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Short communication

Influenza vaccine effectiveness against influenza A during the delayed 2022/23 epidemic in Shihezi, China

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ABSTRACT

After the temporary end of COVID-19 in China in February 2023, the influenza epidemic peaked in March across many Chinese places. We recruited a total of 258 all-age subjects presenting influenza-like illness (ILI) in Shihezi city, China from January 1 to March 16, 2023, and tested for influenza virus infection. Using a test-negative design, we assessed influenza vaccine effectiveness (VE) of 56.3% (95% CrI: 13.6, 73.6) against medically attended, influenza illness during the delayed 2022/23 influenza epidemic. The findings contributed to the continuous monitoring of the influenza vaccine performance across the world, especially in the "post-COVID" pandemic era.

1. Background

Owing to the public health control measures against the COVID-19 pandemic, the landscape for seasonal influenza altered with a lower level of virus activity and decreased incidence compared with pre-pandemic levels observed in many regions including China, where the strict "zero-COVID" strategy has been imposed during epidemics [1]. The influenza epidemic in season 2022/23 was interrupted by the impacts of the historically large-scale COVID-19 epidemic in China after the exit of "zero-COVID" strategy. After the temporary end of the COVID-19 epidemic in China in February 2023, with the rapid growth of influenza infections, the influenza epidemic peaked in early March across many Chinese cities [2].

The general population in China, as elsewhere, has become more susceptible to influenza due largely to the low influenza vaccine coverage under the voluntary vaccination scheme, and lack of natural exposure to the influenza virus since the COVID-19 pandemic in 2020 [3]. In Shihezi, a city with population size of 0.33 million (in 2022) in northern Xinjiang Uygur Autonomous Region, northern China, an influenza epidemic seeded by both influenza A(H1N1)pdm09 and A (H3N2) viruses was detected in early February 2023. Using a test-negative design, we aimed to assess the influenza vaccine effectiveness (VE) against medically attended, laboratory-confirmed influenza A illness.

2. Methods

Nasal or nasopharyngeal specimens, demographic information, and epidemiological data were collected from patients presenting influenza-like illness (ILI) at all community-based clinics and hospitals in Shihezi city, China. As frequently adopted for influenza VE assessment, the ILI was defined as measured fever $\geq$ 37.5 °C plus at least one of the respiratory symptoms such as cough, sore throat, runny nose, chills, fatigue, headache, and dizziness [4,5,6,7]. We excluded children younger than 1 year owing to vaccine eligibility in mainland China.

In each epidemiological week from January 1 to March 16, 2023, more than 5 but less than 50 random-selected specimens collected from patients with ILI were tested for influenza viruses by reverse

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transcriptase PCR. Demographic and epidemiological characteristics including sex, age, ethnicity, body mass index (BMI), ILI symptom onset date, self-reported contact settings, and results of complete blood count test at the specimen collection time were recorded for each subject tested for influenza. The vaccination history of trivalent or quadrivalent inactivated influenza vaccine was collected by directly interviewing each patient or legal guardian of the patient. Subjects with vaccine injected for at least 14 days before the symptom onset date were considered vaccinated.

To address the relatively small sample size, Bayesian logistic regression models were used to estimate VE, with the adjustment for confounders including sex, age (using spline with a degree of freedom at 2), BMI (using spline with a degree of freedom at 2), and symptom onset date (in the form of epidemiological week). The VE was calculated as 1 minus the adjusted odds ratio of vaccination [8]. The statistical uncertainty was assessed by 95% credible interval (CrI) constructed from posterior samples. All statistical analyses were performed in **R** statistical software, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

A total of 258 subjects were identified as eligible for influenza VE assessment between January 1 and March 16, 2023. Among them, 14 received the influenza vaccine and the distribution of vaccine recipients in each age group was as follows: 3 (6.67%) aged 1–6 years, 1 (1.61%) aged 7–17 years, 8 (6.15%) aged 18–64 years, and 2 (9.52%) aged 65 years and above. Statistically evident difference in vaccine uptake among the age groups was not detected in this study, and thus the data analysis included all age groups. No test-positive subject was detected in the first five weeks of 2023. Most of the test-positive subjects were identified in the seventh and eighth epidemiological weeks in February 2023 (Fig. 1). Of the identified subjects, 81 (31.4%) were tested positive for influenza, where all of them were influenza A, with 56 A(H1N1) pdm09 and 25 A(H3N2) viruses (Table 1). Among the 81 test-positive subjects, 43 (53.1%) were aged 7–17 years, and only 3 (3.7%) were aged 65+ years. The majority of test-positive subjects were underweight (42%, 34/81), followed by obese (29.6%, 24/81). According to the self-reported contact settings, most of the influenza transmission events were believed to occur in the school setting, among those aged < 18 years. Only 2 (2.5%) were vaccinated among the test-positive patients, while for test-negative patients, 12 (6.8%) were vaccinated.

We estimated a VE of 56.3% (95% CrI: 13.6, 73.6) against the medically attended, laboratory-confirmed influenza A illness. The VE estimates were 61.3% (95% Crl: 28.3, 79.1) and 41.1% (95% Crl: −8.8, 68.3) against influenza illness caused by A(H1N1)pdm09 and A(H3N2) viruses, respectively. We conducted a sensitivity analysis by restricting data to a total of 170 subjects whose symptom onset dates were on or after week 6 (February 5), and we found an overall VE estimate of 54.1% (95% CrI: 25.3, 83.2).

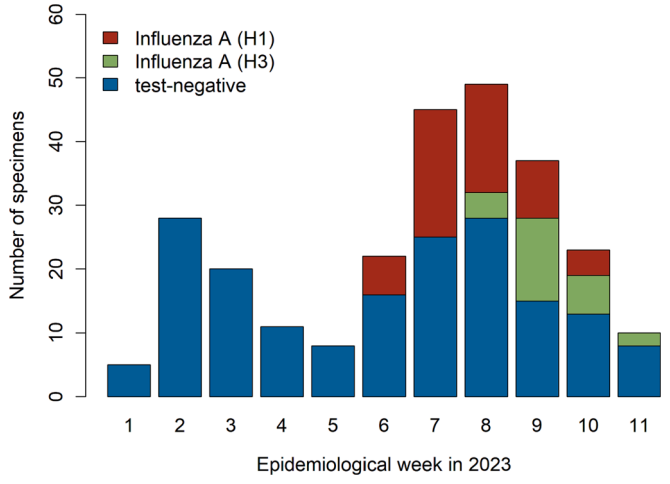

Fig. 1. Weekly number of recruited patients by their ILI onset week in Shihezi city, Xinjiang Uygur Autonomous Region, China, with test-negative or -positive cases for influenza virus ($n = 258$).

Table 1
Demographic and clinical characteristics of testing-positive and -negative patients for influenza virus.

Characteristics	Test-positive participants			Test-negative participants
	H1N1 pdm09	H3N2	Subtotal	
Total, *n* (%)	56 (100%)	25 (100%)	81 (100%)	177(100%)
Sex, *n* (%)				
Male	31 (55.4%)	14 (56.0%)	45 (55.6%)	94 (53.1%)
Female	25 (44.6%)	11 (44.0%)	36 (44.4%)	83 (46.9%)
Age group, *n* (%)				
1–6 years	12 (21.4%)	1 (4.0%)	13 (16.0%)	32 (18.1%)
7–17 years	21 (37.5%)	1 (4.0%)	22 (27.2%)	40 (22.6%)
18–64 years	20 (35.7%)	23 (92.0%)	43 (53.1%)	87 (49.2%)
65 + years	3 (5.4%)	0 (0.0%)	3 (3.7%)	18 (10.2%)
Age, median (IQR)	14 (7, 25)	21 (20, 22)	20 (9, 22)	24.5 (7, 51)
Ethnicity, *n* (%)				
Han	51 (91.1%)	21 (84.0%)	72 (88.9%)	165 (93.2%)
Uyghurs	2 (3.6%)	0 (0.0%)	2 (2.5%)	2 (1.1%)
Hui	1 (1.8%)	2 (8.0%)	3 (3.7%)	4 (2.3%)
Other ethnicities	2 (3.6%)	2 (8.0%)	4 (4.9%)	6 (3.4%)
BMI, *n* (%)				
Underweight: < 18.5	22 (39.3%)	2 (8.0%)	34 (42.0%)	65 (36.7%)
Normal: 18.5–23.0	20 (35.7%)	14 (56.0%)	5 (6.2%)	52 (29.4%)
Overweight: 23.0–27.5	9 (16.1%)	9 (36.0%)	18 (22.2%)	47 (26.6%)
Obese: > 27.5	5 (8.9%)	0 (0.0%)	24 (29.6%)	13 (7.3%)
BMI, median (IQR)	20.05 (16.4, 22.6)	20.8 (20.03, 23.89)	20.45 (17.19, 23.88)	20.81 (16.67, 24.14)
Month of ILI symptom onset in 2023, *n* (%)				
January	0 (0.0%)	0 (0.0%)	0 (0.0%)	64 (36.2%)
February	49 (87.5%)	7 (28.0%)	56 (69.1%)	80 (45.2%)
March	7 (12.5%)	18 (72.0%)	25 (30.9%)	33 (18.6%)
Time interval from ILI onset to specimen collection, *n* (%)				
0–2 day	43 (76.8%)	20 (80.0%)	63 (77.8%)	110 (62.1%)
3–4 day	10 (17.9%)	5 (20.0%)	15 (18.5%)	41 (23.2%)
5–7 day	3 (5.4%)	0 (0.0%)	3 (3.7%)	21 (11.9%)
8 + day	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.8%)
Median interval, (IQR)	1.5 (1.0, 2.0)	2 (1.0, 2.0)	2 (1.0, 2.0)	2 (1.0, 3.0)
Self-reported contact setting, *n* (%)				
Household	6 (10.7%)	0 (0.0%)	6(7.4%)	28(15.8%)
School	33 (58.9%)	21 (84.0%)	54 (66.7%)	23 (13.0%)
Other settings	11 (19.6%)	2 (8.0%)	13 (16.0%)	91 (51.4%)
Unknown	6 (10.7%)	2 (8.0%)	8 (9.9%)	35 (19.8%)
Measures in complete blood count test				
White cell counts, $\times 10^9$/L	5.2 (4.4, 6.7)	6.15 (4.5, 7.8)	5.55 (4.4, 6.8)	6.5 (4.6, 10.1)
Neutrophils, %	34.75 (4.1, 72.9)	54.5 (6.4, 76.6)	47.3 (4.8, 74.6)	45.4 (6.5, 70.6)
Lymphocytes count, $\times 10^9$/L	0.9 (0.6, 1.3)	1.05 (0.8, 1.2)	1.0 (0.7, 1.2)	1.1 (0.8, 1.7)
Vaccination status, *n* (%)				
Unvaccinated	55 (98.2%)	24 (96.0%)	79 (97.5%)	165 (93.2%)
Vaccinated	1 (1.8%)	1 (4.0%)	2 (2.5%)	12 (6.8%)

4. Discussion

The unprecedented surge in influenza A case numbers in the 2023 winter influenza season in China could be explained by the generally lower immunity level against influenza induced by natural infection and vaccination among the population due to the consequences of COVID-19 epidemics. In this study, we found that the influenza vaccination can substantially reduce the risk of medical attendance for outpatients ≥ 1 year old with influenza A H1N1 pdm09 but was less effective in reducing

the risk of attendance for outpatients with H3N2 infection, during the early season phase. Our VE estimates appeared at a similar moderate scale as the VE estimates reported previously in Canada in 2022, which was also during a delayed influenza epidemic under the impacts of the COVID-19 pandemic [9].

Notwithstanding the relatively wide credible intervals due to the small sample size, our point estimates represented the most possible outcomes due to the random sampling method. The VE against the influenza virus varied by season, and there were no existing VE estimates for the A(H1N1)pdm09 in the current influenza season. Nevertheless, our VE estimates against A(H3N2) were comparable with the latest estimates from the Center for Disease Control and Prevention, United States, which reported a VE point estimate of 54% against outpatients with 1–65 years of age and with H3N2 infection for the period from October 2022 to February 2023 [10] given that the VE among elderly (>65 years) is expected to be much lower [11]. The lower VE against H3N2 can be attributed to the circulating strain being significantly antigenically different from vaccine strain and other circulating influenza viruses [12]. The enrolled influenza vaccinees received their vaccine around 1–3 months before the recruitment, and within-season wane of VE was documented elsewhere [13,14]. Therefore, our findings may approach the maximum VE against the influenza A virus.

The coverage for influenza coverage in China remained low in the general population at 2–3% from 2020 to 2022 [15] which was inferior to the coverage during pre-epidemic periods [16] and far below the rate in the United States and European countries [17]. Annual injection of influenza vaccine should be promoted in China to prevent severe complications, in particular among vulnerable and susceptible populations such as children and the elderly, as indicated by the most frequently reported contact setting observed in our study is the school. We will continue to monitor the effectiveness of influenza vaccine against the circulating influenza virus in the near future in a broader sense, including estimating the age-specific VE and against severe outcomes and hospitalizations.

This study had the following limitations. First, a small sample size due to a limited study period cannot yield VE estimates with high statistical credibility, and thus our VE estimates should be interpreted with caution. Second, we did not have data on the genetic or antigenic information of the circulating influenza A(H1N1)pdm09 or A(H3N2) strains in Shihezi. Thus, comparison of the circulating strains in this study to A/Victoria/2570/2019(H1N1)pdm09 and A/Darwin/9/2021 (H3N2) strains cannot be performed, which were included in the 2022/23 northern hemisphere formulation of influenza vaccine. Third, as an observational study other unobserved confounders cannot be adjusted, and thus may influence VE estimates. Fourth, due to a relatively small sample size, this study may suffer sparse data bias with few vaccinated and test-positive subjects. Last, our VE estimates were largely based on protection against influenza A, and we were unable to assess VE against influenza B.

5. Conclusion

We found an evident and moderate level of protection from influenza vaccine against medically attended, influenza A illness, during the delayed epidemic in the 2022/23 influenza season among the general population in Shihezi, China. Our findings highlighted the importance of continuous surveillance on the performance of influenza vaccines.

Disclaimers

Ethics approval

This study was reviewed and approved by the institutional ethics committee of the First Affiliated Hospital of Shihezi University (No.: KJ2023-294-01).

Consent of information collection

Individual verbal consent was obtained from parents or legal guardians of participants when collecting personal information and human samples by governmental healthcare professionals in the field. This study presents no more than minimal risk of harm to all subjects, and involves no procedures for which written consent is normally required outside of the research context. The institutional ethics committee of the First Affiliated Hospital of Shihezi University waived written informed consent, and approved verbal consent for this study.

Data sharing statement

The original database containing confidential patient information cannot be made publicly available. The anonymized data used in this study were available based on reasonable request to the corresponding authors.

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CRediT authorship contribution statement

Yinxia Su: Resources, Data curation, Writing – review & editing, Funding acquisition. **Zihao Guo:** Formal analysis, Writing – original draft, Visualization, Project administration. **Xiu Gu:** Resources, Data curation, Project administration. **Shengzhi Sun:** Writing – review & editing. **Kai Wang:** Methodology, Software, Validation, Formal analysis, Writing – review & editing, Supervision, Funding acquisition. **Songsong Xie:** Methodology, Validation, Resources. **Shi Zhao:** Conceptualization, Methodology, Validation, Visualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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