Open Forum Infectious Diseases

MAJOR ARTICLE

The Effect of Influenza Vaccination on Mortality and Risk of Hospitalization in Patients With Heart Failure: A Systematic Review and Meta-analysis

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Background. Influenza is a major cause of morbidity and mortality in patients diagnosed with heart failure. The aim of this study was to evaluate the effectiveness of influenza vaccination in this population in terms of reduction in all-cause mortality and rate of hospitalization.

Methods. We conducted a systematic review and meta-analysis using PubMed and EMBASE entries from January of 2000 through April 2018. Publication bias was examined using the Egger's regression test. Statistical heterogeneity was examined using the Higgins I^2 statistic. Subgroup analyses were performed to examine the effect of vaccination during the influenza and noninfluenza seasons.

Results. We identified 8 studies that included a total of 82 354 patients with heart failure. In patients with heart failure who were vaccinated against influenza, we found a reduced risk of all-cause mortality (hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.51–0.87). No evidence of publication bias was found, and the effect was more pronounced during influenza season (HR, 0.49; 95% CI, 0.30–0.69), compared with noninfluenza season (HR, 0.79; 95% CI, 0.68–0.89). In terms of heart failure hospitalizations, we did not identify a statistically significant difference between the cohorts (HR, 0.62; 95% CI, 0.00–1.23).

Conclusions. Influenza vaccination was associated with a decreased risk of all-cause mortality in patients with heart failure, and this effect was more prominent during the influenza season.

Keywords. all-cause mortality; heart failure; hospitalization; influenza vaccination.

Despite advancements in the medical field, influenza remains a major cause of infectious morbidity and mortality. Across 5 influenza seasons from 2010 to 2015, the Centers for Disease Control and Prevention (CDC) estimated the number of influenza infection cases in the United States to range from 9.2 million in the 2011–2012 flu season to 35.6 million in the 2012–2013 influenza season [1]. More recently, during the 2016–2017 season, there were 30.9 million cases of influenza infection, with approximately 600 000 hospitalizations [1]. Although the incidence of influenza infection was evenly distributed across all age groups, more than two-thirds of patients hospitalized due to influenza and more than two-thirds of influenza-related deaths were among patients older than 65 years of age [1].

A number of studies have shown the role of influenza in cardiovascular complications, including acute myocardial infarction [2], stroke [3], and the role of influenza vaccine in preventing such events [4, 5]. To more accurately depict the burden of influenza infection, the CDC has expanded the traditional model of pneumonia- and influenza-related deaths (P&I deaths). Deaths secondary to respiratory and cardiovascular complications (R&C deaths) are now included, highlighting the effect of influenza infection in the exacerbation of chronic respiratory and cardiovascular conditions [1]. Notably, the R&C deaths were estimated to be 3 times higher than the rate for P&I deaths [1].

Heart failure accounts for 9% of the total cardiovascular mortality [6]. In the United States, >6.5 million individuals are diagnosed with heart failure each year, with approximately 1 million new cases and 68 000 heart failure–related deaths per year [6]. Heart failure etiologies vary, but the majority of cases are secondary to chronic heart diseases like hypertension and coronary artery disease [7]. The incidence approaches 21 per 1000 population after 65 years of age, and this doubles and

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triples with each 10-year increase in age from 65 to 85 years in males and females, respectively [8]. Respiratory infections are closely related to heart failure exacerbation and may lead to high in-hospital mortality, as shown by a large study of 48 612 patients with heart failure [9]. However, there have been limited studies focusing on the association between heart failure and influenza vaccination, and most of these studies included elderly patients without accounting for cardiovascular morbidity or heart failure at baseline [10–12]. Reports have suggested a protective role of influenza vaccination on the prognosis of patients with heart failure [13], but no large randomized controlled trials or a meta-analysis have been conducted to quantitatively estimate the effectiveness of influenza vaccination in patients with heart failure. We conducted a systematic review and meta-analysis to evaluate the available data on morbidity and mortality outcomes in vaccinated and nonvaccinated patients with heart failure.

METHODS

Our systematic review and meta-analysis followed the guidelines for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [14].

Literature Search

A systematic literature search was conducted for publications in the PubMed and EMBASE databases from January 2000 to March 2018. The following search terms were used: ("Influenza" OR "Flu" OR "Vaccine" OR "Vaccination") AND ("Heart Failure" OR "Congestive Heart Disease" OR "CHF" OR "HF" OR "Cardiac Failure" OR "Ventricular Failure" OR "Myocardial Dysfunction"). Articles not available in English were excluded. Duplicate studies from the 2 databases were excluded using the Systematic Review Accelerator (SRA), which is considered sensitive and specific [15]. Two investigators (S.P. and F.S.) independently identified and reviewed the titles and abstracts of the published studies that appeared in the search. Potentially relevant studies were reviewed in full text. We reviewed the reference lists of relevant articles to identify additional studies.

Eligibility Criteria

To be eligible for our meta-analysis, studies had to fulfill the following criteria: (1) the study population included patients diagnosed with heart failure; (2) the study provided comparative information available in 2 cohorts—influenza-vaccinated and -nonvaccinated patients; (3) vaccination was administered within a year of study enrollment; (4) outcomes reported included all-cause mortality or hospitalization.

Outcomes of Interest

The outcomes of interest included all-cause mortality and the rate of hospitalization among patients with heart failure who were vaccinated and patients who were not vaccinated.

Data Extraction

Data from the eligible studies were extracted independently by 2 reviewers (S.P. and F.S.). We extracted the following information: author, year of publication, study design, country, study duration, follow-up period, study population and size, hazard ratio and/or risk ratio of mortality, and hospitalization in vaccinated and nonvaccinated study groups. Any discrepancies between the reviewers were resolved with discussions and consensus. Heart failure diagnosis was accepted as per the individual studies' definitions.

Quality Assessment

We used the Newcastle Ottawa Scale (NOS) to assess the methodological quality of observational cohort studies [16]. Two investigators (S.P. and F.S.) independently assessed the risk of bias. As our primary outcomes of interest were all-cause mortality and the rate of hospitalization among patients with heart failure, all 8 stars of the Newcastle Ottawa Scale could be assigned. Two investigators (S.P. and F.S.) independently assessed the risk of bias. Studies with an NOS score ≥7 were considered of adequate quality, whereas those with a score <7 were considered of inadequate quality. One study [17] was awarded an NOS score of 7, whereas the rest of the studies were awarded a score of 8.

Data Analysis

All statistical analysis was done using STATA, version 15.1 (StataCorp LLC, College Station, TX). We investigated the effect of influenza vaccination on the risk of mortality and hospitalization in the heart failure population. A subgroup analysis was performed to compare the effects of vaccination in the influenza season and noninfluenza season. We calculated a pooled hazard ratio (HR) with 95% confidence interval (CI) using the data reported in the individual studies. The studies that did not provide extractable data were not included in the meta-analysis and are discussed separately as part of the systematic review. Testing for heterogeneity was performed using the Higgins I^2, which measures the percentage of variation between the studies [18]. The DerSimonian and Laird random-effects model was used to pool the HR due to expected heterogeneity among the individual studies [19]. Publication bias was assessed using Egger's regression test. Statistical significance was set at .05.

RESULTS

Study Selection and Characteristics

A systematic search of the PubMed and EMBASE databases yielded 661 and 2801 articles, respectively (total n = 3462). After exclusion of duplicates and articles that were not available in the English language, the remaining 2674 articles were screened by title and abstract, and we identified 20 articles that were evaluated in full text. Of those, we excluded 4 studies because they did not include information on mortality and

hospitalization. We also excluded 8 studies that focused on a study population different than that specified in our eligibility criteria (4 of these studies focused on an elderly population without heart failure diagnosis at baseline, whereas the remaining 4 studies focused on patients with acute coronary syndrome, chronic kidney disease, diabetes mellitus, and chronic obstructive pulmonary disease, all without a heart failure diagnosis at baseline). No further studies were identified after a manual search of references. The detailed search process and study selection are depicted in Figure 1. In this analysis, we included 8 observational cohort studies [17,20–26] that fulfilled our criteria. The included studies were conducted in the following countries: 2 in Spain [20, 21] and 1 each in Israel [23], Taiwan [24], the United States [26], the United Kingdom [17], and Turkey [22]. In addition, 1 study reported data from 47 countries, including the United States [25]. The study period for 3 of the studies spanned the 2009 influenza pandemic [17, 20, 25], with 1 study identifying the inclusion of pandemic infection in the study population [20]. The International Classification of Diseases (ICD) coding was used to define heart failure in 3 studies [17, 21, 24], whereas the International Classification of Primary Care (ICPC) was used in 1 study [20]. Also, 1 study included patients with a reduction in left ventricular ejection fraction [25], whereas no specific definition of heart failure was found in the remaining 3 studies [22, 23, 26].

The total study population included in our analysis from these 8 studies was 82 354. The mean age of the study population (range) was ≥65 (65–76) years in all studies, except in 1 study [22], which had a mean age of <65 years. Study duration varied from 2 years to 20 years. Among the included studies, 6 studies reported information on all-cause mortality, whereas 4 reported the risk of subsequent hospitalization. One study reported 1-year all-cause mortality hazard ratio [25], 3 studies reported 4-year all-cause mortality hazard ratio in the influenza and noninfluenza seasons separately [20, 21, 24], 1 study reported both 1-year and 4-year all-cause mortality hazard ratio [23], and the last study reported 1-year all-cause mortality odds ratio [26].

In terms of hospitalization, 1 study reported 1-year risk of hospitalization [22], 1 study reported 2-year risk of hospitalization [25], and 1 study reported 4-year risk of hospitalization in the influenza and noninfluenza seasons separately [24]. The last study that reported hospitalization risk, Mohseni et al., followed a self-controlled study design in which the hospitalization rate among individuals with heart failure during the vaccination year was compared with the hospitalization rate in an adjacent

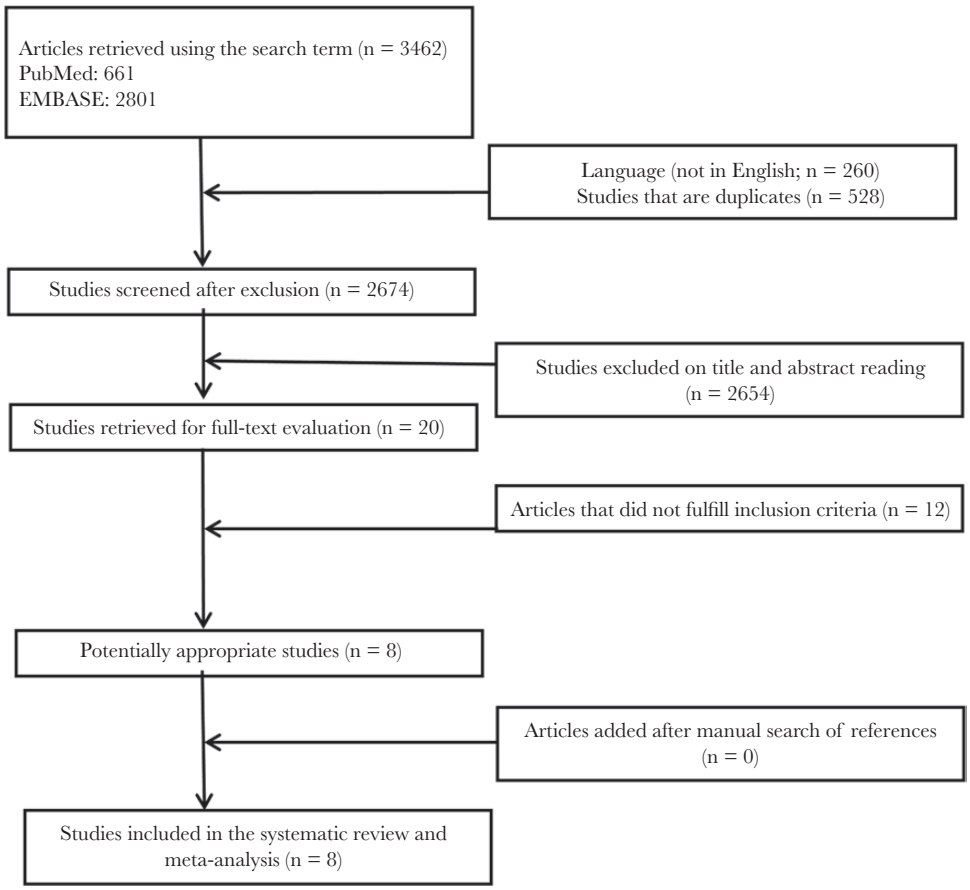

Figure 1. Flow diagram of the study selection.

nonvaccination year for the same individual [17]. The vaccination year was determined based on vaccination status within 12 months before each study year. A summary of individual study characteristics is presented in Table 1.

We used the Newcastle Ottawa Scale to evaluate observational cohort studies. Most of the studies were based on electronic health records, and thus the cohort representation was considered adequate. The 2 cohorts (vaccinated vs nonvaccinated) were comparable, and the baseline comorbidities were compared on all studies, with some using propensity score matching [20, 23, 25] and some using multivariable adjustment [21, 22, 24, 26] to ensure that the cohorts were comparable. Records of influenza vaccination were based on the recall of each individual, and as the recall duration was less than a year, the possibility of recall bias was considered to be low [27]. In terms of exposure duration, as influenza vaccination effects may wane after 6 months [28], even 1-year follow-up, which was followed in most studies, was considered adequate. All the included studies were considered of adequate quality based on the Newcastle Ottawa Scale.

Influenza Vaccination and Mortality

Four out of the 6 studies (16 751 patients) that reported data on mortality were included in the meta-analysis to evaluate the effect of influenza vaccination on mortality [21, 23–25]. There were another 2 studies that reported mortality outcome but could not be used in the meta-analysis because they reported the odds ratio instead of hazard ratio of mortality [26] or compared outcomes between consistently vaccinated and inconsistently or never-vaccinated individuals with heart failure during a 4-year study period [20]. Pooling of the 4 studies showed that influenza vaccination was associated with a decreased risk of mortality in individuals with heart failure 1 year after administration of the vaccine (HR, 0.69; 95% CI, 0.51–0.87) (Figure 2A). No evidence of publication bias was detected by the Egger's test for small study effects (P = .190). Considerable statistical heterogeneity was detected between the included studies (I^2 = 85.5%; Cochran Q value = 20.71; P < .01). In addition, we performed a subanalysis on 2 studies (6388 patients) that reported outcomes separately for the influenza and noninfluenza seasons (January to April for Diego et al., October to March for Liu et al., June to September for Diego et al., April to September for Liu et al., respectively) [21, 24]. The pooled hazard ratio of all-cause mortality during the influenza season was 0.49 (95% CI, 0.30–0.69) (Figure 2B), and during the noninfluenza season, it was 0.79 (95% CI, 0.68–0.89) (Figure 2C). Finally, we separately pooled 2 studies that reported on patients with heart failure only and not chronic heart disease [23, 25], and we found a hazard ratio of 0.81 (95% CI, 0.70–0.92) (Figure 2D).

Influenza Vaccination and Hospitalization

Two out of 3 studies (9055 patients) that reported data on hospitalization secondary to heart failure could be pooled in a meta-analysis [22, 25]. We found that influenza vaccination was associated with lower heart failure hospitalization compared with nonvaccinated individuals with heart failure (HR, 0.62; 95% CI, 0.00–1.23) (Figure 2E). However, the result was not statistically significant. Considerable heterogeneity was detected

Table 1. Study Characteristics

S.No.	First Author	Country	Study Design/ Duration	Study Population (Vaccinated/ Nonvaccinated), No.	Mean Age (Vaccinated/ Nonvaccinated), y	Male % (vaccinated/ Non-Vaccinated)	Intervention (Influenza vaccination)
1.	Kopel et al. 2014 [23]	Israel	Prospective cohort/1 y	1964 (501/1463)	75.8 ± 9.2/74.1 ± 10.6	56% /55%	12 months prior to study
2.	Vardeny et al. 2016 [25]	Global	Prospective cohort/2 y	8399 (1769/6630)	67.9 ± 10.1/62.7 ± 11.5	77.7%/80.2%	12 months prior to study
3.	Liu et al. 2012 [24]	Taiwan	Prospective cohort/4 y	5048 (2760/2288)	74.8 ± 6.3/75.7 ± 7	58.3%/51.8%	12 months prior to each study year
4.	Diego et al. 2009 [21]	Spain	Prospective cohort/4 y	1340 (860/480)	76.7 ± 6.7/75.5 ± 7.6	48%/46.3%	12 months prior to each study year
5.	Blaya et al. 2016 [20]	Spain	Prospective cohort/4 y	3229/2032 (1016/1016)	75.97 ± 9.67/76.53 ± 10.44	38.09%/39.67%	12 months prior to each study year
6.	Wu et al. 2014 [26]	US	Retrospective cohort/7 y	2516 (2087/429)	71.91 ± 10.55/68.3 ± 11.27	98.5%/98.4%	12 months prior to each study year
7.	Mohseni et al. 2017 [17]	UK	Prospective cohort/20 y	59 202	74.7 ± 11.3/74.7 ± 11.3	50.1%/50.1%	12 months prior to each study year
8.	Kaya et al. 2017 [22]	Turkey	Prospective cohort/2 y	656 (265/391)	60 ± 14/63 ± 13	72%/72%	12 months prior to each study year

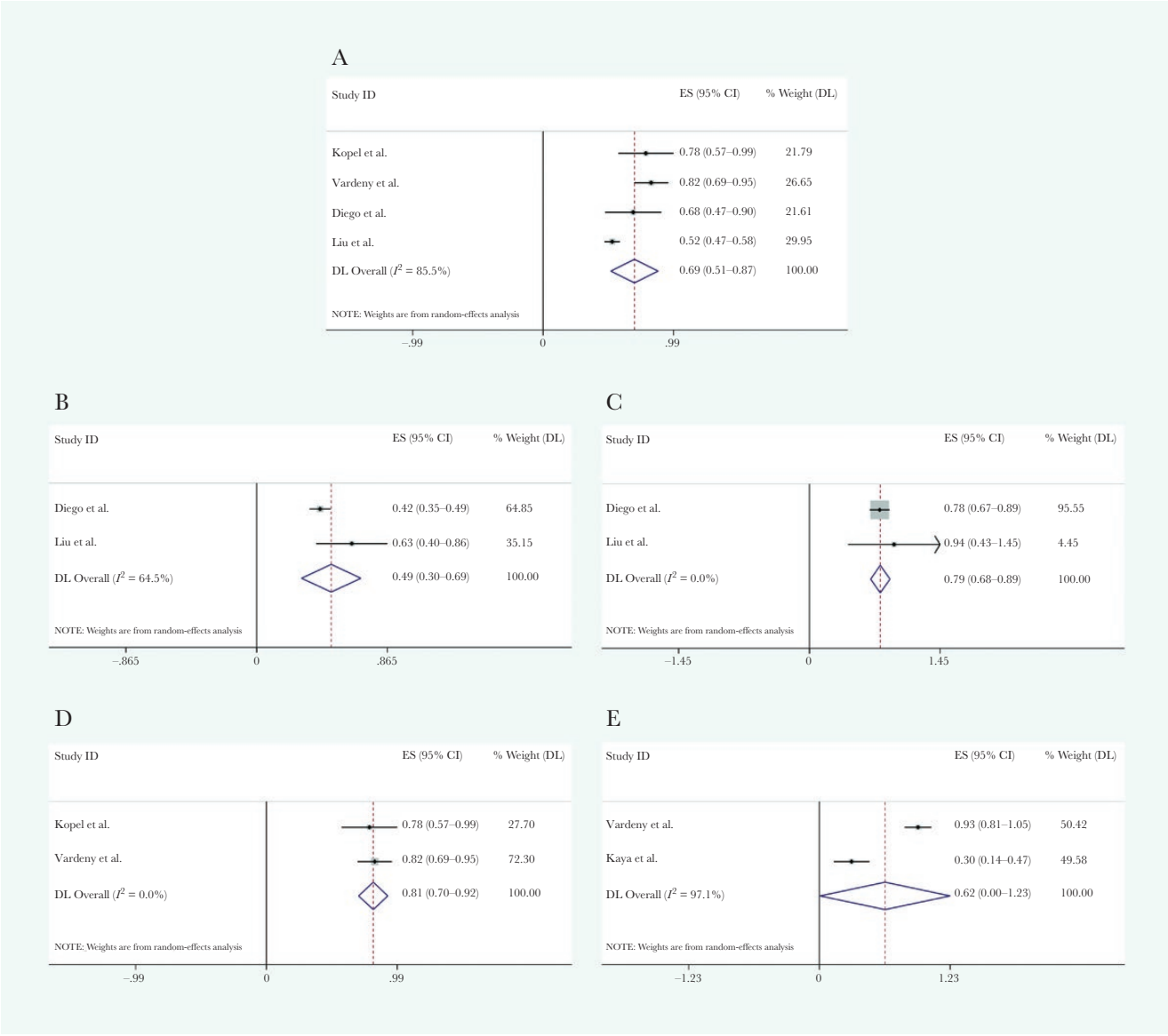

Figure 2. Forest plot showing the effect of influenza vaccination on mortality and hospitalization. A, Effect of influenza vaccination on all-cause mortality. B, Effect of influenza vaccination on all-cause mortality during influenza seasons. C, Effect of influenza vaccination on all-cause mortality during noninfluenza seasons. D, Effect of influenza vaccination on all-cause mortality in patients with heart failure and not chronic heart disease. E, Effect of influenza vaccination on heart failure hospitalization. Abbreviations: CI, confidence interval; DL, DerSimonian and Laird; ES, Effect Size (Hazard Ratio).

in this analysis (I^2 = 97.1%; Cochrane Q value = 34.4; P < .01). Data presented in the study by Mohseni et al. [17] could not be pooled, as a hazard ratio was not provided, and the authors reported a statistically significant decrease in incidence rate of heart failure hospitalization with influenza vaccination in heart failure individuals (incidence rate ratio [IRR], 0.71; 95% CI, 0.68–0.75) (Table 2).

Two studies examined the association of influenza vaccination with all-cause hospitalization in individuals with heart failure [17, 25]. In particular, Mohseni et al. [17] showed that the incidence rate ratio was significantly lower in the vaccinated group (IRR, 0.96; 95% CI, 0.95–0.98), as compared with the nonvaccinated group, whereas Vardeny et al. [25] failed to show a statistically significant difference in all-cause hospitalization between the 2 groups (HR, 1.07; 95% CI, 0.97–1.18) (Table 2). Finally, in terms of cardiovascular hospitalization, 2 studies reported a significant decrease in the risk of hospitalization with the administration of influenza vaccine [17, 24]. Mohseni et al. [17] reported an IRR of 0.73, and Liu et al. [24] reported a hazard ratio of 0.84 and 1.04 in the influenza season and noninfluenza season, respectively (Table 2).

DISCUSSION

In this study, we evaluated the effect of influenza vaccination on all-cause mortality and hospitalization rate among patients with

Table 2. Study Outcomes (Mortality and Hospitalization)

S.No.	First Author	Outcome (Mortality)			Outcome (Hospitalization)		
		Mortality Reported	1-y Mortality HR	4-y Mortality HR	Heart Failure	All-Cause	Cardiovascular
1.	Kopel et al. 2014 [23]	HR 1 y, 0.78 (0.60–1.02); HR 4 y, 0.78 (0.66–0.93)	0.78 (0.60–1.02)	0.78 (0.66–0.93)	-	-	-
2.	Vardeny et al. 2016 [25]	HR, 0.82 (0.7–0.96)	0.82 (0.7–0.96)	-	HR, 0.93 (0.81–1.06)	HR, 1.07 (0.97–1.18)	-
3.	Liu et al. 2012 [24]	HR flu season, 0.42 (0.35–0.49); HR nonflu, 0.78 (0.68–0.9)	-	0.52 (0.47–0.58)	-	-	HR flu, 0.84 (0.76–0.93); HR nonflu, 1.04 (0.91–1.18)
4.	Diego et al. 2009 [21]	HR flu season, 0.63 (0.44–0.91); HR nonflu, 0.94 (0.56–1.58)	-	0.66 (0.47–0.90)	-	-	-
5.	Mohseni et al. 2017 [17]	-	-	-	IRR, 0.71 (0.68–0.75)	IRR, 0.96 (0.95–0.98)	IRR, 0.73 (0.71–0.76)
6.	Kaya et al. 2017 [22]	-	-	-	HR, 0.303 (0.178–0.514)	-	-
7.	Blaya et al. 2016 [20]	HR flu, 0.59; HR preflu, 0.91; HR postflu, 0.75	-	-	-	-	-
8.	Wu et al. 2014 [26]	OR, 0.75 (0.66–0.84)	-	-	-	-	-

Abbreviations: HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio.

preexisting heart failure. In terms of mortality, we found data favoring influenza vaccination in patients with heart failure. Our results suggest that the risk of all-cause mortality is 31% lower in the vaccinated individuals with heart failure, as compared with nonvaccinated patients. This effect is more prominent during influenza seasons compared with noninfluenza seasons (HR, 0.49 vs 0.79, respectively). In terms of hospitalization, we found a pooled hazard ratio of 0.62 favoring influenza vaccination, but this result did not reach statistical significance.

Importantly, we found that all-cause mortality is lower by almost one-third in patients with heart failure who received influenza vaccination, as compared with those who were not vaccinated. Our results are consistent with a retrospective cohort study of a population >75 years of age without baseline heart failure diagnosis [10] and with 2 recent meta-analyses in patients with underlying cardiovascular disease that showed 50% [5] and 66% [29] reduction in cardiovascular deaths. Respiratory infection is a precipitating factor for heart failure exacerbation [9], and studies have repeatedly demonstrated the effectiveness of influenza vaccination in prevention of admissions secondary to influenza like illness and/or lower respiratory tract infection [30]. This decrease in mortality appears to be secondary to a decrease in heart failure exacerbations, and this finding is further supported by the larger decrease in mortality during influenza seasons compared with noninfluenza seasons that we found in our analysis.

There was no statistically significant difference in the rate of hospitalization among vaccinated and nonvaccinated patients with heart failure (pooled HR of 0.62 favoring influenza vaccination), which may be due to the relatively limited number of studies. Furthermore, due to the low power of the included studies, small treatment effects could result in under- or overestimation of the treatment effect [31]. Moreover, individual studies have shown that admission secondary to heart failure or any cardiovascular cause or any other cause is less frequent among vaccinated individuals compared with nonvaccinated individuals [17, 22, 24, 25]. Similarly, studies have reported a decrease in the hospitalization rate after 1 year of influenza vaccination in elderly populations without baseline heart failure diagnosis [11, 12]. From an economic perspective, the total annual direct medical cost burden from heart failure treatment in the United States was estimated to be $30.7 billion in 2012 [6] and is projected to reach $77.7 billion by 2030 [32]. A cost-effectiveness analysis reflecting current practices and costs is needed to address potential health care cost savings from influenza vaccination in patients with heart failure.

Guidelines from professional societies in regards to the use of influenza vaccination have been explicit and uniform (Supplementary Table 1). The European Society of Cardiology (ESC) [33], the American College of Cardiology Foundation (ACCF) [34], and the CDC [35] recommend usage of influenza vaccines in patients with underlying cardiovascular disease, whereas the Heart Failure Society of America (HFSA) specifically recommends the use of influenza vaccines in the heart failure population [36]. Despite this uniformity of published guidelines, the coverage rate remains low [37], and among the elderly population in the United States, the coverage rate has been constantly in the range of 60% to 65%, the latest being 65.3% in the years 2016–2017 [38]. For example, in a large multinational trial among patients with heart failure, the vaccination coverage rate was <20% in more than half of the included countries, with the relevant rate in the United States being

barely above 50% [25]. Given the significant difference in mortality among patients with heart failure who receive the vaccine, it will be important to identify factors that might contribute to the low compliance with the vaccination in this population and implement targeted strategies to increase the vaccination rate.

The findings of this meta-analysis should be interpreted while taking into account potential limitations. First, it should be noted that the studies are not randomized, and as such, our analysis is subject to the potential of "healthy user bias" and confounding factors. However, most of the studies included in our analysis were adjusted using the propensity score matching system, which adds validity to our results. Second, lower ejection fraction and higher New York Heart Association (NYHA) class are independent predictors of increased mortality in patients with heart failure [39, 40]. In our meta-analysis, influenza seemed to increase the mortality of patients with heart failure, but only 2 of the included studies reported the ejection fraction or the NYHA class of their patients. To account for the differences in the severity of heart failure in terms of ejection fraction and/or NYHA class, both studies performed multivariable logistic regression analysis [22, 25]. Future studies with stratification of heart failure severity are needed to minimize and avoid possible confounding. Third, optimal timing of vaccination is needed for maximum benefit [41], and this effect might also be influenced by the vaccine effectiveness, which changes every year [38]. To this effect, a random-effects model was selected to generate a more conservative estimate, and the large sample size (16 751 patients) included in the mortality analysis strengthens our findings. Also, due to the limited number of included studies, we were not able to identify a correlation between the yearly variability of vaccine effectiveness and outcomes such as mortality and hospitalization. Finally, in 2 of the included studies, the study population consisted of both heart failure patients and patients with chronic heart disease. Although it is known that a large part of heart failure diagnosis is secondary to chronic heart disease like hypertension and coronary heart disease [42], it would be ideal to compare the effect of influenza vaccination exclusively in a heart failure population and have undiluted results.

In conclusion, we report that in patients with heart failure, vaccination against influenza provides a statistically significant mortality benefit. This finding highlights the need for stricter implementation strategies of influenza vaccination in this patient population. Future studies should focus on identifying subgroups of patients who are less likely to be vaccinated, the effectiveness of high-dose vaccines, and the subgroups that will have the greatest benefit. Also, an updated cost-effectiveness analysis should incorporate the potential benefit of influenza vaccination, current practices, and the possible decrease in health care cost.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Author contributions. Sanjay Poudel, MBBS: Dr. Poudel conceptualized and designed the study, participated in data review and analysis, participated in data interpretation, reviewed and revised the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Fadi Shehadeh, MEng: Mr. Shehadeh conceptualized and designed the study, participated in data review and analysis, participated in data interpretation, reviewed and revised the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ioannis Zacharioudakis, MD: Dr. Zacharioudakis conceptualized and designed the study, participated in data interpretation, reviewed and revised the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Giannoula S. Tansarli, MD: Dr. Tansarli conceptualized and designed the study, participated in data interpretation, reviewed and revised the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Fainareti N. Zervou, MD: Dr. Zervou participated in data interpretation, reviewed and revised the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Marlos Kalligeros, MD: Dr. Kalligeros participated in data interpretation, reviewed and revised the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Robertus van Aalst, MSc: Mr. van Aalst participated in data interpretation, reviewed and revised the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ayman Chit, PhD: Dr. Chit participated in data interpretation, reviewed and revised the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Eleftherios Mylonakis, MD, PhD: Dr. Mylonakis conceptualized and designed the study, participated in data interpretation, reviewed and revised the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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