

Preplanned Studies

Multicenter Study on the Prevalence of Human Respiratory Syncytial Virus Coinfection and Disease Burden Among Hospitalized Children Aged 5 Years and Younger — 5 Prefecture-level Cities, Zhejiang Province, China, 2018–2023

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Summary

What is already known about this topic?

Human respiratory syncytial virus (HRSV) coinfection with other respiratory pathogens frequently occurs in young children with acute respiratory illness. However, the epidemiological patterns and associated disease burden of HRSV coinfections in pediatric populations remain poorly characterized.

What is added by this report?

Analysis of hospitalized children under 5 years in Zhejiang Province from 2018 to 2023 revealed that 20.4% experienced HRSV coinfections, with bacterial coinfections substantially exceeding viral coinfections (14.1% vs. 5.3%). *M. pneumoniae* and *S. pneumoniae* emerged as predominant bacterial copathogens, while human rhinovirus and cytomegalovirus were the most prevalent viral coinfection agents. HRSV coinfections were associated with significantly higher disease burden compared to HRSV mono-infection [median expense: 4,971.4 Chinese Yuan (CNY) vs. 4,649.1 CNY; $P < 0.05$].

What are the implications for public health practice?

Implementation of comprehensive prevention strategies, including vaccination programs, nonpharmaceutical interventions, and enhanced surveillance of multiple respiratory pathogens, is essential to reduce HRSV coinfections and their associated disease burden during periods of high respiratory pathogen circulation.

The human respiratory syncytial virus (HRSV) belongs to the *Orthopneumovirus* genus within the *Pneumoviridae* family (1) and represents the primary etiological agent of acute lower respiratory tract infections (ALRTIs) in children under 5 years,

immunocompromised individuals, and elderly populations (2–3). Globally in 2019, HRSV was responsible for 33 million ALRTI episodes, resulting in 3.6 million hospitalizations and 101,400 deaths among children younger than 5 years (1). China bears a substantial burden of HRSV infections, accounting for more than 10% of global cases (4).

Advanced diagnostic technologies in hospital settings have revealed an increasing frequency of HRSV codetection with other respiratory viruses (5). Contemporary research indicates that HRSV codetection with other respiratory viruses occurs in 35%–40% of HRSV infections among young children (6–7). However, the impact of viral and bacterial coinfections on the disease burden of HRSV-associated respiratory illnesses remains incompletely understood (8).

This study examined hospitalized children aged ≤ 5 years admitted with influenza-like illness (ILI), acute respiratory infection (ARI), or severe acute respiratory infection (SARI) (Supplementary File 1, available at <https://weekly.chinacdc.cn/>) between January 1, 2018, and August 31, 2023, across eight hospitals in Zhejiang Province. HRSV infection was confirmed through laboratory antigen testing or reverse transcription polymerase chain reaction (RT-PCR). Hospital selection criteria incorporated geographical location, economic development level, and population coverage considerations (Supplementary File 2 Supplementary Table S1, available at <https://weekly.chinacdc.cn/>). Total hospitalization costs encompassed all direct patient expenses during admission, including examination, medication, bed, and treatment fees. To account for temporal cost variations across the 5-year study period, this research applied a 3% discount rate (9) to adjust hospitalization costs from 2018–2022.

This study stratified patients into four categories

based on pathogen infection status: HRSV alone, HRSV+virus, HRSV+bacteria, and HRSV+virus+bacteria. Pathogen positivity rates were compared across these groups, considering gender, age group, pneumonia status, coronavirus disease 2019 (COVID-19) epidemic phases, and hospitalization duration. This study analyzed the pathogen spectrum in HRSV coinfection cases and evaluated the hospitalization duration and total costs associated with the three most prevalent viral and bacterial coinfections.

Statistical analyses were conducted using R software version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was established at $P < 0.05$ (two-tailed).

Between January 2018 and August 2023, the eight

participating hospitals recorded 8,338,484 outpatient and 252,658 inpatient visits across all age groups. Of these, 180,601 patients underwent HRSV testing via nucleic acid or antigen detection methods, yielding 10,956 positive cases (positivity rate: 6.07%). The highest monthly positivity rates were observed in August 2021 (26.9%) and December 2018 (25.9%), while no positive cases were detected in May and June 2020 (Figure 1A).

Among the 7,857 HRSV-positive inpatients aged 5 years and younger included in this study, the median age was 12.0 months [interquartile range (IQR): 4.0–24.0 months], with 65.9% being 12.0 months or younger. Males comprised 60.4% (4,746/7,857) of the cohort, and 80.9% (6,360/7,857) were diagnosed with

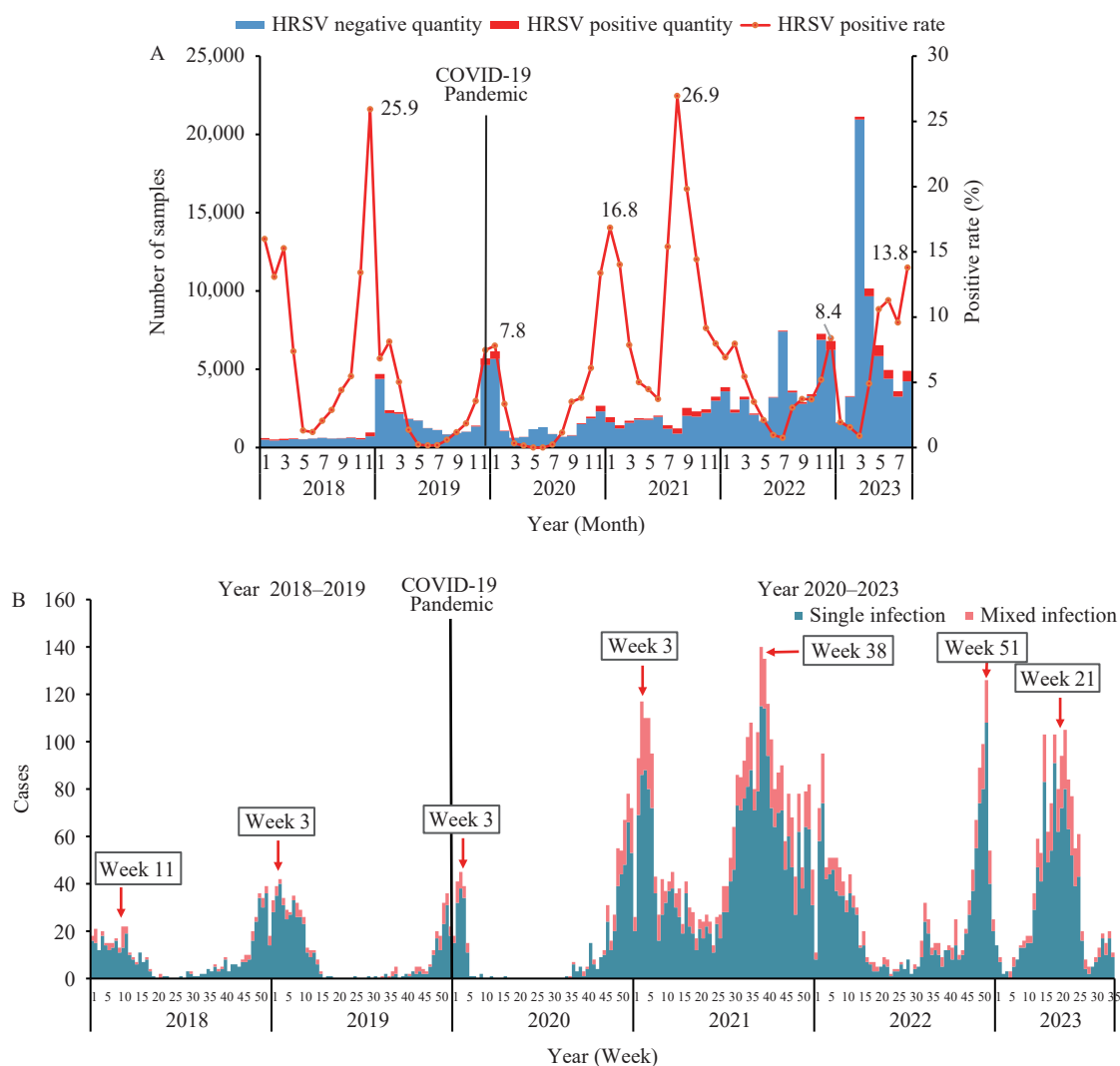


FIGURE 1. The timeline distribution of HRSV monoinfections and coinfections among outpatients and inpatients in Zhejiang Province, China, 2018–2023. (A) Monthly detection rates of HRSV among outpatients and inpatients; (B) Weekly distribution of HRSV monoinfections and coinfections among hospitalized children aged 5 years and younger. Abbreviation: COVID-19=coronavirus disease 2019; HRSV=human respiratory syncytial virus.

pneumonia. HRSV coinfection with other pathogens was identified in 20.4% (1,601/7,857) of cases.

A significant increase in HRSV hospitalizations was observed from 2020 to 2023 compared to 2018–2019 (Figure 1A). The median age of patients during the COVID-19 pandemic period (2020–2023) was significantly higher than in the pre-pandemic period (2018–2019) (17.0 months *vs.* 10.1 months, $P<0.010$). The pandemic period saw a reduction in the proportion of HRSV inpatients aged 0–5 months (from 45% to 28%) and concurrent increases in those aged 13–24 months (from 9% to 15%) and 25–36 months (from 6% to 15%) (Supplementary Figure S1, available at <https://weekly.chinacdc.cn/>).

Compared to HRSV mono-infection cases, patients with coinfections were significantly older (19.7 months

vs. 15.0 months, $P<0.01$) (Table 1). Notable increases were observed in the 13–24 months (13% to 18%) and 25–36 months (12% to 20%) age groups (Supplementary Figure S2, available at <https://weekly.chinacdc.cn/>). Coinfection rates were lower in males compared to females (18.8% *vs.* 22.7%, $P<0.01$) and higher in pneumonia cases compared to non-pneumonia cases (21.9% *vs.* 14.1%, $P<0.01$), Table 1. The highest coinfection rates were observed in patients with hospital stays of 15 days (31.2%), followed by those staying 8–14 days (21.7%) (Table 1).

Among the HRSV inpatients, 14.1% (1,110/7,857) tested positive for at least one bacterial pathogen. Patients with bacterial coinfections demonstrated a substantially higher incidence of pneumonia compared to those with viral coinfections (73.2% *vs.* 22.7%).

TABLE 1. Pathogen positivity rates among hospitalized children aged ≤ 5 years with human respiratory syncytial virus infections in multicenter surveillance, Zhejiang Province, China.

Categories	Number (N=7,857)	Mono-HRSV infection (n1=6,256)	Co-HRSV infection				P
			Total (n2=1,601)	HRSV+virus (n3=418)	HRSV+ba- cteria (n4=1,110)	HRSV+virus+ bactetia (n5=73)	
Proportion, No. (%)	7,857 (100.0)	6,256 (79.6)	1,601 (20.4)	418 (26.1)	1,110 (69.3)	73 (4.6)	–
Gender, No. (%)							
Male	4,746 (60.4)	3,852 (81.2)	894 (18.8)	256 (28.6)	599 (67.0)	39 (4.4)	<0.0001
Female	3,111 (39.6)	2,404 (77.3)	707 (22.7)	162 (22.9)	511 (72.3)	34 (4.8)	
Mean age (months)	15.9	15.0	19.7	16.4	20.9	20.9	
Age group (months), No. (%)							
0–5	2,383 (30.3)	2,085 (87.5)	298 (12.5)	135 (45.3)	150 (50.3)	13 (4.4)	0.035
6–12	2,816 (35.8)	2,225 (79.0)	591 (21.0)	147 (24.9)	421 (71.2)	23 (3.9)	0.663
13–24	1,124 (14.3)	841 (74.8)	283 (25.2)	60 (21.2)	207 (73.1)	16 (5.7)	0.004
25–36	1,039 (13.2)	735 (70.7)	304 (29.3)	56 (18.4)	234 (77.0)	14 (4.6)	0
37–48	376 (4.8)	274 (72.9)	102 (27.1)	14 (13.7)	82 (80.4)	6 (5.9)	0.007
49–60	119 (1.6)	96 (80.7)	23 (19.3)	6 (26.1)	16 (69.6)	1 (4.3)	Reference group
Pneumonia or not, No. (%)							
Yes	6,360 (81.0)	4,970 (78.1)	1,390 (21.9)	315 (22.7)	1,017 (73.2)	58 (4.1)	0
No	1,497 (19.0)	1,286 (85.9)	211 (14.1)	103 (48.8)	93 (44.1)	15 (7.1)	
Period, No. (%)							
Year 2018–2019	1,081 (13.8)	925 (85.6)	156 (14.4)	53 (34.0)	99 (63.5)	4 (2.5)	0
Year 2020–2023	6,776 (86.2)	5,331 (78.7)	1,445 (21.3)	365 (25.3)	1,011 (70.0)	69 (4.7)	
Hospitalization duration (day)							
1–3	950 (12.1)	827 (87.1)	123 (12.9)	43 (35.0)	78 (63.4)	2 (1.6)	0
4–7	5,847 (74.4)	4,605 (78.7)	1,242 (21.2)	290 (23.3)	898 (72.3)	54 (4.4)	0.052
8–14	996 (12.7)	780 (78.3)	216 (21.7)	73 (33.8)	129 (59.7)	14 (6.5)	0.075
>15	64 (0.8)	44 (68.8)	20 (31.2)	12 (60.0)	5 (25.0)	3 (15.0)	Reference group

Note: P comparing mono-HRSV infection *vs.* co-HRSV infection.
Abbreviation: HRSV=human respiratory syncytial virus.

Additionally, the rate of bacterial coinfections was significantly elevated during the 2020–2023 period compared to 2018–2019 (Table 1).

In bacterial coinfection cases, *Mycoplasma pneumoniae* (*M. pneumoniae*) emerged as the predominant pathogen, representing 59.2% of all bacterial detections. This was followed by *Streptococcus pneumoniae* (*S. pneumoniae*) at 25.3% and *Haemophilus influenzae* (*H. influenzae*) at 8.8% (Figure 2).

Among viral coinfections, human rhinovirus (HRV)

was the most frequently detected pathogen, accounting for 27.3% of all viral-positive detections, followed by cytomegalovirus (CMV; 23.8%) and human adenovirus (HAdV; 14.0%) (Figure 2).

Analysis of hospitalization expenses revealed that HRSV coinfection cases, whether viral or bacterial, incurred significantly higher costs (median: 4,971.4, IQR: 3,864.7–6,878.0) compared to HRSV monoinfection cases (median: 4,649.1, IQR: 3,486.6–6,524.9, $P=0.013$). Among all coinfections, CMV was associated with the highest median

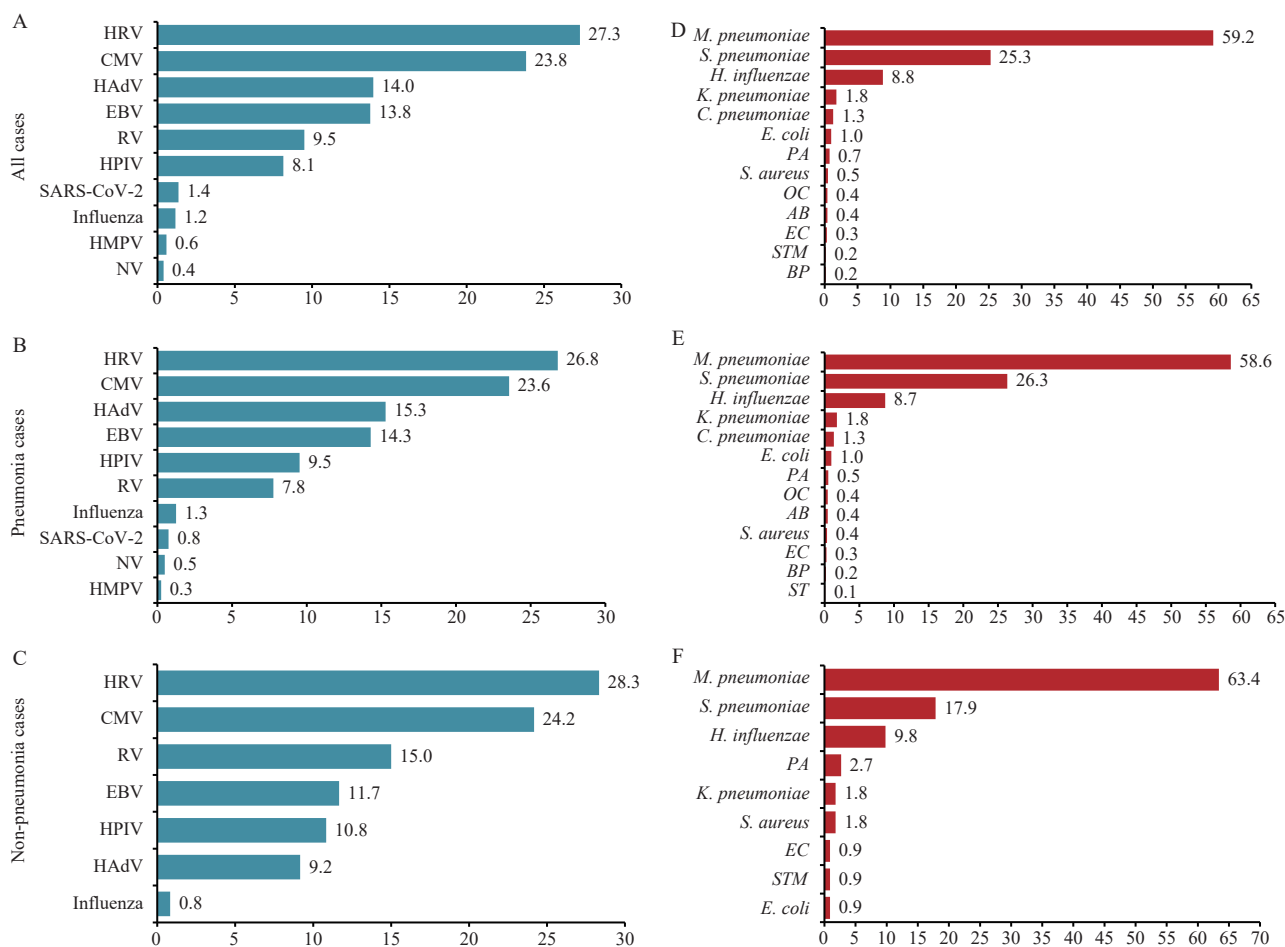


FIGURE 2. Viral and bacterial composition of HRSV-positive hospitalized children aged 5 years and younger in Zhejiang Province, China, 2018–2023. (A) Viral composition in all patients; (B) Viral composition in pneumonia cases; (C) Viral composition in non-pneumonia cases; (D) Bacterial composition in all cases; (E) Bacterial composition in pneumonia cases; (F) Bacterial composition in non-pneumonia cases.

Note: Analysis includes all cases tested for ten viral and 13 bacterial pathogens among HRSV-positive hospitalized children. Bar lengths and accompanying numbers represent the proportion of each pathogen, calculated as the number of positive cases divided by the total number of HRSV-positive cases.

Abbreviation: HRV=human rhinovirus; CMV=cytomegalovirus; HAdV=human adenovirus; EBV=Epstein-Barr virus; RV=rotavirus; HPIV=human parainfluenza virus; COVID-19=coronavirus disease 2019; HMPV=human metapneumovirus; NV=norovirus; *M. pneumoniae*=*Mycoplasma pneumoniae*; *S. pneumoniae*=*Streptococcus pneumoniae*; *H. influenzae*=*Haemophilus influenzae*; *K. pneumoniae*=*Klebsiella pneumoniae*; *C. pneumoniae*=*Chlamydia pneumoniae*; *E. coli*=*Escherichia coli*; *PA*=*Pseudomonas aeruginosa*; *S. aureus*=*Staphylococcus aureus*; *OC*=oral candidiasis; *AB*=*Acinetobacter baumannii*; *EC*=*Enterobacter cloacae*; *BP*=*Bordetella pertussis*; *ST*=*Salmonella typhi*; *STM*=*Salmonella typhimurium*.

hospitalization expense (median: 7,243.6, IQR: 5,459.3–9,569.8) (Figure 3).

Regarding length of stay, cases with viral or bacterial coinfections demonstrated marginally longer durations (median: 5.0, IQR: 4.0–7.0) compared to HRSV mono-infections (median: 5.0, IQR: 4.0–6.0, $P<0.01$). Among viral coinfections, CMV cases exhibited significantly extended hospitalization periods (median: 6.0, IQR: 5.0–8.0, $P=0.003$). In bacterial coinfections, both *S. pneumoniae* (median: 6.0, IQR: 5.0–7.0, $P=0.025$) and *H. influenzae* (median: 6.0, IQR: 5.0–7.0, $P=0.018$) demonstrated comparable prolonged hospital stays (Figure 3).

DISCUSSION

This study analyzed surveillance data from 2018 to 2023, encompassing comprehensive pathogen testing data from 8 hospitals in Zhejiang Province for 10 viruses and 13 bacteria in pediatric inpatients under 5 years of age. This analysis revealed significant patterns in the prevalence, pathogen spectrum, and disease burden of HRSV coinfections in this population.

These findings demonstrate a marked increase in HRSV infections during 2020–2023 compared to previous seasons (2018–2019), with a notable shift in age distribution toward older children within the

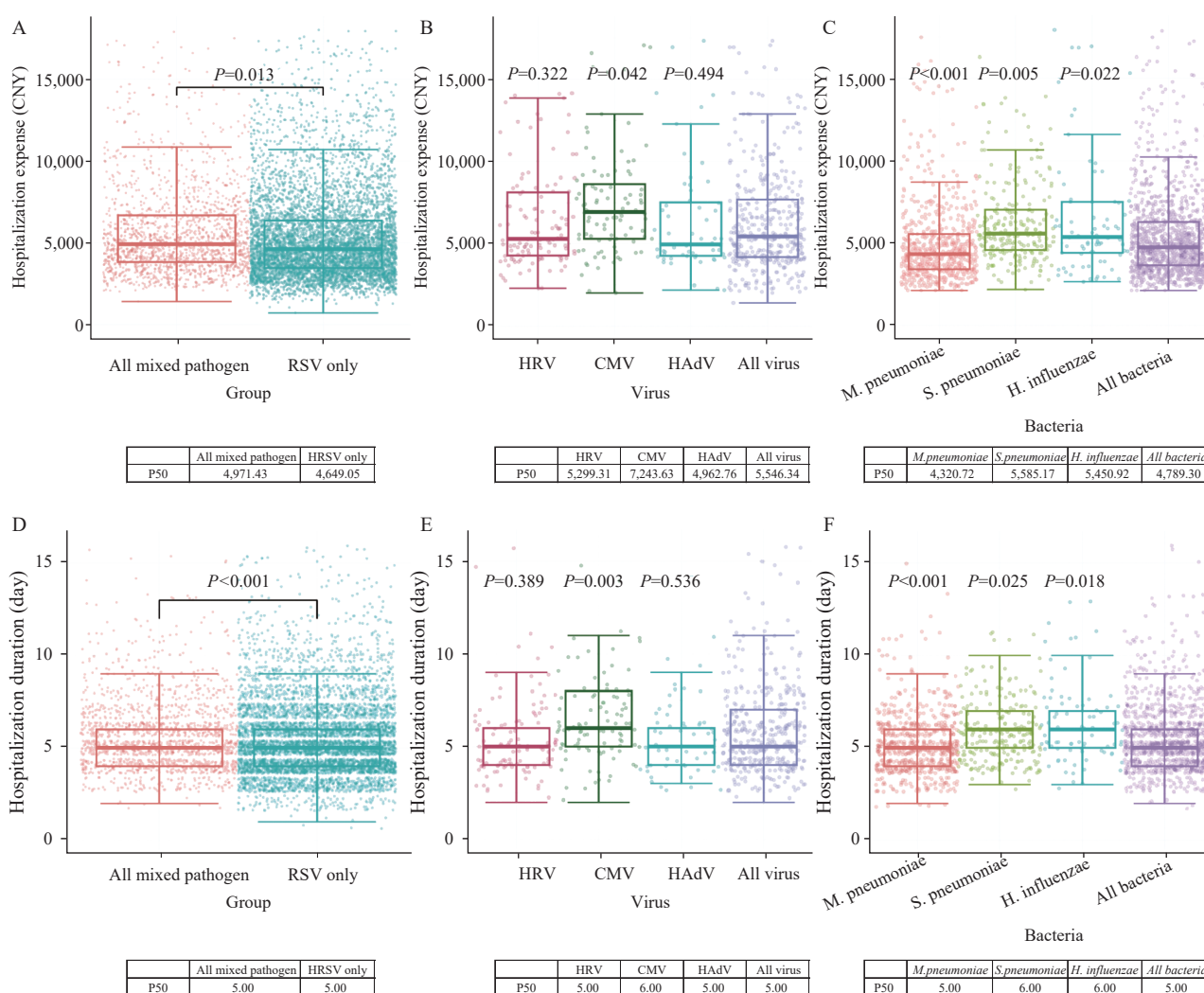


FIGURE 3. Disease burden in HRSV mono- and co-infections among hospitalized children aged 5 years and younger in Zhejiang Province, China, 2018–2023. (A) Hospitalized expense (HRSV only vs. HRSV coinfection); (B) Hospitalized expense (HRSV coinfections with all viruses vs. single virus); (C) Hospitalized expense (HRSV coinfections with all bacteria vs. single bacteria); (D) Hospitalized days (HRSV only vs. HRSV coinfection); (E) Hospitalized days (HRSV coinfections with all viruses vs. single virus); (F) Hospitalized days (HRSV coinfections with all bacteria vs. single bacteria).

Abbreviation: HRV=human rhinovirus; CMV=cytomegalovirus; HAdV=human adenovirus; *M. pneumoniae*=*Mycoplasma pneumoniae*; *S. pneumoniae*=*Streptococcus pneumoniae*; *H. influenzae*=*Haemophilus influenzae*; CNY=Chinese Yuan.

under-5 age group. This pattern suggests that pandemic-related disruptions created increased susceptibility among older children who lacked prior exposure to endemic HRSV (9–10).

The study revealed that HRSV coinfection with other respiratory pathogens was common, affecting 20.4% of all hospitalizations during 2018–2023. Notably, HRSV coinfection rates were substantially higher during 2020–2023 compared to 2018–2019. While the precise mechanism remains unclear, this increase likely relates to both enhanced RT-PCR testing implementation and elevated respiratory pathogen circulation during the COVID-19 pandemic period (11).

Regarding disease status, HRSV coinfections showed significantly higher prevalence in patients with pneumonia compared to those without pneumonia, aligning with Liu et al.'s findings on coinfection patterns in community-acquired pneumonia (12).

This study revealed increased hospital stays and expenses among HRSV coinfections, potentially attributable to the implementation of multiple therapeutic interventions (13–14). These findings underscore the importance of specialized care for hospitalized children with HRSV coinfections. Optimal management should include isolation in separate wards, with particular emphasis on early detection of coinfections through comprehensive testing for HRSV and other common respiratory viruses, especially in infants under 6 months of age.

This study had two primary limitations. First, the analysis of hospitalization expenses excluded indirect costs. Second, selection bias may have occurred as the study included only inpatients with confirmed HRSV infection, excluding those without HRSV detection.

In conclusion, this study demonstrates a significant increase in HRSV coinfections during the COVID-19 pandemic, particularly among patients with pneumonia and those requiring extended hospitalization exceeding 14 days. These coinfections were associated with prolonged hospital stays and elevated healthcare costs. To mitigate future HRSV coinfection incidence and disease burden, public health initiatives should focus on raising awareness among parents and the general public regarding pediatric coinfection risks and prevention strategies. Healthcare providers should implement recommended testing protocols for patients presenting with acute respiratory symptoms to identify HRSV coinfections promptly, potentially reducing infection severity and associated disease burden.

Conflicts of interest: No conflicts of interest.

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SUPPLEMENTARY MATERIAL

Supplementary File 1: The definition of influenza-like illness (ILI), acute respiratory infection (ARI), and severe acute respiratory infection (SARI)

(1) Influenza-like illness (ILI) is a non-specific syndrome defined as fever (temperature of 38 °C or greater) with cough or sore throat. (National Guideline for Institutional Outbreak Management of Seasonal Influenza, 2018 version)

(2) An acute respiratory infection (ARI) is defined as a measured fever of ≥ 38 °C and cough, with onset within the last 10 days. (The World Health Organization (WHO) Global Influenza Programme, <https://www.who.int/teams/global-influenza-programme/surveillance-and-monitoring/case-definitions-for-ili-and-sari>)

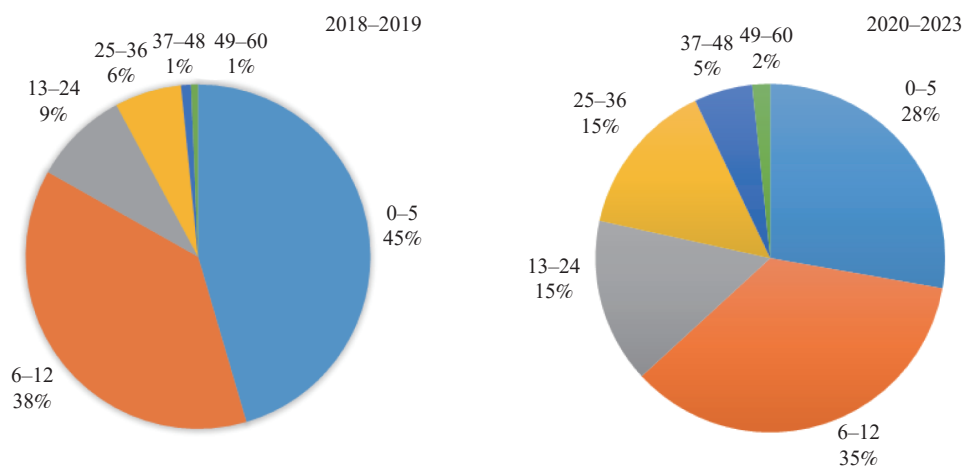
(3) Severe acute respiratory infection (SARI) is defined as ARI with symptoms including cough and fever within 10 days of presentation and with hospitalization. [The World Health Organization (WHO) Global Influenza Programme, <https://www.who.int/teams/global-influenza-programme/surveillance-and-monitoring/case-definitions-for-ili-and-sari>]

Supplementary File 2: The criteria for the selection of eight hospitals in Zhejiang Province, China, in this study

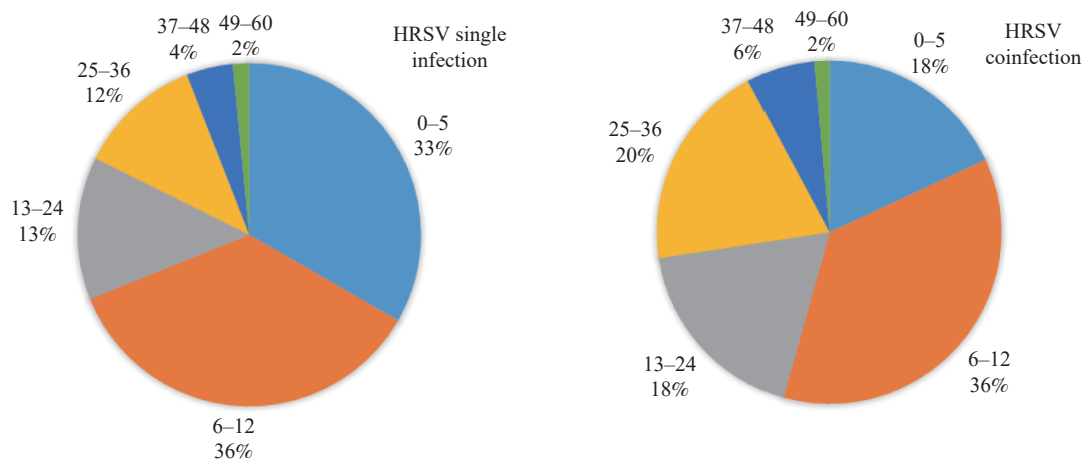
(1) We selected the representative hospitals in the northern, central, southern, and coastal areas of Zhejiang Province, covering rural and urban areas.

(2) We selected different levels of hospital, including provincial-level tertiary hospitals, municipal hospitals, and county-level hospitals.

(3) We included general hospitals and specialized pediatric hospitals.



SUPPLEMENTARY FIGURE S1. The age distribution of hospitalized children under 5 years old infected with HRSV in Zhejiang Province, China (pre-pandemic vs. pandemic period).



SUPPLEMENTARY FIGURE S2. The age distribution of hospitalized children under 5 years old infected with HRSV alone or coinfecting with HRSV in Zhejiang Province, China.

SUPPLEMENTARY TABLE S1. The characteristics of eight hospitals in five prefecture-level cities of Zhejiang Province, China.

Number	Hospital name	Hospital level	Hospital classification	Locations
1	Jiaxing Maternity and Child Health Care Hospital	Level III Grade A	Women and children	Jiaxing City
2	The First Hospital of Jiaxing	Level III Grade A	Comprehensive hospital	Jiaxing City
3	The Second People's Hospital of Jinyun	Level II Grade B	Comprehensive hospital	Lishui City
4	The Maternity and Child Health Hospital of Tonglu	Level II Grade B	Comprehensive hospital	Hangzhou City
5	The First People's Hospital of Tonglu	Level II Grade A	Comprehensive hospital	Hangzhou City
6	Wenzhou Medical College Affiliated Second Hospital Wenzhou Medical College Affiliated Yuying Children's Hospital	Level III Grade A	Women and children	Wenzhou City
7	People's Hospital of Daishan	Level II Grade A	Comprehensive hospital	Zhoushan City
8	Zhoushan Hospital	Level III Grade A	Comprehensive hospital	Zhoushan City