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REVIEW ARTICLE

Legionnaires' disease: A review of emerging public health threats

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ABSTRACT

Legionnaires' disease (LD), caused by the Gram-negative bacterium *Legionella pneumophila*, has emerged as a significant public health concern due to its rising incidence and high morbidity and mortality rates. This review comprehensively examines the etiology, epidemiology, pathogenesis, clinical presentation, diagnosis, treatment, and prevention of LD. The bacterium thrives in aquatic environments, often within biofilms and protozoan hosts, contributing to its resilience and widespread distribution in natural and man-made water systems. Transmission primarily occurs through the inhalation of contaminated aerosols, with immunocompromised individuals, the elderly, and smokers being at heightened risk. Clinically, LD presents as a severe pneumonia with systemic involvement, and its diagnosis often relies on culture, urinary antigen tests, and molecular methods. The treatment landscape is dominated by macrolides and fluoroquinolones, with emerging research into alternative therapies to combat antimicrobial resistance. Effective public health strategies, including rigorous water management practices and infection control measures, are vital in mitigating the risk of outbreaks. This review aims to enhance clinical awareness and inform public health initiatives by elucidating the complex interplay between bacterial virulence, host factors, and environmental conditions that contribute to LD transmission and persistence. A better understanding of these dynamics is crucial for developing robust prevention and control strategies, ultimately reducing the global burden of this potentially life-threatening disease.

Keywords: *Legionella pneumophila*, Legionnaires' disease, pneumonia, public health, waterborne pathogens.

INTRODUCTION

Legionnaires' disease (LD) or legionellosis is a serious public health issue characterized by high morbidity and mortality [1]. *Legionella pneumophila*, a Gram-negative bacterium belonging to the Legionellaceae family, is the source of this illness infection [2]. In addition to LD, another acute non-pneumonic respiratory disease that *L. pneumophila* can cause is Pontiac fever [3]. Pontiac fever is a mild respiratory illness, whereas LD is more severe. *L. pneumophila* is typically found in freshwater settings, where it multiplies rapidly inside free-living amoeba in warm, stagnant water (25°C–45°C) [4]. As it spreads quickly through water-borne transmission, *L. pneumophila* is found worldwide in freshwater habitats [5]. In the US, 8–18,000 persons are hospitalized for LD annually, but only roughly 10% of these patients receive a clinical diagnosis [1].

Following a significant respiratory outbreak among guests of an American Legion conference, the disease known as LD was first identified in 1976 [6]. *Legionella* is

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commonly contracted by inhaling aerosolized water, which is typically found in showers, whirlpool spas, outdoor cooling equipment, humidifiers, sprayers, and respiratory therapy devices [7]. Although aspiration is a significant method of LD transmission, the disease cannot be spread from person to person or by drinking contaminated water [8]. Individuals with compromised immune systems, comorbidities, older people, and smokers are more likely to contract LD [9]. However, most instances (up to 96%) were sporadic and had no known cause.

The symptoms of LD can mimic those of typical pneumonia [10]. These signs often appear after 2–10 days of *L. pneumophila* infection. In some instances, this illness may also have symptoms that affect the digestive system and brain [11–13]. Frequent signs and symptoms of LD include fever, coughing, dyspnea, diarrhea, headache, nausea, stomach discomfort, hemoptysis, and blood coughing [14]. This disorder requires prompt and effective treatment. The rationale is that this condition can lead to several life-threatening complications if not treated. Untreated LD can lead to life-threatening complications, including respiratory failure, septic shock, acute kidney failure, and myocardial infarction [14]. Investigating legionellosis outbreaks is a major priority for public health initiatives, which are followed by source control and investigation [3].

Pneumonia caused by *L. pneumophila* mainly affects people who are immunocompromised, elderly, or have severe diseases [10]. Individuals who have a history of smoking or chronic lung illness, are older than 50 years old, or have immune system disorders are more likely to develop LD [9]. Major origins of LD outbreaks have been identified as environmental risk factors, such as cooling towers or water systems in buildings, including hospitals [15]. The treatment of pneumonia caused by *Legionella* species in both hospital- and community-acquired cases requires early clinical diagnosis and appropriate antibiotic treatment [16]. Diagnosis relies on the isolation and culture of *Legionella* species from clinical specimens. Testing for urinary antigens is still the most commonly used diagnostic procedure [17].

LD requires appropriate attention and treatment because although it is underdiagnosed and underreported, its incidence is increasing annually. The purpose of this review is to explain the etiology, history, reservoir, epidemiology, pathogenesis, immune response, pathology, clinical symptoms, diagnosis, differential diagnosis, transmission, risk factors, public health importance, treatment, antimicrobial resistance, and control of LD. Improved knowledge of the risks linked to LD will enable state and municipal authorities to more effectively target preventive measures and raise clinical awareness of the disease's dangers.

ETIOLOGY

L. pneumophila is catalase-positive, slightly oxidase-positive, and Gram-negative [18]. The ideal growth conditions are 35°C and pH 6.9–7.0. *Legionella* can grow in ambient air, but it thrives in environments with 2.5%–5% carbon dioxide [19]. These bacteria have no anaerobic growth. This organism has never developed on a medium without cysteine. These bacteria require specifically enriched culture conditions for *in vitro*. Yeast extract agar, including charcoal, has been the best developed media to date [20]. The growth of artificial culture media can take up to 10 days [21]. Both the yolk sac of embryonated chicken eggs and the intraperitoneal injection of guinea pigs can be used to isolate this organism [22, 23]. *Legionella* does not use carbs, break down nitrate, or target urea. These bacteria do not appear to contain arginine dihydrolase, lysine, or ornithine decarboxylases. It produces beta-lactamase [24].

L. pneumophila rods are usually 2–3 μm long and have frequently pointed ends when viewed under a microscope [25]. Despite being Gram-negative, this organism is incompatible with the standard Gram stain. Gimenez staining can be used to identify these bacteria, and silver impregnation staining can be applied to tissue [26]. Bacterial cells with high concentrations of branched-chain fatty acids are analyzed by gas chromatography [27]. All organisms evaluated by DNA hybridization were genetically unrelated to *L. pneumophila* at the species and genus level [28]. The differences in clinical features between outbreaks do not appear to be caused by variations in strains. On the basis of variations in their antigens, these organisms are categorized into four serological categories. Group I (prototype strain, Knoxville) included the bulk of isolates, including those from the 1976 Philadelphia outbreak [6]. Little isolates were found in Group II (prototype strain, Togus), Group III (prototype strain, Bloomington), and Group IV (prototype strain, Los Angeles) [29].

HISTORY

The US Centers for Disease Control and Prevention (CDC) and the media first became aware of the existence of *Legionella* species, which are Gram-negative bacteria, during the summer of 1976 after an unprecedented pneumonia outbreak in Philadelphia, Pennsylvania, United States [6]. At the 58th annual conference of the American Legion, 221 guests were afflicted with an uncommon respiratory ailment, of which 34 deaths were reported [30]. The CDC assembled what at the time was the largest team in its history to locate the infection's source due to the significance of the outbreak and the uncertainty surrounding the causal agent. Joseph E. McDade and Charles C. Shepard discovered bacteria as the cause of LD in December 1976 [31]. They found a new genus called *Legionella*, which at the time contained only one known species and a novel Gram-negative rod-shaped bacterium that they named *L. pneumophila*, after the American Legion.

Following the organism's identification, more investigation revealed that *Legionella* had been isolated in 1947 but had not yet undergone further characterization [32]. Moreover, it was demonstrated that *Legionella* was the source of previously unidentified outbreaks of flu-like sickness, including the outbreak that struck Pontiac, Michigan, in 1968 and was subsequently diagnosed as Pontiac fever [33]. Over 65 distinct species are currently recognized in the genus *Legionella*, and our knowledge of the biology and toxicity of these species is growing. Understanding the history of this disease is important to investigate the bacteria reservoir, pathogenesis, treatment, and prevention of transmission further.

RESERVOIRS

L. pneumophila is a symbiotic organism that grows within amebas in aquatic environments [34]. *Legionella* live in water as internal parasites of the protozoa that inhabit there, like ameba. Amebas are frequently found in biofilms and once shielded by a biofilm from *Legionella* and other infections, they are extremely difficult to eradicate [35]. One source of contaminated water in the built environment is the central air conditioning systems found in hotels, business buildings, and hospitals [36]. These bacteria can also reside in evaporative coolers, nebulizers, humidifiers, whirlpool spas, hot water systems, showers, windshield washers, fountains, room humidifiers, ice makers, cooling towers used in industrial cooling systems, and misting systems commonly found in grocery stores' produce departments [37].

These bacteria can also be transmitted from contaminated aerosols generated in hot tubs if disinfection and maintenance programs are not strictly followed [38]. *Legionella* may originate from ornamental fountains, streams, and freshwater ponds [39]. Hotels, fountains, cruise ships, and hospitals with intricate cooling and drinking water systems are specifically linked to this condition [40]. Sterile water must be used because tap water tainted with *Legionella* species can infect respiratory devices such as humidifiers and nebulizers [41]. Exposure to compost and potting mixes is another source of contamination [42]. Therefore, periodic surveillance and monitoring of the wastewater system are crucial due to the specific niche and the rapid spread of bacteria through the water system. Early detection of *Legionella* in wastewater systems and adequate remediation can prevent transmission to humans.

EPIDEMIOLOGY

In 2021, the European LD Surveillance Network reported that the age-standardized notification rate of LD was 9.2 cases/million population, with a range of 0–21.4 cases/million [43]. According to prospective studies, 2%–9% of cases of community-acquired pneumonia (CAP) are caused by *L. pneumophila* [44]. Of the 60 cases of hospital-acquired pneumonia (HAP) in patients in non-intensive care units where the etiology was identified, seven had a diagnosis of *L. pneumophila*-caused HAP [45]. Most cases of LD have a mortality rate of 8%–12%, although this might increase in high-risk situations [46]. The countries with the greatest reported instances of community-acquired LD were Spain, Italy, and France; conversely, the countries with the lowest notification rates (<1 case/million) were Bulgaria, the Czech Republic, Greece, Romania, and Slovakia [47].

The first time that *L. pneumophila* was linked to a significant respiratory outbreak among American Legion conference participants at a Philadelphia hotel was almost 40 years ago [6]. Since its initial description, surveillance programs have been implemented in a number of nations, including Europe, the United States, Canada, New Zealand, Australia, Japan, and Singapore, where the condition is considered reportable [48].

Large epidemics have received the most attention due to their significant impact on public health. In Murcia, Spain, in 2001, 449 individuals were affected by the biggest outbreak ever documented [49]. Cooling towers of buildings and water storage tanks in the city were implicated in the LD community outbreak. Interestingly, epidemiological investigations on the LD outbreak in Murcia indicated that the cooling towers of a hospital located in the northeastern part of the city of Murcia, Spain, were the origins of the community LD outbreak [49]. Based on investigations, most of the cooling system installations in the city area, including hospitals, were not properly maintained. However, after the LD outbreak was reported and the source was identified, urgent measures were taken to maintain the city's cooling systems, such as cleaning, disinfecting, and closing possible contaminated sources. The cooling tower implicated as the major source of the LD outbreak was also subsequently replaced [49].

A massive outbreak of coronavirus disease-19 (COVID-19) that included 128 cases in July 2015 claimed 12 lives in New York [30]. The Michigan Department of Health and Human Services announced the outbreak in January 2016. Since Flint moved to the Flint River for its water supply, officials have reported 87 cases, 10 of which have resulted in fatalities [50]. The Flint LD outbreak was particularly linked to difficulty in treating river water sources due to seasonal variations between high organic (microbial) loads, high magnesium hardness, and high carbon concentrations, which fluctuate mostly during rain events. Most LD cases are sporadic, but these significant outbreaks typically include more people. Of the cases reported to public health authorities, only 4% were related to the outbreak [51].

Travel is a factor in 20% of documented cases of LD [52]. The risk of travel-associated LD (TALD) is predicted to be between 0.0001% and 0.001% per month of stay in a developing nation, based on data obtained in Europe in 2009 [47]. A tendency toward increasing TALD risks from northwest to southeast

Europe was also observed [47]. Greece had the highest risk of TALD at 1.68 incidents per million nights; nevertheless, no domestic TALD cases were reported in Greece in 2009 [53]. Higher levels of prevention, control, and notification are required in countries with high TALD to enhance the diagnosis of LD.

Descriptive epidemiological data from the 1990s showed that between 8,000 and 18,000 hospitalizations were related to community-acquired LD [54]. A greater estimate could result from current data. According to the Occupational Safety and Health Administration, between 10,000 and 50,000 cases of LD are reported annually in the US, with the northeastern states reporting the highest notification rates [1]. In New York City, the number of instances reported to the Department of Health and Mental Hygiene increased by 230% between 2002 and 2011, according to a recent study of 1449 cases [55]. During the same year, 2009 had the highest incidence (2.74 cases/100,000 population), higher than the incidence in the US as a whole (1.5 cases/100,000 people). Only three reported cases of LD in Indonesia have been spread across various regions, including Tangerang, Jakarta, and Bali [56]. The lack of ability to diagnose or identify *Legionella*, including the traits of *L. pneumophila* serogroup from clinical specimens, is assumed to be the cause of the low number of case reports. Research findings indicate that multiple water sources in Palembang have been found to contain *L. pneumophila* bacteria [57]. According to additional research, *L. pneumophila* was detected in swimming pool water samples from Surabaya and in water samples from several hospitals in Jakarta [58, 59].

An efficient notification and surveillance system is essential for the early detection of epidemics, which can spread quickly and impact hundreds of people in a matter of days. However, because affected nations have different diagnosis and monitoring systems, the precise global incidence of LD remains unknown and largely underreported, possibly due to a lack of diagnostic resources, insufficient surveillance systems, or cultural and healthcare system challenges. Understanding the natural history of LD, epidemiological data, and microbiological information are crucial for locating the source and implementing effective control measures. Continuous global and regional surveillance program strategies and the development of rapid diagnostic techniques will be instrumental in preventing further LD outbreaks.

PATHOGENESIS

The pathogenesis of *Legionella* infection begins with the presence of pathogenic bacteria in water sources and human transmission pathways [5]. There is no evidence of person-to-person transmission because *Legionella* does not belong to the normal human bacterial ecology. The infection begins in the lower respiratory tract. *Legionella* is an internal facultative parasite, meaning that it can multiply freely within alveolar macrophages, the principal barrier against bacterial infection in the lungs [60]. Through complement receptors, bacteria attach to alveolar macrophages and are taken up by phagosomal vacuoles. However, the bacteria impede the normal acidification of the phagolysosome and maintain the harmful myeloperoxidase system in the absence of susceptible bacteria by blocking the fusion of lysosomes with phagosomes by an unknown method. Bacteria reproduce within the phagosome, meaning that the cellular compartment becomes a nursery, not a death trap [61]. The cell eventually breaks down, unleashing a fresh batch of bacteria to infect more cells.

Potent chemotactic factors are produced by bacterial growth, complement system activation, and alveolar macrophage death, resulting in the influx of polymorphonuclear monocytes and neutrophils [60]. Transudation of serum and deposition of fibrin in the alveoli are made possible by leaky capillaries. As a result, breathing becomes difficult, and airway damage and pneumonia occur. Macrophages play a role in the spread of bacteria to locations outside the lungs, but an inflammatory reaction is not always the result [62]. The symptoms associated with *Legionella* infection most likely stem from a combination of physical disruptions to blood oxygenation, an imbalance between ventilation and perfusion in the remaining lung tissue, and the release of harmful chemicals from the bacteria and inflammatory cells [63]. Proteases are bacterial agents that may be in charge of tissue destruction [64]. Tumor necrosis factor, which may be in charge of certain systemic symptoms, and interleukin-1, which releases fever from monocytes, are examples of cellular factors [65].

Virulence seems to have multiple causes. Metalloproteases and heat shock proteins found in the cytoplasmic membrane of outer membranes trigger defensive immunological reactions, although they are not necessary for pathogenicity [66]. It has been determined which gene encodes the 29 Kd protein and contributes to cellular infection [60]. Further investigation of factors affecting virulence levels that induce different severity levels in humans. Exploration on both the bacteria and host sides is necessary.

IMMUNE RESPONSE FROM THE HOST

Conditions that weaken both innate and acquired immunity are risk factors for LD. The integrity of physical clearance mechanisms, such as the mucociliary escalator of the tracheobronchial tree, is an important line of defense against serious *L. pneumophila*, which is more common in individuals with chronic heart and lung illness [10]. Non-immunological antibacterial substances such as lysozyme or lactoferrin, which are typically present in respiratory secretions, might be involved [67].

The immunological response that emerges after an infection by *L. pneumophila* involves a delicate equilibrium between the pro- and anti-inflammatory functions of immune cells (Figure 1). The major antibacterial defense against *Legionella* infection is often compromised by the normal activities of recruited blood monocytes and human alveolar macrophages [60]. Mice's alveolar macrophages of mice do not promote intracellular bacterial development, which is one of the key reasons why mice are more resistant to experimental *L. pneumophila* [68]. Because polymorphonuclear leukocytes (neutrophils) do not promote bacterial growth *in vitro* and have only weak bactericidal effects, their involvement in these illnesses is poorly understood [69]. Neutropenia is not a significant risk factor, although treatment with cytokines like gamma-interferon may marginally boost neutrophil bactericidal activity [70]. On the other hand, different types of immunosuppression are the major risk factors for disease in humans. For instance, pneumonia was more likely in patients receiving corticosteroid treatment in a minor outbreak caused by contaminated nebulizers [10].

There is still much to learn about the critical elements of the immune system that protect against legionellosis. *Legionella* is an intracellular facultative pathogen, which is why cell-mediated immunity is the focus of the present study by Cunha and Zamboni [71]. Measuring lymphocyte blastogenesis following exposure to *Legionella* antigens allows physicians to identify infected individuals through their cell-mediated immune response [2]. After an acute infection, lymphocytes begin to develop in the air passages of experimentally infected animals after approximately 5 days. Activated alveolar macrophages or peripheral blood monocytes limit bacterial proliferation *in vitro*, whereas naive alveolar macrophages are conducive to intracellular bacterial development [72]. Treatment with lymphokines generated by selectively stimulated lymphocytes can activate macrophages [73]. An essential mediator is interferon-gamma, which can take the place of lymphokines. It has been proposed that intracellular growth is inhibited when iron entry into phagosomes is restricted, which is a critical growth factor for *Legionella* [74].

Less is known about humoral immunity's function. All immunoglobulin classes are produced following experimental therapy or human infection. *In vitro*, these antibodies perform opsonization tasks that help polymorphonuclear leukocytes, macrophages, and monocytes phagocytose microorganisms [61]. Most *Legionella* strains are not killed by antibodies, although the ability of the cell to phagocytose depends on how the interaction turns out. *L. pneumophila* stimulates the complement system's classical route, which improves phagocytosis even further [75]. In addition, the alternate complement pathway is triggered by *Legionella micdadei*, allowing for the opsonization of this species before the development of an immunologically specific antibody response [76]. Antibodies can be useful or

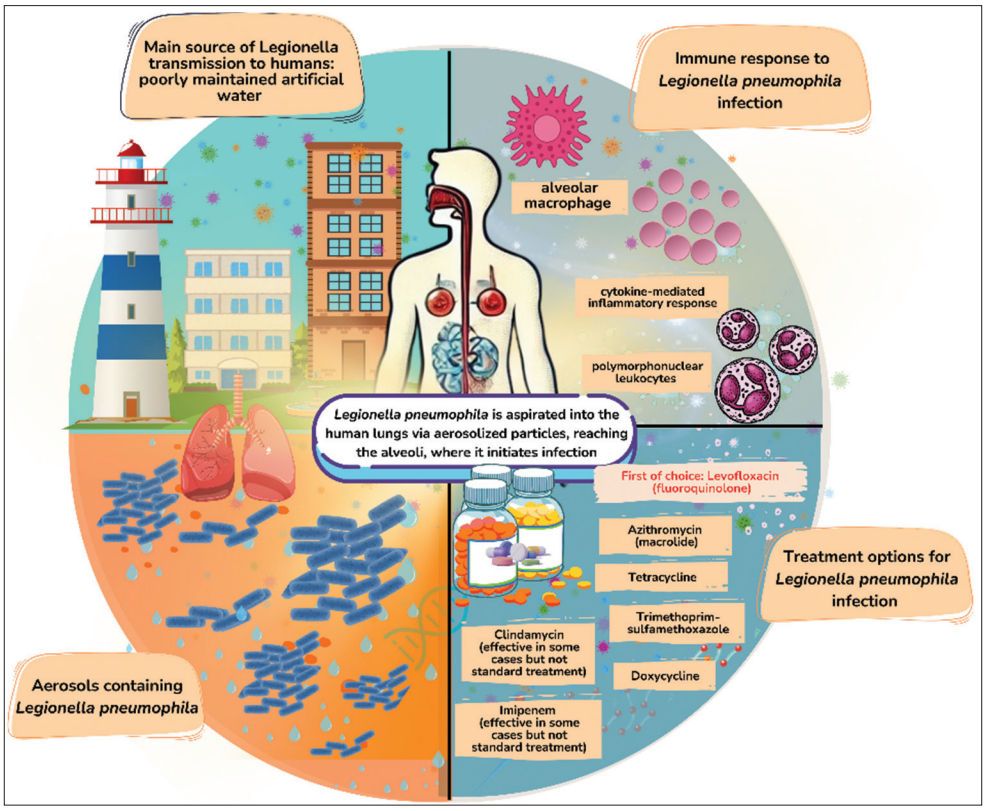

Figure 1: Transmission to recovery: The immune fight against *Legionella pneumophila* should be considered as the treatment of choice [Source: The figure was prepared by Bantari Wisynu Kusuma Wardhani].

harmful, depending on the circumstances, based on *in vitro* data. Studies on animals have confirmed that antibodies have a protective function [76]. Beside the humoral immunity, cellular-type immune responses are also crucial to combat *Legionella* infection [76]. This response can shape the pathology of *Legionella* infection.

PATHOLOGY

The lungs are typically the only organ with pathological signs. It is typical to have serous or serosanguineous pleural effusions, fibrinous pleurisy, and varying degrees of lobar consolidation [77]. Acute fibrinopurulent bronchopneumonia surrounding the respiratory bronchioles is a microscopic finding [78]. Septa alveolaris are typically intact. An extensive dense eosinophilic intra-alveolar proteinaceous and fibrinous exudate is primarily composed of polymorphonuclear leukocytes. Macrophages are commonly encountered. Oxygen toxicity or illness may cause acute diffuse alveolar injury with hyaline membrane development and regenerated type 2 pneumocytes [79].

Bacilli are not visible on common tissue stains. Some of these stains are periodic acid–Schiff stain, Gridley fungus stain, Gomori methenamine silver stain, and Brown–Brenn stain [80]. Gimenez staining works well on both preserved and fresh lungs [81]. The Warthin-Starry stain and Dieterle's silver impregnation stain both clearly identify *L. pneumophila* but are not specific [82]. Under an electron microscope, organisms can be observed inside phagocytic vacuoles, polymorphonuclear leukocytes, alveolar macrophages, and exudate [83]. A direct fluorescent antibody (DFA) test or culture must be used for diagnosis. Before oxygen therapy, a biopsy taken during the 1st week of the disease revealed interstitial pneumonia and acute bronchopneumonia to understand the actual condition because oxygen treatment might influence the pathology appearance [78]. Pathological examination results can help understand the mechanisms of disease and be a valuable tool for identifying disease progression.

MANIFESTATION OF *L. PNEUMOPHILA* INFECTION: CLINICAL SIGNS AND SYMPTOMS

The term "legionellosis" refers to various terms referring to both pneumonic and non-pneumonic human infections caused by *L. pneumophila* [84]. The quantity of bacteria present in the aerosol, virulence factors, and the individual immunological condition of each patient all influence the clinical signs and symptoms of LD. [9]. *L. pneumophila* can cause serious infections and sepsis when they interact with other microbes, such as *Helicobacter cinaedi* and *Streptococcus pneumoniae*, as well as viral diseases like severe acute respiratory syndrome coronavirus 2 [2]. It is interesting to note that Sanchez *et al*. [85] recently revealed that COVID-19 individuals were coinfected with methicillin-resistant *Staphylococcus aureus* and *L. pneumophila* serogroup 1. There are two different kinds of manifestations of this infection: the non-pneumonic form, often known as Pontiac fever, which is a less severe form of infection that includes pneumonia, and LD, which is a feverish, flu-like condition [3]. Furthermore, reports of involvement of the heart, brain, belly (including the gallbladder), joints, and skin in extrapulmonary forms of LD have been published [86]. Furthermore, it is quite uncommon for LD symptoms to be accompanied by exanthema. Eleven cases of legionellosis linked to a rash have been reported in the literature [87].

Pontiac fever is an acute, self-limiting influenza-like illness that typically lasts for 2–5 days. In 1968, at least 144 people were affected by the first known outbreak of this kind of legionellosis in Pontiac, Michigan [33]. The incubation phase begins when the disease first manifests symptoms and typically lasts up to 48 h. Fever, headache, lethargy, and myalgia are the primary symptoms [88]. Pontiac fever is a self-limiting illness that frequently goes untreated. The same bacteria that cause Legionnaire's disease can also cause Pontiac fever; however, pneumonia is not the same as Pontiac fever.

LD is a type of legionellosis pneumonia. Typically lasting between 2 and 10 days, the incubation period can last up to 16 days in certain outbreaks [9]. The illness can cause anything from a cough to potentially dangerous pneumonia. The initial symptoms include fatigue, headache, fever, nausea, and malaise. In addition, some individuals may experience dizziness, disorientation, and myalgia [12]. Typically, the patient experiences a moderate dry cough, which develops into a cough with phlegm in 50% of cases [10]. Approximately one-third of patients presented with hemoptysis. Lung abscesses and pleural empyema occur in certain people with immunological diseases, such as those with systemic lupus erythematosus after kidney transplantation [89]. Patients with LD may present with gastrointestinal signs, such as acute stomach pain and watery diarrhea [11]. In addition to other intracellular infections, *L. pneumophila* frequently induces relative bradycardia during fever. The clinical signs of bacterial pneumonia are rare. In a patient with disseminated *Legionella*, Patel *et al*. [90] reported an even more uncommon LD manifestation: Significant hypertriglyceridemia with rhabdomyolysis.

The intensity of illness, suitability of the first antibiotic treatment, the location where *Legionella* was acquired, and host characteristics (nutrition, immunological state, and co-infections) all affect the mortality rate associated with LD [91]. The mortality rate generally falls between 5% and 10%. However, for immunosuppressed patients who are not receiving treatment, the mortality rate might increase to 40%–80%. Even in the conditions mentioned above, the mortality rate can be reduced to 5%–30% with appropriate care [2]. It is noteworthy to emphasize that nosocomial epidemics with elevated mortality

rates might result from LD associated with healthcare facilities.

In the past, several test abnormalities have been linked to the diagnosis of legionellosis. Acute elevations in creatine phosphokinase levels, elevated liver enzyme levels, hypophosphatemia, and hyponatremia are reported in the legionellosis [92]. Take note that there is a link between severe legionellosis and hyponatremia. The identification and confirmation of clinical and laboratory characteristics unique to *Legionella* infection have remained elusive in clinical trials. Diagnostic specificity is low when considering clinical and laboratory abnormalities separately. A recent study by Beekman *et al*. [93] validated a six-item admission diagnostic scoring system (*Legionella* prediction score) to identify pneumonia caused by *L. pneumophila*. This list of clinical symptoms can be an important tool for diagnosing *Legionella* infections.

DIAGNOSIS

The typical procedure for identifying *Legionella* species involves the cultivation of samples from the lower respiratory tract [16]. Buffered charcoal yeast extract mixed with polymyxin, anisomycin, vancomycin, and dyes is necessary for the first isolation of *Legionella*; the dyes give the bacteria distinct colors, whereas the antimicrobials stop *Legionella* from growing in the presence of other competing organisms [94]. In cases of strong clinical suspicion of LD, urine antigen and *Legionella* culture from respiratory samples are necessary. *Legionella* infections can be quickly and affordably diagnosed by urine antigen testing, which has a sensitivity of 56%–99% [84]. Testing urine antigens provides numerous benefits compared with culture. Urinary antigen tests (UATs) are highly sensitive and specific and are available in a variety of formats, including a rapid immunochromatographic test or a 96-well plate-based enzyme immunoassay. UATs are the most common diagnostic tools for *Legionella* disease in the United States and Europe [95]. However, they are less sensitive to the detection of other *Legionella* species or serogroup, and urinary antigens may persist in some patients for months.

The majority of patients suffering from LD find it difficult to obtain a sufficient sputum specimen; test results can be obtained within 48–72 h of the onset of symptoms and can continue to be positive even after receiving antibiotic therapy for weeks or months; results for urine antigen can be obtained in a matter of hours, while results for cultures take 3–5 days [95]. The primary drawback of urine antigen testing is its high specificity for Lp1 pathogens compared with non-Lp1 bacteria. However, these species and serogroups are responsible for almost 90% of LD cases in the United States [9]. A quick urine antigen test that records result in 15 min is the BinaxNOW (Abbot, USA) *Legionella* Urine Antigen Test. This assay uses an immunochromatographic membrane and has 80% sensitivity and 97%–100% specificity [96].

Legionella infections can also be diagnosed using some other approaches, although these are insensitive and technically challenging. Respiratory specimens stained with fluorescein isothiocyanate (FITC) range in intensity from 25% to 75%. In contrast, a direct culture of clinical specimens cultured with competing microorganisms can accomplish this highly specific (almost 100%) procedure [97]. Polymerase chain reaction (PCR) amplification of DNA from *Legionella* species has been reported in bronchoalveolar lavage, serum, urine, and throat swab specimens obtained from patients with pneumonia [98]. These techniques can amplify DNA from all *Legionella* species and serogroups, but they are not well standardized. PCR has not yet been demonstrated in clinical experience to be more sensitive than culture, and the CDC does not advise routinely using PCR or genetic testing to identify *Legionella* species in clinical specimens.

Detection using DFA can be used in the diagnosis of *Legionella*. This method uses a pool of polyvalent FITC-labeled rabbit anti-*Legionella* conjugates to detect fluorescent bacillary structures in smears or sections [99]. Because all test methods have weaknesses, it is recommended that more than one testing method be used. For example, clinicians may submit sputum in addition to urine to increase the possibility of diagnosing *Legionella*.

DIFFERENTIAL DIAGNOSIS

Clinical diagnosis may be challenging in non-epidemic situations. Extrapulmonary signs such as weakness, non-productive cough, chronic and recurring chills, persistently rising fever, and relative bradycardia should raise the possibility of LD [100]. An unimpressive cough and a small phlegm when dealing with severe pneumonia are something to be concerned about. Compared with simple-to-simple *S. pneumoniae* pneumonia, recurrent chills are more predictive of LD than single chills [101]. *Mycoplasma pneumoniae* infections generally affect younger people, although there is some age overlap, which is more likely to cause persistent coughs [102].

In certain regions, the start of late summer is beneficial, as is immunosuppression, high fever, and corticosteroid use in nosocomial patients. Aspiration pneumonia and other dual infections have also been reported; however, failure to isolate other bacterial pathogens has been suggested [103]. Q fever, psittacosis, influenza, and adenovirus should also be considered [77]. Diffuse interstitial infiltrates are more common in Q fever, and smaller infiltrates are typically seen on chest radiographs in patients with psittacosis than in those with LD [104]. In rare cases, tularemia or pneumonia should also be considered.

TRANSMISSION

Humans contract LD by inhaling aerosols carrying *Legionella*, which are primarily released from contaminated water sources [105]. This transmission method is illustrated in Figure 1. Experts concur that there is no human-to-person transmission of the illness [106]. Nonetheless, a case of a potential transfer from a patient to his caregiver was documented in 2014 [107]. In extremely rare circumstances, direct contact between tainted water and the surgical site can cause the spread of this infection [108]. The optimal temperature range for *Legionella* to develop is between 25°C and 45°C (77°F and 113°F), with a temperature of approximately 35°C (95°F) being ideal. Temperatures >60°C (140°F) can eradicate these microorganisms [109].

Numerous artificial water sources, including hot water tanks, cooling towers, and evaporative condensers in sizable air conditioning systems, like those seen in hotels and big office buildings, are suitable environments for the growth of these bacteria [110]. *L. pneumophila* is currently found in a variety of manmade and natural aquatic settings, such as hot tubs, cooling towers, industrial equipment, home plumbing systems, thermal spas, water pipes, and hospital nasogastric tubes and nebulizers [111]. Research indicates that these microorganisms can infiltrate hot water distribution systems in 12%–70% of hospitals [112].

A 2005 outbreak of LD was reported to have originated from a small ornamental fountain in Rapid City, South Dakota [7]. Furthermore, cooling towers are recognized as primary conduits for the transmission of this illness, primarily due to their capacity to disperse tainted aerosols across extended distances [113]. According to research, the distance at which contaminated cooling towers can travel airborne can reach 1.6–3.2 km, and in a French incident, there were indications of a spread as far as 6 km [114, 115]. The capacity of cooling towers, the absence of efficient control mechanisms, and pervasive environmental contamination are important risk factors in community epidemics. The potential for long-distance airborne transmission of *Legionella* poses significant challenges to public health initiatives aimed at controlling and preventing *Legionella* infection.

RISK FACTORS

The host factors that affect susceptibility to infection and disease severity interact with geographic factors, which are evident in outbreak and seropositivity rates [116]. Naturally, men in their middle to older years dominated the Philadelphia and Los Angeles outbreaks [87, 117]. In other outbreaks, occasional nosocomial cases, and rare occurrences, males also appear to be the predominant gender. Notably, the incidence of LD infection is higher in immunocompromised patients from different hospitals [118]. LD has been reported among patients on chronic dialysis in several hospitals. About 63% of the 241 cases had reported symptoms, and 63% had a serious underlying illness. Renal transplantation, malignancy, and, less commonly, rheumatic disease were the underlying illnesses in 47 immunodeficient patients. Diabetes mellitus, renal disease, lung disease, and organic heart disease are other prevalent underlying illnesses [19]. Smoking and alcoholism are prevalent and can be risk factors in rare cases [16]. Risk factors include the proximity of excavations to one's residence, overnight travel within the previous 2 weeks, and the potential use of air conditioning at home [119].

PUBLIC HEALTH IMPORTANCE

Both the US CDC and the World Health Organization acknowledge the significance of *Legionella* in public health. The number of LD cases recorded in the US has been increasing since 2003; in 2018, approximately 10,000 cases were reported, but the actual number of cases is probably significantly higher [1]. Many suggested contributing causes have been suggested, although the exact explanation of this ongoing growth is unknown. These include aged plumbing infrastructure, increased LD testing, and increased population vulnerability (due to age and other risk factors) [120]. Monitoring water systems in public and healthcare facilities is important to prevent LD outbreaks. This is because *Legionella* can grow in complex water systems in buildings, including healthcare facilities. The individuals at risk include those who are older, smokers, or have certain medical conditions [121]. Routine testing for *Legionella* is an essential part of a water management plan to prevent Legionellosis and protect public health. Routine testing helps detect *Legionella* early, establish baseline measurements, and validate water management programs [122].

In recent years, many prominent *Legionella* outbreaks have garnered media attention. One of the most recent significant outbreaks occurred in New York City, where a single cooling tower in the South Bronx was connected to 138 illnesses and 16 fatalities [30]. It is interesting to note that the existence of *L. pneumophila* isolates that are closely related to the epidemic strain in a number of environmental samples and from earlier Legionnaires outbreaks raises the possibility that the Bronx population harbors an "endemic" strain of the disease. In 2017, two cooling towers at an amusement park in Orange County, California, were connected to 22 cases of LD among 3 park personnel and 19 guests. This was another well-known *Legionella* outbreak connected to cooling towers [123]. After more research, it was discovered that the park had not cleaned its cooling towers according to the correct protocol, which may have contributed to the elevated *Legionella* levels inside the buildings. Travel on cruise ships and lodgings is also connected to outbreaks of LD. A large cruise line neglected to inform guests in 2015 that *Legionella*

had been found in the ship's water supply, resulting in a breakout among those getting off the ship [124]. The investigation revealed that the deck whirlpool was a likely source of contamination. *Legionella* is a widespread contaminant of man-made water systems, as demonstrated by the current outbreak. LD epidemics can result from the colonization of these organisms in water supplies, particularly in establishments such as hospitals and long-term skilled care facilities that accommodate patients who are highly susceptible to serious illness [125]. Many establishments and facilities have been shuttered for extended periods due to the COVID-19 pandemic. Systems with standing water allow *Legionella* (and other biofilm-forming organisms) to grow more easily. There could be a rise in the number of patients with LD once these facilities reopen [126].

TREATMENT

The presence of *Legionella* species within cells affects the effectiveness of antibiotic treatment. *Legionella* infections respond well to recent respiratory fluoroquinolones (particularly levofloxacin) and macrolides (particularly azithromycin) [127]. Results were comparable between people taking fluoroquinolones and those taking macrolides in investigations involving patients with LD (n = 600) [128]. On the other hand, fluoroquinolones are linked to a significantly quicker decrease in body temperature, fewer side effects, and a lower hospitalization rate.

Due to their quicker onset of fever and shorter hospital stays, fluoroquinolones, such as levofloxacin, are frequently the primary choice for patients with immunosuppression or more severe cases. In mild-to-moderate cases, a dose of 500 mg once daily for 7–14 days has been demonstrated to be beneficial; in severe situations, a dose of 750 mg once daily for 5–10 days has demonstrated good benefits. To avoid relapse, immunosuppressed patients may be given an extended medication period of 21 days [127].

Other medications that have been effectively used include trimethoprim-sulfamethoxazole, tigecycline, doxycycline, and tetracycline [129]. Although imipenem and clindamycin are useful in certain situations, they are not considered conventional treatments [130]. Of 1551 patients with CAP in the experiment, 71 had confirmed *L. pneumophila* infection. More than 90% of mild-to-moderate and severe *L. pneumophila* infections in these patients responded well to levofloxacin 500 mg once daily for 10–14 days or 750 mg once daily for 5 days. It is also effective to use 500 mg azithromycin daily after an initial dose of 1 g daily for a duration of 7–10 days. One common recommendation is a 21-day treatment with levofloxacin (750 mg once daily) for immunosuppressed individuals who are very sick when they first arrive [131].

Ongoing investigation into alternative antibiotics and adjunctive therapies effective against antibiotic-resistant *Legionella* strains is essential. This includes studies assessing the efficacy of existing treatments in different stages of infection and among diverse populations, including immunocompromised individuals. For example, omadacycline, a novel tetracycline antibiotic, showed potential benefits for treating *L. pneumophila*. Furthermore, a previous study by Jasper *et al.* [127], and Kato *et al.* [132] demonstrated the *in vivo* efficacy of combining sivelestat, a leukocyte elastase inhibitor, with pazufloxacin, a fluoroquinolone, for the treatment *of L. pneumophila*. Both fluoroquinolones and macrolides are recommended as first-line treatments for *L. pneumophila*, but there is no clear consensus on which is more effective. Some studies have found no significant difference between the two, while others have shown a trend toward one treatment being slightly better [133, 134].

CONTROL

The management of an environment where *Legionella* is likely to flourish is the primary goal of preventive measures against Legionellosis. Ensuring adherence to national standards and codes of practice is crucial in mitigating the danger of infection and subsequent propagation. The best way to prevent LD is to have a healthy lifestyle, which includes limiting exposure to cigarette smoke, using disinfectants to clean water and air pipes, and other practices [135]. In addition, cleaning humidifiers, hot tubs, shower heads, and faucets as these items may harbor *Legionella* [136]. These methods include maintenance, water quality, building operator training, regulation, and enforcement.

In addition, the air conditioner needs to be maintained and cleaned with chlorine regularly, which should be done at least twice a year [137]. A minimum of 50°C must be reached in the water temperature in the faucet, and 60°C must be maintained in the water heater [138]. Steer clear of situations that could lead to water stagnation.

In healthcare settings, cleaning nebulizer medication chambers and making aerosol solutions for nebulizers and humidifiers should only be done with sterile water for clinical practice and infection control [138]. Only sterile water should be used to flush the nasogastric tube in patients who are immunosuppressed and intubated. The use of sterile water is also targeted for respiratory equipment such as bronchoscopes, heating-cooling units, and continuous positive airway pressure [139]. This is extremely important, especially for immunosuppressed subjects, because it can worsen severe pneumonia [139]. Clinical infection control protocols need to be implemented, including how hospitals can better manage water systems and disinfect medical equipment. Disinfectants and cleaning agents that can be used to control *Legionella* include chlorine, chlorine dioxide, ozone, copper, and silver ionization [136]. Chlorine dioxide is

an oxidizing biocide that can be used in drinking water applications [140]. Other ways to manage *Legionella*-contaminated water systems in hospitals include maintaining water temperatures, removing parts of the water system with no or low flow, installing thermostatic mixing valves, recirculating hot or cold water, ensuring that there is a residual disinfectant, cleaning and maintaining water system components, flushing water lines, and descaling shower heads and hoses [141]. In addition, medical equipment can be managed by regularly cleaning it according to the manufacturer's recommendations [142].

In public facilities and environmental settings, to prevent the growth of *Legionella* bacteria in hotels, cruise ships, and public pools, hot water is maintained at a minimum temperature of 120°F (49°C) and continually recirculated, while cold water is maintained below 77°F–113°F (25°C–45°C); keeping water systems and lines clean and in good condition; flushing water lines such as faucets, showers, and tub spouts regularly, especially when not in use; testing and monitoring spa water quality; and conducting water quality and frequency checks [113]. Cruise ships must adapt public hot tub maintenance and operating protocols for private outdoor hot tubs [143].

Surveillance systems help identify new cases, identify epidemiological relationships among cases, and identify the need for outbreak investigations [144]. The notifiable disease database must be updated within three working days of notification of all probable and confirmed cases of *L. pneumophila*, as well as any clusters or outbreaks caused by other species of *Legionella*. Data reporting includes information such as the number of cases, seasonality, geographic distribution, and demographic characteristics [145]. Law enforcement can take action against *Legionella* violations by ensuring that controls are in place and functioning to prevent *Legionella* growth and issuing a Notification of Contravention detailing the law on what needs to be done to stop the violation [110]. Increase awareness among healthcare workers and the public about the risk factors of LD, particularly in those with weakened immune systems. Strengthen water disinfection protocols and promote better maintenance practices in systems such as cooling towers, plumbing, and hot tubs to minimize *Legionella* proliferation.

FUTURE PROSPECTS

The urgent problem in *Legionella*-related diseases is the difficulty of eradicating them in reservoirs due to their ability to "hide" under other protozoa organisms. In such cases, antibiotics and standard disinfection are not sufficient to prevent *Legionella* infection [146]. Moreover, biofilm formation and the potential spread of viable but non-culturable bacteria are also found in recurrent cases of *Legionella* [147]. Thus, an understanding of the mechanism is necessary for formulating chemical or mechanical eradication strategies that target this environmental phase of the bacteria.

Another important aspect that requires further investigation is the role of genetic variability in *Legionella* virulence and antibiotic resistance. Although this aspect has been widely studied in other bacteria, information on *Legionella* is limited. For example, mutations in the *23S ribosomal ribonucleic acid* gene and ribosomal proteins L4 and L22 contribute to macrolide resistance [148]. More investigation is necessary to tailor treatment options.

Promote public health guidelines on managing water systems in hotels, hospitals, and other public spaces, focusing on conditions that favor *Legionella* growth, such as stagnant water and warm temperatures. Investigate the role of biofilms in *Legionella* colonization of water systems and develop strategies to prevent or eliminate biofilm formation. These suggestions are geared toward advancing prevention, diagnosis, and treatment, as well as improving public health awareness and water management practices to control LD.

CONCLUSION

LD, driven by *L. pneumophila*, represents a persistent and evolving threat to public health, characterized by its rising global incidence, severe clinical manifestations, and significant mortality, particularly among vulnerable populations. This review has elucidated the multifaceted aspects of LD, including its etiology, pathogenesis, epidemiology, clinical presentation, diagnostic challenges, therapeutic strategies, and preventive measures. The strength of this study lies in its comprehensive approach, integrating historical perspectives, current clinical practices, and emerging research to provide a holistic understanding of LD and its implications for healthcare systems and public health policies.

However, certain limitations must be acknowledged. The review predominantly relies on published literature and existing clinical guidelines, which may not fully capture regional variations in disease prevalence, diagnostic capabilities, or healthcare infrastructure. In addition, while this study highlights novel therapeutic and preventive approaches, the rapidly evolving nature of bacterial resistance and environmental adaptation of *Legionella* species necessitates ongoing research and validation of these strategies in diverse settings.

Future research should focus on advancing rapid and specific diagnostic techniques, exploring novel antimicrobial agents and treatment modalities, and enhancing the understanding of *Legionella* biofilm formation and persistence in water systems. In addition, public health initiatives must prioritize the development and implementation of robust water management protocols, particularly in high-risk environments such as healthcare facilities, hotels, and large public

infrastructures. Addressing these challenges through interdisciplinary collaboration and innovative research will be critical to reducing the burden of LD and improving public health outcomes globally.

AUTHORS' CONTRIBUTIONS

ARK, BWKW, and NLPID: Drafted the manuscript. IBM, KAF, and DN: Revised and edited the manuscript. HN and DAAK: Drafted and revised the manuscript. MKJK, IF, and SW: Edited the references. All authors read and approved the final version of the manuscript.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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