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ORIGINAL RESEARCH

Epidemiological Changes in Hospitalized Bronchiolitis in Children Under 2 Years of Age in Hangzhou Before and After COVID-19 Restriction Easing

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Background: Bronchiolitis is a common cause of hospitalization in infants under 2 years of age. The epidemiological effects of changes in hygiene and social behaviors during COVID-19 restrictions on the disease is still debated. This study aimed to analyze the changes in the viral etiology of bronchiolitis in Hangzhou during the COVID-19 restriction period (2022) compared to the period following the easing of restrictions(2023).

Methods: This study collected data on patients under 2 years of age who were admitted for bronchiolitis to the Department of Pulmonology at the Children's Hospital, Zhejiang University School of Medicine (Hangzhou) from January, 1, 2022, to December 31, 2023. It also investigated seasonal variations in the incidence of bronchiolitis and pathogen distribution across different years.

Results: This study included a total of 697 children with bronchiolitis, with a median age of 7.5 (4.2–12.0) months. Of these, 68.9% were boys and 31.1% were girls. Compared to 2022, the number of bronchiolitis cases in 2023 (388 versus 309) and their proportion of lower respiratory tract infections (39.1% versus 28.2%) have significantly increased ($p < 0.001$). Whether in 2022 or 2023, respiratory syncytial virus (RSV) was the primary pathogen causing bronchiolitis among children under 12 months of age, while human rhinovirus (HRV) was the main pathogen in children aged 12–24 months. There was a shift in the timing of the peak of several viruses including RSV, human metapneumovirus (HMPV) and parainfluenza virus (PIV) infections in 2023. However, the epidemic trend of HRV presented no significant changes between 2022 and 2023.

Conclusion: The findings suggest that bronchiolitis hospitalizations increased markedly after COVID-19 restriction easing, particularly among children aged 12–18 months. There was a shift in the timing of the peak of several viruses including RSV, HMPV and PIV infections in 2023, emphasizing the need for hospitals to anticipate potential irregularities in time in the future.

Keywords: RSV, COVID-19, bronchiolitis, non-pharmaceutical interventions

Introduction

Bronchiolitis is an acute infection of the lower respiratory tract that affects young children especially under 2 years of age worldwide.[1] The pathology is mainly related to inflammation and obstruction of the distal bronchioles, resulting in airflow limitation and alteration in exhalation capacity, which lead to lung function alterations, mucus hypersecretion, atelectasis and wheezing.[2,3] Evidence suggests that bronchiolitis leads to over 30 million cases of lower respiratory tract infections in children, with 3.2 million hospitalizations, and approximately 59000 deaths worldwide annually.[4,5] This poses a serious threat to the health of infants and young children and imposes a significant burden on society and economy. As an acute respiratory infection, bronchiolitis is generally considered to be a viral illness, and the most

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common viruses is human respiratory syncytial virus (RSV), followed by rhinovirus (RV), influenza, and human metapneumovirus (HMPV).[6,7] Although bacterial pathogens such as *Bordetella pertussis* and atypical pathogens have been reported, their incidence is considerably lower than that of viral infections.[8] Studies have indicated that single viral infections are more common than coinfections with multiple viruses.[9,10] While viral coinfections are associated with longer the hospital stays, they do not increase the need for admission to the pediatric intensive care unit (PICU).[11] The onset of bronchiolitis is seasonal, historically occurring mainly in winter, with peaks in the Northern Hemisphere from December to February and in the Southern Hemisphere from May to July.[12–15] COVID-19 has had profound effects on individuals, societies, and health-care systems. During the COVID-19 pandemic, non-pharmaceutical interventions (NPIs) have been implemented,[16] including personal measures such as home isolation, wearing masks, frequent handwashing, and avoiding crowded places, as well as lengthy whole country lockdowns and travel restrictions, aimed at preventing the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[17] Because of the NPIs, the COVID-19 pandemic has altered the epidemiological pattern of acute respiratory infections globally, affecting the circulation of viruses and the incidence of respiratory infections worldwide.[17–19] Currently, several studies have demonstrated the epidemiological changes of bronchiolitis in children during the COVID-19 pandemic compared to the pre-pandemic period, involving countries such as the England, the US, Spain, Australia, etc.[19–22] However, there are few studies on the changes in the etiology of bronchiolitis after easing of COVID-19 restrictions. According to the Chinese Center for Disease Control and Prevention, COVID-19 restriction policies in China were lifted in December 2022. Therefore, we define 2022 as the pre-COVID-19 restriction easing period and 2023 as the post-COVID-19 restriction easing period.

In this study, we aimed to investigate the impact of NPIs on the epidemiological trends of bronchiolitis by collecting data on hospitalized children under 2 years of age in Hangzhou in 2022 and 2023. This will provide new evidence for the changes in the incidence peaks of various pathogens causing bronchiolitis in the post-pandemic era, contributing to the rational allocation of related medical resources.

Materials and Methods

Study Design and Participants

This single-center, retrospective study included all hospitalized cases of bronchiolitis in children aged 29 days to 2 years, admitted between January 1, 2022, and December 31, 2023, to the Children's Hospital of Zhejiang University School of Medicine. Cases were identified using relevant International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes (eTable 1 in Supplementary information).[23] As the target population for bronchiolitis diagnostic guidelines in most countries is children aged ≤2 years, we selected children between 29 days and 2 years of age as the subjects of our study.[2]

Eligible patients had to undergo nasopharyngeal swab nucleic acid testing for 13 respiratory pathogens upon outpatient clinic visit or hospital admission. Patients were excluded if (1) their hospital electronic medical records are incomplete; (2) they have congenital diseases (such as congenital heart disease, bronchopulmonary dysplasia), auto-immune diseases, tuberculosis, or other underlying diseases that affect immune system function; (3) they have bacterial infections or infections caused by pathogens other than viruses.

Respiratory Virus Detection

The nasopharyngeal swab samples were transported and stored at 2–8°C. Nucleic acids were extracted from the nasopharyngeal swab samples using the TANBead OptiPure Virus Auto Tube (Taiwan Biotoka Nano Technology Co., Ltd.) according to the manufacturer's instructions. The extracted RNA was stored in polymerase chain reaction (PCR) tubes at −80°C until further analysis.

Etiology was determined using a 13-respiratory pathogen multiplex detection kit (Ningbo Hysun Gene Technology Co., Ltd. China) combined with GeXP capillary electrophoresis technology for the simultaneous detection of 13 common respiratory viral targets,[24] including the influenza virus A (InfA), influenza virus A subtype H1N1 (H1N1), seasonal influenza virus A subtype H3N2 (H3N2), influenza virus B (InfB), respiratory syncytial virus (RSV), human rhinovirus

(HRV), human coronavirus (HCoV), human metapneumovirus (HMPV), human adenovirus (ADV), human bocavirus (HBoV), human parainfluenza virus (PIV), *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae.*

Ethics Statement

Ethics approval has been granted (No.KY-2024-0075) by the Research Ethics Committee of the Children's Hospital of Zhejiang University School of Medicine. All the data were collected retrospectively and anonymized in a standardized case report form in the hospital database.

Statistical Analysis

Categorical variables were represented as numbers (%) and frequencies. Since age did not follow a normal distribution, it was expressed as median and interquartile range (IQR). Comparisons between groups were made using $\chi2$ tests and rank-sum tests. A p-value below 0.05 was considered to indicate a statistically significant difference.

Statistical analysis was performed using SPSS version 25.0. To further investigate the seasonal variations in the prevalence of respiratory syncytial virus (RSV) and parainfluenza virus (PIV) infections in children with bronchiolitis across different years, we conducted a subgroup analysis stratified by season: spring, summer/autumn, and winter. The primary outcome was the presence of RSV or PIV, and the key explanatory variable was the year of diagnosis (2022 vs 2023). Logistic regression models were employed to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between the year and viral prevalence. All models were adjusted for age and sex to control for potential confounding factors. Interaction terms were included to assess season-specific effects. Statistical significance was defined as a p-value <0.05, and interaction p-values were reported to evaluate seasonal heterogeneity.

Results

Demographics

There were 697 cases of bronchiolitis that met the inclusion criteria, among 2089 hospitalized children under the age of 2 due to lower respiratory tract infections from January 1, 2022, to December 31, 2023. The median patient age was 7.5 (IQR, 4.2–12.0) months; 31.1% were girls and 68.9% were boys. In 2022, before the easing of COVID19 restrictions, 1096 children under 2 years of age were hospitalized for lower respiratory tract infections, of which 309 cases (28.2%) were bronchiolitis. In 2023, after the easing of COVID-19 restrictions, there were 388 cases of bronchiolitis (39.1%) among 993 hospitalized children with lower respiratory tract infections. The proportion of bronchiolitis cases in 2023 showed a significant increase compared to 2022, with a statistically significant difference (χ^2=27.726, P<0.001). Demographic data were presented in the Table 1.

Table 1 Patients' demographic characteristics

	No. (%) of Bronchiolitis Admissions			
Characteristic	**Overall (n=697)**	**2022 (n=309)**	**2023 (n=388)**	***P* value**
Age, median (IQR), mo	7.5 (4.2-12.0)	7 (4.3-10.0)	8.1(4.2-13.0)	0.093
Age group, mo				
≤6 M	272 (39.0)	125 (40.5)	147 (37.9)	
6-12 M	274 (39.3)	132 (42.7)	142 (36.6)	
12-18 M	86 (12.3)	24 (7.8)	62 (16.0)	0.010
18-24 M	65 (9.3)	28 (9.1)	37 (9.5)	
Sex				
Female	217 (31.1)	96(31.0)	121(31.2)	0.973
Male	480 (68.9)	213(69.0)	267(68.8)	

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Viral Etiology

Based on the etiological and epidemiological data of the pediatric patients in this study, the distribution of viruses by year were reported in Table 2. Our observations revealed that among 697 cases of bronchiolitis, 575 cases of viral infections were detected, with a detection rate of 82.5%. Of these, 505 cases were single-virus infections (72.5%), and 70 cases were mixed-virus infections (10.0%). In 2022, out of 309 cases of bronchiolitis,

259 cases of viral infections were detected, with a detection rate of 83.8%. Among these, 228 cases were single-virus infections (73.8%), and 31 cases were mixed-virus infections (10.0%). While in 2023, 316 cases of viral infections were detected among 388 patients, with a detection rate of 81.4%, in which 277 cases were single-virus infections (71.4%), and 39 cases were mixed-virus infections. There were no statistically significant differences in the viral detection rates and mixed-virus infection rates between 2022 and 2023 ($P > 0.05$). The most common viruses detected was RSV (n=300, 43%), followed by HRV (n=171, 24.5%), PIV (n=60, 8.6%), HMPV (n=58, 8.3%), HBoV (n=34, 4.9%), ADV (n=8,1.1%), HCoV (n=8, 1.1%), Inf (n=6, 0.9%). In addition, there were no significant differences in the detection rates of RSV, HRV, HMPV, PIV, HBoV, ADV and HCoV between 2022 and 2023 ($P > 0.05$). However, the detection rate of Inf increased in 2023 ($P<0.05$).

Age Stratification

The patients were divided into 4 groups based on their age, which were ≤6 months, 612 months, 12–18 months and 18–24 months. The majority of patients were aged ≤6 months and 6–12 months, accounting for 39% and 39.3% respectively. Compared to 2022, there was an increase in admissions among all age groups in 2023, the difference was most notable among children aged 12–18 months ($\chi 2=10.659$, $P<0.05$), in whom the proportion of admissions increased 2-fold in 2023 compared with the pre-COVID19 restriction easing period (Table 1, Figure 1A, 1B). Among patients under 12 months, the most common viral infections were RSV, while in hospitalized children aged 12–24 months, HRV was the most prevalent. Additionally, no significant differences were found in the detection rates of various viruses across different age groups between 2022 and 2023 ($P > 0.05$) (Figure 1C,1D).

Viral Etiology and Gender

The infection rate was higher in male patients (n=480, 68.9%) compared to the females (n=217, 31.1%). Meanwhile, no significant differences were observed in the detection rates of individual viruses between genders, with RSV being the most common one (Figure 2).

Seasonality

According to the meteorological classification in Hangzhou, March to May is defined as spring, June to August as summer, September to November as autumn, and December to February as winter. Before the easing of COVID-19 restrictions, bronchiolitis exhibited a winter-dominant seasonality, with peak hospital admissions in December. However, bronchiolitis in the post-restriction period displayed atypical seasonality (Figure 3A). Further detailed investigation

Table 2 Distribution of pathogens diagnosis during two consecutive years 2022 and 2023

		No. (%) of Bronchiolitis Admissions								
Characteristic		**Positive**	**RSV**	**HRV**	**HMPV**	**HBoV**	**PIV**	**ADV**	**HCoV**	**Inf**
Total (n=697)		575 (82.5)	300 (43.0)	171 (24.5)	58 (8.3)	34 (4.9)	60 (8.6)	8 (1.1)	8 (1.1)	6 (0.9)
2022(n=309)	Total infection cases	259 (83.8)	139 (45)	75 (24.3)	24 (7.8)	19 (6.1)	24 (7.8)	4 (1.3)	5 (1.6)	0 (0.0)
	Single infection cases	228 (73.8)	122 (39.5)	55 (17.8)	20 (6.5)	13 (4.2)	13 (4.2)	2 (0.6)	3 (1.0)	0 (0.0)
	Multiple infection cases	31 (10.0)	17 (5.5)	20 (6.5)	4 (1.3)	6 (1.9)	11 (3.6)	2 (0.6)	2 (0.6)	0 (0.0)
2023 (n=388)	Total Infection cases	316 (81.4)	161 (41.5)	96 (24.7)	34 (8.8)	15 (3.9)	36 (9.3)	4 (1.0)	3 (0.8)	6 (1.5)
	Single infection cases	277 (71.4)	144 (37.1)	69 (17.8)	25 (6.4)	12 (3.0)	24 (6.2)	2 (0.5)	1 (0.3)	0 (0.0)
	Multiple infection cases	39 (10.0)	17 (4.4)	27 (7.0)	9 (2.3)	3 (0.8)	12 (3.0)	2 (0.5)	2 (0.5)	6 (1.5)

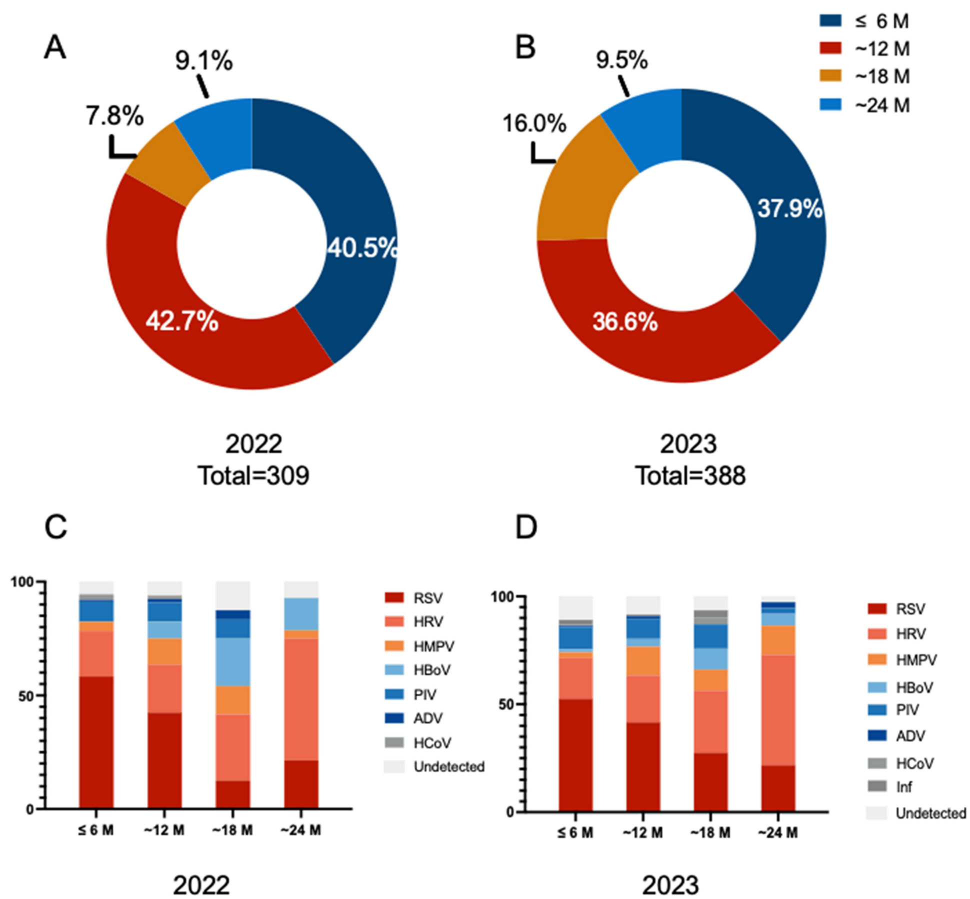

Figure 1 Proportion of different age groups and distribution of various viruses in bronchiolitis hospitalizations in 2022 and 2023. (**A**). Proportion of different age groups in 2022, (**B**). Proportion of different age groups in 2023, (**C**). Distribution of various viruses among different age groups in 2022, (**D**). Distribution of various viruses among different age groups in 2023.

revealed that in 2022, there was a marked reduction in RSV positive cases in April and remained a low level until Autumn, followed by a steady increase, reaching a peak in November and December. However, these trends reversed after the COVID-19 restriction easing, exhibiting an off-season outbreak during the summer, with no notable peak in winter as traditionally observed (Figure 3B). The epidemic trend of HRV presented no significant changes between 2022 and 2023 (Figure 3C). In 2023, there was a shift in the timing of the peak of HMPV infections compared to 2022. In the pre-COVID-19 restriction easing period, the peak detection of HMPV occurred in March to May (Spring), whereas in the postCOVID-19 restriction easing period, the peak occurred in November to December (Figure 3D). Additionally, in 2022, the trend of PIV detection paralleled that of RSV positive cases, while in 2023, the peaks of PIV detection occurred in July and October, showing an earlier timing compared to 2022 (Figure 3E). The logistic regression results revealed significant seasonal variations in RSV and PIV prevalence between 2022 and 2023, adjusted for age and sex. In winter, the odds of RSV infection were significantly lower in 2023 compared to 2022 (OR: 0.35; 95% CI: 0.18–0.69; p=0.003).In summer/autumn, the odds of PIV infection were significantly higher in 2023 compared to 2022 (OR: 2.98; 95% CI: 1.26–7.05; p=0.013).Interaction analyses confirmed significant heterogeneity in seasonal trends for both RSV (p for interaction <0.001) and PIV (p for interaction <0.001) (Figure 4).

Discussion

To our knowledge, this study is the first epidemiological investigation to explore the changes in bronchiolitis pathogens in southeastern China before and after the easing of COVID-19 restrictions. We observed an increase in hospitalizations for bronchiolitis in pediatric patients in 2023 compared to 2022. This analysis confirmed previous reviews showing

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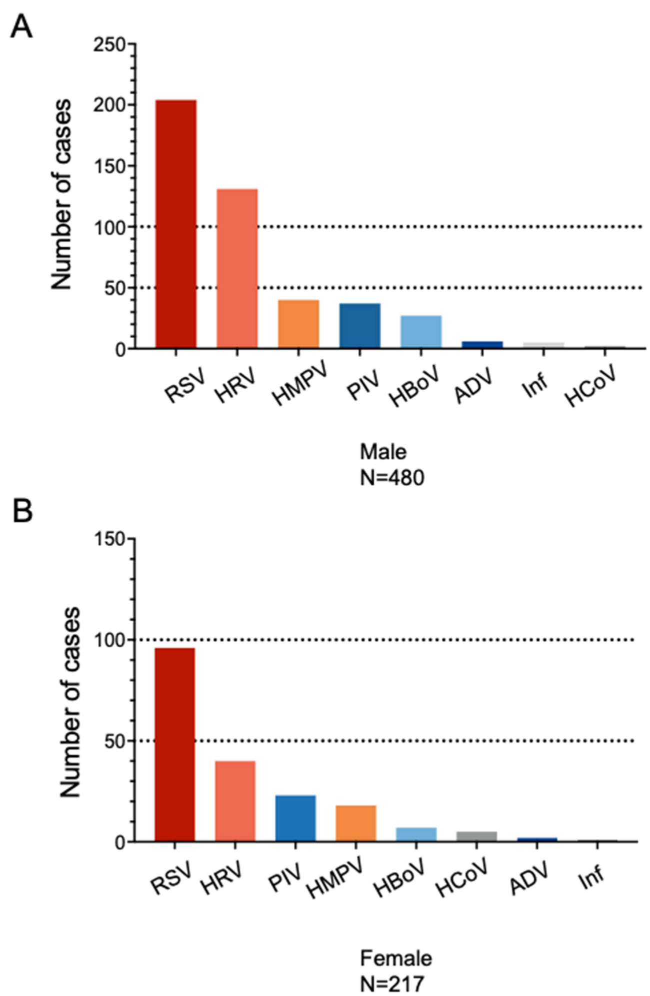

Figure 2 The distribution of viral infections among bronchiolitis hospitalizations by gender. (**A**) Male (**B**) Female.

similar demographic trends.[25] The NPIs, such as mask-wearing, handwashing, and social distancing, may be linked to this reduction in the number of admissions for pediatric respiratory diseases.[26] However, in 2023, as social behaviors came back to normal, respiratory infections exploded when faced a pediatric population with little to no immunity. Besides, during the pandemic control period, the complexity of medical procedures led most patients to prefer visiting nearby community hospitals rather than seeking treatment at higher-level hospitals for mild symptoms. A more interesting discovery was that the increased admissions were seen in all age groups, but the greatest change was in children aged 12 to 18 months. This may be related to the fact that children in this age group needed more outdoor activities, but their compliance with wearing masks was poor, making them more likely to contact with pathogens. The present data also showed that bronchiolitis predominantly affects males, with males accounting for approximately 69% of admissions in both 2022 and 2023. This study supports prior work suggesting that males are a risk factor for severe RSV infection, with boys having a risk ratio of 1.425:1 compared to girls for bronchiolitis. Potential reasons for this difference include sex-based variations in immune responses to infection, as females generally possess a stronger immune system than males.[27,28]

Viral infection is the most common cause of bronchiolitis. An analysis of the virological test results for bronchiolitis in 2022 and 2023 revealed an overall virus detection rate of 82.5%, with a mixed infection detection rate of 10%. RSV remains the primary pathogen for bronchiolitis, with a detection rate of 43.0%, followed by HRV at 24.5%. Further analysis of the total virus detection rate and mixed infection detection rate for bronchiolitis in 2022 and 2023 showed no significant differences. Except for influenza, the differences in the detection rates of individual viruses were not

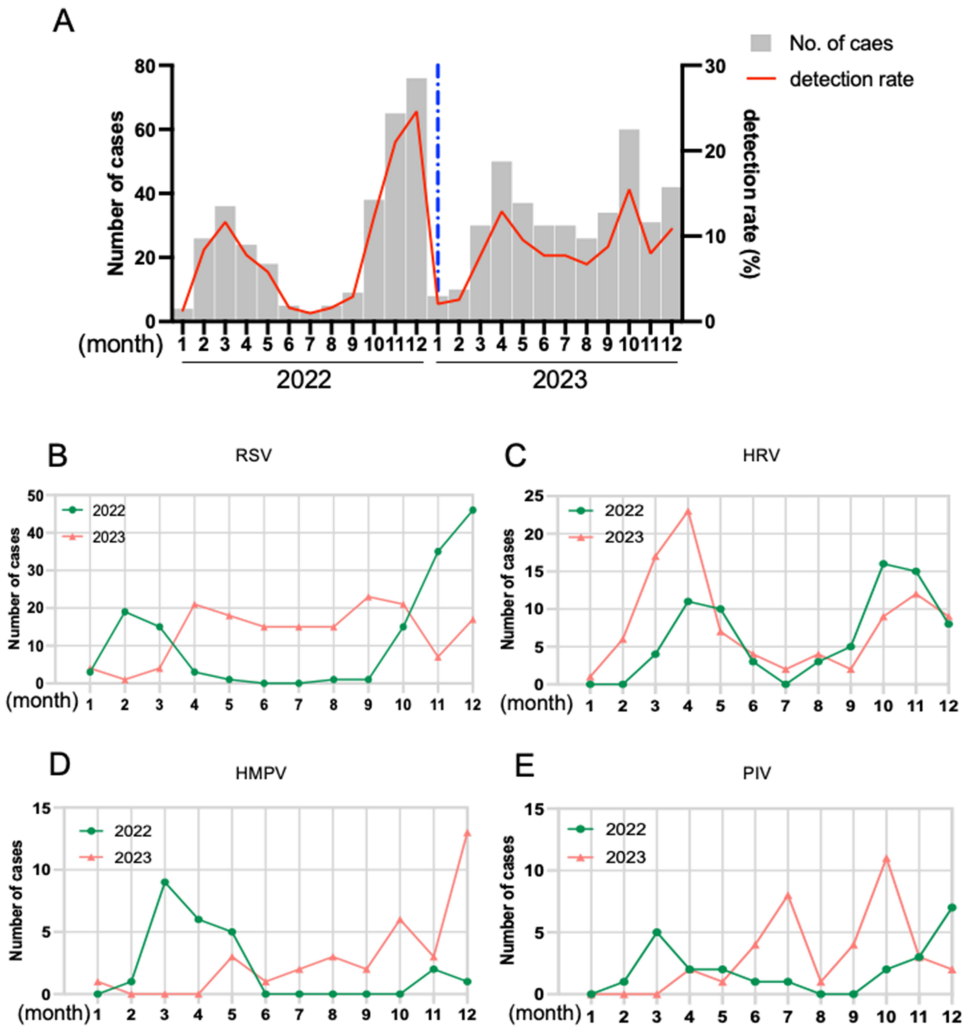

Figure 3 Monthly distribution of common respiratory viruses in 2022 and 2023. (**A**) Monthly distribution of bronchiolitis hospitalizations in 2022 and 2023. Monthly distribution of RSV-positive (**B**), HRV-positive (**C**), HMPV-positive (**D**), PIV-positive (**E**) cases in 2022 and 2023.

statistically significant. Several studies also have demonstrated that during the COVID19 pandemic, the prevalence of influenza was extremely low, a phenomenon related to the stringent preventive measures implemented during the pandemic.[29–31] A further comparison of the age distribution characteristics of children with bronchiolitis revealed different detection rates for various viruses across age groups. Admissions under 12 months had the highest positivity rate for RSV, while children aged 12 to 24 months had the highest detection rate for HRV. In other words, as age increases, the detection rate of RSV in children with bronchiolitis gradually decreases, whereas the detection rate of HRV gradually increases. This trend is consistent with the finding reported by Jartti et al.[6]

Based on the comparison of two consecutive years of data, we found that RSV, the most common pathogen of bronchiolitis, displayed unusual seasonality after COVID19 restriction easing. Before the COVID-19 pandemic, RSV was widely prevalent globally and exhibited significant seasonality. In the Northern Hemisphere, the RSV season typically ran from November to March, peaking in January and February, while in the Southern Hemisphere, it lasted from June to September. In tropical countries, RSV circulated year-round, with peaks during the rainy season.[12,32,33] In this study, the seasonality of RSV positive cases in 2022 remained consistent with previous works, showing a peak during the winter. However, in 2023, after the relaxation of NPIs, an out-of-season RSV epidemic occurred. The summer peak lasted until autumn, while the typical winter peak of RSV infections was absent. Similar changes have been observed in several studies.[17,34,35] This phenomenon may be related to the concept of “immune debt” caused by the

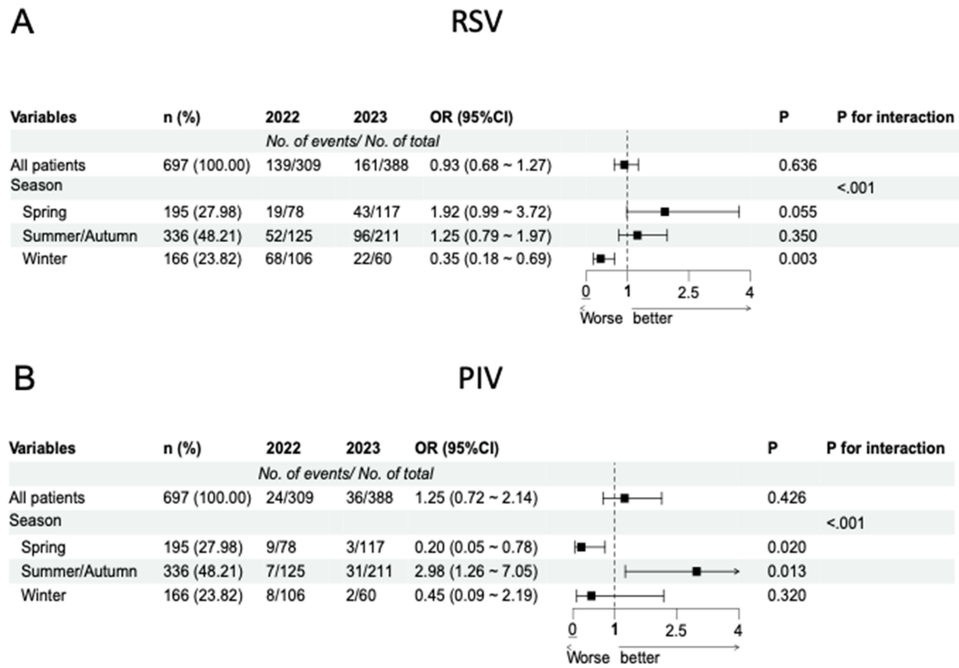

Figure 4 Adjusted Odds Ratios for RSV and PIV Infection by Season in Bronchiolitis Patients: A Subgroup Analysis (2022 vs 2023). (**A**) RSV infection, (**B**) PIV infection.

lifting of NPIs. Although "immune debt" is not a recognized term in medicine and immunology, it has gained attention in the public sphere. It is proposed to describe the paucity of protective immunity arising from extended periods of low exposure to a given pathogen, leaving a greater proportion of the population susceptible to the disease.[36] This immunity debt is particularly concerning for RSV, for which temporary immunity is obtained through exposure to the virus and maternal antibodies wane quickly; without seasonal exposure, immunity decreases, increasing susceptibility to future infections.[37] With no specific treatment against RSV currently, hospitals should prepare for the possibility of an-earlier than-usual increase in bronchiolitis cases and ensure sufficient bed capacity to provide supportive care, notably respiratory support.[38] As the second most common pathogen causing bronchiolitis, HRV showed no significant changes in its epidemic curve over these two years, with peak incidences consistently occurring in the spring and autumn seasons. The epidemiological differences between HRV and RSV can be explained by the differences in their transmission capabilities. RSV is an enveloped virus,[39] whereas HRV is a non-enveloped virus.[40] Compared to enveloped viruses, non-enveloped viruses are generally more virulent, shed from infected individuals for a significantly longer time, can survive in the gastrointestinal tract, and are more resistant to extreme pH, high temperatures, dryness, and simple disinfectants.[41] These factors favor the persistence of these viruses on surfaces and extended shedding among infected individuals, which explains why HRV transmission was only marginally affected by NPIs. Even when these measures were still in place or only partially lifted, HRV transmission returned to traditional levels. In contrast, enveloped viruses exhibit the opposite characteristics and were significantly influenced by NPIs. When NPIs were partially or completely lifted, the transmission of these viruses increased.[42] Apart from RSV and HRV, the seasonality of infections caused by HMPV and PIV has also changed. These findings highlight the importance of sustained interventions and monitoring measures, such as respiratory viral vaccines and monoclonal antibodies, as well as necessary NPIs, in helping reduce the burden of illness. Additionally, the varying epidemic curves of different viruses provide valuable insights for the strategic stockpiling of vaccines and the utilization of antiviral drugs.

In summary, during 2022–2023, the spectrum and epidemiological characteristics of bronchiolitis viruses have changed, presenting new challenges for clinical practice. Our study identified shifts in the timing of peak infections for certain pathogens in the postpandemic era, offering valuable insights for the more efficient allocation of healthcare resources moving forward. A limitation of this study is its single-center, retrospective case collection design, which restricts the generalizability of the findings to broader populations. In addition, due to limitations in sample size and the original data collection, we were unable to conduct seasonal evaluations for all viral types. While RSV and PIV were analyzed in detail, other less prevalent viruses, such as human bocavirus (HBoV) and adenovirus (ADV), were excluded from the subgroup analysis.

Conclusion

In this single-center, retrospective study, bronchiolitis admissions increased following the easing of COVID-19 restrictions compared to the period before, with the most notable rise observed in children aged 12 to 18 months. RSV and HRV were identified as the most significant viruses causing bronchiolitis. RSV was more common in children under 12 months, while HRV was more prevalent in children over 12 months. Compared to 2022, RSV exhibited an atypical epidemic in the summer of 2023, and the usual winter peak did not occur. The epidemic curve of HRV showed no significant changes. The seasonality of bronchiolitis admissions does not yet appear to be stable, and Chinese hospitals should prepare for the possibility of atypical timing in the future.

Abbreviations

RSV, respiratory syncytial virus; HRV, human rhinovirus; HBoV, human boca virus; PIV, parainfluenza virus; HMPV, human metapneumovirus; ADV, adenovirus; HCoV, human coronavirus; Inf, Influenza virus; COVID-19, coronavirus disease 2019; SARSCoV-2, severe acute respiratory syndrome coronavirus 2; NPIs, non-pharmaceutical interventions; PCR, Polymerase chain reaction; IQR, interquartile ranges.work.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the.

Disclosure

The authors declare that there is no conflict of interest regarding the publication of this paper.

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