosocomial outbreak due to a mist ultrasonic humidifier [14–20]. Neonates are especially susceptible to infection given the immaturity of their immune systems.

Intact cell-mediated immunity is important for an effective host response to *Legionella*, and conditions or drugs that impair or suppress cell-mediated immunity increase risk for both infection and morbidity/mortality [21]. In addition to malignancy, both solid organ and hematopoietic stem cell transplantation are associated with increased risk for LD [22]. Immune modulating drugs such as tumor necrosis factor antagonists (e.g., adalimumab) also increase risk of LD as well as infection by other intracellular pathogens [12].

Older persons are at increased risk for pneumonia [23], including LD [11], because of increased risk for aspiration, decreased immune function, and decreased mechanical function of the lungs [23–25]. Additionally, LD risk increases with age, in one study increasing by decade until persons reach their 80s [26•]. Smoking is a well-established risk factor for pneumonia [27, 28] and LD [5•, 10], with increasing risk with amount of cigarettes smoked [29]. Nicotine directly influences both *Legionella* spp. metabolism as well as host macrophage response [30]. Compared with women, the higher smoking prevalence among men may contribute to the higher incidence of LD among men [5•].

Legionella Environment and Epidemiology

Legionella are primarily transmitted from the environment. Infection can occur when *Legionella* have proliferated in a water environment, there is a susceptible human host, and contaminated water is aerosolized and inhaled or aspirated into the lungs [1•, 3] (Fig. 1). While *Legionella* are found in almost all natural water environments, most documented legionellosis cases have resulted from exposure to man-made water systems [1•, 8]. To date, only one case of probable human-to-human transmission of *Legionella* has been documented: in Portugal, a 74-year-old mother developed fatal LD 1 week after caring for her 48-year-old son who was a smoker and contracted LD working as a maintenance worker at a cooling tower complex [31]. The mother had cared for her son in a small, nonventilated room for approximately 8 h while he was very sick and coughing; *L. pneumophila* from mother and son matched by whole genome sequencing [31, 32••]. The rest of this section will discuss the ecology of *Legionella* and then focus on risk factors identified from epidemiologic studies of the past four decades, including conditions that amplify *Legionella* bacteria growth and man-made systems that broadly disseminate *Legionella* via water aerosolization.

Legionella Ecology

Legionella spp. have been isolated worldwide from stagnant and moving surface freshwaters including lakes and streams [33, 34], deep groundwater, and salt water [35, 36]. A few studies have also reported isolation of *Legionella* in rainwater [37–39]. In one study, *L. pneumophila* was cultured from 36% of rainwater samples collected from puddles on roads in Japan [39], the hypothesized source of exposure for a 54-year-old truck driver who developed LD after a car accident during a rainy season in Japan [40]. *Legionella* is able to survive these varied water environments and stressful natural (i.e., pH changes, temperature extremes, nutrient deprivation) and man-made conditions (i.e., chemical disinfectants) in part because the bacteria are able to live intracellularly within free-living and biofilm-associated amoebas, protozoa, or slime molds. In addition to the protective environment that amoeba and biofilm provide, *Legionella* spp. are able to enter into a viable but non-culturable state, with minimal metabolic activity or needs until favorable conditions exist [41, 42]. They also survive a wide range of temperatures (4 C/39 F to 50 C/122 F) and low-oxygen environments despite being obligate aerobes [43, 44].

Some *Legionella* spp., including *L. pneumophila* and *L. longbeachae*, have also been found in soil and compost in several countries, including Australia, New Zealand, Japan, UK, and USA [45–48]. Sporadic cases of LD caused by *L. longbeachae* have been linked to potting soil exposure in these and other countries [45, 49–52]. In Australia and New Zealand, *L. longbeachae* cases have been reported about as or more frequently than *L. pneumophila* cases [53, 54]. A case-control study from Australia found that people were more likely to develop a *L. longbeachae* infection if they ate or drank after gardening without washing hands (OR 29.47) or were near dripping hanging flower pots (OR 8.97) [55]. Recently, an LD outbreak investigation in New Zealand found both *L. pneumophila* and *L. longbeachae* from implicated

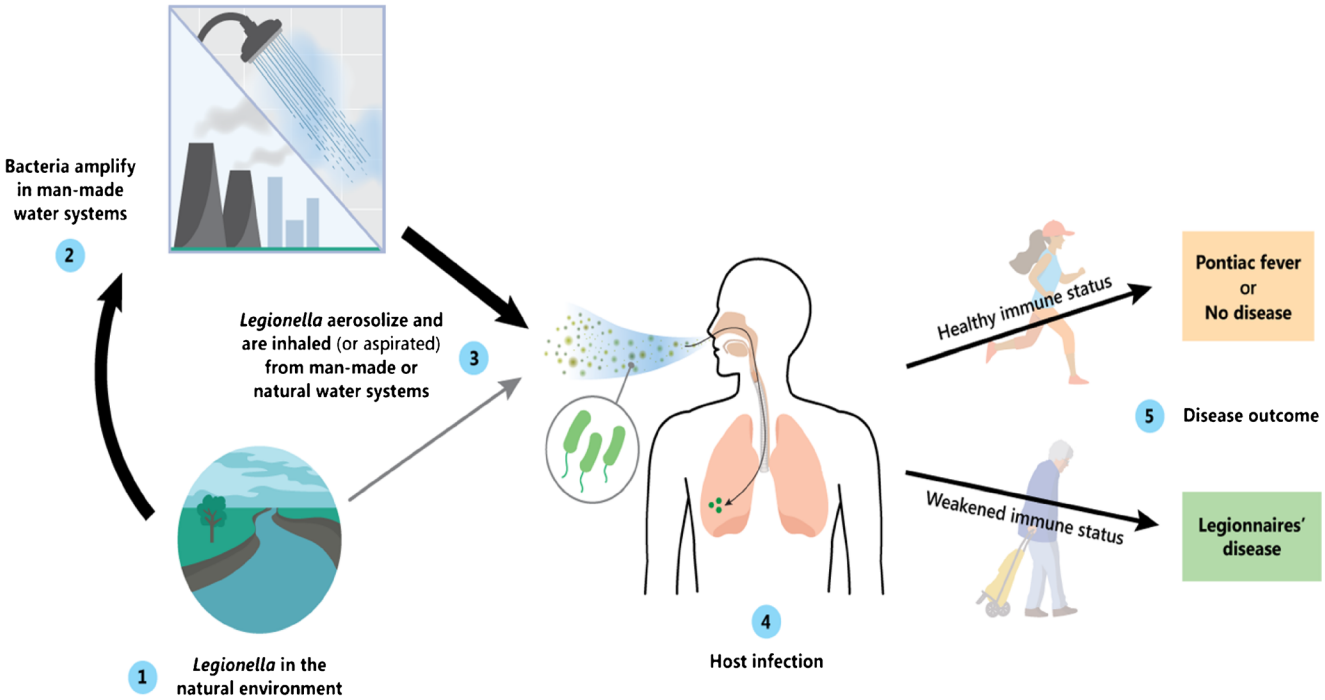

Fig. 1 *Legionella* pathways from water sources to legionellosis. *Legionella* in the natural environment (1) are amplified in man-made water systems (2), and, under favorable conditions (i.e., warm temperature), are aerosolized (3). People are infected most commonly via inhalation of aerosolized *Legionella* (4), with subsequent disease outcome depending on the host immune status (5)

cooling towers suggesting that *L. longbeachae* may also be transmitted through aerosolization of contaminated water [56•].

While *Legionella* bacteria have been isolated from natural water environments around the world, there are relatively fewer reports of legionellosis linked microbiologically with these sources. With the exception of hot springs, discussed in more detail below, the cases linked to the natural water environment generally implicated an aspiration event such as near drowning [57, 58••]. Rather than being a direct cause of legionellosis, natural waters are more often sources of *Legionella* introduction into the man-made water environments such as drinking or cooling systems.

Legionella Amplifiers

Man-made Water Systems

Certain conditions in man-made water systems amplify *Legionella* bacterial proliferation, biofilm formation, and increase legionellosis risk to people. Stagnated water, which exists in dead-end pipes or infrequently used water storage units, is conducive to *Legionella* growth [59]. Biofilm also survive particularly well on copper and other common plumbing materials [60]. Changes in water flow or flushing of water can disrupt biofilm and release *Legionella* downstream [61]; one study reported 125 times greater numbers of *L. pneumophila* in low-use taps, which have more stagnant water and larger changes in water flow, compared with high-use taps [62].

It follows that man-made water systems have been the most commonly implicated causes of legionellosis and are often the primary focus of disease investigation and prevention efforts [58••]. These man-made water systems are extensive and *Legionella* colonization can occur at any point from the municipal water system down to individual components at the building level, including dead-end water storage areas (i.e., water tanks), end-user devices (i.e., faucets), water-disseminating devices (i.e., cooling towers), and the extensive plumbing that connects all components [58••]. One study reported that two thirds of municipal water storage tanks surveyed across 10 US states had *Legionella* detected by real-time polymerase chain reaction (PCR) [63], while another study reported that *Legionella* was detected by PCR at all points in a drinking supply system, from raw untreated surface water through treatment and delivery as potable drinking water at the tap [64]. A study of potable drinking water sources in Germany reported that *Legionella* spp. were detected in one third of 233 buildings tested [65].

High levels of *Legionella* contamination or colonization at the municipal water level without adequate water treatment have the potential for causing large numbers of legionellosis cases, as these systems deliver water broadly to mass populations. As a case in point, an LD outbreak in Flint, Michigan, that occurred between 2014 and 2015 affected 87 people and was attributed to the municipal water supply after an

epidemiologic investigation. This outbreak correlated with a switch in Flint's municipal water supply from adequately chlorinated water from Lake Huron to intermittent or low levels of chlorinated water from the Flint River than recommended [66•].

At the building level, potable water has been linked to sporadic disease and outbreaks, both epidemiologically and microbiologically [67, 68]. A recent review of outbreaks of LD and Pontiac fever reported in the literature from 2006 to 2017 reported that, of 119 outbreaks that reported an attributed source, 42 (30%) were attributed or suspected to be due to potable water/building water systems [69]. And in European countries, of 457 outbreaks of legionellosis reported to the European Working Group for *Legionella* Infections from 2005 through 2008, 163 (36%) were attributed to hot or cold building water systems [70, 71]. However, pinpointing the source of *Legionella* within a building water system is difficult due to the time elapsed since incident exposure, quality, quantity, and location of sampling, bacterial changes and degradation during handling and transportation, and limits of laboratory methods [72].

Warm/Hot Temperature

An important environmental amplifier for *Legionella* growth is warm/hot water temperature. While *Legionella* can survive at a wide range of temperatures, proliferation and virulence are greatly increased between 32 and 40 C (89–104 F), based on in vitro and modeling studies [73–75]. In contrast to the paucity of cases associated with most natural surface waters, there have been multiple LD cases linked microbiologically to hot springs, usually due to bathing or near-drowning events [76–81]. In one case, a 57-year-old man with myelodysplastic syndrome developed LD, presumably from aspiration, after almost a year of drinking water directly from a thermal hot spring contaminated with the same strain of *L. pneumophila* that caused his disease [76].

Similar man-made hot water environments have been associated with outbreaks and sporadic cases of legionellosis. In a literature review of 1977–2018 legionellosis cases and outbreaks associated with recreational waters, Leoni et al. found 1079 cases and 25 outbreaks related to recreational waters including spa pools, some of which use hot spring water; of 25 outbreaks, 20 (80%) involved public spas, including whirlpool spas at hotels and resorts [82].

Up to 24% of reported LD cases in the USA and Europe are associated with domestic or international travel in the 10 to 14 days before illness onset [6, 83, 84]. Follow-up investigation of travel-associated cases clustering with a common hotel, motel, or cruise ship has often implicated recreational spas and whirlpools that were poorly maintained and under chlorinated [85].

An even more common artificial water system maintained at high temperatures ideal for *Legionella* growth is a water heater or a hot water system. *Legionella* have been commonly isolated from building potable hot water systems, with studies showing that 1–94% of tested hot water systems have *Legionella* bacteria [86–90]. This broad range appears to vary by type of building and age of system, with larger, older water systems most frequently and heavily colonized. An Italian study reported 5 (100%) of 5 hospitals, 7 (63.6%) of 11 hotels, 13 (41.9%) of 31 apartments with centralized water heating systems, and none of 28 apartments with independent water heating systems had *L. pneumophila* [90].

Larger, older buildings with centralized water heating systems tend to have complex plumbing and inconsistent and imbalanced hot water requirements in different parts of the building. This leads to multiple, large water tanks and many dead-end systems such as closed pipes, all increasing chances of water stagnation. Over time, buildings pipes and water systems accumulate nutrients, biofilms, and *Legionella* colonization.

The temperature of hot water correlates with extent of colonization. Water heaters with water below 48.8 C (120 F) can lead to increased *Legionella* colonization [91]. Electric water heaters also seem to be colonized more often than gas water heaters, potentially because of uneven water heating in electric tanks and lower temperatures at the bottom of tanks where sediment accumulates [86]. Studies have also found less colonization in instantaneous water heaters, which do not keep a reservoir of hot water, compared with traditional hot water heater tanks [92, 93].

The link between *Legionella* found in these hot water systems and legionellosis has been documented during outbreaks associated with retirement homes, group homes, hotels, and hospitals, where high colonization rates of their large, centralized, complex, and often old water systems were reported [94–96, 97•].

Legionella Aerosolizers and Disseminators

The role of water-aerosolizing and water-disseminating devices is especially important because they substantially increase the risk for legionellosis by converting water into an easily inhaled or aspirated form and spreading it broadly. Showerheads have been proposed as devices that have the optimal mechanisms for causing legionellosis, with the right habitat for biofilm, intermittent hot water running through them, and ability to aerosolize bacteria directly onto an individual. Studies from the UK and Australia have found *Legionella* in 50–75% of household showers sampled, with air sampling also able to detect low levels of *Legionella* by quantitative PCR [98, 99]. Those studies found that increasing age of the showers, decreased frequency of cleaning and decreased frequency of use were associated with *Legionella*

detection, supporting the notion that biofilm production and subsequent disruption at irregular intervals increase risk of *Legionella* mobilization [98, 99]. Besides supporting *Legionella* colonization and growth, showerheads have also been associated with nosocomial disease and community-acquired sporadic LD [100, 101].

While showerheads generally affect one person at a time, other devices can aerosolize and disseminate *Legionella* more broadly. Fountains, humidifiers, and misters have been implicated in causing legionellosis because, once contaminated, they can directly aerosolize water into environments that people frequent [58••, 102]. It is likely that anything that could aerosolize water and draws from a potentially contaminated source could lead to legionellosis. Some past cases, for instance, have been linked to an air-perfused footbath, windshield wiper fluid, car washes, and machinery cooling systems [103–107].

Air conditioning and cooling units that generate a water aerosol have also caused legionellosis. Evaporative coolers use recirculating water to trap heat and release the evaporant into open air, potentially carrying *Legionella* bacteria with it. Evaporative coolers have been linked to legionellosis outbreaks [108–110] with many studies demonstrating *Legionella* bacteria from such systems [58••]. Closed system air conditioners are not designed to generate aerosol and therefore are not considered a risk for legionellosis. However, poorly maintained units with leaking aerosol have been linked with legionellosis cases, including from malfunctioning car air-conditioning units [111, 112].

Cooling towers (CT) are a special, extensively used cooling system that are similar in design to evaporative coolers. CTs have been the most extensively implicated cause of large LD outbreaks. A 2015 review reported that close to half of the available publications on potential or confirmed sources of *Legionella* were related to CTs [58••]. These included the original LD outbreak at the American Legion conference in Philadelphia in 1976 that affected 182 people [7] and a massive LD outbreak in Spain in 2001 with over 800 suspected cases [113].

The capacity of CTs to cause large outbreaks is related to the large amount of warm water being circulated, creating an ideal environment for amplification of *Legionella*. The CTs can then broadly disseminate bacteria through large volume aerosolization into densely populated areas. CTs remove heat by recirculating vast volumes of water (1,000–600,000 gal/min) and exhausting the resultant evaporative hot vapor, with losses of around 1% of circulating water per 5 C of cooling [114]. The distance that the subsequent *Legionella* containing vapor can travel varies with CT height, fan size, relative atmospheric humidity, temperature, and wind speed and direction [115, 116]. Studies have suggested that risk of LD is higher within a mile (1.6 km) from a contaminated CT [117–120]. However, some outbreak investigations and atmospheric dispersion models have suggested that contaminated aerosols can travel over 3.7 miles (6 km) from an implicated CT and cause disease [120, 121]. Results from one recent CDC study demonstrated that, of 196 water samples collected from CTs across the USA, 164 (84%) were PCR-positive for *Legionella*, and *Legionella* were isolated from CTs in seven of the eight regions surveyed [122].

The substantial association between legionellosis and CTs has led to interest in preventive efforts to minimize transmission risk. Since 1987, multiple agencies including federal, state, and local public health departments, the American Society of Heating, Refrigerating and Air Conditioning Engineers (ASHRAE), and the Cooling Technology Institute (CTI), have issued guidelines on the design, maintenance, and operating practices of CTs, with most focusing on disinfection and routine testing [123, 124]. Some agencies have formalized regulations. For example, New York City (NYC) now requires that all CTs, evaporative condensers, and fluid coolers be registered and owners of buildings with CTs to maintain an annual certification and conduct yearly inspections for compliance [125, 126]. This regulation was implemented in response to two large NYC CT outbreaks in 2015; in one outbreak, 138 persons developed LD and 16 died [127•, 128].

Legionella Outbreaks and Transmission in Healthcare Facilities

The hospital setting brings together a large population of susceptible hosts and a large building water system that, if colonized with *Legionella*, can lead to deadly LD outbreaks. Of 27 LD outbreaks investigated by the CDC during 2000–2014, 33% were healthcare associated, including 57% of outbreak-associated cases and 85% of outbreak-associated deaths [2]. In another review by the CDC of definite healthcare-associated LD from 21 state and local health jurisdictions in 2015, cases were reported from 57 long-term care facilities and 15 hospitals, with a case fatality rate of 25% [26•]. Healthcare facilities have complicated water systems that are frequently colonized by *Legionella* spp. [129]. Outbreaks and cases in healthcare settings have been linked to decorative fountains, ice machines, showers, birthing tubs, cooling towers, air conditioners, humidifiers and other respiratory or nasogastric equipment, other potable water sources, and, rarely, dental equipment [18, 96, 97•, 130].

Persons at risk of nosocomial exposure include people residing in skilled nursing facilities; who had recent outpatient visits to healthcare centers, including dialysis units; who had recent surgery; and who were recently hospitalized [96]. In 2017, given the severity of LD outbreaks in healthcare facilities, the Centers for Medicare & Medicaid Services (CMS) required all healthcare facilities in the USA to develop and implement a water management plan that conforms to ASHRAE standards [131]. Facilities with inpatient

hematopoietic or solid organ transplantation programs are recommended to have a water testing program for *Legionella* [132]. In Europe, all buildings are required to have a *Legionella* testing program [133].

Climate

Seasonally, LD is more common in the summer during warmer and more humid months in the USA [134–136]. An increased relative humidity combined with warm temperatures during LD incubation periods appears to have an important effect in both US- and UK-based studies [136–138]. A US nationwide study using data from 1998 to 2011 reported an increased odds (3.1) for community-acquired LD when humidity was > 80% compared with < 50% when temperatures ranged 60–80 F [136]. Risk also increased with greater rainfall during incubation periods [134, 135]. These findings are likely the result of both ecological and human factors, with increased growth of *Legionella* in the environment, increased travel distance and survival of *Legionella* spp. in aerosolized water vapor, and increased use of air conditioners and CTs in warmer, humid climates.

Conclusions

The public health risk and burden of LD will likely continue to increase in the near future given the aging population, increasing number of susceptible persons with immunosuppression and/or co-morbidities, aging plumbing infrastructure, and ubiquity of *Legionella* bacteria. A changing climate will also likely impact *Legionella* ecology and epidemiology in some regions, with expansion of natural and man-made environments and prolongation of the warm and humid season facilitating *Legionella* proliferation. Combined with the increasing urbanization, population density, and cooling system use expected with global warming, more people will likely be exposed to *Legionella*.

Therefore, prevention methods will become ever more important. The recent CMS requirement that all US healthcare facilities implement a water management plan that conforms to the ASHRAE standards will help to reduce LD risk starting with the facilities with the greatest potential for LD outbreaks and substantial fatality. The industries that own and manage travel resorts, hotels, and cruise ships should also consider implementing similar water management plans to decrease LD risk at their facilities to protect both their business and their clients. Research is needed on the effectiveness of water management plans to ensure efficacy in *Legionella* control and prevention of disease.

Along with water management plans, public health action remains essential to control and prevent this potentially severe disease. Patients diagnosed with legionellosis should be reported promptly to public health so that epidemiologic and laboratory investigation and follow-up can be coordinated to identify clusters and potential sources of transmission to prevent additional morbidity and mortality.

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Compliance with Ethical Standards

Conflict of Interest Alexander Yu, Amanda Kamali, and Duc Vugia each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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