



## Review

## Impact of influenza vaccination on healthcare utilization – A systematic review

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## ABSTRACT

**Introduction:** Although a vaccine-preventable disease, influenza causes approximately 3–5 million cases of severe illness and about 290,000–650,000 deaths worldwide, which occur primarily among people 65 years and older. Nonetheless, prevention of influenza and its complications rely mainly on vaccination. We aimed to systematically evaluate influenza vaccine effectiveness at reducing healthcare utilization in older adults, defined as the reduction of outpatient visits, ILI and influenza hospitalizations, utilization of antibiotics and cardiovascular events by vaccination status during the influenza season.

**Methods:** We searched MEDLINE, EMBASE, CINAHL, Cochrane Library and considered any seasonal influenza vaccine, excluding the pandemic (2009–10 season) vaccine. Reviewers independently assessed data extraction and quality assessment.

**Results:** Of the 8308 citations retrieved, 22 studies were included in the systematic review. Overall, two studies (9%) were deemed at moderate risk of bias, thirteen (59%) at serious risk of bias and seven (32%) at critical risk of bias. For outpatient visits, we found modest evidence of protection by the influenza vaccine. For all-cause hospitalization outcomes, we found a wide range of results, mostly deemed at serious risk of bias. The included studies suggested that the vaccine may protect older adults against influenza hospitalizations and cardiovascular events. No article meeting our inclusion criteria explored the use of antibiotics and ILI hospitalizations. The high heterogeneity between studies hindered the aggregation of data into a meta-analysis.

**Conclusion:** The variability between studies prevented us from drawing a clear conclusion on the effectiveness of the influenza vaccine on healthcare utilization in older adults. Overall, the data suggests that the vaccine may result in a reduction of healthcare utilization in the older population. Further studies of higher quality are necessary.

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## 1. Introduction

Influenza contributes directly and indirectly to a large number of hospitalizations and deaths, 90% of which occur in older adults [1]. Influenza vaccination remains the cornerstone of influenza prevention, as recommended by the National Advisory Committee on Immunization [2]. While seasonal vaccination is recommended for everyone, individuals with underlying medical conditions and people 65 years and older, who are at higher risk of complications if infected are prioritized.

Previous systematic reviews on the effectiveness of the influenza vaccine have been published [3–6]. Yet, results have been inconclusive due to methodological flaws and low quality of the included studies. Additionally, there has not been a recent review of studies evaluating the effectiveness of influenza vaccination in older adults. To address this gap in the literature, we conducted a systematic review of the effectiveness of the influenza vaccine in older adults at preventing healthcare utilization and reducing the risk of cardiovascular events, during the epidemic season.

## 2. Method

### 2.1. Protocol registration, search strategy and study selection

Our protocol was registered in PROSPERO (ID: CRD42017073549). We searched five electronics databases (MEDLINE, EMBASE, CINAHL, The Cochrane Library and [www.clinicaltrials.gov](http://www.clinicaltrials.gov)) to identify studies published between January 1st, 2000 and August 31st, 2017. We restricted the literature search to reflect changes in influenza diagnostic methods following 2000. The search strategy was developed in collaboration with a research librarian. The initial search was developed in MEDLINE and adjusted to other databases (Supplementary 1). After removal of duplicates, two reviewers (I.F. and P.D.P.) independently reviewed titles and abstracts, then selected full texts to evaluate the eligibility of each reference. References of identified systematic review on influenza vaccine effectiveness were screened to identify studies missed by the database search. In case of disagreement, a third reviewer was asked to arbitrate (C.Q.). The review process was completed using Distiller SR online software (Evidence Partners Inc, Ottawa, Canada).

### 2.2. Study eligibility

We included observational studies evaluating the effectiveness of influenza vaccine on healthcare utilization and the risk of cardiovascular events in older adults. Studies evaluating adults

65 years of age and older were included. We focused our research question on older adults because they are considered at higher risk of complications if infected. We excluded ecological studies, case reports and case series as these designs do not allow to answer the research question. Only articles in English or French were included. We considered all types of influenza vaccines, except the 2009–2010 pandemic vaccine, as our research question was focused on seasonal influenza. We did not restrict on medical conditions or settings.

We included studies that evaluated participants who had received the influenza vaccine at least 14 days before illness onset. Our primary outcome was healthcare utilization defined as outpatient visits for influenza-like-illness (ILI), hospitalization for ILI (defined as an acute respiratory infection with objectively measured temperature of  $\geq 38$  °C and cough with onset in the last 10 days [7]), hospitalization for influenza (defined as a diagnosis of influenza ICD-9/ICD-10 coded or a laboratory confirmed infection (LCI) by PCR or viral culture), all-cause hospitalization and overall utilization of antibiotics in defined daily doses. The secondary outcome was cardiovascular events during the influenza season. We excluded test-negative study designs as these only include participants tested for influenza, which implies ILI and healthcare utilization for all participants. We only included outcomes that occurred during the influenza season.

### 2.3. Data extraction

A data extraction form was specifically developed for this systematic review. The extraction process was piloted independently by two reviewers (F.T. and P.D.P.) to assess the quality and the consistency of data collection. We extracted the following data: population characteristics; intervention description, vaccine type; outcome definition, number of events by vaccination status; follow-up period, influenza season; and vaccine strains' match. Effect measures extracted included odds ratio (OR), hazard ratio (HR), risk ratio (RR), and vaccine effectiveness (VE) estimates. Meetings were held to compare data extractions and resolve any discrepancies between reviewers. In case of a disagreement, a third reviewer was asked to arbitrate (C.Q.).

### 2.4. Quality assessment

We evaluated studies' risk of bias using the Cochrane tool (ROBINS-I) to assess methodological quality and studies' validity [8]. To be considered at moderate risk of bias due to confounding, it was critical to appropriately control for health status and functional status. If at least one of these confounding factors was not

appropriately controlled for, the study was deemed at serious risk of bias due to confounding. A study was considered at critical risk of bias if both health status and functional status were not appropriately controlled for in the analysis. Functional status was ascertained if details about a diagnosis of dementia and/or mention of a subject's need for assistance in activities of daily living was mentioned [9]. We determined the quality of evidence and strength of recommendations for each clinical outcome using the GRADE tool [10].

### 2.5. Data analysis

A descriptive analysis of the included studies was performed. Forest plots were created for each outcome presented by study design and health status. We tested for heterogeneity between studies stratified by outcomes, using the  $I^2$  statistics (R, version 3.4.3). If the heterogeneity was less than 50%, we proceeded to a meta-analysis as previously stated in the research protocol.

## 3. Results

### 3.1. Study characteristics

Overall, 22 articles were included in the systematic review (Fig. 1) [11–32]. Studies were conducted between the 1994–1995 and the 2016–2017 influenza seasons in Europe (55%), Asia (36%) and America (9%). One (4.5%) study looked at individuals from nursing home facilities [32] and two (9.1%) only included individuals with underlying medical conditions (Table 1) [14,18].

Eight studies looked at outpatient visits [11,12,15–17,22,25,26]; seven at influenza hospitalizations [11,13,17,23,27,28,31]; six at all-cause hospitalizations [17,20,21,24,30] and seven reported cardiovascular events [14,17–21,29]. Four (18.2%) articles reported more than one outcome of interest [11,17,20,21]. We found no article meeting our inclusion criteria for the use of antibiotics and ILI hospitalizations.

### 3.2. Within-Study risk of bias

Overall, two (9%) studies were deemed at moderate risk of bias, thirteen (59%) at serious risk of bias and seven (32%) at critical risk of bias (Table 1). Confounding bias was mostly due to unadjusted statistical estimates and confounding by indication. Possible misclassification, often associated with recall bias, was observed in nine (41%) studies. Eight (36.4%) studies were deemed at risk of bias due to inappropriate handling of missing data in the analysis. Four (18.2%) studies were considered at risk of selection bias due to unclear reporting of selection criteria.

### 3.3. Results of individual studies

#### 3.3.1. Outpatient visit

We extracted eighteen effect measures from eight studies assessing outpatient visits. Almost all estimates were in favour of the intervention, except Kafatos et al's. adjusted vaccine effectiveness (aVE) of people 75 years and older and our calculated OR for Denmark from Kissling's study [22,25]. However, these were not statistically significant.

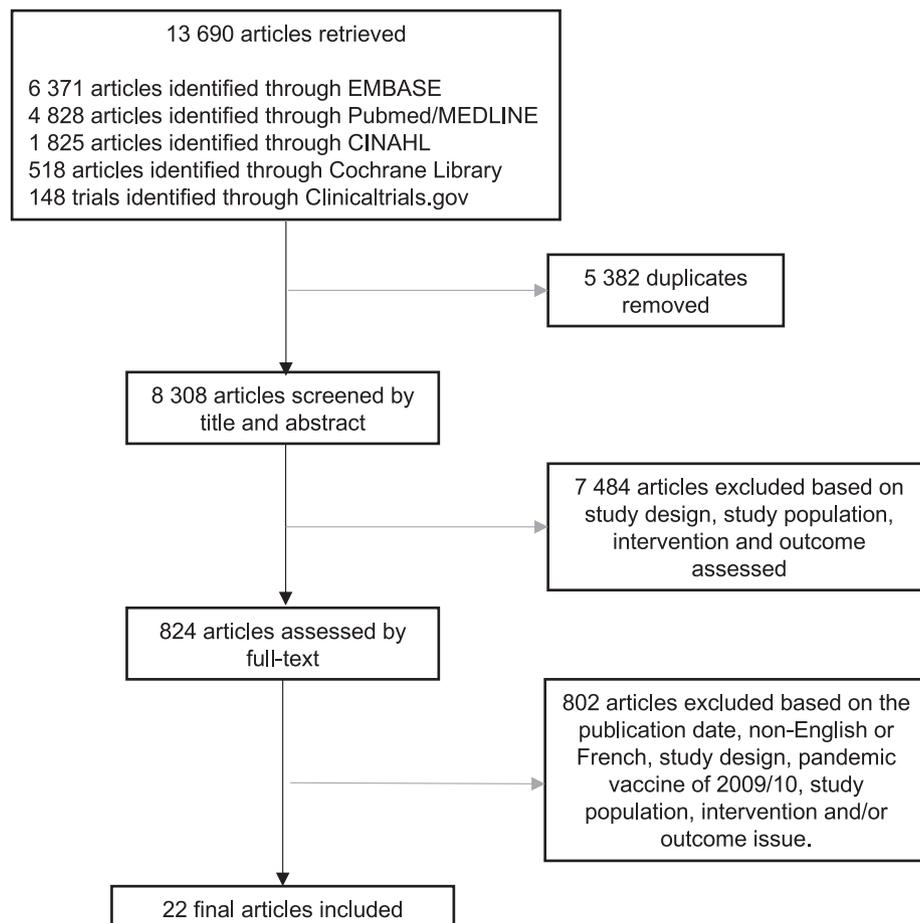


Fig. 1. Study Identification Flow Chart.

**Table 1**  
Summary of the Studies Included in the Systematic Review.

Authors	Year	Study design	Country	Study population	Follow-up period	Vaccine type/match	Outcome measures	Risk of bias
Hergens et al. [12]	2017	Cohort	Sweden	"All individuals aged 65 years and older registered in Stockholm County on 1 October 2016."	10/2016 to 01/2017	TIV/NA	LCI: aHR 0.76 (0.65–0.89)	Serious
			Finland	"All individuals aged 65 to 100 years old permanently living in Finland on 1 October 2016."	10/2016 to 01/2017	TIV/NA	LCI: aHR 0.67 (0.63–0.72)	
Leval et al. [11]	2016	Cohort	Sweden	All individuals aged 65 years and older registered in Stockholm at the start of each season.	10/2011 to 05/2012	TIV/NA	Outpatient cases: aHR 0.86 (0.64–1.17) Inpatient cases: aHR 0.94 (0.68–1.31)	Serious
					10/2012 to 05/2013		Outpatient cases: aHR 0.62 (0.35–1.10) Inpatient cases: aHR 0.48 (0.34–0.69)	
					10/2013 to 05/2014		Outpatient cases: aHR 0.59 (0.33–1.05) Inpatient cases: aHR 0.51 (0.31–0.83)	
					10/2014 to 05/2015		Outpatient cases: aHR 0.89 (0.69–1.15) Inpatient cases: aHR 0.79 (0.68–0.93)	
Havers et al. [13]	2016	Case-control Setting: Community-dwelling	USA	Adults aged 50 years and older in select counties in 10 states (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, 2 sites in New York, Oregon and Tennessee).	10/2010 to 04/2011	NA/Influenza B component well match	65–74 y.o. LCI hospitalization: aVE 61.0% (4.3–84.1) & 75 years and older LCI hospitalization: aVE 57.3% (15.9–78.4)	Moderate
Fang et al. [14]	2016	Cohort	Taiwan	"All patients diagnosed with chronic kidney disease who visited health care facilities in Taiwan over a 10-year period."	01/1999 to 12/2008	NA/NA	65–74 y.o. HF hospitalization: aHR 0.28 (0.18–0.43) & 75 years and older HF hospitalization: aHR 0.33 (0.21–0.50)	Serious
Souty et al. [15]	2015	Case-base	France	Individuals of 65 years and older in metropolitan France.	2010/2011 2011/2012 2012/2013 2013/2014 Early 2014/2015	TIV/Good match Good match Good match Good match Mismatch	ILI cases: VE 55% (41–66) ILI cases: VE 31% (16–43) ILI cases: VE 57% (49–64) ILI cases: VE 57% (37–72) ILI cases: VE 11% (–4 to 23)	Critical
Simpson et al. [17]	2013	Cohort	Scotland	Individuals of 65 years and older registered with practicing practices throughout Scotland.	2000/2001 to 2008/2009	TIV/ 2005/2006 poor match; 2008/2009 good match	ILI cases: aVE 19.3% (–3.3 to 36.9); Influenza-pneumonia hospit.: aVE 11.6% (–2.4 to 23.6); All-cause hospitalization: aVE 13.1% (9.5–16.6); CVD Hospitalization: aVE 12.8% (6.4–8.7)	Moderate

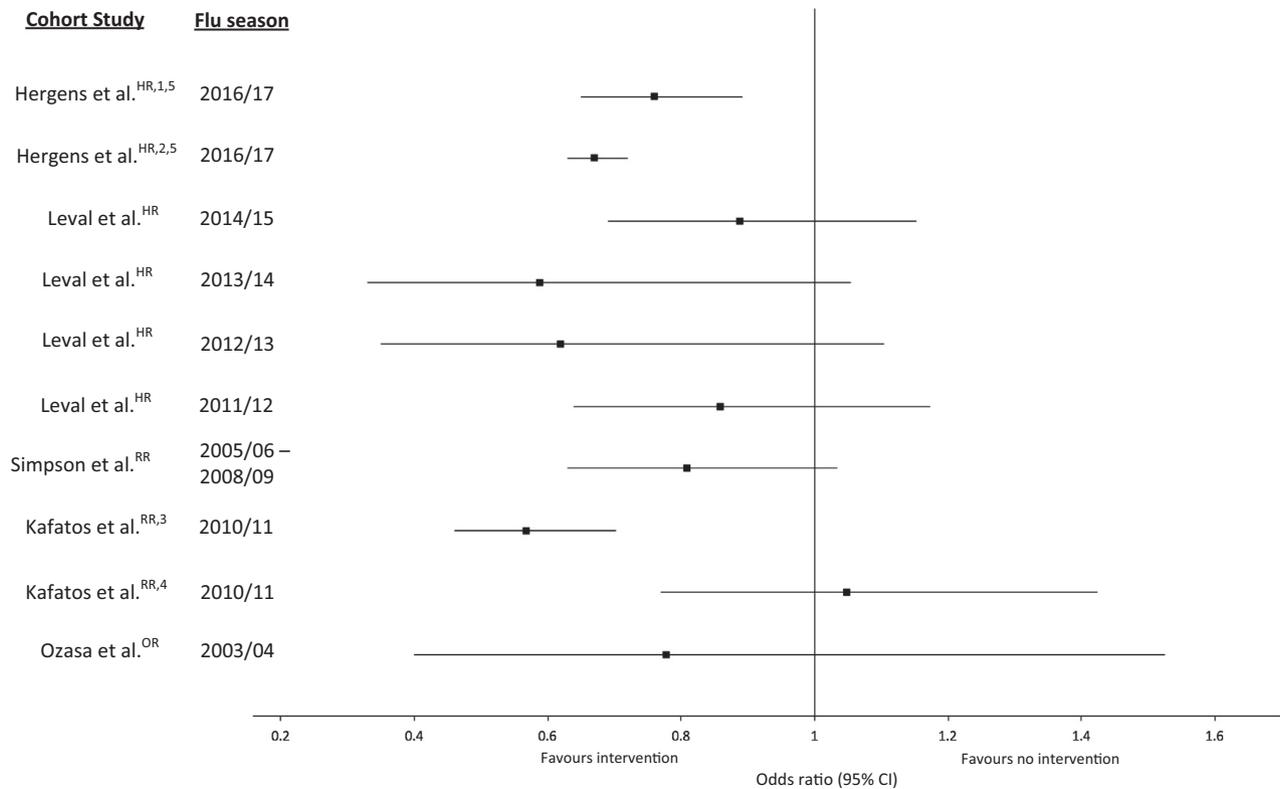
Sung et al. [18]	2014	Cohort	Taiwan	Older patients (55 years and older) with a diagnosis of COPD over a 8-year period.	01/2000 to 12/2007	NA/NA	ACS hospitalization 65–74 y. o.: aHR 0.51 (0.36–0.71) & 75 years and older: aHR 0.31 (0.19–0.50)	Serious
Lin et al. [19]	2014	Case-control	Taiwan	Individuals of 65 years and older from Taiwan's National Health Insurance program in 2006.	2006/2007 to 2008/2009	NA/NA	Stroke hospitalization: aOR 0.80 (0.64–0.98)	Serious
Seo et al. [21]	2014	Case-control	Korea	Patients who visited cardiovascular and pulmonary clinics during the influenza epidemic period.	12/2011 to 05/2012	NA/Good match	People 65 years and older All-cause hospitalization: aOR 0.46 (0.32–0.66) & CVD hospitalization: aOR 0.44 (0.29–0.68)	Serious
Kafatos et al. [22]	2013	Cohort	England and Wales	Patients registered with a practice by 1 September 2010.	09/2010 to 03/2011	TIV/Good match	65–74 y. o. ILI cases: aVE 43.2% (29.7–54.0) & 75 years and older ILI cases: aVE –4.5% (–42.2 to 23.2)	Serious
Falchi et al. [16]	2013	Case-base	France	Individuals covered by the CNAMTS in France.	2010/2011	TIV/Good match	65 years and older ILI cases: VE 51% (35–63) & 65 years and older LCI cases: All influenza viruses VE 49% (–9 to 78); A(H1N1)pdm09 VE 79% (–45 to 99); Influenza BVE 43% (–38 to 78)	Critical
Gasparini et al. [23]	2013	Case-control	Italy	Older adults (>64 years old) residing in Genoa, Italy.	2010/2011	Adjuvanted/Good match	Influenza hospitalization: aOR 0.05 (0.01–0.23); By vaccine type: Inflexal-V aOR 0.05 (0.01–0.37) & Flud aOR 0.12 (0.01–1.39)	Serious
Seo et al. [20]	2013	Case-control	Korea	Patients who visited cardiovascular and pulmonary clinics during the influenza epidemic period.	12/2010 to 02/2011	NA/Good match	People 65 years and older; All-cause hospitalization: aOR 0.48 (0.30–0.78) & CVD hospitalization: aOR 0.27 (0.11–0.66)	Serious
Hottes et al. [24]	2011	Cohort	Canada	Adults of 65 years and older from administrative databases in Manitoba (MIMS and Centre for Health Policy data).	2000/2001 2001/2002 2002/2003 2004/2005	NA/ Good match Good match Good match; Good match;	Overall hospitalization: aVE –16% (–46 to 8) aVE 4% (–28 to 29) aVE 3% (–29 to 27) aVE 30% (9 to 46)	Serious
Kissling et al. [25]	2009	Case-control	Denmark	“Elderly living in selected sentinel GP practice catchment areas in Denmark.”	2005/2006 2008/2009	Good match; TIV/Good match	aVE 3% (–36 to 31) Outpatient visit: OR 1.49 (0.69–3.23)	Critical
			Portugal	“Elderly living in selected sentinel GP practice catchment areas in Portugal.”	2008/2009	TIV/Good match	Outpatient visit: OR 0.78 (0.35–1.75)	
Ozasa et al. [26]	2006	Cohort	Japan	Older adults (65 years and older) living in rural area of Kyoto Prefecture, Japan.	12/2003 to 03/2004	TIV/Mismatch	Outpatient visit: aOR 0.78 (0.40–1.52)	Serious

(continued on next page)

**Table 1** (continued)

Authors	Year	Study design	Country	Study population	Follow-up period	Vaccine type/match	Outcome measures	Risk of bias
Christenson et al. [28]	2004	Cohort	Sweden	All individuals of 65 years and older in Stockholm County, Sweden.	12/1999 to 05/2000	TIV/NA	Influenza hospitalization: OR 0.63 (0.53–0.75)	Critical
Lavallée et al. [29]	2002	Case-control	France	French population aged 60 years and older.	1998/1999 to 1999/2000	TIV/NA	75 years and older Cardiovascular event: aOR 0.65 (0.12–3.56)	Serious
Takahashi et al. [30]	2001	Cohort Setting: Community-dwelling	Japan	All residents of 3 years and older of Kawaura, a rural town in Kumamoto Prefecture, Japan.	12/1999 to 03/2000	TIV/NA	Respiratory disease hospitalization: RR 0.13 (0.04–0.44) & Non-respiratory disease hospitalization: RR 0.32 (0.20–0.50)	Critical
Crocetti et al. [31]	2001	Case-control Setting: Community-dwelling	Italy	Individuals aged 65 years or older, residents in Health District no. 10 in the Tuscany region.	12/1994 to 03/1995	NA/NA	Influenza hospitalization: aOR 0.67 (0.48–0.95)	Serious
Deguchi et al. [32]	2001	Cohort Setting: Nursing home resident	Japan	Individuals older than 65 years who resided in 301 welfare nursing homes in Osaka Prefecture, Japan.	11/1998 to 03/1999	TIV/NA	All-cause hospitalization: VE 82.3%	Critical
Christenson et al. [27]	2001	Cohort	Sweden	People of 65 years and older in Stockholm, Sweden.	12/1998 to 05/1999	TIV/Good match	Influenza hospitalization: VE 46% (34–56)	Critical

Effect measure (95% CI); ACS, Acute coronary syndrome; COPD, Chronic Obstructive Pulmonary Disease; CVD, Cerebrovascular and cardiovascular disease; HF, Heart failure; ILI, Influenza-like-illness; LCI, Laboratory confirmed infection; NA, not available; TIV, trivalent inactivated vaccine; y. o., years old; aHR, adjust hazard ratio; aOR, adjust odds ratio; OR, crude odds ratio; aVE, adjust vaccine effectiveness; VE, vaccine effectiveness; RR, risk ratio.



**Fig. 2.** Effect measure of outpatient visit comparing vaccinated and unvaccinated individuals. <sup>HR</sup> Hazard ratio; <sup>OR</sup> odds ratio; <sup>RR</sup> risk ratio; <sup>1</sup> Sweden population; <sup>2</sup> Finland population; <sup>3</sup> age range: 65–74 years old; <sup>4</sup> age range: 75 years and older; <sup>5</sup> laboratory-confirmed infection.

From the five cohort studies included, three of ten effect measures (30%) showed a protective effect of the influenza vaccine against outpatient visits during the influenza season ( $p < 0.05$ ) (Fig. 2). From the 2016–2017 mid-season analysis, Hergens et al. found that the vaccine was protective against laboratory confirmed infection in Sweden and Finland with adjusted hazard ratios (aHRs) of 0.76 (95% CI: 0.65–0.89) and 0.67 (95% CI: 0.63–0.72), respectively [12]. Leval et al. reported aHRs (95% CI) for the 2011–2012 to the 2014–2015 influenza seasons of 0.86 (0.64–1.17), 0.62 (0.35–1.10), 0.59 (0.33–1.05) and 0.89 (0.69–1.15), respectively [11]. Simpson et al. calculated an aVE against ILI of 19.3% (–3.3 to 36.9) over eight influenza seasons [17]. For the 2010–2011 influenza season, Kafatos et al. reported for both age groups, 65 to 74 years of age and 75 years and older, aVEs (95% CI) of 43.2% (29.7–54) and –4.5% (–42.2 to 23.2), respectively [22]. A Japanese study measured an aOR (95% CI) of 0.78 (0.40–1.52) for the 2003–2004 mismatched influenza season [26].

While we included the Kissling et al. case-control study, we did not extract the reported effect measure. Instead, we calculated crude ORs using the raw data from countries that reported on subjects without healthcare encounters during the 2008–2009 influenza season. The calculated ORs (95% CI) were 1.49 (0.69–3.23) and 0.78 (0.35–1.75) for Denmark and Portugal, respectively.

Two articles showed VE results using a case-base study design [15,16]. Souty et al. estimated the effectiveness of influenza vaccines (95% CI) for the 2010–2011 to early 2014–2015 flu season to be 55% (41–66%); 31% (16–43%); 57% (49–64%); 57% (37–72%) and 11% (–4% to 23%) [15]. Falchi et al. measured a VE (95% CI) of 51% (35% to 63%) for patients presenting with ILI in the 2010–2011 flu season [16]. Furthermore, they estimated a VE (95% CI) of 49% (–9% to 78%) against all influenza viruses for patients with LCI; 79% (–45% to 99%) against A(H1N1)pdm09 infection and 43% (–38% to 78%) against influenza B infection [16].

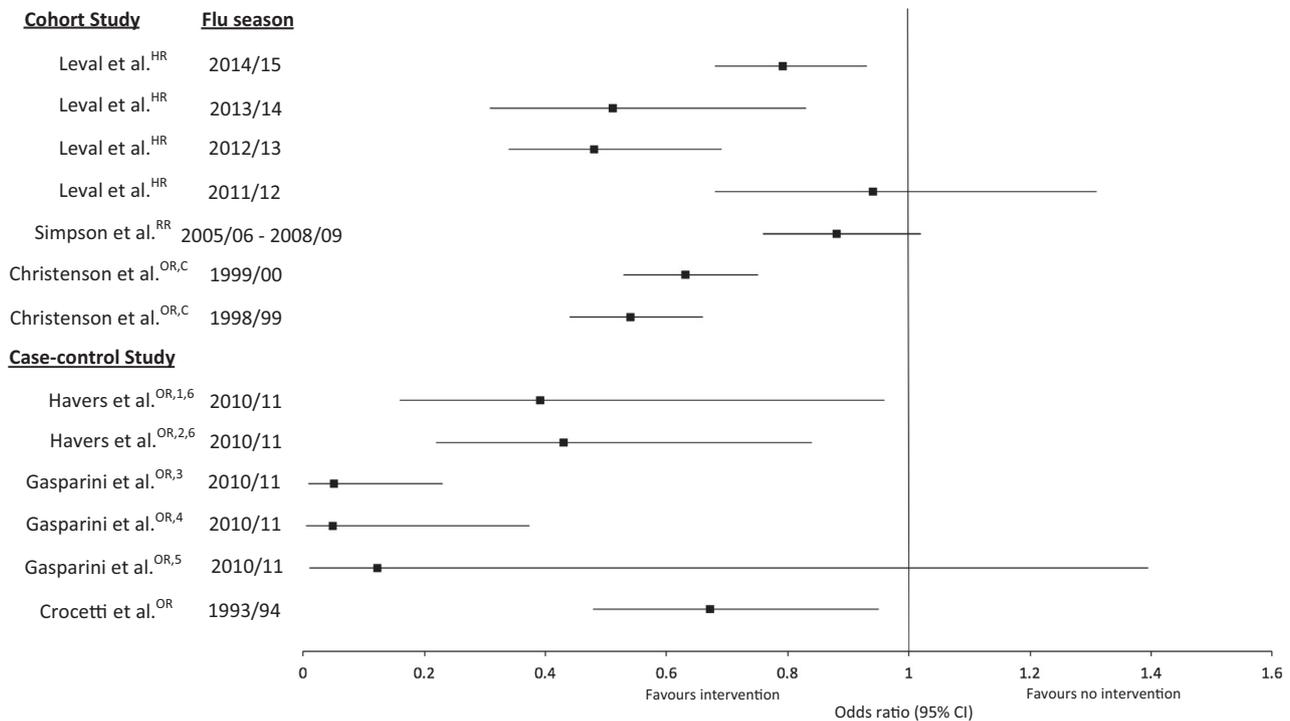
Studies reporting a good match between seasonal vaccine and circulating influenza strains tended to report better VEs [15,16,22]. Studies’ low quality and estimates’ imprecision ( $I^2 = 90%$ ,  $p < 0.01$ ) prevented the pooling of data in a meta-analysis of the effect of the influenza vaccine to prevent outpatient visits in older adults.

### 3.3.2. Influenza hospitalization

For influenza hospitalization, seven studies were included and thirteen effect measures extracted, all in favour of the intervention (Fig. 3).

From four cohort studies, five estimates (71.4%) showed the influenza vaccine to be protective against influenza hospitalization ( $p < 0.05$ ). Among these, two studies looked at the additive effect of influenza and pneumococcal vaccines. Both studies showed a reduction in hospital admission for vaccinated individuals compared to unvaccinated individuals with a VE (95% CI) of 46% (34–56) and OR (95% CI) of 0.63 (0.53–0.75) from the 1998–1999 and 1999–2000 influenza seasons [27,28]. Leval et al. estimated aHRs (95% CI) of 0.94 (0.68–1.31), 0.48 (0.34–0.69), 0.51 (0.31–0.83) and 0.79 (0.68–0.93) for the 2011–2012 to the 2014–2015 influenza seasons [11]. A study from Scotland reported an aVE (95% CI) of 11.6% (–2.4 to 23.6) against influenza and pneumonia hospitalizations [17].

From three case-control studies, five effect measures (83.4%) were in favour of the intervention ( $p < 0.05$ ). Havers et al. estimated that for both age groups, 65 to 74 years of age and 75 years and older, the vaccine was protective against hospitalization for LCI [aVEs (95% CI): 61% (4.3 to 84.1) and 57.3% (15.9 to 78.4)] [13]. Gasparini et al. calculated an adjusted OR (aOR) of 0.05 (0.01–0.37) for Inflflexal V<sup>®</sup>, a trivalent virosome influenza vaccine, and an aOR (95% CI) of 0.12 (0.01–1.39) for Fludax<sup>®</sup>, an adjuvanted influenza vaccine [23]. Crocetti et al. reported an aOR (95% CI) of



**Fig. 3.** Effect measure of influenza hospitalization comparing vaccinated and unvaccinated individuals. <sup>HR</sup> Hazard ratio; <sup>OR</sup> odds ratio; <sup>RR</sup> risk ratio; <sup>C</sup> crude effect measure; <sup>1</sup> age range: 65–74 years old; <sup>2</sup> age range: 75 years and older; <sup>3</sup> regardless of vaccine type; <sup>4</sup> Inflectax V<sup>®</sup> vaccine; <sup>5</sup> Flud<sup>®</sup> vaccine; <sup>6</sup> laboratory-confirmed infection.

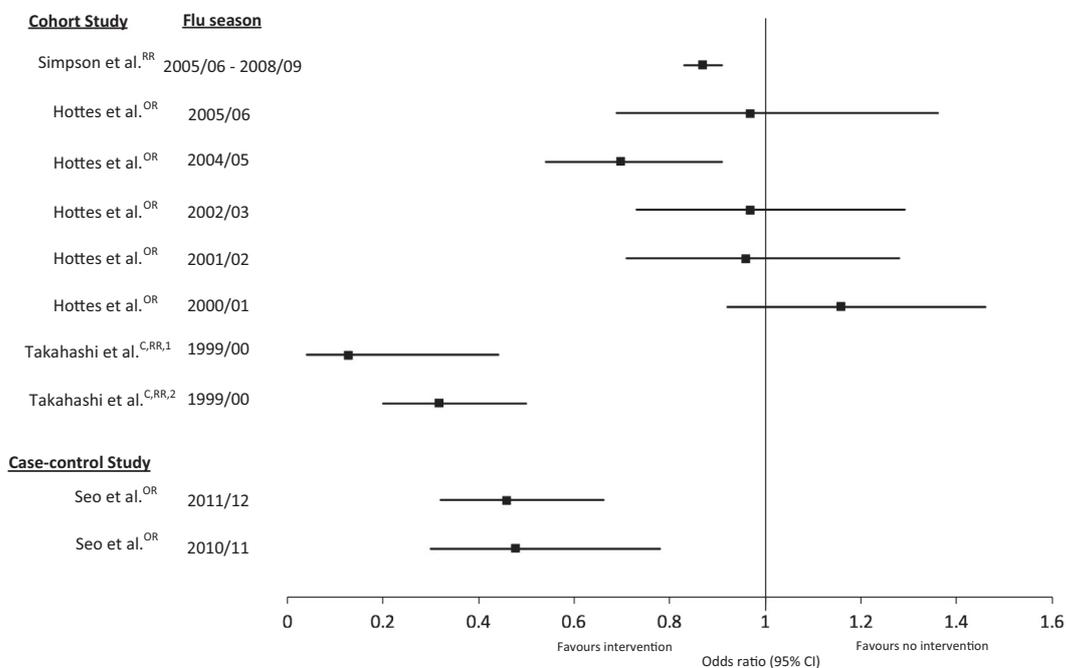
0.67 (0.48–0.95) against influenza hospitalization in older adults [31].

Three studies reported a well-matched vaccine to circulating strains and statistically significant estimates [13,23,27]. Overall, a decreased likelihood of influenza hospitalization was observed. The low quality of evidence and the wide range of results [effect measures of 0.05 to 0.94] hindered the aggregation of data into a meta-analysis ( $I^2 = 93\%$ ,  $p < 0.01$ ).

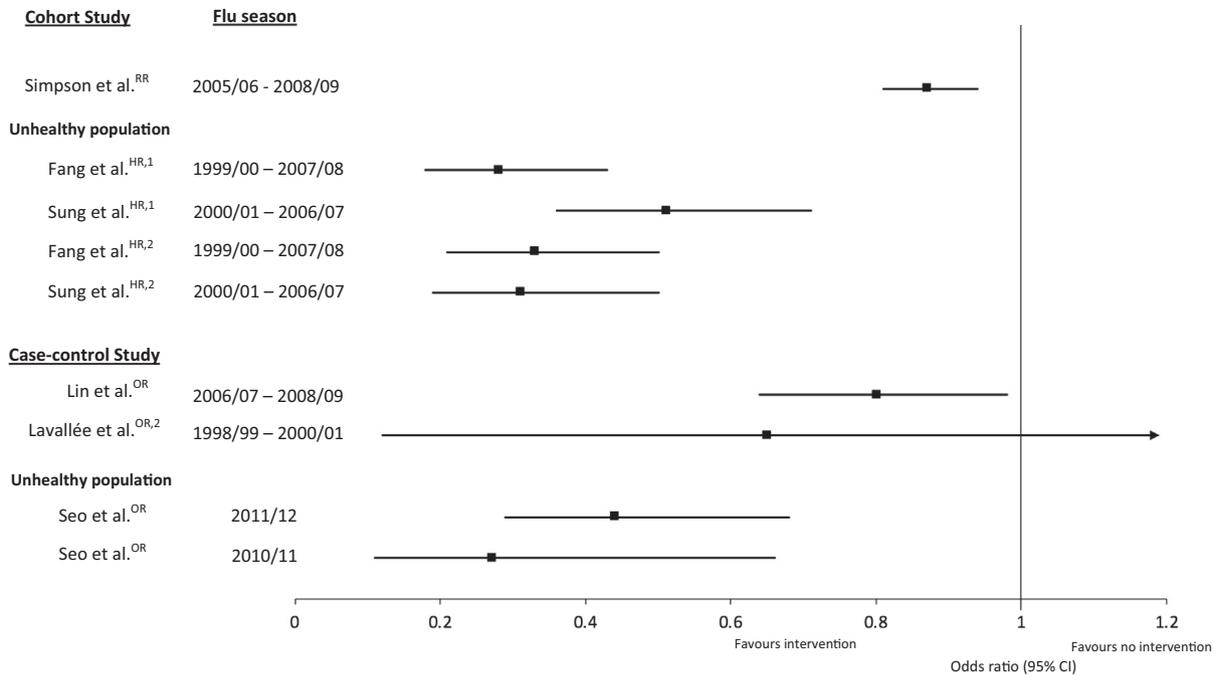
### 3.3.3. All-Cause hospitalization

We included six studies and extracted eleven effect measures. All estimates were in favour of the intervention, except Hottes et al.'s estimates of the 2000–2001 flu season adjusted VE (aVE), but the result was not statistically significant (Fig. 4) [24].

From four cohort studies, four of nine effect measures (44%) showed the vaccine to be protective against all-cause hospitalization ( $p < 0.05$ ). Simpson et al. reported an aVE (95% CI) of 13.14%



**Fig. 4.** Effect measure of all-cause hospitalization comparing vaccinated and unvaccinated individuals. <sup>OR</sup> Odds ratio; <sup>RR</sup> risk ratio; <sup>C</sup> crude effect estimate; <sup>1</sup> respiratory diseases hospitalization; <sup>2</sup> non-respiratory diseases hospitalization.



**Fig. 5.** Effect measure of cardiovascular event comparing vaccinated and unvaccinated individuals. <sup>HR</sup> Hazard ratio; <sup>OR</sup> odds ratio; <sup>RR</sup> Risk ratio; <sup>1</sup> age range: 65–74 years old; <sup>2</sup> age range: 75 years and older.

(9.51 to 16.62) over eight influenza seasons [17]. Hottes et al. reported aVEs (95% CI) of –16% (–46 to 8), 4% (–28 to 29), 3% (–29 to 27), 30% (9–46) and 3% (–36 to 31) for the 2000–2001, 2001–2002, 2002–2003, 2004–2005, 2005–2006 influenza seasons respectively [24]. Takahashi et al. stratified all-cause hospitalization by respiratory disease and non-respiratory disease hospitalizations and obtained RRs (95% CI) of 0.13 (0.04–0.44) and 0.32 (0.20–0.50) [30]. Deguchi et al. found a VE of 82.3% against all-cause hospitalization of nursing home residents [32].

Seo et al. published two case-control studies calculating VE for 2010–2011 or the 2011–2012 influenza season [20,21]. Both showed vaccines to be protective against all-cause hospitalizations for people 65 years and older who visited cardiovascular and pulmonary clinics during influenza epidemic seasons with aORs (95% CI) of 0.48 (0.30–0.78) and 0.46 (0.32–0.66), respectively [20,21].

While the included studies cover a range of respiratory conditions as cause for hospitalization, the results remain inconsistent ( $I^2 = 93\%$ ,  $p < 0.01$ ). As such, we cannot reach a clear conclusion on the effectiveness of the influenza vaccine at reducing all-cause hospitalization in older adults.

### 3.3.4. Cardiovascular events

We included seven studies and extracted nine effect measures on the risk of cardiovascular events during the influenza season, all in favour of the intervention (Fig. 5).

From three cohort studies, we extracted five estimates showing a protective effect of the influenza vaccine against cardiovascular events during the influenza season ( $p < 0.05$ ). Simpson et al. reported aVEs (95% CI) of 12.8% (6.4 to 18.7) against cerebrovascular and cardiovascular disease hospitalization over eight influenza seasons [17]. Fang et al. found that the vaccine was protective against heart failure hospitalization for patients 65–74 years of age and 75 years and older diagnosed with chronic kidney disease with aHRs (95% CI) of 0.28 (0.18–0.43) and 0.33 (0.21–0.50), respectively [14]. Sung et al. reported aORs (95% CI) of 0.51 (0.36–0.71) and 0.31 (0.19–0.50) against acute coronary syndrome

hospitalization for patients 65 to 74 years old and 75 years and older diagnosed with chronic obstructive pulmonary disease during the influenza season [18].

From four case-control studies, three effect measures (75%) showed a protective effect of the influenza vaccine against cardiovascular and/or cerebrovascular events during the influenza season ( $p < 0.05$ ). Lin et al. reported an aOR (95% CI) of 0.80 (0.64–0.98) against stroke hospitalization among older adults [19]. Lavallée et al. found an aOR (95% CI) of 0.65 (0.12–3.56) against cerebral infarction for individuals 75 years and older [29]. Seo et al. reported, for 2011–2012 and 2010–2011, aORs (95% CI) of 0.44 (0.29–0.68) and 0.27 (0.11–0.66) against cardiovascular hospitalizations among patients who visited cardiovascular and pulmonary clinics during influenza epidemic seasons [20,21].

The influenza vaccine seems to reduce cardiovascular events during the influenza season in older adults. Protection appears to be greater for individuals with underlying medical conditions. Nonetheless, because of case definition heterogeneity ( $I^2 = 93\%$ ,  $p < 0.01$ ) and the wide range of results from included studies [ORs of 0.27–0.87], the interpretation should be made with caution.

### 3.4. Risk of bias across studies

We evaluated the quality of evidence and strength of the recommendation of each clinical outcome included in the systematic review using the GRADE approach (Supplementary 2). We obtained very low certainty for outpatient visits, influenza hospitalization, all-cause hospitalizations and our secondary outcome (cardiovascular events) because most studies had serious risk of bias.

## 4. Discussion

Aging is associated with the decline of the immune system and an increased susceptibility to infections and reduced vaccine effectiveness in older adults [33,34]. Seasonal influenza vaccination of

older adults is highly recommended to decrease the disease burden of individuals at higher risk of complications when infected. Above and beyond the prevention of infection, it is important to determine the impact of vaccination on healthcare utilization, from a public health and economic perspective. Therefore, our systematic review focused on older adults as they contribute to a large number of hospitalizations and deaths during the influenza season [1].

We included 22 studies in our systematic review to evaluate VE for four outcomes. We found a modest vaccine effect against outpatient visits for ILI, with many non-statistically significant estimates. We observed a decreased likelihood of influenza hospitalization in a majority (71.4%) of studies looking at a clinical diagnosis of influenza or pneumonia based on ICD-9/ICD-10 codes. For all-cause hospitalization, results inconsistency was obvious even if studies cover a range of respiratory conditions as cause of hospitalization. The influenza vaccine is likely to reduce cardiovascular events with a greater benefit for individuals with underlying medical conditions. Undoubtedly, the magnitude of vaccine protection varies depending on the measured outcomes. Outcome specificity plays a crucial role in VE estimate accuracy. For instance, outpatient visits and all-cause hospitalizations, both unspecific outcomes, gave questionable VE estimates, while the vaccine seemed protective against influenza hospitalization.

Our results are supported by previously published literature. Vu et al. meta-analysis of the influenza VE in older adults living in the community found a small VE against outpatient visits for pneumonia and influenza [6]. An earlier systematic review by Jefferson et al. found that the vaccine was not statistically effective against ILI, but well-matched vaccines prevented hospital admission for influenza and pneumonia. However, findings may be affected by various selection biases [4]. Others have criticized syndromic surveillance emphasizing that ILI, as an outcome, could capture other respiratory pathogens, with similar clinical presentations, not preventable by influenza vaccine resulting in underestimation of influenza VE [35]. LCI, a highly specific outcome, is considered the gold-standard for VE estimates because of high specificity and sensitivity of the RT-PCR test. Since laboratory confirmation is not routinely done during most medical encounters, the alternative to evaluate influenza VE is clinical ICD-9/ICD-10 codes. In 2007, the Armed Forces Health Surveillance Center (AFHSC) developed a case definition for influenza and ILI cases. In 2015, an alternative case definition was proposed for specific ILI surveillance only including codes with at least 75% matched LCI positivity. They obtained high specificity (96%) and moderate sensitivity (62%) when using limited ICD-9-CM codes (488.82, 487.0/1/8) compared to case definition with all fever codes (780.6x) [36]. Consequently, ICD-9/ICD-10 codes included in case definition impact VE estimates reflecting how cases are captured within the data set. Yet, most of the included studies used a wide range of ICD-9/ICD-10 codes in their case definition, undermining outcome specificity and VE estimates.

Finally, our findings for cardiovascular events are supported by Barnes et al.'s meta-analysis, which concluded that the influenza vaccine was associated with a protective effect against acute myocardial infarction with a pooled OR (95% CI) of 0.71 (0.56–0.91) with two (29%) studies that did not restrict the timing of acute myocardial infarction to influenza seasons [37]. However, studies of people with underlying medical conditions showed substantial benefit from the vaccine against cardiovascular events with effect measures ranging from 0.27 to 0.51. Two studies reported that the vaccine protective effect was observed regardless of influenza seasonality; suggesting no relation between influenza virus circulation and cardiovascular event [14,18]. Finally, selection bias might have occurred as none of these studies controlled for frailty and/or disease severity resulting in an overestimation of effectiveness.

#### 4.1. Limitations

Our systematic review has several limitations. We only included studies in English or French and were unable to provide an overall estimate of VE because heterogeneity between studies hindered the aggregation of result into a meta-analysis.

Furthermore, most of the studies were considered at serious and critical risk of bias, mainly due to inappropriate control confounding. Functional status and health status are important confounders known to be associated with a decreased likelihood of vaccination and an increased risk of mortality [9,38,39]. Accordingly, we considered studies without extensive adjustment for health and functional status at critical risk of bias. To improve methodological quality of VE studies, future evaluation of the effectiveness of the influenza vaccine should attempt to adjust for those variables.

Finally, we looked at the reduction of outpatient visits in vaccinated and unvaccinated individuals. To properly answer the research question, it was necessary to exclude test-negative study design which limited the number of studies available. The test-negative study design is a commonly used design to assess VE, as it reduces bias arising from different healthcare-seeking behaviors [40]. This bias was infrequently corrected in studies included in our systematic review. Some countries have publicly funded healthcare systems, which could influence healthcare seeking behaviour. However, most studies did not discuss the possible bias arising from the healthcare seeking behaviour. To evaluate the impact of influenza vaccine on healthcare utilization, future studies should account for individual propensities to seek medical care.

## 5. Conclusion

The available evidence identified was of low quality and the variability of study methodology, limited statistical power, and the unpredictable match between seasonal vaccine and circulatory strains, all prevented the pooling of data. We found modest evidence supporting the influenza vaccine protection against healthcare utilization in older adults. Limited data for people 75 years and older prevent VE interpretation by age group. There remains a need for high-quality studies of influenza VE in older adults. The secondary use of existing administrative and electronic medical record datasets is an attractive alternative to laborious intervention studies. However, to avoid the pitfalls of existing VE studies, it is necessary to evaluate if these data could provide accurate estimates of vaccine effectiveness with good outcome specificity.

#### Conflicts of interest

None of the authors had any conflicts of interest to disclose.

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#### Contribution

PDP and CQ conceived and designed the research protocol. All authors drafted the manuscript and approved the final version submitted for publication.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.04.051>.

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