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Review Article

The Effect of Monovalent Influenza Vaccine on the Risk of Hospitalization and All-Cause Mortality According to the Results of Randomized Clinical Trials: A Systematic Review and Meta-Analysis

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Abstract

Background: In recent years, various studies have been conducted to investigate the role of the influenza vaccine in reducing the risk of hospitalization and mortality; however, the results of these studies are clearly contradictory. Accordingly, we aimed to investigate the effect of monovalent flu vaccines on the risk of hospitalization and all-cause mortality.

Methods: This study was a systematic review and meta-analysis of Randomized Clinical Trial (RCT) studies published in databases (Web of Science (ISI), Scopus, PubMed, Cochrane, Science Direct, Google Scholar) from 1980 to Dec 2022. All analyzes were performed by Stata15 statistical software and the significance level in this study was considered 0.05.

Results: In the initial search, 375 articles were retrieved which, considering the study criteria, finally 8 RCT were included in the meta-analysis of the effects of monovalent Flu vaccine on the risk of hospitalization, and 10 RCT on the risk of all-cause mortality. Based on the results of meta-analysis, the overall Odds Ratio (OR) of hospitalization is equal to 0.71 (95% CI: 0.56-0.90; P <0.001) and the overall OR of all-cause mortality is equal to 0.82 (95% CI: 0.68-0.98; *P*=0.033). There was no publication bias in the study of the effect of monovalent flu vaccine on the risk of hospitalization and all-cause mortality

Conclusion: Getting the flu vaccine can reduce the risk of hospitalization by 29% and the risk of overall death by 18%. Therefore, it may be promising to receive this vaccine as a preventive intervention for deaths and hospitalizations.

Keywords: Influenza vaccine; Hospitalization; All-cause mortality; Meta-analysis

Introduction

Influenza is an acute viral disease of the respiratory system that has a global spread (1). The importance of influenza is in the speed of spreading of its epidemics, the extent and number of patients and the severity of its complications, especially viral and bacterial pneumonia (2). Since this virus

has the ability to create genetic changes, there are always many concerns about the occurrence of pandemics caused by it in the world (3). Influenza pandemics have always been a threat to public health around the world (4).

Influenza viruses can cause mild to severe illness and even death, especially in high-risk individuals such as the elderly, people at risk for cardiovascular disease, stroke, kidney disease, and immune system deficiency diseases (5). Therefore, due to the weak control of this disease by health systems and the resulting severe economic and health damage, it was finally decided to targeted vaccination against influenza (6). According to studies, vaccination is one of the most effective ways to prevent the disease and reduce its medical costs (5).

In recent years, with the improvement of nutrition and health in different communities, we are witnessing an increase in the average age of the population and, in other words, an aging population. In the near future, the elderly will make up the bulk of the world's population. One of the important challenges related to the phenomenon of population aging is the issue of providing health services for this segment of the population (7-11). The elderly are a major consumer of health services due to their reduced physical function and mental vulnerability, and their increase in population is accompanied by an increase in demand for health services (12-14). The treatment costs of the age group over 65 years are more than 5 times the total treatment costs of the age group less than 65 yr (15). In recent years, various studies have been conducted around the world to investigate the role of the influenza vaccine in reducing the risk of hospitalization and mortality due to various diseases in the elderly. A high proportion of these studies have shown that influenza vaccination reduces the risk of hospitalization or mortality in people receiving the vaccine (16-18). However, a number of other studies have shown that receiving the flu vaccine increases the risk of hospitalization (19-21) or death (19, 22) in vaccine recipients. Nevertheless, some studies have shown that the risk of hospitalization or death does not differ between those who receive the vaccine and those who do not (23, 24).

Therefore, the results of studies conducted in this field are clearly contradictory, and based on these studies; no general conclusion can be reached about the effect of influenza vaccine on the risk of hospitalization and all-cause mortality in the people receiving the vaccine. Since one of the best ways to achieve a clear answer to a scientific question in the field of health is to use systematic review and meta-analysis studies using the results of clinical trial investigations, the present study, using the results of researches conducted in this field by systematic review and meta-analysis, investigated the effect of flu vaccine on the risk of hospitalization and all-cause mortality according to the results of randomized clinical trials.

Methods

Type of study and population studied

This systematic review and meta-analysis used data from clinical trial studies to investigate the effect of flu vaccine on the risk of hospitalization and all-cause mortality from 1980 to Dec 2022.

Search strategies

A comprehensive search of the texts published in the databases of Web of Science (ISI), Scopus, PubMed, Cochrane, Science Direct and Google Scholar was performed in the period from 1980 to Dec 2022, in this study, the keywords Influenza Vaccine, Hospitalization and mortality and their synonyms based on PubMed MeSH were used to perform the search.

Moreover, to ensure the availability of all published studies in this regard; the list of references of articles retrieved in the electronic search was reviewed to access related studies. In addition, in order to access articles whose full text could not be received through databases, we contacted the relevant authors by e-mail to receive the full text of the articles. After collecting the documents and articles, their characteristics and abstracts were entered into the Endnote software and duplicate items were removed using this software as well as re-reading the titles. In the next step, by reviewing the titles, articles unrelated to the purpose of the

research were excluded, and then among the remaining studies, by referring to the abstract and also the full text of the article, it was relevant to the purpose of the study. Figure 1 shows the process of identifying and selecting studies as well as how to examine them in order to enter a systematic review and meta-analysis schematically.

Criteria for inclusion and exclusion of clinical trial studies

Only articles from clinical trials that examined the effect of flu vaccine on the risk of hospitalization and all-cause mortality were evaluated. Moreover, the relative risk, risk ratio, or odds ratio of the effect of exposure on the outcomes under consideration should be measured in the article, taking into account the 95% confidence interval (CI), or it should be calculable based on the information in the article. Articles that did not provide sufficient data to calculate the effect size or standard deviation (SD) for the relevant estimates were excluded from the study.

Information extracted from the clinical trial studies

From the final articles included in this study, information such as study title, type of study, name of the first author of the article, year of publication, country of study, sample size, number of exposed and non-exposed groups, duration of follow-up of patients, the status of receiving or not receiving influenza vaccine in participants, hospitalization rate, the incidence of total mortality, RR and OR with 95% CI related to hospitalization and overall mortality, the percentage of women in the study population, the average age of the participants in the study, the prevalence of diabetes, the prevalence of blood pressure and the proportion of smokers; and variables that were adjusted in the multivariate models, were extracted and collected.

In many studies, the vaccine effectiveness (VE) was calculated and presented based on the relevant formula VE = (OR -1) × 100 (25). In these cases, the OR and the relevant 95% CI were calculated based on the presented VE values. In studies where the effect size reports were calculated and presented separately for time or seasonal periods, using the meta-analysis method, an overall effect size was calculated from the presented values and considered in the analysis. Moreover, in studies where the effect size was not reported but information about the number of participants and injected vaccines were available, the effect size and relevant 95% CI were calculated using a 2×2 table.

Evaluating the quality of the Clinical trial studies

To evaluate the quality of studies, the Jadad scale checklist was used due to its quantitative scoring capability (26, 27). This checklist is used to evaluate the quality of randomized clinical trial (RCT) studies. The maximum score that can be given to an article using this checklist is 5 and the minimum is 0. Based on the Jadad scale, scores range from 0 to 2, 3 to 4, and more than 4 were defined for low, moderate, and good-quality articles, respectively (26, 27)

Statistical Analysis

Due to the low incidence of outcomes (hospitalization and mortality), the rate ratio and the risk ratio in various studies were considered as equal of odds ratio (OR). The presence of heterogeneity in the studies included in the meta-analysis was assessed using I^2 or Q-Test (Chi-square). I^2 test was used to report a quantitative amount of heterogeneity. In addition, Forest Plot was used to investigate the heterogeneity graphically. Using the Chi-square test, the differences in the results of the studies entered in the met-analysis were investigated and according to results of this test determined the type of model (fixed or random). Egger's test and Begg's test were used to evaluate publication bias. All analysis were performed by Stata statistical software (version 15.0, Stata Corp, College Station, TX), and the significance level in all tests were considered 0.05.

Results

Clinical trial studies included in the systematic review and meta-analysis

According to Fig. 1; 375 articles were collected by electronic search in databases with keywords created in Mesh with Title/Abstract. By examining the effect size reported in studies related to the purpose of the study, 8 studies for hospitalization (28-35) and 10 studies for general mortality (28-37) were included in the meta-analysis, eight articles reported the effect size associated with hospitalization and mortality (28-35).

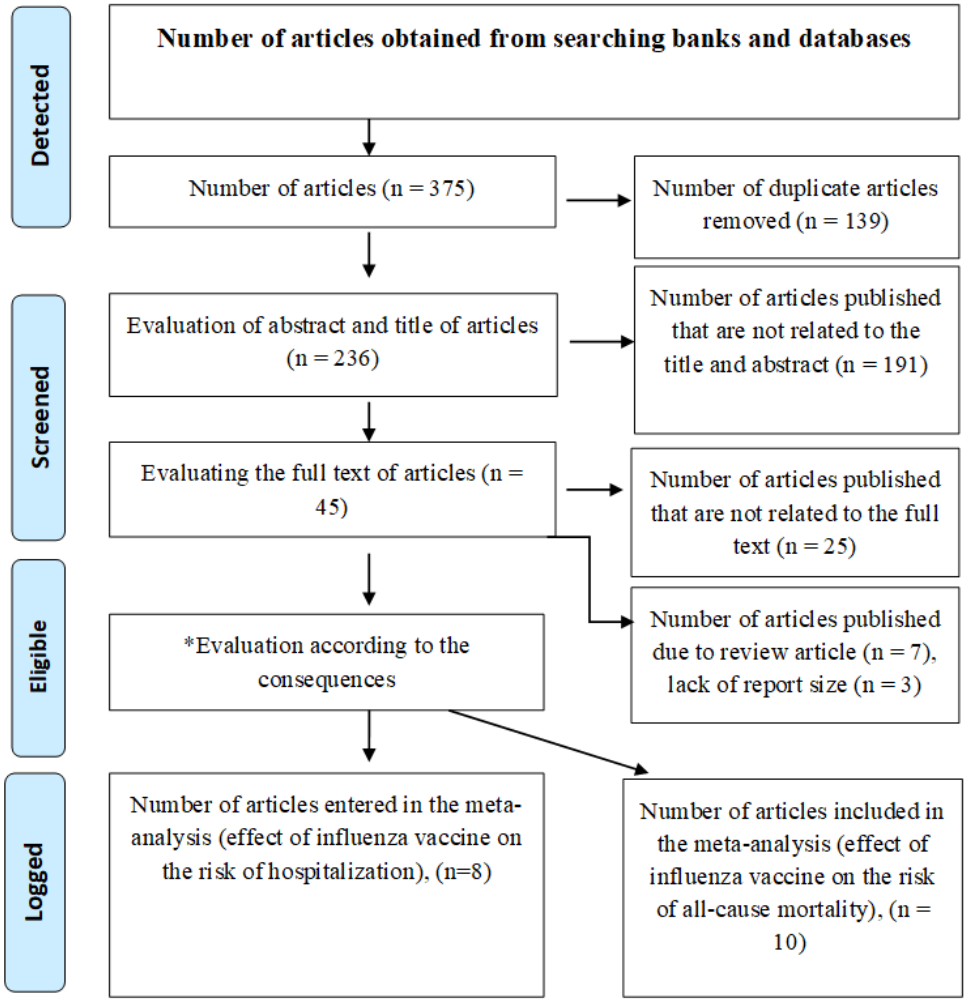

Fig. 1: Diagram of selected clinical trial studies for meta-analysis

Effect of influenza vaccine on the risk of hospitalization

Overall, eight clinical trial studies were conducted to investigate the effect of influenza vaccine on the risk of hospitalization (28-35). These studies were performed on 14,396 people between 1994 and 2022. The follow-up time of participants in different studies varied from 5 to 24 months. Moreover, 6 study are classified in terms of quality assessment in the group of good-quality studies (Table 1). The adjusted variables in the study of the effect of influenza vaccine on the risk of hospitalization in different studies can be seen in Table 2.

Table 1: Characteristics of clinical trial studies included in the meta-analysis to investigate the effect of influenza vaccine on the risk of hospitalization

First author (Reference number)	*Year*	*Country*	*Sample size*	*Mean age*	*Women, %*	*Hypertension, %*	*Diabetes Mellitus, %*	*Smoker, %*	*OR (95% CI)*	*Duration of follow-up*	*Jadad Scale (Score)*
Govaert (29)	1994	Netherlands	1838	65	-	-	-	-	0.42(0.24-0.74)	5 months	5
Flucad(31)	2008	Finland	658	60	26	67	20	18	0.55 (0.22 – 1.37)	10 months	5
IVCAD (33)	2009	Iran	266	54.7	33	83	-	-	1.94 (0.36 – 10.42)	6 months	4
De Villiers (32)	2009	South Korea	3242	69.5	33	57	26	17	0.91 (0.36 – 2.27)	8 months	5
Phrommintikul (34)	2011	Thailand	439	66	43	62	31	12	0.70 (0.57 – 0.82)	24 months	4
FLUVACS (30)	2004	Argentina	292	64.5	28	52	18	44	0.44 (0.28 – 0.71)	24 months	5
Fröbert (35)	2021	Sweden, Denmark, Norway, Latvia, the United Kingdom, Czech Republic, Bangladesh, and Australia	2532	60	18	49	21	35	1.38(0.78-2.49)	12 months	5
Loeb (28)	2022	India-China-Africa	5129	57	51	-	23	-	0.83(0.72-0.97)	12 months	5

Table 2: Adjusted variables in the studies that investigate the effect of influenza vaccine on the risk of hospitalization

First author (Reference number)	*Year*	*Adjusted variables*
Govaert (29)	1994	Age, sex, previous influenza vaccination
Flucad(31)	2008	Age, gender, weight, height, residence, employment status, hypertension, diabetes, smoking, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, creatinine, clinical history, actual treatment, inflammatory markers and infectious burden
IVCAD (33)	2009	Age, sex, previous influenza vaccination, hypertension, diabetes, smoking
De Villiers (32)	2009	Fever ≥37 degrees, cough, sore throat, age, sex, runny nose, stuffy nose, headache
Phrommintikul (34)	2011	Age, sex, serum creatinine, treatment with angiotensin converting enzyme inhibitors and coronary arteries
FLUVACS (30)	2004	Age, sex, anterior infarction, stemi, hypertension, diabetes
Fröbert (35)	2021	-
Loeb (28)	2022	-

Based on meta-analysis of the results of RCT studies included in the meta-analysis (28-35), the OR of hospitalization is equal to 0.71 (CI 95 %; 0.56-0.90, P<0.001), in other words, this meta-analysis show that compared to the people did not receive the flu vaccine, the odds of hospitalization in persons receiving the flu vaccine is reduced by 29%, which is statistically significant (Fig. 2).

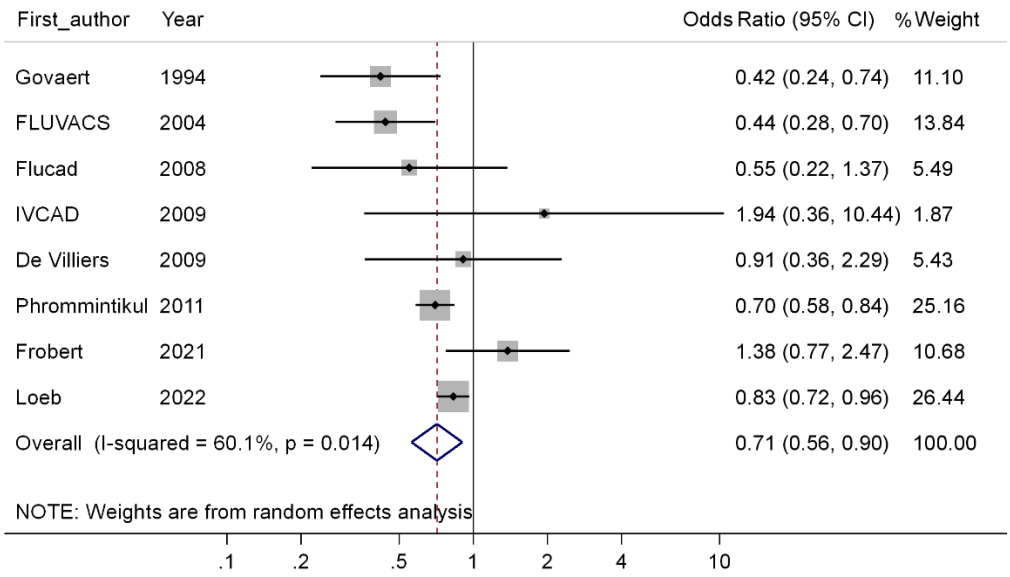

Fig. 2: Forest plot of the effect of receiving the flu vaccine on the risk of hospitalization

Assessment of publication bias in the valuation of the effect of receiving the flu vaccine on the risk of hospitalization according to the results of clinical trial studies

In the study of the effect of receiving the flu vaccine on the risk of hospitalization, using Begg's test (P=0.536) and Egger's test (P=0.790), no Publication bias was observed. The funnel plot of the effect of receiving the flu vaccine on the risk of hospitalization is presented in Fig. 3.

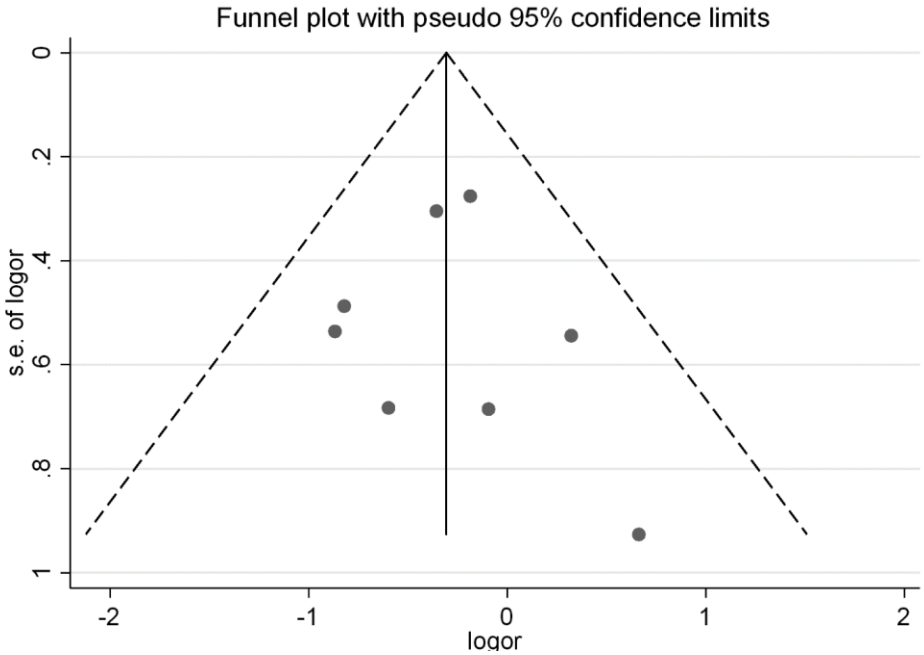

Fig. 3: Funnel plot for evaluation of Publication bias in investigating the effect of receiving the flu vaccine on the risk of hospitalization according to the results of clinical trial studies

Effect of influenza vaccine on the risk of all-cause mortality

In general, ten clinical trial studies (28-37) have been conducted to investigate the effect of influenza vaccine on the risk of all-cause mortality. These studies were performed on 21,155 people between 1994 and 2022. The follow-up time of participants in different studies varied from 5 to 24 months. Moreover, 8 study are classified in terms of quality evaluation in the group of good-quality studies (Table 3). The adjusted variables in the study of the effect of influenza vaccine on the risk of all-cause mortality can be seen in Table 4.

Table 3: Characteristics of the clinical trial studies included in the meta-analysis to investigate the effect of influenza vaccine on the risk of all-cause mortality

First author (Reference number)	*Year*	*Country*	*Sample size*	*Mean age*	*Women, %*	*Hypertension, %*	*Diabetes Mellitus, %*	*Smoker, %*	*OR (95% CI)*	*Duration of follow-up*	*Jadad Scale (Score)*
Govaert (29)	1994	Netherlands	1838	65	-	-	-	-	1.97(0.49-7.84)	5 months	5
FLUVACS (30)	2004	Argentina	292	64.5	28	52	18	44	0.34 (0.17 – 0.71)	24 months	5
FLUCAD (31)	2008	Finland	658	60	26	67	20	18	1.06 (0.15 – 7.56)	10 months	5
IVCAD (33)	2009	Iran	266	54.7	33	83	-	-	0.97 (0.20 – 4.72)	6 months	4
De Villiers (32)	2009	South Korea	3242	69.5	33	57	26	17	1 (0.54 – 1.85)	8 months	5
Phrommintikul(34)	2011	Thailand	439	66	43	62	31	12	0.39 (0.14 – 1.12)	24 months	4
Verhees (37)	2019	Netherlands	2198	67	53	45	3	23	0.96 (0.87 – 1.07)	24 months	5
Fröbert (35)	2021	Sweden, Denmark, Norway, Latvia, the United Kingdom, Czech Republic, Bangladesh, and Australia	2532	60	18	49	21	35	0.59(0.39-0.90)	12 months	5
Langley (36)	2011	North america	4561	50	55	-	-	-	0.17(0.02-1.83)	12 months	5
Loeb (28)	2022	India-China-Africa	5129	57	51	-	23	-	0.91(0.81-1.02)	12 months	5

Based on the results of RCT studies included in the meta-analysis (28-37), the OR of all-cause mortality is equal to 0.82 (95% CI; 0.68 - 0.98, *P*=0.033), in other words, this meta-analysis show that compared to the people who did not receive the flu vaccine, the odds of death in the persons receiving the influenza vaccine decreased by 18%, which is statistically significant (Fig. 4).

Table 4: Adjusted variables in the studies that investigate the effect of influenza vaccine on the risk of all-cause mortality

First author (Reference number)	*Year*	*Adjusted variables*
Govaert (29)	1994	Age, gender, previous influenza vaccination, health status
FLUVACS (30)	2004	Age, sex, anterior infarction, stemi, hypertension, diabetes
FLUCAD (31)	2008	Age, gender, weight, height, residence, employment status, hypertension, diabetes, smoking, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, creatinine, clinical history, actual treatment, inflammatory markers and infectious burden
IVCAD (33)	2009	Age, sex, previous influenza vaccination, hypertension, diabetes, smoking
De villiers (32)	2009	Fever ≥37 degrees, cough, sore throat, age, sex, runny nose, stuffy nose, headache
Phrommintikul(34)	2011	Age, sex, serum creatinine, treatment with angiotensin-converting enzyme inhibitors and coronary arteries
Verhees (37)	2019	Gender, age, smoking status, lung disease, heart disease, diabetes mellitus, and previous vaccinations
Fröbert (35)	2021	Age, gender, st-segment–elevation myocardial infarction, non–st-segment–elevation myocardial infarction, stable coronary artery disease, body mass index, diabetes, smoking, hyperlipidemia, hypertension, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass graft, killip class, number of diseased vessels
Langley (36)	2011	-
Loeb (28)	2022	-

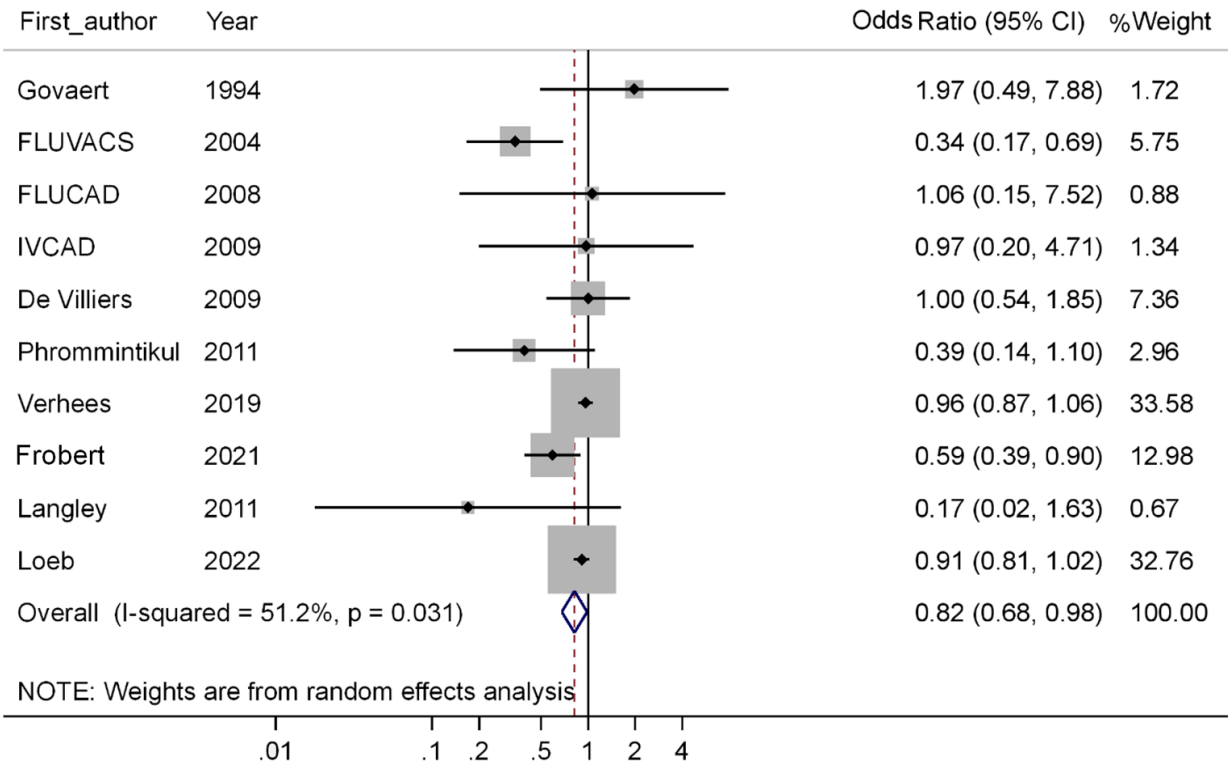

Fig. 4: Forest plot of the effect of influenza vaccine on the risk of all-cause mortality

Assessment of publication bias in the valuation of the effect of influenza vaccine on the risk of all-cause mortality according to the results of clinical trial studies

In the study of the effect of influenza vaccine on the risk of all-cause mortality, using Begg's test (P=0.858) and Egger's test (P=0.145), no Publication bias was observed (Fig. 5).

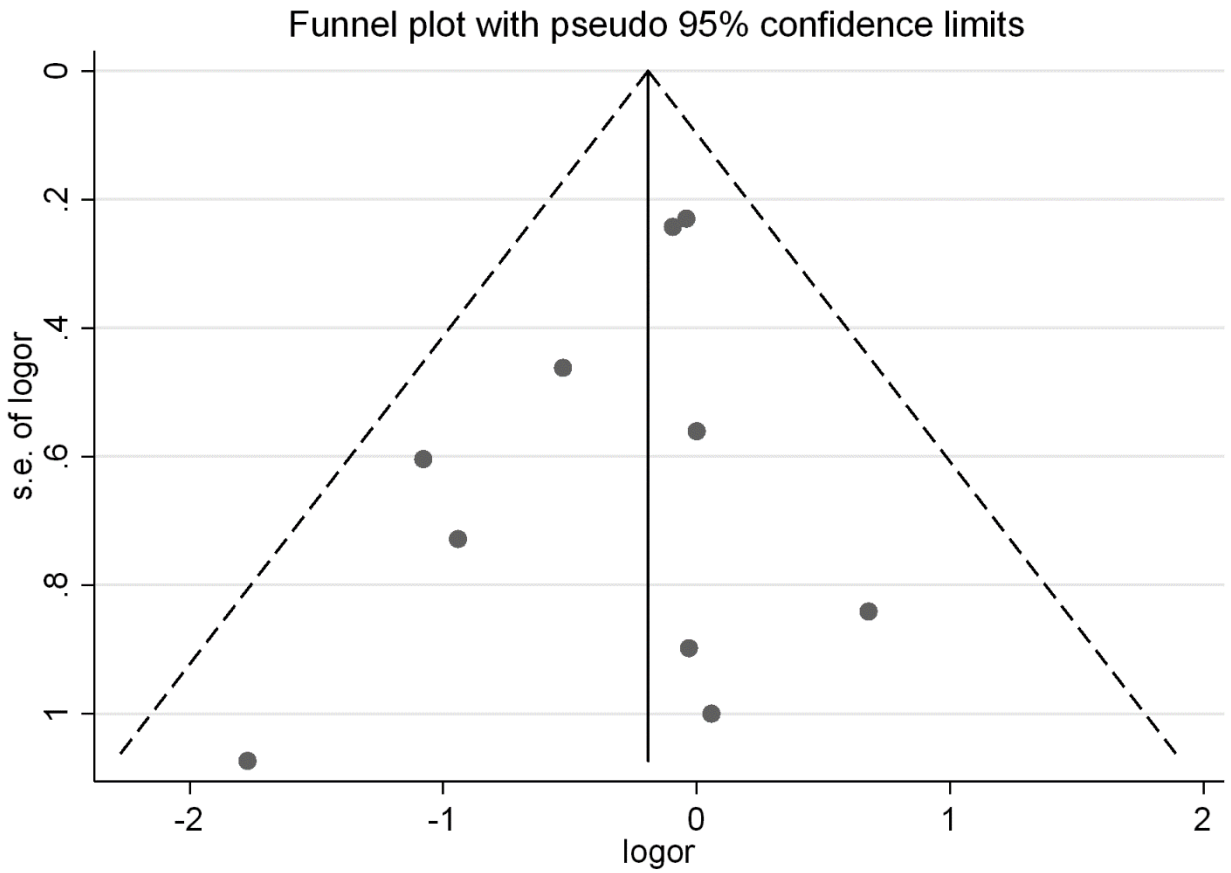

Fig. 5: Funnel plot for evaluation of Publication bias in investigating the effect of influenza vaccine on the risk of all-cause mortality according to the results of clinical trial studies

Discussion

The purpose of this systematic review and meta-analysis was to investigate the effect of influenza vaccine on the risk of hospitalization and all-cause mortality. Based on the meta-analysis of the results of RCT studies included in the meta-analysis (28-37), compared to the individuals who did not receive the flu vaccine, the odds of hospitalization and mortality in people receiving the flu vaccine was decreased by 29% and 18%, respectively. Similarly, a systematic review and meta-analysis by Kyu Rae Lee and et al., entitled "Effect of influenza vaccination on risk of stroke: a systematic review and meta-analysis", showed that receiving the flu vaccine had protective effects against stroke (6).

In the same way, the protective effects of influenza vaccine against the chance of hospitalization or mortality have also been confirmed in other studies, in a cohort study that conducted in patients with ischemic heart disease in Taiwan, influenza vaccine has protective effects against hospitalization and mortality, so that influenza vaccination leads to a reduction in the OR of hospitalization (0.84 (95% CI ; 0.76-0.93)) and mortality (0.42

(95% CI ; 0.35-0.49)) due to cardiovascular diseases (38).

Moreover, in another cohort study was conducted on 4,454 vaccinated diabetic patients and 4,571 unvaccinated diabetic patients. The risk of pneumonia, respiratory failure, the need for intensive care, hospitalization, and overall mortality was assessed during the first year after vaccination. Fewer Pneumonia and respiratory failure are seen in the vaccinated group. Moreover, in the vaccinated group, the rate of hospitalization is 11% lower than the non-vaccinated group (incidence rate of 29.6 vs. 33.1 per 100 people per year) with an adjusted Hazard Ratio (HR) 0.88 (95% CI; 0.81-0.96). In addition, the HR of hospitalization in the intensive care unit in the vaccinated group is equal to 0.30 (95% CI; 0.19-0.47), and the HR of overall mortality is equal to 0.44 (95% CI; 0.36-0.54). Furthermore, in comparison with non-vaccinated group, receiving the flu vaccine led to a reduction of $ 1283 hospitalization costs per person in vaccinated group (39).

In addition, receiving the flu vaccine in the elderly reduced the need for hospitalization as well as the length of hospitalization (40). In most observational studies with a sample size of more than 10,000 people, the protective role of the influenza vaccine in preventing the hospitalization of the elderly has been confirmed (41, 42).

However, some studies have not shown a protective effect of the flu vaccine against the risk of hospitalization or overall mortality. For example, in a study conducted on 1,000 people in Japan, in comparison with non-vaccinated individuals, the HR of hospitalization in vaccinated people is equal to 1.25 (95% CI; 0.29-5.37) (43), which of course this risk increases is not statistically significant. Another study as a prospective cohort study in Hong Kong on 27,469 people found that compared to non-vaccinated people, the HR of hospitalization in the vaccinated individuals was 0.85 (95% CI; 0.61-1.17) (44). However, the reason for the lack of a significant relationship between exposure and outcome in some observational studies (cohort, cross-sectional, case-control, etc.) is probably a random error due to sampling or lack of control of potential confounder variables or the presence of residual confounder. However, in RCT studies, due to the randomization phase, the confounding variables are evenly distributed among the groups under study, if the randomization is performed well and the sample size is appropriate.

Usually, the elderly have a higher prevalence of underlying or chronic diseases such as cardiovascular diseases (35, 37), high blood pressure (35), diabetes (30-32) and blood lipid disorders (31, 32), on the other hand, people who have such chronic diseases are more likely to suffer from more severe forms of the influenza and its complications; that ultimately leads to an increase in the possibility of hospitalization or death in the elderly (29, 31, 33, 35, 37). However, the results of this study show that receiving the influenza vaccine can effectively reduce the chance of hospitalization, which indicates the effectiveness of the vaccine in preventing the disease or preventing severe forms of the disease. This success eventually leads to improve the health of the elderly and reduce treatment costs. Although the primary goal of this study was not to investigate the effect of the influenza vaccine on the risk of hospitalization and mortality exclusively in the elderly, the average age of the participants in all the studies included in the analysis was equal to or greater than 50 years. Therefore, the results of this study can be extended to elderly people as well.

The results of studies on the relationship between influenza vaccination and hospitalization and mortality in the elderly are inconsistent, especially in studies with observational design. Therefore, this study can be very helpful in providing an appropriate answer in this regard based on the result of RCT studies as golden-standard studies in medical science and extracted clear results for evidence-based medicine and scientific medical advice, therefore the results of this study can be very useful in the decision of the elderly to receive the flu vaccine as well as providing preventive advice with health experts based on scientific evidence.

Nevertheless, this study has its limitations. One of the main limitations of this study is the small number of RCT studies that have examined the effect of influenza vaccine on the risk of hospitalization (8 studies) and all-cause mortality (10 studies).

Due to the small number of studies conducted in this field, current studies cannot provide a good pattern of the effect of exposure and the outcomes in different parts of the world.

Conclusion

Getting the flu vaccine can reduce the risk of hospitalization by 29% and the risk of all-cause mortality by 18%. Therefore, receiving this vaccine as a preventive intervention may be promising. However, more clinical studies are needed to evaluate these relationships and their potential contribution to improving health outcomes.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Data availability

The data used in this systematic review and meta-analysis can be retrieved in the tables provided in the text of the article. In addition, the data used for meta-analysis in the present study is freely available in the text of the articles used.

Conflict of interest

The authors declare that there is no conflict of interest.

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