

REVIEW

Influenza vaccination in the elderly: why are the overall benefits still hotly debated?

C. TRUCCHI, C. PAGANINO, A. ORSI, D. DE FLORENTIIS, F. ANSALDI

Department of Health Sciences, University of Genoa, Italy and IRCCS University Hospital San Martino, IST National Institute for Cancer Research, Genoa, Italy

Key words

Influenza vaccine • Vaccine efficacy • Vaccine effectiveness

Summary

The exact magnitude of the benefit of influenza vaccine among elderly individuals is subject of considerable debate. Existing vaccine effectiveness estimates come mostly from observational studies, which may be biased because of difficulties in identifying and adjusting for confounders. In this paper, we examine the potential sources of bias in observational studies of influenza vaccine effectiveness in the elderly and we discuss available

evidence regarding the efficacy and effectiveness of licensed influenza vaccines. Although several methodological criticisms among the available analyses on seasonal vaccines for elderly were identified, overall seasonal influenza vaccines showed relevant efficacy/effectiveness in reducing the risk of influenza and its complications in the elderly, considering different measure of outcome.

Introduction

Influenza infection is associated with considerable yearly morbidity and subjects aged ≥ 65 years are among those at highest risk of serious outcomes [1, 2]. Annual influenza vaccination, that is considered the most effective strategy to prevent influenza by the World Health Organization, is recommended for elderly in many developed countries [3]. However, the exact magnitude of the benefit of the current immunization strategy among older adults is a subject of considerable debate [4-10]. Most estimates of the influenza vaccine effectiveness (IVE) are based on studies using different designs and outcomes, which provided a wide range of IVE estimates in the elderly (adults ≥ 65 years-old) [10, 11]. Furthermore, as most of the IVE studies are observational, they are susceptible to bias. Confounding factors such as comorbidities or functional status can alter the estimates and different methods to adjust for these confounding factors have been suggested [5, 12]. The present study discusses available epidemiological studies estimating IVE and criticisms in the evaluation of influenza vaccine efficacy and effectiveness, defined as the relative reduction in influenza risk after vaccination as established by a randomized placebo-controlled clinical trial (RCT) and the relative reduction in influenza risk in vaccinated individuals in observational studies that used medically attended, laboratory-confirmed influenza as the primary outcome of interest, respectively [13].

Criticisms in the evaluation of influenza vaccine efficacy and effectiveness

WHICH EPIDEMIOLOGICAL STUDY CAN ESTIMATE INFLUENZA VACCINE EFFECTIVENESS?

Not many RCTs on the influenza vaccine efficacy in older adults have been conducted, because of ethical issues concerning interventions that are recommended [14]. In the last two decades, the only large RCT of inactivated influenza vaccine in adults aged ≥ 60 years was conducted during a single season and it was limited to healthy subjects. This RCT demonstrated a reduction in risk of serologically confirmed uncomplicated influenza infection in participants 60-69 years-old, with an estimated efficacy for prevention of serologically-confirmed influenza in symptomatic subjects of 58%, but no strong conclusions about the IVE could be drawn about those ≥ 70 years-old because this RCT was inadequately powered to examine the efficacy of the vaccine in this age group [15]. Moreover, the efficacy evidence in healthy subjects 60-69 years-old may not apply to fragile elderly ≥ 70 years-old because advanced age and the comorbidities are associated with an increased risk of complications and the weakening of the immune system [16-22]. Without satisfactory data from RCTs, estimates of IVE among older subjects result from observational studies, typically from retrospective cohort studies, which may be biased [12, 23]. Many observational studies have compared the risk of hospitalization pneumonia-related and all-cause mortality in vaccinated and unvaccinated elderly during influenza season and have reported significant reductions in risk for vaccinated subjects, with reductions of 50% for all-cause mortality and of 27-33% for pneumonia and influenza hospitalization [24-41]. Some authors interpreted

these results as evidence that influenza vaccine substantially reduces the risk of death and hospitalization in the elderly [11, 42-46]. Nevertheless some studies, as the review published in 2007 by Simonsen et al. [9], state that there is evidence for bias in estimated risk reductions for vaccinated versus unvaccinated elderly in available observational studies, especially those not using laboratory-confirmation as outcome, that is considered the gold standard. Simonsen et al. [9] observed that the finding of reductions $\geq 50\%$ in all-cause mortality for vaccinated elderly during influenza season is implausible, considering that influenza accounts for a maximum of 10% of all deaths during influenza season [47] and, therefore, influenza vaccine could at most prevent 10% of deaths, even if the vaccine efficacy was 100% in the elderly. Furthermore, estimated risk reductions for vaccinated elderly are not specific to seasons with a matching between the circulating and vaccine influenza strains. Nordin et al. reported large reductions in risk of death and hospitalization in vaccinated elderly in the 1997-1998 influenza [33], characterized by a mismatch and during which a RCT found no vaccine effect in healthy adult workers [48]. Moreover, the greatest apparent vaccine benefit has been observed before influenza season, when no effect is expected [5]. Two further studies [5, 47] are of particular interest. In 2005 Simonsen et al. conducted an ecologic study [47] and reported that, despite substantial increases in vaccine coverage (VC) from about 15% in 1980 to $\geq 65\%$ by 2001 in elderly, rates of winter excess morbidity and mortality have not declined during this period. If the estimated mortality reduction of 50% by influenza vaccine is real, the observed excess mortality rate should have decreased with increasing VC [12]. Second, a large cohort study [5] assessed the risk of death and hospitalization in vaccinated and unvaccinated elderly in both influenza and non-influenza periods. The study confirmed that vaccinated subjects 60-69 years-old were at lower risk (44% for all-cause death) during influenza season, but revealed a larger risk reduction before the onset of influenza season (61% for all-cause death), when the IVE is expected to be 0%. Therefore this finding suggests the presence of confounding and any estimated difference in risk between vaccinated and unvaccinated elderly during this period is related to bias. Similar bias were found in pre-influenza estimates of the association between vaccination and other outcomes, including hospitalizations for pneumonia or influenza. Finally, available observational studies about IVE frequently use data from databases, such as the General Practitioners Research database, health care utilization data systems, or those kept by some health maintenance organizations in the United States [12]. In 2005 Schneeweiss and Avorn published a review about general methodological issues that arise using these databases in health research, such as data inaccuracies and residual confounding, but they didn't discuss methodological criticism specific to influenza vaccination [49].

The "case-coverage" or "case-cohort" method is another type of study to estimate IVE. In this case, vaccination rates among cases are compared with those in a similar cohort (which may include individuals who develop cases) over a defined period of time [50]. This method

has been used in a study published in 2008 by Szilagyi et al. that evaluated IVE among children 6-59 months of age during 2 influenza seasons [51]. The authors concluded that this type of study design is "inefficient and may insufficiently account for important factors, such as propensity to seek care" and that it has "important limitations in being able to annually assess IVE".

In recent years, the test-negative design, that is an analogous to the indirect cohort study [50], has arisen as the preferred method for estimating IVE in observational studies [52]. This type of study design consider as study subjects all persons who seek care for an acute respiratory illness (ARI) and who are tested for influenza infection. IVE is estimated from the ratio of the odds of vaccination among subjects testing positive for influenza to the odds of vaccination among subjects testing negative. The main advantage of this study design is that it allows removing differences in health care-seeking behavior between vaccinated and unvaccinated subjects in the study design phase.

WHICH FACTOR MAY INTERFERE WITH VACCINE EFFECTIVENESS ESTIMATES?

Vaccine effectiveness can be measured using different endpoints, each of which has advantages and disadvantages [53]. In the recent past, the most frequently considered endpoints include the incidence of clinically defined influenza-like illness (ILI) and laboratory-confirmed influenza. The methods used to the laboratory confirmation include viral culture, serologic rises between pre and post influenza season samples and molecular methods [53]. Unfortunately, none of these are both specific and sensitive methods. Typically influenza presents with the acute onset of fever, myalgia and cough [54]. The Centers for Disease Control and Prevention (CDC) defined ILI as fever with either cough or sore throat for research purposes [55]. This CDC-ILI definition has high positive predictive value in young adults (86.8%) [56] during periods of high influenza activity, but it is much lower in older adults, who frequently don't have fever and other manifestations of influenza [57, 58]. Furthermore, vaccine impact on severe outcomes such as hospitalization and death may be difficult to measure because of the large sample sizes needed to accurately estimate rare events like these [59]. Conventionally, culture has been considered the gold-standard for the diagnosis of influenza [53]. Nevertheless, viral titers in the respiratory secretions of older adults are generally lower than those of younger adults and children, reducing the sensitivity of culture in this age group when compared with serology and polymerase chain reaction (PCR) [60]. Serology is another common but not sensitive endpoint for estimating IVE. A positive case of influenza is usually defined as a ≥ 4 -fold rise in antibody titers between the pre- and post-season serology [53]. Some authors have suggested that this endpoint might overestimate the efficacy of vaccine because of the "antibody ceiling" phenomena, that could be explained as follows: once antibody titres have increased in response to the vaccine, they could go no higher in response to infection [61]. Furthermore, the association of immune

correlates of vaccine protection with efficacy against disease is not always dependable endpoint [62], particularly weak in young children, the elderly and immunocompromised, i.e. target groups that may respond least well to vaccination [63]. Use of real-time PCR (RT-PCR) with appropriately designed primers and probes for detecting influenza infection has now become the gold standard and it should be the primary end point used in future efficacy studies [64]. The test is highly sensitive, so much so that concerns has been raised that it might detect subclinical infections that are not clinically relevant [64]. Isolation in cell culture must still be used in those RT-PCR positive to further characterize the viruses, but use it alone as an endpoint could result in missed cases and biased results [64, 65].

Potential bias in estimates of influenza vaccine effectiveness

The risk of selection bias in observational studies estimating IVE has been discussed in many available studies [4-6, 8, 9, 12].

Although universally recommended for old subjects, acceptance of influenza vaccine is voluntary and a preferential receipt of vaccine by motivated relatively healthy elderly and a selective underuse by frail elderly were demonstrated [5-7, 9, 12]. Healthy adherer bias may be more noticeable for influenza vaccine than other type of exposures for several reasons. First, limited availability of vaccine (late autumn and winter) may limit the chance for vaccination. Several studies demonstrated that elderly subjects who have a car or can walk to their health care provider's office [66], live with others who can assist them [67], or have fewer functional limitations [6] are more prone to be immunized. A case-control study of all-cause mortality conducted in 824 elderly during influenza season found that severe functional limitation, in particular requiring assistance for bathing, was associated with a 13-fold increased risk of death and a 52% decreased likelihood of vaccination [6]. Therefore, disability appears as a contributing factor in the decision to receive or resist vaccination near the end of life. A further factor that may aggravate bias is the use of all-cause death as a study outcome, because it is nonspecific and so expected vaccine effects are small and thus difficult to distinguish from confounding, which may be large [68]. To differentiate vaccine effects from bias, Fireman et al. has proposed a "difference in differences" approaches [4]: if the flu vaccine really does prevent deaths, then in a large population there should be a detectable difference between: (i) the difference in the odds of prior vaccination decedents and survivors that is observed on days when influenza is circulating and (ii) the difference in the odds of prior vaccination between decedents and survivors that would be expected on the same calendar dates if influenza were not circulating. The implementation of the "difference in differences" approach consisted of tracing the trajectory of the bias over time and comparing the vaccination-mortality association inside flu season with that outside flu

season. Estimated VE against all-cause mortality during 1996-2005 flu seasons was 4.6% (95% CI: 0.7 – 8.3). Although this estimate may seem unsatisfactory, it amounts to approximately 47% of a plausible target: the rise in mortality that would have occurred during flu season had none of the elderly been vaccinated.

Available estimates of influenza vaccine efficacy and effectiveness against lab-confirmed influenza in adults aged 50 years and older obtained by meta-analyses

A considerable body of evidence has been produced on influenza vaccines for different types of virus strains and various populations and settings [69]. Between 1995 and 2011 numerous meta-analyses evaluating the benefits and harms of influenza vaccines mainly in adults and elderly have been published, as an effort to integrate this evidence [13, 44, 70-77]. In 2012 Osterholm et al. [13] published a meta-analysis of RCTs and observational studies that assesses the highest quality evidence about the efficacy and effectiveness of licensed influenza vaccines in the USA using RT-PCR or viral culture to confirm influenza infections. Vaccine efficacy was defined as "the relative reduction in influenza risk after vaccination as established by a RCT". Vaccine effectiveness was defined as "the relative reduction in influenza risk in vaccinated individuals in observational studies (case-control, case-cohort and prospective cohort studies) that used medically attended, laboratory-confirmed influenza as the primary outcome of interest" [50]. Laboratory-confirmed influenza was defined as RT-PCR-confirmed, the preferred diagnostic test for influenza because characterized by high sensitivity and low probability of false positive [78], or culture-confirmed influenza. Trivalent influenza vaccine (TIV) efficacy and effectiveness studies that considered serology endpoints to diagnose influenza were excluded because of bias in case detection in immunized subjects [64, 79]. For all the considered studies, efficacy and effectiveness were evaluated as statistically significant if the 95% CI did not cross 0.

EFFICACY

None of the evaluated RCTs assessing TIV efficacy exclusively considered subjects aged ≥ 65 years-old and this is attributable to ethical issues. For LAIV, the only RCT conducted in adults aged ≥ 60 years-old reported significant overall efficacy (42%, 95% CI: 21-57), but estimated efficacy was lower in subjects aged 60-69 years-old (31%) and higher in those aged ≥ 70 years-old (57%) [80].

EFFECTIVENESS

Several observational studies about influenza vaccines effectiveness have been conducted [13], especially on TIV. Main recent evidences are following described. Since 2007 the European Centre for Disease Prevention and Control (ECDC) has promoted I-MOVE (Influenza Monitoring Vaccine Effectiveness), a network to moni-

tor seasonal and pandemic IVE in the European Union (EU) and European Economic Area (EEA) [81]. Initial phase of I-MOVE network include five case-control and two cohort studies evaluating IVE in 2008-2009 season. The studies were piloted in the network of active General Practitioners (GP)-based influenza sentinel surveillance systems and assessed IVE against laboratory confirmed influenza in community-dwelling elderly [82]. The estimated crude IVE in the pooled analysis was 55.1% (95% CI: 27.8-72.1%). The overall IVE adjusted for study, age, sex, presence of chronic conditions, previous hospitalizations, smoking history, functional status, and previous influenza vaccination was 59.1% (95% CI: 15.3-80.3%). The adjusted IVE in subjects 65-74 year-olds was 65.4% (95% CI: 15.6-85.8%) and 59.6% (95% CI: -72.6-90.6%) in the age-group of ≥ 75 years. Spain participated in I-MOVE project with a case-control study using two different control groups. IVE against laboratory-confirmed influenza in elderly ≥ 65 years was also estimated by Savulescu et al. using the screening method [83]. Both designs (case-control and screening method) were carried out in the frame of the Spanish Influenza Sentinel Surveillance System (SISSS) in 2008-2009 season. Participating sentinel GPs of the framework swabbed all patients who were attended for ILI. Study cases were defined as "ILI patients swabbed and laboratory confirmed for influenza by RT-PCR or culture". The first control group included ILI cases testing negative for influenza (test-negative controls) and the second one comprised patients not having had respiratory symptoms since the beginning of the season (non-ILI controls). The crude estimated IVE was 86% (95% CI: 43-98) and the IVE adjusted for chronic conditions, previous hospitalizations, functional status, smoking, previous influenza and pneumococcal vaccination was 79% (95% CI: -26-96). In the same period Talbot et al. conducted a prospective observational study, published in 2012 [53]. Patients aged ≥ 50 years with respiratory symptoms or fever hospitalized in Davidson County, TN (Nashville) during three influenza seasons (2006-2007, 2007-2008 and 2008-2009) were enrolled and influenza vaccination status was compared in those with and without laboratory-confirmed influenza by RT-PCR to estimate IVE for the prevention of hospitalization. For each of the three evaluated seasons, unadjusted annual estimates were 59.4% (95% CI: -26.7-87%), 61.8% (95% CI: -29.4%-88.7%) and 81.8% (95% CI: 34.8-94.9%), respectively. With propensity-score adjustment, overall IVE for the three influenza seasons was 61.2% (95% CI: 17.5-81.8%).

Available estimates of TIV efficacy and effectiveness against influenza in the elderly obtained by umbrella review

Given that published meta-analyses on influenza vaccine efficacy and effectiveness evaluated different types of vaccines, different age-groups and used different stratified analyses and study selection criteria, it's difficult to obtain a clear picture of vaccine benefits examining sin-

gle meta-analyses [69]. Consequently, in 2012 Manzoli et al. conducted an umbrella review, i.e. an over-arching evaluation of all recent meta-analyses on vaccine efficacy and effectiveness (Fig. 1).

Four meta-analyses including both RCTs and observational studies on TIV conducted in the elderly were discussed [13, 44, 76, 84].

Two meta-analyses estimated vaccine efficacy/effectiveness against laboratory-confirmed cases of influenza (LCC) [13, 84]. Influenza vaccine efficacy estimated by RCTs was 58% (95% CI: 34%-73%), while the estimates of IVE from cohort studies varied from 41% (95% CI: -15%-70%) in the Jefferson et al. meta-analysis, that included only LCC based on serology, to 63% (95% CI: 28%-81%) in the Osterholm et al. meta-analysis, that evaluated a more specific outcome (RT-PCR or culture-confirmed influenza infections only). Concerning clinically confirmed cases (CCC), all considered reviews demonstrated that influenza vaccine confer significant protection. The four evaluated RCTs estimated a summary efficacy of 41%, while the meta-analyses of cohort studies showed an overall IVE ranging from 56% [44] to 24% [84].

Three meta-analyses evaluated also other outcomes [44, 76, 84], demonstrating that TIV was significantly better than placebo in preventing hospitalizations due to influenza or pneumonia. However the estimates varied, ranging from 48% [44] to 27% [84].

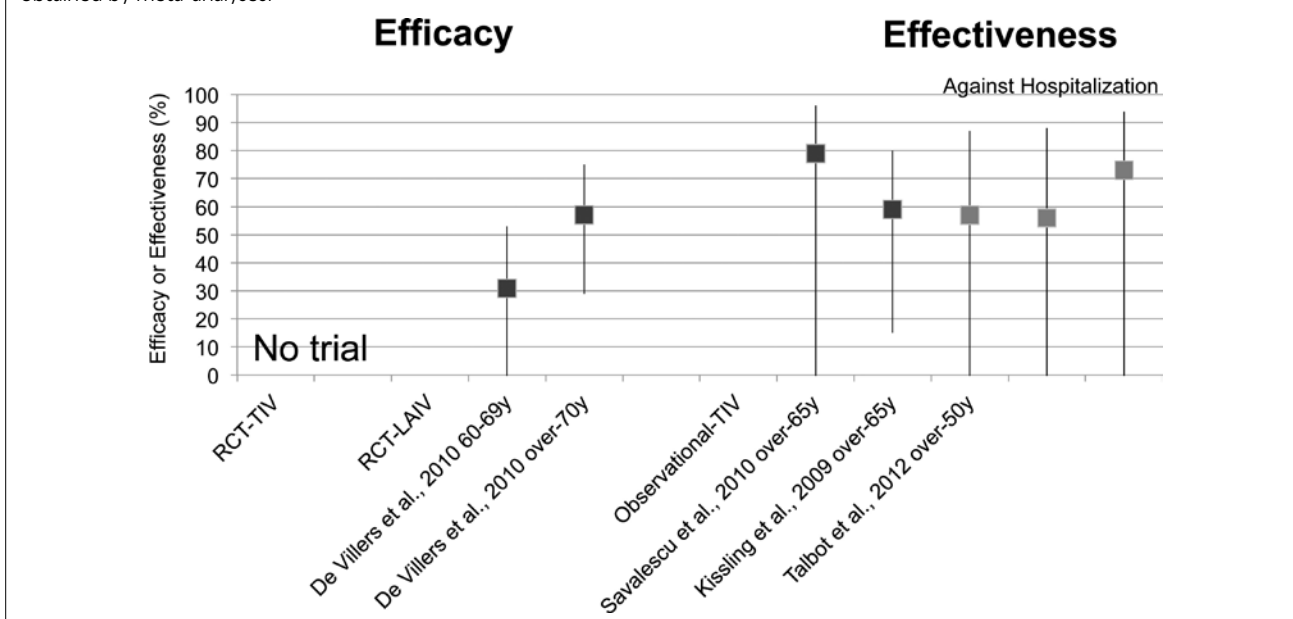
Three meta-analyses considered the outcome mortality [44, 76, 84]. Unexpectedly, the estimates of IVE in preventing mortality due to influenza or pneumonia were similar to those of all-cause mortality [47].

Combining observational studies, all meta-analyses demonstrated a significant reduction of deaths for all causes, with IVE ranging from 68% to 47%.

The effect of vaccination is expected to be higher in case of a good antigenic matching between the circulating and the vaccine strains [85]. However, Gross et al. observed a significant IVE even in seasons in which mismatching was demonstrated [44]. Jefferson et al. [84] observed that IVE in preventing hospitalization due to influenza or pneumonia and all cause mortality was substantially higher in seasons with good matching. Nevertheless, in 2010 Dean et al. published a cluster randomized trial, which demonstrated that influenza vaccine can be effective against disease and severe outcomes despite incomplete vaccine match [86].

Manzoli et al. summarized that Gross et al. [44] and Vu et al. [76] observed that influenza vaccines are effective in preventing influenza cases, hospitalizations and deaths in the elderly, while Osterholm et al. stated that "evidence for protection in adults aged 65 years or older is lacking" [13]. However, the conclusions by Osterholm et al. could be due to the choice of restrictive inclusion criteria [87]. Jefferson et al. stated that "the available evidence is of poor quality and provides no guidance regarding the safety, efficacy or effectiveness of influenza vaccines for people aged 65 years or older," but these observation may be influenced by the evidence of potential biases [84].

Fig. 1. Available estimates of influenza vaccine efficacy and effectiveness against lab-confirmed influenza in adults aged 50 years and older obtained by meta-analyses.



Conclusions

The overall evidences suggest that most influenza vaccines confer relevant protection against naturally acquired infection also in the elderly, who are at increased risk for influenza and complications due to influenza infection [53, 69, 88]. However, the assessment of vaccine benefits is still affected by considerable methodological challenges [88]. There is evidence for the presence of bias in available observational studies estimating the IVE in the elderly and that current adjustment methods could not adequately control it [12]. Some of the outcomes evaluated in the comprehensive umbrella review by Manzoli et al. seem to be surprising when compared, i.e. the large impact on all-cause mortality in the elderly as opposed to far more modest effects against CCC [69]. However, Manzoli et al. concluded that “although several discrepancies among meta-analyses on seasonal vaccines for elderly were identified, most seasonal influenza vaccines show statistically significant efficacy/effectiveness, the magnitude of which, however, largely varied” [69]. The conduct of adequately powered publicly-funded RCTs on elderly could be a solution, but this would be also an expensive and an ethically complex proposal, because the use of influenza vaccines is recommended worldwide from several years [69, 88] and cost-effectiveness issues have to be properly re-assessed in times of economic recession [89].

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■ Correspondence: Filippo Ansaldi, largo R. Benzi 10, 16132 Genoa, Italy - Tel. +39 010 5552333 - E-mail: filippo.ansaldi@unige.it