

Clinical characteristics and factors associated with severe acute respiratory infection and influenza among children in Jingzhou, China

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Background: Influenza is an important cause of respiratory illness in children, but data are limited on hospitalized children with laboratory-confirmed influenza in China.

Methods: We conducted active surveillance for severe acute respiratory infection (SARI; fever and at least one sign or symptom of acute respiratory illness) among hospitalized pediatric patients in Jingzhou, Hubei Province, from April 2010 to April 2012. Data were collected from enrolled SARI patients on demographics, underlying health conditions, clinical course of illness, and outcomes. Nasal swabs were collected and tested for influenza viruses by reverse transcription polymerase chain reaction. We described the clinical and epidemiological characteristics of children with influenza and analyzed the association between potential risk factors and SARI patients with influenza.

Results: During the study period, 15 354 children aged <15 years with signs and symptoms of SARI were enrolled at hospital admission. severe acute respiratory infection patients aged 5–15 years with confirmed influenza (H3N2) infection were more likely than children without influenza to have radiographic diagnosis of pneumonia (11/31, 36% vs 15/105, 14%. $P < .05$). Only 16% (1116/7145) of enrolled patients had received seasonal trivalent influenza vaccination within 12 months of hospital admission. Non-vaccinated influenza cases were more likely than vaccinated influenza cases to have pneumonia (31/133, 23% vs 37/256, 15%, $P < .05$). severe acute respiratory infection cases aged 5–15 years diagnosed with influenza were also more likely to have a household member who smoked cigarettes compared with SARI cases without a smoking household member (54/208, 26% vs 158/960, 16%, $P < .05$).

Conclusions: Influenza A (H3N2) virus infection was an important contributor to pneumonia requiring hospitalization. Our results highlight the importance of surveillance in identifying factors for influenza hospitalization, monitoring adherence to influenza prevention and treatment strategies, and evaluating the disease burden among hospitalized pediatric SARI patients. Influenza vaccination promotion should target children.

*These authors contributed equally to this work.

KEYWORDS

children, influenza, risk factors, severe acute respiratory infection

1 | BACKGROUND

Influenza is an important vaccine-preventable infectious disease that causes significant morbidity worldwide in persons of all ages. Studies conducted in North America, Europe, and Asia have documented that children have particularly high rates of morbidity and influenza-related complications, particularly those aged <2 years.¹⁻³ Although effectiveness varies by season through the interaction of viral and host factors, annual influenza vaccination remains the most effective method for preventing seasonal influenza and related complications.⁴⁻⁷ In the United States, annual influenza vaccination is recommended for all persons aged ≥6 months of age.⁸ In China, availability and use of seasonal influenza vaccine has increased dramatically; nevertheless, the vast majority of Chinese children are not vaccinated annually.⁹

During 2010, in the post-2009 H1N1 pandemic period, we initiated active surveillance for severe acute respiratory infection (SARI) and influenza in a central Chinese city. The highest influenza-associated SARI rates occurred among children aged 6–11 months (3603 and 3805 hospitalizations per 100 000 during 2010–2011 and 2011–2012, respectively) and influenza-associated SARI mostly affected children aged <5 years (2021 hospitalizations per 100 000 during 2010–2011 and 2349 per 100 000 during 2011–2012).¹⁰ We conducted active SARI surveillance in central China to analyze the clinical and epidemiological characteristic of influenza-associated SARI cases, including pneumonia, among pediatric patients aged <15 years.

2 | METHODS

Surveillance was conducted in Jingzhou, Hubei Province, in three general hospitals and one pediatric hospital as previously described.¹⁰ All patients admitted to a surveillance hospital were screened by nurses and physicians for SARI and were considered eligible if the SARI case definition was met within 24 hours of hospital admission. Briefly, we collected demographic, clinical, and outcome data and performed influenza testing for all pediatric patients (aged <15 years) hospitalized for SARI to characterize the epidemiology of severe influenza in children.

2.1 | Case definitions

Children <15 years of age met the case definition for SARI if they had measured elevated temperature (rectal or axillary) ≥37.3°C and at least one sign or symptom of acute respiratory illness, including cough, sore throat, tachypnea, difficulty breathing, abnormal breath sounds on auscultation, sputum production, hemoptysis, chest pain, or

chest radiograph consistent with pneumonia. A laboratory-confirmed influenza case was defined as a SARI patient with a documented positive result of real-time reverse transcription polymerase chain reaction (RT-PCR) assay for influenza, admitted to a participating hospital between April 5, 2010, and April 8, 2012. A pneumonia case was defined as a SARI patient with infiltrates noted on chest radiograph performed at any time during the hospitalization.

2.2 | Data collection

Physicians screened potential case patients for SARI at hospital admission and obtained verbal consent from a parent or guardian for enrollment in the study. Physicians then abstracted data from the medical records of patients meeting the SARI case definition including basic demographic information, past medical history, signs, symptoms, and radiographic results on a structured case report form. At hospital discharge, physicians were required to update the form to include data about outcome and influenza testing results.

2.3 | Laboratory

Nurses collected nasal swabs from pediatric SARI case patients within 24 hours of admission following standardized procedures and were transferred to the Jingzhou Center for Disease Control and Prevention (Jingzhou CDC). At Jingzhou CDC, laboratory confirmation of influenza virus infection was determined by real-time RT-PCR. Handling and testing of specimens has been described in detail elsewhere.¹⁰

2.4 | Analysis

Data were entered into EPIDATA (version 2.0, Odense, Denmark). Descriptive statistics including frequency analysis for categorical variables, medians, and interquartile ranges (IQRs) for continuous variables were calculated. To further examine the association between potential risk factors and SARI, we first performed univariate analysis. For multivariable logistic regression, we included variables with $P < .10$ in univariate analysis or those believed to be potential risk factors associated with the outcome of interest, such as “at least one tobacco smoker in household” and we conducted stepwise backwards variable selection, retaining variables with $P < .05$ after controlling for other risk factors in the logistic regression model. Data were analyzed with SPSS (v17.0; SPSS, Chicago, IL, USA).

2.5 | Human subjects review

This project was approved by the ethical review committees at the Chinese Center for Disease Control and Prevention (China CDC,

Beijing, China) and the Centers for Disease Control and Prevention (US CDC, Atlanta, GA, USA). In response to the 2009 H1N1 pandemic, China's Ministry of Health implemented the 2nd edition of the national protocol in October 2009 to conduct surveillance for influenza-associated hospitalizations and authorized participating hospitals to collect individual patient data and specimens from patients hospitalized with acute respiratory infection. For this project, therefore, participation only required patients or their parent/guardian to provide brief verbal consent.

3 | RESULTS

3.1 | Overall

From April 5, 2010, to April 8, 2012, a total of 37 607 patients aged <15 years were hospitalized in four surveillance hospitals in Jingzhou, and 15 354 (41%) of them met the SARI case definition and 15 354 were enrolled (0.05% refused; Fig. 1). Over the 24-month period, there were increases in influenza activity during summer (August and September), winter (December–February), and spring (March–May) months.

3.2 | SARI patients

The median age of all enrolled SARI patients was 1.9 years (interquartile range [IQR], 0.9–3.3 years), 80% were aged <5 years, and 57% were male. Only 2% of SARI patients had an underlying medical condition, the most common of which was prematurity (2%). Only 1% of influenza patient received monovalent pandemic H1N1 vaccination and 16% patient received seasonal trivalent influenza vaccination (Table 1). severe acute respiratory infection patients

were admitted to the hospital a median of 2 days (IQR, 1–3 days) after illness onset. Cough (61%) and sore throat (27%) were the most frequent symptoms of SARI patients at hospital admission. A quarter of all SARI patients had high fever (temperature $\geq 39.0^{\circ}\text{C}$) at admission. The median length of hospitalization for SARI patients was 5 days (IQR, 3–6). Of these SARI patients, 3 (0.02%) died during hospitalization, and 5 (0.03%) died within 30 days after discharge (Table 2).

3.3 | SARI patients with laboratory-confirmed influenza

Of 14 479 (14 479/15 354, 94%) children who met the SARI case definition and had respiratory specimens collected, 1774 (17, 74/14, 479, 12%) tested positive for influenza viruses. Of the 1774 children with confirmed influenza, 58% were male and 88% were aged <5 years. Nearly all influenza-associated SARI cases were previously healthy, and only 2% had at least one underlying medical condition, the most common of which were low birth weight (1%) and prematurity (1%) among children aged <2 years.

Influenza-associated SARI cases were admitted to the hospital a median of 2 days (IQR, 1–3 days) after illness onset, and presented with fever (temperature $\geq 37.3^{\circ}\text{C}$; 82%), cough (65%), and sore throat (23%; Table 2). Other symptoms included rhinorrhea (18%) and sputum production (8%). Gastrointestinal symptoms (nausea, vomiting, and diarrhea) were uncommon. Twenty-seven percent of influenza cases had high fever (temperature $\geq 39.0^{\circ}\text{C}$) at admission. Complications among influenza-associated SARI patients were very uncommon, but included neurologic disorders (0.2%), respiratory failure (0.1%), cardiac failure (0.1%), and hepatic dysfunction (0.1%). Twenty-one influenza patients were admitted to an intensive care unit, and five required mechanical ventilation. The median length of hospitalization for influenza-associated SARI patients was 5 days (IQR, 3–6); of these, 1 (0.06%) died within 30 days after discharge.

3.4 | SARI patients with and without laboratory-confirmed influenza

Of 14 479 children who met the SARI case definition and had respiratory specimens collected during the study period, 12 705 (88%) tested negative for influenza viruses. The demographic characteristics of patients with and without influenza were similar except those without influenza had a lower median age and a younger age distribution ($P < .05$; Table 1). Influenza cases were more likely to have at least one tobacco smoker in the household and a sick contact with fever or respiratory symptoms than children without influenza ($P < .05$).

Clinical characteristics of pediatric influenza cases and children without influenza were similar. More pediatric influenza cases had cough and rhinorrhea than children without influenza ($P < .05$), while more SARI cases without influenza had gastrointestinal symptoms (nausea, vomiting, and diarrhea) than influenza cases (Table 2). More

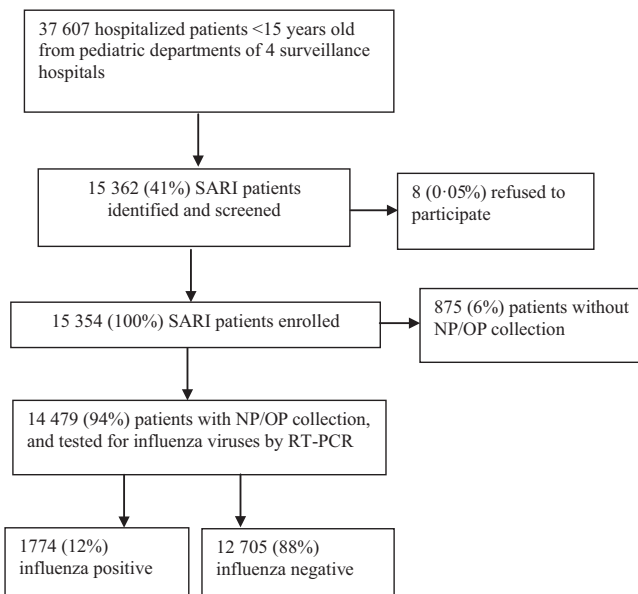


FIGURE 1 Flowchart of case enrollment in active surveillance for severe acute respiratory infection among hospitalized pediatric patients in Jingzhou

TABLE 1 Demographic characteristics and underlying medical conditions of pediatric patients with severe acute respiratory infection with and without laboratory-confirmed influenza, Jingzhou, China, April 5, 2010 to April 8, 2012

Characteristics ^a	Confirmed Influenza (n=1774) (%)	Influenza negative (n=12 705) (%)	P-value ^b	Total ^c (n=15 354) (%)
Male sex	1024 (58)	7248 (57)	.591	8789 (57)
Median (IQR) age (years)	2.5 (1.0–4.3)	1.8 (0.9–3.2)	<.05	1.9 (0.9–3.3)
Age group:				
<6 mo	156 (9)	1099 (9)		1318 (9)
6–11 mo	263 (15)	2684 (21)		3121 (20)
12–23 mo	339 (19)	3042 (24)		3596 (23)
2–4 y	669 (38)	4361 (34)		5318 (35)
5–9 y	300 (17)	1300 (10)		1710 (11)
10–15 y	47 (3)	219 (2)		291 (2)
At least one underlying medical condition	39 (2)	283 (2)	.938	333 (2)
Asthma	3 (0.2)	34 (0.3)	.617	39 (0.3)
Chronic bronchitis	0	8 (0.1)	.607	9 (0.1)
Obesity ^d	4/1016 (0.4)	16/5880 (0.3)	.833	22/7319 (0.3)
Prematurity ^e	17/758 (2)	97/6825 (1)	.507	117/8035 (2)
Low birth-weight ^f	13/758 (2)	67/6825 (1)	.862	82/8035 (1)
Received Influenza vaccination ^g				
Received monovalent pandemic H1N1 vaccination ^h	5/407 (1)	76/2299 (3)	.778	83/2826 (3)
Received seasonal trivalent influenza vaccination ⁱ	151/959 (16)	1116/7145 (16)	.907	1311/8528 (15)
Exposure history				
At least one tobacco smoker in household	308/1182 (26)	1865/8928 (21)	<.05	2294/10 640 (22)
Sick contact with fever or respiratory symptoms ^j	82/1083 (8)	390/8078 (5)	<.05	497/9601 (5)
More than one child living in household in past 3 mo	60 (3)	344 (3)	.106	422 (3)

IQR, interquartile range.

^aData presented as no. (%) of patients unless otherwise indicated. Denominators for testing of fewer patients than full group are indicated. Percentages may not total 100 because of rounding. Data did not include patients without specimens for influenza virus testing.

^bThe P-values are comparisons between "pediatric SARI patients with confirmed influenza infection" and "pediatric SARI patients without influenza infection", and statistically significant as $P < .05$

^cThere were 875 (6%) patients without NP/OP collection.

^dBody mass index (BMI) was calculated for patients with available height and weight data to assess obesity using Chinese criteria (BMI greater than the cutoff values for children aged 2–17 y). BMI was not calculated in children aged <2 y.¹¹

^eDefined as gestational age <37 wk at birth for children aged <2 y.

^fDefined as birth weight of a live born infant of <2500 g for children aged <2 y.

^gAnswered "Yes" to this question, "During the past 12 mo, have you had a flu shot?" which were asked during a face-to-face interview.

^hOf children aged ≥6 mo eligible to receive monovalent pandemic A (H1N1) influenza vaccine.

ⁱOf children aged ≥6 mo eligible to receive seasonal trivalent inactivated influenza vaccine.

^jContact with anyone else with fever or respiratory symptoms defined as having been in close contact (within 1 m) or direct contact of person with fever or respiratory symptoms in the previous 2 wk.

influenza cases had high fever at hospital admission than those without influenza ($P < .05$).

3.5 | SARI cases with pneumonia

Of 2291 SARI patients clinically diagnosed with pneumonia at hospital admission, 1938 (85%) had chest radiography performed, and 1674 (86%) had evidence of pneumonia. The median length of hospitalization for pneumonia cases was 6 days (IQR, 5–8), which was longer ($P < .05$) than children without pneumonia (median 5 days, IQR, 3–6). Among influenza cases, the proportion with cough, sputum production, or Dyspnoea was higher in children with radiologic evidence of

pneumonia compared with those without ($P < .05$; Table 3). However, children without radiologic evidence of pneumonia had higher temperatures ($T > 38^{\circ}\text{C}$) on admission than children with radiologic evidence of pneumonia, but more pneumonia cases had abnormal breath sounds on auscultation than children without pneumonia ($P < .05$).

Of 807 SARI cases with radiologic evidence of pneumonia that were tested for influenza viruses, 246 (30%) were positive, including 145 (59%) with influenza A and 101 (41%) with influenza B (Table 4). Among the influenza A cases, 46 (32%) were due to A(H1N1)pdm09 and 99 (68%) were due to A(H3N2). Among pneumonia cases aged 5–15 years, the proportion associated with A(H3N2) was significantly higher than either A(H1N1)pdm09 or influenza B (Table S3-1).

TABLE 2 Clinical characteristics of pediatric patients with severe, acute respiratory infection with and without laboratory-confirmed influenza, Jingzhou, China, April 5, 2010 to April 8, 2012

Characteristics ^a	Confirmed Influenza (n=1774) (%)	Negative for Influenza (n=12 705) (%)	P-value ^b	Total (n=15 354) ^c (%)
Symptoms at hospital admission				
Cough	1157 (65)	7205 (57)	<.05	8836 (61)
Sore throat	401 (23)	3531 (28)	<.05	4098 (27)
Rhinorrhoea	323 (18)	1748 (14)	<.05	2192 (14)
Sputum production	135 (8)	1089 (9)	.173	1304 (9)
Dyspnoea	39 (2)	556 (4)	<.05	642 (4)
Vomiting	69 (4)	721 (6)	<.05	859 (6)
Diarrhea	28 (2)	540 (4)	<.05	609 (4)
Abdominal pain	27 (2)	186 (2)	.849	228 (2)
Signs at hospital admission				
Temperature (T, °C)				
T<36.0	0	6 (0.05)	<.05	7 (0.05)
36.0≤T<37.0	251 (14)	2071 (6)		2460 (16)
37.0≤T<38.0	373 (21)	3048 (24)		3624 (24)
38.0≤T<39.0	676 (38)	4461 (35)		5459 (36)
T≥39.0	474 (27)	3119 (25)		3804 (25)
Abnormal breath sounds on auscultation	537 (30)	3799 (30)	.751	4579 (30)
Tachypnea	1 (0.1)	25 (0.2)	.361	29 (0.2)
Pneumonia Diagnosis				
Clinically diagnosed as pneumonia at hospital admission	238 (13)	1911 (15)	.071	2291 (15)
Clinically diagnosed as pneumonia at hospital admission and chest radiograph performed	195/238 (82)	1623/1911 (85)	.227	1938/2291 (85)
Radiographic diagnosis of pneumonia	161/195 (83)	1401/1623 (86)	.154	1674/1938 (86)
Chest radiograph performed at hospital admission and during hospitalization	807 (46)	5600 (44)	.262	6841 (45)
Radiographic diagnosis of pneumonia	246/807 (30)	2188/5600 (39)	<.05	2583/6841 (38)
Clinical laboratory findings				
Leucopenia ^d	165/1525 (11)	557/11 055 (5)	<.05	777/13 299 (6)
Leukocytosis ^e	282/1525 (19)	3657/11 055 (33)	<.05	4188/13 299 (31)
Anemia ^f	269/1520 (18)	2313/11 014 (21)	<.05	2748/13 250 (21)
Elevated erythrocyte Sedimentation rate ^g	66/158 (42)	641/1086 (59)	<.05	777/1349 (58)
C-reactive protein >8 mg/L	117/476 (25)	1431/3397 (42)	<.05	1622/4040 (40)
Treatment				
Received antibiotics before hospital admission	670/1343 (50)	4529/9831 (46)	<.05	5490/11 802 (47)
Received antibiotics during hospitalization	1750 (99)	12 461 (98)	.097	15 056 (98)
Received corticosteroids during hospitalization	164 (9)	1591 (13)	<.05	1880 (12)
Received oseltamivir during hospitalization	2 (0.1)	21 (0.2)	1.000	23 (0.1)
Supplemental oxygen required	16 (0.9)	183 (1.4)	.086	216 (1)
Mechanical ventilation	1 (0.1)	2 (0.05)	.324	5 (0.1)
Admitted to ICU	1 (0.1)	18 (0.1)	.722	21 (0.1)
Complications				
Neurologic disorders	3 (0.2)	11 (0.1)	.241	20 (0.1)
Respiratory failure	1 (0.1)	8 (0.1)	1.000	10 (0.1)
Cardiac failure	1 (0.1)	11 (0.1)	1.000	14 (0.1)
Hepatic dysfunction	2 (0.1)	3 (0.01)	.117	7 (0.1)
Clinical course, median days (IQR)				
From illness onset to hospital admission	2 (1-3)	2 (1-3)	.860	2 (1-3)
From hospital admission to discharge or death	5 (3-6)	5 (3-6)	.936	5 (3-6)
Clinical outcome				
Died during hospitalization	0	3 (0.02)	.221	3 (0.02)
Died within 30 d after discharge	1 (0.1)	4 (0.03)	.480	5 (0.03)

ICU, intensive care unit; IQR, interquartile range.

^aData presented as no. (%) of patients unless otherwise indicated. Denominators for testing of fewer cases than full group are indicated. Percentages may not total 100 because of rounding. Data only include patients who provided specimens for influenza virus testing.

^bThe P-values are comparisons between "pediatric SARI patients with confirmed influenza infection" and "pediatric SARI patients without influenza infection", and statistically significant as $P<.05$.

^cThere were 875 (6%) patients without NP/OP collection.

^dDefined as a reduction in the circulating WBC count to $<4000/\mu\text{L}$.

^eDefined as a reduction in the circulating WBC count to $>10\ 000/\mu\text{L}$.

^fDefined as a reduction in the hemoglobin in grams per liter ($\text{Hb}<110\ \text{g/L}$).

^gRaised erythrocyte sedimentation rate defined as $>20\ \text{mm/h}$.

TABLE 3 Clinical characteristics of pediatric severe, acute respiratory infection patients with laboratory-confirmed influenza with and without radiographic diagnosis of pneumonia in Jingzhou, China, April 5, 2010 to April 8, 2012

Characteristics of influenza patients ^a	Case patients with pneumonia (n=246) (%)	Case patients without pneumonia (n=561) (%)	P-value ^b
Symptoms at hospital admission			
Cough	209 (85)	341 (61)	<.05
Sore throat	48 (20)	111 (20)	.928
Rhinorrhoea	40 (16)	103 (18)	.472
Sputum	43 (18)	56 (10)	<.05
Dyspnoea	19 (8)	11 (2)	<.05
Vomiting	4 (2)	25 (5)	.062
Diarrhea	0	11 (2)	.022
Abdominal pain	0	8 (1)	.115
Signs at hospital admission			
Temperature (T, °C)			
T<36.0	0	0	<.05
36.0≤T<37.0	51 (21)	100 (18)	
37.0≤T<38.0	62 (25)	124 (22)	
38.0≤T<39.0	82 (33)	202 (36)	
T≥39.0	51 (21)	135 (24)	
Abnormal breath sounds on auscultation	154 (63)	191 (34)	<.05
Tachypnea	1 (0.4)	0	.305
Clinical laboratory findings			
Leucopenia ^c	14/228 (6)	60/493 (12)	<.05
Leukocytosis ^d	42/228 (18)	85/493 (17)	.753
Anemia ^e	50/229 (22)	80/492 (16)	.070
Raised erythrocyte sedimentation rate ^f	16/33 (49)	28/72 (39)	.355
C-reactive protein>8 mg/L	24/94 (26)	34/154 (22)	.533
Influenza virus type/subtype			
Influenza B	101 (41)	237 (42)	.753
A(H1N1)pdm09	46 (19)	88 (16)	.290
A (H3N2)	99 (40)	236 (42)	.642
Treatment			
Received antibiotics before hospital admission	112/177 (63)	217/411 (53)	<.05
Received antibiotics during hospitalization	245 (100)	558 (100)	.811
Received corticosteroids during hospitalization	35 (14)	54 (10)	.055
Received oseltamivir during hospitalization	1 (0.4)	1 (0.2)	.517
Supplemental oxygen required	4 (2)	6 (1)	.503
Mechanical ventilation	1 (0.4)	0	.131
Complications			
Neurologic disorders	1 (0.4)	1 (0.2)	.517
Respiratory failure	1 (0.4)	0	.305
Cardiac failure	1 (0.4)	0	.305
Hepatic dysfunction	1 (0.4)	0	.305
Clinical course, median days (IQR)			
From illness onset to hospital admission	3 (1–5)	2 (0–3)	<.05
From hospital admission to discharge or death	6 (5–8)	5 (3–6)	<.05
Died during hospitalization	0	0	–
Died within 30 d after discharge	0	1 (0.2)	1.000

ICU, intensive care unit; IQR, interquartile range.

^aData presented as no. (%) of patients unless otherwise indicated. Denominators for testing of fewer cases than full group are indicated. Percentages may not total 100 because of rounding. Data only include patients with specimens for influenza virus testing.

^bThe P-values are comparisons between “pediatric influenza patients with pneumonia” and “pediatric influenza patients without pneumonia”, and statistically significant as P<.05.

^cDefined as a reduction in the circulating WBC count to <4000/μL.

^dDefined as a reduction in the circulating WBC count to >10 000/μL.

^eDefined as a reduction in the hemoglobin in grams per liter (Hb<110 g/L).

^fRaised erythrocyte sedimentation rate defined as exceed up limit as 20 mm/h.

TABLE 4 Demographic characteristics and underlying medical conditions of pediatric severe, acute respiratory infection patients with laboratory-confirmed influenza with and without radiographic diagnosis of pneumonia, Jingzhou, China, April 5, 2010 to April 8, 2012

Characteristics of influenza patients ^a	Case patients with pneumonia (n=246) (%)	Case patients without pneumonia (n=561) (%)	P-value ^b
Male sex	145 (59)	332 (59)	.950
Median (IQR) age (years)	2.3 (0.9–3.7)	2.2 (1.0–4.0)	.542
Age group:			
<6 mo	29 (12)	50 (9)	
6–11 mo	38 (15)	87 (16)	
12–23 mo	43 (18)	124 (22)	
2–4 y	105 (43)	195 (35)	
5–9 y	26 (11)	90 (16)	
10–15 y	5 (2)	15 (3)	
At least one underlying medical condition	7 (3)	9 (2)	.275
Prematurity ^c	2/110 (2)	4/261 (2)	.744
Low birthweight ^d	1/110 (1)	5/261 (2)	.705
Vaccination history ^e			
Received monovalent pandemic H1N1 vaccination ^f	0	2/132 (2)	1.000
Received seasonal trivalent influenza vaccination ^g	31/133 (23)	37/256 (15)	<.05
Exposure history			
At least one tobacco smoker in household	37/160 (23)	102/322 (32)	.051

IQR, interquartile range.

^aData presented as no. (%) of patients unless otherwise indicated. Denominators for testing of fewer patients than full group are indicated. Percentages may not total 100 because of rounding. Data did not include patients without specimens for influenza virus testing.

^bThe P-values are comparisons between “pediatric influenza patients with pneumonia” and “pediatric influenza patients without pneumonia”, and statistically significant as $P < .05$.

^cDefined as gestational age <37 wk at birth for children aged <2 y.

^dDefined as birth weight of a live born infant of <2500 g for children aged <2 y.

^eAnswered “Yes” to this question, “During the past 12 mo, have you had a flu shot?” which were asked during a face-to-face interview.

^fOf children aged ≥ 6 mo eligible to receive seasonal trivalent inactivated influenza vaccine.

^gOf children aged ≥ 6 mo eligible to receive monovalent pandemic A (H1N1) influenza vaccine.

3.6 | Treatment

Forty-seven percent of SARI patients had either been prescribed an antibiotic or self-administered an antibiotic before hospitalization. A higher proportion of influenza-associated SARI cases had been prescribed an antibiotic before admission than those without influenza (Table 2, $P < .05$). Nearly all SARI patients were treated with antibiotics after hospital admission regardless of influenza testing results. Fewer cases of influenza-associated SARI were prescribed corticosteroids during hospitalization than those without influenza ($P < .05$) and 35 (21%) of them had developed X-ray confirmed pneumonia ($P < .05$), which was significantly higher than those influenza cases without corticosteroid treatment. Only 0.1% of SARI cases with laboratory-confirmed influenza received oseltamivir treatment during hospitalization.

3.7 | Risk factors associated with influenza

The results of univariate and multivariable analyses of potential factors associated with influenza among SARI patients are presented in Tables S1–S8. The proportion of SARI cases with a household member who smokes cigarettes in the home or contact with anyone with fever or respiratory symptoms was significantly associated with influenza among young children aged 6–23 months. These two factors were also significantly associated with higher odds of

influenza for children aged 2–4 years and children aged 5–15 years. In multivariable analyses, low birthweight (OR, 6.081; 95% CI, 1.308–28.266) and living with someone who smokes cigarettes in the household (OR, 1.363; 95% CI, 1.047–1.776) were independent risk factors for increased odds of influenza among children with SARI (Table S8).

4 | DISCUSSION

To our knowledge, this is one of the first prospective studies describing laboratory-confirmed influenza among hospitalized children in China. We used data from an active, population-based surveillance system to assess epidemiological and clinical characteristics of hospitalized children with influenza. Our results are consistent with our recent disease burden estimation, which found that influenza was associated with an estimated 2021 SARI hospitalizations per 100 000 during 2010–2011 and 2349 per 100 000 during 2011–2012 among children aged <5 years¹⁰ and other studies outside China.^{12,13} In this study, we observed the low birth weight and living with someone who smokes cigarettes in the household were independent risk factors for increased odds of influenza among children with SARI. We also documented a low percentage (1%–16%) of SARI patients with influenza who had received influenza vaccine. Low antiviral treatment of

influenza and high inappropriate use of antibiotics and corticosteroids were identified from the study.

In 2012, the WHO Strategic Advisory Group of Experts on immunization suggested that children up to 5 years of age should be considered as a target group for annual influenza vaccination.¹⁴ Several national guidelines recommend annual influenza immunization for children.¹⁵⁻¹⁷ However, the vast majority of the Chinese population is not vaccinated annually. Several studies have estimated vaccine effectiveness across influenza seasons and patient care settings using laboratory-confirmed influenza cases and found a significant protective effect for children.¹⁸⁻²³ In our study, we did not document types or doses of vaccine administered, making it difficult to draw conclusions about vaccine effectiveness.

Almost no children with influenza were treated with oseltamivir, even though the drug is well tolerated in children and treatment started within 24 hours of symptom onset provides substantial benefits to children with influenza A infection.²⁴ It is urgent to make oseltamivir more widely available for influenza patients, and educate Chinese clinicians about the clinical benefit of early oseltamivir treatment. More widespread use of rapid molecular assays with high sensitivity could also increase the proportion of children appropriately treated for influenza.

Corticosteroids were prescribed to 9% of influenza patients in this study. In a retrospective cohort study of hospitalized patients with A (H1N1)pdm09 influenza virus infection in China, the early use of glucocorticoids for fever reduction and pneumonia prevention was associated with the subsequent development of critical illnesses, even after adjusting for the presence of underlying diseases or risk factors.^{25,26} Corticosteroids may also prolong influenza viral shedding in the respiratory tract.²⁷ Based on available data, WHO does not currently recommend the use of systemic high-dose corticosteroids for influenza-associated pneumonia.²⁸

While the infections (12%) in this study were caused by influenza viruses, clinicians prescribed antibiotics for almost all SARI patients. While we did not have data to assess the need for antibiotics in our study population, inappropriate antibiotic use is potentially harmful to the community, fostering the growth of antimicrobial-resistant organisms.²⁹ Reducing inappropriate antibiotic use among children in China may be challenging. Physicians may not be willing to wait for viral testing results, influenza testing is not widely available, and, even when widely available as in this study, physicians often did not receive results until at least 48 hours after specimen collection. Parents may also be less willing to accept waiting for test results before antibiotic administration. Indeed, over half of SARI patients were already treated with antibiotics before hospital admission.³⁰

Severe acute respiratory infection patients exposed to tobacco smoke were more likely to have flu as an etiology of SARI. Environmental tobacco smoke or secondhand smoke causes ill health and mortality in children, especially among those under 5 years of age.³¹⁻³³ Exposure to secondhand smoke kills approximately 100 000 people every year in China.³⁴ Reducing secondhand smoke exposure is one of four priorities identified by the World Health Organization for global tobacco prevention and control. China's 12th 5-Year Plan calls for smoke-free public places as part of the major national goal to increase life expectancy.

Despite the significant progress made in tobacco control in China, many children are still exposed to secondhand smoke in their home.

This study is subject to several limitations. First, our study only captured children who met our surveillance case definition for severe acute respiratory infections. Young infants might have fever only without any respiratory symptoms. Second, our study was only able to test for influenza virus infection, and only 12% of pediatric SARI patients had evidence of influenza virus infection. We do not know the etiology of illness among most pediatric SARI patients enrolled in our study.

5 | CONCLUSIONS

Our results highlight the importance of surveillance in identifying factors associated with influenza in hospitalized SARI patients, monitoring adherence to influenza prevention and treatment strategies, and evaluating the year-round disease burden during influenza seasons in central China. Additional research on pediatric SARI patients in China should also incorporate testing for other respiratory pathogens, further elucidate the connection between tobacco exposure and outcomes of SARI, and identify factors that can help clinicians rapidly start antiviral treatment of influenza while reducing inappropriate use of antibiotics and corticosteroids.

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CONFLICTS OF INTEREST

We declare that we have no conflict of interests.

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SUPPORTING INFORMATION

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