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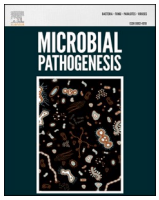

Reemergence of *Mycoplasma pneumoniae* disease: Pathogenesis and new approaches

Hamed Tahmasebi [a], Ali Babaeizad [b], Maryam Mohammadlou [c], Farnaz Alibabaei [b], Seyedeh Zahra Banihashemian [b], Majid Eslami [d,*]

[a] School of Medicine, Shahroud University of Medical Sciences, Semnan, Iran
[b] Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran
[c] Department of Immunology, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran
[d] Department of Bacteriology and Virology, Semnan University of Medical Sciences, Semnan, Iran

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ABSTRACT

The review discusses the recurrence of *Mycoplasma pneumoniae* (*M. pneumoniae*), a bacterium causing atypical pneumonia, primarily affecting Europe and Asia due to climate change, immunity decline, antibiotic resistance, and genetic heterogeneity. The COVID-19 pandemic initially reduced M. pneumoniae cases due to preventative measures, but its reemergence suggests different transmission dynamics and exacerbates clinical severity with co-infections with other viruses. The pathogenicity of *M. pneumoniae* is attributed to its intracellular changes, toxin release, and adhesion processes, which can result in a variety of symptoms and problems. Antibiotics and immunomodulators are used in treatment, and attempts are being made to create vaccines. Effective management of its reappearance necessitates surveillance and preventative measures, especially in the context of co-infections and potential outbreaks. *M. pneumoniae's* resurgence highlights its reliance on a polarized cytoskeletal architecture for host cell attachment and pathogenicity through cytoadherence and cytotoxic agent synthesis. *M. pneumoniae* has returned even though the COVID-19 pandemic originally reduced incidence; this might be because of things like declining immunity and particular pathogenic characteristics. Meteorological factors like temperature and humidity, along with air quality, including pollutants like $PM_{2.5}$ and NO2, increase susceptibility to environmental hazards. During the pandemic, non-pharmaceutical measures decreased transmission but did not eradicate the infection. Epidemics typically occur three to five years apart, emphasizing the need for ongoing study and observation. Antimicrobial resistance is a serious issue, necessitating caution and alternative therapies, especially in macrolides. COVID-19 pandemic lessons, such as mask use and hand hygiene, may help limit *M. pneumoniae* transmission.

1. Revealing *Mycoplasma pneumoniae*: Exploring the reasons behind its resurgence

Infections of the respiratory tract commonly occur as a result of *Mycoplasma pneumoniae*. Atypical characteristics distinguish *M. pneumoniae* from other pathogens: it is one of the smallest self-replicating organisms, has a compact and remarkably stable genome (0.8 Mbp), has no cell wall, grows slowly (with a generation time of 6h), requires close contact for transmission, and has a unique clinical manifestation called atypical pneumonia. Immune responses of the host may play an important role in this atypical pneumonia's pathogenesis [1,2]. There are epidemics every few years in many different climates around the world, with infections occurring all year long [3,4]. Medical and scientific communities have become increasingly concerned about the resurgence of *M. pneumoniae*, which causes atypical pneumonia in humans [5]. Infections caused by *M. pneumoniae* are reemerging due to a variety of factors. The bacterium exhibits a high degree of genetic variability, allowing it to evade the immune system and develop resistance to commonly used antibiotics [6]. The periodic occurrence of epidemics is caused by waning herd immunity or the introduction of new subtypes. Multiple nations in Europe and Asia were simultaneously affected by the most recent epidemic in late 2019–early 2020 [7]. As the population dynamic changes, travel increases, and urbanization increases, the bacterium may be spread more easily [8]. As well, changing

* Corresponding author.
E-mail address: M.eslami@semums.ac.ir (M. Eslami).

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environmental conditions and climate variations may contribute to *M. pneumoniae's* survival and transmission [9]. Globally, *M. pneumoniae* detection decreased markedly after non-pharmaceutical interventions (NPIs) against COVID-19 were introduced in March 2020 [7]. As with other respiratory pathogens, the incidence of *M. pneumoniae* changed markedly in the first year following the introduction of NPIs (1–69 %, 2020-211), similar to the pre-pandemic incidence (86 %, 2017-20) [7,10]. In addition, *M. pneumoniae* incidence decreased by 70 % in the second year, when other respiratory pathogens resurfaced as indicators of community transmission [11,12]. Over 3 years after COVID-19 pandemic restrictions were introduced, *M. pneumoniae* has re-emerged in Europe and Asia. As we know, this delayed reemergence is unique to this pathogen, and it occurred long after NPIs were discontinued. *Mycobacterium tuberculosis* and *Bordetella pertussis*, which had reduced incidence and resurgences that occurred earlier than *M. pneumoniae*, in 2021 and 2022, respectively, were two other respiratory pathogens with sustained declines but earlier resurgences [13,14]. The complicated linkages between numerous health and epidemiological factors are highlighted by the rapid increase in *M. pneumoniae* infections in China following the lifting of COVID-19 restrictions in 2023. Extensive isolation measures were implemented as a result of the pandemic, which decreased exposure to common respiratory viruses and produced an "immunity gap." This gap reduced both individual and group immunity because of fewer pathogen exposures. Populations with less exposure to pathogens, particularly children and young people, were more susceptible to infections once limitations were lifted [15]. Other respiratory viruses, such as respiratory syncytial virus (RSV), also showed same pattern. The pandemic lowered viral co-infections that had previously assisted in the management of bacterial diseases like *M. pneumoniae* and upset regular patterns of pathogen circulation. Once limits were removed, *M. pneumoniae* could spread more readily because non-pharmaceutical interventions (NPIs) reduced viral infections. Furthermore, non-COVID respiratory infections were frequently disregarded by healthcare systems that prioritized treating COVID-19, which resulted in an underdiagnosis or untreated case of *M. pneumoniae*. These situations increased as healthcare services became more concentrated. Due to the increased contact amongst children who had weakened immune systems, the reopening of schools had a role in the spread. All things considered, the rise in *M. pneumoniae* infections serves as a reminder of the substantial changes in respiratory illness patterns that might result from pandemic-related adjustments to pathogen exposure, healthcare goals, and demographic variables [16,17].

2. Exploring *M. pneumoniae's* comeback: insights into pathogenesis

Atypical pneumonia is caused by the bacteria *M. pneumoniae*, which uses a number of immune evasion techniques to spread and persist in infection [18]. These techniques include the following: One prevalent pathogen linked to respiratory illnesses is *M. pneumoniae*. Its pathogenicity is largely dependent on its capacity to adhere to host cells. The P1 protein is the main adhesin in charge of this adherence. This protein specifically interacts with sialoglycoproteins that are found on the respiratory tract's epithelial cells' surface. Because of this organelle, *M. pneumoniae* is able to adhere securely to the membrane of the host cell, maintaining the bacterium's close contact to the host cells. For further invasion steps, this first devotion is necessary. The significance of adherence mechanisms in establishing infection is shown by the pivotal roles played by the attachment organelle and the P1 protein in the pathogenesis of *M. pneumoniae*. These structures enable a tight binding that is important for efficient colonization as well as the bacterium's resistance to host immunological responses. Following attachment, *M. pneumoniae* can penetrate host cells by a mechanism known as "pedestal formation," in which the bacteria alter the cytoskeleton of the host cell to make entry easier. In contrast to several external infections, *M. pneumoniae* possesses the capacity to infiltrate and persist within epithelial cells, offering a shield from extracellular immune reactions [19].

Because of its internal lifestyle, it is able to elude the host's immune responses, which include complement proteins and antibodies that are useful in fighting extracellular diseases. *M. pneumoniae* is protected from parts of the host's antimicrobial defenses and avoids direct exposure to these immune components by living inside the cells. Because of its intracellular presence and resistance to many common immune responses, *M. pneumoniae* is an especially difficult disease to target and eradicate [19]. *M. pneumoniae* has the ability to obstruct apoptotic signaling pathways as well as other host cell signaling pathways. The bacterium increases the duration of infected cells' survival by blocking apoptosis, which improves the bacterium's own persistence and multiplication within the host. The environment within cells restricts the amount of time that bacterial antigens are exposed to immune surveillance systems. This lessens the possibility that extracellular antigen-targeting antibodies and cytotoxic T cells will find and eliminate the target. *M. pneumoniae* is able to evade systemic immune responses, including those involving phagocytes and circulating antibodies, because it may live inside host cells. The intracellular niche offers the bacteria a safe haven from direct immune responses so that it can survive longer. The persistence of inflammation is partly caused by *M. pneumoniae* living inside host cells. Prolonged symptoms and possible tissue damage in the respiratory tract are caused by chronic inflammation resulting from the immune system's continuing response to the infection. Prolonged inflammation can exacerbate the infection, resulting in more severe respiratory symptoms and increasing the difficulty of treatment procedures [19].

In *M. pneumoniae*, the pathogenesis is complex. It causes alterations in intracellular metabolism and ultrastructure in infected cells at the initial stage of infection. Meanwhile, CARDS toxin, hydrogen peroxide and superoxide radicals are released and directly damage host cells. Eventually, inflammation is caused by inflammation in conjunction with HapE enzymes, lipids, lipoproteins, glycolipids, and other components, which induce the production of cytokines. The immune evasion mechanism used by *M. pneumoniae* allows it to survive in the body for a long time, which may lead to more serious clinical manifestations. An important factor in *M. pneumoniae's* pathogenicity is adhesion. This ability relies on a terminal attachment organelle with polarized attachment. Some pathogenic factors, such as toxic effects, require adhesion. Attaching to the bronchial ciliary epithelium surface, *M. pneumoniae* interacts with the host respiratory epithelium, affecting intracellular metabolism and ultrastructure in infected cells, rearranges the cytoskeleton, and depletes host cells of nutrients [20]. As a result of its unique attachment organelle, *M. pneumoniae* tightly binds to the epithelial cells at the host's surface, which is believed to facilitate cell division, adhesion, and cell motility [21]. Sialylated and sulfated oligosaccharide receptors are the main targets of *M. pneumoniae* [22]. *M. pneumoniae* adhesion and sliding can be profoundly affected by the nature and density of host receptors, which impacts their pathogenic mechanisms [23]. It has also been shown that *M. pneumoniae* can cause some extrapulmonary complications in addition to the usual respiratory symptoms [24].

3. Understanding the comeback of *M. pneumoniae* pathogenic insights

M. pneumoniae is best known for its role in community acquired pneumonia pathogenesis especially in 5–7 year old children [25,26]. It accounts for 10–40 % cases of pneumonia among adolescents and children [27,28]. Infection with *M. pneumoniae* can develop to severe cases of pneumonia, bronchitis, heart failure and immune system disturbance if it's not treated in time or doesn't get restricted spontaneously [29,30]. In recent years numerous cases of plastic bronchitis were reported in children as a complication of *M. pneumonia* infection. Plastic bronchitis is an acute condition which happens when bronchial casts are produced

and cause obstruction in tracheobronchial tree. It's often presented with progressive dyspnea, pleuritic chest pain and productive cough and is more likely in patients with an underlying cardiac or pulmonary disease like cyanotic congenital heart disease, cystic fibrosis, sickle cell anemia and neoplasms [28]. Also during COVID-19, reports revealed that co-infection with *M. pneumoniae* aggravate the severity of the symptoms and increase the mortality rate so an accurate surveillance with a proper treatment is absolutely required [31].

M. pneumoniae is a small pathogen which is transferred through respiratory droplets and cause symptoms like sore throat, headache, and cough that can be persistent for weeks. Nose congestion, wheezing and diarrhea are the symptoms mostly seen in pediatric patients. Some cases may get inflicted by extra-pulmonary manifestations in their skin or other organs and experience *Mycoplasma*-induced rash, myocarditis, hepatitis and hemolytic anemia [25,29,32]. A study indicated that children who developed severe *M. pneumonia* infection had elevated respiratory rates with cyanosis and dyspnea. Also multiple lobes of their lung were infiltrated, their general status was compromised and some had extra-pulmonary manifestations [32,33]. Also compared to viral pneumonia, hyperthermia and eosinophilia were more common in mycoplasma infection while the incident rate of hypothermia, vomiting, procalcitonin and lymphocyte level were lower [26]. *M. pneumoniae* is capable of living outside the host cell but it takes nearly 6 weeks for the bacteria to grow in the medium. Due to the absence of a cell wall in *M. pneumoniae,* resistance against B-lactam antibiotic exists so the direct contact between the bacteria and the host cell promotes the molecular exchange on membrane level [25,29].

Although infection with *M. pneumoniae* can happen any time of the year it peaks in summer and the beginning of fall but its epidemic cycle normally occurs each 3–7 years and lasts for 2 years [29,30,34], The last two epidemics happened in 2013 and 2016 [30]. Factors like waning herd immunity or emergence of new subtypes in communities may explain the periodic epidemics. Recent data acquired from prospective surveillance centers assessed the prevalence of *M. pneumoniae* in 24 countries during April 1 to September 30, 2023. This data showed that incident rate of *M. pneumoniae* is more frequent in Europe and Asia than in America and Oceania. The highest reported rate were Denmark, Sweden, and Switzerland in Europe and Singapore in Asia [34]. During COVID-19 pandemic there was a decline in *M. pneumoniae* prevalence. A vast study was carried on in China on a million children aged 1 day to 18 years. The results showed the number of children infected with *M. pneumoniae* has reduced in all ages in 2021 and 2020 compared to 2018 and 2019. The decrease in *Mycoplasma* infection was attributed to the sanitary precautions that were taken seriously during Covid-19 pandemic, measures like avoiding physical contact, wearing mask, following the routine of hand hygiene and staying away from social gatherings [25,27,30]. Therefore these precautions are considered to be significantly essential for the prevention of *M. pneumoniae* infection [25]. Another study that analyzed 34752 CAP-infected children in China, also indicated a significant decrease in positive numbers of *Mycoplasma* infected individuals due to preventive procedures in 2020 but, the positive rate increased once again in July to October in 2021. Withdrawal of limitations and precautions and wide use of Azithromycin during COVID-19 may explain this drastic increase [27]. It's been also reported that humidity and temperature has remarkable impact on *Mycoplasma* survival and 37 °C has been detected as the optimum temperature for its growth. So with the climate changing globally and the temperature rising, the condition for *M. pneumoniae* growth becomes more and more suitable especially in the hot months of the year [30]. As it was explained, preventive measures during COVID-19 epidemic contributed to a substantial decline in *M. pneumoniae* detection but the interesting matter is that the re-emergence of this bacteria occurred long after the non-pharmaceutical interventions were discontinued unlike *M. tuberculosis* and *B. pertussis* which had earlier resurface. Waning and altered herd immunity over time and exclusive features of *M. pneumoniae* like slow growth rate, long incubation period and lower transmission rate might be the reasons of why the re-emergence of this bacteria was delayed [34].

4. Novel approaches and pathogenic mechanisms

M. pneumoniae pathogenesis pathway initiates when the bacteria is attached to the host cell, then it induces the innate immune system. The activation begins and local cytotoxic agents get released and cause inflammation. The infected harmed epithelial cells produce cytotoxic substance that elevate inflammatory cytokines. Besides there's a virulence factor, CARD (community-acquired respiratory distress syndrome) toxin which is produced and contribute to airway dysfunction. In case the substance enter the systemic circulation, involvement of extra-pulmonary organs can be manifested [29]. In addition, MPP can impose destruction through adhesion and membrane fusion and lead to respiratory epithelium necrosis. It also can impair the normal function of cilia. As a result the mucus formation facilitate the inflammation process [28,35].

The uncontrolled use of Macrolides in recent years has led to the emergence of macrolide-resistant *M. pneumoniae* (MRMP) [29,32]. A study of 520 admitted children who were infected with *M. pneumoniae* showed that those with MRMP infection are more likely to develop pleural effusion, increased D-dimer, LDH, lymphocyte count and a longer duration of admission. However the reports have been inconsistent and in some other studies no significant clinical differences were detected between MRMP and MRSP infection [32]. In another study high fever, elevated serum level of LDH, albumin,GOT, interleukin-18, IL-17A, and the CARD toxin in Broncho-alveolar lavage fluid indicated as predictors for refractory form of *Mycoplasma* infection [33]. Patients who have lasting fever and consolidations in their imaging despite receiving macrolide antibiotic for 7 days are about to develop refractory *M. pneumonia*. The complications of this kind can be life threating; bronchitis obliterans, thrombosis and necrotizing pneumonia are some instances that should be noted [26,35,36].

The resistant species were first detected in children in Japan but it's been spreading vastly all around the world especially in Asia [29,32]. The prevalence of MRMP has exceeded 60 % in Asia and over 80 % in China and Korea [35]. Studies revealed that mutations in 23S rRNA of *M. pneumoniae* is responsible for the antibiotic resistance. A2063G appears to be the most prevalent mutation that has been reported so far [29]. The affected mutated region in rRNA has lesser affinity to the macrolides and as a result this antibiotic can't exert its inhibitory effect on protein synthesis of *M. pneumoniae* and block its growth [29]. Now the prevalence of *Mycoplasma* are comparable to pre-pandemic era in Asia and Europe but the progression of this re-emergence isn't easy to anticipate due to the previously reduced exposure but the clinicians should be alarmed about the severe cases of re-emergent infection and its extra-pulmonary complications to present a timely and efficient management [34].

5. Pathogenesis resurfaced: *M. pneumoniae* new frontier

Around 20 mycoplasma species, such as *M. pneumoniae*, require a polarized cytoskeletal structure for attaching to host epithelial cells and surfaces. *M. pneumoniae's* attachment organelle, a unique polarized structure, plays a role in both gliding motility and cell division [37,38]. A distinguishing feature of this organism is its electron-dense core, composed of atypical cytoskeletal proteins and enclosed by a membrane with adhesins embedded on its surface [38]. Preferably, these adhesins bind to sialo-glycoconjugates and sulfated glycolipids on the host cell's surface during *M. pneumoniae* infection, with a particular affinity for the apical microvillar border and ciliated epithelium [39,40]. Absence of host molecules in the secretory cells and mucus makes them unsuitable for attachment. When attachment organelle proteins are mutated, *M. pneumoniae* cells can't properly attach due to structural or functional impairments. The gliding mechanism in *M. pneumoniae* is not yet fully

explained, unlike in certain other motile *Mycoplasma* [37,41].

Examining gliding motility in *Mycoplasma* mobile and other mycoplasmas is unlikely to shed light on how *M. pneumoniae* achieves this, due to the contrasting composition of their adhesins and attachment organelles [40,41]. The absence of virulence in these attachment organelle protein mutants underscores the essential role of this structure in infection colonization and pathogenicity. Scientists have been driven to investigate the proteins of the attachment organelle, specifically P1, due to its crucial involvement in causing sickness. This has led to a focus on using it as a potential treatment or vaccine [39,42].

The connection between carbon metabolism and pathogenicity is evident in the nature of numerous pathogens [43]. Phospholipids in the host's lung epithelia are broken down and used for energy by *M. pneumoniae*. The breakdown of these phospholipids leads to the creation of hydrogen peroxide, an important virulence factor [42,43]. The host cell is susceptible to cellular damage caused by hydrogen peroxide, which triggers lipid peroxidation and can lead to cell lysis. Hydrogen peroxide production, caused by the metabolism of glycerol and glycerol-phosphocholine, is responsible for cytotoxicity in many species of the *Mycoplasma* genus [39,40].

Hydrogen peroxide and the community-acquired respiratory distress syndrome (CARDS) toxin are both significant virulence factors in *M pneumoniae*. Essential for the successful delivery and cytotoxicity of the CARDS toxin, the KELED (Lys-Glu Leu-Glu-Asp) sequence is a distinct feature within its structure [44]. By transferring an ADP-ribosyl group to host target proteins, this toxin induces vacuolization and ultimately results in cell death. Host hemolysis has been linked to virulence due to the involvement of hydrogen sulfide. This virulence factor, produced by *M. pneumoniae* through HapE, serves the purpose of obtaining essential nutrients like amino acids and nucleotides [37,45]. It is possible that this enzyme plays a role in both the production of thiouridine in tRNA and the conversion of cysteine to alanine [46]. Furthermore, HapE is capable of converting cysteine to pyruvate by means of its cysteine decahydrate activity, a practical process that can yield an extra ATP through the oxidation of pyruvate [39,44]. Bacteria are able to communicate with each other through physical contact or by releasing chemicals, which can activate cellular processes such as the creation of virulence factors and biofilms [39,46]. Peptides, lipids, and secondary metabolites are the typical types of chemical substances that are secreted [39,47]. When bacterial cells release them into the environment, they become signaling molecules that attach to specific receptors on neighboring cells, setting off a series of events that regulate cellular functions [42,46].

5.1. Regulatory systems in M. pneumoniae

The phosphotransferase system (PTS) is a regulatory mechanism responsible for simple sugar transport in this organism. It is primarily used for sugars uncommonly found in lung epithelia. *M. pneumoniae* primarily uses lung epithelial phospholipids for energy, as revealed by recent studies on carbon source metabolism [47,48]. Glycerol, along with glycerol-phosphocholine (GPC), both of which are essential components found in phospholipids, are known to enter the process of glycolysis in the form of dihydroxyacetone phosphate (DHAP). The metabolic processes of these molecules give rise to the production of hydrogen peroxide, which serves as a significant virulence factor within the human host [20,49]. The process of glycolysis is a complex metabolic pathway that plays a crucial role in energy production within living organisms. Before GPC can enter the glycolysis pathway as DHAP, it undergoes an important modification [20]. This modification involves the removal of its diester group, which is facilitated by the enzyme known as glycerol-phosphodiesterase GlpQ. This enzymatic reaction is necessary for GPC to be converted into DHAP, ultimately allowing it to continue through the series of reactions that lead to ATP generation and energy release [20,47].

6. Tracking *M. pneumoniae* reemergence

The literature on pediatric *M. pneumoniae* has significantly increased from the late 1990s to the early 2020s [50,51]. This particular subject has recently undergone a remarkable surge in expansion after the year 2018, with an annual increase exceeding many publications. Simultaneously, the appearance of SARS-CoV-2 and its disease, COVID-19, has rapidly swept across the global landscape since its initial documentation in December 2019, establishing it as the most critical public health urgency of the century [37,52]. Governments have implemented strict containment measures to reduce the spread of respiratory illnesses, including movement restrictions, mask-wearing, and promoting hand hygiene. One could argue that the pre-COVID-19 era was accompanied by a *M. pneumoniae* epidemic, which led to inflated incidence rates. This not only provided clinicians with ample clinical data, but also inspired scholars to undertake more foundational research [37,38,53].

M. pneumoniae causes respiratory disease through cytoadherence, a key virulence factor involving close interaction with the mucosal epithelium. It is believed that cytoadherence, along with the generation of peroxide and superoxide radicals, contributes to disease by inducing oxidative stress [20]. Superoxide anions produced by *M. pneumoniae* inhibit catalase in host cells, making the host cell more susceptible to oxidative damage. Patients with *M. pneumoniae*-induced pneumonia are often encountered by doctors, who may exhibit less respiratory distress compared to the extent of their lung involvement [20,49,54]. In various parts of the world, infections are a constant occurrence, and outbreaks happen periodically. Previous data revealed that there was a 1–3-year time frame between *M. pneumoniae* epidemics occurring in Europe [37,54]. The periodic outbreaks of epidemics can be linked to multiple factors, including a decline in herd immunity and the introduction of new subtypes into the population. The last epidemic to occur, which affected several countries in Europe and Asia, took place during the late 2019 to early 2020 period [37,55].

The resurgence of *M. pneumoniae* in Europe and Asia has been brought to light by the global surveillance data, despite the implementation of COVID-19 pandemic restrictions over three years ago. This pathogen's reappearance, which was significantly delayed even after the discontinuation of nonpharmaceutical Interventions (NPIs), is a unique and noteworthy occurrence [37,38]. *M. tuberculosis* and *B. pertussis*, along with *M. pneumoniae*, saw a sustained decrease in cases, but they both resurged earlier. However, it wasn't until 2021 and 2022, respectively, that an increase in reported cases was observed [20,56]. There are many ideas about why the spread of infections changed during the COVID-19 pandemic. Most of them don't relate to *M. pneumoniae* anymore because the number of cases has dropped so much since the NPIs stopped being used [38,53]. It is unlikely that there was a connection between the decline in pneumococcal disease in young children and the suppression of respiratory syncytial virus, *influenza* viruses, and human *metapneumovirus*, as observed for *Streptococcus pneumoniae*. This is because respiratory viruses resurged much earlier, while *M. pneumoniae* was still absent. It has been suggested that the reappearance of M. pneumoniae epidemics could be due to a decrease in herd immunity over time [37,38]. As previously theorized for *M. pneumoniae* epidemics, the decline of herd immunity could also be responsible for the delayed re-emergence. However, there has been no evidence of a reoccurrence in nations where the previous outbreak was noted. Furthermore, PCR did not detect any re-emergence, but there was a decrease in *M. pneumoniae*-specific IgM and IgG antibody levels at locations that provided separate data for PCR and serology, indicating a decline in immunity [37,38,57]. There is a potential link between *M. pneumoniae* and immune-mediated neurological conditions. Secondary vasculitis of the central nervous system can be triggered by infections, as well as inflammatory or autoimmune conditions [57]. In children, *Mycoplasma* can lead to the development of secondary central nervous system vasculitis. Yimenicioğlu, S. et al. found that a patient suffering from encephalitis also had vasculitis affecting both the internal

carotid artery and posterior circulation in their studies. Their findings suggest that although *M. pneumoniae*-related neurological symptoms typically fully resolve, they can also lead to long-term impairments in physical and cognitive abilities with varying levels of severity [58].

7. *M. pneumoniae* resurgence explored

New research has shown a gradual rise in the occurrence of fatal or severe *M. pneumoniae*, potentially due to excessive inflammation. Nonetheless, the precise origins of this immoderate inflammation remain obscure. Many agree that the location of administering antibacterial treatments for *M. pneumoniae* is inconsequential due to its low mortality rate and self-limiting nature [38,57]. Findings from studies as far back as the 1960s have revealed that treating mild *M. pneumoniae* infections can lead to a decrease in pneumonia morbidity and a quicker resolution of symptoms. A recent study in Japan revealed that telithromycin, a ketolide antibiotic, effectively combats 41 clinical strains of *M. pneumoniae*. It has also been reported globally that there are cases of Macrolide-resistant *M. pneumoniae* [37,50,54]. In the past two decades, macrolide-resistant *M. pneumoniae* has been reported in China, Japan, Europe, and the United States, affecting individuals of all ages. Several types of antibiotics have been created to combat infections, with various versions tailored to different age groups affected by the infection. The emergence of drug-resistant *M. pneumoniae* is becoming a growing concern in the treatment of community-acquired pneumonia. It is crucial to monitor the epidemiological patterns of *M. pneumoniae* resistance to various antibiotics in adult patients [53,59].

Regardless, it should be noted that both China and the United States have become prominent for their prolific publication output. A complex system of partnerships has been established through the collaboration of countries. Conversely, the majority of institutions are not clustered in a single location, emphasizing the need to improve collaboration among them [37,53]. While discussing the survival and spread of airborne *M pneumoniae*, it is important to acknowledge the significant role that climate conditions, such as hu.midity and temperature, can play. Nevertheless, these studies have produced conflicting outcomes, indicating that climate may not be the dominant factor in determining *M. pneumoniae* transmission patterns [38,53]. Besides, there were no apparent disparities in the sex distribution of pediatric cases with *M. pneumoniae* infection. Positive cases showed a significant difference based on the age of the affected individuals. Evidence suggests that *M. pneumoniae* infections are more prevalent in children aged 5 and above, but can also occur in younger infants [38,57]. On the other hand, varying studies have proposed increased rates of infection among young children in either preschool or school settings. Several studies have shown that the percentage of hospitalizations due to *M. pneumoniae* infection falls within the reported range of 18–67 %. The significant upsurge observed in 2019 strongly indicates that infections during an *M. pneumoniae* epidemic were notably more severe and intense compared to previous outbreaks [53,57].

8. New strategies in combatting *M. pneumoniae's* resurgence

There has seen a resurgence of *M. pneumoniae* infections which has led to an urgent need for new strategies to combat this pathogen.

Surveillance: The global prospective surveillance is essential for tracing the trend and outbreak of MP infections and alerting clinicians to familiarize themselves with the atypical characteristics of this bacteria for sufficient management and quick response. Although there has been a global survey, from 2017 to 2021, it merely covered 37 sites from 21 countries and there is no national reporting or surveillance system for this infection [37]. Additionally, there is a need for integrated guidelines in order to MP detections and surveillance [38]. Also, in recent years, antimicrobial resistance has become an important issue in management of MP infection, thereby we need an epidemiological surveillance system to cover antimicrobial resistance.

Antibiotic treatment and resistance: Macrolides like azithromycin is deemed a choice treatment for MP infection in children [60]. Due to overuse or inappropriate use of macrolide medications, macrolide-resistant strains have increased dramatically worldwide since 2000, particularly in Asia, where resistance rates have reached 80–90 % [61,62]. In Kue et al. study conducted in southern Taiwan, the rate of macrolide-resistance MP(MRMP) was 88.1 % [63]. Kim et al. showed that the global prevalence of MRMP is approximately 28 % [64]. Clinicians should be cognizant of antibiotic treatment options and the manifestations of MRMP, including persistent fever and/or lack radiological regression, and the possibility of complicated pneumonia [65]. In pediatric MRMP, tosufloxacin was used in Japan, and tetracyclines including minocycline or doxycycline were found to be more effective but it is important to note that they are contraindicated in children aged less than 8 year [66,67]. Appropriate antibiotic prescription and timely diagnosis of the disease are of great importance to reduce the duration of the disease and its severity, as well as the development of MRMP.

Promoting Non-Pharmaceutical Interventions (NPIs): Since some NPIs were implemented in various countries during the COVID-19 pandemic, the outbreak of MP infection experienced a substantial decline. So, some preventive measures like hand washing, improving hand hygiene, mask-wearing by preventing the spread of respiratory droplets, and social distancing by reducing close contact can help to reduce the incidence of this infection [68].

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Data availability

The corresponding author will provide the datasets created during and/or analyzed during the current investigation upon reasonable request.

Ethics approval

This research was done via observation. There is no need for ethical approval for the research.

Consent to participate

All individuals taking part in the study gave their informed consent.

Intellectual Property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Authorship

We confirm that the order of authors listed in the manuscript has been approved by all named authors.

CRediT authorship contribution statement

Hamed Tahmasebi: Writing – original draft, Investigation, Data curation. **Ali Babaeizad:** Software, Formal analysis, Conceptualization. **Maryam Mohammadlou:** Writing – original draft, Investigation. **Farnaz Alibabaei:** Writing – original draft, Resources, Investigation. **Seyedeh Zahra Banihashemian:** Writing – review & editing,

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