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Original Article

Epidemiology of Respiratory Pathogens in Children with Lower Respiratory Tract Infections in Shanghai, China, from 2013 to 2015

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SUMMARY: This study aimed to explore the epidemiology of pathogens in children who were hospitalized with lower respiratory tract infections (LRTIs) at the Children's Hospital of Fudan University, Shanghai, China. Children aged less than 18 years who were hospitalized with LRTIs were enrolled from January 2013 to December 2015. Respiratory specimens were collected for the detection of common respiratory viruses, atypical bacteria, and other bacteria using current laboratory diagnostic tests. The epidemiological characteristics of the respiratory pathogens were analyzed. Of the 10,123 specimens obtained from the patients, 5,966 (58.7%) were positive for at least 1 pathogen. *Mycoplasma pneumoniae* (*M.pneumoniae*) was the most commonly detected pathogen (15.7%), followed by respiratory syncytial virus (RSV) (13.9%). Co-infections were found in 11.4% of patients. Of these co-infections, viral-bacterial co-infections were the most common. The detection rates for the respiratory pathogens varied considerably by age. RSV was the most common pathogen in children aged less than 24 months. Clear seasonal peaks were observed for RSV, *M. pneumoniae*, parainfluenza virus, human metapneumovirus, *Moraxella catarrhalis*, and *Haemophilus influenza* infections. Our findings demonstrate specific epidemiological patterns in children with LRTIs in Shanghai, China.

INTRODUCTION

Lower respiratory tract infections (LRTIs) such as pneumonia and bronchiolitis are a leading cause of morbidity and mortality among children younger than 5 years of age in developing countries (1). Of the 6.3 million children who died in their first 5 years of life in 2013, 0.935 million children died of pneumonia (14.9% of all deaths), resulting in a substantial burden on the health care system (2). The etiology of LRTIs is diverse and complicated. Bacteria such as *Streptococcus pneumoniae* (*S.pneumoniae*), *Haemophilus influenza*(*H.influenzae*), *Staphylococcus aureus*(*S.aureus*), *Moraxella catarrhalis* (*M.catarrhalis*), *Pseudomonas aeruginosa*(*P.aeruginosa*), and other gram-negative bacilli are widely considered the major pathogens responsible for LRTIs (3). Viruses also play an important role in LRTIs, especially in infants younger than 2 years (4). The common viral pathogens include respiratory syncytial virus (RSV), human metapneumovirus (hMPV), influenza virus (FLU) A and B, parainfluenza virus (PIV) 1 to 3 and adenovirus (ADV). The atypical bacterial pathogens that are recognized as childhood respiratory pathogens include *Mycoplasma pneumoniae* (MP), *Chlamydia pneumoniae*, and *Chlamydia trachomatis* (CT) (5). The co-infection of respiratory pathogens is quite common, especially in less developed countries such as China (6).

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The symptoms of patients infected with the above-mentioned pathogens are very similar and lack specificity. A better understanding of the epidemiology of pathogens leading to LRTIs is critical for the successful implementation of prevention, control, and treatment strategies. The prevalence of each respiratory pathogen varies from region to region possibly owing to differences in climate, culture, and geography. China is a large country with varying climatic characteristics in different regions. Although some studies on the epidemiology of LRTIs have recently been reported for local areas of China (7–9), most of these studies investigated only the epidemiology of respiratory viruses, and the epidemiological characteristics of pathogens including bacteria, viruses, and atypical bacteria at the same time have not been previously reported in Shanghai, China.

In this study, we explored the epidemiology of pathogens in children who were hospitalized with LRTIs at the Children's Hospital of Fudan University.

MATERIALS AND METHODS

Study design: A consecutive 3-year prospective study from January 2013 to December 2015 was conducted in Shanghai, a coastal city in China. The inclusion criteria for this study were as follows: (i) children aged less than 18 years, (ii) hospitalization at the Children's Hospital of Fudan University, and (iii) a diagnosis of acute LRTI (ALRTI). A patient was considered to have an ALRTI if they had (a) at least 1 of the following manifestations of acute infection: confirmed fever (38°C), abnormal white blood cell (WBC) differential, leukocytosis (a WBC count of $>$10,000/mL) or leukopenia (a WBC count of $<$4,000/mL), and chills; and (b) at least 1 of the following signs/symptoms of LRTI: sputum, shortness of

breath, lung auscultation abnormality (rale or wheeze), tachypnea, and chest pain.

The patients were divided into 4 groups: under 6 months of age (~6 mo), 6–24 months of age (~24 mo), 2–5 years of age (~5 yr) and more than 5 years of age (>5 yr).

Specimen collection: Respiratory specimens (nasopharyngeal aspirates/bronchoalveolar lavage fluids) were obtained from all the enrolled children within 48 h of admission by trained staff following standard operating procedures. The specimens were immediately transferred to the Clinical Laboratory of the Children's Hospital of Fudan University for respiratory pathogen detection.

Specimen detection: Each specimen was tested for viruses, bacteria, and atypical bacteria. Viruses such as RSV, ADV, PIV, hMPV, and FLU were detected using direct immunofluorescence assay kits according to the manufacturer's instructions (Diagnostic Hybrids, Athens, OH, USA). Bacteria were cultured and isolated using standard microbiological methods. A bacterial pathogen was determined to be present if there was a pure culture in the bacteriological culture dish.

Atypical bacteria such as MP and CT were detected with real-time polymerase chain reaction assays using commercial kits (DaAn Gene,Guangzhou,China) according to the manufacturer's instructions.

Co-infection was defined as the detection of 2 or more respiratory pathogens in any combination.

Statistical analysis: Differences in the pathogen detection rates for the various groups were examined using the χ^2 test. Significance was defined as a p value less than 0.05. Data analysis was performed using STATA version 10 (College Station, TX, USA).

RESULTS

Study population: From January 2013 to December 2015, 10,123 eligible specimens were obtained from children hospitalized with a LRTI. The patient ages ranged from 0 to 18 years, with a median age of 9 months; 4,319 patients were under 6 months of age (~6 mo), 2,624 patients were 6–24 months of age (~24 mo), 2,016 patients were 2–5 years of age (~5 yr), 1,164 patients were over 5 years of age (>5 yr). The study group was 62.1% male. The median length of stay in the hospital was 7 days (interquartile range, 5–11 days). A total of 1,316 children (13%) required intensive care, and 21 children (<1%) died.

Overall detection of respiratory pathogens: Of the 10,123 specimens (9,717 nasopharyngeal aspirates, 406 bronchoalveolar lavage fluids) obtained from children hospitalized with a LRTI, 5,966 (58.7%) were positive for at least 1 pathogen. Viruses, bacteria, and atypical bacteria were detected in 3,176 (31.4%), 2,362 (23.3%), and 1,779 (17.6%) of the specimens, respectively (Table 1). The overall positive rate was lower in 2015 than in the other years ($p < 0.05$), but there was no difference between 2013 and 2014 ($p = 0.06$) (Table 1). MP was the most commonly detected pathogen in the 10,123 specimens (1,594, 15.7%), followed by RSV (1,404, 13.9%), *S. aureus* (637, 6.3%), *S. pneumoniae* (556, 5.5%), PIV (555, 5.5%), and *H. influenzae* (409, 4.0%) (Table 1).

Seasonal outbreaks of pathogens: In general, the seasonality profile of each individual pathogen detected was diverse. RSV, MP, PIV, hMPV, *M. catarrhalis*, and *H. influenzae* showed regular seasonality (Fig. 1).

RSV and *M. catarrhalis* exhibited similar seasonal distributions. Although the seasonal peak of *M. catarrhalis*

Table 1. Detection rates of respiratory pathogens over the course of three years [*n* (%)]

	2013 (*n* = 3,354)	2014 (*n* = 3,403)	2015 (*n* = 3,366)	Total (*n* = 10,123)
Bacteria	899 (26.8)	1,219 (35.8)	1,058 (31.4)	3,176 (31.4)
S. aureus	203 (6.1)	208 (6.1)	226 (6.7)	637 (6.3)
S. pneumoniae	139 (4.1)	241 (7.1)	176 (5.2)	556 (5.5)
H. influenza	84 (2.5)	183 (5.4)	142 (4.2)	409 (4.0)
K. pneumoniae	97 (2.9)	111 (3.3)	101 (3.0)	309 (3.1)
E. coli	119 (3.5)	93 (2.7)	89 (2.6)	301 (3.0)
M. catarrhalis	48 (1.4)	86 (2.5)	65 (1.9)	199 (2.0)
A. baumannii	38 (1.1)	50 (1.5)	68 (2.0)	156 (1.5)
P. aeruginosa	37 (1.1)	36 (1.1)	30 (0.9)	103 (1.0)
Other	97 (2.9)	130 (3.8)	125 (3.7)	352 (3.5)
Virus	747 (22.3)	856 (25.2)	733 (21.8)	2,362 (23.3)
RSV	396 (11.8)	548 (16.1)	437 (13.0)	1,404 (13.9)
PIV	222 (6.6)	161 (4.7)	172 (5.1)	555 (5.5)
ADV	55 (1.6)	76 (2.2)	35 (1.0)	166 (1.6)
FLU	35 (1.0)	58 (1.7)	49 (1.5)	142 (1.4)
hMPV	51 (1.5)	19 (0.6)	50 (1.5)	120 (1.2)
Atypical bacteria	726 (21.6)	536 (15.8)	517 (15.4)	1,779 (17.6)
MP	656 (19.6)	477 (14.0)	461 (13.7)	1,594 (15.7)
CT	75 (2.2)	63 (1.9)	61 (1.8)	199 (2.0)
Total	1,982 (59.1)	2,087 (61.3)	1,897 (56.4)	5,966 (58.9)
Co-infection	350 (10.4)	429 (12.6)	373 (11.1)	1,152 (11.4)

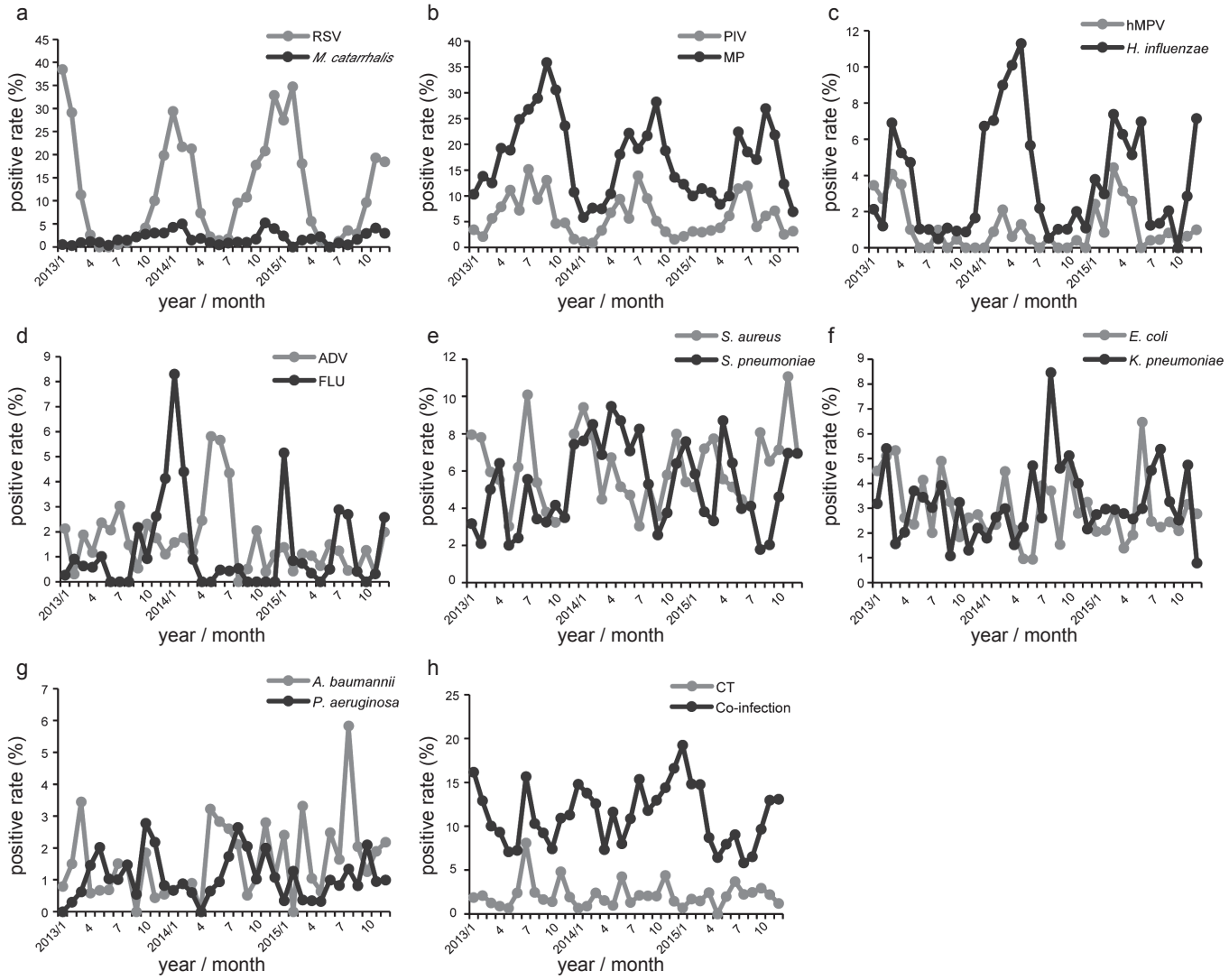

Fig.1. Seasonal distribution of respiratory pathogens from January 2013 to December 2015.

was much lower than that of RSV, both had a high prevalence during the cold season. RSV peaked in winter (January–February), and *M. catarrhalis* peaked in late autumn (November) or winter (Fig. 1a).

In contrast, PIV and MP were detected more often in the hot season and had a low prevalence in winter. PIV peaked in July, and MP peaked in September (Fig. 1b).

H. influenzae had a high prevalence in spring and peaked in March or May. A similar seasonality was observed for hMPV with its peak occurring in March, although its total positive rate was only 1.2% (Fig. 1c).

FLU outbreaks occurred from September 2013 to March 2014 as well as in January, July, August, and December 2015, but its detection rates in the other months were very low. Our study did not find regular seasonality in ADV infections, although a sudden increase in ADV infection was recorded in the summer of 2014 (Fig. 1d).

We did not observe a distinct seasonal pattern for the rest of the pathogens (Fig. 1e, f, g, h).

Co-infections were detected more often in winter (Fig. 1h).

Age distribution of respiratory pathogens: The detection rates of the respiratory pathogens varied considerably by age group (Fig. 2). On the whole, the overall detection rate in the ~24 mo age group was significantly lower than that in the other age groups ($p < 0.05$). Viruses, bacteria, and co-infection had a similar age distribution, which included decreasing detection rates as patient age increased, whereas atypical bacteria showed increasing detection rates as patient age increased (Fig. 2a). RSV was the most common pathogen in very young children aged less than 24 months (Fig. 2b), whereas MP was the most prevalent pathogen among children over 24 months (Fig. 2c).

Three distinct trends in detection rates were observed in the age groups. The type 1 pathogens included RSV, *S. aureus*, *Klebsiella pneumoniae*, *Escherichia coli*(*E. coli*), *Acinetobacter baumannii*(*A.baumannii*), and CT, which showed decreased detection rates with aging. The type 2 pathogens included *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, PIV, and ADV, which showed a peak detection rate in young children (~24 mo or ~5 yr), with no significant difference between the ~24 mo and ~5 yr age groups. The type 3 pathogens included MP and FLU, which showed increased detection rates with aging. There was no clear trend for *P. aeruginosa*, which occurred sporadically in all age groups (Fig. 2b, c, d).

Mixed infection types of the respiratory pathogens: Co-infections with multiple respiratory pathogens were common. There were 1,152 specimens in which 2 or more pathogens were detected, representing 11.4% of the specimens (Table 1), and the types of co-infection were complex (Table 2). Among them, viral-bacterial co-infections were the most common, with 679 samples (accounting for 58.9% of all co-infection samples); followed by atypical bacterial-bacterial co-infections, with 235 samples; and atypical bacterial-viral co-infections, with 151 samples. These data indicate that 28.7% (679/2,362) of the children with viral infections were co-infected with bacteria., and 1,091 specimens showed infection with 2 pathogens. Of these co-infections, the RSV+*S. aureus* co-infection was the most frequent, with 127 samples (accounting for 11.0% of all co-infection samples); followed by RSV+*S. pneumoniae*, with 67 samples; and MP+RSV, with 53 samples. A total of 61 specimens showed infection with 3 pathogens. Of these co-infections, MP+RSV+*S. pneumoniae* was the most frequent co-infection, with 7 samples, followed by MP+RSV+*S. aureus* and MP+RSV+CT (Table 2).

Impact of sex on pathogen detection: Male patients displayed significantly higher detection rates for PIV, *H. influenzae*, and *S. pneumoniae* than female patients. In contrast, female patients displayed significantly higher detection rates for MP. No significant sex difference was observed for the other pathogens (Table 3).

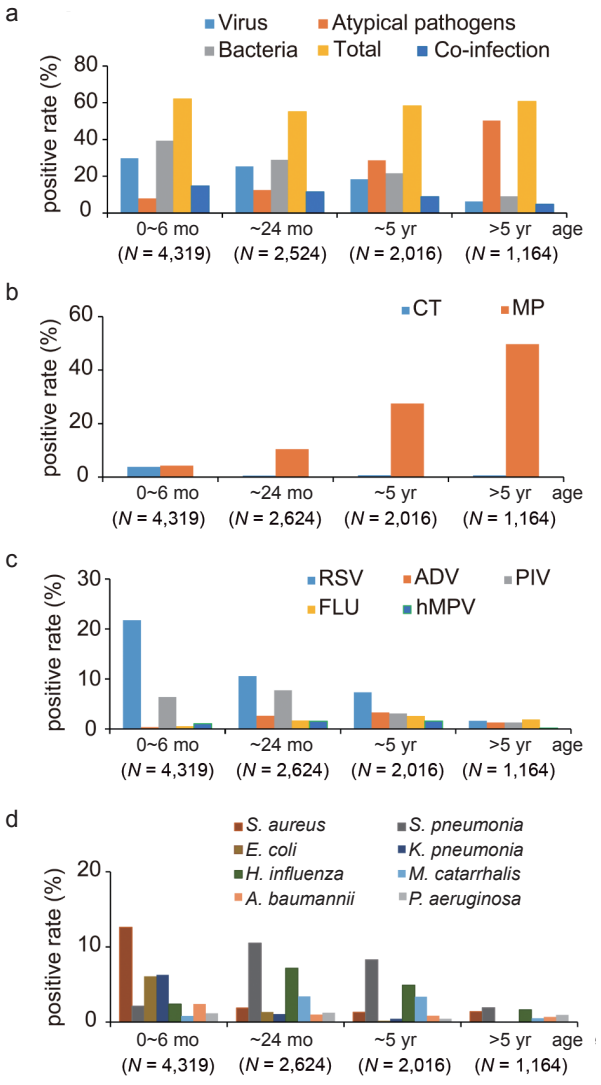

Fig.2. (Color online) Detection rates of respiratory pathogens in hospitalized patients from different age groups. a shows the overall detection rates. b, c and d indicate the detection rates of atypical bacteria, viruses and bacteria in the different age groups, respectively.

Table 2. Common co-infection types of respiratory pathogens (only the common co-infection types are listed)

Co-infection types	Number	Percentage (%)
2 pathogens	1,091	94.7
Virus + Bacteria	679	58.94
RSV + *S. aureus*	127	11.02
RSV + *S. pneumoniae*	67	5.82
RSV + *E. coli*	52	4.51
Other	433	37.59
Atypical bacteria + Bacteria	235	20.40
MP + *S. pneumoniae*	36	3.13
MP + *S. aureus*	35	3.04
MP + *H. influenza*	26	2.26
Other	138	11.98
Atypical bacteria + Virus	151	13.11
MP + *S. pneumoniae*	53	4.60
MP + *S. aureus*	44	3.82
MP + *H. influenza*	16	1.39
Other	38	3.30
Virus + Virus	20	1.74
RSV + PIV	10	0.87
RSV + FLU	3	0.26
RSV + MV	3	0.26
Other	4	0.35
MP + CT	6	0.52
3 pathogens	61	5.30
MP + RSV + *S. pneumoniae*	7	0.61
MP + RSV + *S. aureus*	5	0.43
MP + RSV + CT	3	0.26
Other	46	3.99

Table 3. The prevalence of different respiratory pathogens based on patient gender [*n* (%)]

Pathogen	Male (*n* = 6,289)	Female (*n* = 3,834)	*p* value
RSV	848 (13.48)	533 (13.90)	0.552
ADV	111 (1.76)	55 (1.43)	0.204
PIV	374 (5.95)	181 (4.72)	0.009
FLU	95 (1.51)	47 (1.23)	0.237
hMPV	78 (1.24)	42 (1.10)	0.514
CT	114 (1.81)	85 (2.22)	0.155
MP	933 (14.84)	661 (17.24)	0.001
S. aureus	393 (6.25)	243 (6.34)	0.858
S. pneumoniae	371 (5.90)	186 (4.85)	0.025
H. influenza	279 (4.44)	130 (3.39)	0.010
K. pneumoniae	202 (3.21)	107 (2.79)	0.232
E. coli	186 (2.96)	115 (3.00)	0.904
M. catarrhalis	113 (1.80)	86 (2.24)	0.117
A. baumannii	105 (1.67)	50 (1.30)	0.146
P. aeruginosa	70 (1.11)	33 (0.86)	0.220
Total	3,708 (58.96)	2,257 (58.87)	0.927
Co-infection	724 (11.80)	410 (10.69)	0.090

DISCUSSION

This study is the first to investigate the epidemiology of respiratory pathogens, including viruses, bacteria, and atypical bacteria, in children hospitalized with LRTIs in Shanghai, China. Our results provide a distinctive epidemiological profile of respiratory pathogens in children hospitalized with LRTIs.

In our study, at least 1 pathogen was detected in 58.7% of the children with LRTIs. A multicenter study conducted from January 2010 through June 2012 in the United States showed that pathogens were detected in 81% of children with pneumonia, which is much higher than our results. This difference might be attributed to the year of analysis or differences in the populations studied and methodology (10). Of the pathogens examined, MP was the most common pathogen detected (in 15.7% of the children), which was consistent with previous studies conducted in Nanjing and Wuhan, China (11,12).

The seasonal climate is an important factor that can affect pathogen transmission. The difference in seasonal detection may be related to a region's climate and demographic factors. Our results found regular seasonality for RSV, MP, PIV, hMPV, *M. catarrhalis*, and *H. influenzae*. The detection rate for RSV was highest in winter, consistent with findings reported in Nanjing and Jinan, China (8,11). However, a report from Vietnam showed that RSV was prevalent in summer (13). Wet weather and cold weather are risk factors for RSV infection. Therefore, in temperate climates, RSV activity peaks in the cold winter months, but in tropical and subtropical areas, RSV infection primarily increases in the humid summer months. The detection of MP, PIV, and hMPV was the highest in autumn, summer, and spring, respectively. These results are similar to the findings in Guangzhou, China (14). Nevertheless, a multicenter study conducted in the United States revealed that MP peaked in the winter, and a study conducted in Shenzhen, China, indicated that the detection rate of PIV was highest in autumn (10,15). The reasons for such differences are most likely due to local climate and population differences. In contrast to a study conducted in Zambia, which did not observe a distinct seasonal pattern for any of the analyzed bacteria (16), our study found that *M. catarrhalis* was detected more commonly in the cold season and that *H. influenzae* was detected more often in spring. The discrepancies between this study and the study conducted in Zambia may be attributed to the climate and the enrollment criteria.

We found that the detection rates varied between the different age groups. The incidence of MP steadily increased with age. MP is highly contagious and spreads between people through bodily fluids and airborne droplets from sneezing and coughing. It is most easily spread among people who are in close contact with one another. Thus, the prevalence of MP in the preschool and school groups is higher than that in the infant or toddler groups. CT is a common sexually transmitted pathogen owing to the absence of routine screening and treatment for CT during pregnancy. CT infection during pregnancy can increase the risk of preterm labor, low birth weight, and perinatal mortality (17). Neonatal colonization or infection with CT can lead to early respiratory problems such as pneumonia (18). Thus, the incidence of CT infection primarily occurred in infants younger than 6 months. RSV was the most common viral cause of LRTIs in children, especially children younger than 6 months, and the prevalence of this pathogen decreased with age owing to the maturation of the immune system (19). PIV and other type 2 pathogens showed a peak detection rate in the ~24 mo or ~5 yr groups. A possible explanation for this pattern is that the levels of maternally transmitted antibodies have decreased, while the immune system is not mature enough in these age groups.

Our study also revealed a high incidence of co-infections, representing 11.4% of the specimens. Viral-bacterial co-infections were the most common type of co-infection, and approximately one-quarter of the children with viral infections were co-infected with bacteria. The classic view is that viruses pave the way for bacterial infection, with the underlying mechanism being that respiratory viruses promote bacterial adhesion to respiratory epithelial cells (20). Of the mixed infections with two pathogens, the RSV+*S. aureus*, RSV+*S. pneumoniae* and MP+RSV combinations were the most common, which is consistent with the high detection rates of those pathogens. Thus, the pathogens that have a high incidence in single infections will also have a high incidence in co-infections.

This study has some limitations. The first limitation is the lack of control groups, i.e., groups comprising individuals without LRTIs. Without these groups, we cannot determine whether the microbiological findings reflect true infection with causative agents or merely colonization in coincidentally ill children. This limitation is clearly difficult to address because of ethical issues. Second, some common respiratory pathogens, such as human rhinovirus, human bocavirus, and human coronavirus, were not included in our study, which may lead to underestimation of the viral burden. Third, although the Children's Hospital of Fudan University is one of the largest children's hospitals in Shanghai, China, our findings may not be representative of the entire Shanghai pediatric population or may not be generalizable to other settings. Finally, we studied only hospitalized children, and a study of outpatients might have produced different results.

Conflict of interest None to declare.

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