Review Article

Understanding the unconventional reemergence of *M. pneumoniae* epidemics during the COVID-19 pandemic

Bingjie Liu, Lina Xu, Yuqing Wang, Chuangli Hao, Wujun Jiang

Department of Respiratory Medicine, Children's Hospital of Soochow University, Suzhou, China

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Correspondence to: Wujun Jiang, MD. Department of Respiratory Medicine, Children's Hospital of Soochow University, No. 92 Zhongnan Street, Suzhou 215000, China. Email: jwj8701@suda.edu.cn.

Abstract: Since the implementation of coronavirus disease 2019 (COVID-19) restrictions since 2020, the number of *Mycoplasma pneumoniae* (*M. pneumoniae*) infections in children has significantly decreased. However, after the end of the COVID pandemic, there has been a notable resurgence in *M. pneumoniae* infections, which is particularly unusual in terms of both the number of infections and their severity. The purpose of this article is to review the existing evidence and explore theories that underlying the epidemiological shifts of *M. pneumoniae* following the COVID-19 pandemic, and propose factors contributing to the unconventional resurgence of *M. pneumoniae* infections. Proposed factors include decline of *M. pneumoniae* immunity, circulation of different genetic types and emergence of new macrolide-resistant *M. pneumoniae* (MRMP) variants, immune dysregulation following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and others. Among these factors, the decline in *M. pneumoniae* immunity and the circulation of different genetic types are considered significant contributors. Further research in bacterial genomics and more robust immunology studies are needed to guide the prevention of *M. pneumoniae* infections and the allocation of healthcare resources. International cooperation and information sharing are crucial for understanding the epidemiological changes of *M. pneumoniae*. Further cross-regional collaboration is called to enhance our understanding of the scope of *M. pneumoniae* outbreaks and facilitate a collective response.

Keywords: *Mycoplasma pneumoniae (M. pneumoniae)*; reemergence; waning immunity; coronavirus disease 2019 (COVID-19)

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Introduction

Mycoplasma pneumoniae (*M. pneumoniae*) frequently leads to respiratory tract infections, placing community-acquired pneumonia as the primary burden associated with the disease in children and adults (1). While the majority of pediatric cases of *M. pneumoniae* infections are relatively mild, it is essential to note that some cases can lead to more severe outcomes, such as pleural effusion, bronchiolitis obliterans, bronchiectasis, and atelectasis. Previous studies suggested that there is typically an interval of 2–4 years between epidemics of *M. pneumoniae* in Europe and Asia (2-4). The latest epidemic of *M. pneumoniae* before coronavirus disease 2019 (COVID-19) pandemic occurred in late 2019, affecting multiple nations concurrently, with a predominant impact observed in Europe and Asia (5).

Since 2020, the implementation of non-pharmaceutical interventions (NPIs) to combat COVID-19 has led to a sudden cessation of these epidemics and a notable decrease in the global detection of *M. pneumoniae* (5), as well as other

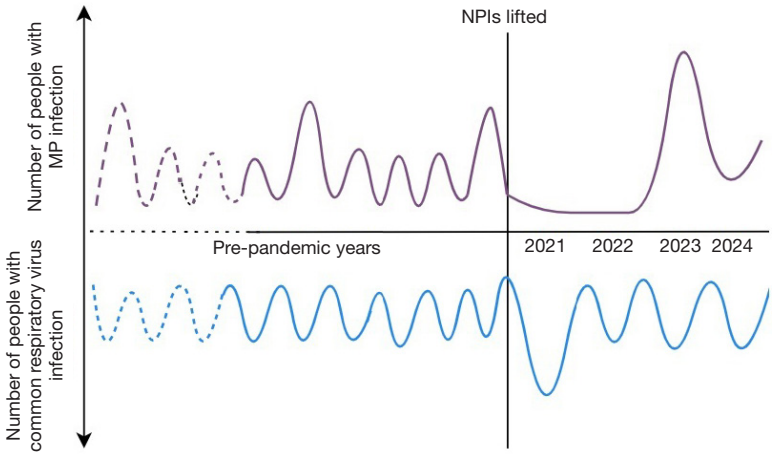

Figure 1 Modelling of *M. pneumoniae* and common respiratory viruses in children before and after the COVID-19 pandemic. The model is based on relevant research data (7,9). During the pandemic, the implementation of NPIs led to a sharp decline in infections. As NPIs were relaxed, the number of infections with common respiratory viruses first increased, until an unconventional outbreak of *Mycoplasma pneumoniae* infections occurred in 2023. COVID-19, coronavirus disease 2019; *M. pneumoniae*, *Mycoplasma pneumoniae*; NPIs, non-pharmaceutical interventions.

respiratory pathogens (6). After the relaxation of major NPIs in many areas, several virus infections emerged and continued to persist, while *M. pneumoniae* did not resurge until 2023. Although the outbreak of *M. pneumoniae* occurred later compared to other viral infections, it follows the usual cycle of 2 to 4 years. However, unlike previous patterns, it is unconventional that there has been a significant increase in the number of cases in multiple regions in 2023, far surpassing the levels observed before the COVID-19 pandemic (7-9) (*Figure 1*).

Documenting and comprehending the atypical alterations in *M. pneumoniae* circulation during the COVID-19 pandemic can contribute valuable insights to shape forthcoming public health responses. The purpose of this article is to review the existing evidence and explore various theories that underpin the atypical shifts in the epidemiology of *M. pneumoniae* during the COVID-19 pandemic.

Decline of *M. pneumoniae* immunity at the population level

At the end of 2019, there was an outbreak of *M. pneumoniae* infection, leading to the population acquiring temporary herd immunity to *M. pneumoniae*. Given the typical three-year interval between *M. pneumoniae* epidemics, this temporary herd immunity likely helped suppress the resurgence of the infection for an extended period. The absence of continuous immune stimulation by *M. pneumoniae* or other respiratory pathogens for extended periods may have expanded the population of immunologically vulnerable individuals, particularly among children. The Pediatric Infectious Disease Group has introduced the concept of an "immunity debt" to explain this phenomenon (10). Waning humoral immunity, characterized by lower antibody titers, could increase the susceptibility to infection, thereby contributing to a higher incidence of respiratory infections (11). The decline in the detection of *M. pneumoniae*-specific immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies may further confirm this point (12).

Our recent study summarized the dynamic changes in *M. pneumoniae* IgG antibodies in children aged 1–14 years before and after the epidemic, and for the first time, provided evidence of *M. pneumoniae* immunity gap following an extended period with low exposure to the microbe (7). In the late stage of the pandemic, the decline in IgG levels was more pronounced in children over 9 years old. Another study confirmed a significant reduction in IgA and IgM levels in the pediatric population during this period (13). Further research is needed to investigate antibody levels against *M. pneumoniae* in adults.

Prior to the introduction of NPIs, children had regular opportunities to be exposed to and develop immunity

against *M. pneumoniae*, following the normal infection cycle. However, during the period when NPIs were implemented in China from 2020 to 2022, susceptible children were not exposed to *M. pneumoniae* infections. As a result, the efficacy of *M. pneumoniae* immunoglobulin G (MP-IgG) antibodies decreased more than expected, resulting in an immune gap. Additionally, infants born during this period had limited exposure to antigens, resulting in a relatively weaker immune response. Therefore, by 2023, the cumulative effect of a new susceptible cohort and the gradual decline in immunity over time widened the immune gap, potentially contributing to a significant increase in the number of affected children.

Circulation of different genetic types and emergence of new macrolide-resistant *M. pneumoniae* (MRMP) variants

The genome of *M. pneumoniae* is highly conserved, and the total number of genes is close to saturation, indicating a relatively restricted pan-genome.

In Switzerland, P1-1 and P1-2 alternate in dominance (14). The United States experienced a shift from P1-1 to P1-2 (15). In East Asia, P1-1 was the initially dominant strain, aligning with reports from Japan, where P1-2 was predominant from 2017 (16).

Recent studies have noted a trend in certain regions of China shifting from P1-1 to P1-2 (17). Particularly post-pandemic, there has been a significant increase in the proportion of P1-2 among school-aged children in China, although this change has not been observed in children, adults, and the elderly (16). This is consistent with a study conducted in Suzhou, where the transition from EC1 in P1-1 to EC2 in P1-2 was observed, showing complete resistance to macrolide antibiotics (18). This suggests a shift in the predominant *M. pneumoniae* patterns, leading to changes in the distribution of macrolide-resistant strains.

Besides, new research in Vietnam has revealed the emergence of a novel C2353T variant, which showed resistance to macrolide antibiotics (19). The known MRMP mutation A2063G is the most prevalent mutation compared with other infrequent mutations (e.g., A2063T/C, A2067G, A2064G, A1290G, and C2617A) (20). Mutations at site 2063 are strongly linked to elevated macrolide resistance levels (21). The circulation of different *MRMP* variants or emergence of new *MRMP* variants may contribute to the recent *M. pneumoniae* infections outbreak among children (18).

As patients with macrolide-resistant infections experience longer duration of fever, prolonged hospital stays, and greater treatment challenges compared to those with macrolide-sensitive infections (21). The transition in genotypes and the emergence of novel variants have increased the number of patients with *MRMP* infections, leading to a rise in hospitalizations due to *M. pneumoniae* infections.

Immune dysregulations following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

SARS-CoV-2 infection elicits a robust immune response that plays a crucial role in clearing the initial infection. This response involves the generation of neutralizing antibodies and the activation of CD4 and CD8 T cells. Neutralizing antibodies can prevent infection and clear pathogens, playing a key role in providing long-term immunity (22). Similar to most acute respiratory virus infections, SARS-CoV-2 infection triggers a neutralizing antibody response (22). However, with the recent emergence of the SARS-CoV-2 Omicron variant, there has been a decrease in the production of neutralizing antibodies. These variants carry numerous protein mutations that can evade broad-spectrum neutralizing antibodies, leading to a compromised immune function, which underscores the increasing immunological importance of T-cell responses targeting conserved epitopes in cellular immunity (23). Compared to other respiratory viruses, the host's immune response to SARS-CoV-2 fails to initiate a robust type I and type III interferon response, while inducing high levels of chemokines and pro-inflammatory cytokines (24). Additionally, despite the effectiveness of interferons in blocking SARS-CoV-2 replication, the virus employs mechanisms to inhibit the induction of endogenous interferons and interferon receptor signaling (25). This reduction in early interferon response can result in an imbalanced host immune response and an inability to clear the virus (24). Consequently, the lack of this interferon response allows for sustained viral replication, leading not only to severe SARS-CoV-2 infection but also to large-scale respiratory viral infection events observed in populations after the lifting of NPIs. Immunological dysregulation may lead to a larger population and more severe *M. pneumoniae* infections. Currently, there is no literature specifically addressing this, but there are reports regarding the impact of immunological dysregulation on viral activity (6). Similarly, a weakened humoral immune response may increase the likelihood of

infection, leading to more infections, increased replication of *M. pneumoniae*, and a higher chance of mutations, thereby resulting in the emergence of new variants that can impact the activity of *M. pneumoniae* infections.

Other potential factors

Changes in the colonization of upper respiratory tract (URT) bacteria in children

The URT colonization includes bacteria, viruses, and *M. pneumoniae*, which interact in a symbiotic or antagonistic manner (26). Changes in URT colonization can affect the infection process through various pathways, for instance, by upregulating adhesion receptors, thereby increasing the binding of certain pathogens to epithelial cells and amplifying the inflammatory response (26). Infection by *M. pneumoniae* initially requires adhesion to the host bronchial epithelium, inducing an inflammatory response in infected cells (27), a process that may also be influenced by URT colonization. A study from South Africa reported changes in URT colonization in children before and after COVID-19 (28), with such changes potentially affecting the current infections of *M. pneumoniae*.

Potential interaction between respiratory viruses and M. pneumoniae

In our country, where NPIs were lifted in 2022, the resurgence of both common respiratory viruses and *M. pneumoniae* occurred in 2023. In 2023, children began experiencing multiple viral infections, including influenza, adenovirus, and respiratory syncytial virus, starting in March (29). The rise in viral infections may have contributed to immunological dysregulation, increasing children's susceptibility to *M. pneumoniae*, which re-emerged following the viral outbreaks. Besides, the co-infection of viruses and *M. pneumoniae* is a common occurrence (30). When compared to a singular *M. pneumoniae* infection, children admitted to the hospital with *M. pneumoniae* along with simultaneous viral infections, particularly adenovirus and influenza, display more severe clinical symptoms and necessitate an extended treatment duration (31). The simultaneous resurgence of multiple viruses, along with *M. pneumoniae*, has further contributed to an increase in hospitalizations.

The impact of environmental factors on M. pneumoniae infection

Meteorological factors and environmental pollutants strengthen the susceptibility to respiratory pathogens, including *M. pneumoniae*, especially in the transmission of *M. pneumoniae* infections. A previous study has shown particulate matter 2.5 ($PM_{2.5}$), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) concentrations have influence on *M. pneumoniae* infections in children (32). Compared to the period of NPIs, exposure to environmental air pollutants post-pandemic may impact the transmission of respiratory pathogens, promoting inflammatory states and leading to immune system dysregulation (33).

Conclusions

This study documents and analyzes the atypical epidemiological changes of *M. pneumoniae* during the COVID-19 pandemic. A sudden decrease in *M. pneumoniae* cases and a significant global reduction in detection rates due to NPIs implemented for COVID-19. However, as these interventions were gradually relaxed, a delayed resurgence of *M. pneumoniae* was observed, with large-scale outbreaks occurring in China in October and November 2023. The resurgence of *M. pneumoniae* infections in children may be associated with various factors as mentioned earlier (*Figure 2*).

In the future, for comprehensive management of *M. pneumoniae*, especially considering the long-term impact of the COVID-19 pandemic, continuous monitoring of immunity levels is crucial. Simultaneously, in-depth research on the relationship between genetic changes in *M. pneumoniae* and antibiotic resistance is essential. *M. pneumoniae* lacks a comprehensive reporting system across all age groups, unlike infectious diseases such as pertussis, with limited research worldwide in adults and the elderly, particularly regarding serological and genetic levels. We call for greater international attention and more discussion on *M. pneumoniae* on a global scale. Cross-regional collaboration will enhance our comprehension of the scope of *M. pneumoniae* outbreaks, facilitate sharing experiences, and enable a collective response. By maintaining vigilance and promoting global cooperation, we can improve strategies for prevention and treatment, ultimately better safeguarding public health.

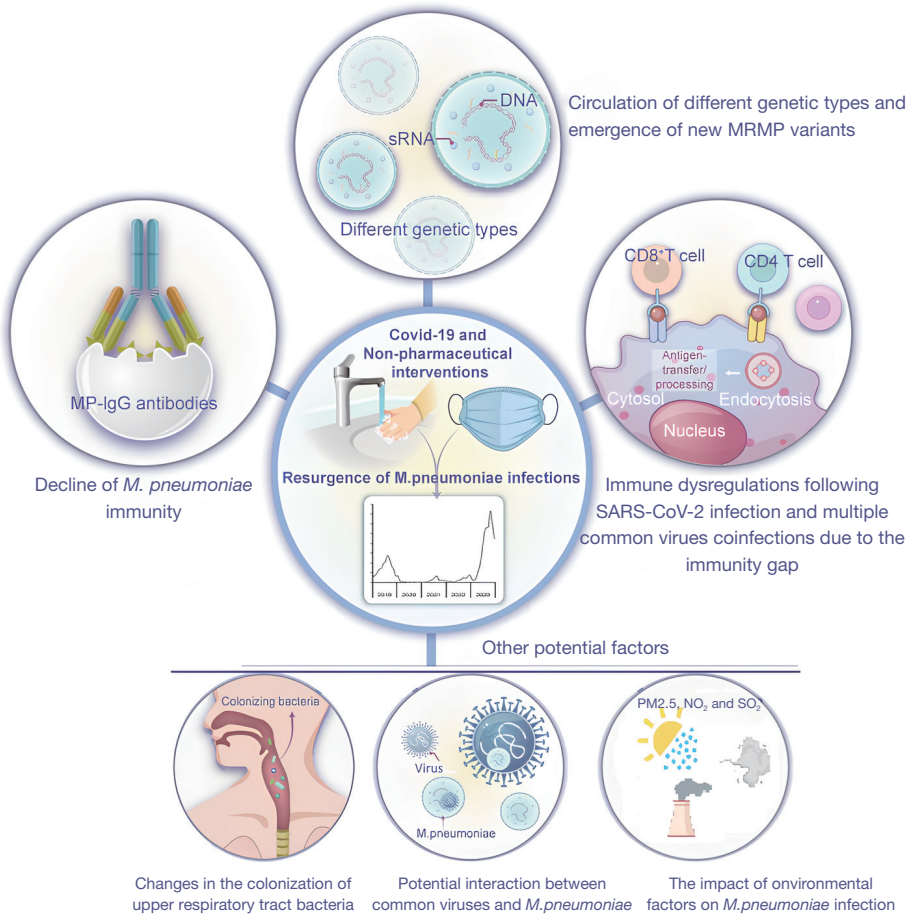

Figure 2 Factors associated with the resurgence of *M. pneumoniae* infections. Decline of *M. pneumoniae* immunity, circulation of different genetic types and emergence of new macrolide-resistant *M. pneumoniae* variants, immune dysregulation following SARS-CoV-2 infection and other factors. COVID-19, coronavirus disease 2019; *M. pneumoniae*, *Mycoplasma pneumoniae*; MP-IgG, *Mycoplasma pneumoniae* immunoglobulin G; MRMP, macrolide-resistant *Mycoplasma pneumoniae*; NO_2, nitrogen dioxide; NPIs, non-pharmaceutical interventions; PM2.5, particulate matter 2.5; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SO_2, sulfur dioxide.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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