Legionella and Legionnaires' Disease: Pathogenesis and Control

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Abstract

A type of bacteria called *Legionella* is responsible for both Pontiac fever, a less serious flu-like sickness, and Legionnaires' disease, a severe form of pneumonia. *Legionella pneumophila*, the main pathogen, grows best in warm water settings including plumbing systems, hot tubs, and cooling towers. Inhaling aerosolized water droplets containing the bacterium causes infection; smokers, the elderly, and those with weak immune systems are more susceptible. By living and proliferating inside amoebae and human macrophages and manipulating host cell processes through a type IV secretion system, *Legionella* circumvents host defenses. Maintaining appropriate water quality, cleaning water systems, and conducting routine monitoring to stop bacterial development are all examples of effective control techniques. In order to stop the spread of illness, public health initiatives concentrate on surveillance, outbreak investigation, and lowering exposure risks in susceptible areas. For the purpose of implementing more focused treatments, it is essential to comprehend the bacterium's survival strategies, especially its capacity for replication inside host cells. Early identification and timely medication are crucial to lowering mortality, even though antibiotic treatment including macrolides or fluoroquinolones are helpful in controlling Legionnaire' disease.

Keywords: *Legionella pneumophila,* Macrophages, Defenses, Immune Systems, Aerosolized

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Introduction

Gram-negative bacteria found in both water and soil naturally are members of the genus *Legionella*. It has the potential to multiply in favorable conditions, such as water temperatures within 20 and 50 degrees celsius, stale water, and the presence of biofilm, if it is brought into facilities via the supply of water. They may invade faucets: head showers, cooling towers, saunas, and fountains in manufactured marine settings, particularly hot water systems found in lodging establishments, nursing homes, hospitals, and other both public and private structures. The low levels of *Legionella* oftenly seen in natural environments can significantly rise in constructed hot water systems with water temperatures below 55 °C. The *Legionella spp.* infections in humans are known to occur when inhalation from aerosols harboring pathogenic germs takes place (Valciņa et al., 2023). Legionellosis, which can manifest as either Legionnaires' disease, a potentially lethal type of pneumonia, or Pontiac fever, a flu-like ailment, is often contracted by breathing aqueous aerosols through shower and similar appliances. Another common cause of nosocomial legionellosis is water ingestion (Bekkelund et al., 2024).

The Gram-negative *Legionella* bacteria have the ability to enter and multiply in both self-sustaining amoebae and mammalian macrophages, as well as to build and flourish in biofilms. *Legionella,* an active intracellular parasite, enters the lung through breathing in particles of infected aerosols. It then infiltrates alveolar macrophages and creates the *Legionella*-containing vacuole for replication, causing damage to tissue and inflammation. With respect to the immune status of those compromised, this virus can cause either a mild, self-limiting, non-pneumonic illness called Pontiac fever or an aggressive form of pneumonia called Legionnaires' disease (Zhu & Liu, 2024). Following an epidemic among members of an American Legion conference in Philadelphia in 1976, *Legionella* was discovered. A form of pneumonia that later came to be recognized as Legionnaires' disease afflicted those impacted (Edelstein & Lück, 2015).

The first local outbreak reported 182 cases and 29 deaths with the majority of patients reporting fever, lung congestion, chest pains, and exhaustion. In 1976, guinea pig inoculation with infected lung tissue from deceased victims led two microbiologists McDade and Shepard to discover LP. The bacteria *L. pneumophila*, which caused Legionnaires' disease, was then discovered (Lupia et al., 2023). Of more than 60 species of *Legionella* known to exist, and 24 of these have the potential to be infectious to humans (Bell et al., 2021; Girolamini et al., 2022). Legionellosis symptoms range from mild fever to fatal pneumonia. The patient's factors and timely care impact Legionnaires' death rates (Frostadottir et al., 2023).

Legionnaires' Disease

Infections transmitted by water belonging to the *Legionella* genera are the cause of Legionnaires' Disease, a form of pneumonia that is frequently quite fatal. Even though almost 20 among the 65 species of *Legionella* that have been identified as infecting humans (Chambers et al., 2021), *L. pneumophila* accounts for over 90% of reported cases, mainly which are transmitted through aerosolized water, with rare instances of person-to-person transmission. It thrives in both natural and artificial water environments like cooling systems and air conditioners (Cruz et al., 2023). The hospital-acquired Legionnaires' disease poses serious outbreak risks and high mortality rates, and patients with impaired immune systems are more vulnerable to severe *Legionella* infections. Compared to 6% for cases not related to healthcare, the United States recorded a 25% case death rate for hospital-associated illnesses in 2015. From 2007 to 2017, the rate of death in Europe from healthcare-acquired legionella cases was three times greater than that from community-acquired infections (Bechmann et al., 2024).

Pathogenesis of Legionnaires' Disease

1. Transmission: The main way that *Legionella* transmits is by water-borne released in aerosol form bacteria, and the probability of transmission is greatest in constructed areas like homes and businesses. Aerosols from tainted warm water can be released by prevalent sources such as cooling systems, hot tubs, showers, and taps. The *Legionella* development is encouraged by elements including retention, warm water, and biofilms in water systems. The Legionnaires' disease is not usually spread from person to individual; rather it is contracted by inhaling infected aerosols (Yao et al., 2024).
2. Entry into Host Cells: Humans that are susceptible acquire the disease by inhaling aerosols containing the pathogens. The alveolar macrophage is a reservoir cell for human infection, where the bacteria prevent phagolysosomal fusion. The *L. pneumophila*'s exceptional capacity to invade a variety of eukaryotic cells alludes to a basic tactic that takes use of basic biological functions. By employing coiling phagocytosis to infiltrate host cells, the bacteria swiftly disrupt organelle migration processes, resulting in the creation of a replicative phagosome where they may proliferate. After eight to ten hours of vegetative development, the bacteria transform into the "mature form," which is a brief, very agile stage (Shames, 2023). Bacteria are taken up by alveolar macrophages and grow in a *Legionella*-specific vacuole that has been modified during infection (Neuber et al., 2024).
3. Intracellular Survival: The *L. pneumophila* loses its flagella soon after entering a host cell, allowing its *Legionella* containing vacuole (LCV) to evade the endocytic pathway through ER-derived vesicles and mitochondria and attracting vesicles produced from the endoplasmic reticulum (ER) by effector-mediated recruitment. Then the LCV becomes peppered with effectors and ribosomes, and rapid replication takes place (replicative phase). When host nutrition run out, *L. pneumophila* exits the host cell and becomes flagellated (transmissive phase). A range of bacterial factors promote *L. pneumophila*'s initial adhesion to host cells. The *L. pneumophila* binds and enters amoebae and mammalian cells more easily due to the rtxA locus, pilEL locus, ladC, and enhC, which produce a type I secretion system, type IV pili, an inner membrane-associated protein, and a periplasmic protein, respectively. Mammal attachment to cells is aided by the porin *L. pneumophila* major outer membrane protein (MOMP) and the collagen-like protein Lcl. Nevertheless, *L. pneumophila* also uses host-related factors, such as Fc receptors and supplement receptors CR1 and CR3, which are activated by MOMP, for adhesion and internalization. Since antibody-mediated inhibition of CR1, CR3, or Fc receptors hinders phagocytosis, complement and Fc receptors are crucial for *L. pneumophila* entrance into macrophages (Chauhan & Shames, 2021).

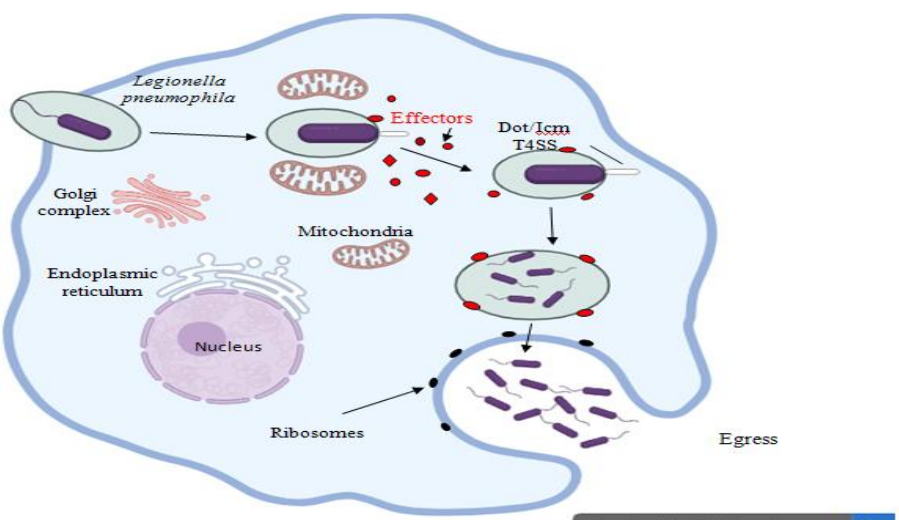

Fig. 1: Mechanism of *Lengionella* (Retrieved from BioRender)

Tissue Damage and Inflammation: As part of the immunological response to the infection, neutrophils, lymphocytes, and macrophages infiltrate the alveolar septa, causing interstitial inflammation in the lung tissue examined histologically in cases of legionnaires' disease. The pneumocyte hyperplasia, intra-alveolar exudates, hyaline membranes, and alveolar edema are important indicators of widespread alveolar injury. The gaseous exchange is hampered by alveolar edema, and fibrosis and further blockage are facilitated by hyaline membranes. The immunological response is reflected in intra-alveolar exudates, which are mostly mononuclear cells. Type I pneumocyte damage is followed by type II pneumocyte hyperplasia. Features such as erythroleukemia phagocytosis, which denotes hemolysis and leukopenia, and the lack of many neutrophils in the alveolar exudate help differentiate legionnaires' disease from other causes of widespread alveolar injury. Because of their internal position inside macrophages, bacteria are challenging to identify using traditional staining techniques. The illness develops in three stages: the proliferative stage (weeks 2-3) with pneumocyte hyperplasia and fibrosis; the fibrotic stage (after week 3) with severe fibrosis and cyst development; and the exudative stage (first week) with edema, hyaline membranes, and exudates. Molecular techniques or immunohistochemistry are used to confirm the diagnosis. The prognosis is correlated with the level of lung injury; higher death rates are associated with more severe damage (Rello et al., 2024).

Alveolar macrophages, the body's main defense against lung infections, consume the bacteria in the lower respiratory tract, which is where a *Legionella* infection begins. Within these macrophages, *Legionella* flourishes as a facultative intracellular pathogen. The bacteria enter phagosomal vacuoles after attaching themselves to the macrophages through complement receptors. Through an unidentified mechanism, *Legionella*, however, stops the normal merging of lysosomes with the phagosome, preventing the acidification that typically takes place and shielding the bacteria from the detrimental impacts of the myeloperoxidase system. This turns the phagosome from a destructive compartment into a reproduction site, allowing the bacteria to grow inside it. New germs that can infect more cells are released when an infected macrophage is ultimately killed.

Control and Prevention of Legionnaires' Disease

1. Water System Maintenance: The *L. pneumophila* persists in artificial water systems by growing inside protozoan hosts, associating with biofilms, and exhibiting resistance or tolerance to disinfectants. While freshwater amoebae serve as its natural eukaryotic hosts, humans are considered incidental hosts (Nisar et al., 2020). Chlorine-based disinfectants, such as chlorine, chlorine dioxide, and monochloramine, are commonly used in potable water systems to control pathogens and ensure water quality during treatment and distribution. While global guidelines, including those from the World Health Organization (WHO), recommend maintaining a chlorine residual of at least 0.2 mg/L at the point of delivery, implementing these standards becomes more challenging in complex building plumbing systems (Xi et al., 2024). Studies show that buildings with hot water systems below 60°C are more susceptible to *Legionella* contamination. As a result, guidelines suggest maintaining healthcare hot water systems above 55°C to help control *Legionella*, though this is aimed at prevention, not elimination (Whiley et al., 2017).

Kinetic analysis and modeling were used to investigate the ozone inactivation of *Legionella* in waste water. Results indicated that changes in germ and COD levels may be predicted by the relationship between ozone concentration, germ concentration, and COD. Ozone and COD reacted and inactivated *Legionella* at the same time, but the COD reaction happened more quickly because ozone oxidizes COD more readily. A larger lnN/N0 and a lower inactivation rate were the results of higher starting COD concentrations. The effectiveness of inactivation was enhanced by higher temperatures. The necessary Ct value for a 99.99% reduction was not consistent because of the nonlinear relationship between the initial ozone concentration and the inactivation rate. Inactivation was more affected by the initial ozone concentration than by contact duration, and increasing contact time was insufficient to counteract a decrease in ozone concentration. Only when the initial ozone concentrations were almost the same were Ct values comparable. The lnN/N0 vs. The Ct curve's inflection point increased with an increase in the starting ozone concentration. Furthermore, a plasma corona used less energy than diamond electrodes coated with boron (Li et al., 2017).

Injecting copper and silver ions into waterways and keeping them at predetermined quantities is known as copper-silver ionization, or CSI. According to laboratory study, CSI can inactivate *Legionella*; nevertheless, the majority of studies on its efficacy were case reports, according to the US EPA review. The bacteria can be shielded by biofilms and amebae, though, and *Legionella* may eventually become resistant. Additionally, using CSI might cause corrosion, especially if the plumbing supplies are insufficient or the water quality is low. Furthermore, amounts of copper and silver may surpass safe limits if improperly managed. To guarantee the safety and efficacy of the system, inductively coupled plasma mass spectrometry (ICP-MS) must be used for continuous monitoring of treated water (Krause, 2024).

2. Cooling Towers and HVAC Systems: Cooling towers (CTs) are specialized heat exchangers designed to dissipate excess heat through the evaporation of water. These systems are commonly used in air conditioning, ventilation, and heating setups in commercial, industrial, residential, and healthcare buildings. Due to factors like semi-open water reservoirs and steady water temperatures within 20-35°C, CTs provide optimal conditions for microbial proliferation and can act as reservoirs for the transmission of harmful pathogens (Wüthrich et al., 2019). Cooling towers (CTs) are considered the primary sources of *Legionella* outbreaks worldwide, primarily due to their ability to release contaminated aerosols over long distances. Major concerns include plume rise/deflection, condensation, and drift deposition, particularly when maintenance and disinfection are inadequate, leading to the growth of *Legionella*. (Girolamini et al., 2023). The occurrence of *Legionella* contamination in cooling tower water (CTWs), especially in CTWs of underground stations and healthcare facilities, is alarming. The detection rate and colony-forming units (CFU/ml) of *Legionella* in CTWs are strongly correlated with air temperature (Trigui et al., 2024). Legionnaires' disease outbreaks have been connected to cooling towers. In 2021, 557 cooling towers in Vancouver, Canada, were the subject of a culture-based investigation of *Legionella pneumophila*. Six of these towers had levels exceeding 1,000 CFU/mL, while 30 towers (5.4%) recorded exceedances, which are defined as findings of 10 CFU/mL or greater. Of the 28 towers that were tested for serogroups, 17 had *L. pneumophila* serogroup 1 (sg1). According to the results, *Legionella* contamination was mostly found in 16 establishments, including two hospitals, indicating that it was highly localized. Nearby city water monitoring stations recorded temperatures below 20°C and a free residual chlorine level of at least 0.46 mg/L in the three months before each exceedance (Radziminski & White, 2023).

3. Risk Assessment: *Legionella* can live in water as planktonic bacteria that float freely or as biofilms that grow on the surface of pipes. In order to withstand severe environments and complicate identification, it can also infect amoebas or change into a viable but non-culturable (VBNC) form. Environmental circumstances, the accessibility of both organic and inorganic nutrients, the presence of protozoa, the

dispersion of microorganisms, the kind of plumbing materials used, and related corrosion products are some of the elements that affect its growth. These elements may also be impacted by water supply and sanitation systems. To improve control strategies and stop colonization, a better knowledge of how *Legionella* behaves with its surroundings in water systems is essential (Sciuto et al., 2021).

4. A study of 100 water samples collected from hospital environments found that 12% were positive for *Legionella* via culture, while 42% tested positive by PCR. Of the PCR-positive samples, 40.47% (17 cases) had concentrations below 10^3 GU/L, 4.76% (2 cases) were in the 10^3 to 10 GU/L range, and 54.76% (23 cases) had concentrations above 10 GU/L. Invasion assays showed that five isolates exhibited higher invasiveness in HeLa cells than the reference strain, while four isolates were similarly invasive, and the remaining isolates showed lower invasiveness. The findings highlight the link between *Legionella* contamination and hospital water systems, underscoring the importance of implementing water monitoring systems to control hospital-acquired infections, particularly *Legionella* outbreaks (Bavari et al., 2022). A quantitative health risk assessment of *Legionella* was conducted in selected hospitals in Tehran, focusing on two exposure scenarios: shower and toilet faucet. From 100 samples collected from toilets and showers in 8 hospitals, *Legionella* was detected in 38 cases (38%). This data was used for quantitative microbial risk assessment (QMRA). The microbial load transmitted by inhalation was estimated based on *Legionella* concentrations in the water. The median length of hospital stay was 3.6 days, and other exposure characteristics, including exposure time and inhalation rate, were taken from previous research. For every exposure event, the infection risk from breathing *L. pneumophila* was evaluated using an exponential model ($\gamma = 0.06$). The infection risk for showers varied from 3.5 to 21.9 cases per 10,000 hospitalized patients, whereas the infection probability for toilet faucets ranged from 0.23 to 2.3 cases per 10,000 at a mean Legionella concentration of 10^3 CFU/L. These values were found to be higher than the WHO recommendations for waterborne pathogens within healthcare settings when compared to acceptable infection risk thresholds established by the US EPA and WHO. Despite the use of treated water in these hospitals, 38% of samples were contaminated with *Legionella*, suggesting that faucets and showers are potential sources of transmission. Our findings emphasize the need for hospitals to address the risk of *Legionella* infection to protect patient health (Kermani et al., 2022). The purpose of the study was to create a scoring system for estimating the potential hazards of environmental contaminants and legionnaires' disease in establishments located throughout the southern Italian region of Apulia. 47 building, water, and air conditioning-related structural and management parameters were evaluated. An overall risk score was determined for each facility using a Poisson regression model based on three outcomes: water samples that tested positive for Legionella (risk score range: 7-54), water samples that tested positive for Legionella with a concentration greater than 1000 CFU/L (risk score range: 22-179,871), and clinical cases of Legionnaires' disease (risk score range: 6-31). Receiver operating characteristic curves were used to calculate the cut-off values for each result: 19 for the first result, 2062 for the second, and 22 for the third. The chance of the corresponding consequences was considerably greater for facilities that exceeded these levels (De Giglio et al., 2021). Samples taken from swimming pools contained *Lengionella spp.* (Zimoch & Paciej, 2020).

5. Personal Protection: As a result of their close interactions with patients, dental healthcare personnel are more susceptible to airborne infectious illnesses. Improving indoor air quality by lowering carbon dioxide levels through efficient ventilation is a crucial element that can greatly affect the risk of disease transmission, either raising or lowering it (Zemouri et al., 2020). Understudied possible origins of community-acquired Legionnaires' disease include unregulated private wells. Adjust the temperature of your water heater to 140 degrees Fahrenheit and to find out how to adjust the temperature of your water heater. Take good care of your water heater. Locate the instruction handbook provided by the manufacturer of your hot water heater. Find out how to properly clean it and how frequently it should be done. Flush with hot water. Legionella may be killed by running shower heads and faucets at 140 degrees Fahrenheit or higher for at least 30 minutes. Be careful. Scalding may result from these temperatures. Hot tubs require meticulous maintenance. Hot tubs that are neglected offer the perfect environment for Legionella to thrive and spread. Find out more at Humidifiers should be used carefully. To lower the danger of exposure to *Legionella* and other infections, workers who manage water systems or who operate in or close to potentially polluted regions should take extra measures. Ensuring that the water system remains in compliance with specified norms or their equivalent is crucial. Considering it can be an origin of contamination, workers should stay away from stale water that has visible coatings and be careful not to aerosolize it. To enable any mist to evaporate, employees should wait at least fifteen minutes after turning off the cooling tower before going inside. When necessary, the proper personal protective equipment (PPE) should also be worn. For example, leather gloves should be worn when working with machinery, rubberized gloves should be worn when using bleach or biocides, and an NIOSH-approved N100 filtering facepiece respirator is advised in cases involving substantial contamination, such as when testing shows levels of Legionella above proposed limits, or in cases where Legionnaires' disease is suspected or confirmed. Employees can greatly lower their chance of coming into contact with dangerous infections by adhering to these recommendations. If there is a chance that workers will come into contact with *Legionella* or other pathogens, they should wear an NIOSH-approved N95 respirator. This covers scenarios such as poor upkeep of the water system, the existence of potentially aerosolized stagnant water, worries about possible infection, or complaints about poor interior air quality. Wearing an NIOSH-approved N95 respirator is still a choice, but it is not required if the water system is kept up to date and there is no water misting. For this reason and to reduce the risk of contamination, all employees should wash their hands with soap and water or use an antibacterial hand sanitizer before consuming food, drinking, smoking, or leaving the place of work.

6. Education and Awareness: The study found that awareness of legionellosis among adults was generally limited. Older individuals and those with lower levels of education were particularly lacking in knowledge about the disease. A notable gap in understanding was evident, especially regarding the methods of diagnosing legionellosis. Public health campaigns that deliver straightforward, easy-to-understand information could be valuable in raising awareness and reducing the impact of the disease (Shalan et al., 2023).

Treatment of Legionnaires' Disease

Despite being underreported, legionellosis is becoming a more significant global public health concern. Research shows a high prevalence and substantial medical expenses. In order to improve epidemiological monitoring, newer, more sensitive tests that may identify other *Legionella spp.* and serogroups are now available. Traditionally, the diagnosis entails finding the *Legionella pneumophila* serogroup 1 antigen in urine. Testing for *Legionella spp*. is recommended when a patient is brought to the hospital with serious community-acquired pneumonia, and early antibiotic therapy that targets *Legionella* is crucial shown in Table 1. Delays in treatment are linked to worse outcomes.

Table 1: First Line therapy for Legionnaires disease

Class of Drug	Antibiotics	References
Macrolide	Azithromycin	
	Erythromycin	(Viasus et al., 2022)
	Fidaxomicin	
	Roxithromycin	
Quinolones	Levofloxacin	(Zhang et al., 2023)
	Ciprofloxacin	
	Moxifloxacin	(Rello et al., 2024)
	Ofloxacin	
	Pefloxacin	(Zhu et al., 2024)
	Trovafloxacin	

500 mg of azithromycin or 750 mg of levofloxacin per day is the starting dosage that is advised. Levofloxacin has been linked to a speedier time to clinical stabilization and a shorter hospital stay (Velazco, 2020).

In addition, in both oral and intravenous formulations, omadacycline is an emerging once-daily aminomethylcycline antibiotic that effectively combats the microorganisms that cause community-acquired bacterial pneumonia and reaches high concentrations in pulmonary tissues. Omadacycline showed similar effectiveness to moxifloxacin in a Phase III study, with 37 patients with legionella pneumophila pneumonia seeing an early clinical success rate of 87% (Zhang et al., 2023) Two factors may contribute to omadacycline's effectiveness by due its ability to bind to the primary tetracycline site on the 30S ribosomal subunit and block the production of bacterial proteins, indicating strong activity against atypical microorganisms like *Legionella pneumophila* and its high ability to break down cellular membranes, which enables it to effectively target and destroy the intracellular pathogen (Zhu et al., 2024). The results of a recent research were consistent with that receiving antibiotics more than a day later increased the likelihood of getting severe pneumonia. ICU transfers were considerably decreased by giving levofloxacin or macrolides within 24 hours of admission, according to that research. Another study also discovered a correlation between increased ICU admission rates and postponed treatment that higher ICU admission rates were linked to postpone therapy (Huh et al., 2022). Legionnaires' disease is a frequent but often underdiagnosed cause of community-acquired pneumonia. However, the use of urine antigen testing and advancements in molecular diagnostics have enhanced detection (Rello et al., 2024). In immunocompromised patients, Legionnaires' disease may progress slowly or fail to resolve, potentially resulting in complications such as lung abscesses and empyema (Pouderoux et al., 2020).

Conclusion

The propensity of *Legionella* bacteria to produce Legionnaires' disease and other respiratory ailments makes them a serious threat to public health. System maintenance, routine monitoring, and disinfection are all essential components of comprehensive water management methods that effectively control and prevent *Legionella* outbreaks. For the purpose of implementing more focused treatments, it is essential to comprehend the bacterium's survival strategies, especially its capacity for replication inside host cells. Early identification and timely medication are crucial to lowering mortality, even though antibiotic treatment including macrolides or fluoroquinolones are helpful in controlling Legionnaire' disease. To lower the prevalence of Legionnaires' illness and sustain susceptible groups, more study into the pathophysiology of *Legionella* and advancements in public health procedures are necessary.

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