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State of the Science Review

Influenza vaccination and COVID-19 infection risk and disease severity: A systematic review and multilevel meta-analysis of prospective studies

Marco Del Riccio MD [a,b,*], Saverio Caini MD PhD [c], Guglielmo Bonaccorsi MD [a], Chiara Lorini PhD [a], John Paget PhD [c,†], Koos van der Velden MD PhD [b], Claudia Cosma MD [d]

[a] Department of Health Sciences, University of Florence, Florence, Italy
[b] Department of Primary and Community Care, Radboud University Medical Centre, Nijmegen, The Netherlands
[c] Research Program Infectious Diseases in Primary Care, Netherlands Institute for Health Services Research (NIVEL), Utrecht, The Netherlands
[d] Medical School of Specialization in Hygiene and Preventive Medicine, University of Florence, Florence, Italy

Key Words:
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Background: In light of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic, the influence of influenza vaccination on the risk and severity of Coronavirus Disease 19 (COVID-19) has been a subject of debate. This systematic review and meta-analysis of prospective studies aim to assess the association between influenza immunization and the risk of SARS-CoV-2 infection and subsequent COVID-19 disease severity.

Methods: A comprehensive search of PubMed and Embase databases was performed to identify prospective studies published before March 2024. We focused on evaluating the effect of influenza vaccination on SARS-CoV-2 infection risk and severe COVID-19 outcomes, such as hospitalization and mortality. The analysis employed a multilevel random effects meta-analysis approach. The risk of bias assessment was conducted using the Newcastle-Ottawa Scale.

Results: From an initial pool of 5,863 records, 14 studies were selected for inclusion. The aggregated data yielded a summary relative risk (SRR) that showed no significant protective correlation between influenza vaccination and SARS-CoV-2 infection risk (SRR 0.95, 95% confidence interval [CI] 0.81-1.11), COVID-19-associated hospitalization (SRR 0.90, 95% CI 0.68-1.19), or COVID-19-related mortality (SRR 0.83, 95% CI 0.56-1.23).

Conclusions: This systematic review and meta-analysis, based exclusively on prospective studies, demonstrates the lack of a proven protective effect of influenza vaccination against COVID-19 and related outcomes. Our results do not support a significant protective effect of influenza vaccination against the risk or severe outcomes of COVID-19.

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BACKGROUND

Since the beginning of the Coronavirus Disease 19 (COVID-19) pandemic, the scientific community has engaged in an ongoing debate regarding the association between influenza vaccination and the risk of contracting Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or developing poor disease outcomes. In particular, prior to the development of a COVID-19 vaccine, questions arose about whether the influenza vaccine could somehow impact susceptibility to SARS-CoV-2 infection.[1,2] This question was prompted by the widespread availability of the influenza vaccine and the consideration that coronaviruses, in general, might exhibit viral interference phenomena, implying that immunization with the influenza vaccine could affect the risk of contracting other respiratory viruses.[3]

The phenomenon of viral interference gained prominence, particularly from a study conducted by Wolff et al,[4] which reported a

* Address correspondence to Marco Del Riccio, MD, Department of Health Sciences, University of Florence, Viale GB Morgagni 48, 50134 Florence (Firenze), Italy.
E-mail address: marco.delriccio@unifi.it (M. Del Riccio).
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significant association between influenza vaccine-induced viral interference and seasonal coronavirus infections. Another study hypothesized that influenza vaccination might increase the risk of contracting COVID-19 or exacerbate its severity.[5] Further subsequent research mostly focused on the opposite direction, suggesting that influenza vaccination could play a protective role against COVID-19 infection and severity,[6,7] citing among the possible explanations the activation of trained immunity.[8] On one hand, these assessments initially raised doubts as to whether the influenza vaccine should be administered; on the other hand, they suggested that the influenza vaccine could represent a possible tool to reduce infections and the severity of COVID-19 disease (at least while waiting for a COVID-19 vaccine to be available), thereby generating confusion. All of this research, in any case, might be not entirely reliable as it was mostly based on retrospective studies and, therefore, subject to potential selection bias and limitations linked to retrospective data collection, as well as a higher susceptibility to confounding variables.[9]

Trying to better understand the relationship between the influenza vaccine and the risk of becoming infected with SARS-CoV-2 or developing related poor outcomes is key for public health and vaccination strategies, so we conducted a systematic review with meta-analysis based exclusively on prospective studies in order to obtain more precise and reliable evidence on this issue. Prospective studies offer significant advantages thanks to an approach that allows for the prevention of potential errors, mitigation of selection bias, the establishment of a clear chronological sequence, and collection of accurate and updated data over time reducing the probability of errors in data collection and improving the validity of the results.

METHODS

The systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[10] The review protocol was developed a priori and registered in a recognized protocol registry (registration code: CRD42023400852).[11]

Research question

The research question was formulated to guide the systematic review process and ensure focused and relevant results. The question was developed using the Population, Exposure, Comparison, Outcome, Type of Study (PECOT) framework, which helped define the key elements of interest. The PECOT components were as follows: P = any population or group; E = vaccination against seasonal influenza; C = non-vaccination against seasonal influenza; O = infections due to SARS-CoV-2 or hospitalization or death due to COVID-19 or other COVID-19-related outcomes; T = prospective studies. In particular, with reference to the requirement for a prospective design, we included studies in which (1) vaccinated and unvaccinated subjects were enrolled and followed up to evaluate the incidence of and/or hospitalization or mortality from COVID-19 (these are prospective cohort studies), or (2) cases (COVID-19 infections, severe infections, hospitalizations, or associated deaths) and corresponding controls were enrolled prospectively from the moment the study started.

Search strategy

A comprehensive and systematic search strategy was developed to identify relevant studies. PubMed and Embase were searched from inception until March 1, 2024. The search terms and keywords were selected based on the research question, included both Medical Subject Headings terms and text words, and were adapted to each database's syntax. The reference list of relevant articles was also explored to identify further potential studies.

Study selection

The study selection process consisted of 2 stages: title/abstract screening and full-text screening. Two independent reviewers (MDR, CC) screened the titles and abstracts of identified articles based on predefined inclusion and exclusion criteria. Articles that met the inclusion criteria or were considered potentially relevant underwent full-text screening. Any discrepancies between the reviewers were resolved through discussion or arbitration by a third reviewer if necessary (SC). The inclusion criteria were specified based on the PECOT components: no further geographical or language restrictions were applied as long as an abstract in English was available to decide on inclusion. Studies published before 2020 were excluded.

Data extraction

A standardized data extraction form was developed to capture relevant information from the selected studies. Data from each included study were extracted and reviewed by the authors in a dedicated meeting to discuss and solve any discrepancies. The following data were extracted from each study, as applicable: (1) study characteristics (author(s), publication year, country); (2) study design and methodology; (3) population characteristics; (4) influenza vaccination status; (5) outcome measures (eg, SARS-CoV-2 infection and hospitalization or death due to COVID-19); (6) statistical details and adjustments; and (7) quality assessment.

The risk of bias in the included studies was assessed using the Newcastle-Ottawa Scale.[12] Two independent reviewers assessed the risk of bias in each study (CC, MDR), and any discrepancies were resolved through discussion or consultation with a third reviewer (SC). The risk of bias assessment aimed to evaluate the internal validity and overall methodological rigor of the included studies.

Statistical analysis

For each of the 3 different considered outcomes (SARS-CoV-2 infection, hospitalization, or death due to COVID-19), a 2-level random effects model was used to account for 2 sources of variance: variance between effect sizes extracted from the same study (level 1) and variance between studies (level 2). This model was used to calculate a summary measure of the effect size for each outcome, and the corresponding 95% confidence intervals (CIs) were calculated by assuming an underlying t distribution.[13] In all analyses, individuals vaccinated against influenza were compared with non-vaccinated, the latter being the reference group; therefore, a summary relative risk (SRR) of less than 1.00 means there is a lower risk of SARS-CoV-2 infection, or hospitalization or death due to COVID-19, and vice versa for SRR greater than 1.00. The I^2 statistic was utilized to quantify the degree of variability of measures of associations across studies, reflecting the extent to which genuine heterogeneity, rather than random chance, contributes to the observed differences.[14] The analyses were performed with RStudio (Version: 2023.06.1+524. Posit team (2023). Rstudio: Integrated Development Environment for R. Posit Software, PBC, Boston, MA. URL http://www.posit.co/), using the "rma.mv" function of the "metafor" package.[15] Forest plots were used to display summary statistics. Publication bias was assessed employing both funnel plots and Egger's regression test.[16] All tests were 2-sided and statistical significance was set at *P* values below .05.

RESULTS

Our search yielded a total of 5,863 non-duplicate records, of which 5,746 were excluded based on their title and abstract and the remaining 117 articles were read in full text (Supplementary File S1).

Table 1
Main characteristics of the articles included in the systematic review and meta-analysis on the effect of influenza vaccination on COVID-19 infection risk and disease severity

First author, year	Country	Study population and design	Study size	Age (years)	Type influenza vaccine and period of administration	% Vaccinated	Follow-up period	Laboratory method	Investigated outcome(s)
Bersanelli, 2020	Italy	Prospective cohort of advanced cancer patients treated with immune-checkpoint inhibitors.	955	Median 69.5, IQR 61-76	Any vaccine, season 2019-2020	50.5	February-April 2020	RT-PCR	Infection
Martínez-Baz, 2020	Spain	Prospective cohort of health care workers.	11,201	Median in the 45-54 category, min 18	Any vaccine, season 2019-2020	34.2	March-June 2020	RT-PCR or antibody rapid test	Infection
Murillo-Zamora, 2020	Mexico	Suspected COVID-19 cases aged ≤15 years followed-up for conclusive results.	1,849	Mean 5.3, max 15	Any vaccine, season 2019-2020	16.1	February-April 2020	RT-PCR	Infection
de la Cruz Conty, 2021	Spain	Consecutive case-series of pregnant women infected with SARS-CoV-2.	1,150	Median 33	Any vaccine administered during pregnancy	38.1	February-November 2020	RT-PCR	Other or mixed outcomes
Giacomelli, 2021	Italy	Prospective cohort of hospitalized COVID-19 patients.	428	Median 61, IQR 50-72	Any vaccine, season 2019-2020	25.5	February-July 2020	Laboratory method not specified	Death, other, or mixed outcomes
Arce-Salinas, 2022	Mexico	Hospital-based case-control study.	560	Mean 61.5, min 18	Any vaccine, season 2019-2020	66.6	NA	RT-PCR	Death
Giner-Soriano, 2022	Spain	General population-based prospective cohort study.	309,039	Mean 49.3	Any vaccine, season 2019-2020	21.6	March-June 2020	RT-PCR + COVID-related ICD-10 code in hospital discharge records	Hospitalization, death
Hosseini-Moghaddam, 2022	Canada	General population-based prospective cohort study.	2,191,543	Mean 75, min 66	Any vaccine, season 2020-2021	57.8	October 2020 to April 2021	RT-PCR	Infection, hospitalization, death
Kristensen, 2022	Denmark	Prospective cohort of health care workers.	35,168	Adults, not specified	Any vaccine, season 2019-2020	31.6	April-October 2020	Enzyme-linked immunosorbent assay	Infection, hospitalization
Mosaed, 2022	Iran	General population-based prospective cohort study.	3,379	Range 20-75	Any vaccine, season 2019-2020	34.7	August 2020 to February 2021	Laboratory method not specified	Infection
Russo, 2022	Italy	Prospective cohort study of subjects who were administered the first COVID-19 booster dose.	618,964	Mean 76.5 (SD 7.5)	Any vaccine, season 2021-2022	58.8	October 2021 to February 2022	Laboratory method not specified	Hospitalization
Seif-Farshad, 2022	Iran	Prospectively accrued COVID-19 cases among health care workers.	620	Mean 44.4, range 9-99	TIV or QIV, August-November 2019	28.9	March-October 2020	RT-PCR or chest CT scan	Hospitalization, death
		Prospectively accrued COVID-19 cases from the general population.	296			7.1			
Domnich, 2023	Italy	Test-negative case-control study among hospitalized SARI patients.	129	Median 77, range 18-101	Any vaccine, season 2021-2022	40.3	NA	RT-PCR	Infection
Taks, 2023	The Netherlands	Immunocompetent adults aged 60 years and older enrolled in a cohort study.	1,919	Mean 67.7	Egg-based inactivated split virion influenza vaccines (season 2020-2021)	56.1	Enrollment April 2020 to May 2021, follow-up 12 months	PCR	Infection

COVID-19, Coronavirus Disease 19; *ICD-10*, International Classification of Diseases, 10th Revision; *IQR*, interquartile range; *NA*, not available; *PCR*, polymerase chain reaction; *QIV*, quadrivalent influenza vaccine; *RT-PCR*, real-time polymerase chain reaction; *SARI*, severe acute respiratory syndrome; *SARS-CoV-2*, Severe Acute Respiratory Syndrome Coronavirus 2; *TIV*, trivalent influenza vaccine.

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Of these, 103 were removed for not matching the inclusion criteria; the main reasons for exclusion were failure to consider influenza vaccination as an exposure of interest (n = 34) and a retrospective nature (n = 46). Eventually, 14 independent studies emerged that successfully met all predefined inclusion criteria and were retained for further analysis (Table 1).[17–30]

When evaluating the risk of bias, the majority of these included studies received high scores ranging from 6 to 9, indicating a generally reliable methodology and a low likelihood of bias (Supplementary File S2).

The 14 articles included in the systematic review were published between 2020 and 2023 and mostly focused on the first 12 months following the appearance of SARS-CoV-2 (n = 10), a period during which no COVID-19 vaccine was available. Specifically, 9 manuscripts examined the impact of influenza vaccines administered during the 2019/2020 winter season. The majority of studies targeted the adult population, with only 1 manuscript, by Murillo-Zamora et al,[19] focusing on children under the age of 16. The studies varied in terms of follow-up period and duration, never exceeding a total of 12 months, as well as in sample size: the case-control study by Domnich et al[29] had the smallest sample size, with 129 included subjects, while the general population-based cohort study by Hosseini-Moghaddam et al[24] included the largest number of subjects, totaling 2,191,543. Lastly, most studies assessed the presence of SARS-CoV-2 infection using real-time polymerase chain reaction (n = 10), with 3 studies considering it as a possible alternative alongside another method.[21,25,26] Regarding the different outcomes, the study by Hosseini-Moghaddam et al reported measures of effect for all outcomes considered by this review, while other studies investigated 1 or 2 outcomes only. Finally, it should be noted that the study by Serif-Farshad reports 2 independent estimates for each of the investigated outcomes (ie, hospitalization and death), as the authors accrued COVID-19 cases in 2 different populations, namely general populations and health care workers (HCWs).

Impact of influenza vaccination on the risk of SARS-CoV-2 infection

Eight studies examined the effect of influenza vaccination on the risk of contracting SARS-CoV-2[6,17–19,24,25,29,30] (Supplementary File S3). Odds ratios and 95% CIs from each study were reported in Supplementary File S3 along with details on variables that were used for adjustment. Being vaccinated against influenza was not significantly associated with a lower risk of SARS-CoV-2 infection: in particular, the SRR comparing the risk between vaccinated and nonvaccinated subjects was 0.95 (95% CI 0.81-1.11) (Fig 1).

A substantial between-studies heterogeneity was found (I^2 = 81%). The test for funnel plot asymmetry yielded a nonsignificant *P*-value of .171, suggesting that there was no strong evidence of publication bias.

Impact of influenza vaccination on the risk of COVID-19 hospitalization

Five studies examined the effect of influenza vaccination on the risk of being hospitalized due to COVID-19[23–25,27,28] (Supplementary File S4), with the study by Seif-Farshad reporting 2 different effect estimates, 1 for the general population and 1 for a group of HCWs. Supplementary File S4 presents odds ratios/hazard ratios and corresponding 95% CIs regarding the risk of COVID-19 hospitalization associated with the influenza vaccine and provides details about the variables used for adjustment in the analyses. In the multilevel meta-analysis, no significant association was found between receiving the influenza vaccine and a reduced risk of being hospitalized due to COVID-19. Specifically, when comparing the risk between individuals who were vaccinated against influenza and those who were not, the SRR was 0.90 (95% CI 0.68-1.19), with high heterogeneity found (I^2 = 97%) (Fig 2).

Impact of influenza vaccination on the risk of dying due to COVID-19

Finally, we included 5 studies that assessed the impact of influenza vaccination on the risk of death due to COVID-19[21–24,28] (Supplementary File S5); also, for this outcome, the study by Seif-Farshad reporting 2 different effect estimates, 1 for the general population and 1 for a group of HCWs. Supplementary File S5 shows studies that analyzed the relationship between the influenza vaccine and the risk of COVID-19 hospitalization. Our multilevel meta-analysis revealed no association between those vaccinated against influenza and a reduced chance of death due to COVID-19 (SRR 0.83, 95% CI 0.56-1.23). High heterogeneity was found also in this case (I^2 = 96%) (Fig 3).

Other outcomes

Five included studies also reported other outcomes (eg, risk of symptomatic COVID-19, risk of critical presentation at admission, risk of severe or very severe COVID-19)[20,21,23–25] (Table 2).

In examining the relationship between influenza vaccination and COVID-19 outcomes, we observed substantial heterogeneity in the reported measures of association. Notably, our multilevel meta-analysis, details of which are not presented here, did not demonstrate a significant reduction in the risk of other COVID-19-related outcomes among those vaccinated for influenza.

DISCUSSION

The recent debate, both in the scientific community and in the media, focusing on the possible association between influenza vaccination and the risk of contracting COVID-19-related hospitalization and poor outcomes, was mainly influenced by systematic reviews and meta-analyses that suggested there might indeed be a protective effect of influenza vaccine against COVID-19 risk of infection and poor outcomes.[8,31–34] Our meta-analysis focused exclusively on prospective studies in order to minimize the risk of bias in the results and found no proven protective effect of influenza vaccination against the COVID-19 burden of disease.

Previous systematic reviews and meta-analyses have put forward several theories to support their conclusions, including the trained immunity activation hypothesis, according to which vaccines could induce an epigenetic reorganization of innate immunity resulting in heterologous protection.[35,36] However, this justification may be less certain in the case of influenza vaccination, as much of the research on trained immunity has focused on specific live attenuated virus vaccines such as the Bacillus Calmette-Guérin, oral polio vaccine, or measles virus vaccine.[37] At present, there are very few scientific studies examining the possible impact of trained immunity on COVID-19 from influenza vaccination.[38] It would be advantageous to conduct further large-scale studies involving the general population and monitor the results over the long term in order to obtain a more complete and accurate assessment of the trained immunity potentially induced by the influenza vaccine. Furthermore, it is important to note that all these meta-analyses mainly used retrospective studies, thus more susceptible to bias and likely to draw incorrect conclusions.

More thoroughly, the meta-analysis conducted by Kapoula and colleagues[31] suggested a lower risk of SARS-CoV-2 infection among those who had received the flu vaccine. However, this association weakened when factors such as age, sex, and comorbidities were taken into account. Another meta-analysis conducted by Wang and colleagues found a lower risk of SARS-CoV-2 infection associated with influenza vaccination but did not significantly link adverse

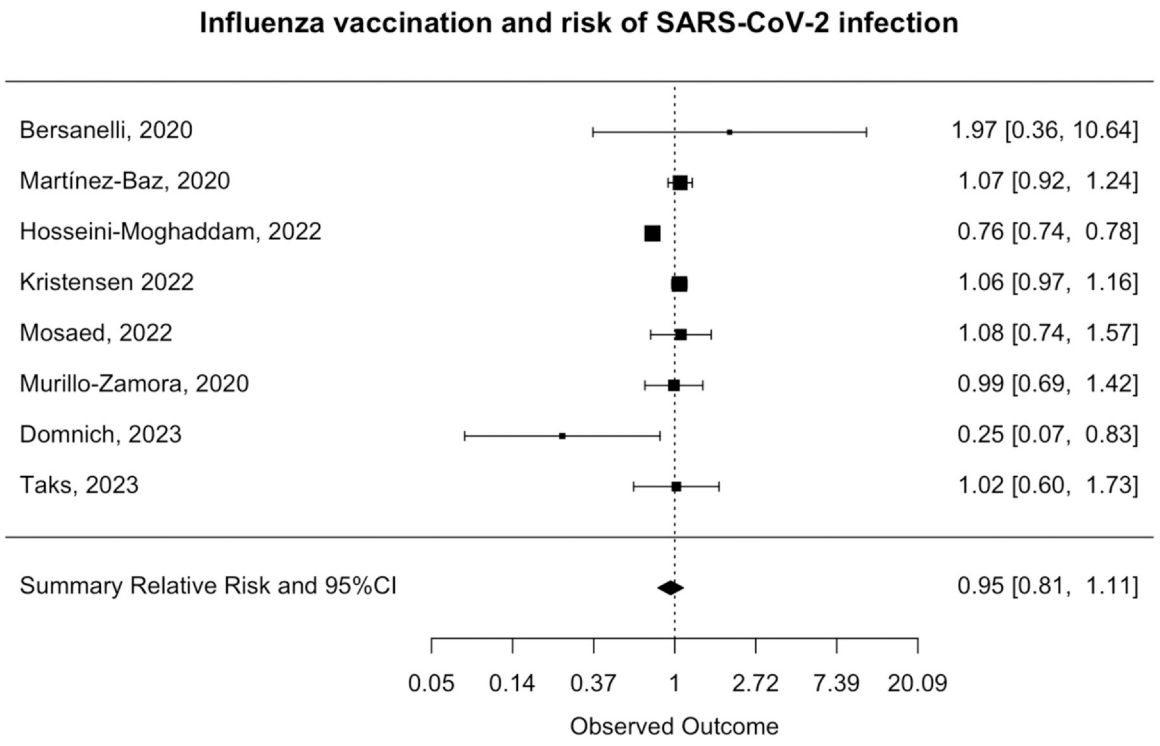

Fig. 1. Forest plot for the association between influenza vaccination and risk of SARS-CoV-2 infection. CI, confidence interval; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

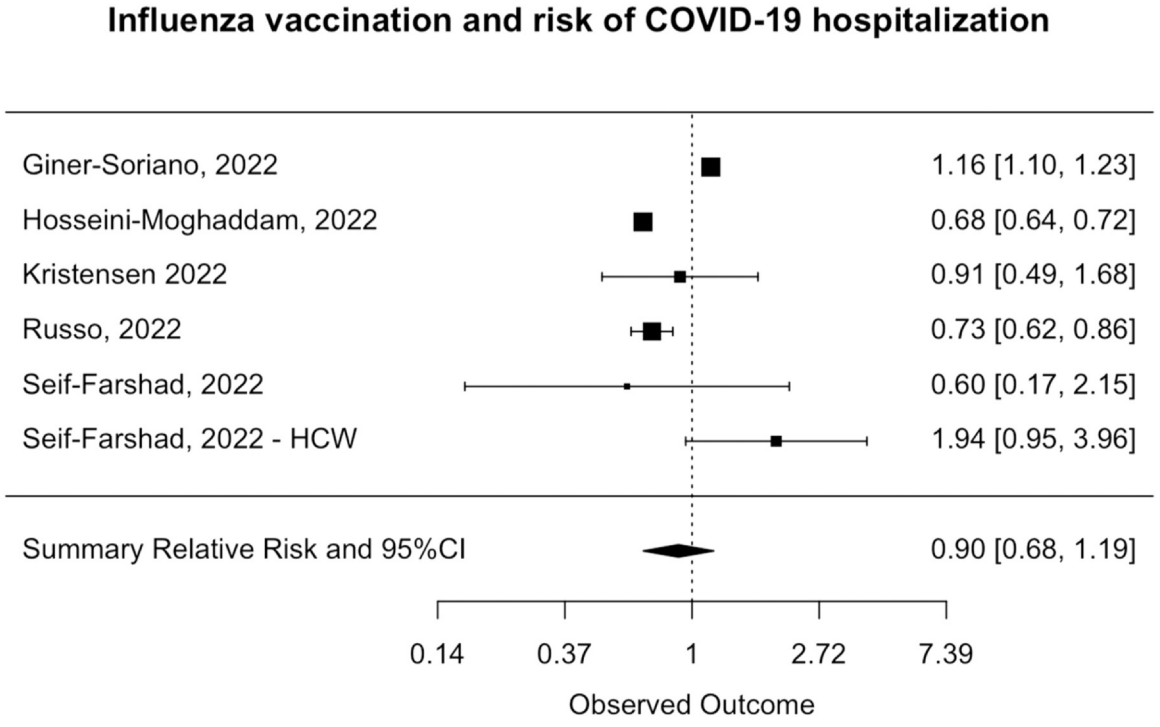

Fig. 2. Forest plot for the association between influenza vaccination and risk of COVID-19 hospitalization. COVID-19, Coronavirus Disease 19; CI, confidence interval.

outcomes such as hospitalization, admission to therapy intensive care, or death. Hypotheses were made to explain these findings, including the possibility that those who had been vaccinated against influenza might better adhere to preventive measures against COVID-19.[8,38] A further meta-analysis by Zeynali Bujani and colleagues[32] suggested that the influenza vaccine could potentially reduce the likelihood of contracting COVID-19, lower hospitalization, intensive care unit admission, and COVID-19-related mortality, which according to the authors, might be due to trained immunity. Similarly, the meta-analysis by Jiang and colleagues[33]

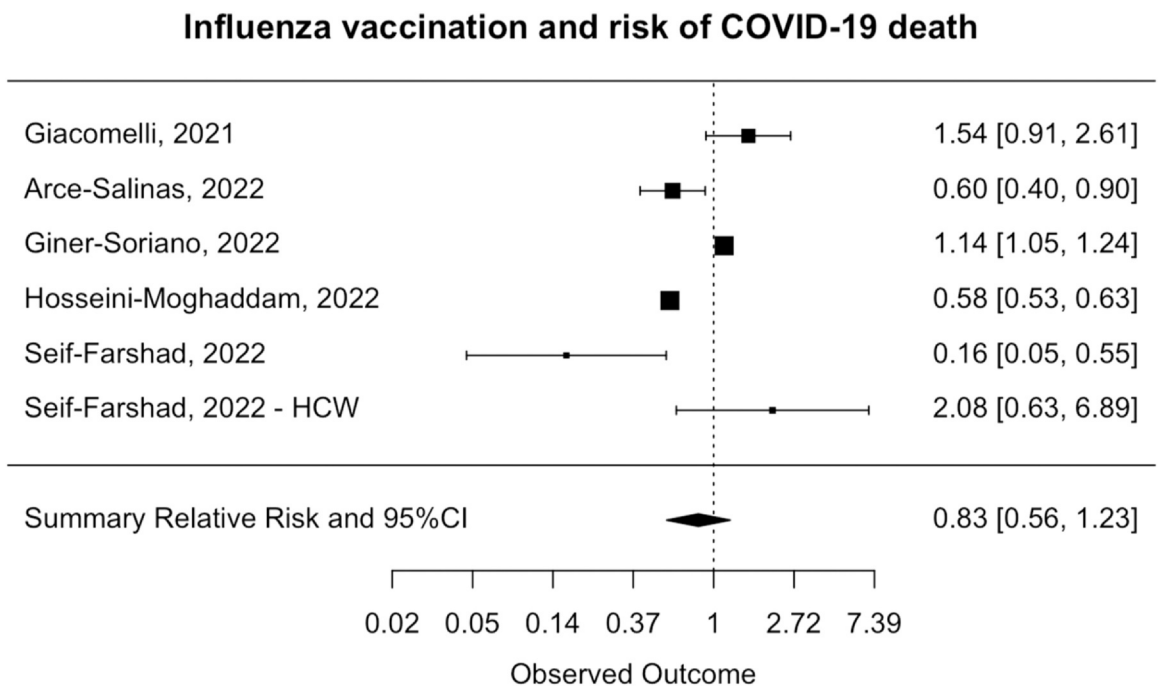

Fig. 3. Forest plot for the association between influenza vaccination and risk of death due to COVID-19. CI, confidence interval; COVID-19, Coronavirus Disease 19; HCW, health care worker.

suggested a role for influenza vaccination in reducing the risk of SARS-CoV-2 infection and disease severity. In contrast, for Su and colleagues,[34] influenza vaccination was associated with a low risk of SARS-CoV-2 infection and hospitalization, but there were no associations with the risk of admission to intensive care or death.

By and large, the results of previous meta-analyses mostly contrast with the results of our meta-analysis. A total of 14 prospective studies published between 2020 and 2023 were included in our study, and in general, influenza vaccination did not appear to confer any protective effect against the COVID-19-related burden of disease. The large variability across studies (design, enrolled population, regional testing policies, diagnostic methods, and others) accounted for the similarly large heterogeneity that we found between study-specific measures of association. Of note, however, we did not find any evidence of publication bias affecting our results.

One notable strength of our study lies in its reliance on prospective studies, which offers several advantages in assessing causality and reducing biases compared to retrospective designs. Prospective studies, by design, minimize recall and selection biases, provide more reliable temporal relationships between exposure (influenza vaccination) and outcomes (SARS-CoV-2 infection, hospitalization, poor outcomes), offer a better control of confounding variables, and enable more accurate and detailed data collection. It is important to underscore the geographic context as well: almost all the studies we included (12 out of 14) were conducted in temperate countries, where the seasonality of respiratory viruses typically coincides with the winter months. This geographical focus, coupled with the fact that the studies investigated outcomes in the immediate winter season after influenza vaccination, ensures a stronger link between vaccination and the observation of outcomes. In temperate regions, the seasonal convergence of influenza vaccination and COVID-19 outbreaks makes our findings even more relevant, as it allows for a more direct examination of the potential impact of influenza vaccination on COVID-19 outcomes during the period of heightened viral transmission. Therefore, our findings contribute to the existing corpus of evidence by offering a more

Table 2
Measures of association and corresponding 95% CIs for the association between influenza vaccination and other COVID-19 related outcomes (not vaccinated subjects are taken as reference group)

Death due to COVID-19				
First author, year	Outcome	Effect estimate	95% CI	Adjusting variables
de la Cruz Conty, 2021	Symptomatic COVID-19	OR 0.99	(0.78-1.26)	None (unadjusted OR from contingency table)
	Severe COVID-19 (pneumonia, complicated pneumonia, shock)	OR 0.95	(0.65-1.36)	None (unadjusted OR from contingency table)
	Very severe COVID-19 (complicated pneumonia, shock)	OR 0.75	(0.26-1.99)	None (unadjusted OR from contingency table)
Giacomelli, 2021	Critical presentation at hospital admission	OR 0.47	(0.24-0.94)	NA
Giner-Soriano, 2022	Pneumonia in COVID-19	OR 1.12	(1.02-1.23)	Age, sex, smoking, comorbidities, other
	Any of pneumonia, hospitalization, or death by COVID-19	OR 1.13	(1.10-1.18)	Age, sex, smoking, comorbidities, other
Hosseini-Moghaddam, 2022	Severe COVID-19 (requiring hospitalization or causing death)	OR 0.66	(0.63-0.70)	Age, comorbidities, other
Kristensen, 2022	Symptomatic COVID-19	OR 1.24	(0.97-1.59)	Age, sex, smoking, comorbidities, other

CI, confidence interval; *COVID-19*, Coronavirus Disease 19; *NA*, not available; *OR*, odds ratio.

robust and temporally accurate assessment of the relationship between influenza vaccination and COVID-19 outcomes.[9] Another strength is that, despite the statistical between-study heterogeneity, the quality assessment revealed a low risk of bias, and the main confounding adjustment factors of most studies were similar, such as age, gender, and comorbidities.

However, there were also several limitations. Firstly, only 1 of the 14 studies included in our review provided exact details regarding which influenza vaccines were administered (eg, high-dose or adjuvanted vaccines) and to which population group, and another one did specify the use of either quadrivalent influenza vaccine or trivalent influenza vaccine.[28,30] Studies were largely heterogeneous in terms of design and inclusion criteria, and in no study was the exact timing of influenza vaccination and SARS-CoV-2 infection (or other outcomes) reported. This heterogeneity, along with differences in patient characteristics and follow-up periods, explains the moderate variation in effect estimates across studies. Moreover, since our analysis primarily focuses on the 2019/2020 influenza season, capturing early variants of COVID-19, this specific focus may limit the direct applicability of our findings to newer strains and ongoing vaccination programs. Furthermore, our findings are based predominantly on data collected before the widespread introduction of COVID-19 vaccines, limiting their applicability to populations who have received these vaccines or those previously infected with COVID-19. The same reason (the studies included in our meta-analysis primarily concluded by May 2021) limits our capacity to assess the effectiveness of influenza vaccination against later circulating strains of SARS-CoV-2, potentially affecting the generalizability of our results to subsequent pandemic phases. Finally, we should also keep in mind that, in general, accurately assessing average influenza vaccine effectiveness can be complicated, as vaccines change annually, as well as the circulating strains. This variability adds a further degree of uncertainty when trying to analyze and compare the results of different studies.[39] Despite these limitations, the existing data provide a sufficiently solid basis to state that there is no evidence to claim a substantial association between receiving the influenza vaccine and the likelihood of contracting COVID-19, or experiencing hospitalization and adverse outcomes.

CONCLUSIONS

Our study may offer valuable insights into vaccination approaches for respiratory viruses. Given the concurrent circulation of influenza and SARS-CoV-2 viruses in an increasingly globalized world, coupled with an aging population and a consequent rise in comorbidities,[40,41] there are challenges to consider. With uneven access to treatments and numerous vulnerable segments of the population, the urgency of deriving robust results becomes paramount: such results are essential to inform public health policies and optimize vaccination strategy planning. Our meta-analysis showed no direct association between influenza vaccination and a reduced risk of COVID-19 outcomes, and this result reinforces the distinct importance of both influenza and SARS-CoV-2 vaccinations. Our findings highlight the importance of effective preventive strategies in public health, with the understanding that vaccines targeting specific viruses may not offer cross-protection against others. These insights hold practical implications for policymakers and health care professionals as they work to enhance public health efforts and minimize the impact of these diseases.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at doi:10.1016/j.ajic.2024.05.009.

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