Preventive Medicine Reports 38 (2024) 102575

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

Review article

Flu vaccine administration in the period before SARS-CoV-2 infection and its outcomes: An umbrella review

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ARTICLE INFO

Keywords:
Influenza vaccination
SARS-CoV-2 infection
COVID-19
Mortality
Hospitalization

ABSTRACT

Objective: The potential association between influenza vaccination and SARS-CoV-2 infection and related outcomes is still controversial. The aim of this umbrella review is to represent the impact of previous influenza vaccination and COVID-19 outcomes using evidence currently available in literature.
Methods: A literature search of MEDLINE, EMBASE, Scopus, Web of Science and Cochrane Library was conducted. The paper selection was conducted using the preferred reporting items for systematic reviews and *meta*-analyses (PRISMA) method by two-blinded authors. The quality of *meta*-analyses was assessed using the AMSTAR 2 scale (A MeaSurement Tool to Assess systematic Reviews). The outcomes investigated were SARS-CoV-2 infection after influenza vaccination, hospitalization, intensive care unit admission, mechanical ventilation and mortality.
Results: The literature research identified 7 ecological studies and 6 *meta*-analyses. All the ecological studies show a negative relationship between influenza vaccination and COVID-19. The *meta*-analyses suggest a protective action of influenza vaccination against SARS-CoV-2 infection. Regarding the outcomes evaluated, only two studies reported a statistically significant reduction of 12% and of 17% in hospitalization and intensive care unit admission, respectively. Regarding mechanical ventilation, three studies showed a risk reduction of 31%, 27% and 28%. A substantial reduction of mortality risk was also observed in one study.
Conclusions: These results suggest that influenza vaccination could be associated with reduced susceptibility to SARS-CoV-2 infection, mechanical ventilation and mortality. Our findings highlighted how the administration of flu vaccine in subjects at risk could lead to a reduction in mortality, particularly in the over 65y.

1. Introduction

Influenza, usually called "the flu", and COVID-19 are contagious respiratory diseases caused by different viruses. COVID-19 is caused by a coronavirus, SARS-CoV-2, while flu by influenza viruses (Centers for Disease Control and Prevention, 2022). Since the first isolation of SARS-CoV-2 in China in January 2020, the COVID-19 pandemic has caused 766,895,075 confirmed cases and 6,935,889 deaths worldwide, as reported by the World Health Organization (WHO) on 24 May 2023 (World Health Organization, 2023) and Italy was one of the countries strongly affected (Altobelli et al., 2022). COVID-19 causes a wide variety of symptoms, such as cough, fatigue, sore throat and headache, that can be in common with the flu. The diseases spread in similar ways, mainly by large and small particles containing the virus expelled when infected subjects cough, sneeze, or talk. However, SARS-CoV-2 and infected subjects seem to be more contagious than influenza viruses. Both diseases can result in severe illness and complications especially in older adults and in fragile subjects (Centers for Disease Control and Prevention, 2022). Co-infections by SARS-CoV-2 and influenza virus increase the risk of death more than twice compared to coronavirus infection alone (Iacobucci, 2020).

Due to the co-circulation of both viruses and to ensure optimal control of influenza during the COVID-19 pandemic, the WHO strongly recommended the prioritization of seasonal influenza vaccination for health workers and older adults, in addition to other risk groups with underlying health conditions and children under 5 years of age (WHO Regional Office for Europe, 2021). Influenza vaccination may have indirect effects on the COVID-19 pandemic by facilitating the diagnosis in

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https://doi.org/10.1016/j.pmedr.2023.102575
Received 11 October 2023; Received in revised form 19 December 2023; Accepted 21 December 2023
Available online 27 December 2023

patients with respiratory disease symptoms, preventing co-infection and reducing the burden of viral pneumonia on the healthcare system (Massari et al., 2021). The Centers for Disease Control and Prevention (CDC) reported that vaccination rates remained well below optimal levels for the 2021–2022 influenza season (Centers for Disease Control and Prevention, 2023).

Some authors have supposed an association between influenza vaccination status and COVID-19-related morbidity, hospitalization and mortality (Marin-Hernandez et al., 2021; Arokiaraj, 2020).

Del Riccio et al. did not find evidence to suggest that influenza vaccine would have a negative impact on patients in terms of SARS-CoV-2 related infections, illness, or deaths (Del Riccio et al., 2020). Pastorino et al. showed that influenza and pneumococcal vaccination were not associated to COVID-19 outcomes considering hospitalization, intensive care unit (ICU) admission and deaths (Pastorino et al., 2021). On the contrary, most studies suggest that flu vaccination is associated with reduced susceptibility or disease severity of COVID-19, mortality and reduced likelihood of ICU admission (Wang et al., 2021; Wilcox et al., 2021; Su et al., 2022; Ragni et al., 2020; Stańczak-Mrozek et al., 2021; Zanettini et al., 2021; Jiang et al., 2022; Candelli et al., 2021; Yang et al., 2021; Al Mosawi et al., 2022; Umasabor-Bubu et al., 2021).

Other two studies reported no impact on COVID-19 prognosis (death and death or ICU admission) but a 13 % statistical reduction in the risk of hospitalization in some Italian geographical areas and in younger subjects (Massari et al., 2021) and no difference in COVID-19 clinical outcomes except for mechanical ventilation, with a significantly lower risk in the influenza vaccinated group (Almadhoon et al., 2022).

Given the many primary studies published, some researchers have conducted ecological studies to suggest a relationship between historic influenza vaccination and COVID-19 (Marin-Hernandez et al., 2021; Zanettini et al., 2021; Moreland et al., 2022; Amato et al., 2020). The disadvantages of ecological works, though, induced researchers to test the association between influenza vaccines and COVID-19 developing *meta*-analyses (Wang et al., 2021; Su et al., 2022; Jiang et al., 2022; Almadhoon et al., 2022; Zeynali Bujani et al., 2021). The objective of our work was to present an umbrella review using evidence currently available in literature to represent the role of COVID-19 on populations who had been administered the influenza vaccine in the period before the pandemic.

2. Materials and methods

The papers included in the umbrella review were sought in MEDLINE, EMBASE, Scopus, Web of Science and Cochrane Library up until 7 June 2023. The research strategy for *meta*-analysis and for ecological studies and the results of each database were reported in supplementary materials, tables S1 and S2.

The selection of works was conducted using the preferred reporting items for systematic reviews and *meta*-analyses (PRISMA) method (Page et al., 2021) by two-blinded authors (P.M.A. and C. M.T.) and PRISMA checklist (Table S1). A methodologist (E.A.) resolved disagreements. The search strategy is reported in Supplementary Tables S2, S3. The quality of *meta*-analyses was assessed using the AMSTAR 2 (Shea et al., 2017). Data quality and data extraction was conducted independently

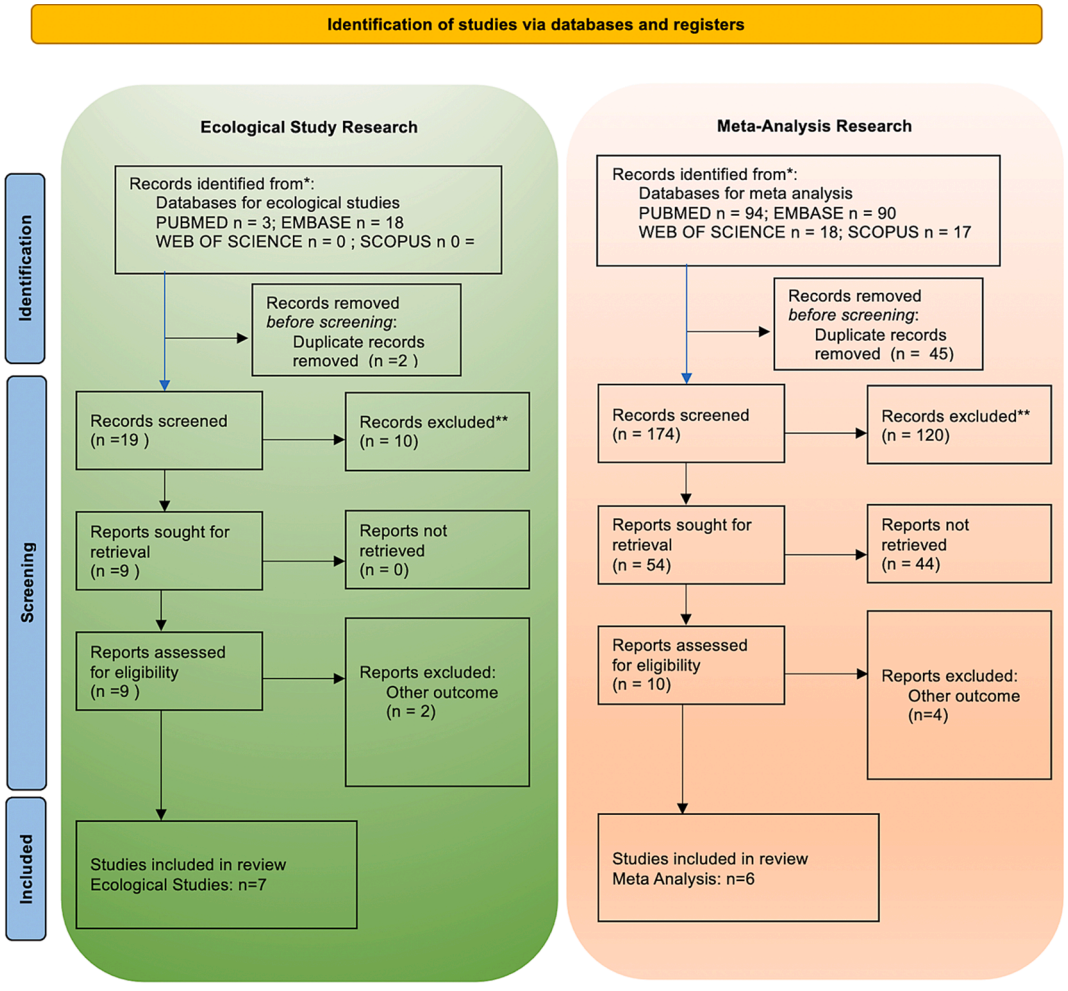

Fig. 1. PRISMA flow-chart reporting literature search and selection regarding ecological studies and *meta*-analyses.

by two authors (P.M.A. and S.M.).

We evaluated the distribution of primary studies included in each *meta*-analysis according to SARS-CoV-2 infection, hospitalization, ICU admission, mechanical ventilation and mortality.

3. Results

3.1. Ecological studies

The literature review highlighted 7 ecological studies of which 4 concerned the USA, 1 South Korea and 2 Italy. The results of the research are represented in Fig. 1, while the studies are described in Table 1.

Regarding the mortality outcome, all studies show a negative relationship between flu vaccination rate and COVID-19 mortality. In Amato et al. the value of the beta coefficient is −3.29 (-5.66; −0.93), p = 0.01 in Marin-Hernandez et al. is −0.0587 (-0.812; −0.20), p = 0.005; both these studies were conducted in Italy. Even in the studies conducted in the USA, a negative relationship is highlighted: Moreland et al. showed the beta coefficient of −5.17 (-7.4; −2.93), p < 0.001 (Moreland et al., 2022); Chen et al. an RR = 0.43 (0.43–0.44), Zanettini et al. a propensity score of 0.88 (0.85–0.91) and Kathe and Wani a Durbin spatial model value of −0.004.

As regards to the relationship between flu vaccination and SARS-CoV-2 seroprevalence, Amato et al. showed a negative relationship with beta = -130 (-198; −62), p = 0.001; instead, compared to SARS-CoV-2 infection, Kim et al. demonstrated a reduction of infections of 9 % (RR = 0.913, 0.838–0.997) while Chen et al showed a reduction of 52 % (RR = 0.48, 0.47–0.48).

Finally, Amato et al also highlighted a negative relationship between influenza vaccination coverage and hospitalization for COVID-19, beta = -4.16 (-6.27; −2.05) and ICU hospitalization beta = -0.58 (-1.05; −0.12) (Table 1).

3.2. Meta-analyses

There are six *meta*-analyses in the literature published in the two-year period 2021–2022. The research results are described in Fig. 1, while Table 2 shows the *meta*-analyses according to author, publication date, number of primary studies and outcomes included A) SARS-CoV-2 infection after influenza vaccination B) hospitalization C) intensive care unit (ICU) D) COVID-19 mortality. We also performed subgroups analysis. Aims, inclusion and exclusion criteria for each *meta*-analysis were reported in Table S4.

SARS-CoV-2 infection after flu vaccination was investigated by 5/6 *meta*-analyses showing a statistically significant reduction in the COVID-19 risk infection in: Zeynali Bujani et al. of 13 %, OR = 0.77 (0.65–0.91), Wang et al., of 14 %, OR = 0.86 (0.79–0.94), Su et al. of 17 %, RR = 0.83 (0.76–0.90), Kapoula et al of 20 %, OR = 0.80 (0.75–0.86), and Jiang et al. of 16 % OR = 0.84 (0.75–0.96) (Table 2, Fig. 2).

Hospitalization was statistically significant only in Kapoula et al., showing a risk reduction of 12 % (OR = 0.88, 0.81–0.95) (Table 2, Fig. 2). ICU admission presented a significant risk reduction only in Jiang et al. work of 17 % (OR = 0.83, 0.72–0.96) (Jiang et al., 2022) (Table 2, Fig. 2). Concerning mechanical ventilation, we found a risk decrease in Jiang et al., Kapula et al. and Almodhoon et al. studies of 31 %, 27 % and 28 %, respectively (Table 2, Fig. 2). Finally, Jiang et al. showed an important risk reduction in mortality outcome (OR 0.69, 0.52–0.93) (Jiang et al., 2022) (Table 2, Fig. 2).

We also described the number and distribution of primary studies according to geographical area considered in each *meta*-analysis (USA = 17, Italy = 12, Spain = 6, Mexico = 4, UK = 3, France = 2, Brazil = 2, Israel = 2, Netherland = 2, Poland = 2, Canada = 1, Denmark = 1, Ecuador = 1, Grace = 1, Iran = 1, Quatar = 1, Serbia = 1, Singapore = 1 and Sweden = 1 (Fig. S1).

3.3. Subgroup analysis

3.3.1. SARS-CoV-2 infection after influenza vaccination

For this outcome, 4/5 *meta*-analyses performed subgroup analyses, with respect to study design, study population, type of anti-flu vaccine administered and diagnostic approach (Table 3).

The cohort studies appeared to be globally significant: in Jiang et al. OR = 0.83 (0.72–0.95), in Kapuola et al. OR = 0.80 (0.75–0.86) and in Su et al. RR = 0.82 (0.73–0.93) Wang et al. highlighted insignificant data, but only on 4 primary studies OR = 0.86 (0.70–1.05).

Cumulative analysis of case-control studies showed significant data for Jiang et al., Kapoula et al., and Wang et al. with the following results, respectively: OR 0.80 (0.60–0.94), OR 0.99 (0.76–1.23), OR 0.89 (0.81–0.99); Su et al. showed non-significant data for case-control studies: RR 0.79 (0.59–1.06) (Table 3).

All subgroup analyses for the cross-sectional studies showed a risk reduction from 24 to 15 % (Table 3).

Table 1
Summary of ecological studies according to influenza vaccination coverage, region or country in which the study was carried out and outcomes.

Authors	Influenza vaccination coverage	Region/ Country	Outcomes				
			Mortality	SARS-CoV-2 seroprevalence	SARS-CoV-2 Infection after influenza vaccination	Hospitalization	ICU
Amato et al., 2020	2019–2020	Italy	r = -3.29 (-5.66; −0.93) p = 0.01	r = -130 (-198; −0.62) p = 0.001	–	r = -4.16 (-6.27; −2.05) p = 0.001	r = 0.58 (-1.05; −0.12) p = 0.017
Marin-Hernandez et al., 2021	2019–2020	Italy	r = -0.587 (-0.812–0.20) p = 0.005	–	–	–	
Moreland et al., 2022	2017	New York	r = -5.17 (-7.4; −2.93) p < 0.001	–	–	–	
Zanettini et al., 2021	2019	USA	Propensity score 0.88 (0.85–0.91)	–	–	–	
Kathe and Wani, 2021	2018–2019	USA	Spatial Durbin Model-0.004	–	–	–	
Kim et al., 2023	2019	South Corea		–	RR = 0.913 (0.838–0.997)	–	–
Chen et al., 2021	2018–2019	USA	RR = 0.43 (0.43–0.44) OR = 0.89 (0.87–0.91)	–	RR = 0.48 (0.47–0.48)	–	–

Table 2
Summary of previous *meta*-analyses results according to publication date, literature research time, number of primary studies, outcomes and subgroups analysis.

Author	Publication date	Literature research time	Number of primary studies included	Outcomes and numbers of primary studies SARS-CoV-2 Infection after influenza vaccination	Hospitalization	ICU admission	Mechanical Ventilation	Mortality	Subgroup analysis
Jiang et al.	2022	April 2022	36	N = 20; OR 0.84 (0.75–0.96); I^2 = 89 %	N = 9; OR 0.87 (0.68–1.10); I^2 = 79 %	N = 10; OR 0.83 (0.72–0.96); I^2 = 61 %	N = 8; OR 0.69 (0.57; 0.84); I^2 = 69 %	N = 15; OR 0.69 (0.52–0.93); I^2 = 79 %	● Study design Diagnostic Approach
Kapoula et al.	2022	April 2022, 30	39	N = 22 OR 0.80 (0.75–0.86) p < 0.01 I^2 = 70.1 %	N = 15 OR 0.88 (0.81–0.95) p < 0.01 I^2 = 95.1 %	N = 11 OR 0.96 (0.88–1.06) p = 0.40 I^2 = 86.0 %	N = 4 OR 0.73 (0.58–0.92) p < 0.01. I^2 = 42.4 %	N = 18 OR 0.90 (0.81–1.01) p < 0.07 I^2 = 78.2 %	● Study design Patients population Diagnostics Age, gender Country
Su et al.	2022	August 2021, 13	23	N = 16; RR 0.83 (0.76–0.90); I^2 =80.8 %	N = 7; RR 0.71 (0.59–0.84); I^2 =89 %	N = 6; RR 0.93 (0.64–1.36); I^2 =89 %	–	N = 7; RR 0.83 0.68–1.01); I^2 =89 %	● Study design Country Vaccine type
Almadhoon et al.	2022	August 2021, 5	13	–	N = 3; RR 0.74 (0.51–1.06); I^2 = 98 % *	N = 6; RR 0.84 (0.44—1.62); I^2 = 95 % **	N = 4; RR 0.72 (0.54; 0.96); I^2 =52 %	N = 7; RR 1.20 (0.71–2.04); I^2 = 98 %	● Country
Wang et al.	2021	March 2021, 10	16	N = 9; OR 0.86 (0.79–0.94); I^2 =89 %	N = 3; OR 0.74 (0.51–1.06); I^2 =89 %	N = 2; OR 0.63 (0.22 1.81); I^2 =89 %	–	N = 3; OR 0.89 0.73 1.09); I^2 =89 %	● Study design Country Vaccine type Sample size
Zeynali Bujani et al.	2021	November 2020, 25	15	N = 9; OR 0.77 0.65–0.91); I^2 = 78.8 %	N = 4 RR = 0.75 0.46–1.28); I^2 = 85.7 %	N = 3 RR = 0.71 0.40–1.27); I^2 = 44.4 %	–	(N = 7 RR = 0.68 0.42–1.11); I^2 = 96.8 %	● Not performed

*Influenza vaccine and COVID-19 hospitalization time N = 4; MD −0.16 (-2.76; 2.45); I^2 = 78 %; **Influenza vaccine and ICU hospitalization time N = 2; MD 0.99 (-2.15; 4.13); I^2 = 0 %.

Regarding the study population, 3 *meta*-analyses performed subgroup analyses. Concerning the general population, three *meta*-analyses showed a risk reduction from 21 % to 16 % (Table 3).

In contrast, the analysis of health care workers showed a risk reduction only in Jiang et al. (8 studies) OR = 0.75 (0.59–0.93). While it is important to underline that there is a risk reduction of 24 % in Jiang et al. OR = 0.76 (0.75–0.77) and of 28 % in the elders in Kapoula et al. OR = 0.72 (0.56–0.92) (Table 3).

Concerning the type of vaccine administered, the quadrivalent showed a reduction of COVID-19 infection of 26 %. On the contrary, the trivalent vaccine revealed non-significant results in both *meta*-analyses: Jiang et al. OR = 1.0 (0.77–1.29); Su et al., RR = 0.89 (0.64–1.23), (Table 3).

For the inactivated vaccine, Jiang et al. found an OR = 0.77 (0.66–0.89) (Table 3).

With respect to diagnostics, subgroup analysis found insignificant results in Jiang et al. In Kapoula et al., however, the PCR had an OR = 0.84 (0.77–0.92) and the other diagnostic methods an OR = 0.74 (0.66–0.83); serology was not significant (Table 3).

Analyses performed by Kapuola et al. on the geographical area considered according to the primary studies revealed significant data in North America and Europe (Table 3).

3.3.1.1. Type of influenza vaccination. This subgroup analysis was performed in two papers (Jiang et al., 2022; Su et al., 2022). In both, the use of the quadrivalent vaccine has shown significant results.

3.3.1.2. Study population. All 3 *meta*-analyses demonstrated significance with regards to the general population, while the results relating to the population of health workers is not significant for 2/3 *meta*-analyses (Jiang et al., 2022; Su et al., 2022; Kapoula et al.,).

3.3.1.3. Diagnostics. In the *meta*-analysis by Jiang et al., no diagnostic methods achieved significant results, while in Kapoula et al. only the diagnosis with PRC presented a significant OR.

3.3.1.4. Region. Only Su et al. work displayed significant results relative to Asian countries (Table 3).

3.3.2. Hospitalization

Regarding this outcome, no subgroup analysis revealed statistically significant data.

3.3.3. Intensive care unit

3.3.3.1. Study design. Only Jiang et al. performed this analysis and statistically significant data are highlighted for both cohort and case-control studies (Table 3).

3.3.3.2. Diagnostics and region. Only Kapuola et al. work performed subgroup analyses that are not significant (Table 3).

3.3.4. Mechanical ventilation

This outcome is evaluated only in Jiang et al. work, considering cohort studies and general population, but not the elderly population (Table 3).

3.3.5. Mortality

Jiang et al. performed a subgroup analysis. As far as the type of population concerned, the data on the elderly is significant, while the

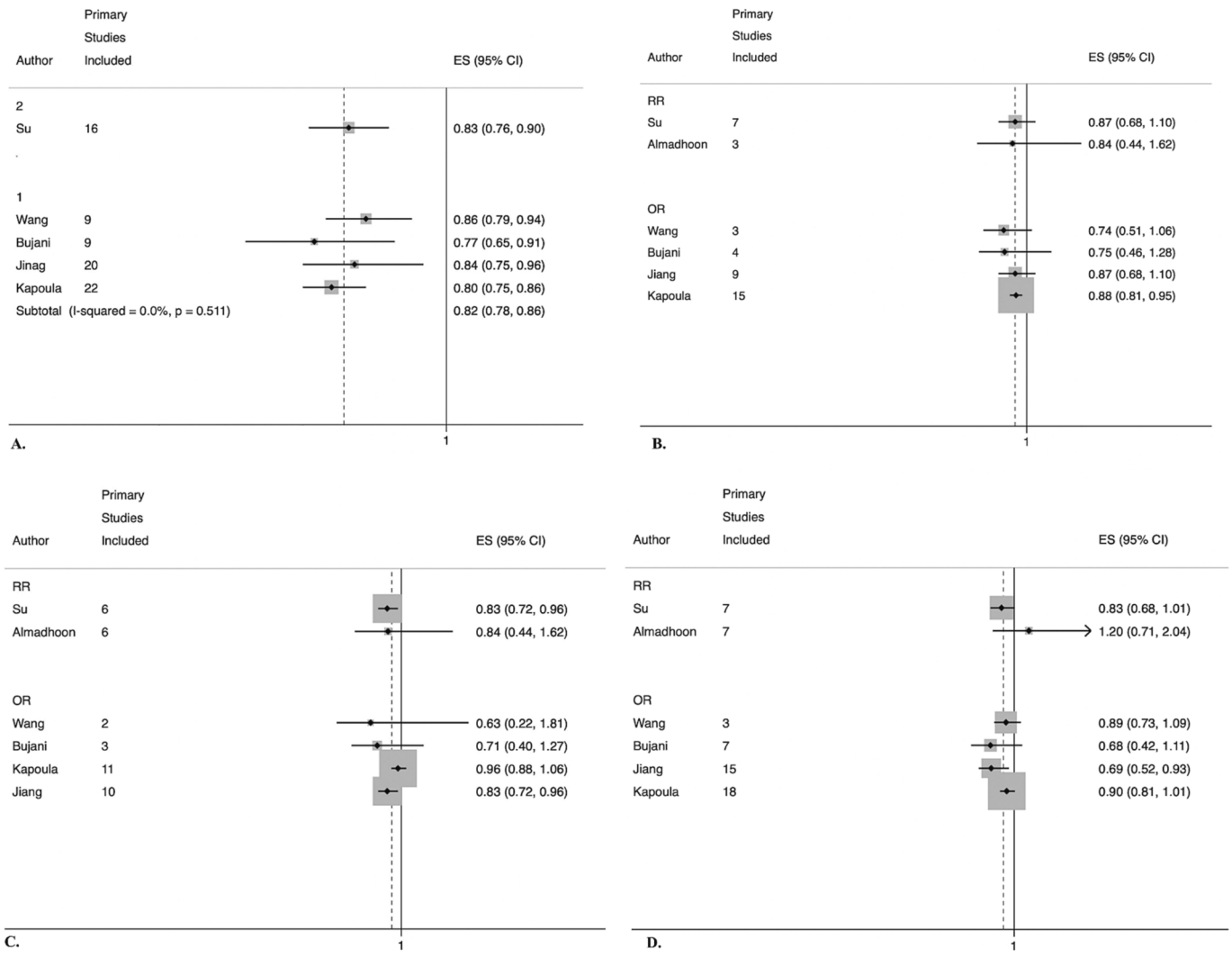

Fig. 2. Meta-analyses results according to outcomes: A) SARS-CoV-2 infection after influenza vaccination B) Hospitalization C) Intensive care unit D) COVID-19 mortality.

data on the general population is at the limit of significance.

Kapoula et al. in our work found insignificant results on diagnostics. While the results on the geographical areas analyzed were in contrast with the results of Almadhoon et al. (Table 3).

3.3.6. AMSTAR 2 bias scale

It should be emphasized that not all *meta*-analyses scored well. Indeed, the *meta*-analysis by Zeynali Bujani et al (score 7/16) presented a "no" to the following important items: 2, 6, 7, 9, 10, 12, 13 14 and 15 (Table 4). While Su et al. had the best score (13/16).

4. Discussion

The present umbrella review refers to the years preceding the start of the administration of the COVID-19 vaccine (tables 1 and S4) which, as is known, was of fundamental importance in reducing hospitalizations in intensive care and mortality in worldwide.

Our study includes seven ecological studies and six *meta*-analyses hypothesizing a possible protective action of influenza vaccination against SARS-CoV-2 infection and its sequelae. The ecological studies present in literature indicate that there is a negative relationship between influenza vaccination and outcomes related to SARS-CoV-2 infection, particularly for mortality. This data appears uniform in the various geographical areas investigated: Italy, USA, and South Korea. Amato et al. related flu vaccination trends in the three-year period preceding the pandemic with SARS-CoV-2 seroprevalence, hospitalization, ICU admission and death attributable to COVID-19, highlighting a robust correlation (Amato et al., 2020). This data is also confirmed in the work of Marin-Hernandez et al. (Marin-Hernandez et al., 2021). Moreland et al. evaluated only New York city and showed that there was indeed a negative correlation between flu vaccination and COVID-19 mortality (Moreland et al., 2022). Of particular interest in this study is the following finding: a negative correlation between the flu vaccine and COVID-19 mortality was highlighted for Whites but was not confirmed for Hispanics and for the elderly. Zanettini et al. and Kathe and Wani conducted ecological studies considering data from all over the USA, confirming the negative correlation between influenza vaccination coverage and COVID-19-related mortality (Zanettini et al., 2021; Kathe and Wani, 2021). Chen et al. evaluated not only mortality, but also the incidence of COVID- 19, showing a negative correlation in both cases, concluding that vaccination coverage above 40 % could guarantee this result. In addition, it was highlighted that the distribution of the flu vaccine was not the prerogative of all social and ethnic categories of the country (Chen et al., 2021). Kim et al. agree in highlighting a negative association between influenza vaccine coverage in the Asian countries examined (Kim et al., 2023). The data derived from ecological studies indicate how the administration of the anti-flu vaccine in subjects at risk has led to a reduction in mortality, particularly in the over 65y (Marin-

Table 3
Subgroups analysis according to outcome considered.

Subgroups Analysis	Author				
	Jiang et al., 2022	Kapoula et al., 2022	Su et al., 2022	Wang et al., 2021	Almadhoon et al., 2022
SARS-CoV-2 INFECTION AFTER INFLUENZA VACCINATION					
Study design					
Cohort	**N = 8 OR 0.83 (0.72–0.95) I^2 = 88 %**	**N = 10 OR 0.80 (0.75–0.86) I^2 = 41.5 %**	**N = 8 RR 0.82 (0.73–0.93) I^2 = 73.2 %**	N = 4 OR 0.86 (0.70–1.05) I^2 = 71.7 %	–
Cohort, prospective		N = 4 OR 0.80 (0.56–1.08) I^2 = 90.9 %			–
Case-control	**N = 3 OR 0.80 (0.60–0.94) I^2 = 0 %**	**N = 3 OR 0.99 (0.76–1.23) I^2 = 51.7 %**	N = 4 RR 0.79 (0.59–1.06) I^2 = 81.8 %	**N = 2 OR 0.89 (0.81–0.99) I^2 = 0.0 %**	
Cross-sectional	**N = 6 OR 0.76 (0.75–0.77) I^2 = 45 %**	**N = 5 OR 0.76 (0.75–0.77) I^2 = 0.0 %**	**N = 4 RR 0.82 (0.71–0.94) I^2 = 82.3 %**	**N = 3 OR 0.85 (0.77–0.95) I^2 = 0.0 %**	
Type of influenza vaccine					
Quadrivalent	**N = 8 OR 0.74 (0.67–0.81) I^2 = 71 %**	–	**N = 4 RR 0.74 (0.65–0.84) I^2 = 0.0 %**	–	
Trivalent	N = 2 OR 1.00 (0.77–1.29) I^2 = 71 %	–	N = 2 RR 0.89 (0.64–1.23) I^2 = 95.9 %	–	
Inactivated	**N = 5 OR 0.77 (0.66–0.89) I^2 = 59 %**	–	–	–	
Unknown			**N = 10 RR 0.84 (0.77–0.93) I^2 = 69.5 %**	–	
Population					
General	**N = 9 OR 0.79 (0.71–0.87) I^2 = 75 %**	**N = 13 OR 0.80 (0.74–0.87) I^2 = 68.4 %**	**N = 11 RR 0.84 (0.77–0.89) I^2 = 73.4 %**		
Health workers	**N = 8 OR 0.74 (0.59–0.93) I^2 = 85 %**	N = 6 OR 0.84 (0.68–1.04) I^2 = 66.6 %	N = 5 RR 0.58 (0.34–1.01) I^2 = 86.4 %		
Elders	**N = 6 OR 0.76 (0.75–0.77) I^2 = 45 %**	**N = 3 OR 0.72 (0.56–0.92) I^2 = 53.8 %**	–		
Diagnostics			–		
HT-PCR	N = 13 OR 0.87 (0.72–1.06) I^2 = 84 %	**N = 15 OR 0.84 (0.77–0.92) I^2 = 57.7 %**	–		
Serological	N = 5 OR 0.90 (0.75–1.08) I^2 = 74 %	N = 2 OR 0.83 (0.38–1.82) I^2 = 37.9 %	–		
Other	N = 5 OR 0.48 (0.19–1.21) I^2 = 90 %	**N = 5 OR 0.74 (0.66–0.83) I^2 = 74.9 %**	–		
Region					
North America	–	**N = 6 OR 0.76 (0.75–0.77) I^2 = 0.0 %**	**N = 4 RR 0.78 (0.74–0.82) I^2 = 33.0 %**	**N = 1 OR 0.76 (0.68–0.85)**	
Asia	–	**N = 3 OR 0.83 (0.77–0.90) I^2 = 0.0 %**	N = 2 RR 0.26 (0.02–2.78) I^2 = 86.4 %	**N = 1 OR 0.79 (0.65–0.96)**	
Europe	–	**N = 13 OR 0.81 (0.70–0.93) I^2 79.7 %**	**N = 10 RR 0.86 (0.78–0.96) I^2 = 65.5 %**	**N = 7 OR 0.91 (0.84–0.98) I^2 = 10.4 %**	
Others	–				
HOSPITALIZATION					
Study design					
Cohort	N = 9 OR 0.87 (0.68–1.10) I^2 = 79 %	–	–	–	
Cross-sectional	–	–	–	–	
Population					
General	N = 8 OR 0.86 (0.66–1.22) I^2 = 82 %	–	–		
Elders	N = 3 OR 1.00 (0.82–1.22) I^2 = 0 %	–	–		
Region					
North America		N = 10 OR 0.93 (0.83–1.04) I^2 = 75.7 %	–		
Asia		–	–		
Europe		N = 5 OR 0.80 (0.63–1.02) I^2 = 73.1 %	–		
Others		–	–		
Diagnostics					
HT-PCR		N = 10 OR 0.87 (0.78–1.02) I^2 = 74.6 %	–		
Serological		N = 5 OR 0.88 (0.67–1.12) I^2 = 90.0 %	–		
Other/Not specified		–	–		
ICU					
Study design					
Cohort	**N = 10 OR 0.83 (0.72–0.96) I^2 = 61 %**	–	–		
Cross-sectional	**N = 2 OR 0.72 (0.68–0.76) I^2 = 49 %**	–	–		
Population					

(*continued on next page*)

Table 3 (*continued*)

Subgroups Analysis	Author				
	Jiang et al., 2022	Kapoula et al., 2022	Su et al., 2022	Wang et al., 2021	Almadhoon et al., 2022
General	**N = 9 OR 0.91 (0.87–0.96) I^2 = 39 %**	–	–		
Elders	N = 4 OR 1.06 (0.71–1.56) I^2 = 37 %	–	–		
Diagnostics					
HT-PCR		N = 9 OR 0.93 (0.84–1.03) I^2 = 58.5 %	–		
Other/Not specified		N = 2 OR 1.12 (0.80–1.57) I^2 = 14.1 %	–		
Region					
North America		N = 4 OR 0.69 (0.47–1.02) I^2 = 10.3 %	–		
Asia		**N = 1 OR 0.76 (0.59–0.98)**	–		
Europe		N = 5 OR 1.05 (0.95–1.16) I^2 = 20.6 %	–		
MECHANICAL VENTILATION					
Study design					
Cohort	**N = 6 OR 0.72 (0.54–0.96) I^2 = 66 %**	–	–	–	
Cross-sectional	–	–	–	–	
Population					
General	**N = 5 OR 0.82 (0.76–0.88) I^2 = 43 %**	–	–	–	
Elders	N = 2 OR 0.96 (0.42–2.17) I^2 = 66 %	–	–		
Mortality					
Study design					
Cohort	**N = 14 OR 0.70 (0.51–0.97) I^2 = 88 %**	–	–		
Cross-sectional	–	–	–		
Population					
General	**N = 14 OR 0.74 (0.55–1.00) I^2 = 86 %**	–	–		
Elders	**N = 3 OR 0.70 (0.51–0.96) I^2 = 0 %**	–	–		
Diagnostics					
RT-PCR	–	N = 14 OR 0.93 (0.82–1.06) I^2 = 80.3 %	–		
Other/Not specified	–	N = 4 OR 0.81 (0.65–1.00) I^2 = 37.1 %	–		
Region					
North America	–	N = 3 OR 0.89 (0.76–1.03) I^2 = 75.3 %	–		N = 2 RR 0.82 (0.60–1.13) I^2 = 49.0 % (*)
Asia	–	**N = 1 OR 0.78 (0.63–0.95) I^2 = 0.0 %**	–		–
Europe	–	N = 12 OR 0.94 (0.80–1.09) I^2 = 75.3 %	–		N = 3 RR 1.87 (1.00–3.49) I^2 = 86.0 % (**)

(*) only USA (**) only Italy.

Table 4
AMSTAR 2 bias scale: summary of results for each *meta*-analysis.

Author	AMSTAR ITEMS																Total AMSTAR score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Jiang et al., 2022	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	10/16
Kapoula et al., 2022	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	10/16
Su et al., 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	13/16
Almadhoon et al., 2022	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	No	No	No	Yes	10/16
Wang et al., 2021	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	12/16
Zeynali Bujani et al., 2021	Yes	No	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No	No	No	No	Yes	7/16

Hernandez et al., 2021; Zanettini et al.,2021; Moreland et al., 2022; Amato et al., 2020; Kim et al., 2023; Chen et al., 2021).

The *meta*-analyses offer an overview of the entire literature, composed exclusively of observational studies produced during the two years of the pandemic. From the first *meta*-analysis by Zeynali Bujani et al. (Zeynali Bujani et al., 2021) we can see that the flu vaccine could have a protective action against SARS-CoV-2 infection. This evidence was constant in all *meta*-analyses (Wang et al., 2021; Su et al., 2022; Jiang et al., 2022, Almadhoon et al., 2022; Zeynali Bujani et al., 2021; Su et al., 2022; Kapoula et al., 2022). A finding accompanying this result is the high degree of statistical heterogeneity present in all *meta*-analyses, despite the progressive inclusion of new primary studies. This result could be linked not so much to the presence of gray literature as to the study designs. In fact, if the subgroup analyses are visualized, it can be seen that the cross-sectional studies show a lower value of the I^2 statistic than the cohort studies. This could be related to the lack of follow-up that cross-sectional studies have. Of particular interest are the results with lower statistical heterogeneity when flu vaccination in the elderly

population is considered, which is known to be recommended (Jiang et al., 2022; Kapoula et al., 2022).

The analysis by geographical area also shows conflicting results, particularly for Europe. This may be linked to the different timing with which the pandemic spread in the old continent and to the public health policies adopted to control the viral spread (Altobelli et al., 2022). Compared to the diagnostic method, this is studied by two *meta*-analyses and the results in this case lean towards the non-significance for the method used (RT-PCR or serological). The difference could lie in the timing of the test, the type of test (RT-PCR, rapid antigen or serological test) and this data could influence the statistical heterogeneity.

The results concerning the remaining outcomes appear more diverse. With respect to the effect of the influenza vaccine on hospitalization for COVID-19, only two *meta*-analyses show significant results (Su et al., 2022; Kapoula et al., 2022). In both, the subgroup analyses do not show significant data for the study design, for the population involved, the geographical area and the diagnostic method. For ICU admission, only one *meta*-analysis shows a significant result (Jiang et al., 2022) (Table 3, Fig. 2).

The data relating to mechanical ventilation in *meta*-analyses (Jiang et al., 2022; Almadhoon et al., 2022; Kapoula et al., 2022) demonstrate significant results with reduced statistical heterogeneity. One could speculate that flu vaccines could stimulate trained innate immune memory so that the local lung immune system is primed for a rapid response against another pathogen such as SARS-CoV-2 (Almadhoon et al., 2022). In particular, the influenza vaccine keeps the immune system primed through Toll-Like Receptor (TLR)-7, an important binding of single-stranded RNA respiratory viruses, including SARS-CoV-2 (Poulas et al., 2020). The underlying mechanisms remain poorly understood, but an induction of the innate immune response following vaccination, that is independent from memory T or B cells, is plausible: this phenomenon is known as “trained innate immunity”. Indeed, it has been demonstrated that the bacille Calmette-Guerin (BCG) vaccination in healthy subjects induces trained immunity and non-specific protection from infections through epigenetic reprogramming of innate immune cells (Kleinnijenhuis et al., 2012).

In the case of the interaction between influenza vaccination and the SARS-CoV-2 virus, the most accredited hypothesis is that the vaccine induces upregulation of the recognition receptors (such as TLRs) on the surface of macrophages, dendritic cells and neutrophils, and modulates the secretion of proinflammatory cytokines (Poulas et al., 2020). The influenza vaccine could stimulate trained innate immune memory so that the local lung immune system is primed for a rapid response against another pathogen such as SARS-CoV-2 (Almadhoon et al., 2022). In particular, the influenza vaccine keeps the immune system primed through TLR-7, an important binding of single-stranded RNA respiratory viruses, including SARS-CoV-2 (Su et al., 2022; Kapoula et al., 2022). Influenza viruses and coronaviruses share some similarities in their evolution, transmission, and pathogenicity, including strategies to control interferon and innate immune responses during infection process (Su et al., 2022; Zeynali Bujani et al., 2021). The vaccine may induce inflammatory and antiviral reactions by establishing similar patterns in receptor identification (Zeynali Bujani et al., 2021). Influenza and SARS-CoV-2 viruses bind to the angiotensin-converting enzyme 2 (ACE-2) (Almadhoon et al., 2022). Influenza vaccination downregulates ACE-2, reducing the binding of SARS-CoV-2 to ACE-2 receptors (Su et al., 2022). Furthermore, Earnest et al. (Earnest et al., 2015) reported that both coronaviruses and low-pathogenic influenza A viruses depend on target cell proteases to cleave viral glycoproteins and prime them for virus-cell membrane fusion, and that anti-tetraspanin antibodies inhibited both (Massoudi and Mohit, 2021).

Finally, it is necessary to make some methodological considerations. All ecological studies show a negative relationship between vaccination and mortality, while only one *meta*-analysis shows a 31 % reduction in mortality. It should be emphasized that ecological studies are subject to the so-called “Ecological Fallacy” or “results from making a causal inference about individual phenomena on the basis of observations of groups” (Morgenstern, 1982). In ecological studies three types of bias can be distinguished: information, selection and confounding. Confounding is a mixing of the effects of other risk factors with the exposure of interest.

In this context, we believe that some limitations should be considered. With regard to ecological studies, the lack of data on the population not vaccinated for influenza; concerning *meta*-analyses, aggregated data with high statistical heterogeneity and limited methodological validity; as shown by the scores on the AMSTAR-2 scale (Table 3), a reduced methodological quality of the primary studies. As also reported by Zdravkovic et al., the quality of COVID-19 publications in the three highest ranked scientific medical journals is below the quality average of these journals (Zdravkovic et al., 2020).

5. Conclusions

The influenza vaccination campaign during the pandemic must be considered important for public health and the sustainability of health systems, for at least two reasons: the first linked to the awareness of the importance of the flu vaccination campaign, a legacy for the future (Bhatt, 2021); the second linked to the fact that both influenza viruses and SARS-CoV-2 not only share transmission modalities, but are potentially fatal for patients with chronic pathologies, such as cardiovascular, respiratory, oncological and metabolic or institutionalized diseases (Petrilli et al., 2020; Gao et al., 2021; Moyo et al., 2020). These findings need to be verified at a later stage of the pandemic.

Ethics approval

No ethics approval was required for this systematic review of literature.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or non-for-profit sectors.

CRediT authorship contribution statement

Paolo Matteo Angeletti: Methodology, Formal analysis, Data curation. **Serena Marchi:** Writing – review & editing. **Claudia Maria Trombetta:** Writing – review & editing. **Emma Altobelli:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2023.102575.

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