

Preplanned Studies

Longitudinal Study of Subsequent Wheezing/Asthma Risk Among Children Hospitalized for Acute Respiratory Infections — Yichang City, Hubei Province, China, 2017–2024

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Summary

What is already known about this topic?

Severe respiratory infections in early life, particularly lower respiratory tract infections, such as bronchiolitis and pneumonia, may increase the risk of subsequent wheezing and asthma.

What is added by this report?

Among the 22,460 children hospitalized for acute respiratory infections in Yichang, 2017–2024, a total of 1,463 subsequently developed wheezing/asthma. Bronchiolitis and pneumonia were associated with the highest subsequent wheezing/asthma risk relative to upper respiratory tract infection or influenza, with excess risk concentrated within the first 2 years after hospitalization; only bronchiolitis remained significantly associated with subsequent wheezing/asthma during the 2 to <4 years period.

What are the implications for public health practice?

Children hospitalized with bronchiolitis or pneumonia should undergo systematic post-discharge follow-up and early asthma screening during the first two years after discharge. Extended follow-up for four years after discharge may be warranted for children hospitalized with bronchiolitis.

cumulative incidence of subsequent wheezing/asthma, with group differences evaluated using the log-rank test. Piecewise Cox proportional hazards regression models were employed to assess the magnitude and timing of risk by ARI type.

Results: Among 22,460 children followed up for a median of 43.5 months, 1,463 developed wheezing/asthma. Hospitalization for bronchiolitis or pneumonia was associated with a significantly higher risk of wheezing/asthma than that for upper respiratory infection or influenza ($P<0.001$), with excess risk concentrated in the first 2 years. During the 2 to <4 years period, only bronchiolitis remained significantly associated with subsequent wheezing/asthma [adjusted hazard ratio (*aHR*)=1.85, 95% confidence interval (*CI*): 1.32, 2.58].

Conclusion: Children hospitalized for bronchiolitis or pneumonia experienced increased subsequent wheezing/asthma, particularly within 2 years of discharge. Structured follow-up and symptom-based asthma screening after discharge are essential, particularly in children with bronchiolitis.

ABSTRACT

Introduction: Acute respiratory infections (ARI) represent a leading cause of hospitalization in early childhood and may increase the risk of subsequent wheezing/asthma. However, longitudinal evidence of this association among Chinese children remains limited.

Methods: A follow-up cohort was established using the Yichang Health Management Big Data Platform, including children born between January 1, 2017, and December 31, 2018, who were hospitalized for ARI. Kaplan–Meier curves were used to estimate the

Asthma is among the most prevalent chronic respiratory diseases in children, and acute respiratory infections (ARIs) represent a leading cause of hospitalization in early life (1). Severe respiratory infections in early childhood may increase the risk of subsequent wheezing and asthma; however, longitudinal evidence from Chinese pediatric populations remains scarce. Moreover, the magnitude and duration of this risk vary according to the infection type and follow-up period (2). Using the Yichang Health Management Big Data Platform, we established a follow-up cohort involving children born between January 1, 2017, and December 31, 2018, who were hospitalized for ARI. This birth period was selected to ensure a sufficient follow-up duration for assessing

subsequent wheezing/asthma outcomes during early childhood, while maintaining the completeness and consistency of longitudinal healthcare records through December 31, 2024. We examined the epidemiological features and temporal patterns of subsequent wheezing/asthma, focusing on variations in risk according to the infection type and follow-up period.

The Yichang Health Management Big Data Platform covers all 13 counties/districts in Yichang, comprising approximately 4.1 million residents. This platform integrates electronic medical records, and healthcare service data from medical institutions across the city, including outpatient and inpatient records. It is routinely maintained through data integration, quality control, and source data verification procedures. Following the removal of personal identifiers, hospitalization records were extracted for children born between January 1, 2017 and December 31, 2018, who were hospitalized for ARIs between January 1, 2017 and December 31, 2024, as identified using the International Classification of Diseases, 10th Revision (ICD-10) codes (J00–J06, J10–J11, J12–J18, J20, and J21). A unique identifier was assigned to each child to link records across institutions and time points, thereby enabling longitudinal follow-up. The first ARI hospitalization was defined as an index event. Repeat hospitalizations occurring within 28 days were considered part of the same infection episode. A 28-day washout period was applied following the index event to reduce the likelihood that wheezing/asthma diagnoses shortly after hospitalization reflected symptoms related to the acute infection episode rather than newly developed disease, consistent with previous epidemiological studies (3–4). The outcome was defined as a subsequent diagnosis of wheezing or asthma (ICD-10: R06.2, J45, and J46) identified from outpatient and inpatient records after the washout period. Follow-up began on day 29 post discharge and continued until the first outcome event or December 31, 2024, whichever occurred first. [Supplementary Table S1](#) (available at <https://weekly.chinacdc.cn/>) provides the specific ICD-10 codes for all diagnoses. The participant selection flowchart is shown in [Supplementary Figure S1](#) (available at <https://weekly.chinacdc.cn/>). This study was exempted from ethical review as it utilized previously collected data that contained no personally identifiable information.

Continuous variables with normal distributions were summarized as means and standard deviations, whereas non-normally distributed variables were reported as medians and interquartile ranges (IQRs). Categorical

variables were presented as frequencies and percentages. Sex differences were compared using the chi-square test, and linear trends across ordered age groups were evaluated using the Cochran-Armitage trend test. Kaplan–Meier analysis was employed to estimate the cumulative incidence of subsequent wheezing or asthma, with between-group differences assessed using the log-rank test. As Schoenfeld residual testing indicated that the proportional hazards assumption was violated for infection type ($P<0.001$), piecewise Cox proportional hazards regression models were fitted across three follow-up intervals: 0 to <2 years, 2 to <4 years, and 4 to <8 years (5). Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were calculated for each stratum. All analyses were conducted using R software (version 4.5.0; R Foundation for Statistical Computing, Vienna, Austria).

As shown in [Table 1](#), 22,460 children hospitalized for acute respiratory infections were included in the analysis, of whom 1,463 developed wheezing or asthma during follow-up. The median follow-up duration was 43.50 months (IQR: 17.25–71.16). Pneumonia was the most prevalent infection type (50.65%), followed by upper respiratory tract infections (26.71%) and bronchitis (15.31%). The distribution of infection types differed significantly between children who did and did not develop subsequent wheezing or asthma ($P<0.001$). Children who developed wheezing or asthma were more likely to be male (61.79% *vs.* 53.14%, $P<0.001$) and younger at the time of ARI hospitalization (median: 1.36 years *vs.* 3.17 years, $P<0.001$). The proportion of children aged 0 to <2 years was higher in the wheezing or asthma group, whereas the proportion aged 5 to <8 years was lower ($P<0.001$). Calendar period of the index ARI hospitalization differed significantly by subsequent asthma status ($\chi^2=457.06$, $P<0.001$), with a higher proportion of children with subsequent wheezing or asthma hospitalized during 2017–2019 and a lower proportion during 2023–2024.

Kaplan–Meier curves revealed significant differences in cumulative wheezing/asthma incidence across infection types (log-rank $P<0.001$) ([Figure 1](#)). Bronchiolitis exhibited the highest cumulative incidence, followed by pneumonia, whereas upper respiratory tract infections and influenza were associated with lower cumulative incidences.

Kaplan–Meier curves showed significant differences in the cumulative wheezing/asthma incidence across infection types. Given that the proportional hazards

TABLE 1. Baseline characteristics of children hospitalized for acute respiratory infections by subsequent wheezing/asthma status, 2017–2024.

Characteristics	Total (n=22,460)	Without subsequent wheezing/asthma (n=20,997)	With subsequent wheezing/asthma (n=1,463)	Statistic	P
Infection type				100.77	<0.001
URTI	6,000 (26.71)	5,685 (27.08)	315 (21.53)		
Influenza	715 (3.18)	691 (3.29)	24 (1.64)		
Pneumonia	11,375 (50.65)	10,565 (50.32)	810 (55.37)		
Bronchitis	3,439 (15.31)	3,245 (15.45)	194 (13.26)		
Bronchiolitis	931 (4.15)	811 (3.86)	120 (8.20)		
Sex				40.81	<0.001
Male	12,062 (53.70)	11,158 (53.14)	904 (61.79)		
Female	10,398 (46.30)	9,839 (46.86)	559 (38.21)		
Birth year				1.78	0.183
2017	11,497 (51.19)	10,723 (51.07)	774 (52.90)		
2018	10,963 (48.81)	10,274 (48.93)	689 (47.10)		
Birth season				5.62	0.132
Spring	5,219 (23.24)	4,896 (23.32)	323 (22.08)		
Summer	5,660 (25.20)	5,310 (25.29)	350 (23.92)		
Autumn	5,795 (25.80)	5,418 (25.80)	377 (25.77)		
Winter	5,786 (25.76)	5,373 (25.59)	413 (28.23)		
Age at first ARI hospitalization, years	2.91 (0.85, 5.18)	3.18 (0.87, 5.30)	1.37 (0.69, 2.85)	—	<0.001
Age group at first ARI hospitalization, years				418.19	<0.001
0–1	9,801 (43.64)	8,866 (42.23)	935 (63.91)		
2–4	6,504 (28.96)	6,048 (28.80)	456 (31.17)		
5–7	6,155 (27.40)	6,083 (28.97)	72 (4.92)		
Calendar period of the index ARI hospitalization				457.06	<0.001
2017–2019	10,085 (44.90)	9,102 (43.35)	983 (67.19)		
2020–2022	6,008 (26.75)	5,611 (26.72)	397 (27.14)		
2023–2024	6,367 (28.35)	6,284 (29.93)	83 (5.67)		

Note: “—” means not applicable. Categorical variables were presented as *n* (%), and age at ARI hospitalization is presented as median (Q1, Q3). Between-group comparisons for infection type, sex, birth year, birth season, and calendar period of ARI hospitalization were performed using the chi-square test; the comparison of age at ARI hospitalization was compared using the Wilcoxon rank-sum test; and the linear trend across ordered age groups was assessed using the Cochran–Armitage trend test.

Abbreviation: ARI=acute respiratory infection; URTI=upper respiratory tract infection.

assumption was violated for infection type, piecewise Cox proportional hazards regression models were applied. As presented in Table 2 and Supplementary Figure S2 (available at <https://weekly.chinacdc.cn/>), bronchiolitis and pneumonia were associated with increased wheezing or asthma risk during 0 to <2 years after hospitalization [*aHR*=3.42 (95% *CI*: 2.48, 4.71) and 2.15 (95% *CI*: 1.75, 2.65), respectively], and bronchiolitis remained associated during 2 to <4 years [*aHR*=1.85 (95% *CI*: 1.32, 2.58)]. No significant associations were observed between ages 4 and 8 years.

DISCUSSION

This study found that children hospitalized for bronchiolitis or pneumonia had a substantially higher subsequent risk of wheezing/asthma than those hospitalized for upper respiratory tract infection or influenza. The excess risk was concentrated primarily within the first two years following hospitalization and gradually attenuated thereafter. Beyond 2 years, only bronchiolitis remained significantly associated with an elevated risk during the 2 to 4 years period, and no significant differences by infection type were detected

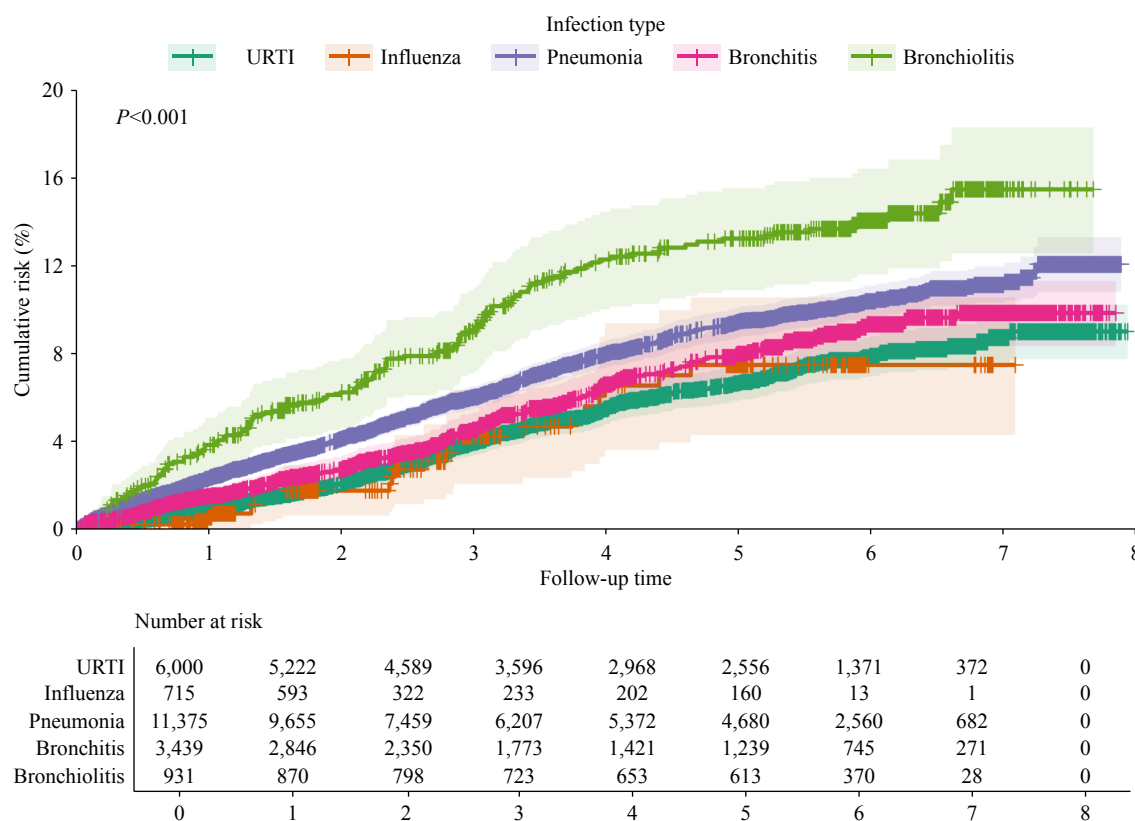


FIGURE 1. Cumulative risk of wheezing/asthma among children hospitalized for different types of acute respiratory infections, Yichang City, Hubei Province, China, 2017–2024.

Abbreviation: ARI=acute respiratory infection; URTI=upper respiratory tract infection.

TABLE 2. Piecewise Cox proportional hazards regression analyses of subsequent wheezing/asthma among children hospitalized for acute respiratory infections, Yichang City, Hubei Province, China, 2017–2024.

Variables	0 to <2 years aHR (95% CI)	2 to <4 years aHR (95% CI)	4 to <8 years aHR (95% CI)
URTI	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Influenza	0.89 (0.47, 1.71)	1.34 (0.74, 2.42)	0.54 (0.13, 2.19)
Pneumonia	2.15 (1.75, 2.65)***	1.16 (0.94, 1.43)	1.07 (0.80, 1.42)
Bronchitis	1.33 (1.00, 1.76)*	1.15 (0.86, 1.53)	1.08 (0.73, 1.61)
Bronchiolitis	3.42 (2.48, 4.71)***	1.85 (1.32, 2.58)***	0.89 (0.51, 1.56)

Note: Hazard ratios were adjusted for sex, birth year, birth season, age at first ARI hospitalization, and the calendar period of the index ARI hospitalization. URTI was used as the reference group.

Abbreviation: aHR=adjusted hazard ratio; CI=confidence interval; Ref=reference; ARI=acute respiratory infection; URTI=upper respiratory tract infection.

* *P* < 0.1; *** *P* < 0.001.

after 4 years.

These findings are broadly consistent with those in the existing literature. Similarly, a recent single-center long-term follow-up study in China reported that children hospitalized for bronchiolitis in early life had an elevated risk of recurrent wheezing (6). A population-based cohort study from Spain demonstrated that early-life bronchiolitis was associated with an increased risk of recurrent wheezing and asthma and that this association was not fully

explained by pathogen type or disease severity (7). In contrast, a smaller longitudinal study conducted in the United Kingdom did not identify a clear direct association between early lower respiratory tract infections and subsequent asthma outcomes (8). This discrepancy may reflect the small sample size, short follow-up duration, and differences in infection severity across the study populations.

Notably, the risk of subsequent wheezing/asthma following ARI hospitalization was concentrated

predominantly within the first 2 years and gradually diminished thereafter. Only bronchiolitis maintained a significant association with increased risk during the 2 to <4 year interval, and no infection type differences persisted beyond 4 years, further underscoring the distinctive link between bronchiolitis and the development of asthma. This temporal pattern aligns with findings from a Scottish cohort study demonstrating that severe RSV-related respiratory infections confer the greatest asthma risk within the first 2 years after infection (4). Accordingly, our results suggest that the first 2 years post-discharge represent a critical follow-up window, with extended monitoring warranted for children hospitalized with bronchiolitis. Some prior studies have reported that the association between early respiratory infections and asthma may persist up to the age of 10 years. The attenuated late effect observed in our study may reflect differences in regional healthcare data systems and diagnostic or healthcare-seeking behaviors. Additionally, as children age, the growing influence of unmeasured host and environmental factors on wheezing/asthma risk may progressively dilute the contribution of early-life infections (9).

One possible explanation for this association is that lower respiratory tract infections, particularly bronchiolitis and pneumonia, involve the small airways and lung parenchyma more extensively than upper respiratory tract infections or influenza, which may be markers of greater airway vulnerability, more intense inflammatory responses, or underlying host susceptibility to recurrent wheezing and asthma (6). In addition, infections occurring during early life may coincide with critical periods of immune and pulmonary development, which may help explain the stronger association observed within the first two years after hospitalization (9–10). However, given the observational design and the absence of detailed data on host, environmental, and immunological factors, these findings should not be interpreted as evidence of a direct causal pathway.

This study had several notable strengths. First, it leveraged real-world medical data with longitudinal linkage across healthcare institutions, yielding a large population-based sample for evaluating long-term outcomes following ARI hospitalization. Second, the application of piecewise Cox proportional hazards regression enabled the capture of temporal variations in wheezing and asthma risk, facilitating the identification of the first two years as a critical follow-up window. Nevertheless, this study had several limitations that

warrant consideration. First, ARI exposure and outcomes were ascertained using ICD-10 codes, which may have introduced coding errors or diagnostic misclassifications. Second, residual confounding from unmeasured factors, including socioeconomic status, family history of atopy, prematurity, and environmental tobacco smoke exposure, cannot be ruled out and might lead to overestimation of the associations. Therefore, our findings should be interpreted as associations rather than definitive causal effects. Future studies should incorporate these variables to delineate the determinants of post-ARI wheezing and asthma more precisely. Finally, the coronavirus disease 2019 (COVID-19) pandemic may have influenced the overall background pattern of ARI hospitalizations during the study period. However, the calendar period analyses suggested that the main associations of interest did not materially change. Because this cohort was derived from a single city and spanned the pandemic period, caution is warranted when generalizing the findings to other regions or pre- or post-pandemic settings.

In conclusion, hospitalization for bronchiolitis or pneumonia was associated with an increased subsequent risk of wheezing or asthma, with the excess risk concentrated primarily within the first two years after hospitalization. These findings support structured respiratory follow-up and symptom-based asthma screening for children hospitalized with bronchiolitis or pneumonia during the first two years after discharge. For children hospitalized with bronchiolitis, an extended follow-up of 4 years after discharge may be warranted. Future studies across diverse regions and cohorts, incorporating more detailed clinical and environmental exposure data, are warranted to strengthen the evidence base for respiratory health management following ARI hospitalization.

Conflicts of interest: No conflicts of interest.

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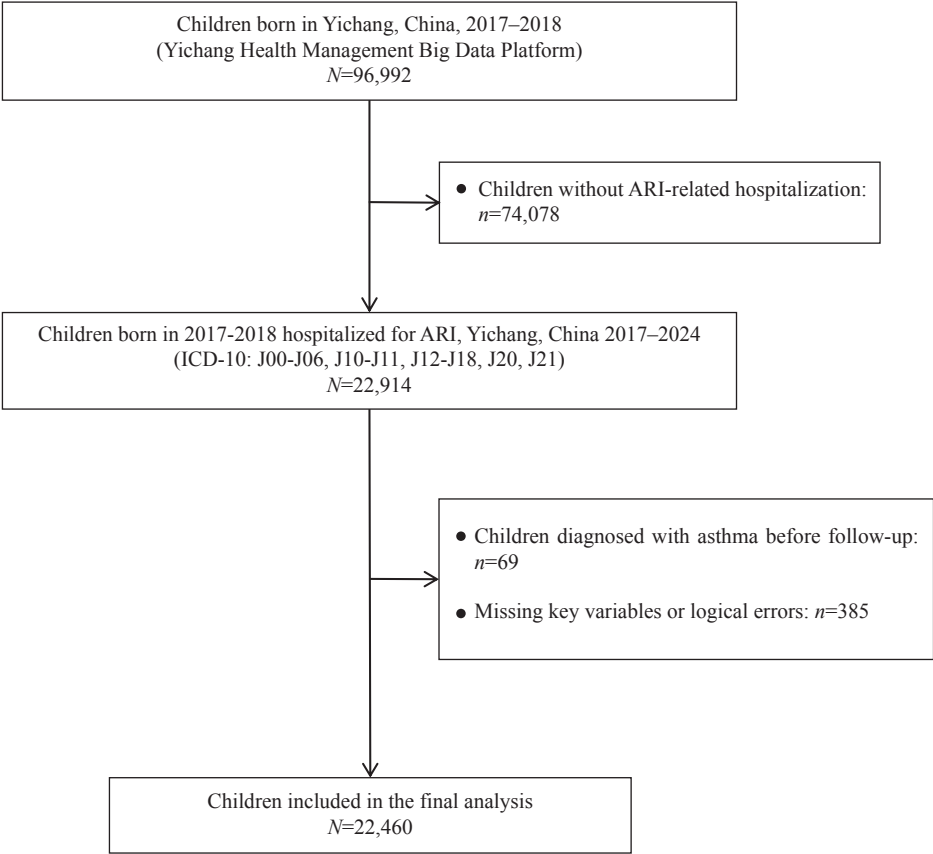
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SUPPLEMENTARY MATERIALS

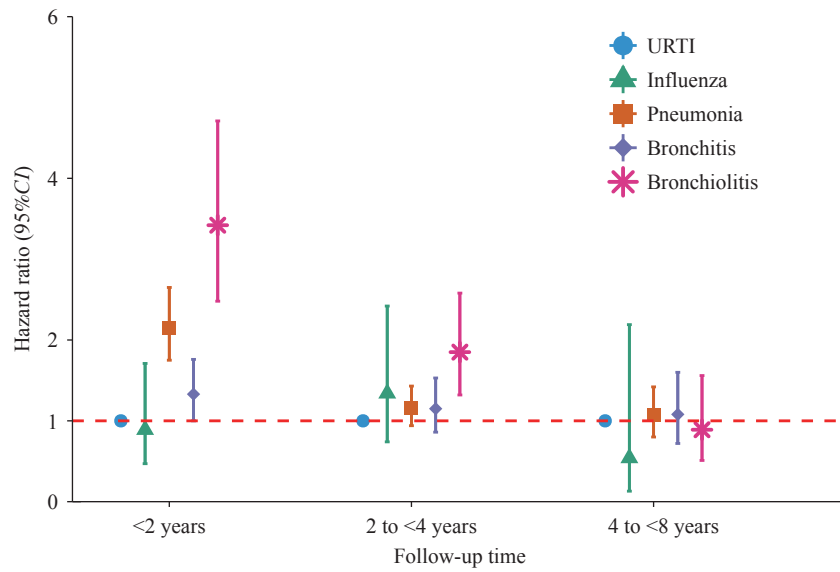
SUPPLEMENTARY TABLE S1. Detailed listing of ICD-10 codes for diseases.

Categories	Subcategories of diseases and corresponding ICD-10 codes
Acute upper respiratory infections	Acute nasopharyngitis [common cold] (J00); Acute sinusitis (J01); Acute pharyngitis (J02); Acute tonsillitis (J03); Acute laryngitis and tracheitis (J04); Acute obstructive laryngitis [croup] and epiglottitis (J05); Acute upper respiratory infections of multiple and unspecified sites (J06)
Influenza	Influenza due to identified influenza virus (J10); Influenza, virus not identified (J11)
Pneumonia	Viral pneumonia, not elsewhere classified (J12), Pneumonia due to <i>Streptococcus</i> (J13), Pneumonia due to <i>Haemophilus influenzae</i> (J14), Bacterial pneumonia, not elsewhere classified (J15), Pneumonia due to other infectious organisms, not elsewhere classified (J16), Pneumonia in diseases classified elsewhere (J17), Pneumonia, organism unspecified (J18)
Bronchitis	Acute bronchitis (J20)
Bronchiolitis	Acute bronchiolitis (J21)
Wheezing	Wheezing (R06.2)
Asthma	Asthma (J45), Status asthmaticus (J46)

Abbreviation: ICD-10=International Classification of Diseases, 10th Revision; ARI=acute respiratory infection.



SUPPLEMENTARY FIGURE S1. Flow chart of study participant selection.
Abbreviation: ARI=acute respiratory infection.



SUPPLEMENTARY FIGURE S2. Forest plot for subsequent wheezing or asthma among children hospitalized for acute respiratory infections in Yichang City, Hubei Province, China, 2017–2024.
Abbreviation: *aHR*=adjusted hazard ratio; *CI*=confidence interval; Ref=reference.