

# Comparative analysis of clinical features and risk factors of severe pneumonia development in pediatric patients hospitalized with seasonal influenza or swine-origin influenza infection

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## Conflict of interest

None declared

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## Abstract

**Background.** The influenza A virus is the most important human pathogen affecting respiratory tract in children and has been prevalent for more than a century.

**Objectives.** To describe epidemiological and clinical features in hospitalized children with acute respiratory infection caused by a novel swine-origin influenza virus (S-OIV) and seasonal influenza virus A (IVA).

**Material and methods.** A total of 1,074 nasopharyngeal aspirate (NPA) samples were collected from children hospitalized with acute respiratory tract infections. The RNAs of S-OIV and seasonal IVA in the samples were examined using real-time polymerase chain reaction (RT-PCR).

**Results.** The presence of IVA was detected in 105 samples (9.8%), including S-OIV in 15 samples (1.4%) and seasonal IVA in the remaining samples (8.4%). The incidence of both viral infections was lower in autumn and winter. The rates of severe pneumonia in patients with S-OIV and seasonal IVA were 6.7% and 15.6%, respectively. In total, 14 out of 90 seasonal IVA-positive cases were categorized as severe pneumonia and 1 out of 15 S-OIV-positive cases as severe bronchiolitis. Five samples were found to have single S-OIV infection among 15 S-OIV-positive cases, while other respiratory viruses were detected in the other 9 samples. Twenty-one samples were found to be single seasonal-IVA-positive among the 90 seasonal-IVA-positive cases. Underlying heart conditions (odds ratio (OR) = 13.60), wheezing (OR = 6.82) and co-infection with adenovirus (OR = 6.21) were risk factors for developing severe pneumonia in seasonal IVA patients.

**Conclusions.** Children younger than 2 years appeared to be susceptible to both kinds of viral infection. Diagnoses of non-severe respiratory tract infection were mainly made for patients with S-OIV and IVA infection. Underlying heart conditions, wheezing and co-infection with adenovirus increase the risk of developing severe pneumonia in seasonal IVA patients.

**Key words:** children, swine-origin influenza virus, seasonal influenza virus A, acute respiratory tract infection

## Introduction

Influenza A virus (IVA) is the most important pathogen of respiratory tract infection in children and has been prevalent for more than a century. The flu has caused epidemics every year and erupts into a global pandemic at intervals of about 40 years.<sup>1</sup> The most common symptoms of flu pediatric patients include fever, cough and sputum.<sup>2</sup> Because of the antigenic drift or antigenic shift of the hemagglutinin and neuraminidase glycoproteins of the influenza viruses, the clinical features vary from year to year. Such is the case with the swine-origin influenza A (H1N1) virus (S-OIV).<sup>3</sup>

In April 2009, the first infection of S-OIV in humans was reported in Mexico, and the virus has rapidly spread across the world, affecting mainly young adults and children. The S-OIV probably resulted from the reassortment of recent North American H3N2 and H1N2 swine viruses (that is, avian/human/swine 'triple' reassortant viruses) with Eurasian avian-like swine viruses.<sup>4</sup> The main presentation of S-OIV was fever, cough, runny nose, nausea, poor feeding, and labored breathing in children,<sup>5</sup> which was more obvious in gastrointestinal symptoms than seasonal influenza. Because of the risk of emerging epidemics and pandemics, influenza always attracts the attention of patients, physicians, health organizations, and the media.<sup>6</sup> Information on the clinical course of children infected with H1N1 is still emerging.<sup>7,8</sup>

In this study, the purpose was to describe the clinical features, laboratory examination results and risk factors of severe pneumonia development in children after seasonal influenza or S-OIV infection, with the respiratory infectious pediatric patients admitted to Children's Hospital of Chongqing Medical University (China) serving as the test subjects.

## Material and methods

### Participants and clinical methods

The study population consisted of 1,074 children under the age of 16 years who were admitted to the Division of Respiratory Medicine at Children's Hospital of Chongqing Medical University between June 1, 2009 and May 31, 2011. During the two-year study period, out of 1,074 pediatric patients, 90 had a confirmed IVA infection and 15 had confirmed S-OIV infection. These 105 pneumonia patients with IVA or S-OIV infection were divided into a severe pneumonia group and a non-severe pneumonia group. The demographic, clinical and laboratory data extracted from medical records for the study included complete blood count, respiratory tract immune fluorescence, sputum culture for bacteria, radiological findings, and epidemiological data, using a standardized datasheet. Subjective symptoms such as headache, sore throat and

myalgia were also assessed, but only in children older than 5 years. The diagnosis of pneumonia and severe pneumonia were mainly based on the guidelines from the Pediatrics Branch Respiratory Study Group of the Chinese Medical Association.<sup>9</sup> The comparison was done between severe pneumonia patients and non-severe pneumonia patients. Clinical and laboratory data was compared between patients with seasonal influenza and those with S-OIV.

All patients or their legal guardians gave informed consent to participate in this study. The study was carried out in accordance with the Helsinki Declaration.

### Laboratory confirmation

All specimens were collected using nasopharyngeal aspirates (NPAs) method. The NPAs were stored at 4°C for a short duration (4–6 h) in the hospital ward; then, they were transported on ice to the Lab for Pediatric Respiratory Medicine of the Children's Hospital of Chongqing, where they were divided into centrifuge tubes and stored at –80°C. DNA and RNA were co-extracted from 200-μL NPA samples using QIAamp® MinElute Virus Spin Kits (Qiagen, Hilden, Germany) according to the manufacturer's instructions, and the samples were eluted in 62 μL of RNase-free water. Then, cDNA was synthesized using a SuperScript® First-Strand Synthesis System for real-time polymerase chain reaction (RT-PCR; Invitrogen, Carlsbad, USA). The RT-PCR was used to detect IVA and S-OIV. Nested PCR assays – providing a higher sensitivity than non-nested PCR – detected parainfluenza viruses (PIVs), respiratory syncytial virus (RSV), human metapneumovirus (hMPV), and Netherlands human coronavirus (HCoV); the PCR method was used to detect Aleutian disease virus (ADV).<sup>9–13</sup> The primers used in the experiments are listed in Table 1.

Table 1. Primers and probes for RT-PCR

Primers and probes	Sequence (5'-3')	Working concentration
IVA forward	AAAGCGAATTCAGTGTGAT	0.2 μM
IVA reverse	GAAGGCAATGTGAGATTT	0.2 μM
IVA probe	GAAAGCCCGGTCCCTCTT	0.1 μM
S-OIV forward	GCACGGTCAGCACTTATYCTTAG	0.2 μM
S-OIV reverse	GTGRGCTGGGTTTCATTGCTC	0.2 μM
S-OIV probe	CYACTGCAAGCCCA**TACACACAAGCAGGCA	0.1 μM

IVA – seasonal influenza virus A; S-OIV – swine-origin influenza virus.

### Statistical analysis

Statistical analyses were performed using SPSS v. 17.0 software (SPSS Inc., Chicago, USA). Data is expressed as mean ± standard deviation (SD), median, percentage, or frequency. The  $\chi^2$  test was used to compare categorical

variables, with Fisher's correction when needed. The t-test was used for comparing continuous variables. To analyze for the risk factors of severe pneumonia, we used multivariate logistic regression. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. A two-tailed p-value of less than 0.05 was considered statistically significant.

## Results

During the two-year study period, out of 1,074 pediatric patients, 90 had confirmed IVA infections and 15 had confirmed S-OIV infections. The age of the IVA patients ranged from 1 to 135 months (median age: 9 months) while the age of the S-OIV patients ranged from 1 to 63 months (median age: 9 months). Of note, there were significantly

more males than females, at a ratio of 2:1 and 4:1 for IVA and S-OIV infections, respectively. Most patients (76.6% and 79.9%, respectively) were younger than 2 years. Approximately 40% of both had an underlying medical condition, such as premature labor, previous respiratory infection ( $\geq 3$ ), asthma, or congenital heart disease. Meanwhile, there were no significant differences regarding demographic characteristics between the IVA and S-OIV groups ( $p > 0.05$ ; Table 2).

The clinical manifestations of IVA or S-OIV infection in the hospitalized pediatric patients are listed in Table 3. The results indicate that there were no significant differences in the symptoms, signs and blood parameters between the IVA and S-OIV groups ( $p > 0.05$ ; Table 3). The most common symptoms of IVA or S-OIV patients at admission were mainly cough (94.4% and 100.0%,

**Table 2.** Demographic characteristics of 90 patients hospitalized with IVA and 15 patients with S-OIV

Characteristic	IVA (n = 90)	S-OIV (n = 15)	p-value
Sex	male, 60 (66.7%) female, 30 (33.3%)	male, 12 (80%) female, 3 (20%)	>0.05
Age groups	>5 years, 7 (7.8%) 2–5 years, 14 (15.6%) <2 years, 79 (76.6%)	>5 years, 1 (6.7%) 2–5 years, 2 (13.4%) <2 years, 12 (79.9%)	>0.05
Median age (range)	9 months (1–135)	9 months (1–63)	>0.05
Underlying medical conditions	34 (37.8%)	6 (40.0%)	>0.05
premature (<37 weeks)	8 (8.9%)	2 (13.3%)	>0.05
previous respiratory infection ( $\geq 3$ )	13 (14.4%)	4 (26.7%)	>0.05
asthma	10 (11.1%)	2 (13.3%)	>0.05
congenital heart disease	7 (7.8%)	0 (0.0%)	>0.05

IVA – seasonal influenza virus A; S-OIV – swine-origin influenza virus.

**Table 3.** Clinical features of 90 IVA patients and 15 S-OIV patients

Clinical feature	IVA (n = 90)	S-OIV (n = 15)	p-value
Symptom			
Cough	85 (94.4%)	15 (100.0%)	0.455
Sputum	63 (70.0%)	7 (46.7%)	0.076
Fever	54 (60.0%)	10 (66.7%)	0.425
Wheezing	29 (32.2%)	5 (33.3%)	0.574
Dyspnea	12 (13.3%)	1 (6.7%)	0.412
Fatigue	6 (6.7%)	0 (0.0%)	0.387
Sore throat	1 (1.1%)	0 (0.0%)	0.857
Headache	2 (2.2%)	0 (0.0%)	0.734
Chest pain	1 (1.1%)	0 (0.0%)	0.857
Abdominal pain	2 (2.2%)	0 (0.0%)	0.734
Sign			
Moist	64 (71.1%)	9 (60.0%)	0.300
Wheeze	39 (43.3%)	5 (33.3%)	0.307
Hemanalysis			
WBC [ $\text{mm}^3$ ]	9926 $\pm$ 4170	9611 $\pm$ 5224	0.915
CRP [mg/dL]	8.569 $\pm$ 27.93	15.83 $\pm$ 38.66	0.483

IVA – seasonal influenza virus A; S-OIV – swine-origin influenza virus; WBC – white blood cell count; CRP – C-reactive protein level.

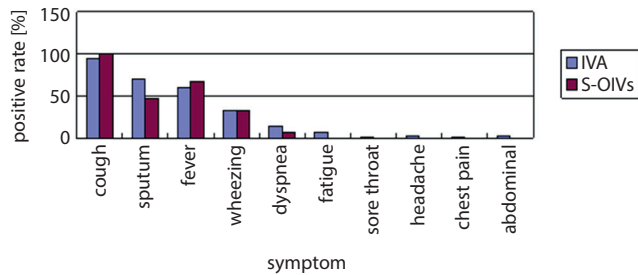


Fig. 1. The symptoms in IVA and S-OIV infection

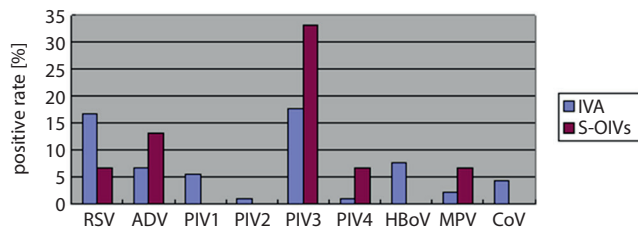


Fig. 2. Viral co-infection in IVA and S-OIV infection

respectively), fever (60.0% and 66.7%, respectively) and sputum (70.0% and 46.7%, respectively). The symptoms of fatigue, sore throat, headache, abdominal pain, and chest pain were rare in both groups of patients (Fig. 1). Physical examination at admission found moist (71.7% and 60.0%, respectively) and wheezing (43.3% and 33.3%, respectively). Detailed blood test results were collected within 24 h of admission. The white blood cell (WBC) count was almost normal, while the C-reactive protein (CRP) level was higher than average, especially in the S-OIV patients.

Out of the 90 IVA-positive cases, 39 (43.3%) had co-infection with other common respiratory viruses, while 9 (60.0%) S-OIV-positive cases had co-infection. The most common co-infection for both was PIVs (25.6% and 40.0%, respectively) – especially PIV3 (17.8% and 33.3%, respectively) – followed by RSV (16.7% and 6.7%, respectively) and ADV (6.7% and 13.3%, respectively). Co-infection with hMPV or HCoV was relatively rare. However, there is a selective bias because S-OIV prefers to mix with ADV, PIV<sub>3</sub>, PIV<sub>4</sub>, and MPV (Fig. 2). Sputum culture was positive in *Streptococcus pneumoniae* (12.2% and 26.7%, respectively), *Hemophilus influenzae* (6.7% and 0.0%, respectively), *Escherichia coli* (6.7% and 0.0%, respectively), and *Klebsiella pneumoniae* (6.7% and 0.0%, respectively) (Table 4). The *S. pneumoniae* co-infection in the IVA group was significantly less common than in the S-OIV group (Table 4;  $p < 0.05$ ). All other concrete data is presented in Table 4.

In order to understand the difference of illness severity between IVA infection and S-OIV infection, we compared the indicators of average inpatient course, number of dyspnea patients, number of severe pneumonia cases, temperatures, and respiratory rates (Table 5). The results revealed that the average inpatient course was significantly longer in the IVA group compared to the S-OIV group (Table 5;  $p < 0.05$ ). However, the other indicators were

Table 4. Co-infection of 90 IVA patients and 15 S-OIV patients

Co-infection	IVA (n = 90)	S-OIV (n = 15)	p-value
Virus			
RSV	6.715 (16.7%)	1 (6.7%)	0.209
ADV	6 (6.7%)	2 (13.3%)	0.491
PIV1	5 (5.6%)	0 (0.0%)	0.455
PIV2	1 (1.1%)	0 (0.0%)	0.320
PIV3	16 (17.8%)	5 (33.3%)	0.256
PIV4	1 (1.1%)	1 (6.7%)	0.424
hBoV	7 (7.8%)	0 (0.0%)	0.328
hMPV	2 (2.2%)	1 (6.7%)	0.526
hCoV	4 (4.4%)	0 (0.0%)	0.535
Sputum culture			
<i>E. coli</i>	6 (6.7%)	0 (0.0%)	0.387
<i>K. pneumoniae</i>	6 (6.7%)	0 (0.0%)	0.387
<i>H. influenzae</i>	6 (6.7%)	0 (0.0%)	0.387
<i>S. pneumoniae</i>	11 (12.2%)	4 (26.7%)	<0.05

IVA – seasonal influenza virus A; S-OIV – swine-origin influenza virus; PIV – parainfluenza viruses; RSV – respiratory syncytial virus; hMPV – human metapneumovirus; hCoV – human coronavirus; hBoV – human bocavirus; ADV – Aleutian disease virus; *E. coli* – *Escherichia coli*; *K. pneumoniae* – *Klebsiella pneumoniae*; *H. influenzae* – *Hemophilus influenzae*; *S. pneumoniae* – *Streptococcus pneumoniae*.

Table 5. Comparison of illness severity between IVA infection and S-OIV infection

Variable	Value		p-value
	IVA (n = 90)	S-OIV (n = 15)	
Average inpatient course [days]	7.73 ± 9.16	5.67 ± 1.29	0.042
Dyspnea case	12 (13.3%)	1 (6.7%)	0.666
Severe pneumonia cases	14 (15.6%)	1 (6.7%)	0.351
Temperature	37.11 ± 0.76	37.44 ± 0.92	0.180
Respiratory rate	42.51 ± 11.54	42.47 ± 10.89	0.857

IVA – seasonal influenza virus A; S-OIV – swine-origin influenza virus.

not significantly different, which does not fully explain whether there is a significant difference in illness severity between IVA infection and S-OIV infection (Table 5).

The patients with severe pneumonia had more co-infection with RSV or ADV, and a higher prevalence of *K. pneumoniae* than the patients with mild pneumonia (Table 6). Severe pneumonia was also more common in patients with underlying conditions, such as congenital heart disease. Patients with severe pneumonia were basically similar in their incidence of the symptoms of cough, fever, sputum, dyspnea, etc. (Table 6). There is no statistically significant difference in WBC counts and CRP levels between severe and mild pneumonia. Meanwhile, in the IVA group, the CHD rate was significantly higher and the incidence of sputum was significantly lower in the severe pneumonia group compared to that of the non-severe pneumonia group (Table 6;  $p < 0.05$ ).

**Table 6.** Risk factors associated with severe pneumonia due to IVA and S-OIV

Variable	S-OIV (n = 15)			IVA (n = 90)		
	severe pneumonia (n = 1)	non-severe pneumonia (n = 14)	p-value	severe pneumonia (n = 14)	non-severe pneumonia (n = 76)	p-value
Sex (male)	1 (100.0%)	11 (78.6%)	0.800	8 (57.1%)	52 (68.4%)	0.298
Age (<2 years)	1 (100.0%)	11 (78.6%)	0.800	13 (92.9%)	56 (73.7%)	0.107
Underlying medical conditions						
Premature labor	1 (100.0%)	2 (14.3%)	0.867	1 (7.1%)	7 (9.2%)	0.638
Previous respiratory infection ( $\geq 3$ )	1 (100.0%)	9 (64.3%)	0.667	7 (50.0%)	44 (57.9%)	0.770
Asthma	0 (0.0%)	2 (14.3%)	0.867	12 (85.7%)	68 (89.5%)	0.484
CHD	0 (0.0%)	0 (0.0%)	1.000	4 (28.6%)	3 (3.9%)	<0.05
Symptoms						
Cough	1 (100.0%)	14 (100.0%)	1.000	13 (92.9%)	72 (94.7%)	0.580
Sputum	0 (0.0%)	7 (50.0%)	0.533	13 (92.9%)	50 (65.8%)	<0.05
Fever	0 (0.0%)	0 (0.0%)	1.000	7 (50.0%)	47 (61.8%)	0.294
Wheezing	1 (100.0%)	4 (28.6%)	0.333	4 (28.6%)	25 (32.9%)	0.508
Dyspnea	0 (0.0%)	1 (7.1%)	0.933	4 (28.6%)	8 (10.5%)	0.088
Fatigue	0 (0.0%)	0 (0.0%)	1.000	1 (7.1%)	5 (6.6%)	0.649
Sore throat	0 (0.0%)	0 (0.0%)	1.000	0 (0.0%)	1 (1.3%)	0.844
Headache	0 (0.0%)	0 (0.0%)	1.000	0 (0.0%)	2 (2.6%)	0.712
Chest pain	0 (0.0%)	0 (0.0%)	1.000	0 (0.0%)	1 (1.3%)	0.844
Abdominal pain	0 (0.0%)	0 (0.0%)	1.000	1 (7.1%)	1 (1.3%)	0.288
Co-infection with virus						
RSV	1 (100.0%)	1 (7.1%)	0.133	5 (35.7%)	10 (13.2%)	0.245
ADV	1 (100.0%)	1 (7.1%)	0.133	2 (14.3%)	4 (5.3%)	0.233
PIV1	0 (0.0%)	0 (0.0%)	1.000	1 (7.1%)	4 (5.3%)	0.580
PIV2	0 (0.0%)	0 (0.0%)	1.000	0 (0.0%)	1 (1.3%)	0.844
PIV3	0 (0.0%)	5 (35.7%)	0.667	4 (28.6%)	12 (15.8%)	0.214
PIV4	0 (0.0%)	1 (7.1%)	0.933	0 (0.0%)	1 (1.3%)	0.844
HBoV	0 (0.0%)	0 (0.0%)	1.000	2 (14.3%)	5 (6.6%)	0.298
MPV	0 (0.0%)	1 (7.1%)	0.933	1 (7.1%)	1 (1.3%)	0.288
CoV	0 (0.0%)	0 (0.0%)	1.000	1 (7.1%)	3 (3.9%)	0.498

IVA – seasonal influenza virus A; S-OIV – swine-origin influenza virus; PIV – parainfluenza viruses; RSV – respiratory syncytial virus; hCoV – human coronavirus; hBoV – human bocavirus; ADV – Aleutian disease virus; CHD – coronary heart disease.

In multivariate analysis (Table 7), independent risk factors for the development of severe pneumonia were co-infection with RSV ( $p = 0.042$ ; OR = 4.245; 95% CI = 1.052–17.128), co-infection with ADV ( $p = 0.029$ ; OR = 7.336; 95% CI = 1.221–44.076), *K. pneumoniae*-positive sputum culture ( $p = 0.022$ ; OR = 7.763; 95% CI = 1.342–44.896), and basic condition of congenital heart diseases ( $p = 0.009$ ; OR = 9.577; 95% CI = 1.777–51.610).

## Discussion

This study compared the characteristics of pediatric patients with seasonal influenza to those with H1N1 infection and analyzed the risk factors for development of severe pneumonia.

Our findings are consistent with other reports in that the clinical features of S-OIV infection are generally similar to those of seasonal influenza infection.<sup>14,15</sup> The most common symptoms were cough, sputum and fever, while the symptoms of fatigue, sore throat, headache, abdominal pain, and chest pain were rare in pediatric patients. Young children cannot formulate complaints, which probably helps explain the less common symptoms.

Studies have previously indicated that many hospitalized patients during the peak periods of seasonal influenza were usually younger than 2 years or older than 65 years.<sup>16,17</sup> In our groups, patients under the age of 2 years represented 79 (76.6%) and 12 (79.9%) cases, suggesting that infants and children under 2 years are the most susceptible group for seasonal influenza and S-OIV in Chongqing.<sup>18</sup> The reason may be that infants and children less than 2 years old lack



**Table 7.** Multivariable analysis of risk factors associated with severe pneumonia

Variable	IVA (n = 90)		Model		
	severe pneumonia (n = 14)	non-severe pneumonia (n = 76)	OR	95% CI	p-value
Sex (male)	8 (57.1%)	52 (68.4%)	0.595	0.192–1.847	0.298
Age (<2 years)	13 (92.9%)	56 (73.7%)	5.141	1.742–48.430	0.107
CHD	4 (28.6%)	3 (3.9%)	9.577	1.777–51.610	<0.05
Symptoms					
Cough	13 (92.9%)	72 (94.7%)	0.138	0.007–2.755	0.580
Sputum	13 (92.9%)	50 (65.8%)	6.330	0.740–54.133	<0.05
Fever	7 (50.0%)	47 (61.8%)	1.321	0.345–5.066	0.294
Co-infection with virus					
RSV	5 (35.7%)	10 (13.2%)	2.360	0.345–16.137	0.245
ADV	2 (14.3%)	4 (5.3%)	1.736	0.136–22.167	0.233
PIV3	4 (28.6%)	12 (15.8%)	2.652	0.446–15.771	0.214
Sputum culture					
<i>E. coli</i>	2 (14.3%)	4 (5.3%)	1.025	0.078–13.405	0.985
<i>K. pneumoniae</i>	3 (21.4%)	3 (3.9%)	3.242	0.336–31.275	<0.05
<i>H. influenzae</i>	1 (7.1%)	5 (6.6%)	0.334	0.006–19.456	0.597
<i>S. pneumoniae</i>	1 (7.1%)	10 (13.2%)	0.299	0.020–4.523	0.383

OR – odds ratio; 95% CI – 95% confidence interval; CHD – coronary heart disease; PIV – parainfluenza viruses; RSV – respiratory syncytial virus; ADV – Aleutian disease virus; *E. coli* – *Escherichia coli*; *K. pneumoniae* – *Klebsiella pneumoniae*; *H. influenzae* – *Hemophilus influenzae*; *S. pneumoniae* – *Streptococcus pneumoniae*.

elastic tissue and mucus gland secretion and have poor cilia movement, which leads to a lower non-specific immune response.<sup>19</sup>

In the comparison of clinical characteristics between IVA and S-OIV patients, we find that the former group has a higher average inpatient course and more cases of dyspnea and severe pneumonia. Although these are not statistically significant, in view of the mere 15 S-OIV-positive cases, it cannot be completely excluded that there is a difference in illness severity between them. According to our data, there is a strong possibility that the pediatric patients with IVA infection have more severe cases than patients with S-OIV. Brundage and Shanks have reported that the replacement of amino acids in the PB2, NS1 and PB1-F2 proteins of the influenza virus has a direct impact on virus virulence.<sup>20</sup> S-OIV possesses fewer pathogenic amino acid sites in the PB2, NS1 and PB1-F2 proteins than IVA, which may be one explanation.

The study shows that the conditions of congenital heart disease, *K. pneumoniae*-positive sputum culture, and co-infection with RSV or ADV are risk factors for developing severe pneumonia. Other reports reveal that mixed IVA pneumonia is 3 times more prevalent than simple influenza pneumonia,<sup>21,22</sup> regardless of the seasonal flu or S-OIV in 2009. The most common bacteria in mixed pneumonia are *S. pneumoniae*, *H. influenzae* and *Staphylococcus aureus* – especially *S. pneumoniae*,<sup>23</sup> which is in accordance with our study.

Influenza pneumonia co-infection with *S. pneumoniae* easily develops into severe pneumonia and raises the mortality rate.<sup>23,24</sup> Two mechanisms for this phenomenon have

been reported. Firstly, animal experiments show that the H1N1 virus mixed with *S. pneumoniae* can induce a synergistic role in enhancing the expression of platelet-activating factor receptor; in consequence, *S. pneumoniae* is easier to adhere to and increases damage to the lungs.<sup>23</sup> Secondly, a mixed infection of the two can upregulate interleukin 1 (IL-1) expression, which reduces the macrophage clearance of *S. pneumoniae*.<sup>24</sup> However, our results suggest that the condition of *S. pneumoniae*-positive sputum culture is not a statistically significant factor, while a *K. pneumoniae*-positive sputum culture ( $p = 0.023$ ; OR = 7.250; 95% CI = 1.311–40.098) is one of the risk factors for the development of severe pneumonia in children hospitalized with respiratory tract IVA infections. This phenomenon has not yet been clearly reported in the literature: only 1 case report has been published in Taiwan, which found that IVA mixed with *K. pneumoniae* in nasopharyngeal carcinoma patients appear to pneumonia and progressive dyspnea.<sup>25,26</sup> In conclusion, the synergistic effect and its mechanism of IVA co-infection with *K. pneumoniae* require further study.

We recognize several limitations in our study. Notably, imaging data was not included, some laboratory values were missing and some symptoms may have been under-reported through poor clinical recognition. Furthermore, the S-OIV-positive cases were too few (only 15 cases) – the relationship between S-OIV and severe pneumonia requires a larger sample size for further study.

The IVA spreads throughout the year, and regional epidemics or worldwide pandemics occur frequently.

As it is one of the most common pathogens in children with respiratory tract infection, determining the prevalence, clinical characteristics and risk factors of severe pneumonia in children with ARIs in Chongqing can be important to its clinical diagnosis, treatment and vaccination.

Although the present study resulted in some interesting findings, there were also limitations. As it is well-known, many risk factors – such as current body weight, birth weight, anemia, and familial diseases – may lead to severe pneumonia in hospitalized pediatric patients. However, these risk factors were not discussed in this study. Therefore, in the following study, we would also investigate the effects of the above risk factors on severe pneumonia.

## Conclusions

The study indicated that the detection rates of S-OIV infection and seasonal IVA were 1.4% and 8.4%, respectively, in children hospitalized with acute airway respiratory infection in Chongqing. Children younger than 2 years appeared to be susceptible to both viruses. A diagnosis of non-severe respiratory tract infection was mainly presented in patients hospitalized with S-OIV and IVA infection in the respiratory medicine division of our hospital. Underlying heart conditions, wheezing and co-infection with adenovirus all increase the risk of developing severe pneumonia in patients with seasonal IVA infection.

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