

# Hospitalizations for Influenza-Associated Severe Acute Respiratory Infection, Beijing, China, 2014–2016

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We analyzed surveillance data for 2 sentinel hospitals to estimate the influenza-associated severe acute respiratory infection hospitalization rate in Beijing, China. The rate was 39 and 37 per 100,000 persons during the 2014–15 and 2015–16 influenza seasons, respectively. Rates were highest for children <5 years of age.

Influenza virus circulates worldwide, causing substantial rates of illness and death (1). In recent years, better estimates of influenza have been possible in low- and middle-income countries because of the development of surveillance systems (2,3).

Beijing is located in northern China in a temperate climate zone. Previous studies used surveillance to estimate the incidence of seasonal influenza infections in Beijing (4). However, hospitalizations associated with influenza have not been evaluated. We aimed to estimate the influenza-associated severe acute respiratory infection (SARI) hospitalization using the methods recommended by the World Health Organization (5).

## The Study

We introduced screening of inpatients for SARI at 2 sentinel hospitals in Beijing during October 2014–September 2016. Throat swabs were collected from all SARI patients with their verbal consent. To explore the characteristics

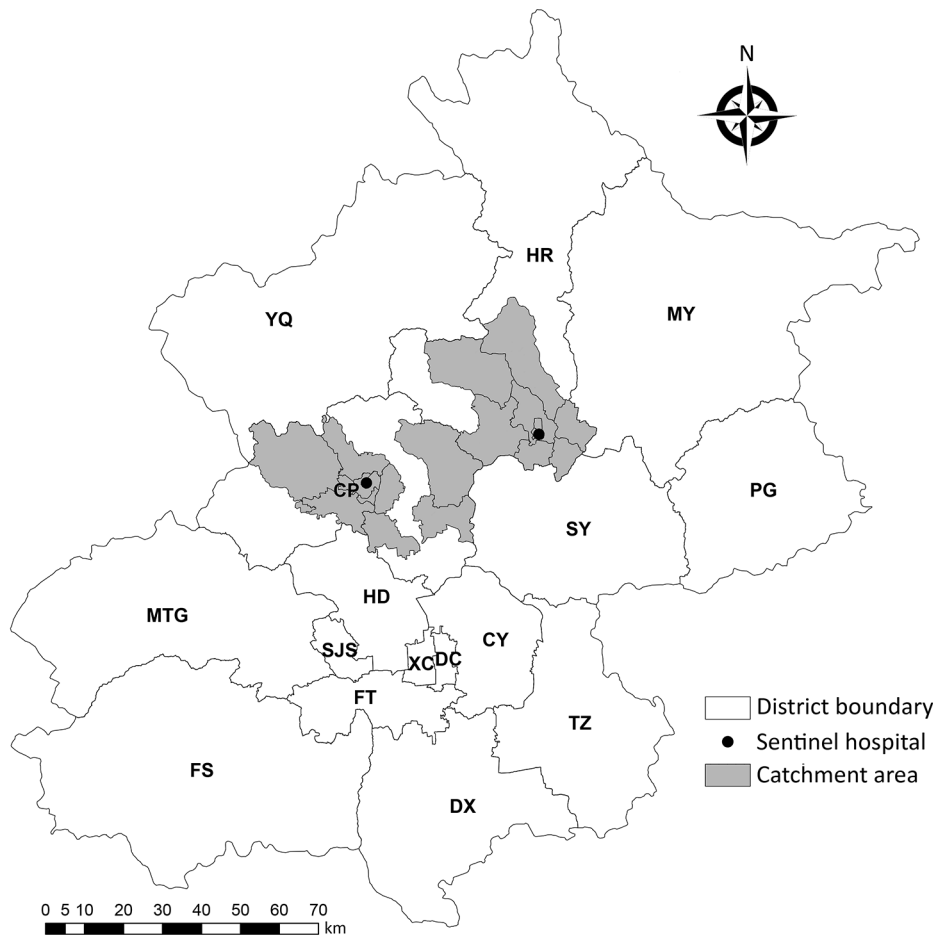
of severe influenza infections, we investigated the demographic characteristics and clinical courses of SARI patients (online Technical Appendix, <https://wwwnc.cdc.gov/EID/article/24/12/17-1410-Techapp1.pdf>).

We estimated the rate of influenza-associated SARI hospitalizations using WHO-recommended methods (5). First, we defined the catchment area of the 2 hospitals. We acquired home address (village or town) of all inpatients hospitalized in 2015 from the hospital discharge registry. Villages and towns from which most ( $\geq 80\%$ ) SARI patients came were defined as the catchment area. We restricted the number of SARI and hospitalized patients to patients residing in the catchment area. Second, we estimated the number of laboratory-confirmed influenza cases among SARI patients residing in the catchment area, adjusting pro rata for the proportion of SARI patients from whom specimens were obtained and tested by age group. Third, we estimated the catchment population size by 5 age groups (<5 years, 5–14 years, 15–24 years, 25–59 years, and  $\geq 60$  years). Catchment populations were obtained from local population statistics (6,7). Next, we obtained the age group-specific annual number of patients with physician-diagnosed pneumonia served by each of the hospitals in the catchment area by examining hospital discharge registers. We adjusted catchment population size pro rata for the proportion of pneumonia patients served by the sentinel site. The rate of influenza-associated SARI hospitalization was estimated as follows:  $([\text{number of laboratory-confirmed influenza SARI patients in catchment area} \div \text{proportion swabbed}] \div [\text{population size of catchment area} \times \text{proportion of pneumonia patients served by the sentinel site}]) \times 100,000$ .

During the study period, 14,523 persons were hospitalized in the 2 sentinel hospitals, including 4,097 SARI patients. Eight towns were identified as catchment areas of the 2 hospitals (Figures 1, 2). Of the 4,097 SARI patients, 3,899 (95.2%) resided in catchment areas and were enrolled. Swabs were collected from 3,130 (80.3%) SARI patients. Of these, 520 tested positive for influenza, resulting in a laboratory-confirmed influenza-positive proportion of 16.6%. Adjusting pro rata, the number of laboratory-confirmed influenza infections was 648 of 3,899 total SARI patients. The 2 hospitals served 93.2% of pneumonia patients in their

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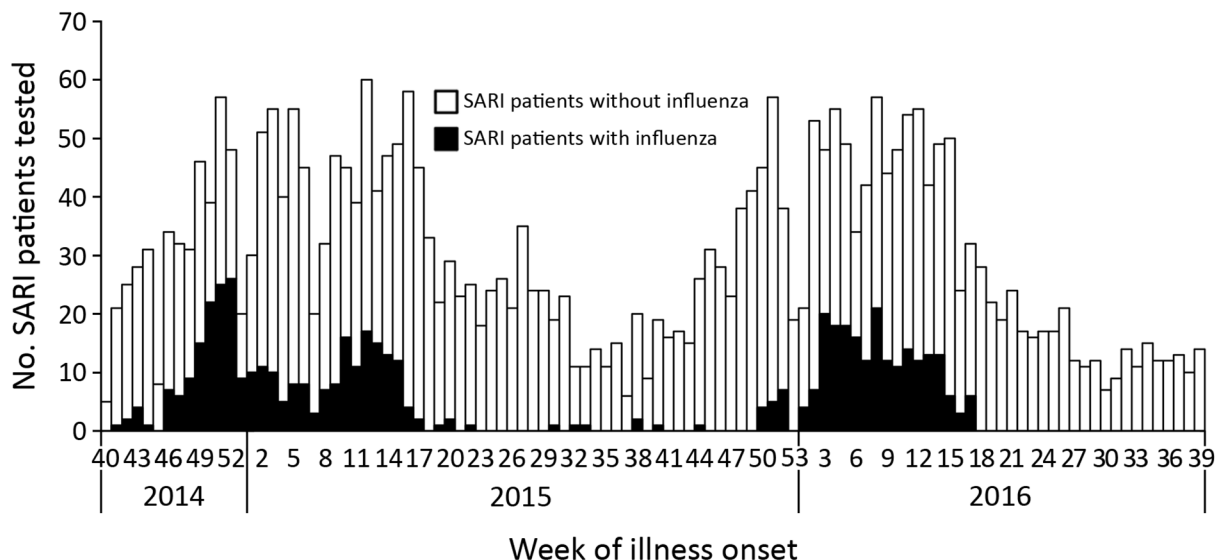
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**Figure 1.** Geographic distribution of sentinel hospitals and catchment areas for surveillance of severe acute respiratory infection, Beijing, China, 2014–2016. CP, Chang Ping; CY, Chao Yang; DC, Dong Cheng; DX, Da Xing; FS, Fang Shan; FT, Feng Tai; HD, Hai Dian; HR, Huai Rou; MTG, Men Tou Gong; MY, Mi Yun; PG, Ping Gu; SJS, Shi Jing Shan; SY, Shun Yi; TZ, Tong Zhou; XC, Xi Cheng; YQ, Yan Qing.

catchment areas. Adjusting pro rata for this proportion provides a total catchment population of 842,895. Overall, the influenza-confirmed SARI hospitalization rate was 39 (95%

CI 35–44) per 100,000 population during the 2014–15 influenza season and 37 (95% CI 33–41) per 100,000 population during the 2015–16 influenza season. The influenza A–



**Figure 2.** Number of total (N = 3130) and influenza-confirmed (n = 520) SARI patients from 2 sentinel hospitals combined, Beijing, China, week 40, 2014–week 39, 2016. SARI, sudden acute respiratory infection.

**Table 1.** Rates of influenza-associated severe acute respiratory infection hospitalizations, Beijing, China

Age group, y	2014–15 influenza season			2015–16 influenza season		
	Influenza A	Influenza B	All influenza	Influenza A	Influenza B	All influenza
<5	223 (176–278)	109 (77–149)	335 (277–401)	286 (233–348)	243 (194–301)	529 (456–611)
5–14	58 (41–80)	61 (43–84)	119 (94–150)	26 (15–42)	72 (53–97)	98 (75–126)
15–24	2 (1–5)	0 (0–3)	2 (1–6)	0	0	0
25–59	5 (3–8)	4 (3–7)	10 (7–13)	3 (2–6)	1 (0–3)	4 (3–7)
≥60	69 (52–88)	38 (26–53)	105 (85–129)	56 (41–74)	10 (5–20)	66 (50–86)
Overall	24 (21–28)	15 (13–18)	39 (35–44)	21 (18–24)	16 (14–19)	37 (33–41)

confirmed SARI hospitalization rate was 24 (95% CI 21–28) per 100,000 population during the 2014–15 influenza season and 21 (95% CI 18–24) per 100,000 population during the 2015–16 influenza season; the influenza B–confirmed SARI hospitalization rate was 15 (95% CI 13–18) per 100,000 population during the 2014–15 influenza season and 16 (95% CI 14–19) per 100,000 population during the 2015–16 influenza season. In both seasons, the rate of influenza-associated SARI was highest for children <5 years of age: 335 (95% CI 277–401) hospitalizations per 100,000 population in the 2014–15 season and 529 (95%

CI 456–611) hospitalizations per 100,000 population in the 2015–16 season. The rate was lowest in the 25–59-year age group: 2 (95% CI 1–6) hospitalizations per 100,000 population in the 2014–15 season and <1 hospitalization per 100,000 population in the 2015–16 season (Tables 1, 2; online Technical Appendix).

### Conclusions

In Beijing, influenza accounted for 16.6% of SARI in the 2 years studied; the hospitalization rate for all ages was 38–39 per 100,000 persons. This finding was much lower than

**Table 2.** Outcomes of SARI patients with and without laboratory-confirmed influenza, Beijing, China, week 40, 2014–week 39, 2016\*

Characteristic	All SARI patients, n = 2,212	SARI patients without confirmed influenza, n = 1,759	SARI patients with confirmed influenza, n = 453	p value†
Sex				
M	1,298 (58.7)	1,030 (58.6)	268 (59.2)	0.816
F	914 (41.3)	729 (41.4)	185 (40.8)	
Age group, y				
0–4	973 (44.0)	778 (44.2)	195 (43.1)	<0.001
5–14	368 (16.6)	260 (14.8)	108 (23.8)	
15–24	40 (1.8)	35 (2.0)	5 (1.1)	
25–59	284 (12.8)	235 (13.4)	49 (10.8)	
≥60	547 (24.7)	451 (25.6)	96 (21.2)	
Underlying medical condition				
>1‡	548 (24.8)	450 (25.6)	98 (21.6)	0.083
Pulmonary diseases§	224 (10.1)	175 (10.0)	49 (10.8)	0.585
Cardiovascular diseases	380 (17.2)	321 (18.3)	59 (13.0)	0.009
Metabolic diseases¶	71 (3.2)	61 (3.5)	10 (2.2)	0.175
Renal dysfunction	22 (1.0)	19 (1.1)	3 (0.7)	0.424
Hepatic dysfunction	10 (0.5)	10 (0.6)	0 (0.0)	0.108
Tumor	31 (1.4)	27 (1.5)	4 (0.9)	0.292
Immune system diseases	1 (0.1)	1 (0.1)	0 (0.0)	0.612
Received influenza vaccine within 1 y	121 (5.5)	90 (5.1)	31 (6.8)	0.15
Treatment				
Antiviral drugs	30 (1.4)	14 (0.8)	16 (3.5)	<0.001
Antibacterial drugs	2,171 (98.2)	1,722 (97.9)	449 (99.1)	0.086
Corticosteroids	214 (9.7)	154 (8.8)	60 (13.3)	0.004
Oxygen therapy	589 (26.6)	492 (28.0)	97 (21.4)	0.005
Mechanical ventilation	12 (0.5)	8 (0.5)	4 (0.9)	0.428
Complication	510 (23.1)	415 (23.6)	95 (21.0)	0.237
Pneumonia	389 (17.6)	321 (18.3)	68 (15.0)	0.106
Median length of hospital stay, d (IQR)	8.8 (8.6–9.0)	9.0 (8.7–9.3)	8.0 (7.5–8.4)	<0.001
Admission to ICU	28 (1.3)	20 (1.1)	8 (1.8)	0.286
Died	9 (0.4)	8 (0.5)	1 (0.2)	0.485

\*Values are no. (%) unless otherwise indicated. The weeks range from 2014 Sep 29 through 2016 Oct 2. ICU, intensive care unit; IQR, interquartile range; SARI, severe acute respiratory infection.

†Calculated by  $\chi^2$  test.

‡Defined as any inpatient stays with admission diagnosis in any of the following diseases, symptoms, or signs: pulmonary disease, cardiovascular disease, chronic metabolic disease, renal dysfunction, hepatic diseases, or tumor.

§Asthma, chronic obstructive pulmonary disease, emphysema, chronic bronchitis.

¶Diabetes, dyslipidemia.

that reported for Jingzhou, a city in central China, in which estimates ranged from 115 to 142 per 100,000 population in the 2010–12 influenza season (8). Although a similar method was used in these 2 studies, they had several differences. First, they estimated the hospitalization rate among different influenza seasons with different influenza activity and circulating strains. Second, the influenza circulation patterns differed (9); Beijing had 1 winter peak, whereas Jingzhou had an additional peak in summer. Moreover, the SARI definition used differed between the studies, with a lower fever threshold of  $\geq 37.3^{\circ}\text{C}$  in their study. As in other studies of age-specific influenza-associated SARI or hospitalization from other regions (3,10,11), we observed the most severe influenza disease in young children (<5 years). This finding underscores a need to consider influenza vaccination programs directed toward young children.

Although influenza B is often considered less severe than influenza A (12), 40.7% of influenza-confirmed SARI patients were influenza B–positive in this study, suggesting influenza B makes up an important component of overall influenza severity. Among the outpatient influenza infections in Beijing, 42.4% were influenza B during our study period, similar to the proportion in SARI patients (41.5%). These results suggest that influenza B is equally as responsible for mild and severe respiratory infections as influenza A.

Our study has some limitations. First, the results have limited generalizability because estimation was based on only 2 hospitals. However, 5 of the other sentinel hospitals are in the business district and serve populations of numerous districts and non-Beijing residents, making the catchment population difficult to estimate. We excluded the remaining 3 suburban sentinel hospitals because they did not have pediatric wards enrolled in SARI surveillance or the quality of their surveillance database was uncertain. Second, 19.7% of SARI patients in our study were not swabbed. We assumed the proportion of influenza-positive among them was the same as among swabbed SARI patients. However, according to clinician descriptions, most of these patients were children <5 years of age. Because the proportion of influenza-positive patients is higher among young children, we might have underestimated overall influenza-associated SARI. Third, because older adults often have complicated illness and not typical SARI symptoms, SARI might be underestimated among the older adult population. Fourth, surveillance covers only respiratory disease–related wards, but SARI patients might be hospitalized in other wards because of influenza complications (13,14), which might have led to underestimation of influenza. Finally, patients with influenza complications requiring admission might have had a relatively long delay from symptom onset to hospitalization, leading to possible false-negative laboratory results, thereby underestimating influenza.

Overall, most SARI patients in this study had influenza A, but the percentage with influenza B was also substantial. The findings of this study expanded knowledge about the impact of severe influenza and challenge the view that influenza B is a mild infection. These findings can be used to inform local policies on influenza prevention and control.

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Ms. Zhang, a PhD candidate in epidemiology in the University of New South Wales, works in the Beijing Municipal Center for Disease Prevention and Control. Her research interests focus on influenza vaccine effectiveness assessment, influenza burden estimation, and risk assessment of influenza and other respiratory infectious diseases.

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# Hospitalization for Influenza-Associated Severe Acute Respiratory Infection, Beijing, China, 2014–2016

## Technical Appendix

### Methods

#### Setting

SARI surveillance has been performed in Beijing since August 2014. Surveillance is conducted in respiratory disease–related wards. This includes pediatric, respiratory, and infectious diseases wards and intensive care units (ICU). Ten general hospitals located in 10 of the 16 districts of Beijing were involved in SARI surveillance from 2014 to 2016. Among them, 5 are located in urban areas, and 5 in suburban areas. In this study, we used data collected from 2 of the 10 sentinel hospitals. The 2 chosen sites are located in suburban areas. The 2 hospitals were selected based on 1) hospitals serving patients of all ages, 2) feasibility of the catchment population estimation, 3) quality of the surveillance database reported—average weekly number of reported SARI patients >5 and confirmed influenza in at least half of the weeks during influenza peak season, and 4) average testing rate of SARI patients was >50% over the study period. The 2 selected hospitals are the largest general hospitals in each of the selected districts in terms of size and medical capability and provide ≈93.2% of pneumonia hospitalization services in each of their catchment areas. The other 8 hospitals were excluded from analysis due to disparities in data quality during the run-in period of surveillance.

## **Patient Enrollment and Data Collection**

Physicians investigated all inpatients from the 2 selected hospitals to complete hospital admission records. They were screened for SARI during this process. SARI was defined based on WHO recommendations (1), “an acute respiratory infection with 1) history of fever or measured fever of  $\geq 38^{\circ}\text{C}$ ; 2) cough; 3) with onset within the last 10 days; 4) and requiring hospitalization.”

The Beijing SARI surveillance protocol obliges the patient’s principal treating physicians to obtain verbal consent from eligible SARI patients, or their guardians, to collect information about demographic characteristics and clinical course within 24 hours of recognizing the patient’s SARI status. Physicians then collect the information while they investigate the patients to complete hospital admittance records. Data include date of admittance, onset of symptoms, influenza vaccination status, treatment, complications, and hospital discharge outcome. Influenza vaccination status is self-reported by the patient, or by their guardian, and verified through vaccination registries for all ages by CDC staff. Discharge outcomes are classified as death during the hospital stay or survival. Patients are not followed up after discharge.

## **Specimen Collection and Testing**

According to the protocol for SARI, trained staff should collect throat specimens from all SARI patients with the patient’s verbal consent. Specimens were collected within 24 hours of admission and stored at  $4^{\circ}\text{C}$  at each ward before transportation to district CDCs for laboratory testing. Specimens were tested using multiplex real-time PCR to detect influenza A(H1N1 and H3N2) and influenza B(B/Yamagata and B/Victoria lineages). RNA extraction was performed from 140  $\mu\text{L}$  samples using QIAamp Viral RNA Mini Kit (QIAGEN, Copenhagen, Denmark). The yield RNA was finally eluted using 50  $\mu\text{L}$  RNase-free water. The viral detection was completed by rRT-PCR using AgPath-ID One-Step RT-PCR kit (Applied Biosystems, Grand Island, NY, USA) and 7500 Fast Real-Time PCR System (Applied Biosystems) using 5  $\mu\text{L}$  of

RNA according to manufacturer's instructions and the WHO's protocol (2). All reactions were run in duplicate. Only those samples that had a cycle threshold cutoff value of  $<35$  or  $>37$  in duplicated tests were regarded as positive or negative, respectively. Otherwise, a retest would be performed to get a confirmed positive or negative result.

## Results

### Characteristics of Influenza and Noninfluenza SARI Cases

Of the 3,130 SARI patients with swab collected, 918 (29.3%) refused to be investigated for clinical information. Among the 2,212 (70.7%) SARI cases with additional demographic and clinical information available, the majority were young children  $<5$  years old (44.0%) or older adults aged  $\geq 60$  years (24.7%). Males accounted for 58.7% of the total SARI cases. Around one quarter (24.8%) had at least 1 underlying medical condition, and 5.5% received the seasonal influenza vaccine. The median duration of hospitalization for SARI cases was 8.8 days (interquartile range [IQR] 8.6–9.0) and 9 cases (0.4%) died during hospitalization.

We compared the clinical characteristics of SARI patients by age group. The proportion of patients with underlying medical condition increased with increasing age, with the highest proportion among older adults ( $\geq 60$  years) at 83.2%. The median duration of hospitalization for SARI cases also increased with age, ranging from 6 days for  $<5$  years children to 12 days for  $\geq 60$  years adults. The 9 deaths were all older adults with a median age of 77 years (IQR 72–80).

When comparing SARI cases with and without confirmed influenza ( $N = 2,212$ ); age, certain medical conditions, treatments and length of hospital stay were significantly different between the 2 groups. SARI cases without confirmed influenza were more likely to have a cardiovascular disease (18.3% versus 13.0%), were more likely to receive oxygen therapy (28.0% versus 21.4%), and were less likely to receive antivirals (0.8% versus 3.5%) and corticosteroids (8.8% versus 13.3%), compared to SARI cases with confirmed influenza. Length



of hospital stay was also significantly higher in SARI cases without confirmed influenza ( $p < 0.001$ ). The proportion of cases admitted to ICU or who died during hospitalization were not statistically significant different between influenza cases and noninfluenza cases (Table 2).

Of the 2,212 SARI patients who were investigated for clinical information, 453 were test positive for influenza viruses. We compared the severity of influenza A to influenza B infection. Around 2.6% (7/265) of influenza A–infected patients were admitted to ICU, compared with 0.5% (1/188) influenza B SARI patients. One patient (0.4%) with influenza A infection died during hospitalization, while all influenza B–infected patients were discharged. The characteristics of SARI patients ( $N = 2,212$ ) and comparison between influenza- and noninfluenza-associated SARI patients are showed in Table 2 and supplementary result 1.

Of note, we found a difference in the age distribution of investigated and noninvestigated SARI patients. A lower proportion of older adults ( $\geq 60$  years) was observed among investigated patients (27.2% vs 39.7%). Moreover, there were a higher proportion of influenza-positive patients among investigated patients (20.5% vs 7.3%). The overall results may have limited generalizability.

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