Original Article

An exceptionally large wave of *M. pneumoniae* infections among children in Tianjin post COVID-19 pandemic

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Background: The coronavirus disease 2019 (COVID-19) pandemic has caused a persistent lowering of *Mycoplasma pneumoniae* (*M. pneumoniae*), which is commonly found in children with respiratory tract infections (RTIs). However, in 2023, we observed an unusually high number of *M. pneumoniae* infections among children from Tianjin, the second largest city in northern China. This study sought to analyze the epidemiological characteristics of children with RTIs caused by *M. pneumoniae* in northern China post COVID-19, in order to provide a theoretical basis for clinical diagnosis and treatment.

Methods: Between January 2019 and December 2023, a total of 78,886 children with respiratory infections from General Hospital of Tianjin Medical University were included in this study. A rapid immunochromatographic assay kit was used to test for *M. pneumoniae* specific immunoglobulin M (IgM) in these patients. The relevant clinical data of *M. pneumoniae*-positive cases were also collected, and analyzed by SPSS software.

Results: Out of the 78,886 samples collected, a total of 11,268 tested positive for *M. pneumoniae* specific-IgM antibody. The average positive rate was 14.3% in the past 5 years. In the year 2023 alone, there were 5,870 *M. Pneumoniae* positive cases, surpassing the combined count from the previous 4 years. The incidence of *M. pneumoniae* had significantly surged since September 2023, peaking at 1,717 cases in November 2023, with a notable surge during the fourth quarter. The prevalence of *M. pneumoniae* infection was primarily observed among children aged 4–6 years and 7–9 years both before and during the COVID-19 pandemic; however, a noticeable increase was observed among children aged 10–14 years after the pandemic ended. Boys exhibited a lower positive rate (13.19%) compared to girls (15.56%). In addition, the proportion of pneumonia cases in 2023 was significantly higher than that in previous years (P<0.001).

Conclusions: Our study revealed that following a prolonged global lowering of *M. pneumoniae* since the COVID-19 pandemic, a significant outbreak had emerged in northern China since September 2023. The proportion of *M. pneumoniae* positive children in the older age group increased in 2023 compared to that observed in 2019. Additionally, there was an increase in the proportion of pneumonia among *M. pneumoniae* positive cases in 2023 compared to the pre-COVID-19 pandemic period.

Keywords: *Mycoplasma pneumoniae* (*M. pneumoniae*); children; coronavirus disease 2019 (COVID-19); post-epidemic; epidemiology

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Introduction

Mycoplasma pneumoniae (*M. pneumoniae*) is a prevalent pathogen commonly associated with upper or lower respiratory tract infections (RTIs) in children. The prevalence of *M. pneumoniae* infection in China is the second highest among bacterial acute respiratory infections, following only *Streptococcus pneumoniae* (*S. pneumoniae*). It accounts for 18.6% of total bacterial infections in the entire population. Moreover, it emerges as the predominant type of bacterial infection among school-age children, accounting for 56.7% (1). Epidemic of *M. pneumoniae* infection occurs every 3 to 7 years (2) and it is responsible for approximately 30% to 40% of community-acquired pneumonia (CAP) in children (3,4). In addition, its epidemiologic characteristics may vary across different age groups, genders and quarters (5,6). Different geographic areas also exhibit distinct pathogen spectrums and epidemiological features. The last epidemic of *M. pneumoniae* occurred from 2015 to 2016 (4,7). The incidence of *M. pneumoniae* infections in China exhibited an upward trend in 2019. However, a cliff decline was observed in 2020 (6,8). Data from a collaborative global network indicated a continued scarcity of *M. pneumoniae* until 2022, prompting the question of its whereabouts (9). Therefore, this study retrospectively analyzed the prevalence of *M. pneumoniae* among pediatric outpatients from 2019–2023 to explore the characteristics of children with *M. pneumoniae* in Tianjin (China), and reported an exceptionally large wave of MP infections post the coronavirus disease-2019 (COVID-19) pandemic in 2023. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-228/rc).

Highlight box

Key findings

- Following a prolonged global lowering of *Mycoplasma pneumoniae* (*M. pneumoniae*) since the coronavirus disease 2019 (COVID-19) pandemic, a significant outbreak had emerged in northern China since September 2023.

What is known, and what is new?

- The COVID-19 pandemic has caused a persistent lowering of *M. pneumoniae* globally until 2022, while other pathogens resurged as an indicator of community transmission.
- An exceptionally large wave of MP infections among children emerged during the third and fourth quarters of 2023 in Tianjin. There was an increase in the proportion of pneumonia among *M. pneumoniae* positive cases in 2023 compared to the pre-COVID-19 pandemic period.

What is the implication, and what should change now?

- Effective strategies are needed for the prevention and management of *M. pneumoniae* in 2024. Identification and control measures should be enhanced for *M. pneumoniae* rare severe cases.

Methods

Study population and samples

A total of 78,886 pediatric patients with respiratory infection, who visited the outpatient/emergency department of General Hospital of Tianjin Medical University, Tianjin, China between January 1st, 2019 and December 31st, 2023, were included in this study. Diagnoses were determined according to the World Health Organization's criteria. Of the 78,886 patients, 42,467 children were male and 36,419 were female. Patients' ages ranged from 1 month to 14 years old. These patients were divided into four groups with 3-year intervals. Peripheral blood was collected from each child for routine blood test. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and received approval from the Ethics Committee of Tianjin Medical University General Hospital (No. IRB2024-WZ-010). It is a retrospective analysis, in which all patient information was reported in an anonymous manner. In accordance with the guidelines set by the Ethics Committee at the Tianjin Medical University General Hospital, individual participant content was waived due to the retrospective nature of the study.

Detection

The *M. pneumoniae* specific immunoglobulin M (IgM) in blood samples collected from 78,886 patients was tested using the rapid immunochromatographic assay kit (manufactured by Zhuhai Lizhu Reagent Co., Ltd., Zhuhai, China) according to the manufacturer's instructions. The blood samples were added to the antigen-coated test strips. A positive result was determined if both a test line and a quality control line appeared within 5–10 minutes after the test. This testing approach showed no significant disparity compared to the passive particle agglutination method when the antibody titer was equal to or greater than 1:160, and repeated tests within three months only recorded once (6).

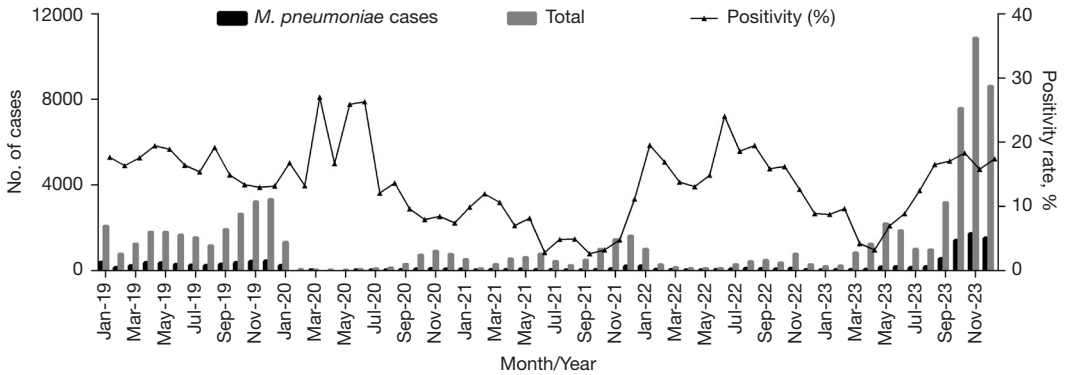

Figure 1 Monthly positive cases and rates (%) of *M. pneumoniae* IgM antibody from 2019 to 2023. *M. pneumoniae*, *Mycoplasma pneumoniae*; IgM, immunoglobulin M.

Statistical analysis

The data analysis was performed using the statistical software SPSS 26.0 (IBM Corp., Chicago, IL, USA). The occurrence of *M. pneumoniae* positive cases was examined across different years, months, quarters, as well as among patients with varying genders, ages, and diagnosis groups. Chi-squared test was employed to compare the variables. A significance level of $P<0.05$ was considered statistically significant.

Results

Annual cases from 2019 to 2023

Of the 78,886 blood samples, 11,268 were positive for *M. pneumoniae* specific-IgM antibody. The average positive rate in the 5 years was 14.3%. The number of *M. pneumoniae* positive cases in 2019 was recorded as 3,635, which subsequently dropped to 518 in 2020, followed by 532 in 2021 and 713 in the year of 2022 (during the COVID-19 pandemic). However, it is noteworthy that the number of *M. pneumoniae* positive cases in 2023 surged to an unprecedented high at 5,870, surpassing the figures observed in previous years and even exceeding the cumulative count of the past 4 years. The corresponding positive rates in each year were 15.7%, 11.6%, 6.6%, 16.4% and 15.1%, respectively.

Epidemiological characteristics of M. pneumoniae over months

Monthly, *M. pneumoniae* dropped dramatically to extremely low levels in February 2020, and kept low levels during the COVID-19 pandemic. Since September 2023, there had been a significant surge in the incidence of *M. pneumoniae*, reaching its peak at 1,717 cases in November 2023, followed by a subsequent decline observed in December 2023 (*Figure 1*).

Epidemiological characteristics of M. pneumoniae in different quarters

The number of *M. pneumoniae* positive cases showed a successive increase in the four quarters of 2023. The positive cases in the first and second quarters of 2023 was lower compared to that in 2019, while it was higher in the third quarter of 2023 compared to the same period in 2019 (828 *vs.* 748). Moreover, there was a significant surge in *M. pneumoniae* positive cases during the fourth quarter of 2023 compare to that in 2019 (4,610 *vs.* 1,209) (*Figure 2*).

Epidemiological characteristics of M. pneumoniae in cases of different age groups

The 11,268 positive cases were aged 7.50±4.18 years (range, 0–14 years). These cases were divided into four groups with 3-year intervals. *M. pneumoniae* infection was predominantly observed in children aged 4–6 and 7–9 years both before and during the COVID-19 pandemic. However, there was a significant increase in the proportion of children aged 10–14 years after the pandemic ($\chi^2=393.897$, $P<0.001$). The positive rate of *M. pneumoniae* in children aged 0–3 years was the lowest both before and after the COVID-19 epidemic (*Figure 3*).

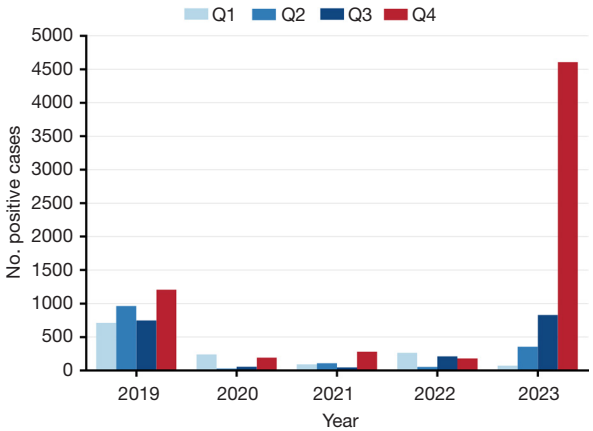

Figure 2 Quarterly positive cases of *M. pneumoniae* IgM antibody from 2019 to 2023. *M. pneumoniae*, *Mycoplasma pneumoniae*; IgM, immunoglobulin M.

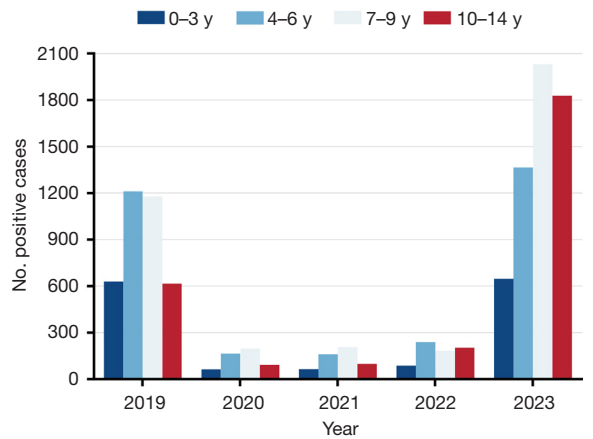

Figure 3 The *M. pneumoniae* IgM antibody positive cases of different age groups from 2019 to 2023. *M. pneumoniae*, *Mycoplasma pneumoniae*; IgM, immunoglobulin M.

Table 1 Sex distribution of patients with *Mycoplasma pneumoniae* infection between 2019 and 2023

Year	Male, %	Female, %	χ^2	P value
2019	14.14	17.43	47.228	<0.001
2020	10.77	12.61	3.629	0.057
2021	6.11	7.14	3.504	0.06
2022	15.54	17.44	2.824	0.09
2023	13.31	15.84	36.265	<0.001
χ^2	240.893	255.585		
P value	<0.001	<0.001		

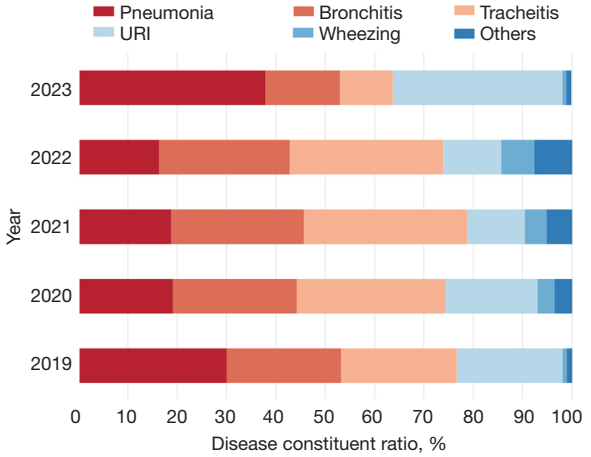

Figure 4 The constituent ratios of *M. pneumoniae* IgM antibody positive cases. URI, upper respiratory infection; *M. pneumoniae*, *Mycoplasma pneumoniae*; IgM, immunoglobulin M.

Epidemiological characteristics of M. pneumoniae in cases of different genders

Among the 11,268 positive cases, 5,600 (49.70%) cases were boys, and 5,668 (50.30%) were girls, with a gender ratio of 1:1. The positive rate (%) of *M. pneumoniae* specific-IgM antibody in blood samples in boys was 13.19% (5,600/42,467), which was lower than that in girls (15.56%, 5,668/36,419), with significant difference (χ^2=90.444, P<0.001). In 2019 and 2023, the annual positive rates in girls were both higher than those in boys, with significant difference (P<0.001). However, there was no significant difference in cases of different genders during the COVID-19 pandemic from 2020 to 2022 (*Table 1*).

The constituent ratios of cases of M. pneumoniae infection

The constituent ratio of *M. pneumoniae* infection cases in 2023 exhibited a significant disparity compared to previous years (χ^2=1,395.770, P<0.001). The highest proportion of *M. pneumoniae* antibody-positive cases was pneumonia, accounting for 37.9% in 2023. Furthermore, the proportion of pneumonia was significantly higher than that observed in previous years (χ^2=263.864, P<0.001). Conversely, the incidence of tracheitis and bronchitis decreased in 2023, while there was a notable rise in the occurrence of upper RTIs (*Figure 4*).

Discussion

M. pneumoniae is a common atypical pathogen that can cause

RTI (10). However, the global prevalence of *M. pneumoniae* has been significantly impacted by the non-pharmaceutical interventions (NPIs) implemented during the COVID-19 pandemic outbreak in late 2019. Global data showed an ongoing scarcity of *M. pneumoniae* until 2022, while other pathogens resurged as an indicator of community transmission (9,11). In our study, an *M. pneumoniae* outbreak was found in Tianjin starting from September 2023, with a peak annual incidence of positive cases (5,870), surpassing the cumulative count of the preceding 4 years. *M. pneumoniae* is usually sporadic, with regional outbreaks every 3 to 7 years, and each outbreak lasts for 1 to 2 years (7,12). The last outbreak of *M. pneumoniae* occurred from 2015 to 2016 (4). The prevalence of *M. pneumoniae* infections in China showed an increasing pattern throughout 2019 (6). However, similar to previous findings (6,7), there was a significant decline in *M. pneumoniae* infections at the beginning of 2020, and since then the prevalence of *M. pneumoniae* remained consistently low. China implemented NPIs in January 2020, followed by numerous countries in March. These measures had been temporally associated with a global and unprecedented suppression of viral and bacterial respiratory infections (13-15). However, as COVID-19 restrictions gradually relaxed in 2021 and 2022, there was a rebound in the transmission of enveloped respiratory viruses such as influenza A virus and respiratory syncytial virus (16). Moreover, non-enveloped viruses like rhinovirus and enterovirus progressively increased after only a few months, reaching pre-pandemic or even higher levels, despite the persistence of NPIs (17,18). Additionally, *Streptococcus pneumoniae* invasive diseases resurged in 2021 (19), while the scarlet fever and invasive Group A *Streptococcus* infections resurged in 2022 (20). However, *M. pneumoniae* remained scarce until summer 2023, which probably attributes to its slow generation time (6 h) and spread rate (incubation period of 1–3 weeks). In our study, *M. pneumoniae* positive cases in 2023 reached 5,870, surpassing the cumulative count of the preceding 4 years. The most recent two epidemics of *M. pneumoniae* occurred from 2015 to 2016 (4) and 2019 respectively. The outbreak may have been influenced by the cyclical nature of *M. pneumoniae* epidemics, which occur every 3–7 years. Furthermore, it should be noted that the present wave of *M. pneumoniae* infections exhibited a significantly higher incidence compared to previous epidemics. The implementation of NPIs may have led to limited exposure to *M. pneumoniae*, resulting in a notable deficit in children's immunity and an increased risk of infection development. Moreover, pathogens such as parainfluenza, adenovirus and influenza B can act as independent risk factors for children *M. pneumoniae* infection (21). These pathogens may also facilitate the infection of *M. pneumoniae* in 2023. Additionally, the recent increased focus on *M. pneumoniae* in the wider media has facilitated voluntary testing for *M. pneumoniae*.

In 2019, the positive numbers of *M. pneumoniae* were higher in both the second and fourth quarters, consistent with the study of Cheng *et al.* in the same period in Beijing (6). However, in 2023, the incidence of *M. pneumoniae* positive cases exhibited a significant surge during the fourth quarter, which can be attributed to the resurgence of *M. pneumoniae* post COVID-19 pandemic beginning in the third quarter of 2023. Based on the previous pattern of *M. pneumoniae* epidemic, it is anticipated that its prevalence will remain elevated until at least 2024 or beyond. Therefore, vigilance towards *M. pneumoniae* should be maintained, especially in the second and fourth quarters of 2024.

M. pneumoniae infection was predominantly observed in children aged 4–6 and 7–9 years both before and during the COVID-19 pandemic. However, there was a significant increase in the proportion of children aged 10–14 years post the pandemic. A single genotype of *M. pneumoniae* is unlikely to be the main cause of the epidemic, as previous research has indicated that both endemic and epidemic spreads of *M. pneumoniae* can involve multiple genotypes (22,23). Therefore, it is possible that the observed age distribution pattern during the two periods could be attributed to interactions between the pathogen and the immune status of the human population. Since the immune system of older children is more fully developed and they are more likely to have been exposed to *M. pneumoniae* in the past, they are protective against *M. pneumoniae* attack in 2019. However, after 3 years absence of *M. pneumoniae* during the COVID-19 pandemic, children of all age groups, including those aged 10–14 years, had limited opportunities to acquire immunity against *M. pneumoniae*, leading to a phenomenon known as 'immunity debt'. Consequently, *M. pneumoniae* positive children aged 10–14 years increased significantly in 2023. Younger individuals had less contact with external environments and thus fewer chances to be exposed to *M. pneumoniae*. This explains why the positive rate of *M. pneumoniae* in children aged 0–3 years was the lowest both before and post the COVID-19 epidemic.

In our study, a significant gender-based disparity was observed both before and post COVID pandemic, with

girls exhibiting higher susceptibility to *M. pneumoniae* compared to boys, consistent with previous findings (6,7,23). However, no significant difference in cases between genders was found during the COVID-19 pandemic, which may be attributed to the limited sample size. The underlying factors contributing to gender disparities before and post COVID pandemic remain unclear. Cheng *et al.* hypothesize that this phenomenon may be explained by disparities in outdoor activity duration between girls and boys (6).

As reported, *M. pneumoniae* infection is usually a form of relatively mild disease and usually self-limiting, but that hit children hard in China last winter (24). In our study, pneumonia accounted the highest proportion of *M. pneumoniae* antibody-positive cases in 2023, reaching 37.9%, followed by upper respiratory infection (URI), bronchitis and tracheitis. Moreover, the proportion of pneumonia in 2023 was significantly higher than that in previous years. This perhaps is due to increased population susceptibility to respiratory infections following 3 years of COVID measures, known as immunity debt. The *M. pneumonia* infection progressed rapidly, and soon progressed from upper RTI to pneumonia in 2023, resulting in a relatively low incidence of bronchitis and tracheitis. Patients with *M. pneumonia* may be at risk of developing severe pneumonia in epidemic times (5). However, only 62 cases of severe pneumonia were found and all occurred in 2023 in our study, which can be attributed to the fact that only outpatients were included in this study.

There are several limitations in this study. First, we assessed the positivity rate by detecting the *M. pneumoniae* specific IgM antibody and did not conduct any nucleic acid testing. As the accuracy of IgM antibody test results can be affected by the timing and duration of antibody production, combining nucleic acid testing with antibody detection provides a more dependable approach for diagnosing (25). Secondly, an extended follow-up period is needed to gain a more comprehensive understanding of the epidemiology of *M. pneumoniae* subsequent to the COVID-19 pandemic.

Conclusions

In conclusion, this study demonstrated that an *M. pneumoniae* outbreak started in September 2023 in Tianjin following a prolonged lowering number of cases due to the COVID-19 pandemic. By comparing the different characteristics of *M. pneumoniae* in 2023 to those of other years, we found that the proportion of *M. pneumoniae* positive children in the older age group increased in 2023. Additionally, there was a notable increase in the proportion of pneumonia cases among those tested positive for *M. pneumoniae* in 2023, indicating the gravity of this outbreak and emphasizing the imperative to enhance identification and control measures for rare severe cases. It is advisable to implement appropriate non-pharmacological preventive measures such as utilization of masks and regular hand sanitization for children in 2024, particularly during the fourth quarters.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-228/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-228/dss

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-228/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-228/coif). The authors have no conflicts of interest to declare.

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. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study has received approval from the Ethics Committee of Tianjin Medical University General Hospital (No. IRB2024-WZ-010). It is a retrospective analysis, in which all patient information was reported in an anonymous manner. In accordance with the guidelines set by the Ethics Committee at the Tianjin Medical University General Hospital, individual participant content was waived due to the retrospective nature of the study.

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