Influenza Vaccination and the Risk of COVID-19 Infection and Severe Illness in Older Adults in the United States

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Abstract

The COVID-19 pandemic is an urgent threat worldwide with no vaccine available. It is important to evaluate whether influenza vaccination can reduce the risk of COVID-19 infection. This is a retrospective cross-sectional study with claims data from Symphony Health database from July 1, 2019, to June 30, 2020. Participants were adults aged 65 years old or older who had received the influenza vaccine between September 1 and December 31 of 2019. The objective was to measure the odds of COVID-19 infection and severe COVID-19 illness after January 15, 2020 among vaccinated and unvaccinated older adults. The adjusted odds ratio (aOR) of COVID-19 infection risk between the influenza-vaccination group and no-influenza-vaccination group was 0.76 (95% confidence interval (CI), 0.75–0.77). Among COVID-19 patients, the aOR of developing severe COVID-19 illness was 0.72 (95% CI, 0.68–0.76) between the influenza-vaccination group and the no-influenza-vaccination group. When the influenza-vaccination group and the other-vaccination group were compared, the aOR of COVID-19 infection was 0.95 (95% CI, 0.93–0.97), and the aOR of developing a severe COVID-19 illness was 0.95 (95% CI, 0.80–1.13). In conclusion, the influenza vaccine may marginally protect people from COVID-19 infection.

Key Points

- Influenza vaccination seems to reduce the risk of COVID-19 infection and COVID-19 illness severity.
- Part of the protective effects of the influenza vaccine may come from the healthy vaccine effect. Preventive health behavior plays a key role in the prevention of COVID-19.
- Regardless of whether the bystander immunity for COVID-19 exists, it is important to receive an influenza vaccination to reduce the risk of a co-infection of influenza and COVID-19.

Introduction

The coronavirus disease of 2019 (COVID-19) has caused a global pandemic and led to over 1 million deaths globally.[1] However, there are currently no specific drugs or vaccines for this disease. Recent evidence suggests that an influenza vaccine may stimulate nonspecific immune responses that reduce the risk of COVID-19 infection or the severity of COVID-19 illness after infection.

Some COVID-19 patients from Wuhan, China, with positive influenza A immunoglobulin M (IgM) had a lower risk of mortality and severe COVID-19 illness compared with those who showed a negative IgM status.[2] Furthermore, in a prospective registry of patients tested for COVID-19 at the Cleveland Clinic in the United States, patients who received the pneumococcal polysaccharide or influenza vaccine correlated with a lower risk of a positive COVID-19 test.[3] An Italian survey suggested that influenza vaccinations in people under 65 years old correlated with a lower rate of a positive SARS-CoV-2 test.[4] Two preprint studies reported that influenza vaccination had a protective effect against COVID-19. In the United States, a county-level study showed that the influenza vaccination coverage rate was negatively associated with COVID-19 mortality in older adults; in Brazil, a patient registry showed that patients who recently received an influenza vaccination had a lower odds of severe illness and mortality from COVID-19.[5, 6]

Older adults and other patients with comorbidities are at greater risk of COVID-19 infection, and they are also more likely to develop severe illness after infection.[7, 8] Given that the influenza vaccine is safe and currently available, it may be a quick and safe option to slow down the COVID-19 pandemic. Limited evidence exists about the association between influenza vaccination and the incidence of COVID-19. Besides, healthy vaccine effect was not considered in prior research. Therefore, it is important to further evaluate the effect of influenza vaccination on risk of COVID-19 infection taking healthy user effect into consideration. Given that older adults are especially vulnerable to COVID-19, the aim of the present study is to evaluate whether influenza vaccination (1) reduces the risk of COVID-19 infection and (2) reduces the severity of illness after being infected by COVID-19 in adults age 65 or older.

Results

The Symphony Health dataset included records from 56 million older adults (**Figure 1**). About 13 million older adults received the influenza vaccination between September 1 and December 31 of 2019. More than 42 million older adults who did not receive an influenza vaccination were selected as a control group for the comparison in Analysis 1. In the same period, 4.7 million older adults received other vaccines (herpes zoster, pneumococcal pneumonia, tetanus, and hepatitis A), and nearly 1.8 million of them had not received an influenza vaccine. These 1.8 million patients were selected as a control group in Analysis 2.

The characteristics of the study cohorts are in **Table 1**. Individuals who had received either an influenza vaccination or other non-influenza vaccination tended to have a lower comorbidity burden compared to individuals who did not receive an influenza vaccination. Among individuals who did not receive an influenza vaccination, 1.2% of them had a COVID-19 infection and 0.02% of them developed severe COVID-19 illness. Those who received an influenza vaccination had a COVID-19 infection rate of 0.9% and a severe case rate of 0.01%. Those who received a vaccination for something other than influenza had a COVID-19 infection rate of 0.98% and a severe COVID-19 illness case rate of 0.01%. Those descriptive statistics show that older adults who received an influenza vaccination had the lowest rate of COVID-19 infection and the lowest severe COVID-19 illness case rate.

Without adjusting for any risk factors, the odds of getting COVID-19 infection for the influenza-vaccination group was 0.72 times that of the no-influenza-vaccination group, with a 95% confidence interval (95% CI) of 0.71–0.73 (**Figure 2**). The adjusted odds ratio (aOR) from the pooled analysis was 0.76 (95% CI 0.75–0.77). The distributions of the aORs and their lower and upper limits from the 2000 subcohorts are shown in **Supplementary Figure S1**. Among COVID-19 patients, the crude odds ratio (OR) of developing severe illness was 0.70 (95% CI 0.66–0.74) in patients who had received an influenza vaccination compared to patients who did not receive an influenza vaccination, and the aOR was 0.72 (95% CI 0.68–0.76).

In Analysis 2, the crude OR of COVID-19 infection between the influenza-vaccination group and other-vaccination group was 0.93 (95% CI 0.92–0.95), and the multivariate aOR was 0.95 (95% CI 0.93–0.97).

Among COVID-19 patients, the unadjusted OR of severe COVID-19 illness was 0.93 (95% CI 0.79–1.10) when the influenza-vaccination group was compared with the other-vaccination group, and the aOR was 0.95 (95% CI 0.80–1.13).

Discussion

In this study, older adults who had received an influenza vaccination were associated with a 24% reduction in the odds of getting a COVID-19 infection and a 28% reduction in the odds of developing a severe COVID-19 illness, compared to older adults who had not received influenza vaccination. When we compared individuals who had received an influenza vaccination to those who received a non-influenza vaccination, the protective effect against COVID-19 infection was reduced from 24% to 5% but remained significant. Receiving an influenza vaccination did not reduce the odds of developing severe illness in patients with COVID-19 infection when compared to receiving a non-influenza vaccination.

Our results suggest that an influenza vaccination seems to have a protective effect against COVID-19 infection, which implies that an influenza vaccination may trigger nonspecific immune responses that help protect against COVID-19 infection. This finding was also consistent with prior evidence that suggested that an influenza vaccination may reduce the risk of a COVID-19 infection or severe COVID-19 illness.[3–6] There is also a hypothesis that immune responses in the influenza vaccine may induce bystander immunity against SARS-CoV-2.[9]

Although receiving an influenza vaccination was associated with a significant reduction in the risk of COVID-19 infection compared to not receiving an influenza vaccination, this effect may come from the healthy vaccine effect because people who were vaccinated may be healthier in general than those who were not vaccinated.[10] In addition, individuals who were vaccinated often have other health behaviors that may prevent the transmission of COVID-19 or reduce the severity of COVID-19 illness. The healthy vaccine effect may be reflected by the result that only a marginal effect was found when we compared the risk of COVID-19 infection between those who received an influenza vaccine and those who received a vaccine against something other than influenza; no difference in the risk of severe COVID-19 illness was observed between the influenza-vaccination group and the no-influenza-vaccination group.

Study Limitation

In this study, we selected four other vaccines that are recommended by the CDC to the older adults as comparators to avoid the healthy vaccine effect. However, vaccines against diseases other than influenza are only administered once in a lifetime or at an interval of many years in between vaccinations. In the present study, only older adults who had received a vaccination after July 2019 could be traced. Therefore, a potential misclassification of this covariate may exist. The results of the comparison between the influenza-vaccination group and the non-influenza-vaccination group should be conservative because individuals were required to have received at least one non-influenza vaccination to be included in the comparison group.

Although the ethnicity and geographic location might affect the incidence of COVID-19 infection, we were unable to adjust for these two variables. In the Symphony Health dataset, 35% of older adults had no ethnic information, and only the first two digits of their zip codes were provided.

Finally, we were unable to implement self-control or case-crossover designs to avoid the healthy vaccine effect because our data only covered one year.[10] However, one important assumption of the case-crossover design is that the outcome event can occur “bi-directionally" (that is, outcomes can occur before and after the exposure), and the event could be reversible.[11] Given that COVID-19 has been newly detected this year, it violates the bi-directional assumption. In short, it is impossible to identify an outcome event (that is, a COVID-19 case) before the exposure (that is, an influenza vaccination) because COVID-19 was not identified before 2020.

Conclusion

The influenza vaccine may only marginally protect people from COVID-19 infection. However, it remains important to receive an influenza vaccination to reduce the risk of a co-infection of influenza and COVID-19. Because influenza and COVID-19 present with similar symptomatology and occupy the same medical resources, the influenza vaccine is crucial in reducing the number of severe influenza patients in order to free up resources that may be necessary to handle another wave of COVID-19 patients.

Methods

This cross-sectional observational study was conducted using the Symphony Health dataset (PRA Health Sciences, Raleigh, NC, USA) from the COVID-19 Research Database.[12] The COVID-19 Research Database was established with Institutional Review Board approval and an exemption from patient consent because it included only data considered to be de-identified by the Health Insurance Portability and Accountability Act (HIPAA), HIPAA-limited data, or non-HIPAA-covered data, along with the strong governance measures in place to control access to all data. The Symphony Health dataset was derived from pharmacy and medical claims from several sources including Medicare, which covers about 280 million patients (almost all older adults), 1.8 million prescribers, and 16,000 health plans in the United States.

We used data collected from July 1, 2019, to June 30, 2020, about older adults (age 65 years old or older). To identify incident COVID-19 cases, we excluded individuals who had received a COVID-19 diagnosis before January 15, 2020. We also excluded individuals who had received an influenza vaccination on or after January 1, 2020, for two reasons. First, it generally takes 14 days for the body to develop antibodies against influenza after vaccination, so we hypothesized that the effect of the influenza vaccination would begin 14 days after the vaccination.[13] Second, although our design is closer to a cross-sectional study, we used the 14-day window to strengthen the temporality between influenza vaccination and COVID-19 infection. All the exposure (that is, influenza vaccination) occurred before the outcome (that is, COVID-19

infection). **Figure 3** shows the timeline of covariate assessment, receipt of influenza or other vaccine, and outcomes.

We classified individuals into an influenza-vaccination group and a no-influenza-vaccination group on the basis of their influenza vaccination status between September 1, 2019, and December 31, 2019. The differences among vaccines were considered as covariates, including trivalent or quadrivalent, live attenuated or inactivated, and with or without an adjuvant. The intranasal influenza vaccine was not recommended to older adults, thus we did not find any intranasal influenza vaccine users in our study sample. The National Drug Codes for the influenza vaccines and other vaccines were from the Centers for Disease Control (CDC).[14] Two outcomes were identified on and after January 15, 2020, in this study: incidence of COVID-19 infection and incidence of severe illness because of COVID-19 infection. These two outcomes follow the U.S. Food and Drug Administration's definition (**Supplementary Figure S1**).[15]

The covariates included in this study were as follows: age 75 or older, gender, vaccinated against a disease other than influenza between July 1 and December 31, whether the influenza vaccine contained an adjuvant, and comorbidities that may increase the risk of COVID-19. The four types of vaccines that are recommended by the CDC and commonly administered to older adults were adjusted in Analysis 1 and served as comparators in Analysis 2 (that is, herpes zoster, pneumococcal pneumonia, tetanus, and hepatitis A). The influenza vaccines included in this study were mainly FLUZONE High-Dose (Sanofi Pasteur Inc.) and FLUAD (Seqirus USA Inc.), which accounted for 56% and 29% of the study sample, respectively. These were the two vaccines that were recommended for older adults by the CDC. The use of other influenza vaccines was never more than 5%. Both vaccines were trivalent in the study period; FLUZONE High-Dose is a vaccine without an adjuvant; FLAUD contains an adjuvant. Thus, we did not control the vaccine valency; instead, we adjusted the appearance of the adjuvant in multivariate analyses because a vaccine adjuvant may reduce COVID-19 severity.[9] Comorbidities were selected according to the CDC's warning about at-risk populations and included asthma, chronic kidney disease with dialysis, chronic lung disease, diabetes mellitus, hemoglobin disorders, immunocompromised, liver disease, serious heart conditions, and severe obesity (**Supplementary Figure S1**).[16]

Two analyses were performed in this study. We first compared the odds of contracting COVID-19 between individuals who received an influenza vaccination versus those who did not (Analysis 1). To clarify the healthy user effect, we repeated the aforementioned analyses by comparing individuals who received an influenza vaccination to those who receive a vaccination other than for influenza (Analysis 2). Vaccines that are recommended for older adults were selected as the comparator (herpes zoster, pneumococcal pneumonia, tetanus, and hepatitis A).

The risk of COVID-19 infection and severe COVID-19 illness were evaluated with univariate and multivariate logistic regressions. To compare the influenza-vaccination group with the no-influenza-vaccination group, we divided the study cohort into 2000 subcohorts because computing efficiency limited the processing of such a large amount of data at once. We calculated the odds ratio in each subcohort and used a meta-analysis approach to get the pooled results. The final result was pooled using

a random-effects model. Data were managed using the Snowflake® data warehouse (Snowflake Inc., San Mateo, CA, USA), and the analyses were performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA).

Declarations

Acknowledgments

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Author contributions

Conceptualization: K.H. and C.C.W.; Designed Research: K.H., S.W.L. and C.C.W.; Performed Research: K.H. and C.C.W.; Analyzed Data: K.H.; Wrote Manuscript- original draft preparation, K.H.; Wrote Manuscript- review and editing, K.H., S.W.L., W.H.S., and C.C.W.

Competing interests

The authors declare no competing interests.

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Table

Table 1. Characteristics of the three study cohorts: no influenza vaccination, influenza vaccination, and vaccination other than influenza

Characteristics	No influenza vaccination	Percent	Influenza vaccination	Percent	Vaccination other than influenza	Percent
N	42 629 666		13 038 311		1 783 969	
Age 75 and older	17 909 748	42	5 568 818	43	671 574	38
Male	19 042 518	45	5 636 245	43	739 562	41
Risk factors						
Asthma	91 734	0.22	31 753	0.24	5052	0.28
Chronic kidney disease with dialysis	43 809	0.10	1787	0.014	888	0.050
Chronic lung disease	1 520 026	3.6	365 723	2.8	50 698	2.8
Diabetes mellitus	4 620 287	11	1 165 787	8.9	175 659	9.8
Hemoglobin disorder	17 624	0.041	4285	0.033	776	0.043
Immunocompromised	214 861	0.50	59 518	0.46	9384	0.53
Liver disease	158 425	0.37	32 516	0.25	5973	0.33
Serious heart condition	3 528 349	8.3	891 346	6.8	122 178	6.8
Severe obesity	1 511 601	3.5	423 755	3.3	67 534	3.8
Other vaccination[1]	34 669 841	81	8 004 874	61	not applicable	
Vaccine with adjuvant	not applicable		3 740 784	29	not applicable	
Outcome						
COVID-19 infection	532 550	1.2	117 467	0.90	17 472	0.98
Severe COVID-19 illness	8540	0.020	1302	0.010	223	0.013

[1]Other vaccines: herpes zoster, pneumococcal pneumonia, tetanus, and hepatitis A.

Figures

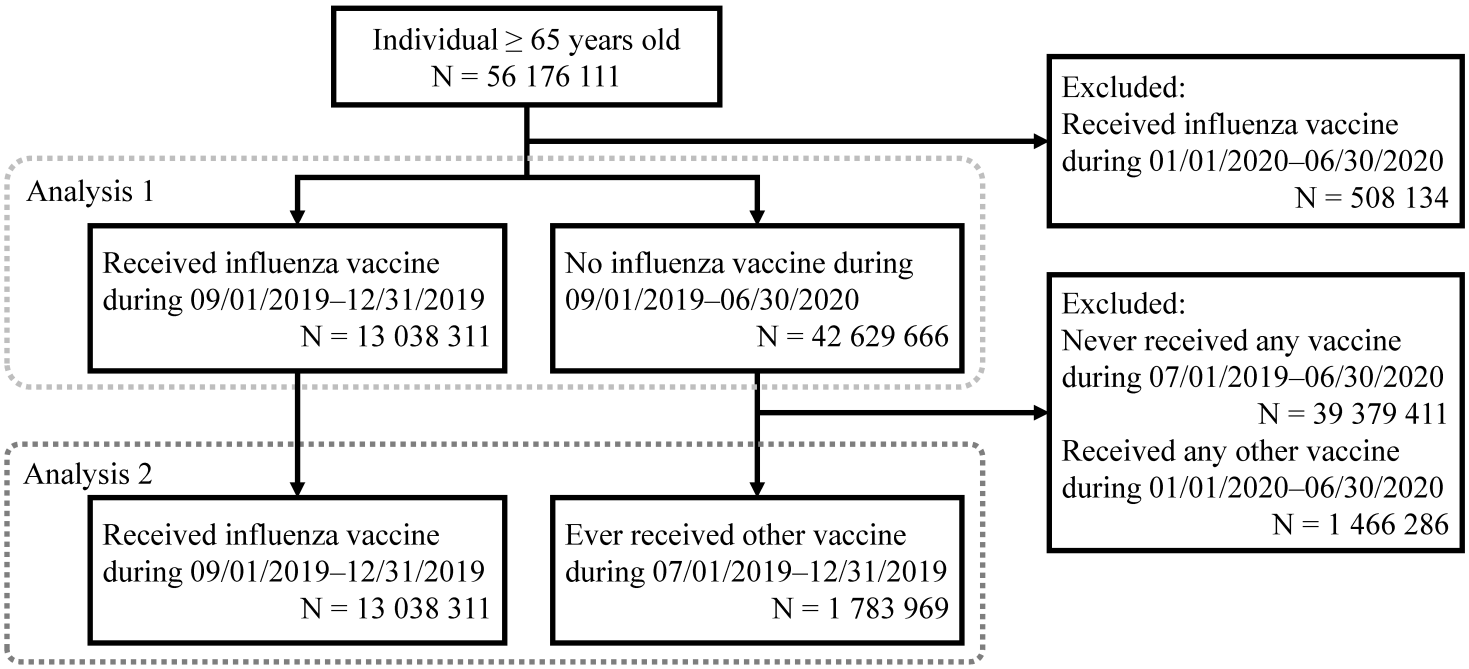
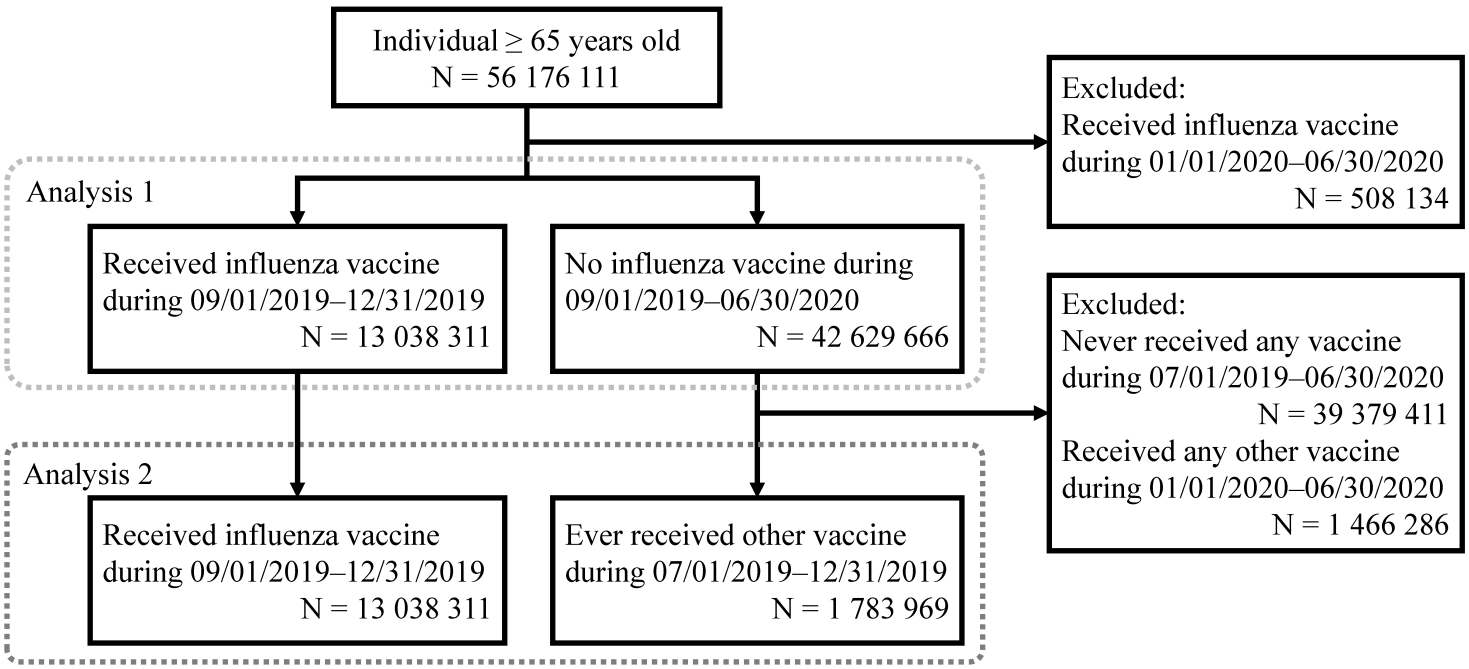


Figure 1

Flow chart of patient selection and comparisons. Analysis 1 compared older adults who received influenza vaccine or not in 2019. Analysis 2 compared older adults who received influenza vaccine or other vaccine in 2019.



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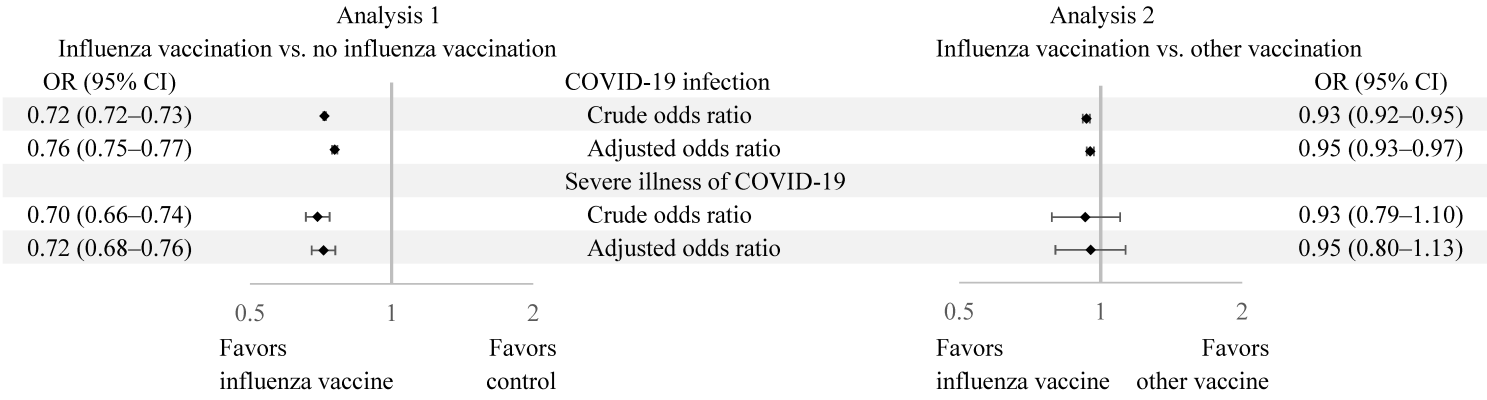
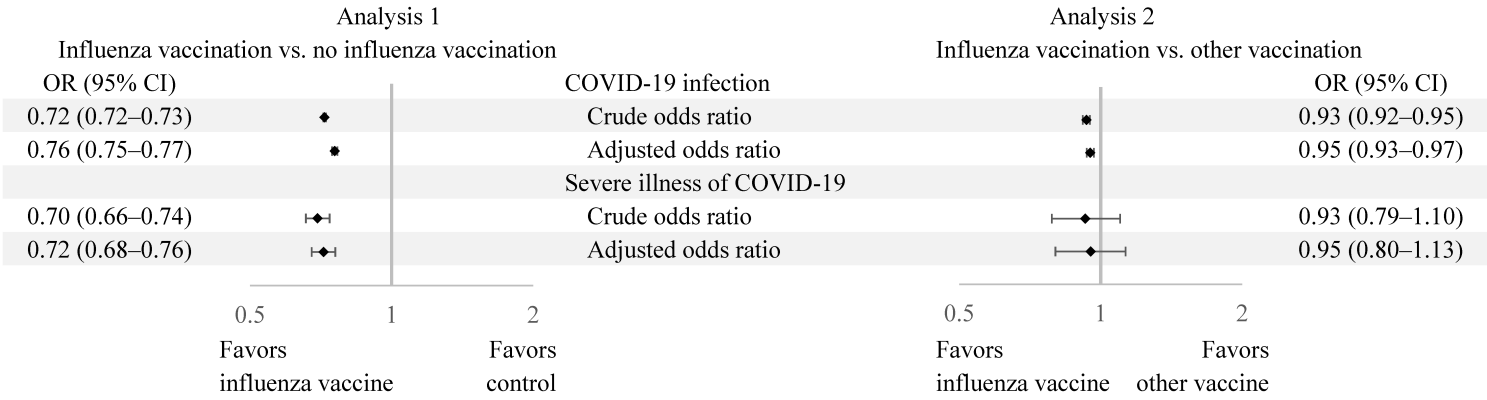


Figure 2

Effectiveness of influenza vaccine for protection against COVID-19 infection and severe COVID-19 illness. Older adults received influenza vaccination had consistent and significant lower odds of COVID-19 infection and severe illness than those who did not receive influenza vaccine, but marginal lower odds than those who received other vaccination. (OR, odds ratio; CI, confidence interval)



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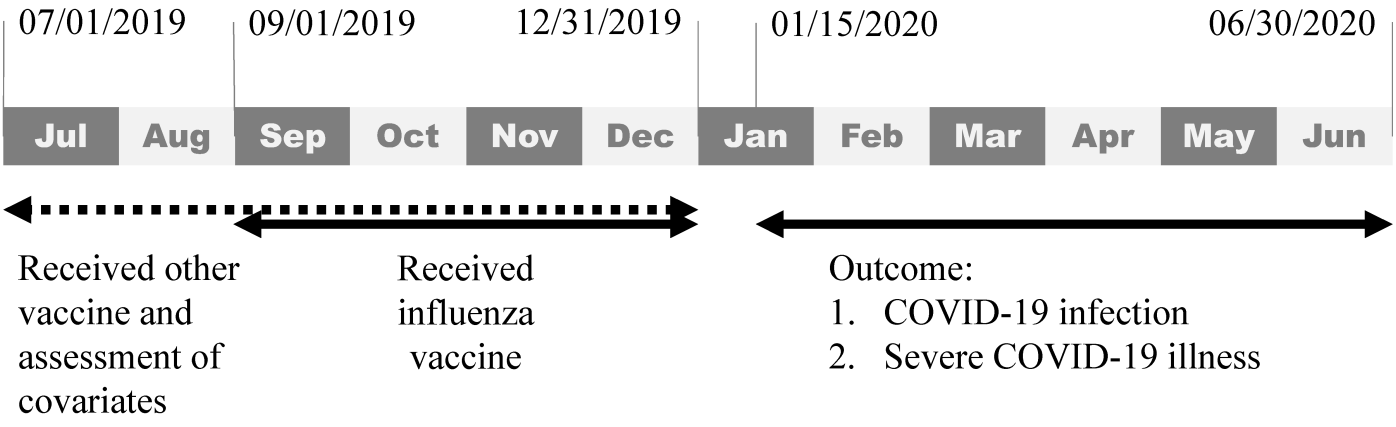

Figure 3

Timeline of covariate assessment, receipt of influenza or other vaccine, and outcomes. The exposure was limited in 2019, including influenza vaccination started on September and other vaccination started on July; outcome was limited between January 15 and June 30 in 2020.

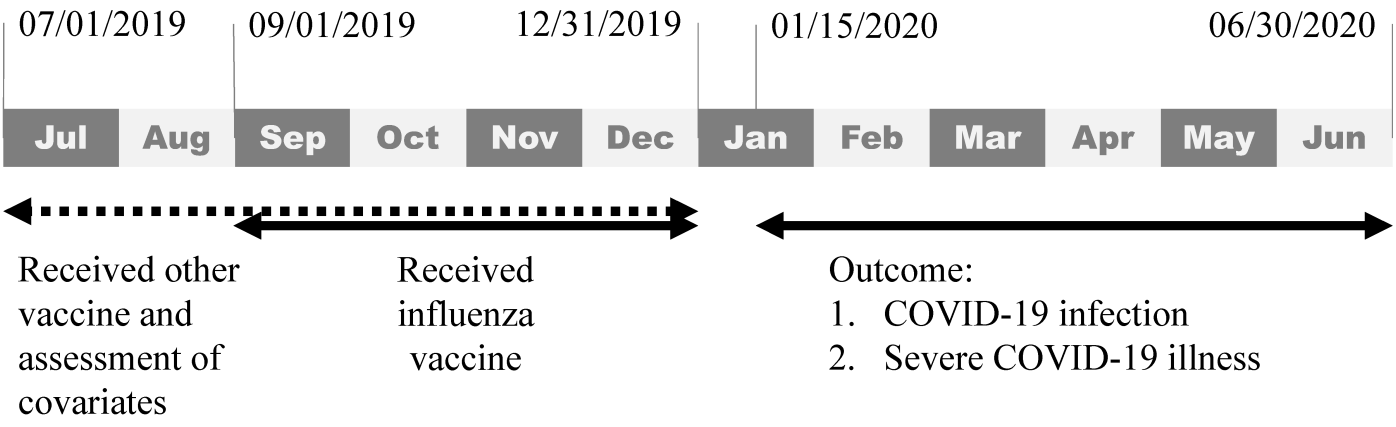

Figure 3

Timeline of covariate assessment, receipt of influenza or other vaccine, and outcomes. The exposure was limited in 2019, including influenza vaccination started on September and other vaccination started on July; outcome was limited between January 15 and June 30 in 2020.

Supplementary Files

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