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A tentative exploration for the association between influenza virus infection and SARS-CoV-2 infection in Shihezi, China: A test-negative study

Songsong Xie [a, 1], Yinxia Su [b, 1], Yanji Zhao [c, 1], Yaling Du [a], Zihao Guo [e], Xiu Gu [d], Jie Sun [f], Mohammad Javanbakht [g], Daihai He [c], Jiazhen Zhang [d], Yan Zhang [d], Kai Wang [h, **], Shi Zhao [i, *]

[a] NHC Key Laboratory of Prevention and Treatment of Central Asia High Incidence Diseases, The First Affiliated Hospital of Shihezi University, Shihezi 832000, China
[b] Department of Medical Engineering and Technology, Xinjiang Medical University, Urumqi 830017, China
[c] Department of Applied Mathematics, Hong Kong Polytechnic University, Hong Kong, 999077, China
[d] School of Medicine, Shihezi University, Shihezi 832000, China
[e] JC School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong, 999077, China
[f] School of Computer Science, Hubei University of Technology, Wuhan 430068, China
[g] Nephrology and Urology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[h] School of Public Health, Xinjiang Medical University, Urumqi, 830017, China
[i] School of Public Health, Tianjin Medical University, Tianjin, 300070, China

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ABSTRACT

The outbreak of respiratory diseases, such as COVID-19 and influenza, has drawn global attention. However, it remains unclear whether the risk of influenza A infection may be affected by the history of SARS-CoV-2 infection. In this study, we conducted a test-negative case-control study, and utilized a logistic regression model to analyze the relationship between SARS-CoV-2 and influenza A infections. Among 258 eligible patient samples with influenza-like illness (ILI), we did not detect a statistically significant association between the history of SARS-CoV-2 infection and the risk of influenza A infection. These findings might indicate that antibodies against COVID-19 acquired through vaccination or natural immunity have not protected against influenza.

* Corresponding author.
** Corresponding author.
E-mail addresses: xiesongsong2007@163.com (S. Xie), yinxia_su@xjmu.edu.cn (Y. Su), yan-ji.zhao@connect.polyu.hk (Y. Zhao), 1147844190@qq.com (Y. Du), guozihao9602@163.com (Z. Guo), 2321173241@qq.com (X. Gu), jiesun2023@163.com (J. Sun), mhmjvbt81@gmail.com (M. Javanbakht), daihai.he@polyu.edu.hk (D. He), zhangjiazhens@163.com (J. Zhang), 3530784589@qq.com (Y. Zhang), wangkaimath@sina.com (K. Wang), zhaoshi.cmsa@gmail.com (S. Zhao).

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[1] These authors contributed equally, and thus they were joint-first authors.

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1. Introduction

After the epidemic of COVID-19 has eased up temporally in China since February 2023, a subsequent outbreak of influenza A infections reached a peak in early March across numerous cities in China. Influenza A is a highly contagious respiratory virus Individuals infected by influenza A virus initially presents with common symptoms such as headache, sore throat, chills, and diarrhea (Tokito et al., 2023). Although the disease prevalent globally with seasonal patterns, it exhibits variability and heterogeneity in its prevalence (Seok et al., 2023). COVID-19 caused by SARS-CoV-2 is characterized primarily by fever, dry cough, and fatigue, with a minor subset of patients exhibiting symptoms in upper respiratory and gastrointestinal tract such as a stuffy or runny nose, and diarrhea (CDC, 2023, pp. 1–11). While the prevalence of COVID-19 in China covered 81.4% population after its outbreak (Tarke et al., 2022), some individuals have been remaining asymptomatic after exposure. Studies have suggested that immune memory generated after COVID-19 infection or vaccination can persist for 3 months to 1 year (Dan et al., 2021; Sette & Crotty, 2022; Wang et al., 2021). Despite COVID-19 and influenza A sharing respiratory transmission routes, the protection provided by vaccination or antibodies induced by infection of one disease against the other remains unclear.

Given that the COVID-19 epidemic preceded the influenza A outbreak in 2023, this study aims to assess the association between prior SAR-CoV-2 infection and testing positive for the influenza virus. This study explored whether the history of SARS-CoV-2 infection can confer protectiveness against the infection of influenza A, and to identify the factors that determine the association between COVID-19 and influenza A susceptibility.

2. Methods

Nasal or nasopharyngeal specimens, demographic information, and epidemiological data were collected from patients presenting with influenza-like illness (ILI) at all community-based clinics and hospitals in Shihezi city, China. As a medical indicator of potential influenza infection, 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 (Bianchi et al., 2023; Cowling & Zhong, 2023; Wu et al., 2022; Zhang et al., 2022). Children under 1 year old were excluded due to influenza vaccine ineligibility in mainland China.

During each epidemiological week from January 1 to March 16, 2023, 5 to 50 randomly selected specimens collected from patients with ILI were tested for influenza viruses by reverse transcription polymerase chain reaction (RT-PCR). Demographic and epidemiological characteristics including sex, age, ethnicity, body mass index (BMI), date of ILI symptom onset, self-reported possible contact settings, history of SARS-CoV-2 infection, and results of complete blood count test at the date of specimen collection were recorded for each case undergone the RT-PCR test.

Descriptive statistics of baseline characteristics were summarized by mean, standard deviation, frequency, and inter-quantile range (IQR). A logistic regression model was used to estimate the odds of observing a test-positive influenza A infectiom given a history of SARS-CoV-2 infection for total subjects and stratified by sex and ages. We used the odds ratio (OR) to evaluate the impact of a history of SARS-CoV-2 infection on the incidence of influenza. The adjusted OR (aOR) was calculated after adjusting for potential confounding variables including sex, age, ethnicity, BMI, date of ILI onset, the time interval from ILI onset to specimen collection, and self-reported contact setting. Wald statistic was applied to assess the statistical significance of the independent variables with significance level of p-value <0.05.

All statistical analyses were performed using **R** statistical software, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Of 258 eligible subjects with specimens collected, 81 (31.39%) tested positive for influenza virus infection. All participants were stratified based on prior SARS-CoV-2 infection. A total of 213 (82.56%) had prior SARS-CoV-2 infection, while 45 (17.44%) did not. There was no statistically significant difference in the proportion of individuals with a history of SARS-CoV-2 infection among those who tested negative, had a positive H1 result, or had a positive H3 result when tested for influenza viruses (Fig. 1).

Table 1 presents the characteristics of cases based on their SARS-CoV-2 infection history. A total of 45 cases without prior infection versus 213 subjects with prior infection were included. No statistically significant differences are performed in sex ($P = 0.679$), age ($P = 0.857$), ethnicity ($P = 0.613$), BMI ($P = 0.288$), or time interval from ILI onset to specimen collection ($P = 0.701$) between the two groups of prior infection. The median age ($P = 0.399$) and median BMI ($P = 0.259$) were 21 years (IQR: 8–38) and 20.76 (IQR: 16.79–23.89) for individuals with prior infection, while the median age and median BMI of those without prior infection were 20 years (IQR: 7–36) and 20.76 (IQR: 15.7–23.44), respectively. Approximately significant difference in the month of ILI onset in 2023 was performed between the two groups ($P = 0.092$). Finally, the effect of self-reported contact setting was not significant between the two groups ($P = 0.240$).

We further performed a logistic regression analysis to assess whether having COVID-19 virus infection history associated with influenza by with and without considering sex, age, ethnicity, BMI, ILI onset time, the time interval from ILI onset to specimen collection, and self-reported contact setting. The result showed there was no significant difference in test status for influenza between those with and without prior SARS-CoV-2 infection (aOR, 0.81; 95% CI, 0.32–2.091). When stratified by

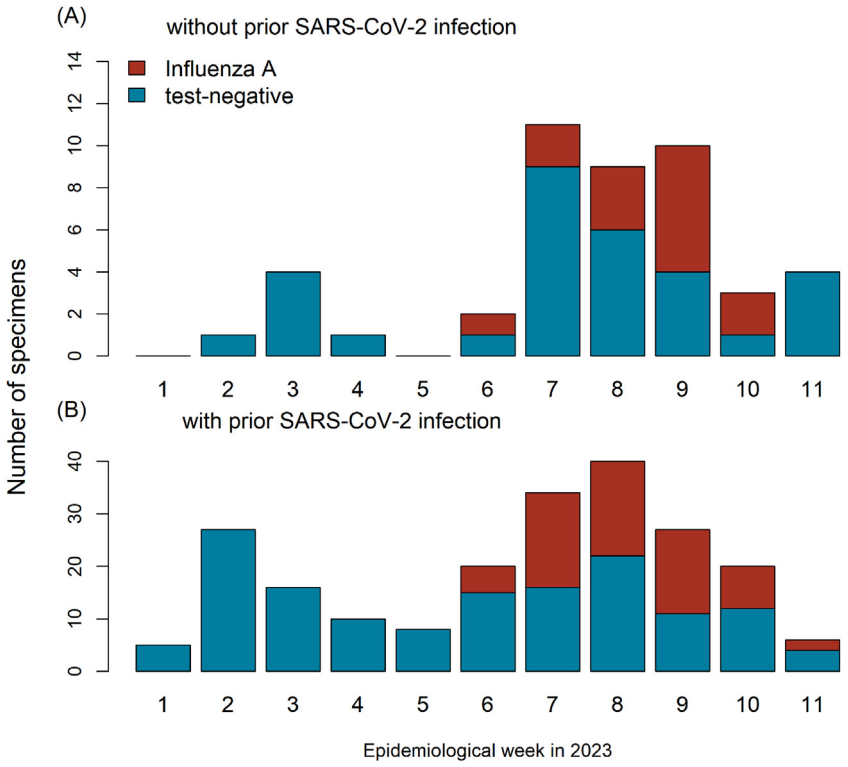

Fig. 1. The number of influenza A detections among eligible patients presenting with influenza-like illness (test-negative, or test-positive) by week of specimen collection, from 1 January to March 16, 2023 (epidemiological weeks from 1 to 11, $n = 258$).

gender, there was no significant difference observed for males (aOR, 0.59; 95% CI, 0.14–2.41). For females, the odds of testing positive for influenza were slightly higher among those with prior SARS-CoV-2 infection, but the difference was not statistically significant (aOR, 1.22; 95% CI, 0.29–5.55). Among subjects aged <18 years, those with prior SARS-CoV-2 infection had higher odds of testing positive for influenza, but the difference was not statistically significant (aOR, 2.80; 95% CI, 0.54–14.60). Among individuals aged 18–59 years (aOR, 0.29; 95% CI, 0.07–1.09), and 60 years or older, there was no significant difference in test status for influenza between those with and without prior SARS-CoV-2 infection. The adjusted odds ratios did not substantially differ from the crude odds ratios, indicating that no confounding variables were present. Overall, these results suggest that there was no significant association between prior SARS-CoV-2 infection and test status for influenza A (Table 2).

4. Discussion

The study findings underscore no significant difference in the positivity rate of influenza test results among individuals previously infected with SARS-CoV-2 or not. The adjusted odds ratios also indicate no significant association between previous SARS-CoV-2 infection and influenza infection, suggesting that the history SARS-CoV-2 infection may not sway the risk of influenza A infection. The mean rate of positive influenza test for men and women previously infected with SARS-CoV-2 was insignificantly and slightly lower or higher than that for those not infected, respectively. For younger participants, there was a slight increase in the rate of positive influenza test results in those previously infected with SARS-CoV-2, but this difference did not reach statistical significance. In older participants, the positivity rate of influenza test results was very low, and the number of positive tests was small, requiring more data to confirm the results in this age group.

Previous research has stated that antibodies generated after SARS-CoV-2 infection or vaccination can provide cross-reactive immunity against diseases caused by coronaviruses and even some other respiratory diseases (Johansson et al., 2021; Kundu et al., 2022). For example, Zhang et al. (Zhang et al., 2021) found that the majority of COVID-19 convalescent individuals maintained SARS-CoV-2 spike S1- and S2-specific antibodies with neutralizing activity against the SARS-CoV-2 pseudotyped virus, and some of the antibodies cross-neutralized SARS-CoV, Middle East respiratory syndrome coronavirus or both pseudotyped viruses. Coincidentally, Andrews et al. found that an influenza H1 hemagglutinin stem-only immunogen elicited a broadly cross-reactive B cell response in humans (Andrews et al., 2023). Similarly, some research findings have shown that antibodies against respiratory diseases caused by the coronavirus do not produce cross-immunity [16,17]. However, there is no research report on the existence of cross-immunity between influenza A and COVID-19. Therefore, it is not clear whether individuals with a history of SARS-CoV-2 infection have a protective effect against H1N1.

Table 1
Demographic and clinical characteristics of with and without COVID-19 virus infection history in Shihezi city, China, from January to March 2023 ($n = 258$).

Characteristics	Subjects by SARS-CoV-2 infection history n (column %)		p-value
	without prior infection	with prior infection	
Total	45 (100%)	213 (100%)	NA
Sex			
Male	26 (57.8%)	113 (53.1%)	0.679
Female	19 (42.2%)	100 (46.9)	
Age group			
0–6 yr	9 (20.0%)	37 (17.4%)	0.857
7–17 yr	12 (26.7%)	50 (23.5%)	
18–59 yr	19 (42.2%)	104 (48.8%)	
60+ yr	5 (11.1%)	22 (10.3%)	
Median age, yr [IQR]	20 [7, 36]	21 [8, 38]	0.399
Ethnicity			
Han	41 (91.1%)	196 (92.0%)	0.613
Uyghurs	0 (0.0%)	4 (1.9%)	
Other ethnicities	4 (8.9%)	13 (6.1%)	
BMI			
Underweight: <18.5	21 (46.7%)	68 (31.9%)	0.288
Normal: 18.5–23.0	11 (24.4%)	75 (35.2%)	
Overweight: 23.0–27.5	11 (24.4%)	54 (25.4%)	
Obese: >27.5	2 (4.4%)	16 (7.5%)	
Median BMI [IQR]	20.8 [15.7, 23.4]	20.8 [16.8, 23.9]	0.259
Month of ILI onset in 2023			
January	6 (13.3%)	58 (27.2%)	0.092
February	25 (55.6%)	111 (52.1%)	
March	14 (31.1%)	44 (20.7%)	
Time interval from ILI onset to specimen collection			
0–1 d	23 (51.1%)	93 (43.7%)	0.701
2–4 d	18 (40%)	96 (45.1%)	
5+ d	4 (8.9%)	24 (11.3%)	
Median interval, d [IQR]	1 (1, 3)	2 (1, 3)	0.421
Self-reported contact setting			
Household	2 (4.4%)	32 (15.0%)	0.240
School	13 (28.9%)	64 (30.0%)	
Other settings	22 (48.9%)	82 (38.5%)	
Unknown	8 (17.8%)	35 (16.4%)	

Note: The significance level used for all tests is $\alpha = 0.05$.

Table 2
Summary of the association between the test status for influenza virus infection and prior SARS-CoV-2 infection.

	Subjects by test status for influenza (row %)		Odds ratio (95% CI)	
	test-negative	test-positive	crude	adjusted[a]
Overall				
without prior SARS-CoV-2 infection	31 (17.5%)	14 (17.3%)	1.0 (reference)	
with prior SARS-CoV-2 infection	146 (82.5%)	67 (82.7%)	1.02 (0.52, 2.09)	0.81 (0.32, 2.09)
among **male subjects**				
without prior SARS-CoV-2 infection	17 (18.1%)	9 (20.0%)	1.0 (reference)	
with prior SARS-CoV-2 infection	77 (81.9%)	36 (80.0%)	0.88 (0.37, 2.25)	0.59 (0.14, 2.41)
among **female subjects**				
without prior SARS-CoV-2 infection	14 (16.9%)	5 (13.9%)	1.0 (reference)	
with prior SARS-CoV-2 infection	69 (83.1%)	31 (86.1%)	1.26 (0.44, 4.17)	1.22 (0.29, 5.55)
among **subjects with age < 18 years**				
without prior SARS-CoV-2 infection	17 (23.3%)	4 (11.4%)	1.0 (reference)	
with prior SARS-CoV-2 infection	56 (76.7%)	31 (88.6%)	2.35 (0.79, 8.73)	2.80 (0.54, 14.60)
among **subjects with age of 18–59 years**				
without prior SARS-CoV-2 infection	10 (12.5%)	9 (20.9%)	1.0 (reference)	
with prior SARS-CoV-2 infection	70 (87.5%)	34 (79.1%)	0.54 (0.20, 1.48)	0.29 (0.07, 1.09)
among **subjects with age 60+ years**				
without prior SARS-CoV-2 infection	4 (16.7%)	1 (33.3%)	1.0 (reference)	
with prior SARS-CoV-2 infection	20 (83.3%)	2 (66.7%)	0.4 (0.03, 9.81)	(not estimated)

[a] Note: The odds ratio (OR) was estimate with the adjustment for co-variables including Sex, Age, Ethnicity, BMI, ILI onset time, the time interval from ILI onset to specimen collection, and self-reported contact setting.

Our primary objective is to assess whether the antibodies generated after the pandemic of COVID-19 can provide protection against currently prevalent influenza A. This study claims no significant association between a history of COVID-19 infection and testing positive for influenza A virus. It suggests that the antibodies generated against COVID-19 may not provide significant protection against influenza and COVID-19 and influenza A may recur in a successive manner as the antibodies gradually diminish in the future. Therefore, specific prevention and treatment measures for these two diseases should be developed, and relevant authorities should formulate tailored prevention and control strategies and develop targeted vaccines.

In summary, the study provides important insights into the relationship between SARS-CoV-2 and influenza. The results reveal insignificant relationship between previous history of SARS-CoV-2 infection and the risk of influenza infection. Understanding the epidemiological characteristics of the disease and its relationship with COVID-19 is critical for future prevention and control efforts, and further researches with adequate data for elders is needed to fully understand the interaction between these two viruses.

5. Conclusions

We found there is no statistically evident association between susceptibility to influenza A and the history of SARS-CoV-2 infection. Additionally, the study identified schools as potential hotspots for influenza transmission, highlighting the need for relevant health education and preventive measures. Understanding the epidemiological characteristics of influenza and its relationship with COVID-19, which emerged before the H1N1 influenza outbreak, is crucial for effective future prevention and control efforts. However, we acknowledge the limitations of our study due to its small sample size of elders, and further investigation is necessary to confirm our findings.

CRediT authorship contribution statement

Songsong Xie: Writing – original draft. **Yinxia Su:** Project administration. **Yanji Zhao:** Formal analysis. **Yaling Du:** Writing – review & editing. **Zihao Guo:** Writing – review & editing. **Xiu Gu:** Writing – review & editing. **Jie Sun:** Writing – review & editing. **Mohammad Javanbakht:** Writing – review & editing. **Daihai He:** Writing – review & editing. **Jiazhen Zhang:** Writing – review & editing. **Yan Zhang:** Writing – review & editing. **Kai Wang:** Supervision. **Shi Zhao:** Conceptualization.

Ethics approval

This study was reviewed and approved by the institutional ethics committee of Xinjiang Medical University.

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 Xinjiang Medical University waived written informed consent, and approved verbal consent for this study.

Declarations of interests

All authors declared no competing interests.

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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