Epidemic characteristics of *Mycoplasma pneumoniae* infection: a retrospective analysis of a single center in Suzhou from 2014 to 2020

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Background: *Mycoplasma pneumoniae* (*M. Pneumoniae*) is a common pathogen of respiratory tract infections, but there is still a lack of detailed investigation on the large sample of *M. Pneumoniae* infection in the all age population. And patients with severe *M. Pneumoniae* pneumonia (SMPP) still have a certain risk of death. How to identify the clinical characteristics and population of patients with SMPP as soon as possible is still an urgent problem in clinical practice.

Methods: Demographic characteristics, patient clinical information, and laboratory data of 81,131 patients with respiratory tract infections (RTIs) in the Affiliated Suzhou Hospital of Nanjing Medical University from 2014 to 2020 were retrospectively collected from all patient records. The serum particle agglutination (PA) test was used to determine *M. Pneumoniae* infection by detecting specific antibodies. The white blood cell count, the proportion of neutrophils and lymphocytes, C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels between children and adults with SMPP were compared by Student's *t*-test; other clinical features were analyzed by χ^2 test or Fisher's exact test.

Results: A total of 81,131 patients with RTIs were included, and 21,582 (26.60%) *M. Pneumoniae* immunoglobulin M (IgM)-positive patients were detected. From 2014 to 2020, the annual proportions of *M. Pneumoniae* RTIs were 23.60%, 28.18%, 38.08%, 27.05%, 23.44%, 25.26%, and 18.33%, respectively. In terms of seasonal distribution, April–June and September–November were the peak seasons of *M. Pneumoniae* infection each year. Children and women have a high proportion of *M. Pneumoniae* infection. The peak age of *M. Pneumoniae* infection was between 4 and 14 years old. There were 301 cases of SMPP, including 281 children and 20 adults (8 cases of pregnant women). Children and pregnant women accounted for a high proportion of SMPP. Children with SMPP had more extrapulmonary symptoms, multilobar infiltrates, and increased CRP and LDH levels compared with adults.

Conclusions: *M. Pneumoniae* infection has seasonal, sex, and age distribution trends. Children and pregnant women accounted for a high proportion of SMPP. Extrapulmonary symptoms, multilobar infiltrates, and increased CRP and LDH levels may be helpful to identify SMPP in children than in adults.

Keywords: *Mycoplasma pneumoniae* (*M. Pneumoniae*); respiratory tract infection (RTI); children; pregnant women; severe *Mycoplasma pneumoniae* pneumonia (SMPP)

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Introduction

Mycoplasma pneumoniae (*M. Pneumoniae*) is a common pathogen of respiratory tract infections (RTIs) worldwide. It is usually sporadic, with regional epidemics every 3 to 5 years, and each epidemic lasts for 1 to 2 years (1,2). Patients may present with a mild self-limiting clinical presentation or convert to radiologically confirmed pneumonia requiring hospitalization. *M. Pneumoniae* pneumonia accounts for approximately 10–30% of cases of community-acquired pneumonia (3-5). In severe cases, it can cause multiple organ damage (6,7). It is of great significance to monitor the epidemic trend of *M. Pneumoniae* infection and analyze the epidemic characteristics. Up to now, domestic studies on epidemiological characteristics have mainly focused on children (8-10).

However, little is known about the epidemiological data of M. Pneumoniae infection among people of all ages in China, especially in some special populations, such as pregnant women. Therefore, in order to better understand the epidemiological characteristics of M. Pneumoniae infection and clinical features of SMPP in Suzhou, we collected the total data of outpatients and inpatients infected with M. Pneumoniae in the recent 7 years of all ages in our hospital, and analyzed the distribution of factors such as gender, age, season, as well as the clinical manifestations of SMPP, in order to facilitate the treatment of M. Pneumoniae infection in clinical practice and identify the population with severe M. Pneumoniae infection. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/ view/10.21037/atm-22-4304/rc).

Methods

Study subjects

From January 2014 to December 2020, a total of 81,131 outpatients and inpatients with RTIs were admitted to Affiliated Suzhou Hospital of Nanjing Medical University, including 40,683 males and 40,448 females (55,658 children and 25,473 adults) aged 0–94 years old (median age: 12 years old). Demographic characteristics, patient clinical information, and laboratory data were collected retrospectively from all patient records. *M. Pneumoniae* RTIs included upper RTIs, bronchitis, bronchopneumonia, and pneumonia. This study protocol was approved by the Medical Research Ethics Committee of the Affiliated

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Suzhou Hospital of Nanjing Medical University (No. KL901299) and strictly followed the Declaration of Helsinki (as revised in 2013). The requirement for informed consent was waived by the committee as our study was an anonymous retrospective review of patient records.

Detection of M. Pneumoniae and protocols

As *M. Pneumoniae* is a common pathogen of respiratory infection, we retrospectively analyzed the situation of *M. Pneumoniae* infection in pediatric patients, respiratory outpatients, and inpatients with RTIs in our hospital. For inpatients, all patients suspected of RTIs were routinely tested for *M. Pneumoniae*-specific immunoglobulin M (IgM). For outpatients, those with dry cough (with or without fever, peripheral white blood cell count <1,000/µL) for more than 1 week (or family members with cough) were also routinely tested for *M. Pneumoniae*-specific IgM. *M. Pneumoniae* infection was confirmed by the detection of *M. Pneumoniae*-specific IgM, which was defined as a single serum *M. Pneumoniae*-specific IgM titer greater than 1:160, or a second seroconversion (a 4-fold increase in antibody titer) (11-13).

Diagnosis of RTIs

RTIs including upper tract infection, bronchitis, bronchopneumonia, and pneumonia were diagnosed based on clinical symptoms (fever, sore throat, cough, sputum, and wheezing, chest tightness) and imaging infiltrates. Severe M. *Pneumoniae* pneumonia (SMPP) was defined as pneumonia with one of the following criteria for severe pneumonia in children and adults with community-acquired pneumonia (14,15): persistent fever >38.5 °C for more than 10 days, radiological deterioration or consolidation present in >2/3 of the lung lobes, intra- and extrapulmonary complications, pulse oxygen less than 92%, and shock.

Statistical analysis

Data were expressed in terms of the mean, count, and percentage. Data analysis was performed using the SPSS 21.0 statistical software package (IBM Corp., Armonk, NY, USA). Continuous data were expressed as mean \pm standard deviation. Continuous variables were analyzed by Student's *t*-test, and categorical variables were analyzed by the χ^2 test or Fisher's exact test. P value <0.05 was considered significant.

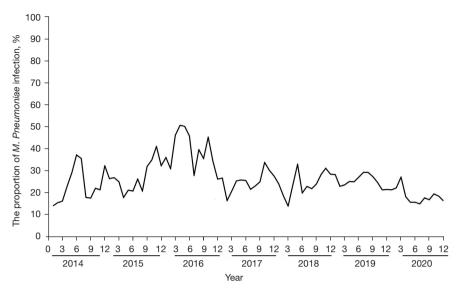


Figure 1 Epidemiological trends of *M. Pneumoniae* infection in adults and children from 2014 to 2020. The positive rate of *M. Pneumoniae* was the highest in 2016 and the lowest in 2020.

Characteristics	Total (n, %)	Children (n, %)	Adult (n, %)	P value*
Year				
2014	1,885/7,988 (23.60)	1,495/5,554 (26.91)	390/2,434 (16.02)	<0.0001
2015	2,985/10,593 (28.18)	2,563/7,011 (36.56)	422/3,582 (11.78)	<0.0001
2016	4,188/10,998 (38.08)	3,574/7,723 (46.28)	614/3,275 (18.19)	<0.0001
2017	3,707/13,704 (27.05)	3,025/8,709 (37.44)	682/4,995 (13.65)	<0.0001
2018	3,092/13,191 (23.44)	2,412/8,641 (27.91)	680/4,550 (14.95)	<0.0001
2019	4,392/17,386 (25.26)	4,189/12,986 (32.25)	203/4,400 (4.61)	<0.0001
2020	1,333/7,271 (18.33)	1,244/5,034 (24.71)	89/2,237 (3.98)	<0.0001
Gender				
Male	9,246/40,683 (22.72)	8,113/27,261 (29.76)	1,133/13,422 (8.44)	<0.0001
Female	12,336/40,448 (30.50)	10,389/28,397 (36.58)	1,947/12,051 (16.02)	<0.0001
P value [#]	<0.0001	<0.0001	<0.0001	

Table 1 Total epidemic characteristics of MP infection in adults and children from 2014 to 2020

*, compared to children and adults; #, compared to males and females. MP, Mycoplasma pneumoniae.

Results

M. Pneumoniae epidemic characteristics from 2014–2020

A total of 81,131 patients with RTIs were suspected of M. *Pneumoniae* infection, of which 21,582 cases were positive for M. *Pneumoniae*-IgM, and the total M. *Pneumoniae* infection proportion was 26.60%. The main clinical symptoms were cough, headache, sore throat,

nasal symptoms, fever, malaise, and a few extrapulmonary symptoms such as skin rash, meningitis, myocarditis, hemolytic anemia, myalgia, digestive symptoms, hemolytic anemia and nephritis. The *M. Pneumoniae* RTI proportions from 2014 to 2020 were 23.60%, 28.18%, 38.08%, 27.05%, 23.44%, 25.26%, and 18.33%, respectively. The *M. Pneumoniae* infection proportion was highest in 2016 and lowest in 2020 (as shown in *Figure 1* and *Table 1*).

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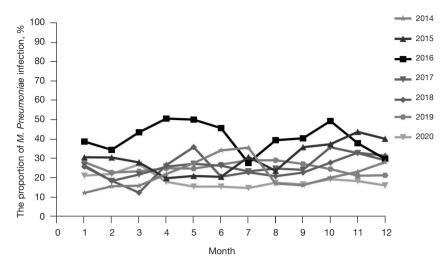


Figure 2 Seasonal distribution of RTI with *M. Pneumoniae* from 2014 to 2020. April to June and September to November were peak months, especially in the epidemic year of 2016. RTI, respiratory tract infection.

Children and adults with M. Pneumoniae RTIs

As shown in *Table 1*, the *M. Pneumoniae* RTIs proportion in children was significantly higher than that in adults in almost every year. The *M. Pneumoniae* RTIs proportions from 2014 to 2020 in children and adults were 26.91% vs. 16.02%, 36.56% vs.11.78%, 46.28% vs. 18.19%, 37.44% vs. 13.65%, 27.91% vs. 14.95%, 32.25% vs. 4.6%, and 24.71% vs. 3.98%, respectively. The epidemic trends of the 2 groups were consistent.

Gender distribution of RTIs with M. Pneumoniae

To investigate the gender distribution of *M. Pneumoniae* infection, we distinguished between gender in the children and adult groups. As shown in *Table 1*, the male and female proportions of *M. Pneumoniae* infection in children were 29.76% and 36.58%, respectively. In adults, the male and female proportions were 8.44% and 16.02%, respectively. The *M. Pneumoniae* RTIs proportion in females was higher than that in males in both children and adults (P<0.0001).

Seasonal distribution of RTIs with M. Pneumoniae

In terms of seasonal distribution, *M. Pneumoniae* was prevalent from January to December, with no obvious trough, but April to June and September to November were the relative peak months, especially in 2016. *M. Pneumoniae* RTIs accounted for 44.4–50.62% from April to June, and 37.95–49.42% from September to November in 2016 (as shown in Figure 2).

Age distribution of RTIs with M. Pneumoniae

Our study included all age groups between 0–94 years old. Because M. *Pneumoniae* is mainly prevalent in children, we set the age group interval for children under 14 years of age at 1 year, and for people aged 14 and above were set to different age groups. From the perspective of age distribution, children and adolescents were the main population of M. *Pneumoniae* infection, among which 4–14-year-olds were the high-risk group. The M. *Pneumoniae* RTIs proportions were from 37.34% to 51.42%. In adults, the M. *Pneumoniae* RTIs proportion decreased gradually after 20 years old, and the proportion of M. *Pneumoniae* RTIs in elderly patients was very low, less than 5% (as shown in Figure 3).

Mycoplasma pneumoniae pneumonia (MPP) and SMPP in children and adults and pregnant and non-pregnant women

As shown in *Table 2*, from 2014 to 2020, there were a total of 2,003 cases of MPP, including 1,757 cases in children and 246 cases in adults. There were 301 cases of SMPP, including 281 cases in children and 20 cases in adults. During this period, 504 pregnant women and 528 non-pregnant women of reproductive age were included. The *M. Pneumoniae* RTIs proportions in women and non-pregnant women were 120/504 (23.81%) and 142/528 (26.90%), respectively.

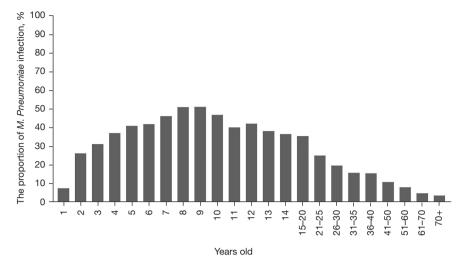


Figure 3 Age distribution of RTIs with *M. Pneumoniae* from 2014 to 2020. Children and adolescents comprised the main population of *M. Pneumoniae* infection, of which those aged 4–14 years old were the high-risk group. In adults, the positive rate of *M. Pneumoniae* decreased gradually after the age of 20, and the positive rate of elderly patients was very low. RTIs, respiratory tract infections.

Table 2 Epidemic characteristics of MPP and SMPP in children, adults and pregnant/non-pregnant women

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Characteristics	MP RTIs (n, %)	MPP (n, %)	SMPP (n, %)	
Children	18,502/55,658 (33.24)	1,757/18,502 (9.50)	281/1,757 (15.99)	
Adult	3,080/25,473 (12.09)	246/3,080 (8.00)	20/246 (8.13)	
P value	<0.0001	0.0075	<0.0001	
Pregnant women	120/504 (23.81)	27/120 (22.50)	8/27 (29.62)	
Non-pregnant women	142/528 (26.90)	28/142 (19.72)	2/28 (7.14)	
P value	0.2551	0.5817	0.0403	

MPP, *Mycoplasma pneumoniae* pneumonia; SMPP, severe *Mycoplasma pneumoniae* pneumonia; MP, *Mycoplasma pneumoniae*; RTIs, respiratory tract infections.

There were 35 cases of MPP (including 8 cases of SMPP) in pregnant women and 30 cases of MPP (including 2 cases of SMPP) in non-pregnant women. The proportion of SMPP in children and pregnant women was higher than that in adults and non-pregnant women (P=0.0403).

Clinical characteristics of SMPP in children and adults

We further analyzed the clinical, laboratory, and radiographic findings of children and adults with SMPP. As shown in *Table 3*, children with SMPP had more extrapulmonary symptoms, lobular infiltrates, and increased C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels compared with adults, which may be related to the secondary immune response of *M. Pneumoniae*. In addition, pregnant women made up nearly half of the adults with SMPP in our study, and their symptoms tended to progress more quickly to lobular infiltrates and pleural effusions, as well as respiratory failure (*Figure 4*).

Discussion

M. Pneumoniae is a prokaryotic microorganism with a size between bacteria and viruses, which can cause epidemics worldwide. In epidemic years, *M. Pneumoniae* can account for 30% to 50% of RTIs (16). Since 2010, *M. Pneumoniae* outbreaks have been reported in several countries, including Europe, the United States, China, and Japan

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Characteristics	Children (n=281)	Adults (n=20)	P value
Clinical presentation (n, %)			
Common symptoms	281/281 (100.00)	20/20 (100.00)	1.0000
Extrapulmonary symptoms	116/281 (41.28)	3/20 (15.00)	0.0306
Laboratory detection (range)			
White blood cells (×10 ⁹ /L)	6.3 (2.8–16.4)	7.9 (3.9–20.1)	0.1026
Neutrophil rate (%)	62.8 (22.4–81.7)	65.4 (30.2–87.2)	0.3801
Lymphocyte rate (%)	28.8 (9.5–65.0)	31.0 (8.1–60.4)	0.4661
C-reactive protein (mg/L)	125.4 (27.1–237.3)	66.3 (10.2–125.6)	<0.0001
LDH (U/L)	447 [150–1,129]	309 [170–620]	0.0032
Imaging manifestations (n, %)			
Unilobar infiltration	83/281 (29.54)	12/20 (60.00)	0.0105
Multilobar infiltrates	198/281 (70.46)	8/20 (40.00)	0.0105
Pleural effusion	115/281 (40.63)	6/20 (30.00)	0.4797

Common symptoms: cough, sputum, headache, sore throat, fever, malaise, chest pain, tachypnea; extrapulmonary symptoms: skin rash, meningitis, myocarditis, hemolytic anemia, myalgia, digestive symptoms, hemolytic anemia and nephritis. SMPP, severe *Mycoplasma pneumoniae* pneumonia; LDH, lactate dehydrogenase.

(2,17,18). From 2014 to 2020, we observed that 26.60% (21,582/81,131) of patients with RTIs were positive for M. Pneumoniae, which was higher than the global incidence of 12% (range, 11-15%) from the Atypical Pathogens Reference Laboratory Database (18). However, the data are basically consistent with the studies in China and Asia (2,8,9,19,20). Our research shows that the M. Pneumoniae RTIs proportion in our hospital increased significantly in 2016, and even exceeded 50% during the epidemic season. In non-epidemic years, the average M. Pneumoniae infection rate was also around 20%, which is thought to be related to the widespread presence of macrolide-resistant M. Pneumoniae in Asia. Interestingly, the proportion of M. Pneumoniae infection decreased significantly in 2020 in our hospital. We speculated that this may be due to the prevalence of novel coronavirus (2019-nCoV), resulting in people changing their living habits, such as generally maintaining social distance and wearing masks, leading to a significant decline in the M. Pneumoniae infection rate. This shows that wearing a mask is a very simple and effective way to prevent cross-infection of M. Pneumoniae.

M. Pneumoniae infection is sporadic throughout the year, but studies have shown that the epidemic of *M. Pneumoniae* was related to temperature and humidity (21). The study in South Korea have shown that *M. Pneumoniae* infection is more common in autumn and winter (22). European data indicate that June to October are the peak epidemic seasons of M. Pneumoniae (23,24). However, studies from Seattle have shown no seasonal differences in M. Pneumoniae infection (25). In China, Gao et al. and Qu et al. reported that the peak season of M. Pneumoniae was mainly in autumn and winter in the north and summer and autumn in the south (26,27). Our results showed that April to June and July to September were the peak months of the M. Pneumoniae outbreak, which is consistent with Qian et al. and Zhang (20,28). According to the epidemic situation of various countries, summer and autumn are the main peak seasons of M. Pneumoniae epidemic.

In our study, the proportion of female *M. Pneumoniae* infection is relatively high in both children and adults, which is consistent with previous research (8,9,25-28). A reasonable explanation may be related to the different levels of activity and immunity between females and males. In children, boys partake in more outdoor sports than girls, especially in school-age children, and girls are more likely to engage in indoor activities during recess, which are relatively closed. Indoor activities over a long period are more conducive to *M. Pneumoniae* transmission. For adults, lower immunity in women than in men may be a factor in susceptibility to *M. Pneumoniae*.

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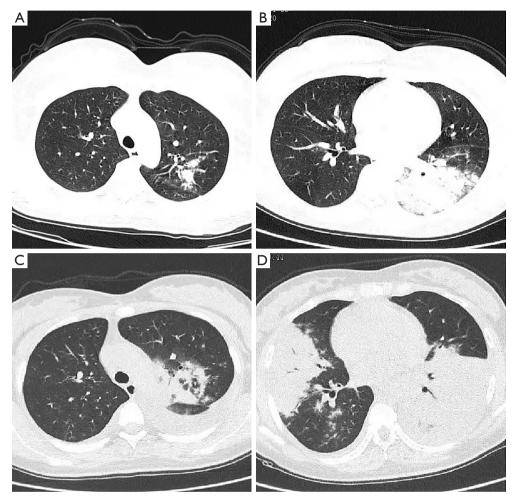


Figure 4 Representative CT images of SMPP in pregnant women. (A,B) Multilobar infiltration and pleural effusion were shown on different levels. (C,D) One week later, the same level of imaging showed deteriorated multilobar infiltration, atelectasis, and increased pleural effusion. CT, computed tomography; SMPP, severe *Mycoplasma pneumoniae* pneumonia.

As shown in *Table 1*, The *M. Pneumoniae* RTIs proportion in children was significantly higher than in adults almost every month. The peak months of *M. Pneumoniae* infection in children and adults were April to June and September to November. Similarly, Qu *et al.* (26) found that the positive rate of *M. Pneumoniae* in children was significantly higher than that in adults (19.7% and 8.9%, P<0.001), and the positive rate in school-age children aged 7–17 was the highest. Kogoj *et al.* (29) reported that the proportions of *M. Pneumoniae* infection in children and adults were 19% and 7%, respectively, and children aged 6–16 years were at serious risk of *M. Pneumoniae* infection. In terms of age distribution, we found that children aged 4–14 years old were the main group, which is consistent with previous studies (26,29). The pathogenic mechanism

of M. Pneumoniae infection is not only direct damage to the human body, but also damage mediated by the immune response (30). The immune system of infants and young children is immature, and the immune response level is low. Therefore, infants younger than 3 years of age show mild or subclinical infection (15). The high proportion of M. Pneumoniae infection among children over the age of 4 may be closely related to their prolonged stay in semi-enclosed settings such as kindergartens and schools.

In our study, we also included pregnant women. Pregnant women have attracted much attention because of their special physiological characteristics. A total of 504 pregnant women were included in this study over the past 7 years. There was no significant difference in the proportion of *M. Pneumoniae* RTIs among pregnant women

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compared with 528 non-pregnant women during the same period. However, the proportion of SMPP in pregnant women was higher than that in non-pregnant women (29.62% vs. 7.14%, P=0.0403).

MPP is usually mild and has a good prognosis, while SMPP is severe and has a long course of disease, with a variety of complications and sequelae, such as atelectasis, bronchiolitis obliterans, and bronchiolitis obliterans. Our study found that children with SMPP had more extrapulmonary symptoms, lobular infiltrates, and increased CRP and LDH levels compared with adults, which may be related to the secondary immune response of M. Pneumoniae. The main pathogenesis is direct damage and indirect immune responses (30,31). In addition to endothelial cells, M. Pneumoniae can adhere to other cells, such as red blood cells and macrophages, which enter multiple organs and cause tissue damage. Besides, M. Pneumoniae activates certain toll-like receptors, especially TLR2, which can also provide injury-related molecular patterns and promote the initiation of inflammatory responses (31). In addition, our research showed that the proportion of SMPP was much higher in children than in adults. Miyashita et al. (32) analyzed 227 adult patients with MPP, among whom 13 had severe SMPP, accounting for 5.7% (13/227). Gao et al. (27) reported that SMPP accounted for about 13.0% of all cases of MPP. Early identification of SMPP in young MPP patients is of urgent clinical value. Studies have shown that fever over 10 days, young children, higher D-dimer level, lung consolidation, massive pleural effusion, necrotizing pneumonia, CRP >60 mg/L, LDH >410 IU/L, and extrapulmonary complications can be used as predictors of SMPP (33-35), which is consistent with our results.

In children, atelectasis, pleural effusion, necrotizing pneumonia, or lung abscess are common in patients with severe SMPP (36). Due to the special status of pregnant women, general imaging examination is not a routine examination. Clinically, according to the recommendation of the American Department of Obstetrics and Gynecology (37), we will also recommend imaging examination for pregnant women with poor treatment response. Our retrospective analysis showed that pregnant women with SMPP also have lobular infiltration and pleural effusion, and often progress rapidly.

Due to the limitations of the study's retrospective design, certain medical data such as medication history, efficacy, and social and economic factors could not be analyzed. In the diagnosis of *M. Pneumoniae*, restricted by our hospital's own

conditions, PCR detection was not carried out, and there may be some deviation in the interpretation of the results. Our hospital is also the designated treatment hospital for women and children in Suzhou. Although thousands of pregnant women and parturients are treated every year, the number of pregnant women in our study was still relatively small. More cases need to be recruited, and more fetal information needs to be collected to analyze the relationship between *M. Pneumoniae* infection and pregnancy outcome. However, because the study included a large number of samples and has been monitored continuously for 7 years, this will make our conclusions more reliable.

Conclusions

In conclusion, our study indicates that *M. Pneumoniae* infection is common in Suzhou. The peak of *M. Pneumoniae* infection occurs in April to June and September to November each year. Children and adolescents aged 4–14 years are the main population of *M. Pneumoniae*. Among the people infected with *M. Pneumoniae*, the proportion of *M. Pneumoniae* infection and SMPP in children are relatively high. Some clinical indicators are needed for the early identification of SMPP.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm. amegroups.com/article/view/10.21037/atm-22-4304/rc

Data Sharing Statement: Available at https://atm.amegroups. com/article/view/10.21037/atm-22-4304/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm. amegroups.com/article/view/10.21037/atm-22-4304/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. The requirement for informed consent was waived by the committee as the

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study was an anonymous retrospective review of patient records. This study protocol was approved by the Medical Research Ethics Committee of the Affiliated Suzhou Hospital of Nanjing Medical University (No. KL901299) and strictly followed the Declaration of Helsinki (as revised in 2013).

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