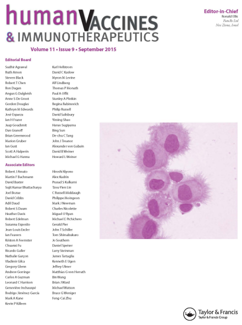

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Abstract

Vaccination represents the most effective intervention to prevent infection, hospitalization and mortality due to influenza. This meta-analysis quantifies data reporting influenza vaccine effectiveness (VE) on influenza visits and hospitalizations of case-control and cohort studies among high-risk groups.

A systematic literature review including original articles published between 2007 and 2016, using a protocol registered on Prospero with No. 42017054854, and a meta-analysis were conducted.

For three high-risk groups (subjects with underlying health conditions, pregnant women and health care workers) only a qualitative evaluation was carried out. The VE quantitative analysis demonstrated a clear significant overall effect of 39% (95%CI: 32%-46%) for visits and 57% (95%CI: 30%-74%) for hospitalization among children. Considering the elderly influenza VE had a

clear effect of 25% (95%CI: 6%-40%) for visits and 14% (95%CI: 7%-21%; $p<0.001$) for hospitalization.

This study showed the high VE of influenza vaccination among high-risk groups, representing a tool for public health decision-makers to develop evidence-based preventive interventions to avoid influenza outcomes.

Keywords

Influenza, vaccine, effectiveness, children, elderly subjects, chronic disease, pregnancy, health care worker, hospitalization, visit.

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List of abbreviation

ALRI = influenza-associated acute lower respiratory infections

GP = general practitioner

HCW = Health Care Worker

ILI = influenza-like illness

OR = Odds ratio

RR = Relative risk

SOT = solid organ transplant

SLR = systematic literature review

VE = vaccine effectiveness

WHO = World Health Organization

Introduction

Influenza is a respiratory infectious disease responsible for thousands of infections, hospitalizations and deaths worldwide.[1-3] Influenza viruses mainly affect lungs, higher and lower respiratory tract, representing one of the main causes of deaths and hospitalization especially during winter seasons.[4,5] In particular, higher morbidity and mortality rates were observed among the elderly, individuals with underlying health conditions, children and pregnant, that are particularly at risk for developing influenza complications, such as bacterial pneumonia.[6-11]

At the same time, health care workers (HCWs) represent a group at higher risk of contracting influenza illness and transmitting the disease to their patients or to the general population.[12-14] Reported estimates of influenza infection among HCWs each season are various (ranging from 20% to 47.5%) and many of them continue working while infected,[13-15] favoring the spread of influenza virus.[13] For these reasons, hospitalized patients could acquire influenza not only from other patients or visitors but also from hospital employees and only high influenza vaccination coverage of health care personnel could prevent nosocomial influenza transmission, reducing influenza-like illness (ILI) mortality among more frail patients.[16,17]

In general, influenza vaccination represents the most effective public health intervention to prevent seasonal influenza infection, hospitalization and mortality.[18-21] All the preventive policies and international guidelines regarding influenza vaccination are primarily focused on protection of individuals at higher risk, by vaccinating themselves or those who could infect them.[19-21]

The principal challenge of this systematic literature review is to analyze studies that reported influenza vaccine effectiveness (VE) data on reducing laboratory confirmed cases, hospitalization, morbidity or mortality due to influenza and to quantify its impact among high-risk groups.

In particular the data were separately discussed among the following major high-risk groups identified in literature: children, subjects with underlying health conditions at any age, pregnant women, HCWs, and the elderly.

Results

Systematic literature review

As illustrated in the flowchart (Figure 1), an initial number of 2,461 articles were retrieved through the selected databases. About one third of the manuscript (n=775/2,461) was identified as duplicates and removed. Through the initial screening of titles and abstracts 1,496 articles were excluded and overall 190 full text articles were assessed for eligibility. A total of 38 studies met all the inclusion criteria of which 13 were included in the qualitative synthesis, whereas 25 took place in the meta-analysis (quantitative synthesis). For three major high-risk groups, namely subjects with underlying health conditions, pregnant women and HCWs, only a qualitative evaluation was conducted. Of note subjects with underlying health condition hadn't the same comorbidities so they weren't pooled together with meta-analysis. At the same time, both for two cohort studies about children/elderly and for case-control studies on pregnant women/HCWs (two studies for each high-risk group), only a qualitative analysis was performed due to limited data available to conduct a quantitative evaluation. Out of the 25 remaining studies, two quantitative synthesis analyses were conducted for the high-risk groups of children and older people (12 manuscripts for children, 9 for the elderly, 4 conducted in both the high-risk groups). Table 1 describes the studies included both in qualitative or quantitative synthesis. In particular, 69% (n=25/36) of them referred to hospitalized patients, while 47% (n=17/36) were conducted in pediatric settings. Furthermore, 83% (n=30/36) of selected studies confirmed influenza vaccination status by at least one objective source of information (registries, electronic dataset, etc) and 78% (n=28/36) were case control studies conducted by using the test-negative design.

Qualitative analysis

Cohort studies conducted among children and the elderly

Only two cohort studies examining effectiveness of influenza vaccine among children and the elderly were selected and included in the qualitative synthesis (Table 1). In particular, Szilagyi PG *et al* evaluated the effect of influenza vaccine on the number of outpatient visits and reported a VE range 7%-52% among children aged 6 to 59 months, during two consecutive influenza seasons (2003-2004 and 2004-2005) in three different American counties.[22] On the other hand, a retrospective cohort study conducted among Ontario residents aged ≥65 years from 1993-1994 through 2007-2008 seasons reported 22% VE for all influenza-associated deaths, 25% VE for deaths occurring within 30 days after and 19% VE for influenza-associated pneumonia/influenza hospitalization, respectively.[23]

Subjects with underlying health conditions

At the end of the revision process of studies that evaluated influenza VE in subjects with comorbidities, 5 case control and 2 cohort studies were selected and included in the qualitative analysis (Table 1). Cheng AC *et al* reported a 51.3% (95%CI: 40.7%-60.1%) reduction of hospitalization due to influenza disease in an Australian population (aged ≥18 years) with at least one chronic condition during 2014 season.[24] In Sidney, a reduction of 83.6% (95%CI: 27.6%-96.3%) for acute myocardial infarction hospitalization was reported, after influenza vaccination, among 599 adults with previous cardiovascular event from 2008 to 2010 influenza seasons.[25] Also, among a Spanish group of subjects aged 18 years or older with high-risk conditions, was reported an adjusted VE of 53% (95%CI: 4%-77%) in reducing hospitalizations during the 2010–2011 influenza season.[26] Furthermore, a reduction of 49% (95%CI: 16%-69%) in hospitalization of a Dutch population 1-84 years old, with a diagnosis of laboratory confirmed A(H1N1)pdm09 influenza and affected by at least one underlying medical condition (pulmonary or cardiac disease, diabetes mellitus, chronic kidney failure, cancer and immunocompromised condition), was observed in 2009-2010 season due to the adjuvanted pandemic vaccine,[27] as also documented by Andrews N *et al* in reducing outpatient visits in England (62%; 95%CI: 33%-78%).[28]

On the other hand, with regard to cohort studies on influenza vaccination effectiveness, Emborg HD *et al* reported a reduction of 49% on general practitioners (GPs) consultation, as well as 44% in hospitalization of subjects <65 years old with underlying chronic diseases in Denmark.[29] Moreover, a study conducted among 64 Spanish solid organ transplant (SOT) recipient, reported an influenza VE of 85% (95%CI: 40%-97%) in reduction the hospitalizations during 2010-2011 season.[30]

Pregnant women

The qualitative analysis included two manuscripts on influenza VE among pregnant women (Table 1). A population based case control study conducted in California and Oregon evaluated prevention of Polymerase chain reaction confirmed influenza cases, in pregnancy, and reported, using influenza-negative controls, a VE of 57% during the 2010-2011 season and 27% during the 2011-2012 season, respectively.[31]

Furthermore, a retrospective cohort study conducted in Western Australia among 34,701 pregnant women reported a VE of 81% (95%CI: 31%-95%) in decreasing emergency department visit for influenza and 65% reduction (95%CI: 3%-87%) in hospital admission of pregnant women, during the 2012 and 2013 influenza seasons.[32]

Health care workers

After the revision process only two manuscripts concerning influenza VE among HCWs were included in the systematic review (Table 1). In detail, a case control study reported a VE of 90.5% (95%CI: 73.5%-97.3%) in reducing emergency department visit for influenza A(H1N1), among the employees of Sao João Hospital of Porto during 2009-2010 season.[33] Another study showed a VE of 70.5% in reducing influenza A(H1N1) hospitalization, among a cohort of Japanese HCWs during 2009-2010 influenza season.[34]

Quantitative analysis

Children

Overall, 7 of the 16 studies included in the meta-analysis evaluated the VE against influenza visits, while 9 focused on influenza hospitalization among children aged 6 months to 18 years.

Considering outpatient or emergency department visits, VE demonstrated a clear significant overall effect of 39% (95%CI: 32%-46%) of influenza vaccines among cases when compared to control children (Figure 2). Since low heterogeneity was present between studies (I^2=48.1%; p=0.052), for this analysis a fixed-effect model instead of a random-effect model was used.

On the other hand, studies evaluating the overall influenza hospitalization VE were analyzed using random effect model. Indeed, using inverse-variance weighting to calculate fixed and random effects summary estimate, there was an higher moment base estimate between studies variance (Chi^2 =0.40; p<0.001). The analysis on influenza hospitalization VE among children (Figure 2) showed a clear overall effect of 57% (95%CI: 30%-74%; p<0.001) even if with a higher between studies heterogeneity (I^2=86.1%; p<0.001). To explain this phenomenon, a meta regression analysis was conducted including independent variables such as studies considering children (<9 years) vaccinated for the first time with at least two doses and hemisphere where the study was conducted. Moreover, other two independent variables integrated the meta regression analysis: mismatch between influenza A or B viruses included in vaccine and influenza viruses A or B circulating among cases and control. As a result, the log odds ratio of influenza hospitalization VE was estimated to decrease of 0.91 (p=0.043) among studies conducted in Northern hemisphere. The estimated between studies variance reduced from 0.40 to null.

Elderly subjects

There was a clear effect of 25% (95%CI: 6%-40%; p=0.012) using fixed effect model, when considering the 3 studies included in meta-analysis on VE for influenza visits among the elderly, although the heterogeneity between studies was very low (I^2=0; p=0.864) (Figure 3).
Additionally, among 10 studies considered about elderly a clear effect of 14% VE (95%CI: 7%-21%; p<0.001) was observed in reducing hospital admission due to influenza with low heterogeneity between studies (I^2=19.2%; p=0.286).

Risk of bias across studies

The symmetry of the funnel plots was examined in order to search for possible publication bias or even heterogeneity. Asymmetry was found for studies reporting influenza hospitalization VE among children (Table 2).

Discussion

This study provide an up-to-date review of VE on reducing measurable outcomes in health care, such as outpatient visits and hospitalization, among five of the most important high-risk groups to which was strongly recommended influenza vaccination.[35] Other reviews beforehand conducted, demonstrated that considerable variations could be observed in reported influenza VE estimates due to differences in circulating viral strains among countries, proportion of influenza strains within one region, type of vaccine used, age-specific vaccine coverage, type of population studied, season definition, case definition, ascertainment of vaccination status, differences in surveillance time-period, variables included or omitted in the statistical model, kind of model, and measured outcomes (admission, outpatient contact or infection).[36-38] For these reasons, our study aimed to generate different model of systematic literature review (SLR) according to high-risk group considered, and to systematize the differences between other variables that make changing influenza VE.

Qualitative analysis

Subjects with underlying health conditions

Subjects with underlying health conditions are recognized as a core group for influenza vaccination administration. Each co-morbidity represents a consistent increasing risk for influenza infection, complications and death. Furthermore, the association of several chronic conditions could enhance the risk for unvaccinated subjects during every influenza season.[18,39] According to main public health authorities, all individuals >6 months old, with at least one chronic illness that represent a risk factor for influenza or complications, should be yearly and actively vaccinated against influenza.[21]

In particular, some case-control studies among subjects with comorbidities reported similar VE values, in the qualitative synthesis analysis, for hospitalization reduction (around 50%) despite different influenza seasons considered.[24,26,27] Moreover, a reduction of 62% in outpatient visits and 84% in acute myocardial infarction hospitalization after influenza vaccination was demonstrated, as described by other authors.[25,28,40] Also a cohort study conducted in Denmark reported a similar VE value (44%) in reducing hospitalization, while another cohort study among SOT found an higher value of VE (85%), evidencing the key role of influenza vaccination in preventing hospitalization in this particular high-risk group.[29,30,41]

Pregnant women

Both studies analyzed in the SLR conducted among pregnant women demonstrated a good VE in decreasing the total number of laboratory confirmed influenza cases,[31] emergency department visits and hospitalizations in different influenza seasons.[32] The consistent difference of VE among vaccinated pregnant women observed in US between the seasons 2010-2011 and 2011-2012 could be due to residual or unmeasured confounding, even if it was similar when stratified by season and influenza virus type.[31] The magnitude effect of influenza vaccination during pregnancy was justified especially by two main factors: the rapid clinical deterioration observed in some patients in respect to the typical course of seasonal influenza, especially when infected with A(H1N1)pdm09 strains,[9,42] and the higher prevalence of cleft lip–palate, neural-tube defects and cardiovascular malformations in newborns of mother with confirmed diagnosis of influenza during the second and/or third month of pregnancy.[43]

Heath care workers

Influenza vaccination of HCWs is the most effective public health strategies for preventing nosocomial influenza transmission and reducing ILI mortality among elderly and high-risk patients, as well as for minimizing absenteeism during annual epidemics.[12,14,16,18]

The two studies included in the SLR throughout the qualitative synthesis were both related to VE during the pandemic influenza season and the use of adjuvanted monovalent influenza vaccine against A(H1N1)pdm09.[33,34] The very high level of VE in reducing emergency department visits and hospitalization for influenza A(H1N1)pdm09 confirmed the specific tropism of pandemic influenza strains for younger people but also the very high efficacy of the influenza vaccines quickly developed worldwide.[44,45]

Quantitative analysis

Children

During each seasonal outbreak, children sustain the highest burden of influenza. A systematic review of the global disease burden of influenza in children >5 years estimated that there were 90 million (95%CI: 49–162 millions) cases during the 2008 influenza season, 20 million (95%CI: 13–32 millions) cases of influenza-associated acute lower respiratory infections (ALRI), and 1–2 million cases of influenza associated severe ALRI, including 28,000 - 111,500 deaths.[46] A review from 1982 to 2012, estimated that influenza resulted in approximately 374,000 (95%CI: 264,000 - 539,000) hospitalizations in children <1 year old, of which 228,000 (95%CI: 150,000 - 344,000) occurred among children <6 months, and 870,000 (95%CI: 610,000 - 1,237,000) in children <5 years of age, annually.[47] According to data of this meta-analysis, influenza vaccination was protective against outpatient visits among children, especially considering studies with children <9 years old and in the US, with a confirmed vaccination status. The lower value of VE for outpatient influenza visits among children, were found by Sullivan SG *et al*.[48] This latter could be due to unadjusted VE by distance of influenza visits and influenza vaccine administration. A combination of two possible mechanisms could explain this reduced VE. Firstly, seasonal variations of circulating viruses, due both to the appearance of another virus type or to the antigenic drift of circulating strains, could be responsible of a partial vaccine mismatch.[49] Secondly, a waning immunity one month after administration of the influenza vaccine was described even among children.[50] Furthermore, to assess vaccination status of enrolled children, this study used a not confirmed method, and this could further reduce the specificity of results on vaccination status. In particular, a study suggested that specificity of self-reported influenza vaccination status can be lowest for young children, whose parents may easily confuse influenza vaccine with other routine childhood vaccines.[49]

Better results about influenza visits VE were reported by Eisemberg KW *et al*,[50] that estimated the influenza VE for children during the 2003-2004 and 2004-2005 seasons, although the matching between circulating influenza viruses and those included in the vaccine was considered suboptimal for both seasons.[51,52]

A better VE was found in reduction of influenza hospitalizations than outpatient influenza visits. Among studies focusing influenza hospitalization VE, the majority were conducted among children aged 6 months to 17 years, in Northern hemisphere, with diagnosis of influenza A or B infection and with a confirmation of vaccination status. Only studies conducted in Southern hemisphere were associated with an increase of influenza hospitalization VE, and this result can be explained because more frequently patients of studies conducted in Southern hemisphere were recruited from tertiary pediatric referral hospital as in Blyth CC *et al* and Dixon GA *et al*.[53,54] These studies may have included more severe infections or complicated comorbidities, when compared to children admitted to more general pediatric wards. Furthermore, a recent global estimates of hospitalization for acute lower respiratory infections, among children <17 years old, including data from systematic review and surveillance platforms, showed that pooled percentages of positivity for influenza among hospitalized children with respiratory illness, varied among World Health Organization (WHO) regions with the highest values in Western Pacific and Southeast Asia (8.5% in both cases) and the lowest in the Americas and Europe (4.6% and 7.1%, respectively).[47] These data confirm a different frequency of severe influenza illness between Southern and Northern hemispheres that could partially explain the VE variability. Even if differences in hospitalization practices, applications of case definitions and factors, such as time from symptom onset to specimen collection, could make detection of influenza viruses more or less likely, and therefore this could bias the outcome.

Elderly subjects

All of the three studies included in VE analysis and concerning the reduction of outpatient visits were conducted among confirmed influenza A and B individuals aged >65 years. More frequently were conducted in Northern hemisphere and the confirmation of influenza vaccine status collected through registries. The better influenza VE among elderly was found in Sullivan SG *et al* even with any limitations.[48] In particular, these authors did not adjust for distance of influenza visit and influenza vaccine administration, and did not collect data on the presence of comorbidities predisposing to severe influenza, such as asthma, obesity and immunocompromising conditions.[48] Failure to adjust for this important confounder may have accounted for the unexpected age effects. In these patients many mechanisms of failed response were related to frailty driven by chronic inflammation and age, even if one more established, but still controversial, explanation is the concept of original antigenic sin.[55] This means that previous exposure to an antigen resulted in a sub-standard immune response, when exposure to a novel but closely related antigen occurs.[56]

In McLean HK *et al* was found a lower value of influenza visits VE among elderly, in particular for influenza A(H3N2).[11] This estimated VE was consistent with laboratory findings from the US national virological surveillance during the same influenza season.[57] Although virological surveillance indicated no antigenic drift between the circulating influenza A(H3N2) viruses and the cell grown reference vaccine virus, the egg-propagated A/Victoria/361/2011 reassortant virus used in vaccine production acquired 3 amino acid changes in the antigenic region of HA (at positions H156Q, G186V and S219Y), which significantly altered its antigenicity.[57] Furthermore, this low VE against A(H3N2) suggests that other factors in addition to immunosenescence, may be important modifiers in this age group.[55] In particular, additional studies are needed to understand the impact of previous infections, vaccinations, and antigenic variability on the risk of illness.[58]

In the elderly influenza VE was lower in hospitalization than outpatient visits. The studies reported in the meta-analysis of influenza hospitalization VE were more frequently among people >65 years old, conducted in Northern hemisphere and regarding trivalent inactivated influenza vaccines. The better influenza hospitalization VE was found by Orellano PW *et al*,[59] even if socioeconomic status, place of residence, medical consultation, or past hospitalizations were not included in this study. This means that severe or mild influenza cases may be different in terms of background characteristics, and this might bias the estimated VE.[55]

On the other hand, lower influenza hospitalization VE was revealed by Gilca R *et al*.[60] This can be consistent with mismatch during 2014-2015 influenza season, when the majority of A/H3N2 strains circulating in the Northern hemisphere were antigenically mismatched to the A/Texas/50/2012 H3N2 vaccine strain.[61] Furthermore, hospitalization VE was evaluated considering a self-reported vaccination status and this may have resulted in exposure misclassification.[49]

Only three studies reporting VE among elderly who received adjuvanted vaccine did not calculate VE by vaccine type.[26,60,72] The authors justified this due to small number of elderly vaccinated with adjuvanted vaccine compared to other trivalent inactivated vaccine. In future, would be beneficial that seasonal VE estimates will be reported by vaccine type to facilitate valid comparisons.

Limits

The studies included in the meta-analyses suffer from a limitation due to a potential overestimation of the vaccination status that could have occurred, since some examined studies used partially or totally referred vaccination status without validation technique. This could assess subjective measures of vaccine uptake that cause recall bias (e.g. past influenza vaccination uptake can be confused with the current one). Investigators who rely on self-reported influenza vaccination status, in particular for young children, should consider the possibility that up to 10% of individuals may be misclassified. So, whenever feasible, vaccination data should be validated by an external source to reduce misclassification.[49]

Also, a possible limit of the present study could be the different vaccine policies and strategies adopted in various countries, as well as the different type of influenza vaccines routinely available. All these factors could have influenced VE reported in different areas.

Regarding asymmetry resulted with influenza hospitalization VE among children, the analysis of funnel plot showed that missing studies were in a top right and bottom left area of significance, so publication bias was unlikely to be the underlying cause of asymmetry.

Conclusion

Influenza represents one of the leading causes of death worldwide. In particular, children, older people, subjects with underlying health conditions, pregnant women and health care workers are groups at higher risk of contracting influenza infection and its complication. Worldwide, vaccination constitutes the only recognized strategy to prevent the spread of influenza viruses as well as human-to-human transmission and infection, and the most important public health authorities strongly recommended vaccine administration among these high-risk groups.

Our SLR and meta-analysis demonstrated the high VE of influenza vaccination in all these high-risk groups, often regardless of season, circulating strain, type of vaccination. Furthermore, the reduction in hospitalization and outpatient visits represent not only a health benefit for individuals vaccinated but also an essential profit for National Health Systems.

Finally, may be suitable that this SLR and meta-analysis aim to provide a tool for public health decision makers in order to develop evidence based preventive interventions to contrast influenza infection, especially among high-risk groups.

Material and methods

Systematic literature review

A SLR was carried out on influenza VE among high-risk groups. They, according to WHO position paper, were identified as people at increased risk of exposure to influenza virus as well as those at particular risk of developing severe disease (i.e. older people, children, people suffering from comorbidities and pregnant women).[35] A written protocol was supplied to all investigators recruited, before starting SLR, and it was registered on Prospero with No. 42017054854 on 19 January 2017. Case-control and cohort studies on influenza health care outcomes, between vaccinated and unvaccinated risk groups, were selected through a SLR using key terms in combination and referred to vaccine/immunization, effectiveness, impact, at risk people and influenza/flu, with medical Subject Headings (MeSH) and MeSH Major Topics included in the syntax. The online databases PubMed/MEDLINE, SCOPUS, EMBASE, ISI Web of Science were considered, as well as the gray literature and a manual search from the references of the articles retrieved and it was performed in January 2017.

Original articles published between 1st of January 2007 and the 31st of December 2016 were retrieved, with restriction criteria applied: articles published in the English language and concerning influenza effectiveness in risk groups. Among all high-risk groups considered, elderly subjects (≥50 years old), children (≤18 years old), subjects with underlying health conditions at any age, pregnant women and HCW were included in the SLR. All influenza vaccines recommended by the WHO were considered to evaluate VE: trivalent inactivated vaccines and live attenuated influenza vaccines.[35] For inclusion, studies were required to focus on at least one countable outcome related to influenza infection: GP or emergency department visits, hospital admission or death. Information were collected from patient consulting medical facilities or medical databases reporting health care outcomes. The following exclusion criteria were also applied during title and abstract screening: articles published in languages other than English, reporting only vaccination information, assessing only vaccination coverage, reporting only vaccination uptake determinants and review articles, trials and qualitative studies.

Other exclusion criteria used during full-text analysis were: no reporting VE, reporting overall VE not specifically defined for high-risk-groups considered in the review, reporting VE not in high-risk-groups and reporting VE on hospitalization or outpatients visit for ILI or acute respiratory infection. Only quantitative studies describing influenza VE among risk-groups were included in the review. Studies were then selected for the qualitative and quantitative analysis.

Variables extraction regarded: cases of influenza among high-risk-groups considered in the SLR, influenza VEs in selected group, laboratory diagnostic procedures for testing for influenza and strategies used to assess vaccination status of each participant. Four investigators independently conducted both a literature search and a systematic review considering the inclusion, eligibility criteria and quality. Incongruity between the investigators was resolved by further discussion, with involvement of an external investigator where necessary.

Meta-analysis

After studies have been selected, reporting number of vaccinated among cases and control and/or influenza incident cases among exposed and unexposed to influenza vaccine, a meta-analysis according to Cochrane guidelines,[62] was conducted on the extracted measures in order to assess the overall effect. Crude ORs and RRs were considered where available. The logarithms were used for the meta-analysis, with exponentiated effect sizes and confidence intervals displayed in the forest plots. Vaccine effectiveness was calculated as VE = [(1-OR)x100] or VE = [(1-RR)x100] and crude ORs or RRs with relative 95% Confidence Interval (95%CI) were estimated for each risk-group.[63]

Pooled estimates were calculated using both fixed effects and DerSimonian and Laird random effects models, weighting individual study results by the inverse of their variances.[64] Forest plots were used to visually assess the pooled estimates and corresponding 95%CI across studies. A test of heterogeneity was performed using a chi-square test at significance level of $p<0.05$ and reported with the I^2 statistic together with a 25%, 50% or 75% cut-off, indicating low, moderate and high heterogeneity, respectively.[65,66]

When the test showed significant heterogeneity, the sources of heterogeneity were explored through pre-specified meta-regression and sensitivity analyses. The following variables were considered for a meta-regression analysis: vaccinated children (<9 years old) who performed, for the first time, two doses of influenza vaccination (yes *vs* no), hemisphere where study was conducted (Northern *vs* Southern), year of study conduction before or after influenza pandemic season (before 2010 *vs* after

2010) and two variables that reported mismatch between influenza A or B viruses included in the seasonal vaccine and circulating viruses among cases and controls or exposed and unexposed (yes *vs* no), respectively. Sensitivity analyses were conducted to examine the contribution of each individual study by evaluating the impact of the outlier studies, eliminating each study from the meta-analysis and comparing the point estimates which included or excluded the study.

The methodological quality of studies included in the meta-analysis was assessed using revised versions of previously validated checklists for quantitative retrospective and prospective studies, as recommended by the Cochrane Collaboration.[62,67]

To assess a potential publication bias, a graphical plot of the logarithm effect estimates versus its standard error, for each study, was employed, and the Egger test was performed.[68,69]

All data were analyzed using the statistical package STATA/MP 14.2 (StataCorp LP, College Station, TX, USA), with the “metan” command used for meta-analysis, “metafunnel”, “metabias” and “confunnel” for publication bias assessment.[70]

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Table 1: Characteristics of included studies on anti-influenza vaccine effectiveness among at risk-group

Reference article	At risk-group	Outcome	Publication year	Influenza season	Age range	Sample size	Country	Influenza vaccine type	Influenza virus diagnsosis among cases	Vaccine status	Study design	Qualitative/Quantitative analysis
Szilagyi PG[22]	children	outpatient visit	2008	from 2003-2004 to 2004-2005	from 6 months to 6 years	10,906	US	trivalent inactivated	A(H3N2)	Confirmed	Cohort	Qualitative
Ridenhour BJ[23]	older	hospitalization/ deaths	2013	from 1993-1994 to 2007-2008	≥ 65 years	21,180,919	Canada	*N.A.*	*N.A.*	Confirmed	Cohort	Qualitative
Andrews N[28]	comorbidity	outpatient visit	2011	2009-2012	<5 and ≥ 65 years	2,153	UK	adiuvated pH1N1	A(H1N1)	Confirmed	Case-control	Qualitative
Emborg HD[29]	comorbidity	outpatient visit / hospitalization	2011	2009-2010	<65 years	388,069	Denmark	adiuvated pH1N1	A(H1N1)	Confirmed	Cohort	Qualitative
MacIntyre CR[25]	comorbidity	hospitalization	2013	from 2008 to 2010	≥ 18 years	599	Australia	trivalent inactivated	A and B	Confirmed	Cohort	Qualitative
Perez-Romero P[30]	comorbidity	hospitalization	2012	2010-2011	>16 years	64	Spain	trivalent inactivated	A(H1N1), A(H3N2) and B	Confirmed	Cohort	Qualitative
Steens A[27]	comorbidity	hospitalization	2011	2009-2011	from 1 to 84 years	10,968	Netherlands	adiuvated pH1N1	A(H1N1)	Confirmed	Case-control	Qualitative
Thompson MG[31]	pregnant women	outpatient visit	2013	2010-2011 and 2011-2012	from 22 to 38 years	492	US	trivalent inactivated	A(H1N1)	Confirmed	Case-control	Qualitative
Regan AK[32]	pregnant women	outpatient visit / hospitalization	2016	2012-2013	≥ 18 years	2,962,374	Australia	trivalent inactivated	A(H1N1)	Confirmed	Cohort	Qualitative
Costa JT[33]	health care workers	outpatient visit	2012	2009-2010	≥ 18 years	245	Portugal	adiuvated pH1N1	A(H1N1)	Confirmed	Case-control	Qualitative
Igari H[34]	health care workers	hospitalization	2011	2009-2013	≥ 20 years	1,817	Japan	adiuvated pH1N1	A(H1N1)	Confirmed	Cohort	Qualitative
Blyth CC[71]	children	outpatient visit	2016	2008 and from 2010 to 2013	from 6 months to 18 years	2,205	Australia	trivalent inactivated	A(H1N1), A(H3N2) and B	Confirmed	Case-control	Quantitative
Sullivan SG[48]	children and	outpatient	2014	2012	< 18 and >65 years	488	Australia	trivalent inactivated	A(H1N1), A(H3N2)	Not	Case-control	Quantitative

	older	visit							and B	confirmed		
Mc Lean HK[72]	children and older	outpatient visit	2014	2012-2013	from 6 months to 17 years and ≥65 years	3,145	US	trivalent inactivated, adiuvated and live attenuated	A(H1N1), A(H3N2) and B	Confirmed	Case-control	Quantitative
Belongia EA[73]	children	outpatient visit	2011	2007-2008	from 6 months to 6 years	412	US	trivalent inactivated	A(H3N2) and B Yamagata	Confirmed	Case-control	Quantitative
Joshi AY[74]	children	outpatient visit	2009	from 1999-2000 to 2006-2007	from 6 months to 6 years	206	US	trivalent inactivated	A(H1N1), A(H3N2) and B Victoria	Confirmed	Case-control	Quantitative
Eisenberg KW[50]	children	outpatient visit	2008	from 2003-2004 to 2004-2005	from 6 months to 6 years	2,534	US	trivalent inactivated	*N.A.*	Confirmed	Case-control	Quantitative
Shuler CM[75]	children	outpatient visit	2007	2003-2004	from 6 months to 6 years	870	US	trivalent inactivated	*N.A.*	Confirmed	Case-control	Quantitative
Chiu SS[76]	children	hospitalization	2016	from 2009-2010 to 2013-2014	from 6 months to 17 years	6,257	Hong Kong	trivalent inactivated	B Yamagata and B Victoria	Not confirmed	Case-control	Quantitative
Blith CC[54]	children	hospitalization	2015	2009 and from 2010 to 2014	from 6 months to 6 years	712	Australia	trivalent inactivated	A(H1N1), A(H3N2) and B	Confirmed	Case-control	Quantitative
Grijalva CC[77]	children and older	hospitalization	2015	from 2009-2010 to 2011-2012	from 6 months to 17 years and ≥65 years	1,806	US	pandemic, trivalent inactivated and live attenuated	A(H1N1), A(H3N2) and B	Confirmed	Case-control	Quantitative
Cowling BJ[78]	children	hospitalization	2014	from 2009-2010 to 2012-2013	from 6 months to 17 years	5,399	Hong Kong	pandemic and trivalent inactivated	A(H1N1), A(H3N2) and B	Not confirmed	Case-control	Quantitative
Ferdinands JM[79]	children	hospitalization	2014	from 2010-2011 to 2011-2012	from 6 months to 17 years	309	US	*N.A.*	A(H1N1), A(H3N2) and B	Confirmed	Case-control	Quantitative
Gilca R[80]	children	hospitalization	2011	2009-2010	from 6 months to 9 years	884	Canada	adiuvated pH1N1	pH1N1	Confirmed	Case-control	Quantitative
Griffin MR[81]	children	hospitalization	2011	2009-2010	from 6 months to 9 years	2,168	US	live attenuated and inactivated pH1N1	pH1N1	Confirmed	Case-control	Quantitative
Dixon GA[53]	children	hospitalization	2010	2008	from 6 months to 6 years	76	Australia	trivalent inactivated	A(H1N1), A(H3N2) and B	Confirmed	Case-control	Quantitative
Orellano PW[59]	children and older	hospitalization	2010	2009	<5 years and >65 years	1,115	Argentina	trivalent inactivated	pH1N1	Confirmed	Case-control	Quantitative
Chen Q[82]	older	outpatient	2014	from 2006-2007 to	≥ 65 years	927	US	trivalent inactivated	A(H1N1), A(H3N2)	Confirmed	Case-control	Quantitative

		visit		2008-2009, from 2010-2011 to 2011-2012					and B			
Havers F[83]	older	hospitalization	2016	2010-2011	>50 years	1,141	US	trivalent inactivated	A(H1N1), A(H3N2) and B	Not confirmed	Case-control	Quantitative
Cheng AC[24]	older and comorbidity	hospitalization	2015	2014	>65 years and ≥16 years for comorbidity	3,217	Australia	trivalent inactivated	A(H1N1), A(H3N2) and B	Not confirmed	Case-control	Quantitative
Gilca R[60]	older	hospitalization	2015	2014-2015	≥ 65 years	314	Canada	adiuvated trivalent inactivated	A(H3N2)	Not confirmed	Case-control	Quantitative
Puig-Barberà J[84]	older	hospitalization	2015	2014- 2015	≥ 65 years	1,108	Spain	trivalent inactivated	A(H3N2)	Confirmed	Case-control	Quantitative
Castilla J[85]	older	hospitalization	2014	2013-2014	>65 years	239	Spain	trivalent inactivated	A(H1N1) and A(H3N2)	Confirmed	Case-control	Quantitative
Kwong JC[86]	older	hospitalization	2013	2010-2011	>65 years	2,230	Canada	trivalent inactivated	A(H1N1), A(H3N2) and B	Confirmed	Case-control	Quantitative
Puig-Barberà J[26]	older and comorbidity	hospitalization	2012	2010-2011	>60 years and ≥18 years for comorbidity	379	Spain	adiuvated trivalent inactivated	A(H1N1), A(H3N2) and B	Confirmed	Case-control	Quantitative
Van Vuuren A[87]	older	hospitalization	2008	2004-2005	≥ 65 years	6,410	South Africa	trivalent inactivated	A(H1N1), A(H3N2) and B	Confirmed	Case-control	Quantitative

Table 2: Analysis for funnel plot asymmetry of studies reporting vaccine effectiveness, estimated by Egger's regression test

	No. studies	**coefficient**	**95% CI**		**p-value**
Vaccine effectiveness on influenza visits among children	9	-0.78	-3.51	1.94	0.520
Vaccine effectiveness on influenza hospitalization among children	10	-3.05	-5.93	-0.18	0.040
Vaccine effectiveness on influenza visits among elderly subjects	3	-1.06	-16.41	14.29	0.541
Vaccine effectiveness on influenza hospitalization among elderly subjects	10	-0.52	-2.35	1.31	0.531

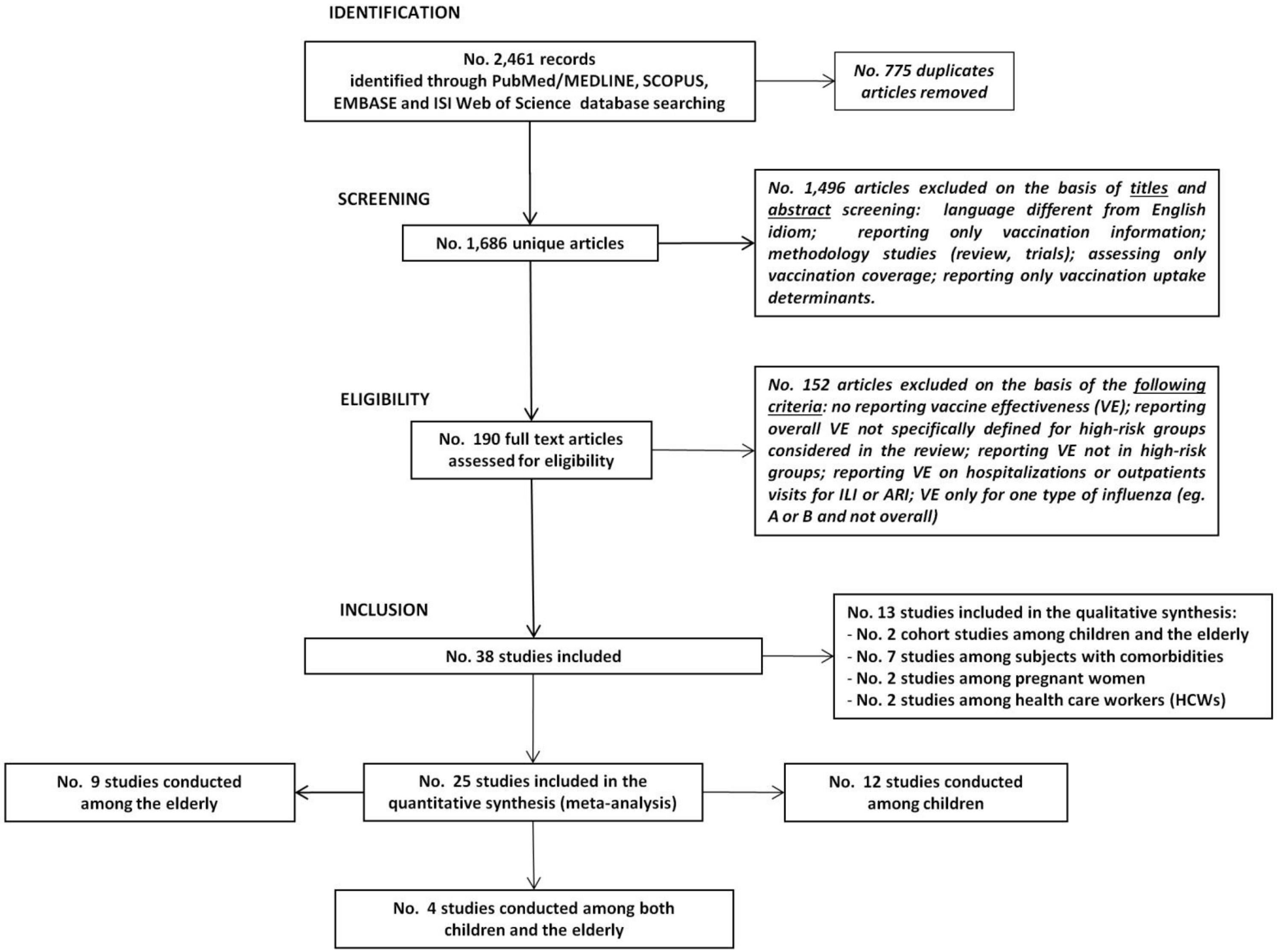
IDENTIFICATION
No. 2,461 records identified through PubMed/MEDLINE, SCOPUS, EMBASE and ISI Web of Science database searching
No. 775 duplicates articles removed
SCREENING
No. 1,686 unique articles
No. 1,496 articles excluded on the basis of titles and abstract screening: language different from English idiom; reporting only vaccination information; methodology studies (review, trials); assessing only vaccination coverage; reporting only vaccination uptake determinants.
ELIGIBILITY
No. 190 full text articles assessed for eligibility
No. 152 articles excluded on the basis of the following criteria: no reporting vaccine effectiveness (VE); reporting overall VE not specifically defined for high-risk groups considered in the review; reporting VE not in high-risk groups; reporting VE on hospitalizations or outpatients visits for ILI or ARI; VE only for one type of influenza (eg. A or B and not overall)
INCLUSION
No. 38 studies included
No. 13 studies included in the qualitative synthesis:
- No. 2 cohort studies among children and the elderly
- No. 7 studies among subjects with comorbidities
- No. 2 studies among pregnant women
- No. 2 studies among health care workers (HCWs)
No. 25 studies included in the quantitative synthesis (meta-analysis)
No. 9 studies conducted among the elderly
No. 12 studies conducted among children
No. 4 studies conducted among both children and the elderly

Figure 2: Forest plot of influenza visits and hospitalization vaccine effectiveness (1-Odds ratio) among children from 6 months to 18 years old

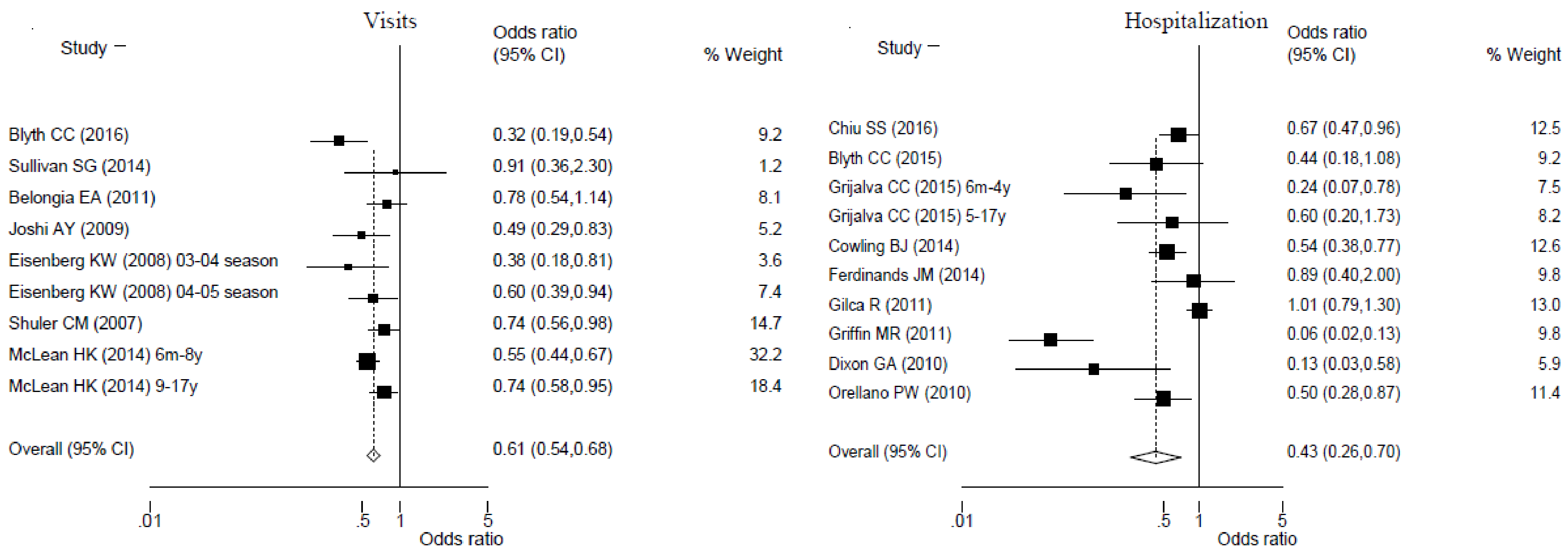

Figure 3: Forest plot of influenza visits and hospitalization vaccine effectiveness (1- Odds ratio) among elderly subjects