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# The efficacy and safety of influenza vaccination in older people: An umbrella review of evidence from meta-analyses of both observational and randomized controlled studies

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ABSTRACT

Vaccination is the main public health intervention to prevent influenza. We aimed to evaluate the efficacy and safety of influenza vaccination including systematic reviews and meta-analyses of observational studies and randomized controlled trials (RCTs). Peer-reviewed systematic reviews with meta-analyses of prospective studies that investigated the association of influenza vaccination with any health-related outcome, as well as RCTs that investigated the efficacy and safety of influenza vaccination, were included. Among 1240 references, 6 meta-analyses were included. In cohort studies of community-dwelling older people influenza vaccination was associated with a lower risk of hospitalization for heart disease and for influenza/pneumonia (strength of evidence: convincing). Evidence in lowering the risk of mortality in community-dwelling older people, of all deaths/severe respiratory diseases in high risk community-dwelling older people and of hospitalization for influenza/pneumonia in case-control studies, was highly suggestive. In RCTs, influenza vaccination, compared to placebo/no intervention, was associated to higher risk of local tenderness/sore arm and to a reduced risk of influenza like-illness. Both these associations showed moderate evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation). In conclusion, influenza vaccination in older people seems safe and effective. Further, the evidence on safety and efficacy of vaccines in this population might benefit by an extension of the follow-up period both in RCTs and in longitudinal studies, beyond the usual 6-month period, in order to be able to evaluate the impact of vaccination on long term outcomes.

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## 1. Introduction

Influenza represents a major cause of morbidity and is responsible for a large number of deaths (291000–646000) every year (Sah et al., 2019). In the United States, over the last 9 years, 28 million cases, 461,111 hospitalizations, and 40,500 influenza-related deaths occurred each year on average (Sah et al., 2019). Among the 6 World Health Organization (WHO) regions, the highest burden of influenza-associated deaths per year is in sub-Saharan Africa, the western Pacific, and southeast Asia. (Iuliano et al., 2018) Notably, most deaths are observed among people aged over 75 years. (Bechini et al., 2020; Iuliano et al., 2018)

Older people are more likely to have chronic conditions that can be exacerbated by influenza. Moreover, influenza can cause secondary infections, such as pneumonia, that is frequently a cause of death (Hardelid et al., 2013).

The World Health Organization (WHO), Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC), and the European Centre for Disease Prevention and Control (ECDC) unanimously recommend influenza vaccination, especially in high-risk groups such as older people and patients with a known medical indication. Worldwide, medical associations support these recommendations or have included them in their clinical guidelines (Sullivan and Cowling, 2019; Verhees et al., 2018).

Vaccination represents the main public health intervention to prevent influenza. (Bechini et al., 2020) The two main types of influenza vaccination widely available are inactivated influenza vaccines (IIV) and live attenuated influenza vaccines (LAIV), whose composition is updated annually by WHO. Those have been traditionally produced to protect against 3 different seasonal influenza viruses (A(H3N2), pandemic A(H1N1) and 1 of 2 influenza B lineage viruses) and are called trivalent vaccines. (World Health Organization, 2012; Rondy et al., 2018) However, recently vaccines which protect against 4 different viruses, namely quadrivalent vaccines, have become available in some countries. (World Health Organization, 2012) Regardless of the type or composition of seasonal influenza vaccine, vaccination should be administered annually to provide optimal protection against infection. (Kassianos et al., 2016; World Health Organization, 2012)

The efficacy of influenza vaccines, currently at 44 % (Sah et al., 2019), is limited by the rapid antigenic evolution of the virus and a manufacturing process that can lead to vaccine mismatch. The US National Institute of Allergy and Infectious Diseases (NIAID) recently identified the development of a universal influenza vaccine with an efficacy of at least 75 % as a high scientific priority (Sah et al., 2019).

Surveys reported that approximately 90 % of physicians think that influenza vaccination in older people is effective and 85 % of general practitioners (GPs) recommend influenza vaccination to their older patients (Klett-Tammen et al., 2016). Among GPs not advising vaccination, 17 % question the efficacy of vaccination. About 70 % of community-dwelling older people with a medical indication believe vaccination is effective (Verhees et al., 2018) and when patients refuse vaccination, this is mainly because they consider themselves healthy or fear side effects (Kan and Zhang, 2018). Vaccination is refused due to uncertainty regarding its efficacy in only 2% of the high-risk patients and approximately 5% of the community-dwelling older people.

Influenza vaccination has shown a moderate preventive effect in older people and a remarkable decrease in morbidity for influenza and pneumonia, respiratory or cardiovascular complications and risk of hospitalization and death. (Jefferson et al., 2005; Kan and Zhang, 2018; Nichol et al., 2007; Ridenhour et al., 2013) In this sense, a Cochrane review (Jefferson et al., 2010) confirmed the safety of the influenza vaccine, but found no convincing evidence for its efficacy. However, a reanalysis of the same data, conducted by Beyer et al., using a biological and conceptual framework, showed significant predictions for the efficacy of the influenza vaccine, thus supporting the ongoing efforts aimed to the vaccination of older people (Kan and Zhang, 2018).

Considering this high grade of uncertainty and the importance of this preventive tool in the older population, the aim of the present work is to evaluate – through an umbrella review with integrated meta-analyses - the strength and credibility of the evidence derived from systematic reviews with meta-analyses on influenza vaccination in older people. Observational and intervention studies will be assessed, in order to obtain a general summary of their importance relative to health outcomes and side effects.

## 2. Materials and methods

### 2.1. Protocol

The protocol of this review is registered on Prospero, with ID: CRD42019134704. For this umbrella review the PRISMA checklist was followed (Liberati et al., 2009).

### 2.2. Data sources and searches

MEDLINE/Ovid, Embase, Cochrane Library and Epistemonikos databases were searched from inception until 12th May 2019 adapting the search strategy from a published Cochrane review (Demicheli et al., 2018). We updated the search on 24th April 2020. In addition, the reference lists of eligible articles were hand searched.

The question for this review was developed using the PICO (Participants, Intervention, Comparator, Outcome) criteria:

- Population: Older people, aged more than 65 years old
- Intervention: Influenza vaccination, any kind, not in combination
- Comparator: Placebo, no treatment
- Outcome: Benefits and harms of influenza vaccination, any health outcome was considered suitable and any outcome measure.

### 2.3. Study selection

We included peer-reviewed systematic reviews with meta-analyses of prospective longitudinal design (i.e. prospective/ cohort or retrospective/ case-control) studies that investigated the association of influenza vaccination with any health-related outcome, as well as RCTs that investigated the efficacy and safety of influenza vaccination.

Restrictions were applied to any population aged > 65 years or with a mean age at least equal to 75 years, independently from the standard deviation. No language restrictions were applied.

Inclusion and exclusion criteria adopted were as follows.

### 2.4. Inclusion criteria

- Meta-analyses that included people aged 65 or older undergoing influenza vaccination including a control group
- Meta-analyses of prospective longitudinal design (i.e. prospective/ cohort or retrospective/ case-control) studies that investigated the association of influenza vaccination with any health-related outcome. Any metric was considered eligible.
- Meta-analyses of randomized controlled trials (RCTs) that investigated the effects of influenza vaccination on any health-related outcome. Any metric was considered eligible.

### 2.5. Exclusion criteria

- Animal or in vitro models.
- Systematic reviews without meta-analyses.
- Conference abstracts.
- No peer-reviewed article

Duplicates exclusion was performed by two independent reviewers (JD, SC). If no consensus was reached, a third independent reviewer solved the conflict (NV).

### 2.6. Data screening

Screening of titles and abstracts (CB, DS, CaB) was piloted and each reference was screened by two reviewers, independently. In case of disagreement, the final decision was reached after consensus with another independent author (JD). The full texts of all potentially eligible articles were then retrieved (GT), and a consensus between two investigators (CB, JD) determined the final eligibility of each reference. If two meta-analyses were available for the same outcome, the largest in terms of studies was included.

### 2.7. Data extraction

The data extraction was piloted. Two independent investigators (CB, JD) extracted the following information for each article: (I) PMID/DOI; (II) first author; (III) year of publication; (IV) number of included studies and the total number of people included in the meta-analysis; (V) population or main condition of patients vaccinated; (VI) effect sizes used in the review; (VII) study design of included primary studies (e.g. case-control, prospective, RCT); (VIII) number of cases (people with the outcome of interest) and controls (without the outcomes) for each study; (IX) number of people randomized to influenza vaccination with the correspondent number of events and number of people randomized to placebo/control and correspondent number of events in intervention meta-analyses; (X) mean follow-up; (XI) mean age of participant population (65–74, 75–84, > 85);(XII) and vaccination type (e.g. adjuvated, not adjuvated etc.)

Next, the study-specific estimated relative risk for health outcomes (risk ratio [RR], odds ratio [OR], hazard ratio (HR), incident risk ratio (IRR), mean difference [MD]), along with the 95 % confidence intervals (CIs) were extracted.

### 2.8. Quality of the meta-analyses

The assessment of the methodological quality of the included meta-analyses was performed using the AMSTAR 2 (Shea et al., 2017). AMSTAR 2 has 16 items leading to an overall AMSTAR 2 score as follows (Shea et al., 2017):

- High: No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- Moderate: More than one non-critical weakness: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
- Low: One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
- Critically low: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

### 2.9. Statistical analysis

For each meta-analysis, the summary effect size and its 95 % CIs were estimated through a random-effects model (Higgins et al., 2009).

The prediction interval (PIs) and its 95 % CI were also estimated, in order to account for between-study effects and estimate the certainty of the association if a new study addresses that same association (Ioannidis, 2009). Finally, it was assessed whether the largest study is statistically significant with 95 % CIs excluding the null (Veronese et al., 2019).

Between-study heterogeneity was estimated by the $I^2$ metric; values > 50 % are indicative of high heterogeneity, while values above 75 % suggest very high heterogeneity (Ioannidis et al., 2007).

In addition, the evidence of small-study effects (i.e., whether small studies would have inflated effect sizes compared to larger ones) was calculated by using the regression asymmetry test developed by Egger and co-workers.(Egger et al., 1997) A p-value < 0.10 with more conservative effects in larger studies than in random-effects meta-analysis was considered as indicative of small-study effects (Sterne et al., 2011).

Finally, the Ioannidis's excess of significance test was applied (Ioannidis and Trikalinos, 2007b). This was applied in order to evaluate whether the number of studies with nominally significant results (i.e. with $p < 0.05$) among those included in a meta-analysis is too large, based on the power that these datasets have to detect effects at $\alpha = 0.05$. The power estimate for each dataset was calculated. The sum of the power estimates of each study provides the expected (E) number of datasets with nominal statistical significance. As described elsewhere, the number of expected 'positive' (i.e., statistically significant) can be compared with the observed (O) number of statistically significant studies through a $\chi^2$-based test. Excess significance for single meta-analysis was considered if $p < 0.10$. The O versus E comparison was done separately for each meta-analysis but was also extended to groups including many meta-analyses after summing the O and E values of each individual meta-analysis.

### 2.10. Criteria for evidence categories for observational studies

For meta-analyses on observational studies evidence was classified according to the following criteria:

- convincing evidence (Class I): more than 1000 cases, significant summary associations per random-effects calculations ($p < 10^{-6}$), no evidence of small-study effects, no evidence of excess of significance, 95 % prediction intervals not including the null and not large heterogeneity (i.e., $I^2 < 50$ %);
- highly suggestive evidence (Class II): more than 1000 cases, significant summary associations per random-effects calculations ($p < 10^{-6}$), and the largest study with 95 % CI excluding the null;
- suggestive evidence (Class III): more than 1000 cases and significant summary associations per random-effects calculations ($p < 10^{-3}$);
- weak evidence: all other associations with $p < 0.05$;
- non-significant associations: all associations with $p > 0.05$ (Ioannidis et al., 2011).

For associations supported by either class I or class II evidence, it was planned to conduct sensitivity analysis by participants' mean age and vaccination type and by considering only studies with a prospective cohort design supported by either class I or class II evidence. However, these analyses were not possible since the information regarding mean age/vaccination type/study design were missing or too homogenous (i.e. included only cohort studies and used the same type of vaccination).

### 2.11. Criteria for evidence categories for RCTs

Evidence from meta-analyses of RCTs was assessed in terms of the

significance of the summary effect, using a p-value < 0.05 as statistically significant and applying the GRADE assessment (Guyatt et al., 2008).

### 2.12. Criteria for grading the evidence

In case of overlapping outcomes, investigated in both meta-analyses of observational studies and meta-analyses of RCTs, it was planned to examine whether the direction and statistical significance of the associations and respective effects were reported concordantly (or not) across the different study types.

## 3. Results

### 3.1. Systematic literature search

As reported in Fig. 1, 1240 references/studies were identified with 6 meta-analyses included (Demicheli et al., 2018; Domnich et al., 2017; Kopsaftis et al., 2018; Poudel et al., 2019; Tsivgoulis et al., 2018; Udell et al., 2013) in this umbrella review for a total of 50 independent outcomes.

### 3.2. Meta-analyses of observational studies

As reported in Table S1, the majority of meta-analyses included community-dwelling older people (n = 25/38). Other populations investigated were patients with CVD (cardiovascular diseases) or COPD (chronic obstructive pulmonary disease). The analyses concerning the observational studies took account of 38 different outcomes. A total of 33 were addressed utilizing cohort studies, while 5 were addressed only by case-control studies. The median length of the follow-up was 4.5 (range 1.5–12) months.

The median number of studies included in meta-analyses of observational studies was 4 (range: 2–27), the median number of participants was 38,000 (range: 498 − 2 452 601), and the median number of cases was 2 171 (range: 5–10 370).

Overall, 25/38 (= 66 %) meta-analyses reported nominally significant summary results with a p-value < 0.05, and, among them, nine associations survived to the application of the more stringent p-value ($P < 10^{-6}$).

Heterogeneity among studies was absent in 16/38 outcomes ($I^2$ < 50 %); high in 7 outcomes ($I^2$ between 50 and 75 %) and very high in 15 outcomes ($I^2$ > 75 %). Only three associations presented 95 %-PIs excluding the null value and only one outcome presented an excess statistical significance bias. The small-study effects bias was present in 3/38 outcomes. The largest study was significant in 25/38

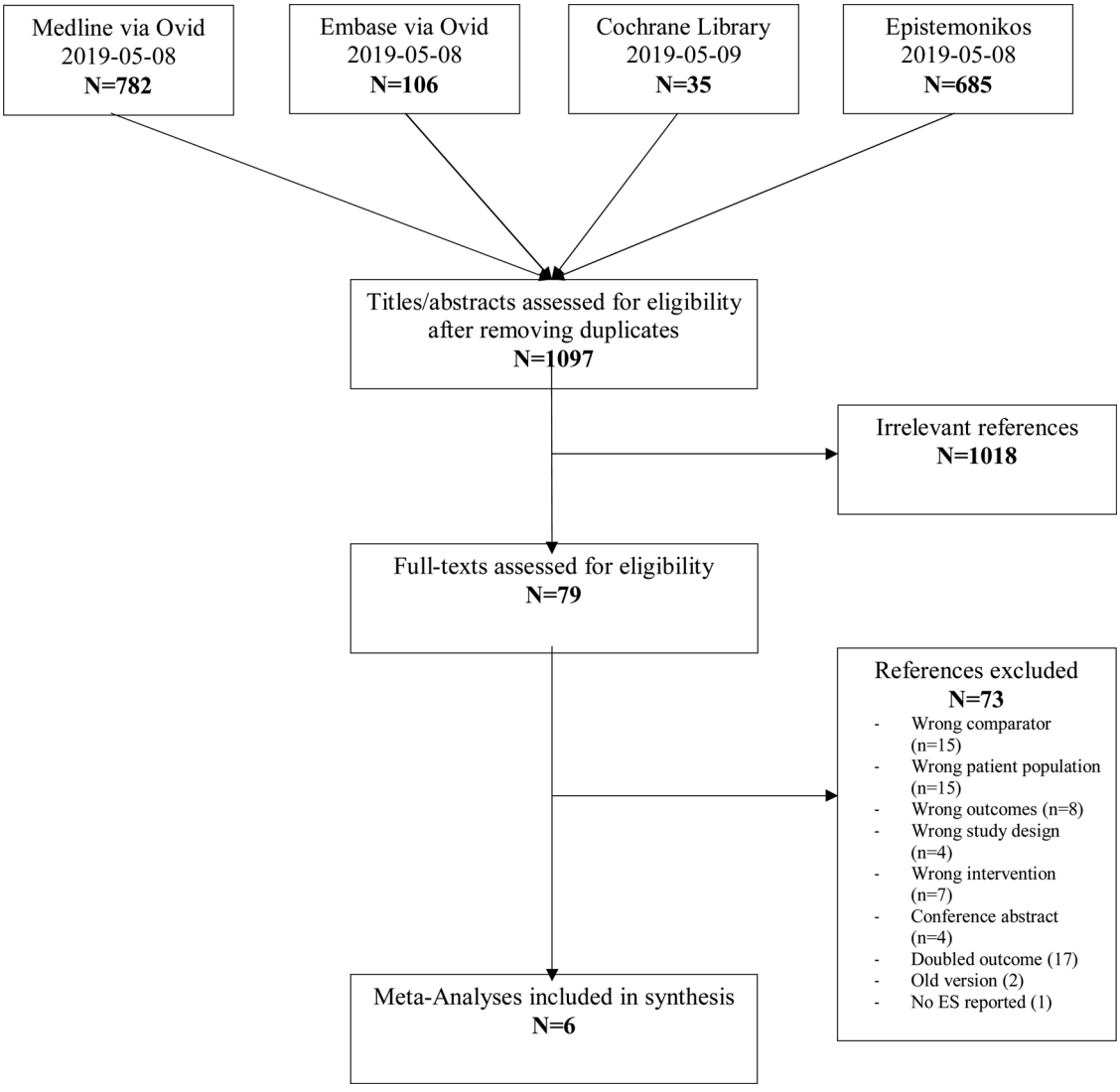


**Fig. 1.** PRISMA flow-chart.

**Table 1**
GRADE evidence for randomized controlled trials investigating influenza vaccination (vs. placebo/no treatment) in older people.

| Outcomes | № of participants (studies) | Certainty of the evidence (GRADE) | Relative effect (95 % CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with placebo/no comparison | Risk difference with influenza vaccination |
| **Local tenderness/sore arm in older people** | 2560 (4 RCTs) | ⨁⨁⨁◯ MODERATE [a] | **RR 3.559** (2.609–4.856) | 37 per 1 000 | **95 more per 1000** (60 more to 143 more) |
| **Influenza- like illness in healthy 65+ years** | 2047 (2 RCTs) | ⨁⨁⨁◯ MODERATE [a] | **RR 0.576** (0.418 to 0.796) | 98 per 1 000 | **41 fewer per 1000** (57 fewer to 20 fewer) |
| **MACE in older people with recent ACS** | 789 (3 RCTs) | ⨁⨁◯◯ LOW [b] | **RR 0.449** (0.324 to 0.623) | 231 per 1 000 | **127 fewer per 1000** (156 fewer to 87 fewer) |
| **MACE in older people with CHD** | 6469 (5 RCTs) | ⨁⨁◯◯ LOW [b] | **RR 0.641** (0.476 to 0.864) | 47 per 1000 | **17 fewer per 1000** (24 fewer to 6 fewer) |
| **Late exacerbation per participant in older patients with COPD** | 180 (2 RCTs) | ⨁⨁◯◯ LOW [c] | – | | MD **0.392 lower** (0.611 lower to 0.173 lower) |
| **Total exacerbations per participant in older patients with COPD** | 180 (2 RCTs) | ⨁⨁◯◯ LOW [c] | – | | MD **0.365 lower** (0.648 lower to 0.081 lower) |

*__The risk in the intervention group__ (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95 % CI). **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference.
GRADE Working Group grades of evidence.
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanations.
a. Unclear risk of bias in all RCTs included.
b. All RCTs with high risk of bias.
c. very small number of trials (only 2) and participants (< 200 in both arms).
Abbreviations: COPD -chronic obstructive pulmonary disease; MACE – major adverse cardiovascular events; ACS- acute coronary syndrome; CHD chronic heart disease.

outcomes available (= 66 %).

Based on the credibility criteria widely used for assessing the evidence of observational studies, two outcomes, assessed only by a cohort study methodology, reported a convincing (class I) evidence. These included the lower risk of hospitalization for heart disease (OR = 0.728; 95 %CI: 0.658 − 0.806) and for influenza or pneumonia (OR = 0.729; 95 %CI: 0.670 − 0.790) observed in older community-dwelling people in association with the use of influenza vaccination. A highly suggestive evidence (class II) was assigned to the lower risk of mortality in community-dwelling older people (OR = 0.526; 95 %CI: 0.457 − 0.606); to all deaths/severe respiratory diseases in high risk community dwelling older people (OR = 0.603; 95 %CI: 0.488 − 0.745) and to hospitalization for influenza or pneumonia in case-control studies (OR = 0.590; 95 %CI: 0.474 − 0.735) observed in subjects immunized against influenza (Table S1). However, 20/38 outcomes were rated as weak.

### 3.3. Meta-analyses of RCTS

As reported in Table S2, the populations considered were in 7 meta-analyses people with a previous cardiovascular disease, other 7 were on people with COPD, 6 included healthy older people, two did not specify any condition. Meta-analysis of RCTs reported on 22 outcomes. The median number of studies was 3 (range: 2–5), the median number of participants was 1418 (range: 97 − 6 469), and the median number of cases (i.e. people having the outcome of interest during the follow-up period) was 97 (range: 9–246). The median length of the follow-up was 8.9 months (range < 1-12).

Overall, 6 outcomes of 22 reported nominally significant summary results as p-value < 0.05. Heterogeneity among studies was modest, having only 3/22 outcomes with a high heterogeneity ($I^2$ > 50 %). Only one outcome presented 95 % PIs excluding the null value. Two outcomes presented an excess statistical significance bias and no study reported a small-study effects bias. For only four outcomes the largest study in terms of participants was statistically significant (p < 0.05) (Table S2).

As fully reported in Table 1, using the GRADE approach for the outcomes reporting a p-value < 0.05 in the random-effect model, the use of influenza vaccination, compared to placebo/no intervention, was associated with a moderate risk of local tenderness/sore arm in 2 560 older people (RR 3.559; 95 %CI: 2.609–4.856) and to a reduced risk of influenza- like illness in 2 047 healthy older people (RR = 0.576; 95 %CI: 0.418 − 0.796). The other four outcomes (i.e. the incidence of the major cardiovascular events in older people with recent acute coronary syndrome or with coronary heart disease and the incidence of total/late exacerbations in older people with chronic obstructive pulmonary disease) reached only a low certainty of the evidence.

### 3.4. Risk of bias

According to AMSTAR-2, all the meta-analyses included, both on observational and interventional studies, were evaluated as having a critically low rating. This was due mainly because the risk of bias was not accurately assessed and the sources of funding for the included studies were not reported or declared (Table S3). On the other hand, each meta-analysis included clearly stated the question in align with the PICO criteria, and the inclusion and exclusion criteria. Moreover, the method adopted for statistical analysis, and risk of bias were coherent.

### 3.5. Overlapping outcomes

We were not able to find any overlapping outcome between intervention and observational studies.

## 4. Discussion

The present review aimed to provide a comprehensive overview of efficacy and safety of influenza vaccination in older adults, by incorporating evidence from meta-analyses of observational studies and RCTs. In this umbrella review, including 6 meta-analyses (Demicheli et al., 2018; Domnich et al., 2017; Kopsaftis et al., 2018; Poudel et al., 2019; Tsivgoulis et al., 2018; Udell et al., 2013) and 50 independent outcomes, it was found that influenza vaccination is significantly associated with several positive effects. In observational studies, a convincing evidence for the use of influenza vaccination in lowering the risk of hospitalization for heart disease and for influenza or pneumonia in community-dwelling older people was found. A moderate strength of evidence supported the use of influenza vaccination in preventing influenza-like illness (ILI) in healthy older people in RCTs.

Our review, including recent meta-analyses and findings not previously reported may represent a significant evidence for further research and policies development.

The present work supports and expands on a recent review by Demichelis Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo, which considers studies up to 2017 and is focused on the reduction of influenza and ILI, by including studies assessed in several additional meta-analyses. Moreover, the present review considered (I) cardiovascular outcomes emerging on a population of patients with cardiovascular diseases, such as heart failure, described in Udell's and Poudel's meta-analyses.(Poudel et al., 2019; Udell et al., 2013) and (II) the impact of influenza vaccination on mortality and hospitalization in older patients with heart failure. (Fukuta et al., 2019; Poudel et al., 2019; Rodrigues et al., 2020)

Overall, the quality of influenza vaccines studies involving older people is very low and it consequently affects the quality of meta-analyses. The use of pre-established tools for quality assessment, which rely on the data reported in the included meta-analysis can result in biases and shortcomings (Ioannidis and Trikalinos, 2007a). Secondly, using the AMSTAR 2-score to assess the meta-analyses, several potential biases were identified, mainly driven by the risk of bias that was not accurately assessed and the sources of funding not declared. Moreover, since the meta-analyses included studies with significant differences in design, population and other basic characteristics, one might claim that large heterogeneity may be a concern. For this reason, the present review used an $I^2$ < 50 % as one of the criteria for class I evidence (convincing) for observational studies and the same was done for intervention trials, in order to assign the best-evidence grade only to robust associations without bias. However, $I^2$ estimates can also carry substantial uncertainty (Ioannidis et al., 2008) and clinical heterogeneity may be substantial even in the absence of statistical heterogeneity. Another limitation of this work was that it was not possible to assess different typologies of vaccines used in single studies as this information was not reported. Indeed, different vaccination types may have different efficacy. Finally, due to the lack of specific information, it was also not possible to carry out the sensitivity analyses planned in the protocol and, therefore, one cannot exclude that influenza vaccination could lead to different effects in selected populations, such as very old adults. In this sense, the type of vaccines used for immunizations and the types of interventions were not clearly indicated in the original meta-analyses.

The assessment of adverse effects was found to be overall limited. A possible explanation to this could be ascribed to the selection criteria defined for the study designs, that tend not to fit best for very rare outcomes such as less commonly reported adverse effects. The only significant association observed between the influenza vaccination and adverse events was higher risk of local tenderness/sore arm, while the other 4 adverse events outcomes (i.e. headache, malaise, fever, upper respiratory tract symptoms) did not reach a statistical significance.

Although acute influenza infection is an independent risk factor for fatal and non-fatal cardiovascular events and other pathologies, the

mechanism underlying this risk is less clear. It is argued that it may be linked to triggering the rupture of a plaque, to the fluid overload in heart failure, consensual myocarditis, arrhythmias, or the susceptibility of frail and vulnerable patients (Udell et al., 2013). Nevertheless, coagulopathy seems to be the major trigger for acute myocardial infarction (Estabragh and Mamas, 2013).

Influenza vaccination seems to have an overall moderate preventive effect. The findings of the present umbrella review indicate that implementing vaccination programs for older people may help reduce hospitalization for influenza or pneumonia, as well as heart disease. The susceptibility of the target population is a key issue in the evaluation: the vaccination in high risk groups is more cost-effective than in low-risk groups, because of the higher rates of complications, which are costly and impact quality of life (Brydak et al., 2012). In the present review, it was not possible to find data on cost-effectiveness of influenza vaccination, as the review focused on health outcomes, basing this work on efficacy and safety of influenza vaccination. The effects of vaccination of cohorts of community dwelling patients may avoid a consistent number of hospitalization, in patients with COPD, MACE, at high risk or in healthy patients, leading indirectly also to a reduction of expenses that makes vaccination policy a particularly cost-effective strategy (Lugner et al., 2012). Cost-effectiveness offered by the vaccination could be significant if the follow-up timing (that was identified in 6 months or less for most of the studies in this umbrella review) could be protracted for longer times. In the meta-analyses of RCTs this review found follow-up intervals ranging from 48 h to 1 year, depending on the investigated outcomes. Namely, follow-up was shorter in studies aiming at analyzing the potential side effects and harms of vaccination, whilst studies investigating endpoints like death or cardiovascular events (Poudel et al., 2019; Tsivgoulis et al., 2018; Udell et al., 2013) had a longer follow-up period, up to 1 year.

In observational studies, mainly included in Demicheli's analysis (Demicheli et al., 2018), it was found that often shorter follow-up periods were reported, whilst in some cases the time indication was limited to a generic epidemic period, without any further information.

In conclusion, this umbrella review summarized the current state of the evidence regarding safety and efficacy of influenza vaccination in older adults, finding that influenza vaccination is associated with several positive outcomes. This work reinforces the importance of promoting the use of influenza vaccination in older adults by public health authorities. Further, the evidence on safety and efficacy of vaccines in this population might benefit by an extension of the follow-up period both in RCTs and in longitudinal studies, beyond the usual 6-month period, in order to be able to evaluate the impact of vaccination on long term outcomes.

## Contributors

Jacopo Demurtas, Gabriel Torbahn, Stefania Maggi, Nicola Veronese and Lee Smith had full access to all the data in the study. Jacopo Demurtas, Gabriel Torbahn, Stefania Maggi and Nicola Veronese conceptualized the study. Jacopo Demurtas, Stefania Maggi, Charlotte Beaudart, Stefano Celotto, Nicola Veronese and Lee Smith designed the study. Gabriel Torbahn and Nicola Veronese searched the literature. Charlotte Beaudart and Dolores Sanchez Rodriguez screened the articles for inclusion and exclusion, Jacopo Demurtas and Cafer Balci conducted data extraction. Nicola Veronese and Lee Smith conducted data analyses. Stefano and Daniele Celotto provided quality assessment. Nicola Veronese and Jacopo Demurtas drafted the initial tables. Jacopo Demurtas drafted the initial manuscript. Nicola Veronese and Gabriel Torbahn provided methodological supervision. All authors contributed to interpretation of data and critical revision of the manuscript for important intellectual content.

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## Dissemination declaration

Dissemination to these groups is not possible/applicable.

Data sharing

The statistical code is available from the corresponding author upon request.

## Declaration of Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no conflict of interest.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2020.101118.

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