# Epidemiology of Respiratory Pathogens Among Children Hospitalized for Pneumonia in Xiamen: A Retrospective Study

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## ABSTRACT

***Objectives***: To investigate the etiology of common respiratory pathogens in children < 2 years of age hospitalized with pneumonia in Xiamen from 2014 to 2017.

***Methods***: The medical records of 5581 children with pneumonia were retrospectively reviewed. Direct immunofluorescent test was used for respiratory virus testing. Bacteria were detected by conventional culture method. The results of pathogen detection at admission were analyzed as well as the clinical outcomes of children.

***Results***: The burden of hospitalized children with pneumonia was highest among infants < 6 months old (58.2%). Respiratory syncytial virus (RSV) was the most common respiratory virus (26.0%) followed by parainfluenza (4.8%) and adenovirus (3.2%). *Haemophilus influenzae* was the most common bacteria detected (16.6%) followed by *Moraxella catarrhalis*

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(13.4%), *Staphylococcus aureus* (13.0%), *Streptococcus pneumoniae* (12.3%), *Escherichia coli* (5.1%) and *Klebsiella pneumoniae* (4.8%). Notably, RSV and *K. pneumoniae* were detected more frequently in severe pneumonia (35.0% and 10.9%) versus mild pneumonia (25.6% and 4.6%), with higher rates of ICU admissions, longer hospital stays and higher hospital costs compared to those infected with other respiratory pathogens.

*Conclusions*: Among children < 2 years of age hospitalized with pneumonia in Xiamen, RSV was the most common respiratory virus, while *H. influenzae* and *S. pneumoniae* remained the predominant bacterial pathogens detected. Considering the low implementation rate of vaccines against pneumococcal and Hib pneumonia in China, there is an urgent need to increase both vaccination rates to reduce pneumococcal and Hib disease burden.

**Keywords:** Respiratory pathogens; Children; Pneumonia; Xiamen

### Key Summary Points

*Why carry out this study?*

Recent epidemiological studies of pneumonia pathogens have rarely been reported in China.

The pathogen spectrum of pneumonia in children may change greatly because of the introduction of vaccines against bacterial pneumonia and influenza in China in recent years.

*What was learned from the study?*

The burden of hospitalization of children with pneumonia was highest among infants < 6 months old in Xiamen.

Among children < 2 years of age hospitalized with pneumonia in Xiamen, RSV was the most common respiratory virus, while *H. influenzae* and *S. pneumoniae* remained the predominant bacterial pathogens detected.

## DIGITAL FEATURES

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## INTRODUCTION

Pneumonia is the disease with the highest morbidity and mortality among children < 5 years of age worldwide [1]. Pneumonia among children contributes to a high disease burden in China. A systematic review estimated the annual incidence of clinical pneumonia in China to be 84 episodes per 1000 children under 5 years of age (95% confidence interval: 40.0–166.0), accounting for approximately 5% of all clinical pneumonia and severe pneumonia cases worldwide in 2015 [2]. The annual incidence of community-acquired pneumonia requiring hospitalization was highest among children < 2 years of age [3].

Knowledge of the pathogens that cause pneumonia and severe pneumonia is needed to improve clinical management and promote the rational use of antibiotics [4]. Respiratory virus infections, such as RSV, influenza virus (flu), adenovirus (ADV) and parainfluenza viruses (PIVs), are the most common causes of pneumonia [5]. In addition, one-fourth to one-third of pneumonia cases are attributed to partially gram-positive (*S. pneumoniae* and *S. aureus*) and gram-negative bacteria (*H. influenzae*, *M. catarrhalis*, *E. coli*, *K. pneumoniae* and *Pseudomonas aeruginosa*) [6–8].

The majority of epidemiological studies of pneumonia pathogens were conducted in China before 2015 [9–12]. However, the etiology of pneumonia in children may have changed significantly because of the introduction of vaccines against bacterial pneumonia (*H. influenzae type b* [Hib] and *S. pneumoniae*) and influenza in China in recent years. This retrospective study investigated common respiratory pathogens in children < 2 years of age hospitalized for pneumonia in Xiamen from 2014 to 2017, providing basic data on the etiological changes of pneumonia in China.

# METHODS

## Study Population

From 1 October 2014 to 30 September 2017, the medical records of children hospitalized for pneumonia at Xiamen Maternal and Child Health Hospital were retrospectively reviewed. Subjects meeting the following criteria were included: (1) age ≤ 2 years old; (2) discharge diagnosis included pneumonia. Children were excluded if their first three discharge diagnoses did not include pneumonia. The diagnosis criteria for pneumonia in children in this study were as follows: (1) radiographic evidence of pulmonary infiltrates; (2) at least three of the following symptoms: fever (body temperature ≥ 38.0 °C), shortness of breath (≥ 60 breaths/min for infants < 2 months old, ≥ 50 breaths/min for breaths/min for children 2–-12 months of age and ≥ 40 breaths per min for children 12–24 months old), cough, auscultation findings (rhonchi, crackles or bronchial breath sounds) or chest tightness. Severe childhood pneumonia was defined if the child with pneumonia had severe ventilation dysfunction, intrapulmonary (e.g., acute respiratory failure, acute respiratory distress syndrome, pneumothorax, pyothorax, pulmonary abscess, etc.) or extrapulmonary (e.g., anemia, septic shock, viral encephalitis, hemolytic uremic syndrome, etc.) complications.

This study was approved by the Ethics Committee of Xiamen Maternal and Child Health Hospital and the School of Public Health of Xiamen University and was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Medical records were de-identified of all personally identifiable information.

## Data Collection

The following information was collected from medical records: (1) basic information: age, sex and date of admission; (2) results of pathogen testing at admission: RSV, influenza virus A and B (Flu A and Flu B), parainfluenza virus type 1, 2 and 3 (PIV I, II and III) and adenovirus (ADV) were tested by direct immunofluorescent test (Diagnostic Hybrids, Inc., USA) with nasal swabs; sputum, blood, pleural fluid, and/or bronchoalveolar lavage specimens were tested for typical bacteria (*S. pneumoniae*, *H. influenzae*, *S. aureus*, *M. catarrhalis*, *K. pneumoniae* and *E. coli*, etc.) using conventional culture method; (3) outcome: ICU admission, length of hospital stay and hospitalization cost.

## Statistical Analysis

For categorical variable comparation, $\chi^2$ test or Fisher exact test was used. All tests were two-tailed, and $P$ values of < 0.05 were considered statistically significant. All statistical analyses were performed with SPSS 20 (SPSS Inc., Chicago, IL, USA). Graphs were generated by GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA).

# RESULTS

## Study Characteristics

From October 1, 2014, to September 30, 2017, a total of 5581 children < 2 years of age hospitalized with pneumonia were included in this study. Of these, 220 (3.9%) cases were classified as severe pneumonia. The median age was 4.4 months (IQR 1.4–10.5). The main population of pneumonia was infants < 6 months of age (58.2%). In addition, the rate of severe pneumonia was higher among them than

**Table 1** Characteristics of children with severe pneumonia

| Characteristics | Severe pneumonia (N = 220) no. (%) | P |
|---|---|---|
| Age, months | 2.85 (1.6–6.0) | < 0.001 |
| Median, (IQR)[a] | | |
| (0–6 m) | 164 (5.1) | |
| [6–12 m) | 29 (2.5) | |
| [12–24 m] | 27 (2.3) | |
| Sex | | 0.240 |
| Male | 136 (3.7) | |
| Female | 84 (4.4) | |
| Season of admission | | 0.578 |
| Spring | 60 (3.6) | |
| Summer | 59 (4.0) | |
| Autumn | 45 (3.8) | |
| Winter | 56 (4.6) | |
| Year of admission | | 0.002 |
| Oct. 2014–Sept. 2015 | 69 (3.6) | |
| Oct. 2015–Sept. 2016 | 59 (3.1) | |
| Oct. 2016–Sept. 2017 | 92 (5.3) | |
| ICU admission | | < 0.001 |
| No | 50 (1.0) | |
| Yes | 170 (32.5) | |
| Hospital stay (median, IQR) | 9 (7–13) | < 0.001 |
| < 7 days | 45 (1.2) | |
| ≥ 7 days | 175 (9.1) | |
| Hospitalization costs (median, IQR) (USD) | 1818.1 (1319.0–2938.3) | < 0.001 |
| < 600 | 1 (0) | |
| ≥ 600 | 191 (7.5) | |

[a] *IQR* interquartile range. *P* values were calculated by $\chi^2$ test as appropriate

among children aged 6–24 months (5.0% vs. 2.5%, $P < 0.001$). The male-to-female ratio was 1.87. More pneumonia (30.2%) occurred in Spring (March to May) (Table 1). The rate of severe pneumonia cases (5.3%) was highest from October 2016 to September 2017.

### Etiologic Agent Distribution

Of the 5581 children with pneumonia, viral or bacterial pathogens were detected in 3768 (67.5%), viral pathogen only in 1810 (32.4%), one viral pathogen only in 810 (14.5%), viral-viral co-detection in 70 (1.3%), bacterial-viral co-detection in 930 (16.7%) and bacterial pathogen only in 1958 (35.1%) (Table 2). RSV was the most common respiratory virus (26.0% of cases) followed by parainfluenza (4.8%) and adenovirus (3.2%). Bacteria were found in 51.7% of the children with pneumonia. *H. influenzae* (16.6%) had the highest detection rate followed by *M. catarrhalis* (13.4%), *S. aureus* (13.0%), *S. pneumoniae* (12.3%), *E. coli* (5.1%) and *K. pneumoniae* (4.8%). Notably, RSV and *K. pneumoniae* were detected more frequently in severe pneumonia (35.0% and 10.9%) versus mild pneumonia (25.6% and 4.6%) (Fig. 1).

RSV was more common in infants with pneumonia < 6 months of age than in older children (27.6% vs. 24.8%, $P < 0.001$), as were *S. aureus* (19.0% vs. 5.0%, $P < 0.001$), *K. pneumoniae* (7.2% vs. 1.6%, $P < 0.001$) and *E. coli* (7.5% vs. 1.8%, $P < 0.001$). Parainfluenza was more common in children with pneumonia > 6 months old than in infants with pneumonia (6.2% vs. 3.8%, $P < 0.001$), as were adenovirus (4.8% vs. 2.1%, $P < 0.001$), *M. catarrhalis* (16.4% vs. 11.2%, $P < 0.001$) and *S. pneumoniae* (20.1% vs. 6.6%, $P < 0.001$) (Table 3). Pneumonia peaked annually in the spring (March to May) (Fig. 2). Seasonal peaks of RSV occurred in late winter (February) and late summer (August). RSV circulated throughout the year, with positive rates ranging from 6.9 to 49.5%. There were no clear seasonal patterns for other viruses, with lower detection rates in each season (Fig. 2A). Furthermore, *M. catarrhalis* was detected frequently in winter, while *H. influenzae* showed a seasonal peak in spring (Fig. 2B).

**Table 2** Detection of viral and bacterial pathogens

| Pathogens | No. (%) |
| --- | --- |
| Viral pathogen only | 1810 (32.4) |
| One viral pathogen only | 810 (14.5) |
| Viral-viral co-detection | 70 (1.3) |
| Bacterial-viral co-detection | 930 (16.7) |
| Bacterial pathogen only | 1958 (35.1) |
| Pathogen undetectable | 1813 (32.5) |

## Outcome of Children Hospitalized for Pneumonia

The rate of ICU admission was 9.4% (523/5581) among all children with pneumonia. The median length of hospital stay was 6 days (IQR 4–7), with median hospital charge of $629.2 (IQR 457.5–889.9). Infants with pneumonia < 6 months of age had a higher rate of ICU admission (12.4% vs. 5.2%, 5.2%), longer hospital stay (6 days vs. 5 days, 5 days) and higher hospital costs ($730.1 vs. $557.9, $507.2) compared to children with pneumonia aged 6–12 and 12–24 months. In terms of viral pathogens, the rate of ICU admissions for children with
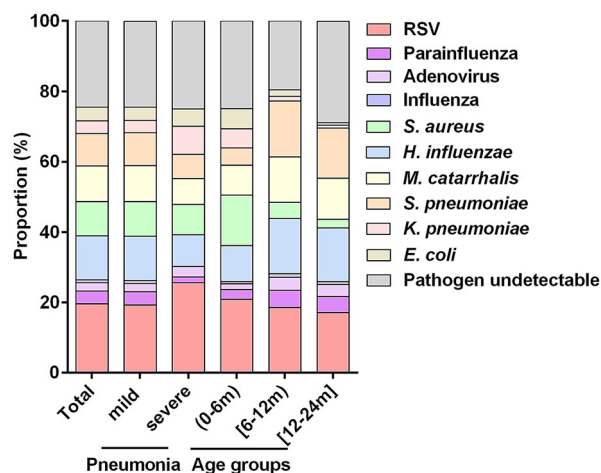


**Fig. 1** Proportion of respiratory pathogens among mild and severe pneumonia cases and different age groups (October 2014–September 2017)

RSV infection (12.5%) was much higher than for children with ADV (9.8%), flu (6.8%) and PIV (3.6%) infections. The median length of hospital stays for children infected with RSV was 6 days, which was longer than for children infected with ADV (5 days), flu (4 days) and PIVs (5 days). In addition, the median hospitalization cost per child with RSV infection was $672.76, higher than for children with other virus infections. For bacterial pathogens, children with *K. pneumoniae* infection had the highest rate of ICU admission (15.3%) and the highest hospitalization costs (median $795.7, IQR 580.1–1101.6) (Fig. 3).

## DISCUSSION

This retrospective study revealed that the burden of hospitalization for children with pneumonia was highest in infants < 6 months of age in Xiamen. Viruses were detected in 32.4% of children with pneumonia, and bacteria were detected in 51.7%. RSV was the most common respiratory virus (26.0%), and *H. influenzae* was the most commonly detected bacterium (16.6%).

RSV was detected more frequently in infants with pneumonia < 6 months of age than in older children with pneumonia (27.6% vs. 23.8%). In other studies, RSV was detected in approximately 17.3–24.6% of children with pneumonia < 5 years of age using PCR assays in China, with a higher detection rate in younger children with pneumonia [12–14], which was similar to our study. Parainfluenza, adenovirus and influenza were detected in 4.8%, 3.2% and 1% of children separately, slightly lower rates than in other regions of China [12, 14, 15]. In contrast to RSV, these three pathogens were more commonly found in older children with pneumonia. RSV infection occurred more frequently in early infancy [16]. Although infants < 6 months acquired maternal RSV-specific antibodies that provide protection, RSV-specific neutralizing antibodies decayed rapidly and provided protection only during the first 3 months of life [17, 18]. However, maternally derived influenza [19–21], ADV [22–24] and PIV [25] specific neutralizing antibodies can protect

**Table 3** Distribution of respiratory pathogens among different age groups, sex and pneumonia

| Pathogens | All cases N = 5581 NO. (%) | Pneumonia | | | Age | | | |
|---|---|---|---|---|---|---|---|---|
| | | Mild (N = 5361) NO. (%) | Severe (N = 220) NO. (%) | P | (0–6 m) (N = 3246) | [6–12 m] (N = 1163) | [12–24 m] (N = 1172) | P |
| Virus | 1810 (32.4) | 1724 (32.2) | 86 (39.1) | 0.031 | 1045 (32.2) | 410 (35.3) | 355 (30.3) | 0.034 |
| RSV | 1451 (26.0) | 1374 (25.6) | 77 (35.0) | 0.002 | 895 (27.6) | 304 (26.1) | 252 (21.5) | < 0.001 |
| Male | 958 (66.0) | 908 (66.1) | 50 (64.9) | | 577 (64.5) | 220 (72.4) | 161 (63.9) | |
| Female | 493 (34.0) | 466 (33.9) | 27 (35.1) | | 318 (35.5) | 84 (27.6) | 91 (36.1) | |
| Parainfluenza | 267 (4.8) | 262 (4.9) | 5 (2.3) | 0.075 | 122 (3.8) | 80 (6.9) | 65 (5.5) | < 0.001 |
| Male | 193 (72.3) | 188 (71.8) | 5 (100) | | 85 (69.7) | 59 (73.8) | 49 (75.4) | |
| Female | 74 (27.7) | 74 (28.2) | 0 (0) | | 37 (30.3) | 21 (26.2) | 16 (24.6) | |
| Adenovirus | 178 (3.2) | 169 (3.2) | 9 (4.1) | 0.437 | 67 (2.1) | 60 (5.2) | 51 (4.4) | < 0.001 |
| Male | 125 (70.2) | 120 (71.0) | 5 (55.6) | | 46 (68.7) | 42 (70.0) | 37 (72.5) | |
| Female | 53 (29.8) | 49 (29.0) | 4 (44.4) | | 21 (31.3) | 18 (30.0) | 14 (27.5) | |
| Influenza | 56 (1.0) | 56 (1.0) | 0 (0) | 0.172 [a] | 27 (0.8) | 17 (1.5) | 12 (1.0) | 0.180 |
| Male | 41 (73.2) | 41 (73.2) | 0 (0) | | 19 (70.4) | 12 (70.6) | 10 (83.3) | |
| Female | 15 (26.8) | 15 (26.8) | 0 (0) | | 8 (29.6) | 5 (29.4) | 2 (16.7) | |
| Bacteria | 2888 (51.7) | 2778 (51.8) | 110 (50.0) | 0.597 | 1675 (51.6) | 664 (57.1) | 549 (46.8) | < 0.001 |
| H. influenzae | 928 (16.6) | 901 (16.8) | 27 (12.3) | 0.077 | 445 (13.7) | 258 (22.2) | 225 (19.2) | < 0.001 |
| Male | 625 (67.3) | 610 (67.7) | 15 (55.6) | | 292 (65.6) | 190 (73.6) | 143 (63.6) | |
| Female | 303 (32.7) | 291 (32.3) | 12 (44.4) | | 153 (34.4) | 68 (26.4) | 82 (36.4) | |
| S. aureus | 727 (13.0) | 701(13.1) | 26 (11.8) | 0.587 | 616 (19.0) | 76 (6.5) | 35 (3.0) | < 0.001 |
| Male | 476 (65.5) | 460 (65.6) | 16 (61.5) | | 404 (65.6) | 51 (67.1) | 21 (60.0) | |
| Female | 251 (34.5) | 241 (34.4) | 10 (38.5) | | 212 (34.4) | 25 (32.9) | 14 (40.0) | |
| M. catarrhalis | 746 (13.4) | 724 (13.5) | 22 (10.0) | 0.134 | 363 (11.2) | 212 (18.2) | 171 (14.6) | < 0.001 |
| Male | 500 (67.0) | 483 (66.7) | 17 (77.3) | | 234 (64.5) | 147 (69.3) | 119 (69.6) | |
| Female | 246 (33.0) | 241 (33.3) | 5 (22.7) | | 129 (35.5) | 65 (30.7) | 52 (30.4) | |
| S. pneumoniae | 685 (12.3) | 664 (12.4) | 21 (9.5) | 0.208 | 215 (6.6) | 261 (22.4) | 209 (17.8) | < 0.001 |
| Male | 473 (69.1) | 459 (69.1) | 14 (66.7) | | 136 (63.3) | 192 (73.6) | 145 (69.4) | |
| Female | 212 (30.9) | 205 (30.9) | 7 (33.3) | | 79 (36.7) | 69 (26.4) | 64 (30.6) | |
| K. pneumoniae | 269 (4.8) | 245 (4.6) | 24 (10.9) | < 0.001 | 234 (7.2) | 22 (1.9) | 13 (1.1) | < 0.001 |
| Male | 186 (69.1) | 172 (70.2) | 14 (58.3) | | 160 (68.4) | 18 (81.8) | 8 (61.5) | |
| Female | 83 (30.9) | 73 (29.8) | 10 (41.7) | | 74 (31.6) | 4 (18.2) | 5 (38.5) | |
| E. coli | 286 (5.1) | 271 (5.1) | 15 (6.8) | 0.245 | 245 (7.5) | 31 (2.7) | 10 (0.9) | < 0.001 |
| Male | 183 (64.0) | 175 (64.6) | 8 (53.3) | | 156 (63.7) | 21 (67.7) | 6 (60.0) | |
| Female | 103 (36.0) | 96 (35.4) | 7 (46.7) | | 89 (36.3) | 10 (32.3) | 4 (40.0) | |

[a] Fisher exact test
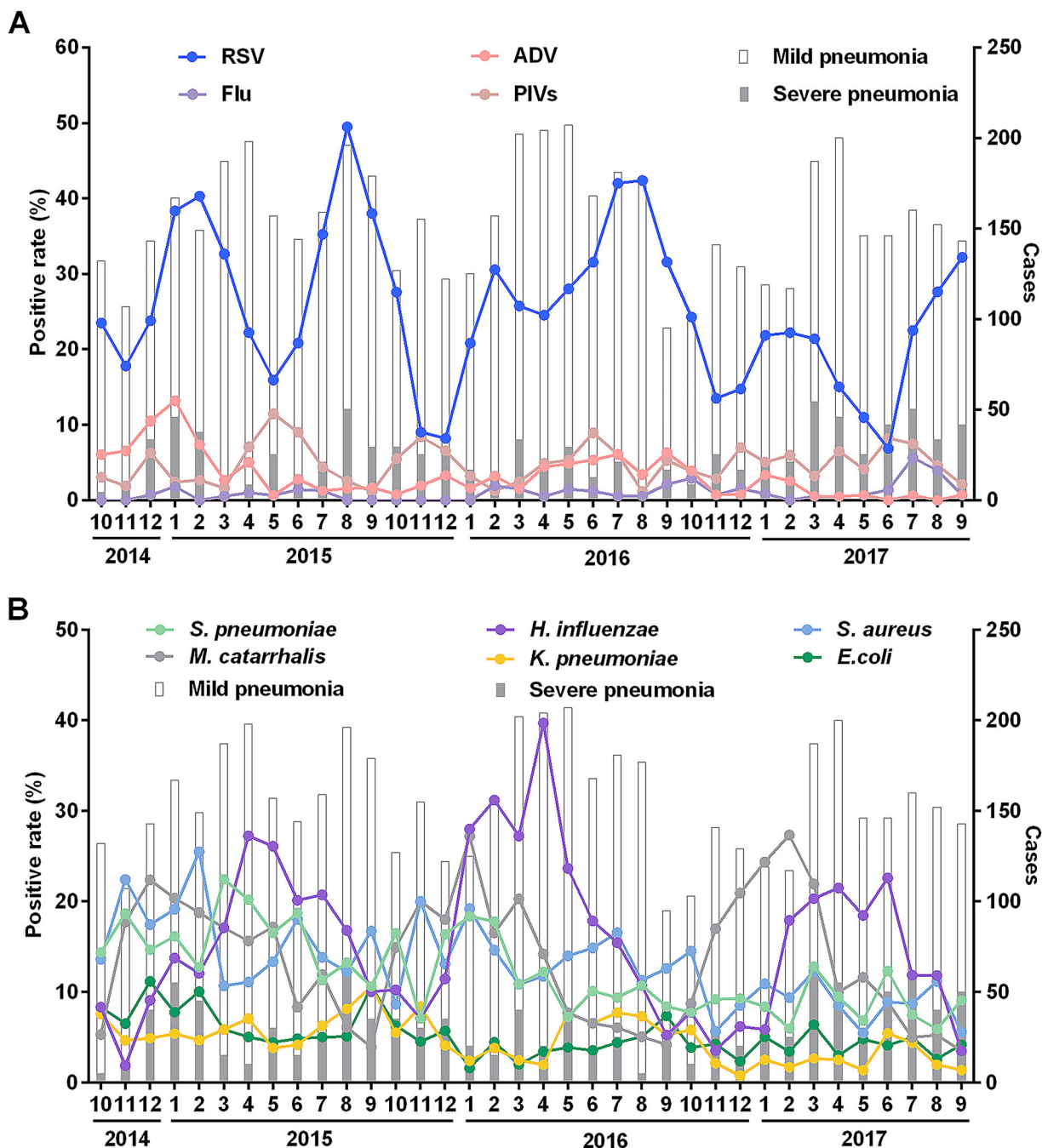
Fig. 2 Seasonal distribution of respiratory pathogens (October 2014–September 2017). **A** Detection rate of RSV, ADV, flu and PIVs during the study period.

**B** Detection rate of *S. pneumoniae*, *H. influenzae*, *S. aureus*, *M. catarrhalis*, *K. pneumoniae* and *E. coli* during the study period

newborn infants < 6 months old from infection with these viruses. Therefore, most infections with influenza, ADV and PIVs [26] usually occurred in children between 7 and 36 months of age. Prolonged and exclusive breastfeeding can transfer maternal antibodies and protect infants against respiratory tract infections [27, 28]. Another strategy to increase maternal
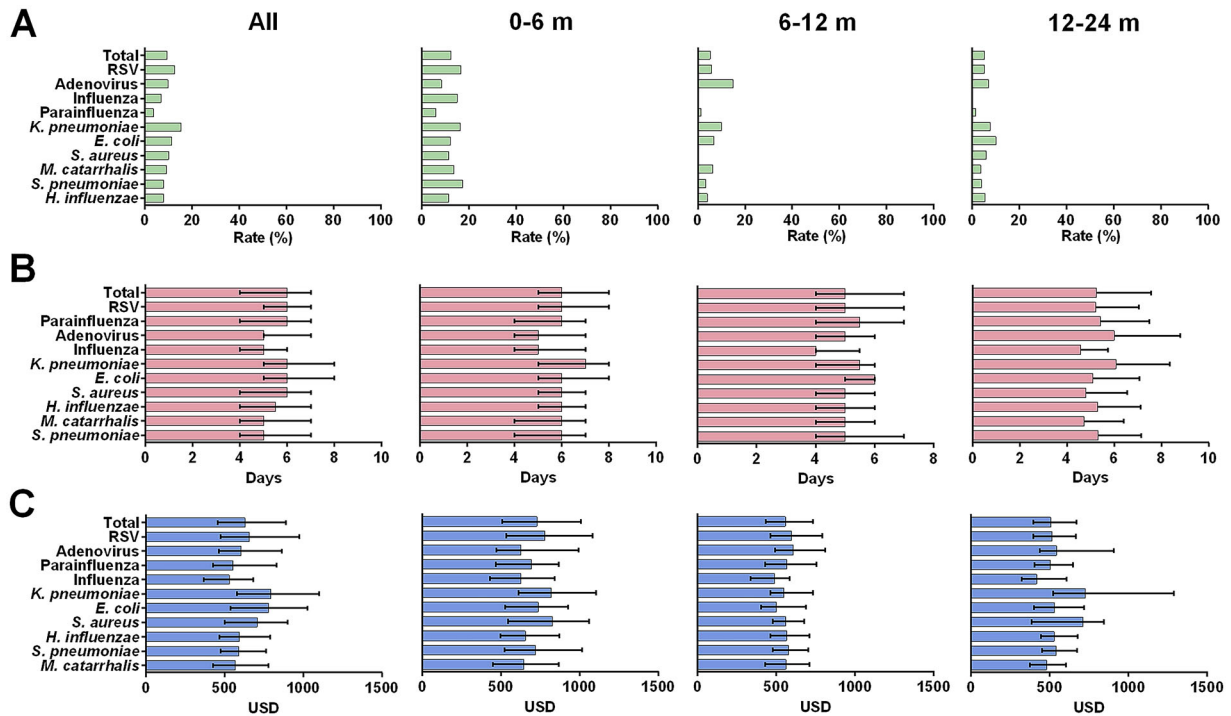
**Fig. 3** Outcome of children infected by major respiratory pathogens. **A** Rate of ICU admission; **B** median hospital stay ≥ 7 days (bars: IQR); **C** median hospital charges ≥ $600 (bars: IQR)

antibodies in infants is immunization during pregnancy, which is recommended in various countries for influenza, pertussis and tetanus vaccination programs [29–31]. In addition, group B *Streptococcus* and RSV vaccines for pregnant women are under development, which will contribute to the prevention of respiratory infectious diseases in children [32].

The proportion of bacterial detection was higher in our study (57.1%) than in other studies (15–46.2%) [3, 33–35]. The most frequently detected bacterial agents included *H. influenzae* (16.6%), *M. catarrhalis* (13.4%), *S. aureus* (13.0%), *S. pneumoniae* (12.3%), *E. coli* (5.1) and *K. pneumoniae* (4.8%), which were generally reported as the major microbes inducing bacterial pneumonia [6, 7, 12, 36]. It is worth noting that *H. influenzae* and *S. pneumoniae* remained the main bacterial agents after the introduction of a vaccine against bacterial pneumonia. Brian et al. reported that there were 294,000 pneumococcal deaths and 29,500 Hib deaths in HIV-uninfected children aged

1–59 months in 2015 globally [37]. The widespread use of pneumococcal and Hib vaccine has dramatically reduced pneumococcal and Hib cases and deaths. However, the implementation rates for both vaccines are relatively low in China (2–7%) [37, 38], and there is an urgent need to increase the vaccination rates to reduce pneumococcal and Hib disease burden in China.

Among children hospitalized for the virus, RSV-positive children contributed to a higher burden of disease, with higher rates of ICU admission, longer hospital stay and higher hospitalization costs compared with those infected by other respiratory viruses, as previously reported [39–42]. Children with RSV infection had a 14-fold increased risk of severe pneumonia [8], and approximately 45% of hospital admissions and in-hospital deaths due to RSV infection occurring in children < 6 months old [43]. In addition, despite low detection rates in children, *K. pneumoniae* was detected more frequently in severe pneumonia

and had the highest rate of ICU admission and hospital charges. The burden of disease was also higher in hospitalized children < 6 months of age than in children aged 6–24 months, which may be related to the higher rate of RSV [43] and *K. pneumoniae* in children < 6 months old [44].

There were some limitations in our study. First, this was a retrospective study of children hospitalized with pneumonia in a single center in Xiamen. Second, this study was confined in partial pathogens and more pathogens such as human rhinovirus, coronavirus, human metapneumovirus, human bocavirus, cytomegalovirus, *Bordetella pertussis*, *Mycoplasma pneumoniae*, *Chlamydia trachomatis*, *Legionella* spp., *Salmonella* spp., etc., should be considered and identified in future studies [8, 45]. Third, we cannot exclude the presence of viral and bacterial coinfection, nor can we establish a causal relationship between bacteria and pneumonia. In addition, *Streptococcus pneumonia, H. influenza, M. catarrhalis, S. aureus* and *E. coli,* etc., may be part of normal flora or colonizers in the upper respiratory tract, so bacteria detected in this study may not be the cause of pneumonia [46, 47]. Additionally, nasal swabs were detected by direct immunofluorescence rather than RT-PCR, which has better sensitivity and specificity.

# CONCLUSIONS

The burden of hospitalization for children with pneumonia was highest among infants < 6 months old in Xiamen. Among children < 2 years of age hospitalized with pneumonia in Xiamen, RSV was the most common respiratory virus, while *H. influenzae* and *S. pneumoniae* remained the predominant bacterial pathogens detected. Considering the low implementation rate of vaccines against pneumococcal and Hib pneumonia in China, there is an urgent need to increase both vaccination rates to reduce pneumococcal and Hib disease burden.

# ACKNOWLEDGEMENTS

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

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