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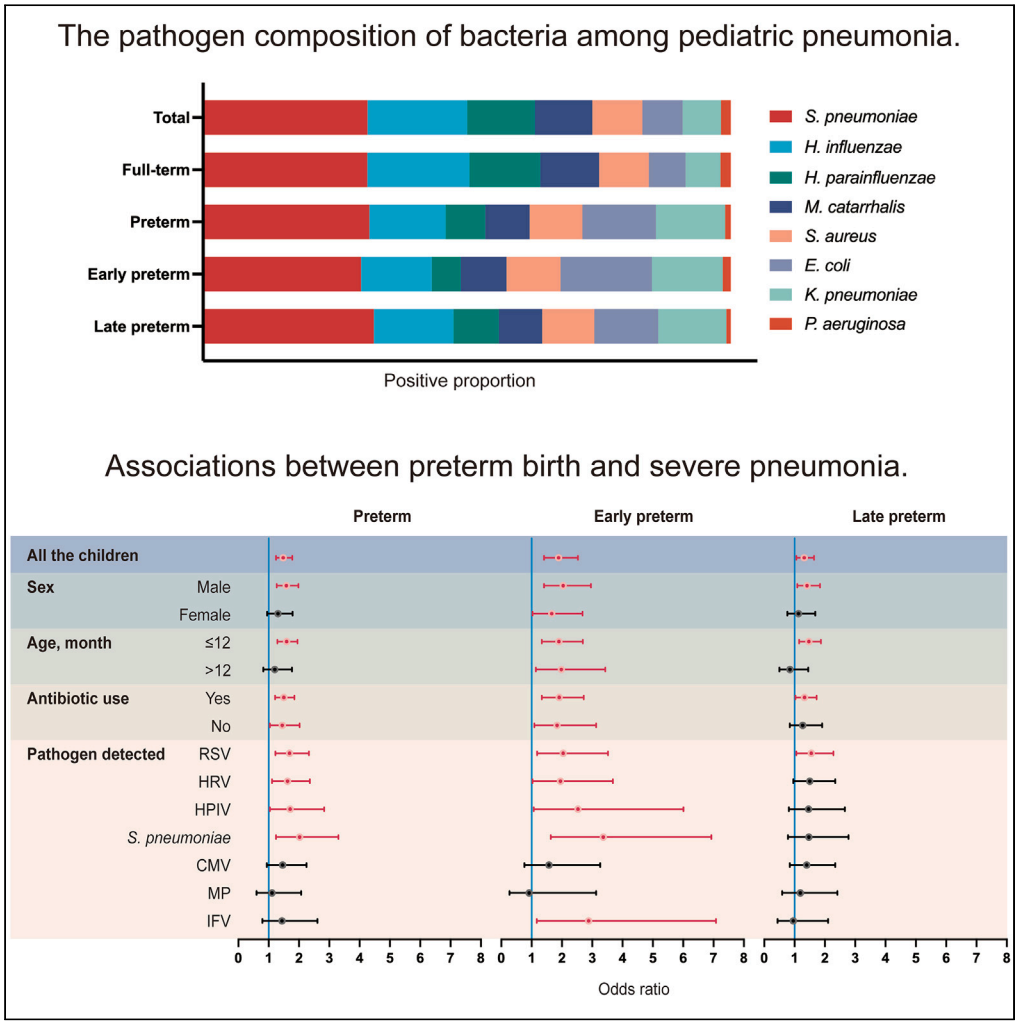

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Highlights

The positive rates for all the viral pathogens were comparable

Preterm birth has an impact on the detection of bacterial pathogens

Preterm birth is a risk factor for severe pneumonia among children

Complicated interactions were found between preterm birth and pathogen infection

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Preterm birth and detection of common respiratory pathogens among pediatric pneumonia

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SUMMARY

Pneumonia complicated by preterm birth is related to adverse clinical sequelae from the neonatal period to childhood. Children with pneumonia during 2009–2021 were enrolled at the Children's Hospital of Chongqing Medical University. Altogether 20 respiratory pathogens were detected and compared. Among 8,206 children, 779 were in the preterm group with 246 of early-preterm and 533 of late preterm. The positive rates for all viral pathogens were comparable between the preterm group and the full-term group. For bacterial pathogens, higher positive rates for *Escherichia coli* and *Klebsiella pneumoniae* were observed in the preterm group. Severe pneumonia developed in 16.52% of all, which was higher in the preterm group than in the full-term group. A significantly higher rate of severe pneumonia was observed in the early-preterm group compared to the late-preterm group. Preterm birth has an impact on the detection of bacterial pathogens in children and is a risk factor for severe pneumonia.

INTRODUCTION

Pneumonia is one of the leading causes of death from childhood infectious diseases globally, with an estimated 1.2 billion episodes and 1.4 million progressing to severe pneumonia each year, especially in low- and middle-income countries.[1] According to the World Health Organization (WHO) data, about one in ten babies is born preterm worldwide,[2] and pneumonia complicated by preterm birth was related to adverse clinical sequelae from the neonatal period to childhood,[3,4] ranking the leading cause of death in children under five years old,[5] and the 2nd among all the causes of death.[6] Etiological studies of pneumonia showed a higher prevalence of respiratory pathogens detected in children born preterm than those from full-term children, featured by a higher presence of human adenovirus (HAdV) and human parainfluenza virus (HPIV) infections among preterm pediatric patients than among full-term patients according to one study performed in Spain.[7] Gestational age at birth was also showed to be strongly associated with pneumonia-related hospitalizations in childhood, especially in infants with gestational age <28 weeks.[8]

China had the second-highest percentage of preterm births in the world. In 2014, the estimated number of preterm births exceeded one million, accounting for 7.8% of all preterm births worldwide.[9] Notably, after the implementation of the two-child policy in 2016, an increased rate of preterm births has been observed.[10] A retrospective study in China from 2009 to 2018 reported a 4.3% neonatal mortality rate for preterm infants due to pneumonia.[11] Despite this large burden of preterm birth and the adverse effect on disease, critical gaps remain in our knowledge about pneumonia in preterm children. Contemporary estimates of the incidence and microbiologic causes were largely performed in the general pneumonia patients, with no diagnostic testing performed systematically and thus detailed etiologic data are lacking on this special group of patients. This study was conducted based on the hypothesis that preterm birth, especially early-preterm birth, is a risk factor for severe pneumonia in children with pneumonia, and has an impact on the detection rate of some pathogens.

RESULTS

Study participants

From June 2009 to June 2021, a total of 8,206 pediatric patients with pneumonia meeting the criteria were enrolled in the study. There were more males (64.96%) than females (35.04%). The median age of the patients was 9 months (IQR 4–21), with 38.52% aged ≤6 months, while 23.28%, 16.79%, and 21.41% in the 7–12 months, 13–24 months, and >24 months groups, respectively. Among them, 779 (9.49%) were categorized into the

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Table 1. Demographic characteristics of the children with pneumonia compared between the full-term and preterm groups

Characteristics	Total n (%)	Full-term n (%)	Preterm n (%)	p-value
Sex				0.426
Male	5331 (64.96)	4835 (65.10)	496 (63.67)	
Female	2875 (35.04)	2592 (34.90)	283 (36.33)	
Age, month				<0.001
≤6	3161 (38.52)	2833 (38.14)	328 (42.11)	
7–12	1910 (23.28)	1703 (22.93)	207 (26.57)	
13–24	1378 (16.79)	1245 (16.76)	133 (17.07)	
>24	1757 (21.41)	1646 (22.16)	111 (14.25)	
Underlying diseases				
Asphyxia history	306 (3.73)	189 (2.54)	117 (15.02)	<0.001
Congenital heart disease	1721 (20.97)	1495 (20.13)	226 (29.01)	<0.001
Congenital airway dysplasia	167 (2.04)	135 (1.82)	32 (4.11)	<0.001
Anemia	587 (7.15)	516 (6.95)	71 (9.11)	0.026
Malnutrition	173 (2.11)	150 (2.02)	23 (2.95)	0.085
Wheezing history	1681 (20.49)	1512 (20.36)	169 (21.69)	0.379
Asthma history	237 (2.89)	220 (2.96)	17 (2.18)	0.216
Eczema history	1497 (18.24)	1379 (18.57)	118 (15.15)	0.019
Season of disease				0.462
Spring (from March to May)	2026 (24.69)	1842 (24.80)	184 (23.62)	
Summer (from June to August)	1913 (23.31)	1744 (23.48)	169 (21.69)	
Autumn (from September to November)	1875 (22.85)	1689 (22.74)	186 (23.88)	
Winter (from December to February)	2392 (29.15)	2152 (28.98)	240 (30.81)	
Antibiotic use				0.258
Yes	5765 (70.25)	5204 (70.07)	561 (72.02)	
No	2441 (29.75)	2223 (29.93)	218 (27.98)	

preterm group, comprising 246 (3.00%) of the early-preterm and 533 (6.50%) of the late-preterm group. All the other 7,427 (90.51%) children were defined as the full-term group. A significantly higher proportion of patients >24 months was observed in the full-term group than in the preterm group (22.16% vs. 14.25%, $p < 0.001$), while comparable between the early-preterm group and the late-preterm group (15.45% vs. 13.70%, $p = 0.516$) (Tables 1 and S1). The asphyxia history and congenital airway dysplasia were more commonly presented in the preterm group than in the full-term group, and likewise in the early-preterm than the late-preterm group (all $p < 0.001$) (Tables 1 and S1). Overall, 29.15% of the pneumonia episode developed during the winter season (from December to February). Antibiotic treatment was applied to 70.25% of the patients, with a comparable rate between the preterm and full-term groups ($p = 0.258$).

Pathogen detection in preterm birth and full-term birth inpatients

All the recruited patients were sampled and tested for 10 viruses and CP/MP, while 91.9% (7542/8206) of the patients were tested for all the eight bacteria. The positive rate was 75.04% (6158/8206) for viral pathogens, 45.09% (3401/7542) for bacterial pathogens, and 16.60% (1362/8206) for CP/MP, respectively (Figure 1A). Among the tested viruses, the highest positive rate was observed for RSV (29.22%), followed by HRV (22.47%), HPIV (15.73%), CMV (14.31%), and IFV (10.60%) (Figure 1B). MP was detected with a higher rate than CP (13.34% vs. 4.62%) (Figure 1C). *S. pneumoniae* was the most frequently determined (15.27%) among the bacterial pathogens (Figure 1D).

At least one positive detection was obtained in 89.22% of the preterm birth patients (695/779): one or more positive detection for virus in 666 patients (85.49%), one or more positive bacteria in 363 (46.60%), positive detection for bacteria and virus in 265 (34.02%), and CP/MP in 104 (13.35%). Significant differences were observed between the preterm group and the full-term group for the positive rate for viral and bacterial

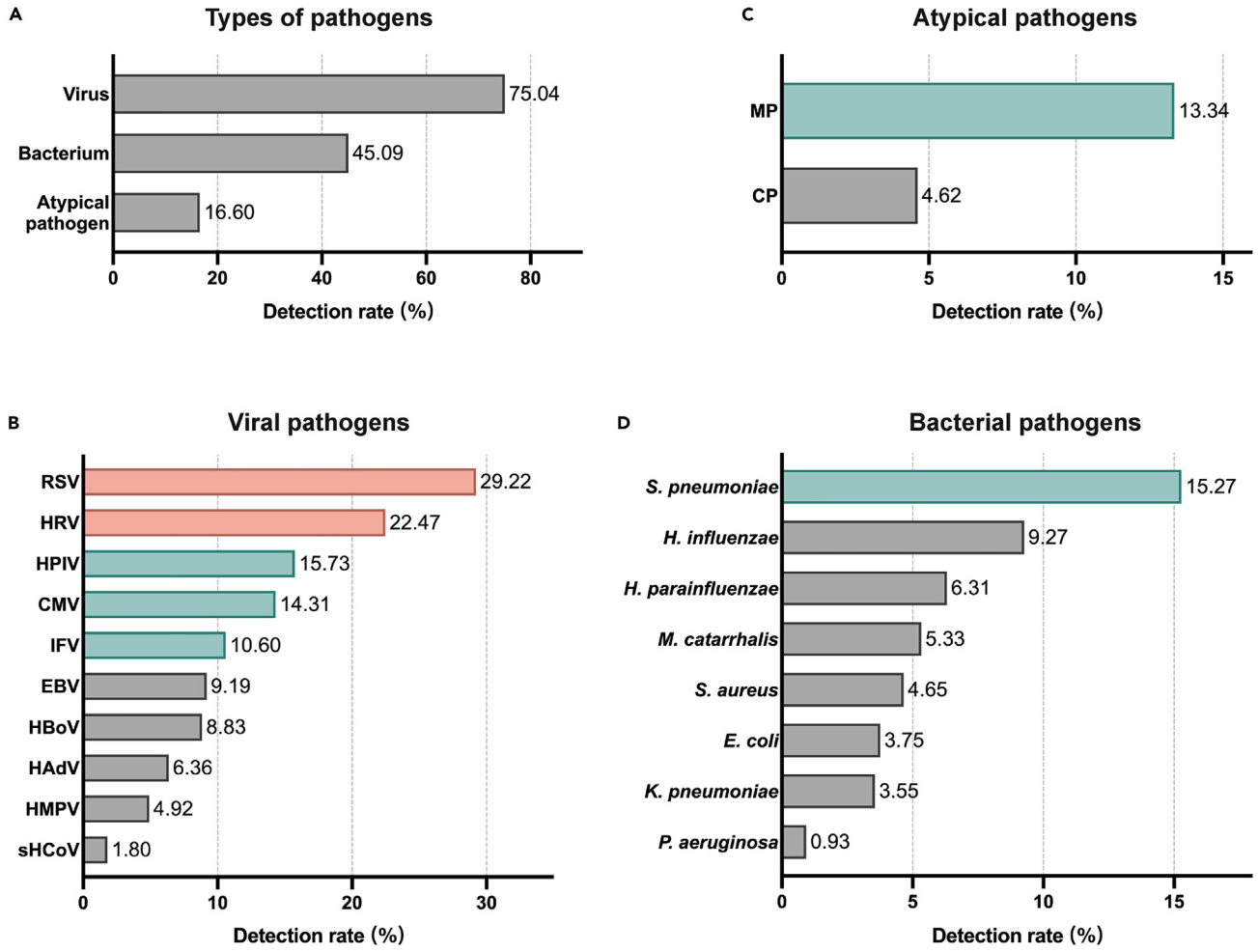

Figure 1. The positive rate of twenty respiratory pathogens in pediatric pneumonia

(A) The positive rates of different categories of pathogens including viruses, atypical pathogens, and bacteria.

(B) The positive rates of viral pathogens. The orange bars represent positive rates >20%, and the green bars represent positive rates between 10% and 20%.

(C) The positive rates of atypical pathogens. The green bar represents the positive rate between 10% and 20%.

(D) The positive rates of bacterial pathogens. The green bar represents the positive rate between 10% and 20%.

pathogen co-infection, and MP/CP infections, while not observed for the single viral or bacterial positive rate (both $p < 0.05$) (Table 2).

When the pathogen was separately compared, we observed a significantly higher prevalence of *E. coli* and *K. pneumoniae* in patients with preterm birth as a whole, in contrast with a significantly lower prevalence of *H. influenzae* and *H. parainfluenzae* in patients with preterm birth. The prevalence of all the viral pathogens was comparable between patients with preterm and full-term. However, discrepant findings were observed when patients were further grouped by age, gender, and preexisting conditions, for

Table 2. Positive rate compared between the full-term and preterm groups

Type of pathogens detected	Total n (%)	Full-term n (%)	Preterm n (%)	p-value
At least one pathogen	7381 (89.95)	6686 (90.02)	695 (89.22)	0.477
One or more viral pathogens	6983 (85.10)	6317 (85.05)	666 (85.49)	0.743
One or more bacterial pathogens	4065 (49.54)	3702 (49.85)	363 (46.60)	0.085
Both viral and bacterial pathogens	3065 (37.35)	2800 (37.70)	265 (34.02)	0.043
MP/CP	1362 (16.60)	1258 (16.94)	104 (13.35)	0.010

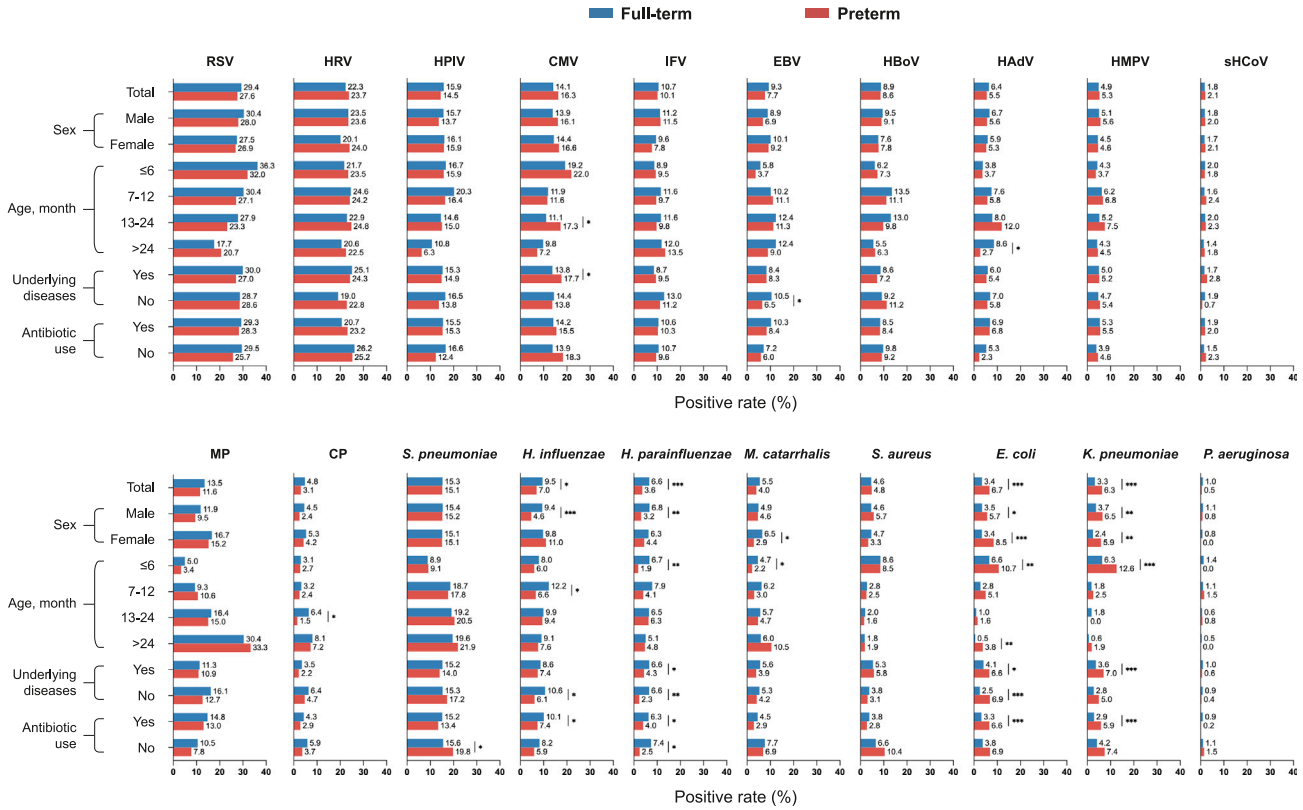

Figure 2. The positive rate of twenty respiratory pathogens in pediatric pneumonia compared between full-term and preterm birth

The positive rate of each pathogen by sex, age group, underlying disease, and antibiotic use. p values were used to determine the differences between the full-term versus the preterm groups. * p value<0.05, ** p value<0.01, and *** p value<0.001.

example, a higher prevalence of CMV was observed in the preterm patients, but only limited to those aged 13–24 months and those with preexisting conditions. A higher prevalence of *E. coli* and *K. pneumoniae* was observed in the preterm birth patients, but not in those aged >7 months or those receiving no antibiotic therapy (Figure 2). Notably, significantly lower prevalence of HAdV and EBV were observed in the preterm group than in the full-term group, but limited to patients >24 months and those without underlying disease, respectively.

Among the 246 patients with early-preterm birth patients, at least one pathogen was detected in 222 (90.24%) patients, one or more viruses were detected in 205 patients (83.33%), one or more bacteria in 123 (50.00%), both bacterial and viral pathogens in 89 (36.18%), and CP/MP in 28 (11.38%). All the prevalence was comparable between children with early-preterm and late-preterm birth (Tables S2).

When the pathogen was separately compared, we observed a significantly higher prevalence of HAdV and *E. coli* in the early-preterm group than in the late-preterm group, by contrast, a lower prevalence of HPIV in the early-preterm patients without underlying disease and those receiving antibiotics therapy (Figure 3).

When taken together, the top-ranking pathogens determined in the preterm patients were RSV, HRV, CMV, HPIV, and IFV, which differed slightly from the full-term patients (RSV, HRV, HPIV, CMV, and IFV). The five top-ranking bacterial pathogens were *S. pneumoniae*, *H. influenzae*, *E. coli*, *K. pneumoniae*, and *S. aureus*, which differed from the full-term patients (*S. pneumoniae*, *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis*, and *S. aureus*) (Figure 4 and Table S3). In patients with early-preterm birth and late-preterm birth, the viruses were consistent in their top five ranking, while for bacterial detection, *E. coli* showed a slight up-ranking from 4th in the late-preterm to 2nd in the early-preterm group. (Figure 4 and Table S4).

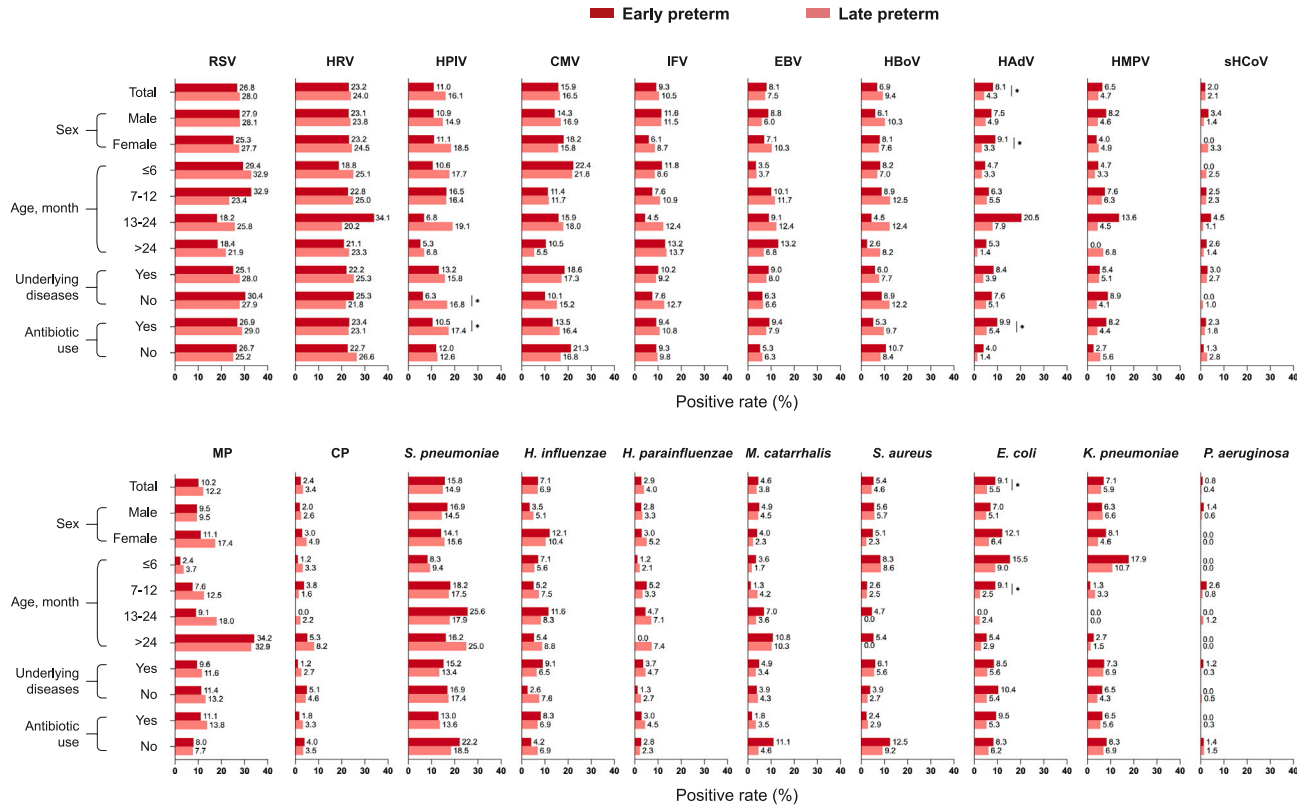

Figure 3. The positive rate of the twenty respiratory pathogens in pediatric pneumonia compared between the early-preterm and late-preterm groups

The positive rate of each pathogen by sex, age group, underlying disease condition, and antibiotic use. p values were used to determine the differences between the early-preterm group versus the late-preterm group. * p value<0.05, ** p value<0.01, and *** p value<0.001.

Preterm birth and development of severe pneumonia

Severe pneumonia developed in 16.52% (1356/8206) of all pneumonia patients, with a higher proportion in the preterm than in the full-term group (23.36% [182/779] vs. 15.81% [1174/7427]; *OR* = 1.48, *95% CI* 1.24–1.78, p < 0.001), also higher in the early-preterm group (27.24% [67/246]; *OR* = 1.89, *95% CI* 1.41–2.53, p < 0.001) and in the late-preterm group (21.58% [115/533]; *OR* = 1.32, *95% CI* 1.06–1.64, p = 0.014) than in the full-term group when adjusted by sex, age group, underlying diseases, and antibiotic use (Figure 5 and Table S5). A significantly higher prevalence of severe pneumonia was observed in the early-preterm group compared to the late-preterm group (*OR* = 1.49, *95% CI* 1.03–2.15, p = 0.033).

When each specific pathogen, sex, age group, underlying diseases, and antibiotic use were included in the analysis, RSV (*OR* = 1.57, 95%*CI* 1.08–2.30, p = 0.019) and HMPV (*OR* = 2.27, 95%*CI* 1.08–4.77, p = 0.030) were associated with a significantly higher prevalence of severe pneumonia among the preterm children (Table S6). For all pathogens tested, only one species being detected (231/779, 29.65%), two species being detected (279/779, 35.82%), and three and more species being detected (178/779, 22.85%) were not observed to be associated with a significantly higher prevalence of severe pneumonia among the preterm children (Table S7).

Subgroup analysis demonstrated a significant association between preterm birth and a higher prevalence of severe pneumonia, only among those of male gender, aged ≤12 months, and with the positive detection of RSV, HRV, HPIV, or *S. pneumoniae*, but not among female, aged>12 months and positive detection for CMV, MP, or IFV (Figure 5 and Table S5). Early-preterm birth was associated with a significantly higher prevalence of severe pneumonia in almost all subgroups, except for those with CMV or MP positive detection. By contrast, the association between late-preterm birth and significantly higher severe pneumonia was only observed in children of male, aged ≤12 months, with antibiotic use, or with positive detection of RSV (Figure 5 and Table S5).

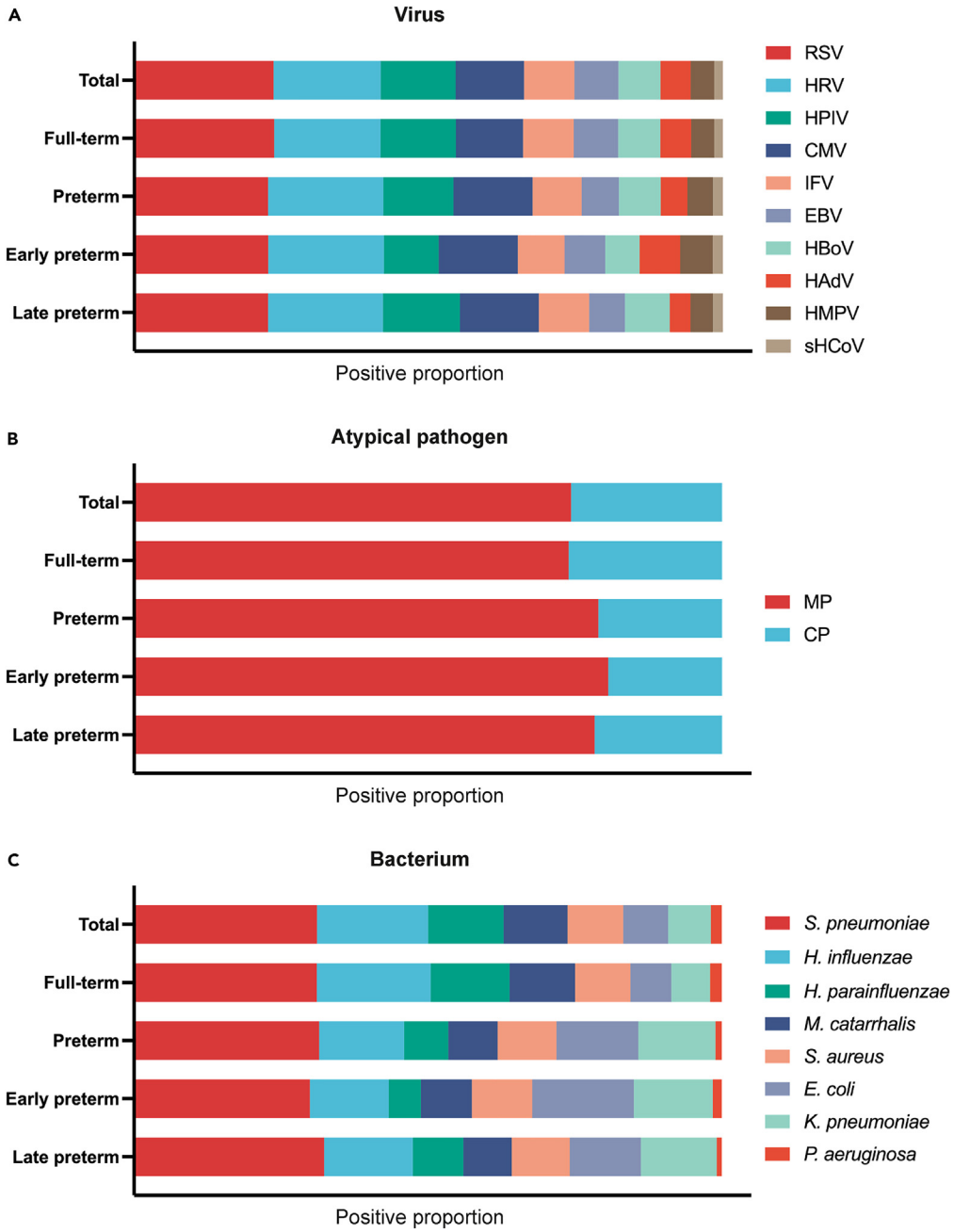

Figure 4. The pathogen composition among pediatric pneumonia in terms of preterm birth

(A) Viral pathogens.

(B) Atypical pathogens.

(C) Bacterial pathogens.

The interaction effect of preterm birth and positive detection for each of the respiratory pathogens was explored by using severe pneumonia as the outcome, sex, age group, underlying disease condition, and antibiotic used as the covariates (Table 3). Significant interaction was observed between preterm birth and positive detection for RSV, HAdV, HMPV, CMV, *K. pneumoniae*, and *S. aureus* (all $p < 0.05$), with the greatest effect observed for *S. aureus* (*OR* = 2.90, 95%*CI* 1.48–5.69, p = 0.002), followed by HAdV (*OR* = 2.84, 95%*CI* 1.48–5.44, p = 0.002) and HMPV (*OR* = 2.79, 95%*CI* 1.44–5.41, p = 0.002), while not observed for other pathogens. Significant interaction was observed between early-preterm birth and positive detection for RSV (*OR* = 2.11, 95%

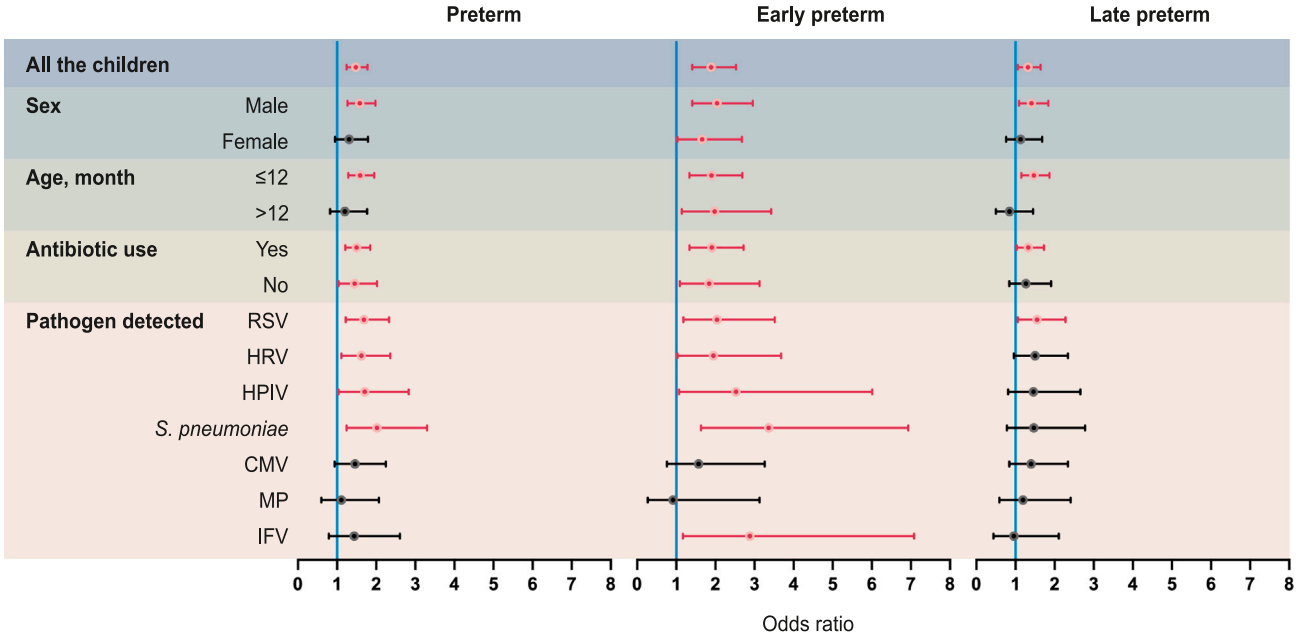

Figure 5. Association between preterm and severe pneumonia stratified by sex, age, antibiotic usage, and respiratory pathogen detection

Seven pathogens with an overall positive rate >10% were selected for analysis. The full-term group was used as the reference group, and the differences in the prevalence of severe pneumonia between the preterm, early-preterm, and late-preterm groups and the reference group were compared separately. The odds ratio for severe pneumonia in the preterm, early-preterm, and late-preterm groups compared to the full-term group is demonstrated.

CI: 1.15–3.86, p = 0.016), HMPV (*OR* = 3.76, 95%*CI* 1.30–10.92, p = 0.015), and *S. pneumoniae* (*OR* = 2.19, 95% *CI* 1.02–4.71, p = 0.046), while not observed for other pathogens (Table S8).

DISCUSSION

In this study, by analyzing 12-year surveillance data on pediatric pneumonia, we have demonstrated a comprehensive analysis on preterm birth and respiratory infection. Based on the detection of ten viral pathogens and eight bacterial pathogens, we determined a comparable prevalence of bacterial and viral pathogens in the preterm and full-term patients, except for higher positive rates of *E. coli* and *K. pneumoniae* among preterm patients. However, we indeed showed a novel role of respiratory infection among the early-preterm patients in severe pneumonia development, as well as complicated interactions that arise between early-preterm and respiratory infection.

As we have currently displayed in the subgroup analysis, preterm birth was a risk factor for severe pneumonia development among children aged ≤12 months, but not for those aged >12 months, which may be related to the relatively defective development of the immune system before 12 months of age in children born preterm compared to the full-term due to invasive operations, such as indwelling catheters, and mechanical ventilation in the neonatal period.[12,13] It is unknown when the immune system is trained to mature after birth in preterm children, however, it has been suggested that differences in the development of the immune system between full-term and preterm children persisted within the first year of life.[14] IgG is the only maternal-derived immunoglobulin in the body at birth and is involved in the humoral immune response.[15] IgG levels at birth are proportional to gestational age and are lower in preterm than in full-term infants.[16–21] Children born preterm also have lower absolute lymphocyte counts[22] or relative counts of helper T lymphocytes[23] than full-term children of the same age within one year of birth. All the aberrant immunity taken together, rendered an increased susceptibility to infection and more severe disease in the first year of life. Also, immune deficiencies increase the chance of nosocomial infections in preterm children during each hospitalization, such as two of the most common hospital-acquired infections, *E. coli* and *K. pneumoniae*,[24] which were also observed to be more frequently detected in preterm children than in term children in this study.

In pediatric patients with severe pneumonia, RSV was the most frequently detected pathogen, and HPIV also had a high predictive value for etiologic attribution. In addition, HRV ranked high in the detection

Table 3. Interaction between preterm birth and positive detection of respiratory pathogens on severe pneumonia development

Positive detection	*OR* (95% *CI*)[a]	p-value
Respiratory syncytial virus (RSV)	2.19 (1.60, 2.98)	<0.001
Human adenovirus (HAdV)	2.84 (1.48, 5.44)	0.002
Human parainfluenza virus (HPIV)	1.09 (0.68, 1.75)	0.714
Influenza virus (IFV)	1.29 (0.73, 2.26)	0.378
Human bocavirus (HBoV)	1.16 (0.61, 2.19)	0.650
Seasonal human coronavirus (sHCoV)	0.99 (0.28, 3.55)	0.991
Human Metapneumovirus (HMPV)	2.79 (1.44, 5.41)	0.002
Human rhinovirus (HRV)	1.42 (0.99, 2.02)	0.054
Cytomegalovirus (CMV)	1.60 (1.06, 2.40)	0.024
Epstein-Barr virus (EBV)	0.84 (0.40, 1.79)	0.658
Chlamydia pneumonia (CP)	2.47 (0.99, 6.16)	0.053
Mycoplasma pneumonia (MP)	1.11 (0.61, 2.02)	0.736
Streptococcus pneumoniae	1.49 (0.94, 2.35)	0.088
Haemophilus parainfluenzae	1.44 (0.57, 3.63)	0.442
Klebsiella pneumoniae	1.88 (1.01, 3.48)	0.046
Escherichia coli	0.87 (0.42, 1.82)	0.717
Moraxella catarrhalis	1.38 (0.55, 3.46)	0.490
Staphylococcus aureus	2.90 (1.48, 5.69)	0.002
Haemophilus influenzae	1.18 (0.58, 2.38)	0.648
Pseudomonas aeruginosa	1.72 (0.18, 16.81)	0.642

[a]The *OR* and 95% *CI* were calculated by performing logistic regression model using severe pneumonia as the outcome, sex, age group, underlying diseases, and antibiotic use as covariates. The reference group was the full-term group.

rate of severe pneumonia cases in children. *S. pneumoniae* is the most frequently identified bacterial pathogen in children with very severe pneumonia requiring hospitalization.[25] Patients with childhood pneumonia infected with several pathogens, including RSV, HRV, HPIV, and *S. pneumoniae*, are more likely to develop severe disease, and preterm birth is a risk factor for severe pneumonia. Therefore, we suspect that the association between preterm birth and severe pneumonia in patients who tested positive for these pathogens is significantly due to a combination of these causes. In addition, defects in the development of the respiratory[26] and immune systems of children born preterm and insufficient maternal provision of antibodies (IgG) at birth may be associated with preterm birth leading to more severe pneumonia.

Respiratory bacteria-bacteria and bacteria-virus interactions on disease outcome are extensively studied;[27,28] however, the interaction between preterm birth and the impact of pathogens on clinical outcomes remains unclear. In this study, significant interactions were observed between preterm birth and the positive detection of several pathogens, i.e., HAdV, HMPV, and *S. aureus* in severe pneumonia. The potential mechanisms underlying such interactions are elusive, however, the detection of these pathogens demands greater attention for children of preterm birth.

In conclusion, preterm birth, especially early-preterm birth, was a risk factor for severe pneumonia. Under the context of an increasing number of children surviving preterm births globally,[11] the current findings might assist in improved therapeutic or preventive strategies for pneumonia in such a special group of patients.

Limitations of the study

The study is subject to several limitations. First, the specimens used for testing were nasopharyngeal aspirates, in which the pathogens detected may be derived from coincidental upper respiratory tract infections and were not the pathogens responsible for pneumonia.[29] The detection of lung aspirates is the gold standard, but invasive procedures limit its use.[29,30] Second, the different methods of detection of respiratory pathogens may lead to bias. For example, sputum or blood cultures and IgM tests have limited sensitivity, which may lead to missed detections. Third, this study did not include other variables that may have an

impact on severe pneumonia, such as BMI and secondhand smoke exposure, in the multifactorial analysis, which may have biased the results. In addition, the study was single-center, which may be another limitation. However, close to 40% of the children hospitalized in the monitoring hospital were from multiple provinces in southwestern China, and the monitoring period spanned a long period of time, so the results of the study may still be representative. We did not perform the multivariate analysis of the interaction between preterm birth and respiratory pathogens on the development of severe pneumonia due to the low detection rate for each pathogen to avoid poor model-fitting.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2023.107488.

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AUTHOR CONTRIBUTIONS

X.-R.W. analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft. J.D., S.-S.Z., and X.-A.Z. performed the experiments, prepared figures and/or tables, and approved the final draft. Q.-B.L., L.R., W.L., and E.-M.L. conceived and designed the experiments, authored or reviewed drafts of the paper, and approved the final draft.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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REFERENCES

1. Chopra, M., Mason, E., Borrazzo, J., Campbell, H., Rudan, I., Liu, L., Black, R.E., and Bhutta, Z.A. (2013). Ending of preventable deaths from pneumonia and diarrhoea: an achievable goal. Lancet *381*, 1499–1506.

2. WHO (2012). Born Too Soon: The Global Action Report on Preterm Birth (World Health Organization Copyright © World Health Organization).

3. Chen, C.H., Wen, H.J., Chen, P.C., Lin, S.J., Chiang, T.L., Hsieh, I.C., and Guo, Y.L. (2012). Prenatal and postnatal risk factors for infantile pneumonia in a representative birth cohort. Epidemiol. Infect. *140*, 1277–1285.

4. Sonego, M., Pellegrin, M.C., Becker, G., and Lazzerini, M. (2015). Risk factors for mortality from acute lower respiratory infections (ALRI) in children under five years of age in low and middle-income countries: a systematic review and meta-analysis of observational studies. PLoS One *10*, e0116380.

5. Liu, L., Oza, S., Hogan, D., Perin, J., Rudan, I., Lawn, J.E., Cousens, S., Mathers, C., and Black, R.E. (2015). Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet *385*, 430–440.

6. Guo, X., Li, X., Qi, T., Pan, Z., Zhu, X., Wang, H., Dong, Y., Yue, H., and Sun, B. (2021). A birth population-based survey of preterm morbidity and mortality by gestational age. BMC Pregnancy Childbirth *21*, 291.

7. García-Garcia, M.L., González-Carrasco, E., Quevedo, S., Muñoz, C., Sánchez-Escudero, V., Pozo, F., Casas, I., and Calvo, C. (2015). Clinical and Virological Characteristics of Early and Moderate Preterm Infants Readmitted With Viral Respiratory Infections. Pediatr. Infect. Dis. J. *34*, 693–699.

8. Coathup, V., Carson, C., Kurinczuk, J.J., Macfarlane, A.J., Boyle, E., Johnson, S., Petrou, S., and Quigley, M.A. (2021). Associations between gestational age at birth and infection-related hospital admission rates during childhood in England: Population-based record linkage study. PLoS One *16*, e0257341.

9. Chawanpaiboon, S., Vogel, J.P., Moller, A.-B., Lumbiganon, P., Petzold, M., Hogan, D., Landoulsi, S., Jampathong, N., Kongwattanakul, K., Laopaiboon, M., et al. (2019). Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Global Health *7*, e37–e46.

10. Deng, K., Liang, J., Mu, Y., Liu, Z., Wang, Y., Li, M., Li, X., Dai, L., Li, Q., Chen, P., et al. (2021). Preterm births in China between 2012 and 2018: an observational study of more than 9 million women. Lancet Global Health *9*, e1226–e1241.

11. Yu, X., He, C., Wang, Y., Kang, L., Miao, L., Chen, J., Zhao, Q., Huang, X., Zhu, J., Liang, J., et al. (2021). Preterm neonatal mortality in China during 2009–2018: A retrospective study. PLoS One *16*, e0260611.

12. Cason, C., D'Accolti, M., Campisciano, G., Soffritti, I., Ponis, G., Mazzacane, S., Maggiore, A., Risso, F.M., Comar, M., and Caselli, E. (2021). Microbial contamination in hospital environment has the potential to colonize preterm newborns' nasal cavities. Pathogens *10*, 615.

13. Quinello, C., Silveira-Lessa, A.L., Ceccon, M.E.J.R., Cianciarullo, M.A., Carneiro-Sampaio, M., and Palmeira, P. (2014). Phenotypic differences in leucocyte populations among healthy preterm and full-term newborns. Scand. J. Immunol. *80*, 57–70.

14. Sharma, A.A., Jen, R., Butler, A., and Lavoie, P.M. (2012). The developing human preterm neonatal immune system: a case for more research in this area. Clin. Immunol. *145*, 61–68.

15. Baxter, D. (2010). Impaired functioning of immune defenses to infection in premature and term infants and their implications for vaccination. Hum. Vaccine *6*, 494–505.

16. Ballow, M., Cates, K.L., Rowe, J.C., Goetz, C., and Desbonnet, C. (1986). Development of the immune system in very low birth weight (less than 1500 g) premature infants: concentrations of plasma immunoglobulins and patterns of infections. Pediatr. Res. *20*, 899–904.

17. Hobbs, J.R., and Davis, J.A. (1967). Serum gamma-G-globulin levels and gestational age in premature babies. Lancet *1*, 757–759.

18. Melville, J.M., and Moss, T.J.M. (2013). The immune consequences of preterm birth. Front. Neurosci. *7*, 79.

19. van den Berg, J.P., Westerbeek, E.A.M., Berbers, G.A.M., van Gageldonk, P.G.M., van der Klis, F.R.M., and van Elburg, R.M. (2010). Transplacental transport of IgG antibodies specific for pertussis, diphtheria, tetanus, haemophilus influenzae type b, and Neisseria meningitidis serogroup C is lower in preterm compared with term infants. Pediatr. Infect. Dis. J. *29*, 801–805.

20. van den Berg, J.P., Westerbeek, E.A.M., van der Klis, F.R.M., Berbers, G.A.M., and van Elburg, R.M. (2011). Transplacental transport of IgG antibodies to preterm infants: a review of the literature. Early Hum. Dev. *87*, 67–72.

21. Resch, B., Resch, E., and Müller, W. (2013). Should respiratory care in preterm infants include prophylaxis against respiratory syncytial virus infection? The case in favour. Paediatr. Respir. Rev. *14*, 130–136.

22. Berrington, J.E., Barge, D., Fenton, A.C., Cant, A.J., and Spickett, G.P. (2005). Lymphocyte subsets in term and significantly preterm UK infants in the first year of life analysed by single platform flow cytometry. Clin. Exp. Immunol. *140*, 289–292.

23. Walker, J.C., Smolders, M.A.J.C., Gemen, E.F.A., Antonius, T.A.J., Leuvenink, J., and de Vries, E. (2011). Development of lymphocyte subpopulations in preterm infants. Scand. J. Immunol. *73*, 53–58.

24. Rangelova, V., Raycheva, R., Kevorkyan, A., Krasteva, M., and Dermendzhiev, T. (2020). Surveillance of Nosocomial Infections in a Bulgarian Neonatal Intensive Care Unit. Folia Med. *62*, 753–761.

25. Pneumonia Etiology Research for Child Health PERCH Study Group (2019). Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. Lancet *394*, 757–779.

26. Bogdan, R.D., Bohiltea, R.E., and Toma, A.I. (2022). Respiratory Follow Up of the Premature Neonates-Rationale and Practical Issues. J. Clin. Med. *11*, 1746.

27. Nickbakhsh, S., Mair, C., Matthews, L., Reeve, R., Johnson, P.C.D., Thorburn, F., von Wissmann, B., Reynolds, A., McMenamin, J., Gunson, R.N., and Murcia, P.R. (2019). Virus-virus interactions impact the population dynamics of influenza and the common cold. Proc. Natl. Acad. Sci. USA *116*, 27142–27150.

28. Chen, J., Hu, P., Zhou, T., Zheng, T., Zhou, L., Jiang, C., and Pei, X. (2018). Epidemiology and clinical characteristics of acute respiratory tract infections among hospitalized infants and young children in Chengdu, West China, 2009-2014. BMC Pediatr. *18*, 216.

29. Shi, T., McLean, K., Campbell, H., and Nair, H. (2015). Aetiological role of common respiratory viruses in acute lower respiratory infections in children under five years: A systematic review and meta-analysis. J. Glob. Health *5*, 010408.

30. Howie, S.R.C., Morris, G.A.J., Tokarz, R., Ebruke, B.E., Machuka, E.M., Ideh, R.C., Chimah, O., Secka, O., Townend, J., Dione, M., et al. (2014). Etiology of severe childhood pneumonia in the Gambia, West Africa, determined by conventional and molecular microbiological analyses of lung and pleural aspirate samples. Clin. Infect. Dis. *59*, 682–685.

31. Wo, Y., Lu, Q.B., Huang, D.D., Li, X.K., Guo, C.T., Wang, H.Y., Zhang, X.A., Liu, W., and Cao, W.C. (2015). Epidemical features of HAdV-3 and HAdV-7 in pediatric pneumonia in Chongqing, China. Arch. Virol. *160*, 633–638.

32. Wang, Z.B., Ren, L., Lu, Q.B., Zhang, X.A., Miao, D., Hu, Y.Y., Dai, K., Li, H., Luo, Z.X., Fang, L.Q., et al. (2021). The Impact of Weather and Air Pollution on Viral Infection and Disease Outcome Among Pediatric Pneumonia Patients in Chongqing, China, from 2009 to 2018: A Prospective Observational Study. Clin. Infect. Dis. *73*, e513–e522.

33. WHO (2013). WHO Guidelines Approved by the Guidelines Review Committee (World Health Organization Copyright © World Health Organization).

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
STATA version 17	StataCorp LLC, USA	https://www.stata.com

RESOURCE AVAILABILITY

Lead contact

Further requests for information, data, and code should be directed to the lead contact, Qing-Bin Lu (qingbinlu@bjmu.edu.cn).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- Data: All the data reported in this paper will be shared by the lead contact upon request.
- Code: Reasonable requests for coding used in this study is available by the corresponding author upon request.
- All other items: Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

The study was conducted at the Respiratory Medicine Department, Children's Hospital of Chongqing Medical University (CHCMU), a tertiary care children's hospital and the largest one in southwestern China, serving patients from several southwestern provinces.[31] Surveillance of respiratory pathogens was conducted among hospitalized patients (age <16 years) with pneumonia during 2009–2021 according to a standard operating protocol, which included guidelines for patient enrollment, specimen collection, laboratory testing, and data recording during the study period.[32]

Pneumonia was defined by the presence of patchy alveolar opacities on chest radiographs with the presence of cough, dyspnea, or tachypnea (in infants, >50–60 breaths/min; in older children, >40 breaths/min). Severe pneumonia was defined if pneumonia was complicated by hypoxemia (maintenance of SaO_2 <92% in air) or increasing respiratory and pulse rates with clinical evidence of respiratory distress and exhaustion with or without elevated $PaCO_2$.[33]

Written informed consent was obtained from the legal guardians of the children in the monitoring cohort, and the study was reviewed and approved by the Ethics Committee of CHCMU (Permit number 2015-77).

METHOD DETAILS

Demographic information collection

Preterm birth was defined as gestational age <37 weeks,[2] among whom early-preterm and late-preterm groups were further defined as born at ≤33 weeks and born at 34–36 weeks. Those with gestational age ≥37 weeks were defined as full-term. Underlying diseases included asphyxia history, congenital heart disease, congenital airway dysplasia, anemia, malnutrition, wheezing history, asthma history, and eczema history.

Specimen collection and laboratory examination

Nasopharyngeal aspirates, sputum, and blood were obtained from patients within 24 hours of admission. Nasopharyngeal aspirates were used for the detection of eight viral pathogens, i.e., respiratory syncytial virus (RSV), HAdV, HPIV, influenza virus (IFV), human bocavirus (HBoV), seasonal human coronavirus

(sHCoV), human metapneumovirus (MPV), human rhinovirus (HRV), as well as *chlamydia pneumoniae* (CP). DNA/RNA was extracted for the amplification by polymerase chain reaction (PCR), reverse transcription PCR, real-time PCR, real-time reverse transcription PCR, within 24 hours of collection or, if not feasible, stored at -80°C for later detection. Infection of cytomegalovirus (CMV), Epstein-Barr virus (EBV), and *mycoplasma pneumoniae* (MP) was determined by the test of Immunoglobulin M (IgM) in serum. Infections by bacterial pathogens were confirmed by sputum culture or blood culture. Among the positive culture results, eight bacterial pathogens were included in this study, i.e., *Streptococcus pneumoniae* (*S. pneumoniae*), *Hemophilus parainfluenzae* (*H. parainfluenzae*), *Haemophilus influenzae* (*H. influenza*), *Moraxella catarrhalis* (*M. catarrhalis*), *staphylococcus aureus* (*S. aureus*), *escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Pseudomonas aeruginosa* (*P. aeruginosa*).

QUANTIFICATION AND STATISTICAL ANALYSIS

Descriptive statistics were performed with normally distributed continuous variables described by mean and standard deviation (SD), non-normally distributed continuous variables described by median and interquartile range (IQR), and categorical variables described by frequency and proportion. Chi-square test or Fisher exact test was used to compare the differences in categorical variables between groups. Logistic regression model was used to calculate the odds ratio (*OR*) and 95% confidence interval (*CI*). Covariates for the logistic regression model included sex, age group, underlying diseases, and antibiotic use. Statistical analysis was performed in STATA version 17 (StataCorp LLC, USA). All tests were two-sided with p-value < 0.05 as statistically significant.

ADDITIONAL RESOURCES

None.