Infection and Drug Resistance

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REVIEW

Legionellosis: Global Epidemiology and Current Perspectives on Diagnosis and Treatment

Jianwen Ma[1,*], Tingyan Dong[2,*], Fei Li[3], Chunmei He[4], Biyun Li[4], Zhenyu Liu[5]

[1]Department of Respiratory and Critical Care Medicine, Linxia Hui Autonomous Prefecture People's Hospital, Linxia, Gansu, People's Republic of China; [2]Guangzhou College of Commerce Research Center for Healthy Aging and Social Economic Development, Guangzhou, Guangdong, People's Republic of China; [3]Department of Pharmacy, The Second People's Hospital of Futian District, Shenzhen, Guangdong, People's Republic of China; [4]Department of Respiratory and Critical Care Medicine, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, People's Republic of China; [5]Department of Pharmacy, Shenzhen Nanshan People's Hospital, Shenzhen, Guangdong, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhenyu Liu, Department of Pharmacy, Shenzhen Nanshan People's Hospital, Shenzhen, Guangdong, People's Republic of China, Email 234899343@qq.com; Biyun Li, Department of Respiratory and Critical Care Medicine, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, People's Republic of China, Email 18811779689@163.com

Abstract: The genus *Legionella*, first identified in 1977, comprises environmental Gram-negative intracellular bacteria that cause *Legionellosis*. Ubiquitous in freshwater and artificial water systems, *Legionella* species have an unclear global incidence, with reported cases likely significantly underestimated. Travel-associated Legionnaires' disease (TALD) has increased recently and become a surveillance priority. For diagnosis, culture remains the gold standard but is time-consuming. Urinary antigen testing enables rapid screening, yet is mainly restricted to *L. pneumophila* serogroup 1. Molecular diagnostics, particularly PCR, offer high sensitivity and detect multiple serogroups, facilitating early diagnosis. Therapeutically, macrolides and fluoroquinolones constitute the mainstay of treatment, though evidence supporting combination therapy remains limited. Increasing reports of antimicrobial resistance underscore the need for strengthened antibiotic stewardship and global surveillance. Future efforts should prioritize large-scale epidemiological studies, diagnostic standardization, treatment optimization, and resistance monitoring to reduce disease burden.

Keywords: *Legionella*, *Legionellosis*, epidemiology, resistance, treatment

Introduction

Legionella, a Gram-negative intracellular parasite, exists in freshwater habitats. It was initially isolated and characterized as a "rickettsia-like" microorganism in 1947. However, it was not until 1977 that it was recognized as the causative pathogen, and the same serogroup, responsible for a serious pneumonia outbreak that occurred in Philadelphia, USA, in 1976.[1,2] This outbreak resulted in a total of 182 cases and 29 fatalities (a case fatality rate of 16%).[3] *Legionellosis*, an acute human illness primarily caused by *L. pneumophila*, presents in two distinct clinical forms: Legionnaires' disease (a severe, pneumonia-associated systemic illness) and Pontiac fever (a milder, self-limiting, non-pneumonic febrile illness). Legionnaires' disease is characterized by high fever, cough, dyspnea, and radiographic evidence of pneumonia; it may progress rapidly to respiratory failure and multiorgan dysfunction. With appropriate antimicrobial therapy, the case fatality rate ranges from 10% to 15%.[4] Pontiac fever resembles influenza-like illness and is characterized primarily by fever, myalgia, and headache. Pontiac fever is a nonlethal and self-limiting condition.[5] To date, 58 species and 3 subspecies within the genus *Legionella* have been identified. Among them, *L. pneumophila* serotype 1 is the predominant pathogen responsible for *Legionellosis*, accounting for over 80% of reported cases.[6] Since the 1976 outbreak in Philadelphia, an increasing number of *Legionella* infection cases associated with communities, healthcare facilities, and travel have been reported worldwide.[7] According to the 2021 Global Burden of Disease (GBD) study, the global age-standardized DALY rate and mortality ratefor *Legionella* infections were 24.74 and 0.86 per 100,000 population, respectively; among adults aged 70 years and older, these rates exceeded 100 and 8 per 100,000, confirming

https://doi.org/10.2147/IDR.S603565
Received: 14 February 2026
Accepted: 1 April 2026
Published: 9 April 2026

a disproportionately high disease burden in the elderly.[8] Meanwhile, antimicrobial resistance has been detected in environmental *Legionella* isolated from China and other countries. Given that Legionnaires' disease frequently progresses to severe pneumonia, delayed or inadequate treatment poses a life-threatening risk, particularly among immunocompromised individuals.[9] This paper presents a narrative review of current literature on *Legionellosis*. In light of its evolving epidemiology and the emerging threat of antimicrobial resistance, we integrate recent findings on disease burden, diagnostic challenges, and resistance mechanisms to inform clinical practice, guide public health interventions, and identify priorities for future research.

Microbiology and Pathogenicity

Legionella is an environmental pathogen. It is a small, Gram-negative, aerobic bacillus that does not form spores or capsules.[10] *Legionella* proliferates in freshwater environments within a temperature range of 25 to 45 °C, with an optimal growth temperature of approximately 37 °C. When the temperature exceeds 42 °C, colony counts of all strains decline.[11] *L. pneumophila*, an aquatic bacterium, primarily replicates within protozoa (amoebae). Cysteine auxotrophy is a key phenotypic characteristics of *Legionella pneumophila*.[12,13] Additionally, *L. pneumophila* adheres to biotic and abiotic surfaces and forms structured, matrix-enclosed microbial communities known as biofilms, which enhance its environmental persistence.[14] Accumulating evidence indicates that biofilms formation is strongly associated with *Legionella* transmission and outbreak occurrence. Biofilms augment bacterial virulence and impair host immune defenses through multiple mechanisms.[15–17]

Legionella infections are primarily transmitted via inhalation of aerosols contaminated with the bacteria; person-to-person transmission has not been convincingly documented.[18,19] The pathogenesis of *Legionellosis* begins with bacterial attachment to host phagocytic cells, particularly alveolar macrophages, and subsequent intracellular replication. Upon entering the human respiratory tract, *Legionella* activates key virulence mechanisms: it establishes a specialized replicative niche known as the Legionella-containing vacuoles (LCV) and expresses genes encoding the type IV secretion system (T4SS), thereby evading lysosomal fusion and degradation, which facilitates persistent intracellular infection.[20]

Among *Legionella* species, *L. pneumophila* is the predominant cause of human infection, accounting for 80–90% of reported cases globally, mainly serogroup 1 (Sg 1). Notably, *Legionella longbeachae* accounts for approximately 1% of global cases; however, in Australia and New Zealand, it causes 50–60% of locally acquired infections. An increasing number of *Legionella longbeachae* infections have also been reported in Europe.[21,22] Due to their relative rarity and the lack of diagnostic reagents, other subtypes such as *L. pneumophila* Sg 3 and Sg 6, *L. bozemanii*, and *L. micdadei* may cause disease but are rarely reported.[23,24]

Clinical Manifestations

Legionnaires' disease (LD) is an atypical pneumonia with an incubation period of 2–10 days.[25] Clinical manifestations depend on inhaled bacterial load, virulence factors, and host immune status.[26] Clinically, it is difficult to distinguish pneumonia caused by *Legionella* from that caused by common respiratory pathogens. Mild cases may only present with cough, whereas severe cases can progress rapidly to life-threatening pneumonia.[27] Pulmonary manifestations of *Legionellosis* are nonspecific and often subtle in the early disease phase. Common symptoms include fever > 38.8°C (67–100%), cough (41–92%), dyspnea (36–56%), and radiographic findings such as pulmonary consolidation or pleural effusion.[28–31] Some immunosuppressed patients (such as organ transplant or SLE patients) may develop lung abscesses and empyema.[32]

Extrapulmonary manifestations of *Legionellosis* carry clinical and diagnostic importance. Gastrointestinal symptoms, including watery diarrhea (with or without abdominal pain), may present as isolated features of the disease.[33] Among central nervous system manifestations, experience headache accompanied by confusion is the most common presentation in patients with *L. pneumonia* infection.[34] The typical cardiac manifestation is pulse-temperature dissociation (such as relative bradycardia, Faget sign), which is uncommon in typical bacterial pneumonias.[35] *Legionella* has been implicated in culture-negative endocarditis; however, this remains a rare complication.[36] Myalgia frequently accompanies fever and chills but is typically mild. Severe myalgia should raise suspicion for influenza-related diagnosis.[37] Additionally, nonspecific laboratory abnormalities can be helpful, such as hyponatremia, mildly elevated liver enzyme levels, unexplained

microscopic hematuria, and abnormally elevated serum creatinine.[38,39] Beekman et al validated a *Legionella* prediction scoring system based on six items admission criteria, which aids in the early identification of *Legionella* pneumonia in clinical practice.[40]

Pontiac fever is a nonfatal, self-limiting, influenza-like illness associated with exposure to *Legionella*. The first outbreak caused by *Legionella* was reported in Pontiac, Michigan, in 1968, affecting at least 144 individuals. Its incubation period is 24–48 hours, and symptoms typically resolve within 2–5 days; the illness is characterized primarily by fever, myalgia, and headache. Antibiotic treatment is generally unnecessary.[41,42]

Epidemiology

Legionella strains capable of causing human infection are widely distributed in natural water sources and anthropogenic environments. However, the global incidence of *Legionellosis* remains poorly characterized. Due to the large differences in disease recognition, diagnostic capacity, and surveillance infrastructure, reported case counts are subject to significant underascertainment. Consequently, epidemiological interpretations of *Legionellosis* incidence data require cautious interpretation.[43]

Globally, the reported incidence of Legionnaires' disease continues to rise in countries with robust surveillance systems (Table 1). In the United States, the age-standardized average incidence increased from 0.48 cases per 100,000 population during 1992–2002 to 2.71 cases per 100,000 in 2018.[44] In Canada, 1401 cases of *Legionellosis* were reported between 1978 and 2006, corresponding to a crude average incidence rate of 0.41 cases per 100,000 person-years.[45] In all EU and European Economic Area countries, *Legionellosis* is a notifiable disease. The European Centre for Disease Prevention and Control (ECDC) established the European *Legionellosis* Surveillance Network (ELDSNet) in 2010. Reported *Legionellosis* incidence across Europe ranges from 0.1 to 30 cases per million population, reflecting substantial intercountry variation.[46] Most reported data on *Legionella* infections in Europe originate from Western European countries. France, Germany, Italy, and Spain collectively account for 70% of notified cases, despite representing only 50% of the total EU population. Spain ranks among the European countries with the highest reported incidence of *Legionellosis*. A study analyzing 13,472 samples from 465 hospitals in Spain reported a *Legionella* detection rate was 65.4%.[47] Notably, following the French government's 1987 mandate requiring case notification, reported *Legionellosis* cases rose steadily, peaking in 2005 at 2.5 cases per 100,000 residents, which is twice the average incidence in Europe. Subsequently, France implemented comprehensive source-control measures, leading to a decline in incidence to 2.0 cases per 100,000 residents by 2008.[48,49] The Netherlands launched the National *Legionella* Outbreak Detection Project (NLODP) in 2002. Between 2002 and 2012, 1991 confirmed legionellosis cases were reported, and 1484 trace back

Table 1 Global Epidemiological Characteristics of Legionnaires' Disease

Country/Region	Incidence (per 100000 Population)	Main Types of Pathogens	Serotype
America	2.71	*L. pneumophila*	Sg1, ST1, ST367, ST461
Canada	0.41	*L. pneumophila*	Sg1, ST2858, ST378
Spain	Positive rate: 65.40%	*L. pneumophila*	ST1, ST578, ST23
France	2.0	*L. pneumophila*	Sg1, clinical: 95.4% environment: 28.2%
Italy	Positive rate: 19.80%	*L. pneumophila*	Clinical Sg2–15 74%, ST23 is most common
Germany	Positive rate: 20.07%	*L. pneumophila*	Sg1, ST62
Australia	2.1	*L. longbeachae*	Unknown
New Zealand	2.7	*L. longbeachae*	Unknown
Japan	0.2–0.7	*L. pneumophila*	ST23, ST120, ST138
South Korea	0.74	*L. pneumophila*	Sg1-15
Singapore	0.28	*L. pneumophila*	Unknown
Thailand	Unknown	*L. pneumophila*	Urban: *L. pneumophila* Sg1 2–5% Rural: *L. longbeachae*
China	Unknown	*L. longbeachae*	Sg1, ST1, ST15, ST461
Hong Kong	0.9	*L. longbeachae*	Unknown

https://doi.org/10.2147/IDR.S603565

investigations were conducted, yielding a positive rate of 24.7%.[50] In addition, the United Kingdom, Portugal, Switzerland, Norway, Greece, etc. have all reported cases of *Legionella* infection.[51–55] *Legionellosis* incidence in Australia (2.1 per 100,000) exceeds the national average (1.5 per 100,000);[56] New Zealand reports an annual incidence of 2.7 per 100,000.[57] In Asia, the incidence rates in Japan, South Korea and Singapore are 0.2–0.7, 0.74, 0.28 cases per 100,000 people, respectively.[58–60] In 1982, the first domestically acquired case of *Legionella* infection in China was discovered in Nanjing. Subsequently, numerous *Legionella* infection-related cases were reported, mostly sporadic.[61] Since there is no mandatory requirement to report *Legionella* infection cases in China, data on *Legionella* infection remain limited. In Hong Kong, China, *Legionellosis* has been a notifiable infectious disease since 1994. The incidence of *Legionella* is 0.9 cases per 100,000 people, showing an upward trend year by year.[62]

The composition of the susceptible population for *Legionellosis* is evolving along with changes in the global population structure. High-risk factors for Legionnaires infection include men over 50 years old, smokers, and individuals with underlying diseases such as diabetes, cancer, or immunosuppression; however, anyone can develop *Legionellosis*.[63–65] With the accelerated global aging process and the increasing number of immunocompromised individuals, the size of the susceptible population for *Legionellosis* continues to expand, presenting new challenges for disease prevention and control. In addition, *Legionellosis* shows a seasonal pattern, with summer and early autumn being the most common times of year for infection. Research has shown that warm and humid climates are associated with an increased incidence of *Legionellosis*.[66,67] This feature suggests that global climate change may further affect the spatiotemporal distribution of this disease.

Legionellosis develops as sporadic cases or as outbreaks. According to the sources of infection, *legionellosis* is usually classified into community-acquired (CALD), travel-associated (TALD), or healthcare-associated (HALD). In recent years, the number of TALD cases, and ship-associated events, occur repeatedly, making them a key focus of monitoring.[68] Hotel-associated cases are typically associated with hotel cooling towers and/or potable water systems, while ship-related cases are most frequently linked to hot tubs.[69] Consistent with European data, most *L. pneumophila* strains isolated from German patients belong to clones that have emerged worldwide.[70] In Singapore, the proportion of imported cases has increased from 6.2% to 27.3%, usually associated with overnight stays in public places.[60] Differences exist in the distribution of infection sources across countries. In Japan, Public baths are the main source of infection.[71] Australia and New Zealand have reported an increase in Long Beach *Legionella* infections associated with potted plants and compost.[72]

Globally, *L. pneumophila* is the primary pathogen, with regional variations in serotypes and genotypes. In Valencia, Spain, ST1, ST578, and ST23 were the most prevalent sequence types among 1088 samples.[73] In France, *L. pneumophila* serogroup 1 accounts for 95.4% of clinical isolates but only 28.2% of environmental isolates. The most common non-*L. pneumophila* species, *L. anisa*, is more prevalent in the environment (13.8%) than in clinical samples (0.8%).[74] A 2002–2017 study in northeastern Italy tested 18,104 water samples and reported a 19.8% *Legionella* positivity rate; 50.8% of 63 medical institutions yielded positive results. *L. pneumophila* Sg 2–15 dominated hospitals (>74%), whereas Sg 1 predominated in swimming pools (82%). ST23 was the most common genotype in Italy.[75,76] Among 76,200 warm-water samples from 24 southern German regions, 15,300 (20.07%) were *Legionella*-positive. *L. pneumophila* constituted 84% of isolates, with marked regional variations.[77] Furthermore, the disease burden caused by *Legionella longbeachae* is particularly prominent in countries in the Southern Hemisphere.[72] *L. longbeachae* is prominent: 59% in Australia,[78] 51.0% in New Zealand,[57] exceeding *L. pneumophila* and showing marked regional difference, suggesting significant differences in the composition of pathogen spectra across regions. In Japan, *L. pneumophila* is predominant, with common sequence types including ST23, ST120 and ST138.[71] In South Korea, *L. pneumophila* is predominant, accounting for 85%.[59] In Thailand, *L. pneumophila* serogroup 1 accounts for 2–5% of urban cases. By contrast, it is rare in rural areas, where *Legionella longbeachae* is more common.[79] In China, a study detected *Legionella* in 22.43% (129/575) of water samples and 9.28% (41/442) of soil samples, with *L. pneumophila* accounting for 75%.[80]

The global epidemiology of *Legionellosis* shows significant regional heterogeneity, and its true disease burden is shaped by the interplay of multiple factors, including surveillance systems, diagnostic capacity, demographic structure, climatic conditions, and pathogen distribution. While current data reflect the epidemiological trends in some regions, their comparability and completeness at a global level still require systematic improvement. Despite revealing the

epidemiological characteristics of certain areas, existing data face substantial challenges in global comparability and completeness, highlighting an urgent need for further integration and optimization.

Diagnosis

The diagnosis of *Legionellosis* is based on a combination of clinical and radiological features as well as laboratory tests. Currently, the detection methods for *Legionella* include serology and antibody testing, bacterial culture, urinary antigen testing, and nucleic acid amplification testing.[81,82] Every method has its own merits and drawbacks (Table 2).

Serological testing for *Legionella* infection is a valuable epidemiological tool. A variety of serological detection techniques, such as indirect immunofluorescence assay (IFA), enzyme immunoassay (EIA), and microagglutination testing, are used to detect *Legionella* pathogens, with a sensitivity of 78% −90%.[83–85] Since the antibodies identified in serological diagnosis are usually a mixture of immunoglobulin A (IgA), M (IgM), and G (IgG), testing for all three antibody classes is recommended to maximize sensitivity.[86] Specific IgM antibodies are unreliable biomarkers for acute infection. Because IgM antibodies may persist for a long time and seroconversion often take several weeks, this delayed kinetics represents the main limitation of serological testing. In most cases, a four-fold increase in antibody titer is observed within 3–4 weeks.[87] Obtaining samples too early can lead to false-negative results. In practice, clinicians are encouraged to simultaneously test serum samples during the acute phase and 3 weeks after the onset of the disease.[88] Data suggest that even the best commercial assays have a positive predictive value of only about 50%, especially in regions where *L. pneumophila* serogroup 1 infections are less common.[89,90]

Detecting soluble *Legionella* antigen in urine samples is a rapid method for diagnosing early *Legionella* infections and is also a useful tool for investigating *Legionellosis* outbreaks. This method was first reported shortly after the 1976 epidemic but was not widely accepted as a routine diagnostic method or incorporated into the international case definition for confirmed cases until the mid-1990s.[91] It detects the lipopolysaccharide component of the cell wall of *L. pneumophila*. Antigen is typically detectable in urine within a few days of disease onset and persists for several days to weeks. Currently, urinary antigen testing accounts for 70–80% of diagnosed cases in Europe and the United States, with a sensitivity of up to 80%-90%. However, This method may miss up to 40% of cases caused by non-serogroup 1 *L. pneumophila*.[92,93] Japan's Ribotest Legionella (2019) enables broader detection and may improve early diagnosis and prognosis for non-serogroup 1 infections, though its efficacy requires further validation. Notably, prolonged antigen excretion in immunocompromised or critically ill patients can yield false-positive results, whereas

Table 2 *Legionella* Diagnostic Methods and Limitations

Method	Principle/Target	Advantage	Limitation
Serological testing	Detection of antibodies (IgA, IgM, IgG)	Retrospective study. epidemiological studies. sensitivity 78%–90%. Simple operation. Easy access to samples. Non-invasive.	not reliable for acute infection. Serum transformation takes 3–4weeks. low positive predictive value (~50%). in areas where non-serogroup 1 infections are common.
Urinary antigen test (UAT)	Detectslipopolysaccharide of *L. pneumophila* serogroup 1 in urine	Rapid. sensitivity 80%–90%. Non-invasive.	Only detect serotype 1. false positives and false negatives. Negative result cannot rule out infection.
Culture	Isolationof *Legionella* from clinical specimens on selective media	Gold standard. strain identification and antimicrobial susceptibility testing.	Requires experienced laboratories. Difficult to get qualified respiratory specimens. slow (3–5 days). low cost-effectiveness.
PCR/mNGS	PCR: nucleic acid amplification. mNGS: metagenomic sequencing	PCR: High specificity (95–100%); rapid. detects all species and serogroups. mNGS: useful for mixed infections and immune- compromised patients	PCR cannot assess bacterial viability; less effective for non-respiratory samples. mNGS expensive, lacks standardized interpretation, not yet routine

https://doi.org/10.2147/IDR.S603565

approximately 8% of patients may test false negative due to absence of urinary antigen excretion. A negative result does not exclude *Legionella* infection, and repeat testing is recommended when clinically indicated.[84,94,95]

The cultivation and isolation of *Legionella* from clinical specimens remains the gold standard for diagnosis.[96] Studies have shown that *Legionella* can be isolated from 66% of cases. If samples are collected within 2 days of admission, *Legionella* can be isolated from 80% of cases.[97] However, many factors limit the sensitivity of culture. First, experienced laboratories are required for the isolation and cultivation of *Legionella*. A survey by the College of American Pathologists showed that up to two-thirds of microbiology laboratories in the United States are unable to cultivate pure *L. pneumophila* isolates. Similarly, in China, the number of such laboratories is extremely limited.[98] Second, the use of selective agar and sample pretreatment (heat or acid) is not straightforward. Given the relatively low prevalence of *Legionellosis*, these methods lack sufficient cost-effectiveness, and culture requires 3–5 days.[99] In addition, to improve the specificity of pneumonia diagnosis caused by pyogenic bacteria, laboratories usually reject sputum specimens containing squamous epithelial cells or few polymorphonuclear leukocytes. Some patients with *Legionellosis* produce little sputum or non-purulent sputum, and it is crucial to culture such specimens immediately.[100,101]

Polymerase chain reaction (PCR) is a molecular method capable of detecting all known *Legionella* infections. It is characterized by high specificity, sensitivity, and rapid turnaround time. The application of PCR overcomes limitations related to pathogen viability and species identification, with a specificity of 95%-100%. However, PCR is not ideal for detecting non-respiratory samples such as urine and serum. In addition, this method makes it difficult to evaluate the activity of pathogenic bacteria (after exposure to antibiotics).[102,103] Moreover, metagenomic next-generation sequencing (mNGS), as a revolutionary technology, is applicable to critically ill patients with rapidly progressive *Legionella* infections and concomitant infections, especially providing clinical guidance for the management of immunosuppressed patients. However, due to its high cost and the lack of a standardized interpretation standard, mNGS has not yet been adopted as a routine clinical diagnostic tool.[104]

Advances in detection technology have improved *Legionella* diagnostics. Novel biomarkers such as ribosomal proteins L7/L12 and interleukin-17A (IL-17A) show strong diagnostic potential.[105] CRISPR-Cas-based detection enables strip-based readout within 30 minutes with single-copy sensitivity, making it highly suitable for emergency and primary care settings.[106] Loop-mediated isothermal amplification (LAMP) offers excellent sensitivity and holds promising potential for portable applications.[107] Targeted next-generation sequencing (tNGS) combines high sensitivity, high throughput, and low cost and may further enhance diagnostic accuracy through integration with dynamic primers.[108]

Antibacterial Treatment

The high mortality rate of *Legionellosis* without timely treatment underscores the clinical priority principle: early diagnosis and prompt, effective antibiotic therapy, along with management of complications such as respiratory failure, hepatic and renal dysfunction, and neurological involvement.[109] *Legionella* is an intracellular pathogen residing in tissues and alveolar macrophages, which means that anti-*Legionella* drugs should accumulate and be biologically active within cells.[110] The IDSA/ATS guidelines recommend that, when treating bacterial community-acquired pneumonia, antibiotics covering atypical pathogens should be considered. For *Legionella*, macrolides (such as azithromycin, clarithromycin) and quinolones (such as levofloxacin, moxifloxacin) are recommended as first-line treatments, and other drugs such as doxycycline, rifampicin, and compound sulfamethoxazole.[111,112] New-generation antibiotics —including sitafloxacin (a novel fluoroquinolone), omadacycline (a new-generation tetracycline), and lefamulin (a pleuromutilin)—exhibit potent antibacterial activity and broaden the available therapeutic options[113] (Table 3).

However, there are no prospective randomized trials comparing the clinical outcomes of patients after treatment with levofloxacin and azithromycin.[114] A meta-analysis compared the efficacy of fluoroquinolones and macrolides as monotherapy for *L. pneumonia*. A total of 21 studies involving 3,525 patients were included. No significant differences were observed between the two groups in clinical cure rate, time to defervescence, length of hospital stay, and recovery from complications. Moreover, no significant difference in mortality reduction was found between patients treated with fluoroquinolones and macrolides (6.9% vs 7.4%; pooled OR = 0.94, 95% CI: 0.71–1.25; P = 0.66). Owing to patient heterogeneity, subgroup analyses stratified by patient population, disease severity, and ICU admission status could not be performed.[115] Kato et al's meta-analysis compared the effectiveness and safety of the two treatments. The results showed

Table 3 Stratified Severity-Based Treatment for Legionnaires' Disease

Disease Severity	First-Line Therapy	Duration	Combination Therapy	Special Considerations
Mild to moderate pneumonia	Macrolide or Quinolones	5–7 days	Not routinely recommended	Monotherapy is standard.
Severe pneumonia	Macrolide or Quinolones	10–14 days	Combination therapy may be considered: Macrolide +Quinolones	Preferred regimen: Quinolones are recommended without contraindications. Combination therapy is indicated for refractory severe pneumonia, especialy in comorbid or immunecompromised patients.
Immunocompromised hosts (organ transplant, chemotherapy)	Quinolones or macrolides	21 days	Based on severity	Immunocompromised patients require prolonged, aggressive therapy to reduce relapse and poor outcomes.

that the cure rates of the two groups were comparable, but the overall and 30-day mortality rates of macrolides were higher than those of fluoroquinolones. Compared with macrolides, fluoroquinolones significantly shortened hospital stay in patients with *Legionella pneumonia*.[116] In addition, when a meta-analysis subgroup pooled data on severe *Legionella pneumonia*, it was found that mortality was significantly lower among patients treated with fluoroquinolones alone than among those treated with macrolides (72.8% vs 30.8%, p = 0.027), whereas length of hospital stay and complication rates were comparable.[117] Currently, the included studies are mainly observational and lack randomized controlled trials; moreover, clinical cure is not among the reported outcomes. This suggests that the available evidence cannot robustly determine whether fluoroquinolones are superior to macrolides, and meaningful comparisons are limited to mortality outcomes. Therefore, in the absence of contraindications, fluoroquinolones may be a preferred choice for reducing mortality, particularly in critically ill patients.[118]

The evidence supporting the benefits of combination therapy for *Legionella* infection is limited. Monotherapy with azithromycin or fluoroquinolones remains the standard treatment for patients with *Legionella* infection[119] Chahin et al recommend combination therapy with fluoroquinolones and azithromycin in patients with severe pneumonia, especially those with significant comorbidities and immunocompromised hosts who have failed conventional treatment.[120] It should be noted that combination therapy increases the risk of adverse reactions, such as Q-T interval prolongation.[121,122] For confirmed cases of moderate to severe *Legionella pneumonia*, treatment with levofloxacin or azithromycin for 7 to 10 days is recommended. For immunocompromised patients, the treatment course should be extended to 21 days.[123,124]

Antimicrobial resistance in *Legionella* represents an emerging yet underappreciated threat to clinical management and public health. Although traditionally considered uniformly susceptible to macrolides and fluoroquinolones, evidence from environmental surveillance and clinical isolates reveals a more complex resistance landscape.[125] In China, Jia et al found that among 149 *L. pneumophila* serogroup 1 strains, 25 environmental isolates were resistant to azithromycin, yielding a resistance rate of 16.78% (25/149). Upregulation of the efflux pump lpeAB gene was associated with reduced azithromycin susceptibility in these 25 strains.[126] The resistance-nodulation-division family (RND family) efflux pump LpeAB, the most well-studied resistance determinant in *L. pneumophila*, actively extrudes azithromycin, leading to a 2–4-fold MIC increase, and has been widely investigated in environmental isolates.[127] Polish researchers isolated a non-serogroup 1 *L. pneumophila* strain resistant to azithromycin from the water supply system of a sanatorium; it also showed reduced sensitivity to ciprofloxacin and rifampicin.[128] Minetti et al studied 107 *L. pneumophila* serogroup 1 strains from clinical and related environmental sources in Portugal. Among them, 12 isolates had an azithromycin minimum inhibitory concentration (MIC) exceeding the provisional highest wild-type (WT) MIC by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Nine of these isolates exhibited negative lpeAB expression, implying the existence of other uncharacterized mechanisms underlying drug resistance. Some isolates showed a reduced sensitivity to fluoroquinolones, including 4 isolates with MIC values above the breakpoints of all tested antibiotics; however, sequencing of the gyrA and parC gene revealed no mutations in the quinolone resistance-

determining regions.[129] Environmental *Legionella* exhibit diverse resistance mechanisms. Although LpeAB-mediated low-level resistance is common, it does not explain elevated MICs in clinical strains, implying unknown links in resistance evolution from environment to clinical settings. Water environment may be an important reservoir of drug resistance genes of *Legionella*, posing a potential public health risk. Monitoring antimicrobial resistance in environmental isolates has significant predictive value for forecasting clinical risks. Meanwhile, pathogens can develop resistance during clinical treatment, and antibiotic exposure can accelerate the emergence of resistance. In 2014, Bruin et al first isolated ciprofloxacin-resistant *L. pneumophila* from clinical specimens. The resistance mechanism may be related to a mutation in the gyrA gene (amino acid position 83). Although no fluoroquinolone (FQ) resistance breakpoint has yet been established for *Legionella*, this isolate was regarded as FQ-resistant due to the poor clinical response to antibiotic therapy and prolonged hospital stay.[130] Shadoud et al used next-generation sequencing to monitor the proportion of gyrA(83) mutant strains in two Legionnaires' disease patients treated with fluoroquinolones. The mutant proportion increased markedly from 1.05% at baseline to 94% post-treatment. Fluoroquinolone resistance in *Legionella* is primarily mediated by mutations in the quinolone resistance-determining regions (QRDR) of gyrA/gyrB (DNA gyrase) and parC/parE (topoisomerase IV). The gyrA T83I mutation (248C→T) is the most clinically relevant, conferring an 8-fold increase in ciprofloxacin MIC.[131] This suggests that extremely low-frequency resistant mutants preexist in wild-type populations, which rapidly expand to become dominant under antibiotic selection pressure, ultimately resulting in treatment failure. We reported 3 patients with confirmed severe *L. pneumophila* pneumonia who did not respond to initial treatment with moxifloxacin. We attempted to culture *L. pneumophila* from the patients to evaluate its resistance to conventional antibiotics such as moxifloxacin, but this was unsuccessful due to their critical condition and laboratory limitations. We speculated that the occurrence of bacterial resistance may be related to the repeated moxifloxacin use in patients with recurrent infections or with subtherapeutic moxifloxacin concentrations resulting from renal insufficiency and hypoalbuminemia.[132] Conventional susceptibility testing relies on culture, which is often unavailable due to clinical or laboratory constraints, leading to underdiagnosed resistance. An integrated environment–clinical network is thus needed to clarify resistance gene transmission, guiding regional empirical therapy, delaying resistance, and improving outcomes.

Conclusions and Outlook

Over the past 50 years, substantial progress has been made in understanding *Legionella* biology and *Legionellosis*; however, critical knowledge gaps remain. Future priorities include epidemiological studies to better define disease burden across populations, standardized diagnostics capable of detecting non-*L. pneumophila* species, and the use of lung microbiota sequencing to inform novel prevention and control strategies. Optimal treatment regimens remain uncertain, with insufficient evidence to guide monotherapy versus combination therapy. However, conducting such trials is challenging due to limitations including clinical operations and inadequate sample size. There is an urgent need to establish an integrated environment–clinical network to monitor resistant *Legionella* strains and their role in therapeutic failure, with direct implications for antimicrobial stewardship and resistance monitoring. Addressing these priorities will be essential to advancing both clinical management and public health strategies for *Legionellosis*.

Data Sharing Statement

The manuscript includes all data generated during this study.

Disclosure

The authors declare no competing interests in this work.

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