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Mycoplasma pneumoniae Infection: Epidemiological Characteristics, Current Status of Antimicrobial Resistance and Genotyping Research Progress

Dafei Liang[1*], Wei Fu[2*], Mei Ye[1], Yuhua Wan[1], Yuwen Guo[1], Hong Chen[1], Jida Li[2#]

[1]Zunyi Maternal and Child Health Hospital, Zunyi, China
[2]Institute of Zoonosis, College of Public Health, Zunyi Medical University, Zunyi, China
Email: [#l]ijida198485@163.com, 904689923@qq.com, 19185612525@163.com, 706975141@qq.com, 298283503@qq.com, 642095065@qq.com, 292646401@qq.com

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Abstract

Mycoplasma pneumoniae is a primary pathogen causing respiratory infections in children and adults. Compared to adults, children have an immature immune system, making them the core population susceptible to *Mycoplasma pneumoniae* infection. Clinical manifestations are primarily characterized by cough and fever; severe cases may progress to respiratory distress, pulmonary embolism, bronchiolitis obliterans, and myocarditis, leading to serious adverse outcomes with significant variation in disease severity. In recent years, research into *Mycoplasma pneumoniae* infection has achieved several breakthroughs: the iterative upgrading of novel detection technologies and molecular typing systems has further deepened our epidemiological understanding, while the publication of whole-genome sequences for a large number of strains has provided crucial evidence for elucidating pathogenic mechanisms. The widespread prevalence of acquired resistance to macrolide antibiotics has further complicated clinical management and prognosis. Currently, *in vitro* antimicrobial susceptibility testing methods have been standardized, and tetracyclines and quinolones are effective alternatives for resistant strains. This review systematically summarizes key advances in *M. pneumoniae* research, focusing on three main areas: epidemiological characteristics, the current status of antibiotic resistance, and genotyping. It integrates multicenter clinical data and molecular biology research findings from both domestic and international sources to provide a theoretical reference for precision clinical diagnosis and treatment, epidemic prevention and control, and scientific research.

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*They are contributed equally to this article.
#Corresponding author.

Keywords

Mycoplasma pneumoniae, Macrolide Resistance, Epidemiology, Genotyping, Pediatric Respiratory Infections

1. Introduction

Mycoplasma pneumoniae is one of the three major bacterial pathogens responsible for acute respiratory infections (ARI), accounting for 18.6% of cases [1], and is also a primary causative agent of community-acquired pneumonia (CAP) [2]. Children are at a critical stage of growth and development, with immature immune systems, making them significantly more susceptible to *Mycoplasma pneumoniae* than adults. Typical symptoms following infection include persistent cough, fever, and sore throat, and pulmonary imaging reveals bronchitis and interstitial pneumonia. In severe cases, children may develop serious complications, such as pleural effusion, pulmonary embolism, acute respiratory distress syndrome (ARDS), and conformational bronchitis, and some may also experience extrapulmonary complications affecting the nervous and cardiovascular systems [3]. Epidemiological data indicate that *Mycoplasma pneumoniae* infection accounts for 10% - 40% of childhood community-acquired pneumonia (CAP), with this proportion exceeding 50% in some years [4]. Since 2023, multiple provinces in China, including Hebei, Shandong, and Liaoning, have witnessed the outbreak of an epidemic. The positive detection rate of *Mycoplasma pneumoniae* infection has doubled compared to previous years, and the incidence of severe cases and extrapulmonary complications has significantly increased [5]-[7]. In 2023, the total per-patient economic burden for pediatric patients hospitalized with *Mycoplasma pneumoniae* pneumonia in Qingdao, Shandong Province, exceeded 50,000 yuan [8]. In municipal hospitals in Shanghai, the annual average length of stay for pediatric patients with MPP ranged from 5.85 to 13.4 days, with per-admission costs ranging from 8026 to 15,660 yuan [9]. The above data indicate that *Mycoplasma pneumoniae* infection poses a serious threat to children's health, survival, growth, and development and imposes a heavy financial burden and care pressure on affected families, making it a significant global public health issue.

1.1. Clinical Hazards and Public Health Implications of *Mycoplasma pneumoniae* Infection in Children

Mycoplasma pneumoniae lacks a cell wall and is a prokaryotic microorganism with a small genome capable of self-replication, characterized by high infectivity and pathogenic diversity [10]. In children, infection typically causes mild upper respiratory tract infections but may progress to severe pneumonia, with a high risk of multi-systemic and extrapulmonary complications, such as myocarditis, encephalitis, hemolytic anemia, and disseminated intravascular coagulation. Some severe cases may result in long-term lung damage or even life-threatening events due to embolism [11]. From a public health perspective, *Mycoplasma pneumoniae* infection is characterized by covert transmission, clustering and periodic outbreaks. According to data from a pediatric medical center, co-infection with rhinoviruses and adenoviruses is the most common form of *Mycoplasma pneumoniae* infection, with a co-infection rate of 14.96%, further increasing the risk of transmission and complicating prevention and control [12]. *Mycoplasma pneumoniae* infection leads to repeated patient visits, hospitalization, and inappropriate clinical use of antimicrobial agents, which in turn further contributes to the evolution and spread of drug-resistant strains. Consequently, the prevention, control, and research of *Mycoplasma pneumoniae* infection are both essential and urgent.

1.2. The Association between the Epidemiology, Antimicrobial Resistance and Genotyping of MP

Research on *Mycoplasma pneumoniae* has identified three key areas of focus: clinical diagnosis and treatment, and epidemic prevention and control, all of which are closely interlinked. Studies on epidemiological characteristics form the foundation of prevention and control; in recent years, data from multicenter studies have revealed the regional distribution of infections, seasonal variations, and the prevalence of mixed infections, thereby providing a basis for targeted prevention and control. The latest antimicrobial resistance surveillance indicates a strong association between dominant genotypes and resistance mutations. Relevant studies have found that tetracyclines demonstrate superior efficacy to macrolides [13] [14]. Genotyping technology serves as a crucial bridge, linking the macro-epidemiological trends of pathogens to their microevolutionary characteristics. In addition to traditional ompA genotyping, whole-genome capture sequencing has revealed two distinct lineages of *Mycoplasma pneumoniae*: P1-1 and P1-2 [15]. The application of genotyping techniques, such as one-dimensional convolutional neural networks (1D-CNNs) combined with Raman spectroscopy, has overcome the limitations of traditional methods, namely, low resolution and limited throughput, thereby offering new approaches for the rapid diagnosis of *Mycoplasma pneumoniae* pneumonia. In particular, the combination of Raman spectroscopy and 1D-CNNs captures the unique ‘spectral fingerprint’ of bacteria and utilizes deep learning models to automatically extract features, enabling rapid, culture-free identification of strains [16]. In contrast, high-throughput sequencing technologies, such as multiplex amplicon sequencing and probe-capture sequencing, along with novel molecular diagnostic platforms, including HyTaq-LAMP and multiplex microfluidic digital PCR, are driving *Mycoplasma pneumoniae* typing research from a single dimension to a multidimensional approach [17] [18]. This not only enables the simultaneous detection of P1 genotyping, MLST genotyping, and 23S rRNA resistance mutation sites, but also significantly enhances the capacity for direct testing of clinical samples, providing effective tools for monitoring strain dynamics, tracing sources of infection, and guiding precise clinical drug therapy.

2. Epidemiological Characteristics of *Mycoplasma pneumoniae* Infection

2.1. Overall Incidence Trends of MP Infection

Surveillance data indicate that since 2023, the number of *Mycoplasma pneumoniae* cases has begun to rise gradually worldwide. Prospective surveillance data from 24 countries across Europe, Asia (Singapore), the Americas, and Oceania confirm that *Mycoplasma pneumoniae* is re-emerging cyclically on a global scale [19]. Further analysis revealed that, in this global epidemic, school-aged children (5 - 14 years) accounted for the highest proportion of infections, reaching 62.3%, and the proportion of severe cases (requiring hospitalization, with respiratory failure or extrapulmonary complications) increased by 12.5% compared to the previous cycle, suggesting that the *Mycoplasma pneumoniae* strains in this epidemic may be associated with greater disease severity [20].

A survey covering 30 tertiary Class A hospitals across 10 first-tier and provincial capital cities including Beijing, Shanghai, Guangzhou and Chongqing shows that from June to July 2023, the positive detection rate of *Mycoplasma pneumoniae* among outpatient cases reached 25.4%, which is nearly twice the rate of 8.7% in the same period of 2022 and 67.1% higher than the rate of 15.2% in the same period of 2019; 50% of children in respiratory wards were diagnosed with *Mycoplasma pneumoniae* pneumonia, with 8.3% of cases requiring admission to the intensive care unit (ICU) [21]. Major complications included pleural effusion, lung abscess, and *Mycoplasma pneumoniae* encephalitis, and the resistance rate to macrolide antibiotics (such as azithromycin) was as high as 91.2% [22]. In Shanghai, the MP antigen positivity rate in pediatric outpatient clinics from July to August 2023 was 22.1%, representing a 179.7% increase compared to the same period in 2022. In Guangzhou, the number of hospitalized pediatric MP pneumonia cases from June to September 2023 increased by 1.8 times compared to the same period in 2022, and the epidemic season began 1 - 2 months earlier than in previous years [23]. In Chongqing, the positive detection rate for pediatric MP infections reached 20.3% in the third quarter of 2023, with pre-school children (aged 3 - 6) accounting for the highest proportion of infections (45.6%), which is presumed to be related to increased group activities in kindergartens and a heightened risk of cross-infection [24]. In Hebei Province, the MP positivity rate reached 28.8% in 2023, a fourfold increase compared to 2021 (7.0%). In Liaoning Province, the infection rate rose sharply after August 2023, with a significant increase in the number of severely ill children and complications. In Gansu Province, the number of pediatric outpatient visits from January to October 2023 reached a record high [25].

In the United States, MP accounted for 8% of MP infections among hospitalized children between 2018 and 2024 and was the most frequently detected pathogen in CAP among children aged five years and older [26]. In South Korea, the detection rate of macrolide-resistant strains rose continuously between 2000 and 2011, with severe cases accounting for 23.12% of the epidemic in 2023 [27]. Surveillance in South Africa from 2012 to 2015 showed that the prevalence of MP among patients with acute respiratory infections (ARI) reached 1.6%, significantly higher than in the general population [28]. Regarding the epidemic cycle, influenced by adjustments to epidemic prevention and control measures and the resumption of population mobility, the traditional 3 - 5 year cycle has shortened to 2 - 3 years, and the number of sporadic cases in non-epidemic years has continued to increase, forming a composite epidemic pattern of "cyclical outbreaks + year-round sporadic cases". A comprehensive analysis of domestic and international data shows that the incidence of *Mycoplasma pneumoniae* infection in children is on a continuous upward trend, with 2023 marking the peak epidemic year in many countries worldwide.

2.2. Seasonal Epidemic Characteristics

The seasonal patterns of *Mycoplasma pneumoniae* infection exhibit significant regional variations, and a shift in seasonal patterns has been observed in recent years. In northern China, the peak incidence period remains in autumn and winter (November to February of the following year), whereas in southern China, it is predominantly in summer and autumn. In Hebei Province, the proportion of positive cases in autumn and winter exceeds 60%, which is associated with the cold, dry environment and increased transmission resulting from indoor gatherings. Data from a retrospective study covering Shanxi in North China indicate that *Mycoplasma pneumoniae* infection is predominantly seen in autumn and winter, with the highest positivity rate occurring in December (47.83%) [29]. In southern regions (Fujian, Hainan, and Suzhou), the peak incidence is mostly in summer and autumn (June-September), with a sharp decline in Fujian following the 2023-2024 MP outbreak; In the Suzhou region, the positivity rate peaked in August [30]; some subtropical regions show no distinct seasonal peak, with the summer positivity rate (41.34%) being slightly higher than in other seasons [31]; studies have found that MP infections in Europe can occur throughout the year, with a peak in winter [32]; weakening of seasonal patterns in tropical regions: Findings from a Thai study clearly indicate that MP infections exhibit no distinct seasonal characteristics [33]; in 2023, disrupted seasonal patterns were observed in many parts of the world; for instance, Gansu Province experienced peaks in patient visits during spring, summer, and autumn, which is speculated to be related to fluctuations in population immunity following the pandemic.

2.3. Patterns of Cyclical Epidemics

The cyclical patterns of *Mycoplasma pneumoniae* infection in children have fluctuated owing to the impact of the pandemic, with the traditional 3 - 5 year epidemic cycle shortening to 2 - 3 years. 2023 marked a global peak year for *Mycoplasma pneumoniae* epidemics. Data from 65 monitoring sites across 29 countries (including the Americas and Oceania) indicated that *Mycoplasma pneumoniae* re-emerged globally in the second half of 2023, with all four global regions (Europe, Asia, the Americas, and Oceania) simultaneously entering an epidemic phase, and a global average detection rate of 11.47%. In China, MP positivity rates in Fujian, Hebei, Liaoning, and other regions increased by 30% - 50% compared to the previous year, and the duration of the epidemic extended to 10 - 12 months. The intensity of infection during peak years has increased significantly; in Shandong Province, the *Mycoplasma pneumoniae* positivity rate reached 89.72% in 2021, the highest on record. Concurrently, the rate of co-infection rose during the peak of the epidemic; in Fujian Province, the co-infection rate reached 14.96% in 2024, a significant increase compared to 2023 (12.62%), with co-infection between MP and rhinovirus or adenovirus being the most common. According to data from the European Center for Disease Prevention and Control (ECDC), an increase in the incidence of respiratory infections caused by *Mycoplasma pneumoniae* has been observed in six European countries, primarily among school-aged children [34]. In Denmark, *Mycoplasma pneumoniae* epidemics typically occur approximately every four years, although they may also persist for two to three consecutive seasons. Analysis of Danish national surveillance data indicates that the number of *Mycoplasma pneumoniae*-positive cases nationwide has been rising steadily since October 2023, exhibiting explosive growth, with the previous peak in prevalence occurring in February 2020 [35].

2.4. Regional and Population Distribution

2.4.1. Regional Variations in Prevalence

In terms of geographical distribution, China exhibits the pattern of "higher prevalence in the north than in the south, higher in urban areas than in rural areas, and higher in the east than in the west." The MP positivity rate among children in the northern provinces (Shandong, Hebei, and Liaoning) generally ranged from 25% to 30%, whereas in the southern provinces (Fujian, Hainan, and Guangdong), it ranged from 15% to 25%. The MP positivity rate among children with respiratory infections in urban areas was 26.09%, which was higher than the 10.17% recorded in rural areas [36]. Key influencing factors include climatic conditions (the cold, dry climate of the north favors pathogen survival), population density (higher risk of cluster transmission in urban areas), and the standard of medical testing (higher detection rates in urban areas). The Asian region (China, Japan, and South Korea) is a high-prevalence area, with positivity rates significantly higher than those in European and American countries, a situation linked to the overuse of macrolide antibiotics and high population density in the region [37]. In the United States, the MP positivity rate among hospitalized children was 8% between 2010 and 2012, whereas in several European countries (Germany, France, and the Netherlands), the positivity rate remained between 5% and 15% [38] [39].

2.4.2. Age Distribution Characteristics

The age distribution of *Mycoplasma pneumoniae* infections continues to show that preschool-aged children (3 - 6 years) and school-aged children (7 - 14 years) constitute the high-risk groups, accounting for 70% - 80% of total cases. The positivity rate among school-aged children in Hebei Province reached 54.5%, whereas the detection rate among children aged 60 months and above in the Suzhou region was 70.25% [40]. The reasons for this high incidence include children in these age groups beginning group living arrangements (nursery and school), resulting in frequent close contact; their immune systems are developing but not yet mature, leading to insufficient specific immunity; and their wide range of activities increases the probability of exposure to the pathogen [41]. It is worth noting that during the 2023 epidemic period, the age of affected children was relatively higher; the mean age of the epidemic group (5.41 ± 2.76 years) was higher than that of the non-epidemic group (3.86 ± 2.33 years), and the incidence of pulmonary consolidation was higher in the older age group. Simultaneously, the incidence of severe disease among infants and young children under 5 years of age was significantly higher than that in other age groups, with longer hospital stays and more complications [42].

2.4.3. Differences in Susceptibility among Populations Based on Gender, Underlying Conditions, etc.

With regard to gender, data from studies in multiple regions indicate that the infection rate is higher among girls than boys. According to data from 122,984 pediatric inpatients with acute respiratory infections in Suzhou, China, the MP positivity rate among girls (22.9%) was significantly higher than that among boys (19.4%) [43]. In Vietnam, the risk of boys contracting *Mycoplasma pneumoniae* was almost half that of girls (OR = 0.62) [44], which may be related to the developmental characteristics of the female immune system. Furthermore, the presence of underlying medical conditions is a key factor influencing susceptibility to *Mycoplasma pneumoniae* and the severity of the disease. A systematic review and meta-analysis covering hospitalized pediatric patients in China showed that clinical indicators associated with disease severity (such as persistent high fever, hypoxemia, and extensive pulmonary consolidation) were significantly associated with the risk of complications from *Mycoplasma pneumoniae* pneumonia [45]. A further multicenter cohort study from Türkiye, published in 2025, confirmed that among 400 hospitalized pediatric patients, 27.5% had underlying conditions, the most common being asthma or reactive airway disease, neurological disorders, and haematological and oncological diseases; these children were more prone to severe manifestations and adverse clinical outcomes [46]. Another study found that the rate of MP co-infection in children with Kawasaki disease reached 38.9%, with older age and longer disease duration being associated with higher rates, suggesting a reciprocal influence between underlying conditions and MP infection [47]. Furthermore, the risk of MP infection is significantly elevated in children with HIV. Relevant studies indicate that the prevalence of pathogenic Mycoplasma infection in HIV-infected individuals is as high as 65.69%, and that patients with lower CD4+ T-lymphocyte levels have an even higher rate of Mycoplasma infection, suggesting a strong association between immunodeficiency and Mycoplasma infection [48]; a finding that aligns with the observation that impaired immunity is a key driver of MP re-emergence [49]. The above findings indicate that children with underlying conditions, such as asthma, congenital heart disease, malnutrition, and immunodeficiency, face a significantly increased risk of developing complications, such as severe pneumonia, pulmonary consolidation, and pleural effusion, following infection with *Mycoplasma pneumoniae*. Furthermore, children with these comorbidities have a 2-4-fold higher risk of infection and are more likely to develop severe disease.

2.5. Transmission Routes and Epidemiological Factors

2.5.1. Primary Routes of Transmission

Mycoplasma pneumoniae is primarily transmitted via respiratory droplets and close contact. It is highly contagious and can spread insidiously. When patients cough or sneeze, they expel droplets containing the pathogen, which can cause infection at close range, making this one of the primary modes of transmission [50]; transmission via close contact can occur through contaminated hands, toys, cutlery, and other objects. *Mycoplasma pneumoniae* can be transmitted even during the incubation period (1 - 3 weeks), and the carrier rate among asymptomatic individuals varies considerably across different studies (2.2% - 21%), making them an important source of silent transmission. Furthermore, co-infection with influenza viruses may be associated with enhanced the transmissibility and pathogenicity of MP through synergistic effects and is associated with more severe symptoms [51] [52].

2.5.2. Environmental Factors

Environmental factors (including population density, climate change, indoor ventilation, and air quality) directly influence the intensity of *Mycoplasma pneumoniae* outbreaks. Higher population density correlates with greater transmission efficiency, and urban centers and large childcare facilities are high-risk settings for cluster outbreaks. An investigation into a *Mycoplasma pneumoniae* pneumonia outbreak revealed that air velocity was significantly lower on floors with poor ventilation layouts, and the risk of transmission during indoor group activities increased fourfold [53]. A Belgian study of indoor air in 21 community settings confirmed that high CO_2 concentrations and inadequate natural ventilation are independent risk factors for the detection of respiratory pathogens; an average of 3.9 pathogens were detected per sample, with 85.3% of samples testing positive for at least one pathogen. Under a ventilation rate of two air changes per hour (ACH), the infection risk for susceptible individuals was 2.43 times higher with mixed ventilation and 1.30 times higher with natural ventilation than with displacement ventilation [54].

Climate change alters transmission risks by affecting pathogen survival and children's behavioral patterns. A study based on nearly half a century of *Mycoplasma pneumoniae* surveillance data from 1958 to 2025 found that environmental variability can sustain the epidemic cycle of *Mycoplasma pneumoniae* infection, whereas non-pharmaceutical interventions (such as COVID-19 control measures) significantly disrupt the regular epidemic cycle [55].

Air quality is also closely associated with *Mycoplasma pneumoniae* infections. A study conducted in Wuhan between 2014 and 2022 demonstrated that elevated O_3 levels increased the incidence of *Mycoplasma pneumoniae* infection [56]. A study from the Paediatric Intensive Care Unit (PICU) at Hunan Children's Hospital further quantified the association between pollutant concentrations and severe MP: when $PM2.5 \geq 35\ \mu g/m^3$, $PM10 \geq 50\ \mu g/m^3$, and $NO_2 \geq 25\ \mu g/m^3$, for every $10\ \mu g/m^3$ increase, the relative risk (RR) of severe MP was 1.28, 1.31, and 2.04, respectively [57].

2.5.3. Socio-Behavioural Factors

Social behavioral factors are a key cause of cluster outbreaks. Childcare centers, schools, and other settings with high concentrations of children are the primary venues for *Mycoplasma pneumoniae* outbreaks. A US national surveillance study covering 2021-2023 showed that *Mycoplasma pneumoniae* outbreaks occurred almost exclusively in closed communities or congregate settings, such as schools, universities, hospitals and long-term care facilities, with the 2023 outbreak concentrated primarily in large urban areas [58]. Furthermore, the implementation of control measures directly influences the outbreak scale. Institutions that strictly enforce morning and afternoon health checks, isolation of cases, and ventilation and disinfection can shorten the duration of outbreaks and limit their spread. Monitoring data indicate that during the COVID-19 pandemic (2020-2022), the prevalence of MP decreased significantly due to the implementation of strict non-pharmaceutical interventions (such as social distancing, mandatory mask-wearing, and school closures), whereas following the lifting of restrictions (2022-2024), the prevalence rose sharply to 56.03% [59].

In 2023, the adjustment of post-pandemic prevention and control measures, the recovery of population mobility, and the full reopening of childcare institutions and schools became the key contributing factors to the outbreak of *Mycoplasma pneumoniae*. Research findings indicate that these factors exhibit a temporal correlation with the outbreak. MP infections in China exhibited a trend of delayed outbreaks, which was associated with the lifting of pandemic control measures and increased clustered contact following the resumption of schools. This phenomenon has been termed 'immunity debt' by international scholars.

3. Current Status and Mechanisms of Antibiotic Resistance in Paediatric *Mycoplasma pneumoniae*

3.1. Global Epidemiological Characteristics of Antibiotic Resistance

3.1.1. Overall Trends in Antimicrobial Resistance Rates and Regional Variations

Antibiotic resistance of *Mycoplasma pneumoniae* in children is primarily driven by macrolides. The situation regarding resistance in China is severe, with a macrolide resistance rate as high as 97.1%, mainly driven by the A2063G mutation in the 23S rRNA gene, with the P1-1 genotype being predominant (87.3% - 94.9%) [60]. Globally, resistance rates in Asia are significantly higher than in Europe and the Americas. According to CDC surveillance data, the global prevalence of macrolide resistance in *Mycoplasma pneumoniae* is approximately 28%; however, there are significant regional variations: approximately 12% in Canada, approximately 80% in China, an average of approximately 5% in Europe (with Italy having the highest rate at 20%), over 50% in Japan, and less than 10% overall in the United States [61].

In China, the resistance of *Mycoplasma pneumoniae* to macrolides presents significant regional variations. The resistance rate is the highest in Beijing, reaching 74.5%, 100% in Shanghai, and as low as 20% in Gansu [62]. A study analyzing the data of *Mycoplasma pneumoniae* isolates from 10 provinces and municipalities in China found that all isolates carried the A2063G resistance mutation, showing high resistance to macrolides but remaining sensitive to tetracyclines and quinolones [63]. In clinical practice, tetracyclines and fluoroquinolones can be used as alternative therapeutic regimens for patients infected with macrolide-resistant *Mycoplasma pneumoniae*, but both have application restrictions in pediatrics. Tetracyclines are the first-line treatment for children aged 8 years and older; for younger children, they are only indicated for severe cases of pneumonia. Considering safety concerns, these drugs should only be used for special and life-threatening cases under the supervision of specialist physicians [64].

3.1.2. Association between Dominant Genotypes and Resistant Strains

The distribution of resistant strains is strongly linked to predominant genotypes. Studies indicate that the predominant genotype for MP in both the Western Pacific and European regions is P1-1, whilst ST3 dominates in the Western Pacific region based on MLST typing. Macrolide resistance rates are highest among P1-1, MLVA 4572 and ST3 [65].

Globally, drug-resistant strains are predominantly concentrated within specific subtypes. A study conducted during the 2024-2025 outbreak in Canada revealed that the P1-1 subtype accounted for 81% of cases, with a resistance rate (29.9%) significantly higher than that of the P1-2 subtype (7.7%), suggesting that the association between the P1-1 subtype and drug resistance is consistent across region [66]. Multistate surveillance data from the United States between 2012 and 2018 showed that the P1-2 subtype accounted for 59.8% (with the P1-1 subtype accounting for 40.2%), and the resistance rate of the P1-1 subtype (12.9%) was also significantly higher than that of the P1-2 subtype (5.5) [67]. In South Korea, almost all macrolide-resistant strains were of the ST3 type (98.3%), and the resistance rate rose from 0% during the first outbreak to 84.4% during the fifth outbreak [68]. In Japan, resistant strains are mainly concentrated in ST3, and with the emergence of susceptible types such as ST7 and ST33, the resistance rate has fallen from 86.2% during the 2011-2012 outbreak to 11.3% in 2018-2019 [69].

Among the resistant strains isolated in the UK in 2024, 67% were of the ST3 type, showing high homology with strains prevalent in East Asia [70].

The above findings indicate that P1-1 (ompA II) and ST3 are the molecular types most closely associated with macrolide resistance globally. Studies from multiple countries consistently show that the resistance rate for P1-1 is significantly higher than that for P1-2, with resistant strains almost exclusively concentrated in the ST3 genotype. In East Asia (China, Japan, South Korea), ST3 is the dominant genotype, and resistance rates have remained persistently high; in North America and Europe, the genotype distribution is more diverse, and resistance rates are relatively lower. Fluctuations in resistance rates are directly related to shifts in the predominant genotypes.

3.1.3. Mechanisms of Resistance to Macrolide Antibiotics

Macrolide antibiotics exert their antibacterial effects primarily by inhibiting protein synthesis through binding to the 23S rRNA domain of the bacterial 50S ribosomal subunit [71]. Traditionally, it was believed that they prevented all protein elongation by physically blocking the nascent peptide exit tunnel (NPET); however, recent studies have shown that macrolides are in fact context-specific translational modulators: drug-bound ribosomes allow some nascent peptides to pass through the NPET, but translation stalls only when specific amino acid sequences—namely, macrolide-binding motifs(MAMs) (e.g. Lys/Arg-X-Lys/Arg), due to the synergistic allosteric effect of the macrolide and the nascent peptide on the peptidyl transferase centre (PTC), preventing it from catalysing the formation of specific peptide bonds; the kinetic parameters of the drug-ribosome interaction determine the antibiotic's capture efficiency and bactericidal activity.

Mycoplasma pneumoniae exhibits diverse mechanisms of resistance to macrolide antibiotics, including point mutations in the 23S rRNA gene, ribosomal protein mutations, and activation of efflux pumps [72] [73].

1) Core mechanism: point mutations in the 23S rRNA gene. Point mutations in the V region of the 23S rRNA are the primary mechanism, accounting for over 90% of resistant strains. From a molecular perspective, these mutations may weaken the allosteric inhibition of macrolides on peptide bond formation by altering the structure of the NPET and the kinetics of drug-ribosome interactions, thereby allowing resistant strains to bypass translation arrest.

2) Secondary mechanism: ribosomal protein mutations. Mutations in the ribosomal protein L4 and L22 genes are relatively rare and primarily cause low-level resistance.

3) Efflux pump mechanisms: Efflux pump activation is relatively rare in *Mycoplasma pneumoniae* resistance in China. A study in Beijing showed that, out of 72 isolates, 2 were found to harbor the efflux pump genes msrA/B and mefA; following treatment with the inhibitor reserpine, the MIC decreased to one-quarter of the original value, confirming the involvement of efflux pumps in resistance development [74]. This aligns with earlier findings in pediatric populations, where a subset of macrolide-resistant isolates also exhibited an efflux mechanism, likely

belonging to the ABC transporter family. Furthermore, independent genomic analyses have identified mutations in the macB efflux gene, with efflux‑pump inhibitors significantly reducing MICs in some isolates. Collectively, these data suggest that efflux pumps may contribute to macrolide resistance as an auxiliary mechanism alongside classical 23S rRNA point mutations. Despite these findings, it is important to note that efflux-associated resistance remains a rare, secondary pathway; the primary clinical driver continues to be 23S rRNA domain V mutations (especially A2063G) [75].

4) Correlation between resistance phenotypes and clinical outcomes. Studies indicate that mutations at positions 2063 or 2064 in domain V of the 23S rRNA gene are the primary mutations associated with resistance.

3.2. Factors Influencing Drug Resistance

3.2.1. Clinical Antibiotic Misuse

The inappropriate use of antibiotics is a major factor in the development of resistance. A Chinese longitudinal genomic epidemiological study revealed that two prevalent macrolide-resistant clones (T1-2-EC1 and T2-2-EC2) carry the 23S rRNA A2063G mutation, whose expansion coincided closely with the widespread adoption of azithromycin for the treatment of paediatric community-acquired pneumonia in China in the early 2000s, providing direct evidence that antibiotic selection pressure drives the expansion of resistant clones [76]. Macrolide resistance is primarily driven by antibiotic overuse and clonal expansion, particularly in sequence type 3 (ST3) strains [77]. Studies have found that the widespread use of macrolide antibiotics is associated with an increase in genetic mutations resulting from the widespread transmission of MP [78]. These findings indicate that, globally, the overuse of antibiotics is closely associated with the expansion of resistant clones (particularly ST3), and that resistance rates correlate positively with the intensity of antibiotic use. Once established, resistance possesses a stable capacity for transmission and the potential for persistent resurgence; this is a key factor behind the persistently high resistance rates in Asia and the continued high levels of resistance observed following the 2023 pandemic.

3.2.2. Cross-Transmission of Resistant Strains

The cross-transmission of drug-resistant strains is a major factor in the rapid rise in resistance rates. Drug-resistant strains spread through inter-regional movement, leading to a simultaneous increase in resistance rates across multiple locations. Studies have shown that the T1-2-EC1 drug-resistant clone prevalent in China in 2023 spread rapidly and intermingled across different provinces, with phylogeographic analysis confirming the inter-regional dispersal capacity of drug-resistant strains [79] [80].

Furthermore, co-infections may enhance the transmission efficiency of drug-resistant strains. A 2023-2024 study of paediatric inpatients with *Mycoplasma pneumoniae* pneumonia in Russia revealed that 62% of patients had viral co-infections, with human parainfluenza virus (47%) and SARS-CoV-2 (12.4%) being the most common [81]. Co-infections may indirectly facilitate the transmission of drug-resistant strains by altering the host immune response or increasing bacterial shedding.

3.2.3. Evolution of MP Genes and Adaptive Mutations

The *Mycoplasma pneumoniae* genome is small (approximately 820 kb) and structurally simple, encoding around 600 protein-coding genes. Due to the absence of a complete DNA repair system, its genomic stability is low, making it prone to spontaneous mutations [82]. Under antibiotic selection pressure, strains carrying resistance mutations such as the 23S rRNA A2063G mutation possess a survival advantage, proliferating rapidly and displacing susceptible strains to form dominant resistant populations [83]. Whole-genome sequencing studies conducted in China between 2021 and 2024 further confirmed that during the resurgence of MP in 2023-2024, the proportion of the P1-1/ST3 lineage rose from 41.9% in 2021 to 84.0% in 2024, representing clonal replacement, with all isolates carrying the A2063G mutation [84].

Studies indicate that the competitive advantage of resistant strains stems not only from resistance mutations but may also be associated with enhanced adaptability linked to specific genotypes. A whole-genome sequencing analysis identified specific mutations in the L4 gene (C162A, A430G) and the CARDS toxin gene (T1112G) in P1-2 strains, whilst all cases of severe pneumonia were infected with drug-resistant strains; two of these strains exhibited multicopy gene phenomena associated with conserved functional domains of the DUF31 protein family [85].

3.3. Impact of Antimicrobial Resistance on Clinical Management

3.3.1. Increased Risk of Treatment Failure and Prolonged Disease Course

Macrolide resistance is significantly associated with increased treatment failure rates. The clinical course is significantly prolonged in paediatric patients with resistant infections. Relevant studies in China have shown that, compared with the susceptible group, the resistant group had a total fever duration prolonged by 5.1 days, a total cough duration prolonged by 4.4 days, a disease duration prolonged by 5.2 days, and a hospital stay prolonged by 5.3 days (all $P < 0.05$) [86] [87]. Japanese research data confirm that the median duration of fever in the resistant group was 8 days, significantly longer than the 5 days observed in the susceptible group ($P = 0.019$) [88].

Studies have found that children infected with macrolide-resistant strains exhibit clinical features such as persistent fever, prolonged antibiotic treatment, and an insignificant reduction in MP-DNA load following macrolide therapy [89]. Furthermore, the proportion of children with drug-resistant infections receiving glucocorticoids and second-line antibiotics increased significantly, and the risk of complications and sequelae also rose accordingly [90].

3.3.2. Increased Incidence of Severe Infection

Infections caused by drug-resistant strains are closely associated with severe pneumonia. *Mycoplasma pneumoniae* resistant to macrolides (MRMP) infections are significantly associated with prolonged fever duration, extended hospital stays, and a higher proportion of severe cases. A study of hospitalised children conducted in 2023-2024 showed that the incidence of pulmonary consolidation (74.7% vs 42.5%), the incidence of extrapulmonary complications (47.4% vs 32.5%) and the incidence of refractory pneumonia (31.6% vs 11.3%) were all significantly higher in the MRMP group than in the non-resistant group ($P < 0.05$) [91]. A 2023-2024 multicentre study across 13 hospitals in South Korea found that the MR resistance rate reached as high as 89.1%; in the macrolide combination therapy group, the median duration of fever was 8 days and the length of hospital stay was 5.0 days, both significantly longer than in the monotherapy group ($P < 0.001$) [92]. Furthermore, MRMP infection has been reported to be associated with serious complications such as plastic bronchitis and Kawasaki disease, suggesting shared inflammatory pathways [93].

3.3.3. Adjustments to Clinical Treatment Strategies

Given the current prevalence of resistance, treatment strategies have shifted from "empirical first-line macrolides" to "individualised treatment guided by susceptibility testing". In clinical practice, macrolide antibiotics remain the first choice for mild, susceptible infections; for severe, resistant infections, doxycycline combined with glucocorticoids may be used to enhance efficacy [94]. Furthermore, resistance gene testing (23S rRNA A2063G/A2064G) can rapidly identify resistant strains and guide drug selection. Studies have shown that in paediatric patients whose initial treatment fails and who are promptly switched to oral doxycycline, hospital stay and duration of fever are significantly reduced, and radiological outcomes are improved. Currently, a consensus has been reached on a stepwise treatment protocol for drug-resistant infections: if macrolide therapy proves ineffective after 3 days, switching to tetracyclines or quinolones should be considered; for refractory cases, glucocorticoids and intravenous immunoglobulin should be administered in combination.

4. Genotyping Methods and Characteristics of *Mycoplasma pneumoniae* in Children

4.1. Common Genotyping Methods

4.1.1. Diagnostic Testing and Genotyping of *Mycoplasma pneumoniae*

Diagnostic testing approaches and molecular genotyping platforms are two core technologies for research on *Mycoplasma pneumoniae*, which differ in detection purpose, result interpretation and nomenclature system.

Diagnostic testing methods (e.g., conventional PCR, real-time quantitative PCR, loop-mediated isothermal amplification, antigen detection, etc.) are mainly used to rapidly confirm the presence of *Mycoplasma pneumoniae* in clinical specimens.

By contrast, genotyping methods (e.g., P1 gene-based PCR-RFLP, multilocus sequence typing (MLST), multiple-locus variable-number tandem repeat analysis

(MLVA), whole-genome sequencing (WGS), multiplex amplicon sequencing, etc.) aim to achieve molecular-level identification of isolates. Different genotyping methods produce distinct nomenclature for typing results: for example, P1 typing (based on ompA gene variants), sequence type (ST), MLVA typing (represented by the repeat number of each VNTR locus), as well as detection of macrolide resistance-associated mutations such as A2063G [95]. Genotyping enables identification of the specific strain causing *Mycoplasma pneumoniae* infection and detection of whether the strain carries resistance determinants, and it plays a critical role in outbreak source tracing, epidemiological surveillance and antimicrobial resistance monitoring.

4.1.2. Classical Genotyping Methods

Genotyping based on sequence variations in the P1 adhesion protein gene is the core method for the molecular genotyping of *Mycoplasma pneumoniae*. Based on differences in the P1 gene sequence, *Mycoplasma pneumoniae* can be classified into two major subtypes: P1-1 and P1-2. Common genotyping methods include nested PCR, PCR-RFLP (restriction fragment length polymorphism of PCR products), rapid cycle PCR, and real-time PCR with high-resolution melting curve analysis [96]. Among these, PCR-RFLP is the most widely used classical typing method, which classifies strains by detecting sequence variations in the RepMP4 and RepMP2/3 repeat regions of the P1 gene. However, due to the high genetic homogeneity of the *Mycoplasma pneumoniae* genome, the discriminatory power of the PCR-RFLP method is limited, making it difficult to identify subtle variations within subtypes.

4.1.3. Novel Genotyping Techniques and Other Methods

In addition to traditional methods, some novel typing techniques offer distinct advantages: The combination of Raman spectroscopy and one-dimensional convolutional neural networks (1D-CNN) enables rapid strain classification with strong noise resistance and an accuracy rate of 98.0%, making it suitable for rapid clinical diagnosis. This technique classifies samples of the two main genotypes of *Mycoplasma pneumoniae*, M129 and FH, achieving an accuracy rate of 98.0% in spectral data superimposed with Gaussian noise, and 97.0% under Poisson and multiplicative noise, respectively.

MLST (multilocus sequence typing) offers high resolution and enables cross-laboratory comparison, making it suitable for global strain evolutionary analysis. An MLST scheme for *Mycoplasma pneumoniae* developed in 2015 is based on eight housekeeping genes (ppa, pgm,gyrB, gmk, glyA, atpA, arcC, adk). Analysis of 55 clinical isolates and two reference strains (M129, FH) identified 12 sequence types (STs), demonstrating superior resolution compared to traditional P1 typing and MLVA typing. A public database (pubmlst.org/mpneumoniae) has been established to support global data sharing [97].

Whole-genome sequencing (WGS) enables precise analysis of the association between drug-resistance mutations, virulence genes and genotypes, and is a core technology for outbreak tracing and in-depth scientific research [98] [99]. Next-generation sequencing-based multiplex amplicon sequencing technology can simultaneously perform p1 genotyping, orf6 genotyping, multi-locus sequence typing (MLST) and 23S rRNA resistance mutation detection, thereby achieving comprehensive coverage of *Mycoplasma pneumoniae* genotyping [100].

SNAP shot technology is based on single nucleotide polymorphism (SNP) genotyping; it offers high resolution and is simple to operate, making it suitable for small-scale studies. This method utilises eight SNP loci identified through whole-genome sequencing to analyse 140 clinical isolates, identifying a total of nine SNP genotypes. Its discrimination index (HGDI) reached 0.836, which is higher than the 0.583 achieved by the MLVA-4 genotyping method, and can be directly applied to clinical sample testing without the need for sequencing steps [101].

4.2. Distribution of Major Genotypes and Epidemiological Characteristics

4.2.1. Predominant MP Genotypes Worldwide

Globally, the predominant genotype in both the Western Pacific and European regions is P1-1, whilst in MLST typing, ST3 dominates the Western Pacific region [102]. The drug-resistant strains prevalent in China in 2023 were primarily two macrolide-resistant clusters, T1-2-EC1 and T2-2-EC2, both belonging to the P1-1 genotype; an MLST study in Japan from 2002 to 2016 showed that ST3 was the predominant sequence type, accounting for 74.6% of macrolide-resistant strains [28]; surveillance data from 2018 to 2019 indicated that the resistance rate had fallen to 11.3%, with the predominant genotypes shifting to ST7 and ST33. A study in South Africa from 2012 to 2015 detected P1-1, P1-2 and variants of P1-2, with all strains being susceptible to macrolide antibiotics [103].

4.2.2. Genotypic Characteristics in Clustered Outbreaks

In cluster outbreaks, the genotypes of the strains were highly consistent, confirming that a single resistant strain can trigger transmission. In the 2013 P1-2c outbreak in Russia, 32 samples from two towns were all genotyped as P1-2c; no macrolide resistance-associated mutations were detected in this outbreak, consistent with the epidemiological characteristics of low resistance rates in Northern Europe.

Japanese surveillance data indicate that MP genotypes exhibit cyclical changes, with P1-1and P1-2 alternating as the dominant circulating strains every 89 years. Between 1995 and 2005, the dominant genotype in Japan shifted from P1-2 to P1-1 [104] [105]. MP genotypes in China also exhibit a dynamic trend of shifting from type I to type II [106].

4.3. Clinical and Research Significance of Genotyping

4.3.1. Tracing the Source of Infection and Transmission Chains

Genotyping is a key technique for tracing the origins of clustered outbreaks. P1 genotyping can determine whether an outbreak stems from a single transmission chain, whilst whole-genome sequencing can precisely identify the first imported case. Molecular genotyping techniques are of significant value in characterising epidemiological evolution and detecting mutations associated with drug resistance, and serve as an important tool for controlling MP outbreaks [107]. Concurrently, MP whole-genome analysis has been achieved through probe-capture sequencing technology, providing technical support for outbreak tracing [108]. Internationally, whole-genome sequencing has been widely applied in outbreak investigations and transmission chain tracing. Systematic geographical analysis can reveal the transmission pathways of drug-resistant strains across different regions, providing a basis for formulating precise prevention and control strategies.

4.3.2. Association between Genotype and Clinical Phenotype

There is a significant association between genotype and clinical phenotype, as well as antimicrobial resistance. Research data indicate that among 261 paediatric patients with MPP, the P1-1 genotype accounted for 73.56% (192 cases), whilst the P1-2 genotype accounted for 26.4% (69 cases);the proportion of children with the P1-1 genotype requiring bronchoscopic intervention (54.2%) was significantly higher than that of the P1-2 genotype (17.4%, $P < 0.001$), suggesting that the P1-I strain may be associated with severe manifestations such as airway mucus plugs and atelectasis [109]. Antibiotic-resistant genotypes are significantly associated with clinical treatment outcomes, and rapid detection of resistance mutations is of great significance in guiding the rational use of antibiotics [110].

4.3.3. Vaccine Development

Genotyping provides the core basis for vaccine development. Vaccine targets should focus on the conserved antigens of the predominant genotype (P1-1 type), such as the conserved regions of the P1 and P30 proteins, to ensure coverage of mainstream drug-resistant strains. Studies have shown that an mRNA vaccine designed based on four conserved antigens of MP, when administered intranasally, can induce potent mucosal immunity and provides broad-spectrum protection against both P1-1 and P1-2strains.

Immunoinformatics-based vaccine design studies have further confirmed that multi-epitope vaccines based on conserved epitopes of the P1 protein can effectively activate the immune response. The constructed multi-epitope candidate vaccine exhibits a binding affinity of −21.7 kcal/mol with TLR4 and achieves a global HLA population coverage of 50.69%, demonstrating good potential for broad-spectrum protection. Currently, significant progress has been made in the development of vaccines targeting conserved antigens of MP. Genotyping provides crucial support for the optimisation of vaccine targets and the evaluation of efficacy; identifying the dominant genotypes circulating globally and their evolutionary patterns provides a scientific basis for the development of broadly effective vaccines.

5. Conclusions and Outlooks

5.1. Conclusions of Key Research Findings

5.1.1. Key Characteristics of MP Epidemiology in Children and Priorities for Prevention and Control

In 2023, China experienced a nationwide outbreak of MP infections among children, with a significant rise in the positivity rate. Regional variations were observed, characterised by a higher incidence in the north during autumn and winter and in the south during summer and autumn. School-aged children (3 - 14 years) constituted the primary group affected, with girls showing a higher infection rate than boys. Childcare centres and schools were identified as the main sites of cluster transmission. The rate of co-infections continues to rise, with co-infections with rhinoviruses and adenoviruses being the most common. Prevention and control efforts must prioritise enhanced monitoring, ventilation and disinfection in settings with high concentrations of children, as well as the isolation of cases. There is a need to strengthen testing for antibiotic resistance genes and the management of rational antibiotic use, whilst establishing early warning models that take climate and environmental factors into account.

5.1.2. The Serious Situation of Antibiotic Resistance and Key Breakthroughs in Prevention and Control

Antimicrobial resistance epidemics have emerged to varying degrees worldwide, with the P1-1 genotype (ompA II) being the predominant resistance genotype and A2063G the core mutation type. Tetracyclines demonstrate superior efficacy to macrolides and offer reliable safety, making them the preferred alternative for patients with drug-resistant infections. Key control strategies include standardising antibiotic use, establishing a national drug resistance surveillance network, promoting rapid drug resistance gene testing, and achieving precise medication use guided by antimicrobial susceptibility testing.

5.1.3. The Core Value of Genotyping in MP Research

Genotyping is a key technology linking epidemiology, antimicrobial resistance and clinical phenotypes. OmpA/P1 genotyping is the mainstream method, whilst novel technologies such as MLST, whole-genome sequencing and multiplex amplicon sequencing have enhanced the resolution and speed of genotyping. Genotyping enables the precise tracing of infection transmission chains, reveals associations between genotypes and drug resistance or severe disease, provides targets for vaccine development, and serves as a vital tool for epidemiological investigations, optimisation of clinical diagnosis and treatment, and scientific research.

5.2. Current Research Gaps

5.2.1. Lack of Multi-Centre, Large-Sample Longitudinal Epidemiological Data

Existing studies are predominantly single-centre, cross-sectional data, with a lack of nationwide, multi-centre longitudinal surveillance, making it difficult to accurately grasp long-term trends in infection and resistance rates; regional data is fragmented, preventing the formation of a globally unified epidemiological profile; and there is insufficient research into the synergistic pathogenic mechanisms and transmission patterns of mixed infections.

5.2.2. Insufficient In-Depth Analysis of Resistance Mechanisms

Existing research focuses on classic mutations in the 23S rRNA gene, with limited studies on novel resistance genes, ribosomal protein mutations, and efflux pump systems; the mechanisms of adaptive evolution in resistant strains, as well as the co-evolution of virulence and resistance, remain unclear; research on the transmission dynamics of resistant strains is insufficient, making it difficult to comprehensively analyse the patterns of resistance spread.

5.2.3. Research on the Causal Relationship between Genotype and Clinical Outcomes Needs to Be Strengthened

Most studies involve correlation analyses between genotypes and clinical phenotypes, with a lack of large-scale cohort studies to confirm causal associations between genotypes and severe disease, resistance, or prognosis; the guidance value of genotypes for clinical diagnosis and treatment has not yet been standardised, making it difficult to translate them into routine clinical indicators; vaccine development remains focused on traditional antigens, and progress on novel vaccines targeting resistant strains is slow.

5.3. Future Research Directions and Outlooks

5.3.1. Establishment of a Global Multicentre Surveillance and Early Warning Network

Leveraging international public health cooperation platforms, a global surveillance and antimicrobial resistance early warning network for paediatric MP infections should be established. This network would integrate data from multiple centres to monitor infection rates, resistance rates and changes in genotype distribution in real time, and construct big data early warning models based on climate, environment and population mobility, thereby enabling early warning of clustered outbreaks and outbreaks of resistant strains.

5.3.2. Deepening Research into Resistance and Transmission Mechanisms

Utilising multi-omics technologies (genomics, transcriptomics, metabolomics) to identify novel resistance genes; elucidating the evolutionary pathways, transmission patterns, and co-evolutionary mechanisms of virulence and resistance in resistant strains; clarifying the impact of antibiotic selection pressure and environmental factors on the evolution of resistance; and conducting studies on the transmission kinetics of resistant strains to provide a theoretical basis for delaying the emergence of resistance.

5.3.3. Optimising Treatment Regimens and Vaccine Development

Conduct multicentre clinical trials to identify active ingredients and targets, and promote personalised treatment regimens; develop multivalent vaccines covering prevalent drug-resistant genotypes (P1-1/ST3), and advance the development of novel antimicrobial agents; formulate precision medication guidelines based on genotyping and antimicrobial susceptibility testing to reduce treatment failure rates.

5.3.4. Promoting New Typing and Detection Technologies

Promote the clinical adoption of technologies such as rapid drug resistance gene detection and whole-genome sequencing, simplifying operational procedures and reducing costs; establish a database linking genotypes, clinical phenotypes and drug resistance to enable genotype-based early risk assessment and medication guidance, thereby establishing precision diagnosis and treatment for MP infections and reducing the economic burden on healthcare.

6. Limitations

Variations in diagnostic methods (e.g., serology, polymerase chain reaction, antigen detection) across different studies may lead to discrepancies in the reported positive rates. Second, differences in the intensity and frequency of surveillance across regions may bias observed epidemiological trends. The absence of a unified definition for severe or refractory *Mycoplasma pneumoniae* pneumonia restricts direct comparisons of complication incidence and clinical outcomes. Most existing data included in this review are derived from retrospective, single-center or cross-sectional studies, rather than prospective, multi-center longitudinal cohort studies, which limits the validity of causal inference.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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