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EDITORIAL

Current *Mycoplasma pneumoniae* epidemic among children in Shanghai: unusual pneumonia caused by usual pathogen

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Mycoplasma pneumoniae (*M. pneumoniae*), primarily transmitted through respiratory droplets when infected individuals cough or sneeze, is a common cause of community-acquired pneumonia, especially among school-age children and adolescents. The infection occurs endemically with an epidemic peak every few years. The worldwide incidence confirmed by direct test methods was reported to be 8.61% between 2017 and 2020 across all age groups [1]. During the coronavirus disease 2019 (COVID-19) pandemic, from 2020 to 2021, the incidence decreased to 1.69% due to non-pharmaceutical interventions (NPIs) [1]. Until 2022, despite the relaxation or discontinuation of NPIs, reductions in incidence continued to be seen in 20 countries across Europe, Asia, the Americas, and Oceania [2]. In China, there was initially a consistent trend in the number of patients with *Mycoplasma pneumoniae* pneumonia (MPP) both before and after the pandemic [3–6]. After that, an unusually different pattern was observed starting in 2021. Typically, *M. pneumoniae* infection presents with symptoms of fever and cough, often accompanied by sore throat, coryza, and occasionally, headache [7]. From April 2020 to early December 2022, has been among the strictest, longest approaches to tackling the pandemic anywhere in the world. Such a long-term NPI has caused a potential for more severe respiratory pathogens epidemics due to a so-called immunity debt. With the lifting of NPI policy, China has experienced peaks in influenza viruses, respiratory syncytial virus (RSV), and *M. pneumoniae* over the past year. Notably, *M. pneumoniae* has undergone a prolonged non-seasonal epidemic, gaining prevalence from April and reaching its peak from October to November. The vast majority of the children, especially infants and preschool children, who have not been exposed to these respiratory pathogens, become a susceptible population that is so large that a sizable unseasonal outbreak occurs when a previously usual respiratory pathogen begins circulating. Therefore, the recently reported spike in respiratory illnesses, especially pneumonia in children is mostly caused by *M. pneumoniae* infection. Additionally, macrolide-resistant *M. pneumoniae* infection also complicates the clinical treatment of this MPP epidemic [8–10].

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Shanghai serves as a vital medical hub for the Yangtze River Delta. Here, we provide an overview of pediatric MPP admissions in 36 municipal hospitals in Shanghai and focus on sharing the data from the Children's Hospital of Fudan University, the Children's National Medical Center, where a surveillance mechanism was established to monitor MPP transmission in children for the benefit of treating MMP pediatric patients.

Trends of *Mycoplasma pneumoniae* infection in children admitted to Shanghai municipal hospitals

Data from the Shanghai Hospital Medical Quality Assessment and Improvement Platform, authorized by Shanghai Hospital Development Center, illustrated the trend of *M. pneumoniae* infection in the last 5 years (Fig. 1) as well as the prevalence of respiratory pathogens between January 2023 and November 2023 (Fig. 2). In 2019, there were 7859 hospitalized patients with MMP in 36 municipal hospitals, with 1114 patients of severe MPP (SMPP). Amid the COVID-19 pandemic, the absolute number of MPP and SMPP patients sharply declined due to the strict intervention measures implemented. Since 2023, there has been a notable increase, surpassing the previous trend. Moreover, the overall proportion of SMPP is increasing, and there is a trend toward shifting the focus away from children's specialized hospitals to general hospitals.

Clinical profiles of *Mycoplasma pneumoniae* infection

In response to the epidemic and based on the previous experience [11], a dedicated ward in Children's Hospital of Fudan University was opened for the implementation of standardized diagnosis and treatment protocols. Patients were diagnosed with MPP if they met all the following criteria [12, 13]: (1) had evidence of acute respiratory tract infections, accompanied by chest radiography-proven pneumonia [13]; (2) a fourfold or greater increase in MP antibody titers of paired sera, or > 1:160 titer of single serum MP antibody, or MP-DNA(+) or MP-RNA(+) [14]. The diagnosis of SMPP is made in MPP patients with either of the following criteria: (1) high fever (> 39 °C) for more than 5 days or fever for more than 7 days without a declining trend in peak temperature; (2) hypoxemia (maintained an SaO_2 < 92% on room air); (3) increasing respiratory and pulse rates with clinical evidence of respiratory distress and exhaustion with or without a raised $PaCO_2$; (4) signs of intrapulmonary infection, such as moderate to large pleural effusion, large area

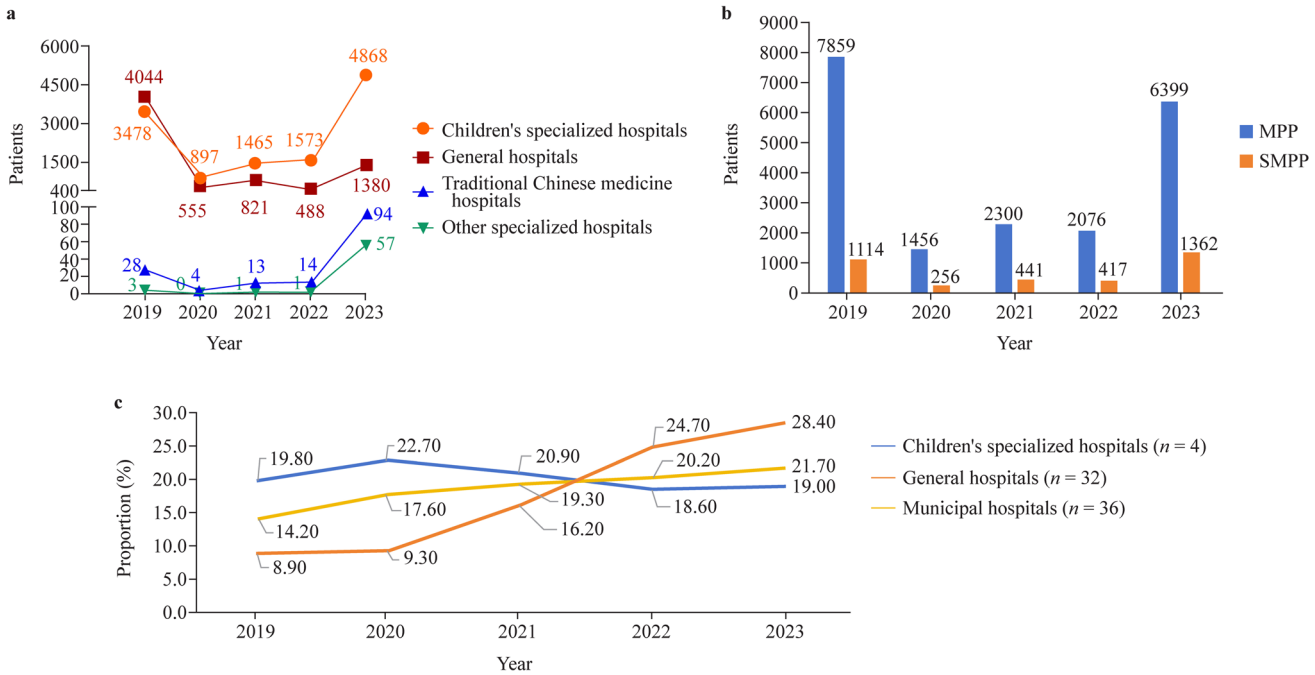

Fig. 1 Typical trend of *Mycoplasma pneumoniae* infection in the last five years. **a** Hospitalized MPP visits in different types of municipal hospitals; **b** hospitalized MPP visits categorized by disease severity; **c** proportion of SMPP visits, illustrating the time trends of pediatric MPP patients from 2019 to 2023. All the data were collected from 36 municipal hospitals in Shanghai. The data for the years 2019–2022 represent the entire year, while the data for 2023 are available for the period from January to September. *MPP Mycoplasma pneumoniae* pneumonia, *SMPP* severe *Mycoplasma pneumoniae* pneumonia

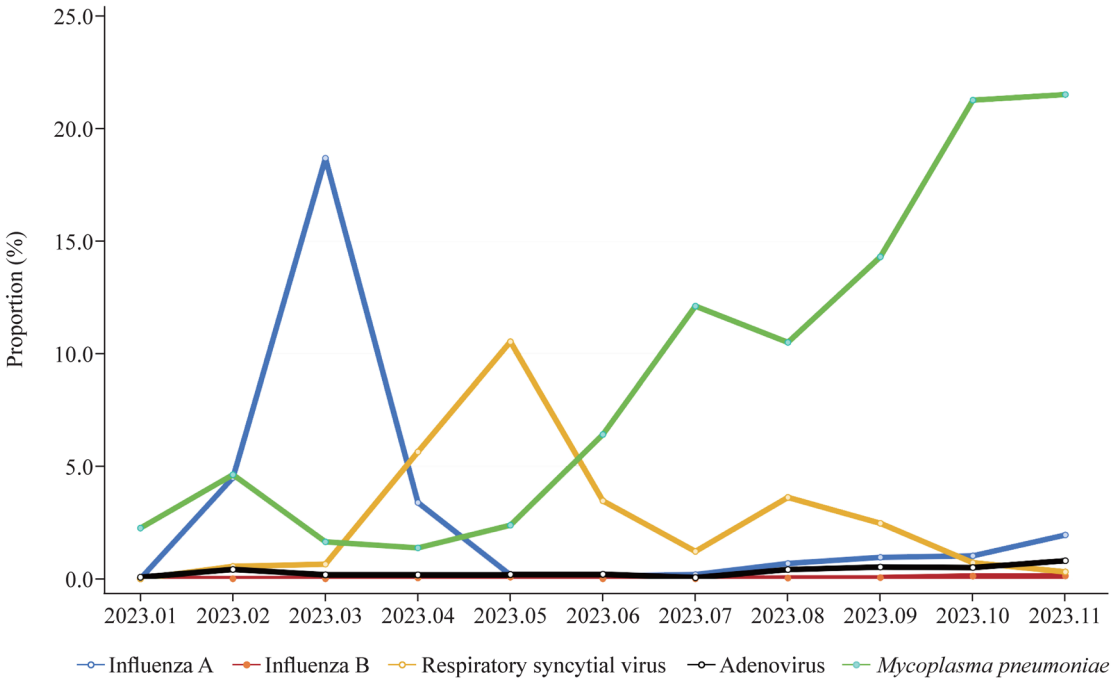

Fig. 2 Chart of trends in the prevalence of influenza A, influenza B, respiratory syncytial virus, adenovirus and *Mycoplasma pneumoniae* among children with pneumonia in Shanghai between January 2023 and November 2023. The data were collected from children's specialized hospital in Shanghai

of pulmonary consolidation, plastic bronchitis, pulmonary embolism, necrotizing pneumonia, and acute asthma exacerbations; and (5) signs of extrapulmonary complications, such as meningoencephalitis, ascending (i.e., Guillain–Barré) paralysis, myopericarditis, erythema multiforme, autoimmune hemolytic anemia, hemophagocytic syndrome, or disseminated intravascular coagulation. From August 1, 2023, to September 30, 2023, 494 patients with MPP were admitted to the newly opened ward. We analyzed the data of these admitted patients.

Demographic characteristics

Of the 494 admissions, 252 (51%) were males, and 124 (25.1%) were classified as having SMPP. The median age was 6 years (interquartile range: 4–9), ranging from 12 months to 13 years. A total of 295 (59.7%) patients were observed in children aged 5 and above, with 78 (26.4%) of these children having SMPP. Among 199 MPP patients under 5 years, 46 (23.1%) patients had SMPP. Eighty-seven (43.7%) MPP patients were under 3 years old, with 19 (19.5%) of them having SMPP. This revealed that *M. pneumoniae* infection is still reported as somewhat uncommon in children under 5 years of age, as was shown in an earlier study [15], but a growing trend of incidence in younger children under 5 years of age can be observed, as in recent reports before the COVID-19 pandemic [16].

Symptoms and signs

A total of 489 (99%) patients presented fever. Among them, 372 (76.1%) experienced high fever (≥ 39 °C), while 105 (21.5%) had extremely high fever (≥ 40 °C). The average duration of fever across all grades was 9.21 ± 6.93 days. Based on pulmonary auscultation, wet rales were detected in 254 (51.4%) patients, whereas dry rales were present in 39 (7.9%). Wheezing was observed in 43 (8.7%) patients, and in 11 (2.2%), shortness of breath was reported. Among seven (1.4%) patients with dyspnea, five presented "three depression signs" (supraclavicular fossa, suprasternal fossa, intercostal space).

Among the MPP patients, 367 (99.2%) had a high fever (≥ 39 °C), and 73 (19.7%) experienced an extremely high fever (≥ 40 °C). The average duration of fever in this group was 8.92 ± 6.97 days. A total of 171 (46.2%) patients had wet rales, whereas 27 (7.3%) patients had dry rales. Twenty-nine (7.8%) patients reported wheezing. Of the SMPP patients, 122 (98.4%) had a high fever (≥ 39 °C), with 46 (37.1%) experiencing an extremely high fever (≥ 40 °C). The average duration was 10.15 ± 7.98 days. Wet rales were found in

83 (66.9%) patients, while 12 (9.7%) patients exhibited dry rales. Fourteen (11.3%) patients had wheezing.

Laboratory characteristics

All patients underwent the following laboratory tests during their hospital stay: complete blood counts, C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, etiological indicators, and specific immunological indicators. Pulmonary injuries associated with refractory MPP or SMPP occur owing to excessive host immune responses rather than direct microbial damage. LDH is generally considered to be a reliable biomarker of refractory MPP [9], and D-dimer and CRP are statistically significant biomarkers to predict refractory MPP in Chinese pediatric patients [17]. MPP patients with higher levels of D-dimer had more severe clinical manifestations [18], and they were more likely to develop refractory MPP [19]. According to the data collected in our hospital, SMPP patients tended to have higher CRP levels than non-SMPP patients (10.76 vs. 7.77; $P < 0.05$), while the levels of Ferr and interferon-γ showed no significant difference between the two groups. Out of 264 (49.8%) patients with abnormal LDH levels, 80 (64.5%) had SMPP, and 166 (44.9%) had non-SMPP. The average LDH value for patients with SMPP was 434 ± 245 U/L. while the average LDH value for non-SMPP patients was 373 ± 74.0 U/L. Furthermore, 136 (27.5%) patients exhibited elevated levels of D-dimer, with 55 (44.4%) having SMPP and 81 (21.9%) having non-SMPP. The average D-dimer value for SMPP patients was 1.55 ± 1.60 mg/L, whereas the average D-dimer value for non-SMPP patients was 0.913 ± 0.424 mg/L.

Although *M. pneumoniae* culture is the gold standard for diagnosis, due to the special culture conditions and slow growth, it is not implemented for *M. pneumoniae* detection. The greatest number of positive tests was obtained with direct test methods followed by a combination of PCR and serology or serology alone (only immunoglobulin M was considered if all isotypes were reported). Moreover, compared with non-SMPP patients, SMPP patients had a higher number of MP-DNA copies.

Complications and concomitant infections

Of 124 (25.1%) patients experiencing intrapulmonary complications, pleural effusion ($n = 123$, 24.9%) was most common, followed by acute asthma exacerbations ($n = 12$, 2.4%), plastic bronchitis ($n = 5$, 1.0%), and necrotizing pneumonia ($n = 5$, 1.0%). Furthermore, we identified five patients of secondary pulmonary embolism, a less common occurrence in infection-acquired thrombophilic states [20, 21]. This highlights the need for increased awareness in patients where chest pain persists despite therapy, especially in the absence of tachypnea and hypoxemia. Extrapulmonary complications were also noted, with secondary liver dysfunction being the most prevalent ($n = 26$, 5.3%). Complications affecting the nervous system, circulatory system, and blood system were each less than 1%. Additionally, 240 patients exhibited T-cell immune dysfunction, and among them, 68 (54.8%) had SMPP.

Real-time−polymerase chain reaction was conducted on nasal swabs to detect the presence of respiratory pathogens, including adenovirus (ADV), rhinoviruses (RV), human bocavirus (HBoV), parainfluenza virus (HPIV), RSV, metapneumovirus (HMPV) and influenza A and B viruses. Influenza A virus and ADV were more commonly to be detected with *M. pneumoniae* [22]. Strong and highly statistically significant antagonistic interspecies interactions were detected between *M. pneumoniae* and influenza virus infections [23]. Of our 499 MPP patients, seven (1.4%) were found to have concurrent bacterial infections, among which *Streptococcus pneumoniae* coinfection ($n = 5$, 1.0%) was the most prevalent, followed by *Staphylococcus aureus* ($n = 2$, 0.4%) and *Pseudomonas aeruginosa* ($n = 2$, 0.4%). Moreover, 13 patients were infected with influenza A, 40 with ADV, 28 with HBoV, 70 with RV, 30 with HPIV, 25 with HMPV, 13 with H3N2, and 29 with RSV. SMPP patients were more likely to be coinfected with RV than non-SMPP patients, but the coinfection situation with other viruses was not different between the groups.

Treatment of *Mycoplasma pneumoniae* pneumonia

According to the guidelines, the priority treatment for *M. pneumoniae* infection is macrolide antibiotics, which can also be prescribed for patients with clinical findings. Nevertheless, due to the absence of a cell wall, a characteristic that sets *Mycoplasma* apart from other pathogenic bacteria, the use of appropriate antibiotics may not always lead to the resolution of symptoms, and the widespread use of macrolides have also caused treatment resistance [9, 24]. Therefore, macrolide-resistant *M. pneumoniae* has become increasingly prevalent. From 2016 to 2019, the reported resistance rate was approximately 80%–90% in Asian countries, including China, Japan, and South Korea [25–27]. In some cases, patients may experience persistent fever and clinical deterioration, which can even progress to severe disease [28, 29]. As a result, quinolones and tetracyclines, in addition to other regimens such as corticosteroids and immunoglobulin, can be considered alternative treatment options for macrolide-resistant *M. pneumoniae*. Our hospital commenced testing for resistance genes A2063G and A2064G in MPP patients concerning the use of macrolide antibiotics in June 2023. A total of 434 MMP patients underwent these tests, yielding a resistance gene positivity rate of 80%. Among the 124 SMPP patients, 97 (88.2%) tested positive, a significantly higher rate compared to non-SMPP patients.

Out of the 494 MPP patients, 155 (31.3%) patients received specific quinolones or tetracyclines, with 71 (57.2%) of them being SMPP patients.

Mechanism behind the surge of respiratory infections in children: pandemic-related immunity gap or others?

We conclude that both the "see-sawing" features and "upsurging" patterns have been observed in *M. pneumoniae* infections, indicating that a notable increase in MPP cases among children may be imminent. Immunity debt take effects in the current unusual *M. pneumoniae* infection in children in China. "Immunity debt" is defined as a paucity of protective immunity raises concerns regarding susceptibility to infectious diseases [30]. Previously, an immunity debt was observed during the 2009 H1N1 influenza pandemic on RSV seasonality. A delayed onset of the RSV epidemic occurred initially, followed by a subsequent surge in the following year [31]. Similarly, children's lack of exposure to various infectious pathogens during the COVID-19 pandemic lockdown has an impact on their developing immunity. It has been reported that innate immune cells, which are a critical part of the immune system activated to battle COVID-19, remain altered for at least a year after infection [32]. This finding suggests that these cells may play a role in some of the lingering symptoms associated with long COVID-19, and other studies also revealed that T cells and inflammatory factors in the body remained at elevated levels [8, 33]. The immunological mechanisms of SMPP and the activation of related cells following COVID-19 infection, along with elevated levels of inflammatory factors, are connected and warrant further investigation. This is not clear, and more studies are needed to confirm the connection. T-cell activation, cell-mediated inflammatory damage, and cytokine-driven proinflammatory environments in the respiratory tract are essential immunological mechanisms that induce SMPP [34].

In conclusion, since June 2023, Shanghai has experienced peak epidemiology in *M. pneumoniae* infection. Severe clinical manifestations were more frequently observed. The strains are mainly macrolide-resistant *M. pneumoniae*, which increases the difficulty of treatment. Delayed effective antimicrobial treatment is associated with prolonged and/or more severe disease. The appropriate prescription of antibiotics, as well as the rapid and accurate diagnosis of MPP, is helpful for patient treatment. Advocating disease awareness within the community and among healthcare professionals is beneficial. Establishing a standardized and practical monitoring system for respiratory pathogens, including influenza viruses, respiratory syncytial viruses, *M. pneumoniae*, and adenoviruses, is crucial. The system can offer timely and scientific evidence for developing a global strategy on infection prevention and control. Early case detection enables prompt treatment, ultimately reducing the severity and mortality rates.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval Not needed.

Conflict of interest No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article. The authors have no conflict of interest to declare.

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