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The Association Between Previous Influenza Vaccination and COVID-19 Infection Risk and Severity: A Systematic Review and Meta-analysis



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Introduction: The association between influenza vaccination and COVID-19 remains controversial. This meta-analysis aimed to investigate whether influenza vaccination reduces the susceptibility and severity of SARS-CoV-2 infection.

Methods: A systematic literature search of PubMed, Web of Science, the Cochrane Library, Embase, China National Knowledge Infrastructure, SinoMed, Wanfang Data Knowledge Service Platform, and China Science and Technology Journal VIP Database was conducted from database inception to August 2021. The pooled RR with 95% CI was used to estimate the effect of influenza vaccination on COVID-19. The I^2 value was used to assess heterogeneity. If $I^2 > 50\%$, the random-effects model was used as the pooling method.

Results: A total of 23 published articles with 1,037,445 participants were identified. This meta-analysis showed that influenza vaccination was associated with reduced risk of COVID-19 infection (RR=0.83, 95% CI=0.76, 0.90) and hospitalization (RR=0.71, 95% CI=0.59, 0.84), although not significantly associated with intensive care unit admission and death (risk of intensive care unit admission: RR=0.93, 95% CI=0.64, 1.36; risk of death: RR=0.83, 95% CI=0.68, 1.01). Further analysis suggested that the tetravalent influenza vaccine may be associated with a reduced risk of COVID-19 infection (RR=0.74, 95% CI=0.65, 0.84).

Discussion: The results suggest that influenza vaccination is associated with reduced susceptibility to or disease severity of COVID-19 and that influenza vaccination may reduce the risk of COVID-19 and improve clinical outcomes.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since first appearing in late 2019, COVID-19 has quickly spread around the world. By September 2021, the total number of cases worldwide had exceeded 220 million, resulting in >4 million deaths.¹ With the recent emergence of new and more infectious SARS-CoV-2 variants, a long-term integrated approach to the COVID-19 pandemic seems to be an effective intervention in the absence or reduction of vaccine protection.² Although multiple COVID-19

vaccines are available, access to vaccines remains a serious problem for some parts of the world. In the absence

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of a vaccine, SARS-CoV-2 and influenza viruses have the potential to spread in parallel in areas with a low rate of COVID-19 vaccination during the fall and winter.³ Animal studies have suggested that an indirect etiological immunity induction pathway may exist between the influenza vaccine and COVID-19.⁴ A Brazilian study showed that influenza vaccine may protect against SARS-CoV-2 infection by training innate immunity.⁵ The influenza viruses and SARS-CoV-2 viruses have evolutionary proximity, and the SARS-CoV-2 spike protein shares common features with Class 1 viral membrane fusion proteins.^{6,7} Influenza viruses and coronaviruses share some similarities in their strategies to control interferon and innate immune responses.⁸ Influenza vaccination also has an indirect effect by reducing the burden of respiratory infections on the national health system and facilitating differential diagnosis of respiratory infection-related diseases.⁹ Therefore, some studies have suggested that influenza vaccination could be used as a temporary measure to reduce the severity of COVID-19,^{6,10} especially in conjunction with vaccines against SARS-CoV-2 or in populations where the SARS-CoV-2 vaccine is not yet available.

Previous studies have shown an association between influenza vaccination status and COVID-19-related morbidity, hospitalization, and mortality.^{6,10} In a cohort study, influenza vaccination was found to be associated with lower disease severity and mortality among patients with COVID-19.⁵ Modeling and hypothesis development studies also indicated a potential link between influenza vaccination and reduced rates of COVID-19 infection.^{11–14} In a study based in Italy, it was found that the higher influenza vaccination rates were, the fewer the deaths from COVID-19. With a 1% increase of influenza vaccination among adults aged >65 years, the regional death rate owing to COVID-19 decreased by 0.3450.¹⁰ By contrast, Fink and colleagues⁵ and de la Cruz Conty et al.¹⁵ did not observe an association between influenza vaccination and hospitalization and intensive care unit (ICU) admission for patients with COVID-19. Therefore, the purpose of this meta-analysis was to assess the association between previous influenza vaccination and COVID-19 on the basis of the available evidence.

METHODS

The reporting of studies included in this systematic review and meta-analysis followed the PRISMA guidelines.¹⁶ In addition, this meta-analysis was registered on March 29, 2021 in the International Prospective Register of Systematic Reviews (<https://www.crd.york.ac.uk/prospero/>, registration number: CRD42021235490).

Search Strategy

The literature search was completed before August 13, 2021 for relevant articles from the following databases: (1) PubMed, (2) Cochrane Library, (3) Web of Science, (4) Embase, (5) SinoMed, (6) China National Knowledge Infrastructure, (7) Wanfang Data Knowledge Service Platform, and (8) China Science and Technology Journal VIP Database. The relevant retrieval strategy was as follows: (*Influenza vaccination OR Influenza Vaccine OR Trivalent Influenza Vaccine OR Quadrivalent Influenza Vaccine*) AND (*COVID19 OR COVID-19 Virus Disease OR SARS-CoV-2 Infection OR Coronavirus Disease 2019*). Relevant Chinese technical terms for the Chinese databases were used to search for published articles. Furthermore, references of all relevant articles and reviews were retrieved to search for additional eligible studies. The detailed search strategy is described in the [Appendix](#) (available online).

Inclusion and Exclusion Criteria

Inclusion criteria. A first screening was performed on the basis of the title and abstract. Then, a second round of screening was performed on the basis of full text. A third screening was carried out to identify and remove papers from the same study. Studies that met the following criteria were included: (1) the exposure factor was influenza vaccine; (2) the outcome events were the infection rate of COVID-19 and hospitalization or ICU admission or death owing to COVID-19; (3) RRs or ORs or hazard ratios (HRs) and 95% CIs or data to calculate them were provided; and (4) if there were multiple publications from the same population, the study with larger sample sizes or greater information yield was selected.

Exclusion criteria. To ensure this meta analysis was scientific and reasonable, we have developed corresponding exclusion criteria. Study exclusion criteria were as follows: (1) the data were unavailable or not adequate to analyze; (2) duplicate literature; (3) abstracts only, the full text of the study was not available; (4) comments, letters to the editor, or case reports; and (5) people who received an influenza vaccine after confirming COVID-19 infection.

Data Extraction

After deleting duplicates, all abstracts and titles were filtered independently by 2 investigators to remove articles not meeting inclusion criteria. Two independent investigators extracted data from the included articles. Data extraction included first author name, year of publication, study location, study type, adjusted confounding factors, influenza vaccination status, and relevant outcome events. The raw data were also extracted, including the number of patients and relevant outcome events in the influenza vaccination group and unvaccinated group; the number of influenza vaccinations for the patient group with COVID-19 and without COVID-19; adjusted confounders; and adjusted and unadjusted RRs, ORs, or HRs with corresponding 95% CIs. Any unresolved discrepancies regarding relevant literature data extraction issues were resolved through discussion with a third investigator.

Quality Assessment

According to the Agency for Healthcare Research and Quality, the Newcastle–Ottawa Scale and 11-item Prevalence Study Quality checklist are recommended to assess the quality of the included case–control studies, cohort studies, and cross-sectional studies.¹⁷ Using

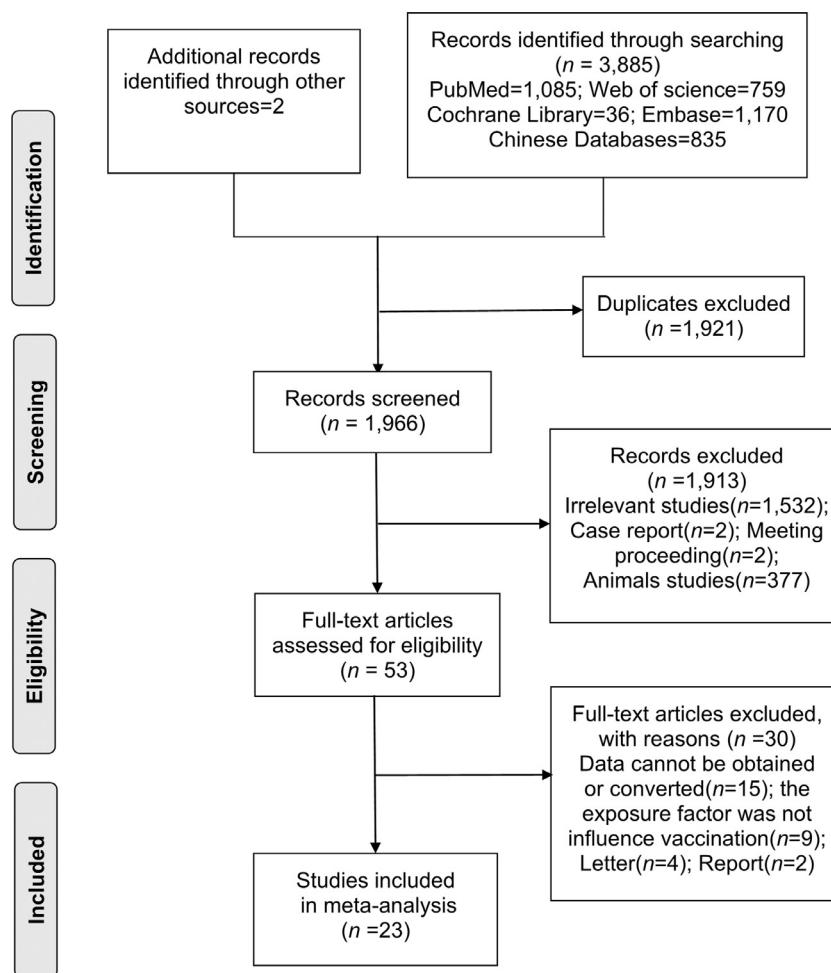


Figure 1. Flow diagram of the study search and selection process.

the Newcastle–Ottawa Scale, the quality of the included studies was rated as follows: low quality (0–3), moderate quality (4–6), or high quality (7–9). For cross-sectional studies, this study used a list of 11 items for quality assessment. The quality of the studies was assessed as follows: low quality (0–3), moderate quality (4–7), and high quality (8–11). If there were differences in the investigators’ assessment of the quality of the study, a discussion or consultation was conducted with a third investigator to reach a conclusion.

Statistical Analysis

Statistical analyses of all data were performed with Stata, version 14.0. The extracted data were used to calculate a pooled RR with 95% CI to assess the association between influenza vaccination status and the risk of COVID-19 infection, hospitalization, and death in patients with COVID-19. HRs were considered approximations of RRs.^{18,19} Where necessary, ORs were transformed into RRs with the formula: $RR = OR / ([1 - P_0] + [P_0 \times OR])$, where P_0 is the incidence of the outcome of interest in the nonexposed group.²⁰ The SE of the resulting converted RR was then determined with the following formula: $SE \log(RR) = SE \log(OR) \times \log(RR) / \log(OR)$, which could also be used to calculate the upper and lower limits of the CI by applying this formula to the upper and lower confidence limits of the adjusted OR.²¹ If the

study did not report a risk estimate for influenza vaccination, the risk estimate was calculated using raw data from influenza vaccination according to the type of study. Subgroup analyses were conducted in terms of study design, study location, whether the study adjusted for confounding factors, influenza vaccine types, and study population for the association between influenza vaccine and risk of COVID-19. Heterogeneity analysis among studies was assessed using Cochran’s Q chi-square test and I^2 statistics. If $I^2 > 50\%$, the random-effects model was used as the pooling method. Otherwise, the fixed-effects model was used.²² Meta-regression was adopted to investigate whether study characteristics explained the heterogeneity of results among studies.²³ A sensitivity analysis was conducted by omitting 1 study at a time to determine whether the omission of the study influenced the overall results.²⁴ Assessment of publication bias was quantitatively assessed by Begg’s test and Egger’s test,²⁵ and $p < 0.05$ was considered statistically significant. When the study size or sample size is small, Egger’s test is limited.²⁶

RESULTS

A total of 3,887 studies met the initial search criteria. After 3 rounds of screening, a total of 23 studies^{3,5,15,27–46}

Table 1. Associated Risks and Publication Bias Between Influenza Vaccination and the Risk of COVID-19 Infection

Subgroups	Number of studies	RR (95% CI)	I square, %	p for Egger's test	p for Begg's test
All study	16	0.83 (0.76, 0.90)	80.8	0.226	0.117
Study design					
Cohort study	8	0.82 (0.73, 0.93)	73.2	0.783	0.805
Cross-sectional study	4	0.82 (0.71, 0.94)	82.3	0.507	1.000
Case-control study	4	0.79 (0.59, 1.06)	81.8	0.226	0.174
Region					
North America	4	0.78 (0.74, 0.82)	33.0	0.145	0.174
Asia	2	0.26 (0.02, 2.78)	93.1	<0.01	0.317
Europe	10	0.86 (0.78, 0.96)	65.5	0.371	0.421
Vaccine type					
Influenza vaccine (unknown)	10	0.84 (0.77, 0.93)	69.5	0.247	0.325
Tetavalent influenza vaccine	4	0.74 (0.65, 0.84)	0.0	0.321	0.174
Trivalent influenza vaccine	2	0.89 (0.64, 1.23)	95.9	<0.01	0.317
Study population type					
General population	11	0.84 (0.77, 0.89)	73.4	0.025	0.983
Special population ^a	5	0.58 (0.34, 1.01)	86.4	0.132	0.327
Adjusted age					
Yes	11	0.86 (0.79, 0.94)	82.8	0.170	0.142
No	5	0.68 (0.53, 0.88)	80.0	0.031	0.586

Note: Boldface indicates statistical significance ($p < 0.05$).

^aSpecial population includes healthcare workers, patients with advanced cancer, and hospital employees.

met the inclusion criteria. The detailed process of literature screening is shown in Figure 1.

In this meta-analysis, 23 published articles comprising 1,037,445 participants were finalized, involving 14 cohort studies, 4 case-control studies, and 5 cross-sectional studies. A total of 12 of the 16 studies on the association between influenza vaccination and SARS-CoV-2 infection included adjusted estimates. The adjusted variables included in the studies were generally age, sex, and comorbidities, but these were not the same across studies. Patients who received their last influenza vaccine >12 months before the diagnosis of COVID-19 and those who received influenza vaccine after diagnosis of COVID-19 were not included in this study. The Newcastle-Ottawa Scale scores of included studies were ≥ 7 , and the scores of the 11-item Prevalence Study Quality checklist were ≥ 8 . Appendix Table 1 (available online) (outcome indicators were COVID-19 infection, hospitalization, ICU admission, and death) shows the detailed characteristics of the included studies.

In total, this study extracted unadjusted and adjusted RRs, HRs, or ORs from the original data for 23 studies for synthesis. Of these, 16 studies^{3,27–41} examined the association between influenza vaccination and the risk of COVID-19 infection, 7 studies^{28,30,34,40,42–44} examined the association between influenza vaccination and the risk of hospitalization in patients with COVID-19, 5 studies^{15,34,43–45} assessed the association between

influenza vaccination and the risk of ICU admission in patients with COVID-19, and 6 studies^{5,40,42,43,45,46} explored the association between influenza vaccination and the risk of death in patients with COVID-19. The results showed that influenza vaccination was associated with a reduced risk of COVID-19 infection (RR=0.83, 95% CI=0.76, 0.90, $I^2=80.8\%$). Among patients with COVID-19, those who received an influenza vaccine within 12 months before the diagnosis of COVID-19 had a lower risk of hospitalization (RR=0.71, 95% CI=0.59, 0.84, $I^2=87.7\%$). However, no association between influenza vaccination and ICU admission (RR=0.93, 95% CI=0.64, 1.36, $I^2=58.8\%$) or death (RR=0.83, 95% CI=0.68, 1.01, $I^2=90.3\%$) was observed. All of these studies adopted a random-effects model. The main results are shown in Figure 2.

A subgroup analysis of COVID-19 infection risk was also performed on the basis of the included studies. When grouped by study design, the pooled RR was 0.82 (95% CI=0.73, 0.93, $I^2=73.2\%$) for cohort studies, 0.79 (95% CI=0.59, 1.06, $I^2=81.8\%$) for case-control studies, and 0.82 (95% CI=0.71, 0.94, $I^2=82.3\%$) for cross-sectional studies. The pooled RRs differed on the basis of study location. The pooled RR was 0.78 (95% CI=0.74, 0.82, $I^2=33.0\%$) on the basis of 4 studies in North America, 0.26 (95% CI=0.02, 2.78, $I^2=93.1\%$) on the basis of 2 studies in Asia, and 0.86 (95% CI=0.78, 0.96, $I^2=65.5\%$) on the basis of 10 European studies. Considering the

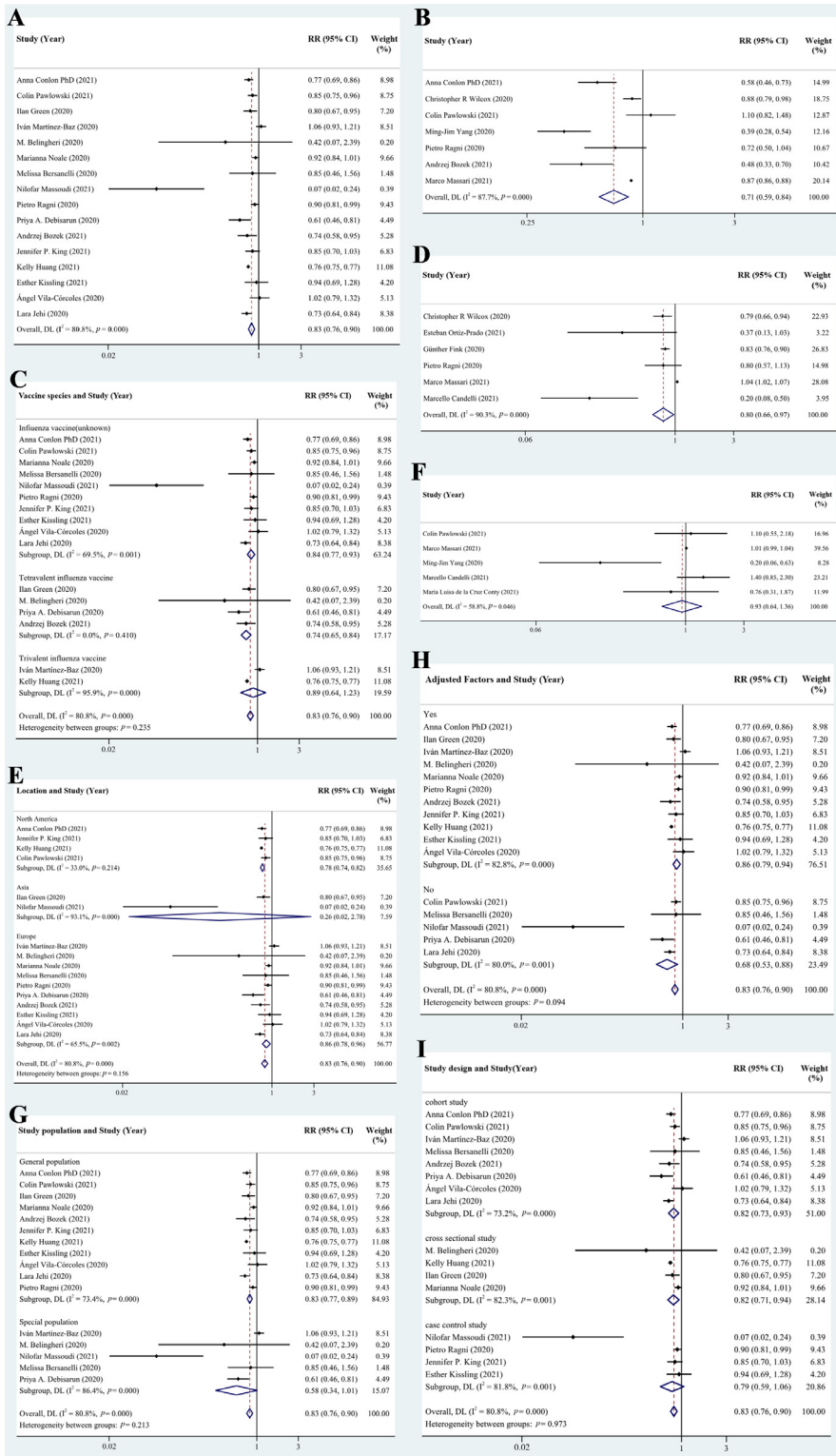


Figure 2. Forest plot of the RR with corresponding 95% CIs from studies on (A) influenza vaccine and COVID-19 infection, (B) influenza vaccine and the risk of death in COVID-19 patients, (D) influenza vaccine and the risk of ICU in COVID-19 patients, and (F) influenza vaccine and the risk of hospitalization in patients with COVID-19. Forest plots for subgroup analysis on the association between influenza vaccination and SARS-CoV-2 infection were analyzed by random-effects model: (C) grouped by study design, (E) grouped by region, (G) grouped by vaccine type, (H) grouped by study population, and (I) grouped by adjustment for age. ICU, intensive care unit.

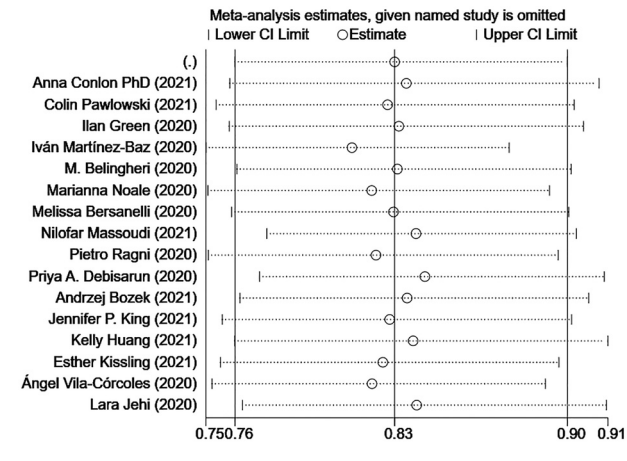


Figure 3. Sensitivity analysis of the association between influenza vaccination and COVID-19 infection by omitting studies one by one.

influence of confounding factors on the study results, this meta-analysis grouped on the basis of age adjustment, and the pooled RR values were 0.68 (95% CI=0.53, 0.88, $I^2=80.0\%$) for combined unadjusted age and 0.86 (95% CI=0.79, 0.94, $I^2=82.8\%$) for adjusted age. The heterogeneity of the studies was significantly lower after adjusting for confounders, but both groups showed that the influenza vaccine was associated with a reduced risk of COVID-19 infection. Further subgroup analysis of influenza vaccine types showed that tetravalent influenza vaccine may be associated with reduced risk of COVID-19 (RR=0.74, 95% CI=0.65, 0.84, $I^2=0.0\%$). For study population type, a statistically significant association was found in the general population, and the pooled RR was 0.83 (95% CI=0.77, 0.89, $I^2=73.4\%$). Detailed results of the subgroup analysis are summarized in [Table 1](#) and [Figure 2](#).

The heterogeneity of most studies was high, and this study used the random-effects model as the pooling method. Study heterogeneity was influenced by study area and influenza vaccine type on the basis of subgroup analysis. Possible influencing factors are the difference in population composition and economic level in the study area. However, the meta-regression did not find any factors with special effects, and [Table 1](#) shows the detailed results of the heterogeneity analysis.

Sensitivity analyses were conducted by excluding studies one by one to test the stability of the association and possible sources of statistical heterogeneity. The pooled RRs suggested that the results of this study were stable and reliable, and [Figure 3](#) shows the detailed results of the sensitivity analysis by omitting studies one by one on influenza vaccination and COVID-19 infection. In addition, no publication bias was detected by Begg's test and Egger's test. In this study, the p -value of

Begg's test was 0.226, and the p -value of Egger's test was 0.177. The funnel plot visual was asymmetric ([Appendix Figure 1](#), available online). The detailed Begg's and Egger's test results are shown in [Table 1](#).

DISCUSSION

The results of this meta-analysis indicate that influenza vaccination may be associated with a reduced risk of SARS-CoV-2 infection. In addition, influenza vaccination was associated with a reduced risk of hospitalization in patients with COVID-19, but no association was found with the risk of ICU admission and death. The lack of statistical association between influenza vaccination and ICU admission and death could possibly be owing to most patients being elderly. There may be an association between patient age and prognosis, and as age increases, these patients may have a higher risk of infection and a higher number of comorbidities, which seems to explain the statistically insignificant results of vaccinated patients entering the ICU and dying. Second, the number of original studies on ICU admission and death was small, and the potential mechanisms of association between influenza vaccination and COVID-19 disease severity need to be further explored. The results of this meta-analysis are supported by those of previous relevant studies. Some studies conducted in the U.S. and Italy have shown an inverse relationship between influenza vaccination coverage and seroprevalence of SARS-CoV-2 and hospitalization.^{10,47} Compared with unvaccinated individuals, those who agree to be vaccinated for influenza were more likely to take a proactive stance to prevent COVID-19 infection, including wearing protective masks properly, respecting social distancing, and the use of other personal protection equipment during the pandemic.

The mechanism of the association between influenza vaccination and SARS-CoV-2 infection is not yet clear. However, Lee and colleagues⁴⁸ proposed a hypothetical training immune mechanism that seems to explain the protective effect of influenza vaccine against COVID-19. Recent studies suggested that influenza vaccination could mitigate the severity of COVID-19, either by modulating the immune response or by reducing the risk of coinfections.^{5,10} The structure, binding receptor, and induced immune response pattern of the influenza vaccine are similar to those of SARS-CoV-2.^{49–52} Related studies have shown that the binding of the coronavirus spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor, its cellular binding site, leads to ACE2 downregulation. However, influenza vaccination is also able to downregulate ACE2, and this dual inhibition may have reduced the risk of the disease.^{6,53} There is also a potential for cross-reaction between influenza

virus and SARS-CoV-2, and the protective immune response induced by influenza vaccination helps to reduce the severity and transmission of COVID-19.⁴⁵ The influenza vaccine activates toll-like receptor cells on the surface of macrophages, dendritic cells, and neutrophils, keeping the immune system primed and activated before SARS-CoV-2 invasion, which is conducive to the early discovery of SARS-CoV-2.^{10,54} Immune cell counts, such as dendritic cells and megakaryocytes, are similar after vaccination compared with those before vaccination, and some of the most prominent transcriptional changes have been observed in CD14⁺ monocytes. This change strengthens the host defense against SARS-CoV-2.⁵⁵ Related studies have shown that certain vaccines lead to protection against other infections through trained immunity for up to 1 year and in the case of live vaccines for up to 5 years.⁵⁶ Furthermore, influenza vaccination itself would generate sustained immunity that overall enhances immunity against SARS-CoV-2. However, the specific mechanisms of the association between influenza vaccination and COVID-19 should be investigated further.

Subgroup analysis was performed to clarify this relationship in more detail. In the subgroup analysis of vaccine types, the tetravalent influenza vaccine may have a potential protective effect against COVID-19 infection, which is consistent with the findings of several studies.^{27,32} Compared with the trivalent influenza vaccine, the tetravalent influenza vaccine increases immunogenicity against other strains without affecting vaccine safety.⁵⁷ In an *in vitro* model, a tetravalent influenza vaccine was shown to induce trained immunity and improve immune cell responsiveness to SARS-CoV-2 stimulation. Different types of influenza vaccines use different adjuvants and induce different training immunization programs. Compared with the trivalent influenza vaccine, Debisarun et al.²⁷ found an enhanced antiviral response after quadrivalent influenza vaccination. However, the number of studies investigating the effects of different influenza vaccine subtypes on COVID-19 was relatively small, and more studies are needed to confirm the association between different influenza vaccine subtypes and COVID-19.

In the subgroup analysis based on study location, this study found a statistically significant association in the U.S. and Europe. The timing of influenza vaccination campaigns, which population groups are prioritized for vaccination, and the timing and severity of SARS-CoV-2 circulation may also have contributed to this variability. For the study design, a statistically significant association was found in the cohort study and cross-sectional study but not in the case-control study. In the subgroup analysis of the study population, statistically significant

associations were found in the general population but not in the special population, probably because of its small sample size. This study performed subgroup analyses on the basis of whether the original study adjusted for confounders. The analysis resulted in significantly less heterogeneity in this study after adjusting for confounders, but both groups showed that the influenza vaccination was associated with a reduced risk of COVID-19 infection. The higher heterogeneity of unadjusted correlates may have amplified the protective effect of influenza vaccine. However, certain groups, such as healthcare workers, are at significantly higher risk of exposure to SARS-CoV-2 than other workers, so healthcare workers are strongly recommended to receive influenza vaccination to reduce hospitalization and aid in the differential diagnosis of COVID-19,³⁸ especially in areas where the COVID-19 vaccine supply is limited.

There were some significant strengths to this meta-analysis. First, this meta-analysis includes published studies with more participants than individual cohort, case-control, or cross-sectional studies, increasing the statistical power. Second, this is the first study exploring the relationship between different influenza vaccine types and COVID-19, which provides more reliable and practical evidence for clinical practice and further research. In addition, the main confounding factors of adjustment of most studies were similar, such as age, sex, and comorbidities. Finally, this study adopted a random-effects model to calculate the pooled RRs, and sensitivity analysis showed that no individual study had an excessive influence on the pooled effect. Therefore, the results were more reasonable, stable, and convincing. This meta-analysis concluded that influenza vaccination is associated with a reduced risk of SARS-CoV-2 infection. The results of this study are the same as those of a previous meta-analysis.⁵⁸ However, in regard to improving clinical outcomes, this study obtained different results. This study's results suggest that influenza vaccination is associated with a reduced risk of hospitalization among patients with COVID-19, which may be owing to the larger number of studies this study included.

Limitations

This meta-analysis also has several limitations. First, the evidence of the correlation between influenza vaccination and COVID-19 is mainly based on observational studies. Observational studies only generate hypotheses⁵⁹; therefore, further studies with more appropriate designs are still needed to verify this study's findings. Second, the small number of studies included in this meta-analysis on influenza vaccination and the risk of hospitalization, ICU admission, and death in patients with COVID-19 lacked sufficient data to conduct

subgroup and sensitivity analyses. Third, considering the completeness of the data and inappropriate statistical methods, this study was not included in the gray literature database in the search strategy, which may have caused some bias to the findings. Fourth, owing to the limited authority of the retrieval system used in this study, literature other than Chinese and English could not be obtained. This study focused only on the findings of the literature on influenza vaccines and COVID-19 in both Chinese and English. Therefore, there may be a potential language bias in the study results. A more comprehensive study will be conducted when more literature is available in other languages. Finally, although most of the studies included in this meta-analysis controlled for the underlying confounders, this study was unable to adjust for all potential and unrecognized confounders, which may have an impact on the associations this study observed. Because of these limitations, further studies should be conducted to confirm these preliminary findings.

CONCLUSIONS

The results of this meta-analysis suggest that influenza vaccination is associated with a reduced risk of COVID-19 infection. In addition, among patients with COVID-19, those who had previously received influenza vaccine had better clinical outcomes. In the dual epidemics of influenza and COVID-19, influenza vaccination is recommended universally and should still be promoted to reduce the impacts on the healthcare system regardless of whether COVID-19 vaccination is available. However, more studies are still needed to confirm and further clarify this study's findings, and more in-depth studies are needed to explain the potential mechanisms by which influenza vaccines can reduce the risk of COVID-19 infection and disease severity.

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SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at <https://doi.org/10.1016/j.amepre.2022.02.008>.

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