Received: 5 September 2023 | Accepted: 13 December 2023

DOI: 10.1002/jmv.29343

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Vaccination against influenza viruses reduces infection, not hospitalization or death, from respiratory COVID-19: A systematic review and meta-analysis

Antonio E. Pontiroli[1] | Francesco Scovenna[1] | Valentina Carlini[2] | Elena Tagliabue[3] | Jimmy Martin-Delgado[4,5] | Lucia La Sala[2,6] | Elisabetta Tanzi[1] | Ivan Zanoni[7]

[1]Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milan, Italy

[2]Laboratory of Cardiovascular and Dysmetabolic Disease, IRCCS MultiMedica, Milan, Italy

[3]IRCCS MultiMedica, Value-Based Healthcare Unit, Milan, Italy

[4]Hospital Luis Vernaza, Junta de Beneficiencia de Guayaquil, Guayaquil, Ecuador

[5]Instituto de Investigacion e Innovacion en Salud Integral, Universidad Catolica de Santiago de Guayaquil, Guayaquil, Ecuador

[6]Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, Milan, Italy

[7]Harvard Medical School, Division of Immunology and Division of Gastroenterology, Boston Children's Hospital, Boston, Massachusetts, USA

Correspondence

Antonio E. Pontiroli, Dipartimento di Scienze della Salute, Università degli Studi di Milano, Ospedale San Paolo, 20142 Milan, Italy.
Email: antonio.pontiroli@unimi.it

Lucia La Sala, Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, Milan, Italy; IRCCS MultiMedica, 20138 Milan, Italy.
Email: lucia.lasala@multimedica.it

Funding information

National Institutes of Health; Burroughs Wellcome Fund; Fondazione Romeo ed Enrica Invernizzi; Ministero della Salute, Ricerca Corrente to IRCCS MultiMedica; NIH, Grant/Award Numbers: 2R01AI121066, 2R01DK115217, 1R01AI165505, 1R01AI170632; Old STAR Program, Grant/Award Number: CRI3888

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 and has brought a huge burden in terms of human lives. Strict social distance and influenza vaccination have been recommended to avoid co-infections between influenza viruses and SARS-CoV-2. Scattered reports suggested a protective effect of influenza vaccine on COVID-19 development and severity. We analyzed 51 studies on the capacity of influenza vaccination to affect infection with SARS-CoV-2, hospitalization, admission to Intensive Care Units (ICU), and mortality. All subjects taken into consideration did not receive any anti-SARS-CoV-2 vaccine, although their status with respect to previous infections with SARS-CoV-2 is not known. Comparison between vaccinated and not-vaccinated subjects for each of the four endpoints was expressed as odds ratio (OR), with 95% confidence intervals (CIs); all analyses were performed by DerSimonian and Laird model, and Hartung-Knapp model when studies were less than 10. In a total of 61 029 936 subjects from 33 studies, influenza vaccination reduced frequency of SARS-CoV-2 infection [OR plus 95% CI = 0.70 (0.65–0.77)]. The effect was significant in all studies together, in health care workers and in the general population; distance from influenza vaccination and the type of vaccine were also of importance. In 98 174 subjects from 11 studies, frequency of ICU admission was reduced with influenza vaccination [OR (95% CI) = 0.71 (0.54–0.94)]; the effect was significant in all studies together, in pregnant women and in hospitalized subjects. In contrast, in 4 737 328 subjects from 14 studies hospitalization was not modified [OR (95% CI) = 1.05 (0.82–1.35)], and in 4 139 660 subjects from 19 studies, mortality was not modified [OR (95% CI) = 0.76 (0.26–2.20)]. Our study emphasizes the importance of influenza vaccination in the protection against SARS-CoV-2 infection.

KEYWORDS

covid-19, epidemiology, hospitalization, infection, influenza, influenza vaccination, influenza vaccine, intensive care units, meta-analysis, mortality, sars-cov-2, vaccines

1 | INTRODUCTION

Since early reports, severe COVID-19 has been found to be more frequent in the elderly, in patients with diabetes mellitus, obesity, or pre-existing cardiovascular diseases, and it has been associated with development of cardiovascular diseases.[1–4]

Many studies focused on the similarities, differences, and relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the influenza viruses (in particular influenza A virus) that cause influenza. SARS-CoV-2 and influenza share some aspects of pulmonary symptomatology[5–7] and, in the case of co-infection with these two viruses, the prognosis of COVID-19 has been shown to be worse.[8–16]

During the COVID-19 pandemic, a significant reduction of influenza cases has been observed worldwide,[17–23] likely as a result of the social distance measures adopted to contain the spread of SARS-CoV-2[24,25]; in addition, influenza vaccination has been strongly recommended,[26] mainly to avoid SARS-CoV-2 and influenza virus co-infections. It is of particular interest whether influenza vaccination directly affects the severity of COVID-19. Previous epidemiological studies performed in 2020 in Italy, a country highly affected by the first wave of COVID-19, have shown that influenza vaccination was associated with a lower rate of SARS-CoV-2 infection and with lower mortality.[27–30] A systematic review of October 2020 focused on the possible association between influenza vaccination and SARS-CoV-2 infection confirmed that, in the majority of the 12 studies considered, influenza vaccination was associated with a lower rate of infection and lower severity of COVID-19.[31] Nevertheless, these findings were only partially confirmed in two more recent meta-analyses, performed in 13 and 23 studies, respectively.[32,33] These latter meta-analyses showed that influenza vaccination was associated with a reduced risk of infection and hospitalization, but that influenza vaccination did not significantly affect the admission to intensive care units (ICU) or the death rate. These somewhat contrasting data give a potent mandate to extend the analysis on the association between influenza vaccination, SARS-CoV-2 infection, and COVID-19 severity.

Beside influenza vaccination, other vaccines, such as the BCG[34,35] or pneumococcal[36] vaccine, have been evaluated for their efficacy in reducing the SARS-CoV-2 infection and/or disease severity, yielding contrasting results. Overall, as of today, no consensus has been reached about the effects of influenza vaccination on the infection with SARS-CoV-2.

The aim of this study is to understand how influenza vaccination affects COVID-19 development and severity. To achieve this goal, we performed a meta-analysis of all available studies that took into consideration the association between influenza vaccination and SARS-CoV-2 infection, as well as the association between influenza vaccination and hospitalization, admission of infected patients to ICU, and mortality. Notably, at sensitivity analysis, we also took into consideration five different groups of individuals: (i) health care workers; (ii) the general population; and special populations such as (iii) elderly individuals; (iv) poor health individuals (subjects at high-risk of influenza complications, kidney transplant patients, advanced-cancer patients); (v) pregnant women. Our analyses demonstrate that influenza vaccination reduces the frequency of SARS-CoV-2 infection and the admission to ICU, but it has only a small effect on the severity of COVID-19, as shown by frequency of hospital admission and, above all, mortality.

2 | MATERIALS AND METHODS

2.1 | Search strategy and inclusion criteria

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[37] Eligible studies were prospective and retrospective studies, both cohort and case-control studies reporting infection in influenza vaccinated and not-vaccinated subjects; in addition, eligible studies were those reporting hospitalization, admission to ICU and mortality in influenza vaccinated and not-vaccinated subjects. Three authors (A. E. P., F. S., and L. C.) independently searched relevant literature in databases including PubMed, Embase, and Cochrane Library from inception until January 31, 2023. The following keywords were used for disease and intervention: Influenza vaccine or Flu Vaccine or Influenza vaccination or Flu vaccination, and COVID-19 or SARS-CoV-2. The title and abstracts written in English language were reviewed to recognize eligible studies. Additional studies were also manually searched through the references cited in reviews. If the results of one study were reported in more publications, only the most recent and complete data were included in analysis. When required, authors of the studies were also contacted by mail to obtain more details. The following studies were excluded: descriptive studies, editorials, review articles, systematic reviews and meta-analyses, case reports, and studies that did not provide risk ratios or effect sizes. Decisions on trials to include were taken by the authors (A. E. P., F. S., and L. C.), and disagreements were resolved by discussion. The reason for exclusion of other trials was specified (lack of details, no controls, Figure 1). In total: 51 studies, 33 studies for infection (with 37 comparison arms),[38–70] 14 studies (with 14 comparison arms) for hospitalization,[43,46,53,54,57,69,71–78] 11 studies (with 11 comparison arms) for admission to ICU,[42,53,54,73,77–79] and 19 studies (with 20 comparison arms) for mortality[43,53,57,61,69,75–78,80–88] fulfilled the inclusion criteria. Tables 1A,B,C,D show details of studies included in this meta-analysis. The protocol of the meta-analysis has been registered (Prospero, CRD42023400802). The following data were extracted: authors, year of publication, country, type of study, mean age of participants. For each group additional items were extracted: population (kind of subjects), method of diagnosis, season of vaccination, date of event, distance in months between vaccination and event, kind of vaccine employed.

2.2 | Quality assessment

Quality of reports was assessed independently by reviewers according to Newcastle-Ottawa Quality Assessment Scale (NOS) for Cohort Studies.[89] The NOS scale is based on a "star system" in which a study is judged from three broad perspectives: study group selection, group comparability, and ascertaining the outcome of interest. The variables

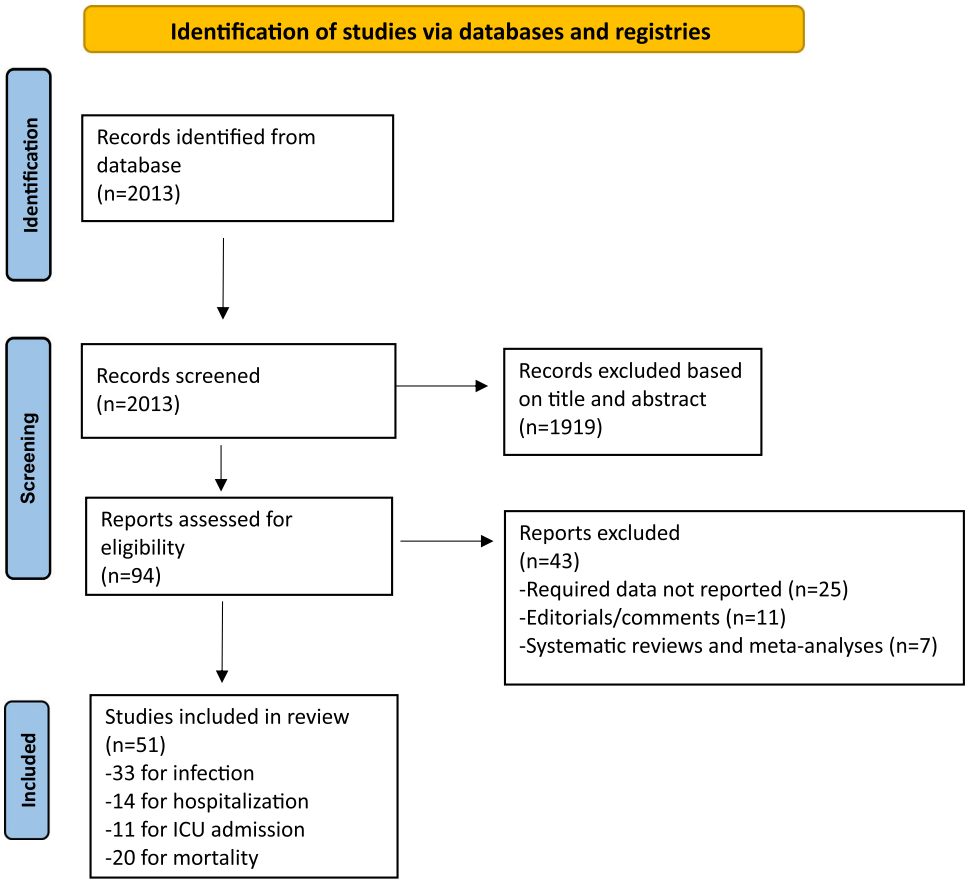

FIGURE 1 Flow-chart of the analysis performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA). After screening of literature according to search terms, most papers were excluded for reasons indicated in the squares.

considered are: risk of bias linked to the selection of participants, confounding variables, performance, detection and measurement of exposure, attrition and reporting biases. Since there is not yet a validated version of the NOS for cross-sectional studies, a specially designed scale was used to evaluate them. Disagreement for the quality assessment was resolved by discussion. A score was eventually built, classifying the research articles as poor, intermediate, or good quality, based on the number of the above criteria available for each publication. The NOS score of each study is reported in Tables 1A–D.

2.3 | Statistical analysis

Comparison between Flu-vaccinated and not-vaccinated subjects for each of the four endpoints (frequency of infection, hospitalization, admission to ICU, and mortality) was expressed as odds ratio (OR), with 95% confidence intervals (CIs); all analyses were performed by a random-effects model according to DerSimonian and Laird.[90] When studies were ≤10, the Hartung-Knapp model was used to confirm analysis.[91] Heterogeneity was assessed through Q and I^2 statistics for each comparison, and potential sources of heterogeneity were discussed where appropriate.[92] Heterogeneity was considered statistically significant for a $p < 0.05$. Sensitivity analyses were performed to evaluate sub-group effects, as well as to evaluate distance of vaccination to the event of interest (be it frequency of infection, hospitalization, admission to ICU, and mortality), and to evaluate the effect of different kinds of vaccine, when available. Through meta-regression, we evaluated the possible role of several patients' and study characteristics on the frequency of endpoints. This was done independently of statistically significant heterogeneity. The dependent variable was the frequency of the event of interest (be it frequency of infection, hospitalization, admission to ICU, and mortality). The role of each covariate in heterogeneity was expressed by Wald test estimated by the meta-regression. The following covariates were included in the meta-regression analysis: number of subjects enrolled, age, kind of study (prospective or retrospective), distance of vaccination to the event of interest, method for diagnosis, kinds of vaccine, quality of studies (NOS). Meta-regression was performed considering all studies together. In a secondary analysis, we also evaluated the existence of a potential publication bias, that means the tendency of authors and editors to publish studies in which the experimental results achieved statistical significance, more favorably than in studies in which the results were not significant, which would ultimately introduce bias into the overall published literature.[93] Funnel-plot asymmetry was evaluated by using the Egger's test for small study effects through the meta-bias routine.[94] All statistical analyses were performed by Stata 17 (Stata Corporation) for MacIntosh.

TABLE 1A Studies evaluating the association between influenza vaccination and SARS-CoV-2 infection.

Study	Year	country	Kind of study	Sample size	Mean age	Population	Method for diagnosis	Vaccine	Vaccination season	NOS
Jehi[38]	2020	US	PC	11 672	Nd	General	RT-PCR	Nd	2019–2020	8
Vila-Corcoles[39]	2020	Spain	RC	1547	65.8	age > 50	RT-PCR	Nd	2019–2020	7
Caban-Martinez[40]	2020	US	CS	203	Nd	Fireworkers and nurses	IgG and IgM	Nd	2019–2020	5
Noale[41]	2020	Italy	CS	6680	44.2 and 70.8 (2 cohorts)	Age < and >65 (2 cohorts)	RT-PCR	Nd	2019–2020	6
Caratozzolo[42]	2020	Italy	RC	848	79.7	Dementia	RT-PCR and antigenic	Nd	2019–2020	5
Zein[43]	2020	US	RC	13 220	55.4	General	Nd	Inactivated 4 v	2019–2020	7
Martinez-Baz[44]	2020	Spain	RC	9745	Nd	Healthworkers	RT-PCR and antigenic	Inactivated 3 v	2019–2020	7
Bersanelli[45]	2020	Italy	PC	955	69.5	Cancer	RT-PCR	Nd	2019–2020	6
Ragni[46]	2020	Italy	CC	17 608	Nd	General	RT-PCR	Inactivated 4 v, 3 v with adjuvant	2019–2020	7
Belingheri[47]	2020	Italy	CS	3 520	Nd	Healthworkers	RT-PCR	Inactivated 4 v	2019–2020	7
Green[48]	2020	Israel	CS	22 563	39.2	General	RT-PCR	Inactivated 4 v	2019–2020	8
Massoudi[49]	2021	Iran	CC	261	39.5	Healthworkers	RT-PCR	Inactivated 4 v	2019–2020	6
Rivas[50]	2021	US	RC	6087	41.4	Healthworkers	IgG	Nd	2019–2020	6
Kissling[51]	2021	Europe	CC	1887	Nd	General	RT-PCR	Nd	2019–2020	6
Erismis[52]	2021	Turkey	RC	203	Nd	Healthworkers	Nd	Nd	2019–2020	5
Conlon[53]	2021	US	RC	27 201	47.2	General	RT-PCR	Nd	2019–2020	8
Pawlowski[54]	2021	US	RC	25 582	74.6	General	RT-PCR	HD, IN, 4 v	2019–2020	8
Fernandez-Prada[55]	2021	Spain	CC	188	64.6	General	RT-PCR	Nd	2019–2020	7
Kowalska[56]	2021	Poland	CS	5376	43.9	General	IgG and IgM	Inactivated 4 v	2019–2020	6
Bozek[57]	2021	Poland	RC	2303	53.7	Age > 40 and <60	RT-PCR	Inactivated 4 v	2019–2020	8
Huang[58]	2021	US	CS	55 667 977	Nd	Age > 65	Nd	HD, 3 v with adjuvant	2019–2020	7
King[59]	2021	US	CC	1736	38	General	RT-PCR	Nd	2019–2020	8
Alkathlan[60]	2021	SA	CS	424	Nd	Healthworkers	Nd	Nd	2019–2020	4
Xiang[61]	2021	UK	PC	30 835	Nd	General	RT-PCR	Nd	2019–2020	8
Pépin[62]	2021	Canada	CC	2985	54.5	Healthworkers and General (2 cohorts)	RT-PCR	Inactivated	2019–2020	6
Debisarun[63]	2021	Netherl	RC	17 755	Nd	Healthworkers	RT-PCR	Inactivated 4 v	2019–2020 and 2020–2021	6

TABLE 1A (Continued)

Study	Year	country	Kind of study	Sample size	Mean age	Population	Method for diagnosis	Vaccine	Vaccination season	NOS
Shosha[64]	2022	Bahrain	RC	3563	40.6	Healthworkers	RT-PCR	Live attenuated 4 v	2019–2020	7
Domnich[65]	2022	Italy	RC	2561	46.8	Healthworkers	RT-PCR	Inactivated 4 v	2020–2021	6
Satir[66]	2022	Turkey	PC	232	44.5	Kidney transplant	RT-PCR	Inactivated 4 v	2019–2020	7
Alòs[67]	2022	Spain	RC	429 537	Nd	High risk people	RT-PCR and antigenic	Inactivated 3 v/4 v	2020–2021	7
Van Laak[68]	2022	Ned	PC	223 580	63.8	High risk people	GP	Nd	2019–2020	7
Hosseini-Mogaddham[69]	2022	Canada	PC	4 471 348	Nd	Age > 66	RT-PCR	Nd	2019–2020 and 2020–2021 (2 cohorts)	7
Tayar[70]	2023	Qatar	CC	2576	Nd	Healthworkers	RT-PCR	Inactivated 4 v	2020–2021	7

Note: Authors (and references), year of publication, country, kind of study, sample size, mean age, population studied, method for diagnosis, kind of vaccine, vaccination season, and Newcastle Ottawa Scale (NOS) are reported.

Abbreviations: CC, Case Control; CS, Cross Sectional; H, high dosage; IN, intranasal; Ned, Netherlands; nd, not determined; PC, Prospective Cohort; RC, Retrospective Cohort; SA, Saudi Arabia; UK, United Kingdom; US, United States; 3 v, trivalent; 4 v, tetravalent.

3 | RESULTS

Based on 33 papers analyzed, total subjects evaluated for the effect of influenza vaccination on SARS-CoV-2 infection were 61 029 936, of which 15 950 169 were vaccinated, and 45 079 687 were not vaccinated. Vaccinated subjects received one of the following influenza vaccines: i) tetravalent (n = 152 924); ii) trivalent (n = 12 900 000); iii) trivalent/tetravalent (n = 198 499). For 2 532 262 subjects it was not possible to determine the type of influenza vaccine that was administered. All the subjects taken into consideration did not receive any anti-SARS-CoV-2 vaccine, although we cannot exclude previous infections with SARS-CoV-2 in the populations analyzed.

Influenza vaccination was associated with a reduced frequency of SARS-CoV-2 infection, as shown in Table 2A and Figure 2. When sub-group analyses were performed, we found that the effect of influenza vaccination was significant in health care workers, in the general population, in elderly subjects, and in poor health individuals, when all the studies were considered together (Table 2A and Supporting Information S1: Figure 1). Nevertheless, more restrictive models (Hartung & Knapp) show a more conservative effect (Table 2A). Vaccination took place between October and December, with no difference between different populations, and the distance was around 5 months (1–11 months) between vaccination and infection (5.1 ± 2.35 months, hospitalization (5.0 ± 1.41 months), admission to ICU (5.0 ± 1.33 months), and death (5.5 ± 1.37 months), with no differences between various populations; in sensitivity analysis, the time distance between influenza vaccination and the positivity to SARS-CoV-2 was also of relevance in all studies, as well in health care workers and in the general population (Table 2A and Supporting Information S1: Figure 2). Moreover, the protection against SARS-CoV-2 infection in individuals that received the tetravalent influenza vaccine (Table 2A, Supporting Information S1: Figure 3, Supporting Information S1: Figure 4), but not other types of influenza vaccines (Supporting Information S1: Figure 5), was significant in all studies, both in health care workers and in the general population. In all studies, a short distance from influenza vaccination and the use of tetravalent vaccine appeared to exert a synergistic effect against infection with SARS-CoV-2 (Table 2A, Supporting Information S1: Figure 6).

Based on 14 papers analyzed that reported the information, total subjects evaluated for effect of influenza vaccination on hospitalization were 4 737 328, of which 2 602 803 vaccinated and 2 134 525 not vaccinated. Influenza vaccination was not associated with effect on hospitalization of infected subjects, as shown in Table 2B, Figure 3. Only two studies, one of which was performed in elderly, showed a significant effect.

Based on 11 studies analyzed that reported the information, total subjects evaluated for effect of influenza vaccination on ICU admission were 98 174, of which 44 553 were vaccinated and 53 621 were not vaccinated. Influenza vaccination was associated with a significant reduction of ICU admission, as shown in Table 2C and Figure 4. The effect was significant in all studies together, in pregnant women and in

TABLE 1B Studies evaluating the association between influenza vaccination and hospitalization due to COVID-19.

study	year	country	Kind of study	Sample size	Mean age	Population	Method for diagnosis	Vaccine	Vaccination season	NOS
Ilic[41]	2020	Serbia	RC	107	39.1	Healthworkers	RT-PCR	3 v, 4 v	2019–2020	7
Zein[43]	2020	US	RC	13 220	55.4	General	Nd	Inactivated 4 v	2019–2020	7
Ragni[46]	2020	Italy	CC	17 608	Nd	General	RT-PCR	4 v, 3 v with adjuvant	2019–2020	7
Conlon[53]	2021	US	RC	27 201	47.2	General	RT-PCR	Nd	2019–2020	8
Pawlowski[54]	2021	US	RC	25 582	74.6	General	RT-PCR	HD, recombinant 4 v, IN	2019–2020	8
Bozek[57]	2021	Poland	RC	2303	53.7	General	RT-PCR	Inactivated 4 v	2020–2021	8
Hosseini-Mogaddham[69]	2022	Canada	PC	4 471 348	Nd	Age > 66	RT-PCR	Nd	2019–2020 and 2020–2021 (2 cohorts)	7
Gobbato[72]	2020	Italy	RC	3010	60.0	General	Nd	Nd	2019–2020	7
Yang[73]	2021	US	RC	2005	43.6	General	Nd	Nd	2019–2020	8
Wilcox[74]	2021	UK	RC	6921	52.4	General	RT-PCR	Nd	2019–2020	8
Greco[75]	2021	Italy	RC	952	71.5	General	RT-PCR	Nd	2019–2020	8
Massari[76]	2021	Italy	PC	115 945	Nd	General	RT-PCR	Nd	2019–2020	8
Taghioff[77]	2021	US	RC	75 754	52.6	General	Nd	3 v, IN, Inactivated	2019–2020 and 2020–2021	8
Giner-Soriano[78]	2022	Spain	RC	309 039	49.3	General	RT-PCR or suspected cases	Nd	2019–2020	8

Note: Authors (and references), year of publication, country, kind of study, sample size, mean age, population studied, method for diagnosis, kind of vaccine, vaccination season, and Newcastle Ottawa Scale (NOS) are reported.

Abbreviations: CC, Case Control; CS, Cross Sectional; H, high dosage; IN, intranasal; Ned, Netherlands; nd, not determined; PC, Prospective Cohort; RC, Retrospective Cohort; SA, Saudi Arabia; UK, United Kingdom; US, United States; 3 v, trivalent; 4 v, tetravalent.

TABLE 1C Studies evaluating the association between influenza vaccination and admission to intensive care unit due to COVID-19.

Study	Year	Country	Kind of study	Sample size	Mean age	Population	Method for diagnosis	Vaccine	Vaccination season	NOS
Zein[43]	2020	US	RC	13 220	55.4	General	Nd	4 v	2019–2020	7
Conlon[53]	2021	US	RC	27 201	47.2	General	RT-PCR	Nd	2019–2020	8
Pawlowski[54]	2021	US	RC	25 582	74.6	General	RT-PCR	HD, 4 v, IN	2019–2020	8
Yang[73]	2021	US	RC	2005	43.6	General	Nd	Nd	2019–2020	8
Taghioff[77]	2021	US	RC	75 754	52.6	General	Nd	3 v, IN, inactivated	2019–2020 and 2020–2021	8
De La Cruz Conty[79]	2021	Spain	PC	1150	33.0	Pregnant women	RT-PCR	Nd	2019–2020	7
Candelli[80]	2021	Italy	RC	602	60.6	General	RT-PCR	Nd	2019–2020	8
Umasabor-Bubu[81]	2021	US	RC	588	68.4	General	RT-PCR	Nd	2019–2020	7
Fernandez Ibanez[82]	2021	Spain	RC	410	70.7	General	RT-PCR	Nd	2019–2020	8
Kline[83]	2021	US	RC	149	58.1	General	RT-PCR	Nd	2019–2020	8
Paganoti[84]	2022	Brasil	RC	3119	30.1	Pregnant women	RT-PCR or antigenic	Nd	2020–2021	7

Note: Authors (and references), year of publication, country, kind of study, sample size, mean age, population studied, method for diagnosis, kind of vaccine, vaccination season, and Newcastle Ottawa Scale (NOS) are reported.

Abbreviations: CC, Case Control; CS, Cross Sectional; H, high dosage; IN, intranasal; Ned, Netherlands; nd, not determined; PC, Prospective Cohort; RC, Retrospective Cohort; SA, Saudi Arabia; UK, United Kingdom; US, United States; 3 v, trivalent; 4 v, tetravalent.

TABLE 1D Studies evaluating the association between influenza vaccination and mortality due to COVID-19.

Study	year	country	Kind of study	Sample size	Mean age	Population	Method for diagnosis	Vaccine	Vaccination season	NOS
Zein[43]	2020	US	RC	13 220	55.4	General	Nd	Inactivated 4 v	2019–2020	7
Conlon[53]	2021	US	RC	27 201	47.2	General	RT-PCR	Nd	2019–2020	8
Bozek[57]	2021	Poland	RC	2303	53.7	General	RT-PCR	Inactivated 4 v	2020–2021	8
Xiang[61]	2021	UK	PC	27 147	Nd	General	RT-PCR	Nd	2019–2020	8
Hosseini-Mogaddham[69]	2022	Canada	PC	4 471 348	Nd	Age > 66	RT-PCR	Nd	2019–2020 and 2020–2021	7
Wilcox[74]	2021	UK	RC	6921	52.4	General	RT-PCR	Nd	2019–2020	8
Greco[75]	2021	Italy	RC	952	71.5	Age > 66	RT-PCR	Nd	2019–2020	8
Massari[76]	2021	Italy	PC	115 945	Nd	General	RT-PCR	Nd	2019–2020	8
Taghioff[77]	2021	US	RC	75 754	52.6	General	Nd	3 v, IN, inactivated	2019–2020 and 2020–2021	8
Giner-Soriano[78]	2022	Spain	RC	309 039	49.3	General	RT-PCR or suspected cases	Nd	2019–2020	8
Candelli[80]	2021	Italy	RC	602	60.6	General	RT-PCR	Nd	2019–2020	8
Umasabor-Bubu[81]	2021	US	RC	588	68.4	Age > 66	RT-PCR	Nd	2019–2020	7
Fernandez Ibanez[82]	2021	Spagna	RC	410	70.7	Age > 66	RT-PCR	Nd	2019–2020	8
Kline[83]	2021	US	RC	149	58.1	General	RT-PCR	Nd	2019–2020	8
Paganoti[84]	2022	Brasil	RC	3119	30.1	Pregnant women	RT-PCR or antigenic	Nd	2019–2020 and 2020–2021	7
Azzi[85]	2020	US	PC	229	59.0	Kidney transplant	RT-PCR and IgG	Nd	2019–2020	5
Ortiz-Prado[86]	2020	Ecuador	CC	9468	44.9	General	RT-PCR	Nd	2019–2020	7
Angulo-Zamudio[87]	2021	Mexico	RC	1737	46.8	General	RT-PCR	Nd	2019–2020	8
El-Qutob[88]	2021	Spain	RC	255	68.4	Age > 66	RT-PCR	Nd	2019–2020	7

Note: Authors (and references), year of publication, country, kind of study, sample size, mean age, population studied, method for diagnosis, kind of vaccine, vaccination season, and Newcastle Ottawa Scale (NOS) are reported.

Abbreviations: CC, Case Control; CS, Cross Sectional; H, high dosage; IN, intranasal; Ned, Netherlands; nd, not determined; PC, Prospective Cohort; RC, Retrospective Cohort; SA, Saudi Arabia; UK, United Kingdom; US, United States; 3 v, trivalent; 4 v, tetravalent.

hospitalized subjects, when the two latter groups were considered together, and in the general population when age was <50 years; the effect was even greater when pregnant women, hospitalized subjects, and general population with age < 50 years were combined Table 2C, Supporting Information S1: Figure 7).

Based on 19 studies that reported the information, total subjects evaluated for effect of influenza vaccination on mortality were 4 139 660, of which 2 703 073 were vaccinated and 1 436 587 were not vaccinated. Influenza vaccination was not associated with a significant effect on mortality, as shown in Table 2D and Figure 5; an effect was only observed in one study in pregnant women, and in one study in which the distance from influenza vaccination and SARS-CoV-2 infection was <4 months; however, combination of the two studies did not show any effect.

Newcastle Ottawa Scales (NOSs) were generally high, indicating a good quality of the studies. No significant meta-regression appeared for any of the endpoints (frequency of infection, hospitalization, admission to ICU, and mortality) and patients' and study characteristics. No publication bias appeared for any of the comparisons. However, heterogeneity was virtually always very high, as reported in Tables 2A–D.

4 | DISCUSSION

In 2020, when vaccines against SARS-CoV-2 were not yet available, preventive measures such as face masks and social distancing were the only remedies to combat COVID-19. A nonspecific protection against

TABLE 2A Effect of influenza vaccination on SARS-CoV-2 infection in all studies and in different populations.

	Dersimonian	Hartung & Knapp	Studi	Cochran Q, *p*
All studies	**0.70 (0.65–0.77)**		37	1486, *0.001*
Distance < 7 months	**0.71 (0.64–0.78)**		29	1217, *0.001*
Any vaccine	**0.71 (0.62–0.80)**		19	893, *0.001*
4 v Vaccine	**0.60 (0.48–0.74)**		15	264, *0.001*
4 v.1 Vaccine	**0.57 (0.49–0.67)**		13	69, *0.001*
4 v Vaccine and distance < 7 months	**0.58 (0.48–0.70)**	**0.51 (0.29–0.87)**	10	65, *0.001*
4 v.1 Vaccine and distance < 7 months	**0.56 (0.45–0.68)**	**0.47 (0.26–0.86)**	9	62, *0.001*
Health care workers	**0.59 (0.43–0.81)**		13	115, *0.001*
Distance < 7 months	**0.57 (0.40–0.82)**		11	101, *0.001*
Any vaccine	**0.55 (0.37–0.81)**	0.50 (0.23–1.06)	8	105, *0.001*
4 v Vaccine	**0.50 (0.36–0.70)**	**0.43 (0.20–0.95)**	7	42, *0.001*
4 v.1 Vaccine	**0.46 (0.32–0.65)**	**0.38 (0.15–0.93)**	6	37, *0.001*
4 v Vaccine and distance < 7 months	**0.51 (0.35–0.75)**	0.43 (0.17–1.09)	6	39, *0.001*
4 v.1 Vaccine and distance < 7 months	**0.45 (0.30–0.69)**	0.36 (0.12–1.11)	5	35, *0.001*
General population	**0.77 (0.62–0.95)**		13	297, *0.001*
Distance < 9 months	**0.78 (0.63–0.98)**		12	291, *0.001*
Any vaccine	0.69 (0.47–1.01)	**0.69 (0.48–0.98)**	6	195, *0.001*
4 v Vaccine	**0.60 (0.54–0.66)**	**0.60 (0.51–0.71)**	5	5.4, NS
4 v.1 Vaccine	**0.60 (0.54–0.65)**	**0.60 (0.51–0.71)**	5	5.4, NS
4 v Vaccine and distance < 7 months	**0.56 (0.51–0.62)**	**0.56 (0.50–0.64)**	3	0.29 NS
4 v.1 Vaccine and distance < 7 months	**0.53 (0.51–0.62)**	**0.56 (0.50–0.64)**	3	0.29, NS
Elderly people	**0.79 (0.71–0.88)**	0.85 (0.60–1.21)	5	179, *0.001*
Distance < 9 months	**0.79 (0.71–0.88)**	0.85 (0.60–1.21)	5	179, *0.001*
Any vaccine	**0.72 (0.71–0.72)**	*0.72 (0.71–0.72)*	1	nd
Sick people	**0.44 (0.30–0.65)**	0.42 (0.09–1.89)	6	383, *0.001*
Distance < 7 months	**0.30 (0.13–0.72)**	0.31 (0.03–3.16)	5	341, *0.001*
Any vaccine	0.94 (0.81–1.10)	0.89 (0.65–1.22)	4	39, *0.001*
4 v Vaccine	0.89 (0.66–1.20)	0.84 (0.49–1.42)	3	23, *0.001*
4 v.1 Vaccine	0.83 (0.49–1.42)	0.70 (0.39–1.27)	2	0.12, NS
4 v Vaccine and distance < 7 months	0.99 (0.73–1.34)	0.99 (0.71–1.38)	2	17, *0.001*
4 v.1 Vaccine and distance < 7 months	**0.84 (0.74–0.96)**	**0.84 (0.74–0.96)**	1	nd

Note: Sensitivity analysis for all studies and for different populations are shown (distance from vaccination to infection, type of vaccine employed). When studies are less than 10, Dersimonian and Hartung & Knapp models were used. Significant effects at either Dersimonian or Hartung & Knapp models are in bold.
Abbreviations: 4 v, tetravalent vaccine; 4 v.1, inactivated or attenuated tetravalent vaccine.

SARS-CoV-2 was initially hypothesized for the BCG vaccine, whose favorable effects on child mortality went beyond prevention of child TBC.[95] However, the efficacy of BCG vaccine has not been confirmed in spite of early reports.[34,35] The influenza vaccination was strongly recommended since the beginning of the pandemics to avoid co-infections[26]) and early studies highlighted a possible association between influenza vaccination and a reduced SARS-CoV-2 infection.[27–30] Since influenza almost disappeared during the 2020 season[17–23] and thus the prevention of co-infection could not explain this possible protective effect of the influenza vaccination on COVID-19, it was hypothesized that influenza vaccination directly played protective roles against SARS-CoV-2 infection. The ensuing studies on the association between influenza vaccination and SARS-CoV-2 infection and COVID-19 severity were the basis for this meta-analysis.[38–88]

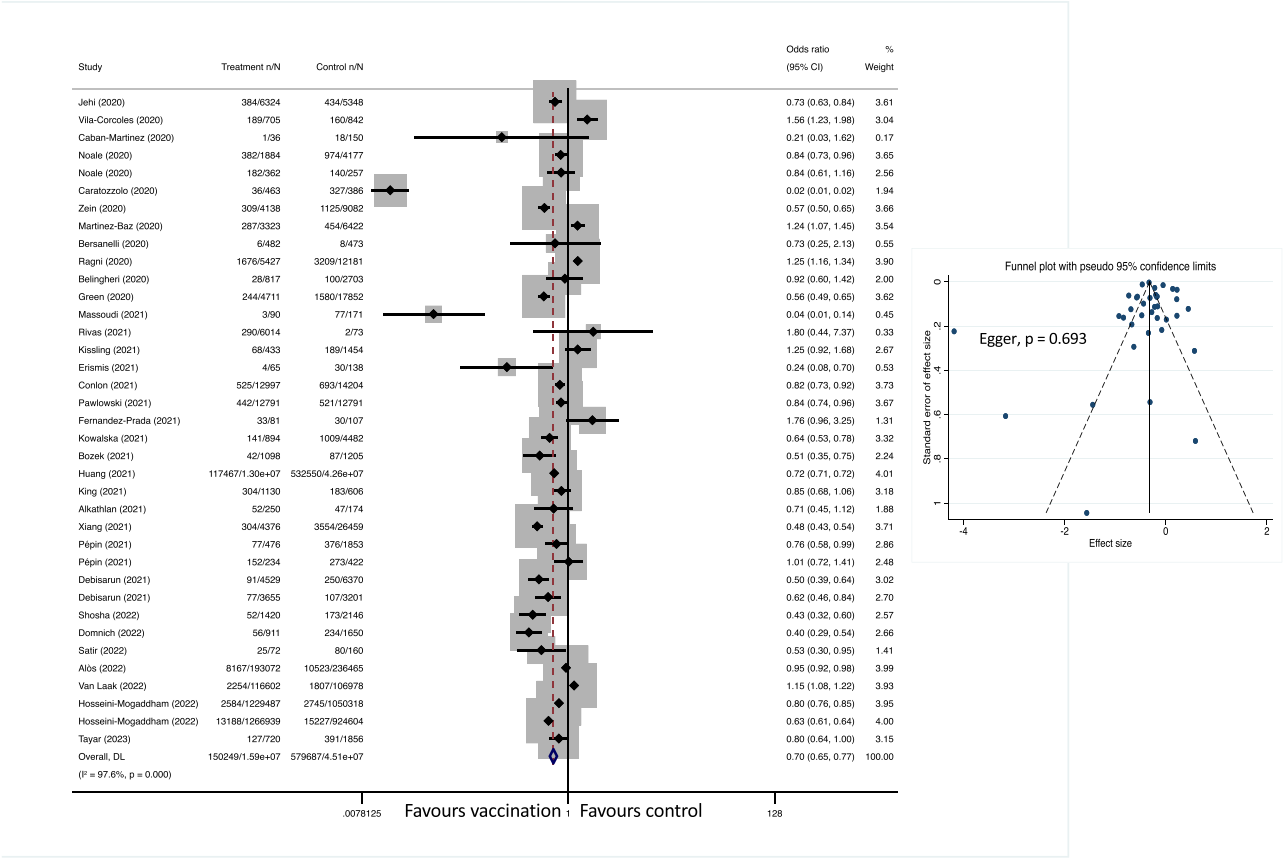

FIGURE 2 Frequency of SARS-CoV-2 infection and influenza vaccination. Left panel: forest plot of pooled hazard ratios of SARS-CoV-2 infection in vaccinated and not vaccinated subjects. Right panel: funnel plot with Egger detection of small bias effect. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 2B Effect of influenza vaccination on hospitalization in all studies and in different populations.

	Dersimonian	Hartung & Knapp	Studi	Cochran Q, *p*
All studies	1.05 (0.82–1.35)		14	1249, *0.001*
distance <4.5 months	**0.54 (0.52–0.57)**	**0.53 (0.37–0.75)**	2	0.2, NS
General population	1.15 (0.92–1.45)	1.14 (0.74–1.73)	9	340, *0.001*
distance <7 months	1.18 (0.89–1.57)	1.17 (0.73–1.87)	9	313, *0.001*
Healthworkers	0.71 (0.27–1.87)	0.71 (0.27–1.87)	1	nd
Elderly	0.88 (0.49–1.58)	0.86 (0.40–1.87)	4	86, *0.001*
distance <4.5 months	**0.54 (0.52–0.57)**	**0.53 (0.37–0.75)**	1	nd

Note: Sensitivity analysis for all studies and for different populations are shown (distance from vaccination to hospitalization). When studies are less than 10, Dersimonian and Hartung & Knapp models were used. Significant effects at either Dersimonian or Hartung & Knapp models are in bold.

The main findings of our meta-analysis are that influenza vaccination reduces the frequency of SARS-CoV-2 infection but has very small effects on severity of COVID-19 in infected subjects, as shown by frequency of hospital admission and mortality. Nevertheless, isolation in ICU appeared to be reduced for several populations analyzed. In particular:

4.1 | Influenza vaccination reduces the frequency of SARS-CoV-2 infection

Coming from the analysis of 33 studies (for a total of 37 comparison arms and over 60-million individuals), this result supports and extends previous observations and reviews.[31–33]

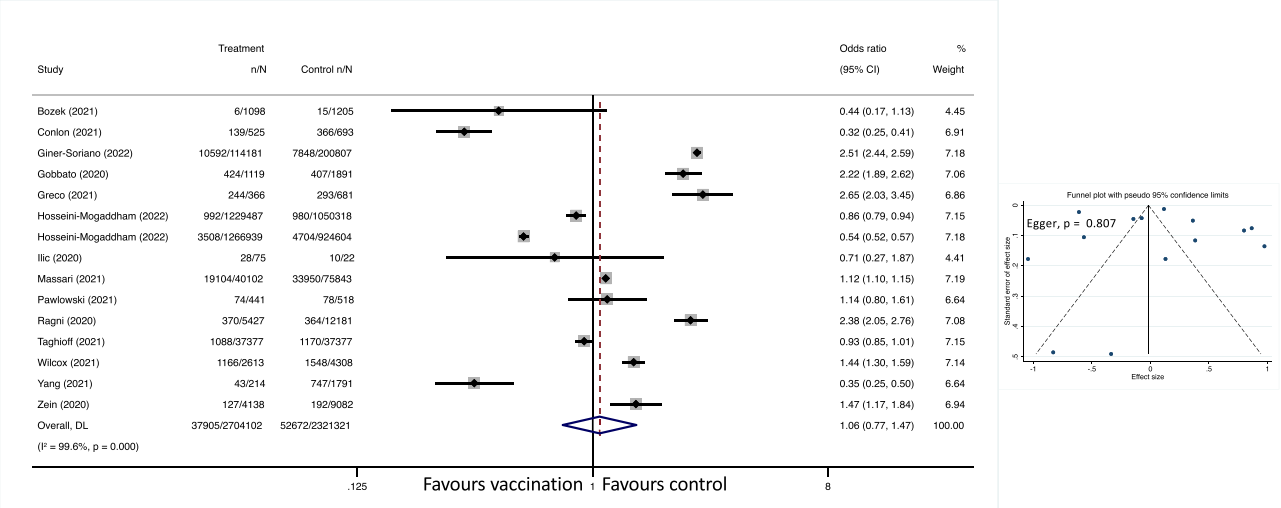

FIGURE 3 Frequency of hospitalization in SARS-CoV-2 infected subjects and influenza vaccination. Left panel: forest plot of pooled hazard ratios of hospitalization due to COVID-19 in vaccinated and not vaccinated subjects. Right panel: funnel plot with Egger detection of small bias effect. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 2C Effect of influenza vaccination on admission to Intensive Care Units in all studies and in different populations.

	Dersimonian	Hartung & Knapp	Studi	Cochran Q, *p*
All studies	**0.71 (0.54–0.94)**		11	47, *0.001*
Age < 60 years	**0.69 (0.49–0.96)**	0.65 (0.37–1.14)	7	34, *0.001*
Age < 50 years	**0.44 (0.22–0.87)**	0.43 (0.18–1.02)	4	19, *0.001*
General population	0.77 (0.51–1.19)	0.75 (0.41–1.37)	7	37, *0.001*
Age < 60 years	0.63 (0.36–1.10)	0.63 (0.36–1.10)		33, *0.001*
Age < 50 years	**0.27 (0.17–0.41)**	**0.25 (0.12–0.52)**	2	0.55 NS
Pregnant women	**0.74 (0.61–0.90)**	**0.74 (0.61–0.90)**	2	0.0, NS
Hospitalized subjects	**0.46 (0.30–0.70)**	**0.42 (0.20–0.89)**	2	0.58, NS
Pregnant women + Hospitalized subjects	**0.61 (0.44–0.85)**	**0.57 (0.34–0.97)**	4	4, NS
Pregnant women + Hospitalized subjects + General population aged < 50 years	**0.44 (0.28–0.70)**	**0.43 (0.23–0.78)**	6	21, *0.001*

Note: Sensitivity analysis for all studies and for different populations are shown (age. Combined populations). When studies are less than 10, Dersimonian and Hartung & Knapp models were used. Significant effects at either Dersimonian or Hartung & Knapp models are in bold.

The novelty of our findings is represented by the different populations examined (health care workers, general population, elderly individuals, poor health individuals, and pregnant women), by the analysis of the vaccines used (tetravalent vs others), and by the possible interaction of type of vaccine and distance from vaccination. When the information about the type of influenza vaccine employed was described, we could not identify any difference in the effect of tetravalent vaccine and of inactivated tetravalent vaccine. In all studies, a short distance from influenza vaccination and use of tetravalent vaccine appeared to exert a synergistic effect against infection with SARS-CoV-2. These data support the hypothesis of the existence of a direct effect of the influenza vaccination on SARS-CoV-2 infection. This effect can be either specific or nonspecific, as discussed below.

4.2 | Influenza vaccination has negligible effects on severity of COVID-19 in infected subjects

4.2.1 | Hospitalization

Only two studies out of 14, in which subjects were elderly people vaccinated less than 4.5 months earlier, showed a significant effect of influenza vaccination against hospitalization.

4.2.2 | ICU admission

In contrast to hospitalization, influenza vaccination had a significant effect on prevention of ICU admission; this applied to all studies, to

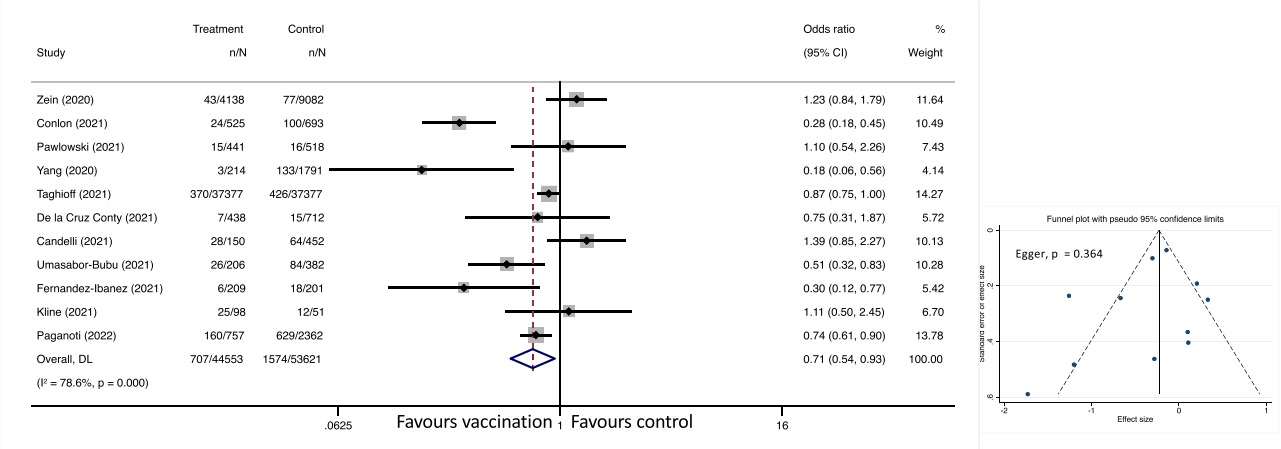

FIGURE 4 Frequency of admission to intensive care units in SARS-CoV-2 infected subjects and influenza vaccination. Left panel: forest plot of pooled hazard ratios of admission to Intensive Care Units due to COVID-19 in vaccinated and not vaccinated subjects. Right panel: funnel plot with Egger detection of small bias effect. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 2D Effect of influenza vaccination on mortality in all studies and in different populations.

	Dersimonian	Hartung & Knapp	Studi	Cochran Q, *p*
All studies	0.76 (0.26–2.20)		20	24 920, *0.001*
Distance < 5 months	0.75 (0.06–9.28)	0.75 (0.17–3.23)	7	17 978, *0.001*
Distance < 4 months	**0.01 (0.01–0.01)**	**0.01 (0.01–0.01)**	1	nd
Pregnant women	**0.39 (0.28–0.53)**	**0.39 (0.28–0.53)**	1	nd
General population	0.98 (0.51–1.89)		12	3473, *0.001*
Distance < 5 months	1.36 (0.63–2.96)	1.34 (0.56–3.24)	4	205, *0.001*
Age > 65 years	0.56 (0.04–7.83)	0.56 (0.0–14.32)	5	3820, *0.001*
Distance < 5 months	0.14 (0.01–19.20)	0.14 (0.01–131.68)	2	219, *0.001*
Distance < 4 months	**0.01 (0.01–0.01)**	**0.01 (0.01–0.01)**	1	nd
Hospitalized subjects	0.79 (0.08–7.82)	0.79 (0.06–9.77)	2	28, *0.001*
Pregnant women + age > 65 years with distance < 4 months	0.57 (0.27–1.21)	0.57 (0.23–1.42)	2	421, *0.001*

Note: Sensitivity analysis for all studies and for different populations are shown (distance from vaccination to death, age). When studies are less than 10, Dersimonian and Hartung & Knapp models were used. Significant effects at either Dersimonian or Hartung & Knapp models are in bold.

the general population below the age of 50 years, to pregnant women, to hospitalized patients, and the effect was even more significant when the three latter categories were combined.

4.2.3 | Mortality

Only two out of 20 studies showed some effect of influenza vaccination on mortality caused by SARS-CoV-2, one in pregnant women, the other in elderly people vaccinated by less than 4 months; interestingly, combination of the two studies did not significantly change the results of our analysis.

4.3 | The possible mechanisms of action

At present, there is no explanation for the preventive effect of influenza vaccination against SARS-CoV-2 infection. Influenza viruses (mainly represented by influenza A virus) and SARS-CoV-2 are different viruses, although they share routes of transmission and part of pulmonary symptomatology.[5–7]

Therefore, a direct effect on SARS-CoV-2 of the adaptive immune response (antibody production and/or T cell responses) elicited by influenza vaccination seems unlikely.

An alternative mechanism to explain the protection of influenza vaccination against the infection with SARS-CoV-2 might be

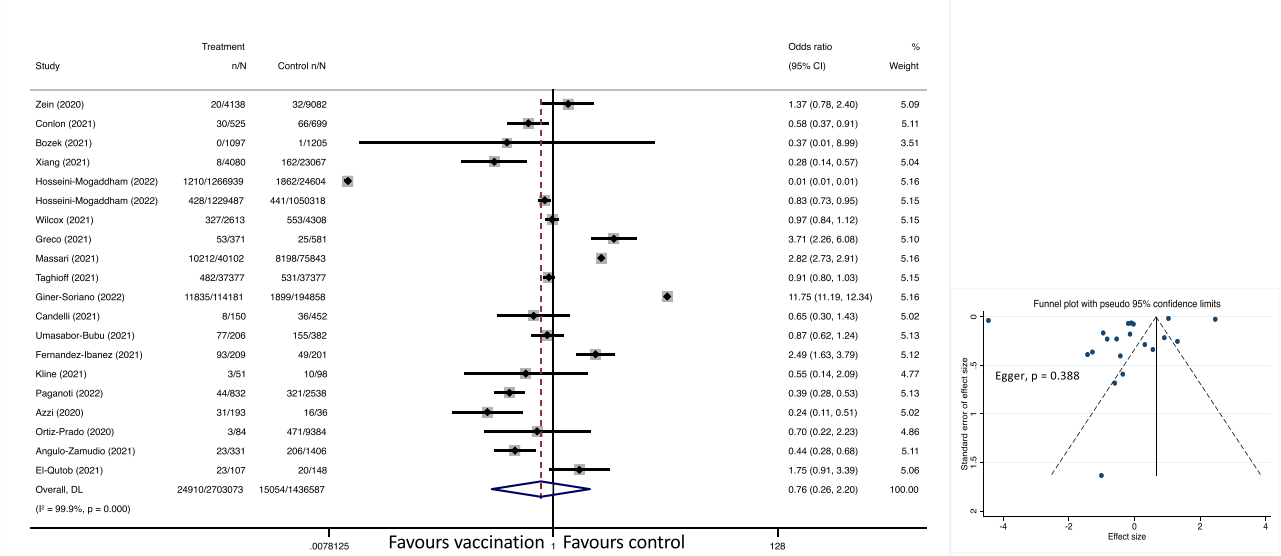

FIGURE 5 Mortality in SARS-CoV-2 infected subjects and influenza vaccination. Left panel: forest plot of pooled hazard ratios of mortality due to COVID-19 in vaccinated and not vaccinated subjects. Right panel: funnel plot with Egger detection of small bias effect.

represented by trained immunity.[96] Trained immunity is a phenomenon that potentiate the responses of innate immune cells such as macrophages, neutrophils, and dendritic cells via the induction of "memory-like" features that are induced in response to infections or vaccines.[96–98] These memory-like responses lead to enhanced protection upon (re)encounter with the same, or a non-related, microorganism. The existence of trained immunity was initially proposed for the BCG vaccine.[96] Children, who are not in the general indications for influenza vaccines, were very little infected during the first year of the SARS-CoV-2 pandemic; the increased interferon responses in children[99,100] would protect against SARS-CoV-2 even in the absence of trained immunity, not necessary because of a strong primary response of the host.

Vaccines usually affect adaptive immunity, namely B and T lymphocytes. In the case of trained immunity, infections and vaccines can re-program cells of innate immunity, with a possible improvement of the nonspecific response to other infections. This protective effect appears to be long-lasting (between 3 months and 1 year, although, for live vaccines, the protection against heterologous infections has been shown up to 5 years) and reminds adaptive immune memory, although without antigen-specificity.[101] Influenza vaccination can stimulate the activity of NK cells, which are innate immune lymphocytes that rapidly respond to an infection[98,102] involved in the elimination of virus-infected cells by shaping the adaptive response mediated by T-cells, and that have been shown to bear a certain level of "memory."[103,104] Activated NK cells are relevant source of INF-g which has a crucial role in instructing $CD8^+$ T cell expansion and contraction, as adaptive immune responses to several pathogens, including viruses.[105,106] In severe SARS-CoV2 infection, NK cells are hypo-responsive,[107] and the anti-SARS-CoV2 vaccination (based on mRNA technology) transiently stimulates high production of NK cells and B cell.[107]

In one study,[63] influenza vaccination was associated with changes of monocytes and CD4+ lymphocytes, in spite of no change of total circulating leukocytes, and with the downregulation of mediators of the systemic inflammatory response and an increased production of anti-inflammatory cytokines. Intriguingly, a similar mechanism, based on regulation of inflammation, has been suggested for a totally different drug, metformin, that was able to reduce the risk of severe COVID-19 and of long COVID.[108]

Interferons might be a key factor in the interaction between influenza vaccination and SARS-CoV-2 infection; different types of interferons are produced in the lungs of COVID-19 patients based on disease severity and location along the respiratory tract.[109,110] It is thus possible to speculate that the transient induction of interferons that follows influenza viruses encounter, or the influenza vaccination may affect the capacity of the host to control the infection with SARS-CoV-2.[111–113]

Our data demonstrate that the protective effect of influenza vaccination fades over time. Influenza vaccines have been shown to induce interferons to different extents,[111–113] suggesting that the broad capacity of interferons, produced in response to influenza vaccine, to "interfere" with the spread and/or replication of viruses may explain the cross-protection against SARS-CoV-2 observed in individuals that were recently vaccinated against influenza.

An additional factor may be represented by the "healthy vaccinee" (or "healthy user") effect, that can act as a confounding factor. Motivated subjects, together with voluntary vaccination, might also observe in a more proper and strict way other sanitary measures, that can by themselves prevent infection, leading to an over-evaluation of the activity of the influenza vaccines.[114] In particular, one study[70] was aimed at reducing differences between general population and health care workers in the approach to vaccination. In agreement with this observation, the effect of

influenza vaccines was somewhat more evident in health care workers than in the general population.

5 | LIMITATIONS

There are several limitations to this meta-analysis. First, no controlled trial was available, and only prospective cohort studies, retrospective cohort studies, case control studies, and cross-sectional studies were available. Second, we should consider that the incidence and severity of SARS-CoV-2 infections have changed from 1 year to the next during the pandemic, and that the severity has particularly decreased in 2022; although the extent and complexity (in terms of geographic location and period of sampling) of the cohorts utilized for this study cannot take into account the changes in the pathogenicity associated with the emergence of new variants of concern,[115] the associations we identified seem to hold true regardless of these differences.

A further limitation is that studies showing a relationship between frequency of vaccination and diffusion of infection could not be considered because they did not show crude data.[27–30] Third, the type of vaccine used was known only for a limited number of individuals, and therefore an analysis of this aspect was not possible across all our analyses. Fourth, we applied two models of analysis, and some of the comparisons were statistically significant only with one of the models. On the other hand, the quality of studies, as assessed through the NOS was elevated, with a few exceptions, and no publication bias was evident. Finally, even though all subjects in the studies did not receive any anti-SARS-CoV-2 vaccine, we had no information about previous infections with SARS-CoV-2, and, with few exceptions,[44,45,51,57,59,65,82,83] about recent infections with the influenza virus, and we had no data on the possible involvement of the cardiovascular system in the studies evaluated.[1–4]

6 | CONCLUSION

Influenza vaccination was associated with reduced rate of SARS-CoV-2 infection in the majority of studies examined. In contrast, influenza vaccination seems to exert minimal effects on the severity of COVID-19, as assessed through rates of hospitalization and death rates. Of note, influenza vaccination reduced the admission to ICU for several populations analyzed. Our data, thus, show that influenza vaccination prevents the infection with SARS-CoV-2, but that, upon infection, it does not alter the response of the host to this new coronavirus. This preventive effect might be of relevance for individuals with co-morbidities, in particular patients with or at risk of cardiovascular diseases.[1–4] Overall, our analysis reveals the importance, together with other preventive measures, of influenza vaccination against COVID-19, that reduces the impact of SARS-CoV-2 and of similar viruses on the general population and of more exposed subjects.[116]

AUTHOR CONTRIBUTIONS

Antonio E. Pontiroli, Lucia La Sala, Ivan Zanoni and Elisabetta Tanzi conceived the study. Francesco Scovenna, Valentina Carlini, Jimmy Martin-Delgado, searched and screened studies published, and Francesco Scovenna used the material for his MD Thesis. All authors judged and discussed the material gathered. Elena Tagliabue performed all statistical analysis. Antonio E. Pontiroli, Lucia La Sala and Ivan Zanoni wrote the first draft, and all authors discussed the draft, and approved the final manuscript.

ACKNOWLEDGMENTS

The authors wish to thank “Fondazione Romeo ed Enrica Invernizzi” Milan, Italy for the support, and Regione Lombardia (Milan, Italy) as data source. This study was supported by a grant (Ricerca Corrente) of the Italian Ministry of Health (Ministero della Salute) to IRCCS MultiMedica. Ivan Zanoni is supported by NIH grants 2R01AI121066, 2R01DK115217, 1R01AI165505, 1R01AI170632, and contract no. 75N93019C00044, Lloyd J. Old STAR Program CRI3888, and holds an Investigators in the Pathogenesis of Infectious Disease Award from the Burroughs Wellcome Fund.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding authors on the basis of reasonable request.

ETHICS STATEMENT

This study was exempt from ethics approval as only data from previously published studies were retrieved and synthesized.

ORCID

Antonio E. Pontiroli http://orcid.org/0000-0002-8217-7672
Jimmy Martin-Delgado http://orcid.org/0000-0003-4384-9197
Elisabetta Tanzi http://orcid.org/0000-0002-4119-701X

REFERENCES

1. Alkundi A, Mahmoud I, Musa A, Naveed S, Alshawwaf M. Clinical characteristics and outcomes of COVID-19 hospitalized patients with diabetes in the United Kingdom: a retrospective single centre study. *Diabetes Res Clin Pract*. 2020;165:108263. doi:10.1016/j.diabres.2020.108263
2. Chiumello D, Pozzi T, Storti E, Caccioppola A, Pontiroli AE, Coppola S. Body mass index and acute respiratory distress severity in patients with and without SARS-CoV-2 infection. *Br J Anaesth*. 2020;125(4):e376-e377. doi:10.1016/j.bja.2020.07.006
3. Liu Y, Wu S, Qin M, Jiang W, Liu X. Prevalence of cardiovascular comorbidities in coronavirus disease 2019, severe acute respiratory syndrome, and Middle East respiratory syndrome: pooled analysis of published data. *J Am Heart Assoc*. 2020;9:e016812.
4. Aghagoli G, Gallo Marin B, Soliman LB, Sellke FW. Cardiac involvement in COVID-19 patients: risk factors, predictors, and complications: a review. *J Card Surg*. 2020;35:1302-1305.
5. Jiang C, Yao X, Zhao Y, et al. Comparative review of respiratory diseases caused by coronaviruses and influenza A viruses during

epidemic season. *Microb Infect*. 2020;22(6-7):236-244. doi:10.1016/j.micinf.2020.05.005
6. Petersen E, Koopmans M, Go U, et al. Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. *Lancet Infect Dis*. 2020;20(9):e238-e244. doi:10.1016/S1473-3099(20)30484-9
7. Clementi N, Ghosh S, De Santis M, et al. Viral respiratory pathogens and lung injury. *Clin Microbiol Rev*. 2021;34(3):e00103-20. doi:10.1128/CMR.00103-20
8. Rubin R. What happens when COVID-19 collides with flu season? *JAMA*. 2020;324(10):923-925. doi:10.1001/jama.2020.15260
9. Petti S, Cowling BJ. Ecologic association between influenza and COVID-19 mortality rates in european countries. *Epidemiol Infect*. 2020;148:e209. doi:10.1017/S0950268820002125
10. Pinky L, Dobrovolny HM. SARS-CoV-2 coinfections: could influenza and the common cold be beneficial? *J Med Virol*. 2020;92(11):2623-2630. doi:10.1002/jmv.26098
11. Capone A. Simultaneous circulation of COVID-19 and flu in Italy: potential combined effects on the risk of death? *Int J Infect Dis*. 2020;99:393-396. doi:10.1016/j.ijid.2020.07.077
12. Xiang X, Wang Z, Ye L, et al. Co-infection of SARS-COV-2 and influenza A virus: a case series and fast review. *Current Medical Science*. 2021;41(1):51-57. doi:10.1007/s11596-021-2317-2
13. Tramuto F, Mazzucco W, Maida CM, et al. COVID-19 emergency in sicily and intersection with the 2019–2020 influenza epidemic. *J Prev Med Hyg*. 2021;62(1):10. doi:10.15167/2421-4248/jpmh2021.62.1.1870
14. Cheng Y, Ma J, Wang H, et al. Co-infection of influenza A virus and SARS-CoV-2: a retrospective cohort study. *J Med Virol*. 2021;93(5):2947-2954. doi:10.1002/jmv.26817
15. Chotpitayasunondh T, Fischer TK, Heraud JM, et al. Influenza and COVID-19: what does co-existence mean? *Influenza Other Respir Viruses*. 2021;15(3):407-412. doi:10.1111/irv.12824
16. Achdout H, Vitner EB, Politi B, et al. Increased lethality in influenza and SARS-CoV-2 coinfection is prevented by influenza immunity but not SARS-CoV-2 immunity. *Nat Commun*. 2021;12(1):5819. doi:10.1038/s41467-021-26113-1
17. Servick K. Coronavirus creates a flu season guessing game. *Science*. 2020;369(6506):890-891. doi:10.1126/science.369.6506.890
18. Sullivan SG, Carlson S, Cheng AC, et al. Where has all the influenza gone? the impact of COVID-19 on the circulation of influenza and other respiratory viruses, Australia, March to September 2020. *Euro Surveill*. 2020;25(47):2001847. doi:10.2807/1560-7917.ES.2020.25.47.2001847
19. Sunagawa S, Iha Y, Kinjo T, Nakamura K, Fujita J. Disappearance of summer influenza in the Okinawa prefecture during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. *Respirat Investigat*. 2021;59(1):149-152. doi:10.1016/j.resinv.2020.10.010
20. Varela FH, Scotta MC, Polese-Bonatto M, et al. COVIDa study group Absence of detection of RSV and influenza during the COVID-19 pandemic in a Brazilian cohort: likely role of lower transmission in the community. *J Glob Health*. 2021;11:05007. doi:10.7189/jogh.11.05007
21. Eisen AKA, Gularte JS, Demoliner M, et al. Low circulation of influenza A and coinfection with SARS-CoV-2 among other respiratory viruses during the COVID-19 pandemic in a region of Southern Brazil. *J Med Virol*. 2021;93(7):4392-4398. doi:10.1002/jmv.26975
22. Kuitunen I. Influenza season 2020–2021 did not begin in Finland despite the looser social restrictions during the second wave of COVID-19: a nationwide register study. *J Med Virol*. 2021;93(9):5626-5629. doi:10.1002/jmv.27048
23. Dhanasekaran V, Sullivan S, Edwards KM, et al. Human seasonal influenza under COVID-19 and the potential consequences of influenza lineage elimination. *Nat Commun*. 2022;13(1):1721. doi:10.1038/s41467-022-29402-5
24. Chan KS, Liang FW, Tang HJ, Toh HS, Yu WL. Collateral benefits on other respiratory infections during fighting COVID-19. *Medicina Clínica (English Edition)*. 2020;155(6):249-253. doi:10.1016/j.medcle.2020.05.019
25. Li Q, Wang J, Lv H, Lu H. Impact of China's COVID-19 prevention and control efforts on outbreaks of influenza. *BioScience Trends*. 2021;15(3):192-195. doi:10.5582/bst.2021.01242
26. "Poster: Influenza during the COVID-19 pandemic - why it's important to get vaccinated against influenza." Accessed June 5, 2023.
27. Petti S, Cowling BJ. Ecologic association between influenza and COVID-19 mortality rates in European countries. *Epidemiol Infect*. 2020;148:e209. doi:10.1017/S0950268820002125
28. Amato M, Werba JP, Frigerio B, et al. Relationship between influenza vaccination coverage rate and COVID-19 outbreak: an Italian ecological study. *Vaccines*. 2020;8(3):535. doi:10.3390/vaccines8030535
29. Marín-Hernández D, Schwartz RE, Nixon DF. Epidemiological evidence for association between higher influenza vaccine uptake in the elderly and lower COVID-19 deaths in Italy. *J Med Virol*. 2021;93(1):64-65. doi:10.1002/jmv.26120
30. Pedote PD, Termite S, Gigliobianco A, Lopalco PL, Bianchi FP. Influenza vaccination and health outcomes in COVID-19 patients: a retrospective cohort study. *Vaccines*. 2021;9(4):358. doi:10.3390/vaccines9040358
31. Del Riccio M, Lorini C, Bonaccorsi G, Paget J, Caini S. The association between influenza vaccination and the risk of SARS-CoV-2 infection, severe illness, and death: a systematic review of the literature. *Int J Environ Res Public Health*. 2020;17(21):7870. doi:10.3390/ijerph17217870
32. Almadhoon HW, Hamdallah A, Elsayed SM, et al. The effect of influenza vaccine in reducing the severity of clinical outcomes in patients with COVID-19: a systematic review and meta-analysis. *Sci Rep*. 2022;12(1):14266. doi:10.1038/s41598-022-18618-6
33. Su W, Wang H, Sun C, et al. The association between previous influenza vaccination and COVID-19 infection risk and severity: a systematic review and meta-analysis. *Am J Prev Med*. 2022;63(1):121-130. doi:10.1016/j.amepre.2022.02.008
34. Escobar LE, Molina-Cruz A, Barillas-Mury C. BCG vaccine protection from severe coronavirus disease 2019 (COVID-19). *Proc Nat Acad Sci*. 2020;117(30):17720-17726. doi:10.1073/pnas.2008410117
35. Pittet LF, Messina NL, Orsini F, et al. BRACE Trial Consortium Group Randomized trial of BCG vaccine to protect against Covid-19 in health care workers. *N Engl J Med*. 2023;388(17):1582-1596. doi:10.1056/NEJMoa2212616
36. Kapoula GV, Vennou KE, Bagos PG. Influenza and pneumococcal vaccination and the risk of COVID-19: a systematic review and meta-analysis. *Diagnostics*. 2022;12(12):3086. doi:10.3390/diagnostics12123086
37. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and Meta-Analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
38. Jehi L, Ji X, Milinovich A, et al. Individualizing risk prediction for positive coronavirus disease 2019 testing. *Chest*. 2020;158(4):1364-1375. doi:10.1016/j.chest.2020.05.580
39. Vila-Córcoles Á, Ochoa-Gondar O, Torrente-Fraga C, et al. Evaluation of incidence and risk profile for suffering Covid-19 infection by underlying conditions among middle-aged and older adults in tarragona. *Rev Esp Salud Publica*. 2020;94:e202006065.
40. Caban-Martinez AJ, Schaefer-Solle N, Santiago K, et al. Epidemiology of SARS-CoV-2 antibodies among firefighters/paramedics of a

US fire department: a cross-sectional study. *Occup Environ Med*. 2020;77(12):857-861. doi:10.1136/oemed-2020-106676

41. Noale M, Trevisan C, Maggi S, et al. The association between influenza and pneumococcal vaccinations and SARS-Cov-2 infection: data from the EPICOVID19 Web-Based survey. *Vaccines*. 2020;8(3):471. doi:10.3390/vaccines8030471
42. Caratozzolo S, Zucchelli A, Turla M, et al. The impact of COVID-19 on health status of home-dwelling elderly patients with dementia in east lombardy, Italy: results from COVIDEM network. *Aging Clin Exp Res*. 2020;32(10):2133-2140. doi:10.1007/s40520-020-01676-z
43. Zein JG, Whelan G, Erzurum SC. Safety of influenza vaccine during COVID-19. *J Clin Transl Sci*. 2020;5:e49. doi:10.1017/cts.2020.543
44. Martínez-Baz I, Trobajo-Sanmartín C, Arregui I, et al. Influenza vaccination and risk of SARS-CoV-2 infection in a cohort of health workers. *Vaccines*. 2020;8(4):611. doi:10.3390/vaccines8040611
45. Bersanelli M, Giannarelli D, De Giorgi U, et al. Symptomatic COVID-19 in advanced-cancer patients treated with immune-checkpoint inhibitors: prospective analysis from a multicentre observational trial by FICOG. *Ther Adv Med Oncol*. 2020;12:1758835920968463. doi:10.1177/1758835920968463
46. Ragni P, Marino M, Formisano D, et al. Association between exposure to influenza vaccination and COVID-19 diagnosis and outcomes. *Vaccines*. 2020;8(4):675. doi:10.3390/vaccines8040675
47. Belingheri M, Paladino ME, Latocca R, De Vito G, Riva MA. Association between seasonal flu vaccination and COVID-19 among healthcare workers. *Occup Med*. 2020;70(9):665-671. doi:10.1093/occmed/kqaa197
48. Green I, Ashkenazi S, Merzon E, Vinker S, Golan-Cohen A. The association of previous influenza vaccination and coronavirus disease-2019. *Hum Vaccines Immunother*. 2021;17(7):2169-2175. doi:10.1080/21645515.2020.1852010
49. Massoudi N, Mohit B. A case-control study of the 2019 influenza vaccine and incidence of COVID-19 among healthcare workers. *J Clin Immunol*. 2021;41(2):324-334. doi:10.1007/s10875-020-00925-0
50. Rivas MN, Ebinger JE, Wu M, et al. BCG vaccination history associates with decreased SARS-CoV-2 seroprevalence across a diverse cohort of health care workers. *J Clin Invest*. 2021;131(2):e145157. doi:10.1172/JCI145157
51. Kissling E, Hooiveld M, Brytting M, et al. Absence of association between 2019-20 influenza vaccination and COVID-19: results of the european I-MOVE-COVID-19 primary care project, March-August 2020. *Influenza Other Respir Viruses*. 2021;15(4):429-438. doi:10.1111/irv.12839
52. Erismis B, Karabela SN, Eksi F, et al. Annual influenza vaccination effect on the susceptibility to COVID-19 infection. *Cent Eur J Public Health*. 2021;29(1):14-17. doi:10.21101/cejph.a6573.
53. Conlon A, Ashur C, Washer L, Eagle KA, Hofmann Bowman MA. Impact of the influenza vaccine on COVID-19 infection rates and severity. *Am J Infect Control*. 2021;49(6):694-700. doi:10.1016/j.ajic.2021.02.012
54. Pawlowski C, Puranik A, Bandi H, et al. Exploratory analysis of immunization records highlights decreased SARS-CoV-2 rates in individuals with recent non-COVID-19 vaccinations. *Sci Rep*. 2021;11(1):4741. doi:10.1038/s41598-021-83641-y
55. Fernández-Prada M, García-González P, García-Morán A, Ruiz-Álvarez I, Ramas-Diez C, Calvo-Rodríguez C. Antecedentes personales y vacunales como factores asociados a la infección por SARS-CoV-2. *Med Clin (Barc)*. 2021;157(5):226-233. doi:10.1016/j.medcli.2021.02.011
56. Kowalska M, Niewiadomska E, Barański K, Kaleta-Pilarska A, Brożek G, Zejda JE. Association between influenza vaccination and positive SARS-CoV-2 IgG and IgM tests in the general population of katowice region, Poland. *Vaccines*. 2021;9(5):415. doi:10.3390/vaccines9050415
57. Bozek A, Kozłowska R, Galuszka B, Grzanka A. Impact of influenza vaccination on the risk of SARS-CoV-2 infection in a middle-aged group of people. *Hum Vaccines Immunother*. 2021;17(9):3126-3130. doi:10.1080/21645515.2021.1913961
58. Huang K, Lin SW, Sheng WH, Wang CC. Influenza vaccination and the risk of COVID-19 infection and severe illness in older adults in the United States. *Sci Rep*. 2021;11(1):11025. doi:10.1038/s41598-021-90068-y
59. King JP, McLean HQ, Belongia EA. Risk of symptomatic severe acute respiratory syndrome coronavirus 2 infection not associated with influenza vaccination in the 2019-2020 season. *Influenza Other Respir Viruses*. 2021;15(6):697-700. doi:10.1111/irv.12880
60. Alkathlan M, Khalil R, Alhemaidani MF, et al. Trends, uptake, and predictors of influenza vaccination among healthcare practitioners during the COVID-19 pandemic flu season (2020) and the following season (2021) in Saudi Arabia. *J Multidiscip Healthc*. 2021;14:2527-2536. doi:10.2147/JMDH.S330029
61. Xiang Y, Wong KCY, So HC. Exploring drugs and vaccines associated with altered risks and severity of COVID-19: a UK biobank cohort study of all ATC Level-4 drug categories reveals repositioning opportunities. *Pharmaceutics*. 2021;13(9):1514. doi:10.3390/pharmaceutics13091514
62. Pépin J, De Wals P, Labbé AC, et al. Influenza vaccine during the 2019-2020 season and COVID-19 risk: a case-control study in québec. *Can Commun Dis Rep*. 2021;47(10):430-434. doi:10.14745/ccdr.v47i10a05
63. Debisarun PA, Gössling KL, Bulut O, et al. Induction of trained immunity by influenza vaccination - impact on COVID-19. *PLoS Pathog*. 2021;17(10):e1009928. doi:10.1371/journal.ppat.1009928
64. Shosha SH, Ajlan DI, Al-Ghatam R. Does influenza vaccination help reduce incidence of COVID-19 infection among hospital employees? *Medicine*. 2022;101(2):e28479. doi:10.1097/MD.0000000000028479
65. Domnich A, Orsi A, Sticchi L, et al. Effect of the 2020/21 season influenza vaccine on SARS-CoV-2 infection in a cohort of Italian healthcare workers. *Vaccine*. 2022;40(12):1755-1760. doi:10.1016/j.vaccine.2022.02.013
66. Satir A, Ersoy A, Demirci H, Ozturk M. Influenza and pneumococcal vaccination and COVID-19 in kidney transplant patients. *Transpl Immunol*. 2022;75:101693. doi:10.1016/j.trim.2022.101693
67. Alòs F, Cánovas Zaldúa Y, Feijóo Rodríguez MV, Del Val Garcia JL, Sánchez-Callejas A, Colomer À. Does influenza vaccination reduce the risk of contracting COVID-19? *J Clin Med*. 2022;11(18):5297. doi:10.3390/jcm11185297
68. van Laak A, Verhees R, Knottnerus JA, Hooiveld M, Winkens B, Dinant GJ. Impact of influenza vaccination on GP-diagnosed COVID-19 and all-cause mortality: a Dutch cohort study. *BMJ Open*. 2022;12(9):e061727. doi:10.1136/bmjopen-2022-061727
69. Hosseini-Moghaddam SM, He S, Calzavara A, Campitelli MA, Kwong JC. Association of influenza vaccination with SARS-CoV-2 infection and associated hospitalization and mortality among patients aged 66 years or older. *JAMA Network Open*. 2022;5(9):e2233730. doi:10.1001/jamanetworkopen.2022.33730
70. Tayar E, Abdeen S, Abed Alah M, et al. Effectiveness of influenza vaccination against SARS-CoV-2 infection among healthcare workers in Qatar. *Journal of Infection and Public Health*. 2023;16(2):250-256. doi:10.1016/j.jiph.2022.12.016
71. Ilic I, Zdravkovic M, Timcic S, Stojanovic DU, Bojic M, Loncar G. Pneumonia in medical professionals during COVID-19 outbreak in cardiovascular hospital. *Int J Infect Dis*. 2021;103:188-193. doi:10.1016/j.ijid.2020.11.156

72. Gobbato M, Clagnan E, Burba I, et al. Clinical, demographical characteristics and hospitalisation of 3,010 patients with Covid-19 in friuli venezia giulia region (Northern Italy). A multivariate, population-based, statistical analysis. *Epidemiol Prev*. 2020;44(5-6 suppl 2):226-234. doi:10.19191/EP20.5-6.S2.122
73. Yang MJ, Rooks BJ, Le TTT, et al. Influenza vaccination and hospitalizations among COVID-19 infected adults. *The Journal of the American Board of Family Medicine*. 2021;34(suppl):S179-S182. doi:10.3122/jabfm.2021.S1.200528
74. Wilcox CR, Islam N, Dambha-Miller H. Association between influenza vaccination and hospitalisation or all-cause mortality in people with COVID-19: a retrospective cohort study. *BMJ Open Respir Res*. 2021;8(1):e000857. doi:10.1136/bmjresp-2020-000857
75. Greco S, Bella A, Bonsi B, et al. SARS-CoV-2 infection and H1N1 vaccination: does a relationship between the two factors really exist? A retrospective analysis of a territorial cohort in ferrara, Italy. *Eur Rev Med Pharmacol Sci*. 2021;25(6):2795-2801. doi:10.26355/eurrev_202103_25441
76. Massari M, Spila-Alegiani S, Fabiani M, et al. Association of influenza vaccination and prognosis in patients testing positive to SARS-CoV-2 swab test: a Large-Scale Italian Multi-Database cohort study. *Vaccines*. 2021;9(7):716. doi:10.3390/vaccines9070716
77. Taghioff SM, Slavin BR, Holton T, Singh D. Examining the potential benefits of the influenza vaccine against SARS-CoV-2: a retrospective cohort analysis of 74,754 patients. *PLoS One*. 2021;16(8):e0255541. doi:10.1371/journal.pone.0255541
78. Giner-Soriano M, de Dios V, Ouchi D, Vilaplana-Carnerero C, Monteagudo M, Morros R. Outcomes of COVID-19 infection in people previously vaccinated against influenza: population-Based cohort study using primary health care electronic records. *JMIR Public Health Surveill*. 2022;8(11):e36712. doi:10.2196/36712
79. de la Cruz Conty M, Encinas Pardilla M, Garcia Sanchez M, et al. Impact of recommended maternal vaccination programs on the clinical presentation of SARS-CoV-2 infection: a prospective observational study. *Vaccines*. 2021;9(1):31. doi:10.3390/vaccines9010031
80. Candelli M, Pignataro G, Torelli E, et al. Effect of influenza vaccine on COVID-19 mortality: a retrospective study. *Intern Emerg Med*. 2021;16(7):1849-1855. doi:10.1007/s11739-021-02702-2
81. Umasabor-Bubu OQ, Bubu OM, Mbah AK, Nakeshbandi M, Taylor TN. Association between influenza vaccination and severe COVID-19 outcomes at a designated COVID-only hospital in brooklyn. *Am J Infect Control*. 2021;49(10):1327-1330. doi:10.1016/j.ajic.2021.04.006
82. Fernández Ibáñez JM, Morales Ballesteros MC, Fernández Anguita MJ, Galindo Andúgar MÁ, Arias Arias Á, Barberá-Farré JR. Influence of influenza vaccine and comorbidity on the evolution of hospitalized COVID-19 patients. *Medicina Clínica (English Edition)*. 2022;158(12):603-607. doi:10.1016/j.medcle.2021.06.022
83. Kline A, Trinh LN, Hussein MH, et al. Annual flu shot: does it help patients with COVID-19? *Int J Clin Pract*. 2021;75(12):e14901. doi:10.1111/ijcp.14901
84. Paganoti CF, Rodrigues AS, Francisco RPV, Costa RA. The influenza vaccine may protect pregnant and postpartum women against severe COVID-19. *Vaccines*. 2022;10(2):206. doi:10.3390/vaccines10020206
85. Azzi Y, Parides M, Alani O, et al. COVID-19 infection in kidney transplant recipients at the epicenter of pandemics. *Kidney Int*. 2020;98(6):1559-1567. doi:10.1016/j.kint.2020.10.004
86. Ortiz-Prado E, Simbaña-Rivera K, Barreno LG, et al. Epidemiological, socio-demographic and clinical features of the early phase of the COVID-19 epidemic in Ecuador. *PLoS Neglected Trop Dis*. 2021;15(1):e0008958. doi:10.1371/journal.pntd.0008958
87. Angulo-Zamudio UA, Martínez-Villa FM, Leon-Sicairos N, et al. Analysis of epidemiological and clinical characteristics of COVID-19 in northwest Mexico and the relationship between the influenza vaccine and the survival of infected patients. *Front Public Health*. 2021;9:570098. doi:10.3389/fpubh.2021.570098
88. El-Qutob D, Nieto M, Alvarez-Arroyo L, Carrera-Hueso FJ. Is there any effect of flu vaccine on the SARS-CoV-2 infected patients? *Vacunas*. 2022;23(2):71-76. doi:10.1016/j.vacun.2021.09.001
89. Wells GA, Shea B, Higgins JP, Sterne J, Tugwell P, Reeves BC. Checklists of methodological issues for review authors to consider when including non-randomized studies in systematic reviews. *Research Synthesis Methods*. 2013;4(1):63-77. doi:10.1002/jrsm.107
90. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin Trials*. 1986;7:177-188.
91. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. *Stat Med*. 2003;22(17):2693-2710. doi:10.1002/sim.1482
92. Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J Royal Stat Soc Ser*. 2009;172:137-159.
93. Kim SY, Park JE, Lee YJ, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol*. 2013;66:408-414.
94. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-634.
95. Higgins JPT, Soares-Weiser K, López-López JA, et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *BMJ*. 2016;355:i5170. doi:10.1136/bmj.i5170
96. Netea MG, Joosten LAB, Latz E, et al. Trained immunity: a program of innate immune memory in health and disease. *Science*. 2016;352(6284):aaf1098. doi:10.1126/science.aaf1098
97. Ziogas A, Netea MG. Trained immunity-related vaccines: innate immune memory and heterologous protection against infections. *Trends Mol Med*. 2022;28(6):497-512. doi:10.1016/j.molmed.2022.03.009
98. Netea MG, Ziogas A, Benn CS, et al. The role of trained immunity in COVID-19: lessons for the next pandemic. *Cell Host Microbe*. 2023;31(6):890-901. doi:10.1016/j.chom.2023.05.004
99. Loske J, Röhmel J, Lukassen S, et al. Pre-activated antiviral innate immunity in the upper airways controls early SARS-CoV-2 infection in children. *Nature Biotechnol*. 2022;40(3):319-324. doi:10.1038/s41587-021-01037-9
100. Yoshida M, Worlock KB, Huang N, et al. Local and systemic responses to SARS-CoV-2 infection in children and adults. *Nature*. 2022;602(7896):321-327. doi:10.1038/s41586-021-04345-x
101. Netea MG, Domínguez-Andrés J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol*. 2020;20(6):375-388. doi:10.1038/s41577-020-0285-6
102. Dou Y, Fu B, Sun R, et al. Influenza vaccine induces intracellular immune memory of human NK cells. *PLoS One*. 2015;10(3):e0121258. doi:10.1371/journal.pone.0121258
103. Mujal AM, Delconte RB, Sun JC. Natural killer cells: from innate to adaptive features. *Annu Rev Immunol*. 2021;39:417-447. doi:10.1146/annurev-immunol-101819-074948
104. Wimmers F, Donato M, Kuo A, et al. The single-cell epigenomic and transcriptional landscape of immunity to influenza vaccination. *Cell*. 2021;184(15):3915-3935. doi:10.1016/j.cell.2021.05.039
105. Tewari K, Nakayama Y, Suresh M. Role of direct effects of IFN-γ on T cells in the regulation of CD8 T cell homeostasis. *J Immunol*. 2007;179(4):2115-2125. doi:10.4049/jimmunol.179.4.2115

106. Sercan Ö, Stoycheva D, Hämmerling GJ, Arnold B, Schüler T. IFN-γ receptor signaling regulates memory CD8+ T cell differentiation. *J Immunol*. 2010;184(6):2855-2862. doi:10.4049/jimmunol.0902708
107. La Sala L, Gandini S, Bruno A, et al. SARS-CoV-2 immunization orchestrates the amplification of IFNγ-Producing T cell and NK cell persistence. *Front Immunol*. 2022;13:798813. doi:10.3389/fimmu.2022.798813
108. Bramante CT, Buse JB, Liebovitz DM, et al. Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial. *Lancet Infect Dis*. 2023;23(10):1119-1129. doi:10.1016/S1473-3099(23)00299-2
109. Sposito B, Broggi A, Pandolfi L, et al. The interferon landscape along the respiratory tract impacts the severity of COVID-19. *Cell*. 2021;184(19):4953-4968. doi:10.1016/j.cell.2021.08.016
110. Zanoni I. Interfering with SARS-CoV-2: are interferons friends or foes in COVID-19? *Current Opinion in Virology*. 2021;50:119-127. doi:10.1016/j.coviro.2021.08.004
111. Legebeke J, Lord J, Penrice-Randal R, et al. Evaluating the immune response in Treatment-Naive hospitalised patients with influenza and COVID-19. *Front Immunol*. 2022;13:853265. doi:10.3389/fimmu.2022.853265
112. Chong Z, Karl CE, Halfmann PJ, et al. Nasally delivered interferon-λ protects mice against infection by SARS-CoV-2 variants including omicron. *Cell Rep*. 2022;39(6):110799. doi:10.1016/j.celrep.2022.110799
113. Kastenschmidt JM, Sureshchandra S, Jain A, et al. Influenza vaccine format mediates distinct cellular and antibody responses in human immune organoids. *Immunity*. 2023;56:1910-1926. doi:10.1016/j.immuni.2023.06.019
114. Shrank WH, Patrick AR, Alan Brookhart M. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. *J Gen Intern Med*. 2011;26(5):546-550. doi:10.1007/s11606-010-1609-1
115. Markov PV, Ghafari M, Beer M, et al. The evolution of SARS-CoV-2. *Nat Rev Microbiol*. 2023;21(6):361-379. doi:10.1038/s41579-023-00878-2
116. Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. *BMC Infect Dis*. 2021;21(1):855. doi:10.1186/s12879-021-06536-3

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pontiroli AE, Scovenna F, Carlini V, et al. Vaccination against influenza viruses reduces infection, not hospitalization or death, from respiratory COVID-19: a systematic review and meta-analysis. *J Med Virol*. 2024;96:e29343. doi:10.1002/jmv.29343