Review

A systematic review of the evidence on the effectiveness and risks of inactivated influenza vaccines in different target groups

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\textbf{A R T I C L E  I N F O}

Article history:
Received 3 June 2011
Received in revised form 27 July 2011
Accepted 1 August 2011
Available online 12 August 2011

Keywords:
Influenza
Inactivated vaccine
Efficacy
Effectiveness
Healthy
Co-morbidity

\textbf{A B S T R A C T}

\textbf{Purpose:} To systematically review the evidence regarding the efficacy, effectiveness and risks of the use of inactivated influenza vaccines in children, healthy adults, elderly individuals and individuals with co-morbidities such as diabetes, chronic lung disease, cardiovascular disease, kidney or liver disease and immune suppression.

\textbf{Methods:} The Cochrane database of systematic reviews was searched for relevant reviews and supplemented with searches of the Cochrane Central Register of Controlled Trials database and Medline. Two reviewers independently assessed review and trial quality and extracted data.

\textbf{Results and conclusions:} The inactivated influenza vaccine has been proven effective in preventing laboratory-confirmed influenza among healthy adults (16–65 years) and children (≥6 years) (GRADE A evidence). However, there is strikingly limited good-quality evidence (all GRADE B, C or not existing) of the effectiveness of influenza vaccination on complications such as pneumonia, hospitalisation and influenza-specific and overall mortality. Inconsistent results are found in studies among children younger than 6 years, individuals with COPD, institutionalised elderly (65 years or older), elderly with co-morbidities and healthcare workers in elderly homes, which can only be explained by bias of unknown origin. The vaccination of pregnant women might be beneficial for their newborns, and vaccination of children might be protective in non-recipients of the vaccine of all ages living in the same community (one RCT, Grade B evidence).

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0264-410X/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2011.08.008
1. Introduction

The vaccines currently used against seasonal influenza contain antigens against three influenza strains (A/H1N1, A/H3N2 and B), which are altered yearly to target the strains that are predicted to circulate in the upcoming season (WHO) [1].

In Europe, only inactivated vaccines, i.e., “killed” whole virion, split virion (fragmented envelopes) or subunit (purified envelope antigens) vaccines are used [2]. More recently, and especially for the A/H1N1 pandemic influenza strain, new (adjuvanted) vaccines were introduced worldwide. Live attenuated vaccines have been available in the United States of America since 2003 but were only recently approved for use in the European Union [3]. The immune response to inactivated influenza vaccines, which is measured by counting haemagglutinin antibodies in the serum, begins one week after vaccination and peaks between 2 and 4 weeks [4]. After vaccination with an inactivated vaccine, the protective immune response lasts for 6–12 months in healthy adults [5]. In general, children and elderly individuals have lower immune responses [4].

The yearly influenza vaccination of at-risk individuals became common practice worldwide after the Second World War [6]. Elderly individuals (65 or older), who account for approximately 90% of all influenza-related deaths [7], chronically ill individuals regardless of age and children with chronic acetylsalicylic acid (ASA) intake are the most important target groups [8]. Until now, the European guidelines have not found enough evidence to target other groups, but caregivers, health care workers and pregnant women are strongly advised to receive vaccinations [8]. In general, the European Guidelines [8] are more conservative than those in the United States of America [9]. An extensive literature search was performed to evaluate vaccination against seasonal influenza in primary care. We looked for evidence of efficacy (against laboratory-proven influenza only, unless stated otherwise), effectiveness (against clinically defined influenza-like illness, unless stated otherwise) and potential risks of the use of inactivated vaccines in several target groups: adults (16–65 years), healthy children (younger than 16 years), elderly (65 years or older), pregnant women, healthcare workers and individuals of all ages with chronic medical conditions.

2. Methods

2.1. Search strategy

The Cochrane database of systematic reviews was queried using the keyword “influenza vaccine”. After checking the inclusion dates in the systematic reviews withheld, a Cochrane Central Register of Controlled Trials search was performed from 2006 to April 2011 using the keywords “influenza and vaccin” [all fields]. Additionally, a PubMed search (Medline) of publications from January 1, 2006, to March 30, 2011, was conducted with the following search strategy: “(‘influenza vaccines’ [MeSH Terms] OR “influenza” [All Fields]) AND ‘vaccines’ [All Fields]) OR “influenza vaccines” [All Fields] OR “(influenza” [All Fields] AND “vaccine” [All Fields]) OR “influenza vaccine” [All Fields]) AND “humans” [MeSH Terms] AND (Clinical Trial [ptyp] OR Meta-Analysis [ptyp] OR Practice Guideline [ptyp] OR Randomised Controlled Trial [ptyp] OR Clinical Trial, Phase IV [ptyp] OR Comparative Study [ptyp] OR Controlled Clinical Trial [ptyp] OR Guideline [ptyp]).” BM and FG selected appropriate publications from this search on the basis of title/abstract and full text by applying the inclusion and exclusion criteria discussed below.

Only studies of seasonal influenza were considered for inclusion. Because live attenuated vaccines are not yet available in Europe, we restricted our review to trivalent inactivated vaccines (TIV). The most recent Cochrane reviews and systematic reviews published after the inclusion date of the latest Cochrane review were withheld. Guidelines and cost-effectiveness studies were excluded, as they have been discussed elsewhere [10]. Studies published in languages other than English or French were excluded, as were immune response studies. Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) with clinical endpoints (efficacy and/or effectiveness versus placebo or no intervention) that were not yet included in a Cochrane review were withheld. Cohort studies, case-control studies and observational studies not included in Cochrane reviews were not discussed. Reviews that were not systematic and non-randomised trials with inappropriate bias control or without adequate control groups were also excluded.

Evidence for the following target groups was identified: healthy individuals (adults, children, elderly, pregnant women, caregivers
2.2. Study quality appraisal

The overall quality of each study was evaluated by BM and FG. After determination of the hierarchal value of the study design (meta-analysis, systematic review, RCT, cohort study, case-control study), the quality of systematic reviews was assessed using AMSTAR [11]. The risk of bias in the additionally retrieved RCTs was assessed using the “Risk of bias tool” in the Cochrane Handbook for Systematic Reviews of Interventions [12]. In cases of disagreement, EV’s evaluation was used.

Evidence quality was graded using the GRADE classification method [13,14].

2.3. Outcome measures

Efficacy (against laboratory-proven influenza) and effectiveness (against influenza-like illness, as defined by the original trial protocol) are expressed in percentages and were calculated from the original publications using the following rule: \( E = (1 - RR) \times 100 \). In some cases, other measures, such as odds ratio, hazard ratio or mean difference, were used.

3. Results

3.1. Included publications

Our search results are described in Fig. 1. Eleven Cochrane reviews, one additional meta-analysis, 14 RCTs and 3 CCTs were included (Table 1).

3.1.1. Quality appraisal of the systematic reviews

In general, the Cochrane reviews are of excellent or good quality according to the AMSTAR checklist [11]. Recently updated Cochrane reviews (with a higher number of existing RCTs) gave more details and used more recently recommended tools in their quality appraisals (i.e., the risk of bias tool from Higgins [12] rather than Jadad scores [16]). Although a thorough search was conducted in an attempt to find unpublished studies, funnel plots to assess publication bias were seldom used, with the exception of the latest update of the Cochrane systematic review by Thomas et al. [17] and the new Cochrane systematic review by Cheuk et al. [18].

The review by Anema et al. [19], which was not a Cochrane review, was rated as medium quality. These authors did not perform a quality assessment of the included studies and pooled 3

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**Fig. 1.** Flow of information in the literature search (PRISMA) [15].
Table 1 Yield of literature search for different target groups.

<table>
<thead>
<tr>
<th>Target groups</th>
<th>Systematic reviews (SR)</th>
<th>RCTs after inclusion date of SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy adults (16–65 years)</td>
<td>1 Cochrane SR [1] – search up to June 2010</td>
<td>4 RCTs [2–7]</td>
</tr>
<tr>
<td>Pregnant women/newborn</td>
<td>0 SR</td>
<td>1 RCT [13]</td>
</tr>
<tr>
<td>Elderly (&gt;65 years)</td>
<td>1 Cochrane SR [14] – search up to October 2009</td>
<td>0 RCT</td>
</tr>
<tr>
<td>Health care workers/elderly in homes</td>
<td>1 Cochrane SR [15] – search up to September 2009</td>
<td>0 RCT</td>
</tr>
<tr>
<td>General practitioners/dentists</td>
<td>0 SR</td>
<td>1 RCT [16] – 1 CT [17]</td>
</tr>
<tr>
<td>COPD</td>
<td>1 Cochrane SR [18] – search up to May 2009</td>
<td>0 RCT</td>
</tr>
<tr>
<td>Asthma</td>
<td>1 Cochrane SR [19] – search up to September 2007</td>
<td>0 RCT</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>1 Cochrane SR [20] – search up to July 2006</td>
<td>0 RCT</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1 Cochrane SR [21] – search up to February 2007</td>
<td>0 RCT</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>1 Cochrane SR [22] – search up to January 2008</td>
<td>1 RCT [23]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0 SR</td>
<td>0 RCT</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>0 SR</td>
<td>0 RCT</td>
</tr>
<tr>
<td>Liver disease</td>
<td>0 SR</td>
<td>1 RCT [24]</td>
</tr>
<tr>
<td>HIV</td>
<td>1 SR [25] – search up to Jun 2007</td>
<td>1 RCT [26]</td>
</tr>
<tr>
<td>Chemotherapy + oncohematologic diseases</td>
<td>1 Cochrane SR [27] – search up to February 2007</td>
<td>0 RCT</td>
</tr>
<tr>
<td>Lupus, reumatoid arthritis, transplant patients</td>
<td>1 Cochrane SR [28] – search up to May 2010</td>
<td>0 RCT</td>
</tr>
</tbody>
</table>

studies with different designs (1 RCT and 2 cohort studies). This was regarded as inappropriate because there existed a high clinical heterogeneity.

3.1.2. Quality appraisal of the additional trials

The included publications by Monto et al. [20], Ohmit et al. [21,22] are in fact three reports from the same study protocol performed during three consecutive years (2004–2005; 2005–2006; 2006–2007). In this study, as well as that of Madhi et al. [23], the reporting randomisation, allocation concealment, blinding and the handling of incomplete outcome data were of good quality (Fig. 2). The studies of Jansen et al. [24] and Zaman et al. [25] were of high methodological quality, except for some problems with outcome measurement (lack of rapid point-of-care influenza tests in the beginning of the follow-up period in the Zaman study; not all RTI cases were swabbed for PCR testing in the Jansen study) that affected the intervention and control groups equally. In the studies of Barett et al. [26], Frey et al. [27], Jackson et al. [28] and Loeb et al. [29] the randomisation, allocation concealment and blinding were adequate, but they analysed results only per protocol or in a modified intention to treat, resulting in follow-up losses ranging up to 15% [29]. The studies of Hui et al. [30], Marchisio et al. [31], Phrommittikul et al. [32] and Song et al. [33] were randomised trials, but allocation was not concealed (no control intervention). Thus, information bias due to underreporting of ILI by vaccinated participants might have occurred. The studies of Anar et al. [34], Michiels et al. [35] and Ochiai et al. [36] were not randomised and not blinded. In the studies of Michiels et al. [35] and Ochiai et al. [36], statistical adjustments were made for the most important confounders. This was not the case for the Anar study [34], with a consequent high risk of bias and unreliable results, and this study was excluded for this reason. We referred to the original publications for quality appraisal for RCTs that were included in the selected Cochrane systematic reviews.

3.2. Specific effects of influenza vaccination in different target groups

3.2.1. Healthy adults (16–65 years)

A Cochrane systematic review on influenza vaccination in healthy adults by Jefferson et al. [2] included 34 trials (n = 34,573) with inactivated vaccines. Reliable evidence (Grade A) was generated on the basis of these trials. Efficacy was 73% if the vaccine was well matched to the circulating strain and/or consistent with WHO recommendations and 44% if the vaccines did not match the
circular strain (Table 2). However, the effectiveness of influenza vaccines was only 30%, even when consistent with the WHO recommendations and the circulating strains (Table 2). No effectiveness was shown when the circulating strain was unknown or did not correspond to the WHO recommendations.

The number of visits to a physician, length of illness (number of days) and number of days off work were not reduced by influenza vaccination when no distinction was made between a good or bad match of the vaccine with the circulating strains. In contrast, a statistically significant effect was found during years with a good match. Compared with placebo or non-vaccinated groups, vaccination did not reduce hospitalisation or pneumonia. Vaccination did not influence drug prescription (e.g., an antibiotic).

The adverse effects mentioned in the Cochrane review [2] encompassed local tenderness and pain (RR 3.11, 95%CI: 2.08–4.66), skin rash (RR 4.01, 95%CI: 1.91–8.41) and myalgia (RR 1.54, 95%CI: 1.12–2.11). Serious side effects were described, including ocular respiratory syndrome (bilateral conjunctivitis, cough, dyspnea, wheezing, dysphagia, hoarseness) (one study) and Guillain-Barré syndrome estimated at 1.6 cases per 1 million additional vaccinations (3 cohort studies). There was no evidence for other demyelinating diseases (two case-control studies).

Four additional trials, reported in six publications [20–22,26–28], compared a trivalent inactivated influenza vaccine to a placebo in healthy adults (Table 3). The efficacy ranged between 49% and 75%. In the second year of the Ohmit study [22], no efficacy was shown because there was little influenza circulation. The studies of Frey et al. [27] and Barrett et al. [26] demonstrated that the efficacy of the cell culture-derived trivalent inactivated influenza vaccine was comparable to that of the classic egg-derived inactivated vaccines. Effectiveness was included as an outcome in one trial, where it was given as 27% (95%CI: 15–38%) [27]. Adverse effects were similar to those mentioned in the Cochrane review.

3.2.2. Healthy children (younger than 16 years old)

In a Cochrane systematic review by Jefferson et al. [37], the quality of evidence in healthy children was moderate. New evidence might change these results (Grade B).

An efficacy of 69% was found in children older than 6 years (Table 4); the studies evaluated here did not include enough participants to demonstrate efficacy in younger children. No efficacy was seen in children under two years in one RCT performed during two consecutive years when the vaccine was a good match of the circulating influenza strains. The effectiveness of inactivated vaccines in preventing influenza-like infection (all ages) is only 36% (95%CI: 24–46%) (n = 19,388) compared with placebo or no intervention. No evidence for or against effectiveness was found for children younger than 2 years. Even the cohort studies included in this systematic review, which have slightly higher point estimates of efficacy and effectiveness, were unable to show a significant effect of the inactivated vaccine in children younger than two years. All RCTs included evaluated one injection in efficacy outcomes. However, two doses are not more effective than one dose. With respect to school absenteeism, otitis media and pneumonia, no benefit of inactivated influenza vaccines was demonstrated. Adverse effects mentioned in the Cochrane review [37], e.g., local reactions and fever, appeared to be more prevalent in the vaccinated group. Safety data in children under 2 years were absent.

Since September 2007, three new studies on the efficacy and/or effectiveness of inactivated influenza vaccines among children have been published. The RCT of Jansen et al. [24] was of good quality and compared three groups: pneumococcal conjugate vaccine + TIV, TIV + placebo and hepatitis B vaccine + placebo in children between 1 and 6 years of age with a history of RITs. The efficacy between TIV + placebo (n = 187) and the control group (n = 195) was 51% (95%CI: 3–75) and the effectiveness was not significant. Episodes of AOM during the influenza season were reduced by 71% (95%CI: 30–88). No effect on primary care visits or number of antibiotic

### Table 2
Summary of RCTs in healthy adults included in the Cochrane systematic review of Jefferson et al. [2] on the effect of inactivated influenza vaccine versus placebo or no vaccine on different outcomes.

<table>
<thead>
<tr>
<th>Number of studies/participants</th>
<th>Outcome – incidence of influenza in placebo</th>
<th>Conditions</th>
<th>Efficacy – effectiveness (95%CI)</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 8/n = 11,285</td>
<td>Proven influenza – 3.9%</td>
<td>Good match*</td>
<td>73% (54–84)</td>
<td>A</td>
</tr>
<tr>
<td>N = 6/n = 10,331</td>
<td>Proven influenza – 2.4%</td>
<td>Bad match</td>
<td>44% (23–59)</td>
<td>A</td>
</tr>
<tr>
<td>N = 10/n = 5984</td>
<td>Influenza-like illness – 30.5%</td>
<td>Good match</td>
<td>30% (17–41)</td>
<td>A</td>
</tr>
<tr>
<td>N = 9/n = 12,062</td>
<td>Influenza-like illness – 9.6%</td>
<td>Bad match</td>
<td>No significant effect</td>
<td>A</td>
</tr>
<tr>
<td>N = 1/n = 1179</td>
<td>Physicians visits</td>
<td>Good match</td>
<td>42% (9–63)</td>
<td>A</td>
</tr>
<tr>
<td>N = 1/n = 1130</td>
<td>Physicians visits</td>
<td>Bad match</td>
<td>No significant effect</td>
<td>A</td>
</tr>
<tr>
<td>N = 3/n = 3670</td>
<td>Illness days</td>
<td>Good match</td>
<td>0.48 (–0.62 to –0.34)</td>
<td>A</td>
</tr>
<tr>
<td>N = 1/n = 1130</td>
<td>Illness days</td>
<td>Bad match</td>
<td>No significant effect</td>
<td>A</td>
</tr>
<tr>
<td>N = 4/n = 4263</td>
<td>Working days lost</td>
<td>Good match</td>
<td>0.21 (–0.36 to –0.05)</td>
<td>A</td>
</tr>
<tr>
<td>N = 1/n = 1130</td>
<td>Working days lost</td>
<td>Bad match</td>
<td>No significant effect</td>
<td>A</td>
</tr>
<tr>
<td>N = 2/n = 2933</td>
<td>Pneumonia</td>
<td>Good or bad match</td>
<td>No significant effect</td>
<td>A</td>
</tr>
<tr>
<td>N = 5/n = 14,877</td>
<td>Hospitalisation</td>
<td>Good or bad match</td>
<td>No significant effect</td>
<td>A</td>
</tr>
</tbody>
</table>

* Match, similarity between vaccine and circulating wild type influenza virus strains (during the consequent epidemic).

### Table 3
Summary of RCTs (since January 2006) on the effect of inactivated influenza vaccine versus placebo on different outcomes in healthy adults.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year of publication/number of participants</th>
<th>Outcome/incidence of influenza in placebo/match of virus strain</th>
<th>Effectiveness (95%CI)</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohmit et al. [21]</td>
<td>2006/n = 728</td>
<td>Proven influenza – 7.8% – bad match</td>
<td>75% (42–90)</td>
<td>A</td>
</tr>
<tr>
<td>Ohmit et al. [22]</td>
<td>2008/n = 1205</td>
<td>Proven influenza – 1.8% – good match</td>
<td>No significant effect</td>
<td>A</td>
</tr>
<tr>
<td>Monto et al. [20]</td>
<td>2009/n = 1138</td>
<td>Proven influenza – 10.8% – good match (except for B)</td>
<td>68% (46–81)</td>
<td>A</td>
</tr>
<tr>
<td>Jackson et al. [27]</td>
<td>2010/n = 7462</td>
<td>Proven influenza – 1.6% – good match (except for B)</td>
<td>49% (20 to 7)</td>
<td>A</td>
</tr>
<tr>
<td>Frey et al. [26]</td>
<td>2010/n = 11,257</td>
<td>Proven influenza – 3.6% – good match (except for B)</td>
<td>CCIV*: 70% (55 to 7)</td>
<td>A</td>
</tr>
<tr>
<td>Barrett et al. [25]</td>
<td>2011/n = 7236</td>
<td>Proven influenza – 2.2% – good match</td>
<td>CCIV*: 63% (47 to 7)</td>
<td>A</td>
</tr>
</tbody>
</table>

* CCIV, cell cultured derived inactivated subunit influenza vaccine; TIV, egg derived inactivated subunit influenza vaccine.
prescriptions was shown. The study of Marchisio et al. [31] was of moderate quality, comparing the use of inactivated influenza vaccine with no treatment in 180 children (1–5 years) with a history of recurrent acute otitis media (AOM). These authors showed an effectiveness of 34% against AOM (p < 0.001) and 13.2% against the number of antibiotic courses (p < 0.001), but they found no effectiveness against Ili, days with fever or days lost from school. No efficacy results were given. A controlled trial (not randomised, not blinded) by Ochiai et al. [36] studied inactivated influenza vaccination among 2265 Japanese children younger than 6 years of age and showed no effectiveness against Ili. No results of efficacy were reported and confirmation of influenza was not included. In a cluster randomised trial, Loeb et al. [29] evaluated the effectiveness of influenza vaccination of children (23 months to 15 years) for the entire community. Efficacy against laboratory-confirmed influenza in non-recipients of the vaccine (n = 2326) (primary outcome) was 61% (95%CI: 8–83%), indicating an effect of immunisation on the transmission of influenza. A good match was seen between transmission strains and vaccine strains. No efficacy could be shown between the influenza-vaccinated and control group (n = 947). Effectiveness against Ili was not included. The side-effects in the trials above did not differ from those in the Cochrane review.

3.2.3. Pregnant women and newborns

In an RCT conducted by Zaman et al. [25], the benefit of vaccinating pregnant women for their newborn babies (<6 m) was evaluated in Bangladesh. An efficacy of 63% (95%CI: 5–85%) and an effectiveness of 29% (95%CI: 7–46%) against all respiratory tract infections with fever were shown for the newborns. Effectiveness in the mother was 36% (95%CI: 4–57%). No results were published on outcomes such as hospitalisation, pneumonia and mortality (Grade B).

3.2.4. Elderly (65 years or older)

According to a Cochrane systematic review by Jefferson et al. [38] on influenza vaccination in the elderly, evidence from RCTs (Table 5) has been limited and poorly reported. The effectiveness and efficacy of influenza vaccination in a mixed population of elderly were 41% and 58%, respectively. Insufficient evidence exists to show an effect on the incidence of pneumonia or on total mortality. No evidence was found regarding an effect on mortality from influenza or pneumonia.

In cohort studies conducted among healthy, community-dwelling elderly, no studies addressing the effectiveness of influenza vaccination could be retrieved. No significant efficacy was shown. Effectiveness rates against pneumonia and hospitalisation for influenza or pneumonia were 41% and 50%, respectively. No effectiveness could be found against specific mortality from influenza or pneumonia or on overall mortality.

In cohort studies conducted among community-dwelling elderly who are at risk for influenza complications, no studies on effectiveness could be retrieved. No significant efficacy was shown. No effect on the incidence of pneumonia was found. Effectiveness rates on hospitalisation for influenza or pneumonia, specific mortality from influenza or pneumonia and overall mortality were 26%, 8% and 61%, respectively.

When evaluating cohort studies conducted among elderly individuals living in nursing homes, significant heterogeneity in the data was observed, even within the same influenza season and within the same institution. The overall effectiveness was 24%. The efficacy was not significant. Effectiveness rates against pneumonia and on hospitalisation for influenza or pneumonia were 47% and 49%, respectively. Effectiveness on mortality from influenza or pneumonia and on overall mortality were 54% and 60%, respectively.

The apparently high effectiveness of the vaccines in preventing death from all causes in cohort studies compared to RCTs among elderly with co-morbidities and institutionalised elderly may reflect a baseline imbalance in health status and other systematic differences in the two groups of participants. This makes this evidence unreliable (Grade C).

There was no statistical difference between the vaccine and control groups in terms of systemic side effects. Local reactions such as tenderness, swelling and redness at the injection site were more frequent in the vaccinated group.

3.2.5. Health care workers in residential nursing homes

A Cochrane systematic review by Thomas et al. [17] compiled evidence regarding the influenza vaccination of health personnel working in nursing homes and its effect on the elderly in their care.

In RCTs, 86% of influenza-like infections were prevented among the elderly who were vaccinated (Table 5), but this effect was not significant among elderly who were not vaccinated. Influenza vaccination of health care workers did not significantly prevent proven influenza in the vaccinated or unvaccinated elderly, nor did it protect against lower respiratory infections or mortality from pneumonia. Paradoxically, however, vaccinating healthcare workers promoted an effectiveness of 34% on total mortality in the elderly.

One cohort study in the Cochrane review [17] (n = 12,742) reported the effectiveness of vaccination of healthcare workers in preventing influenza-like infections as 61% for the vaccinated elderly (95%CI: 53–67%) (n = 6591) and 74% for un-vaccinated elderly (95%CI: 38–89%) (n = 6151).

3.2.6. General practitioners (GPs) and dentists

Our own controlled trial (2006, n = 262) [35] showed that vaccination of GPs is particularly effective in young physicians (30 years: adjusted OR 0.35 (95%CI: 0.13–0.96); efficacy: 0.10 (95%CI: 0.01–0.75)) (Grade B). Another randomised trial by Hui et al. [30] studied 346 dental students and staff members of the faculty of dentistry, University Kebangsaan in Malaysia and showed an effectiveness of 53% (p = 0.002) of vaccination. Remarkably, this study also reported an effectiveness of 72% (p = 0.03) against Ili among family members and housemates. Influenza was not confirmed by laboratory testing.

3.2.7. Individuals with COPD

In a Cochrane systematic review by Poole et al. [39] on influenza vaccination in individuals suffering from COPD, the effect on the total number of exacerbations per patient corresponded to a
weighted mean difference of −0.37 (95%CI: −0.64 to −0.11). An efficacy of 81% (95%CI: 52–93%) against respiratory infections that were subsequently identified as influenza-related was found (2 studies, n = 180).

No significant effectiveness against non-specific respiratory infections and/or exacerbations could be shown. No effect was seen on hospitalisations or overall mortality (2 studies, n = 180). Furthermore, no significant differences in numbers of adverse events were found between the vaccinated and unvaccinated group. One study by Anar et al. [34] published after the inclusion date of the Cochrane review was retrieved, but we considered the results to be unreliable because of methodological problems (cf Section 3.1.2).

3.2.8. Individuals with asthma

In a Cochrane systematic review conducted by Cates et al. [40] that focused on influenza vaccination in children (over two years of age) and adults with stable asthma, no effect was found on the incidence, duration or severity of influenza-related asthma attacks (1 study, n = 696). Furthermore, no improvement in lung function during influenza-positive weeks was found (n = 41 children).

A Finnish study of adults with asthma (n = 328) showed that the vaccine and control responses were similar in terms of peak flow, symptom scores, daily medication, oral corticosteroid use and hospitalisation in the 8 months after vaccination, but the incidence of influenza was low, with only one confirmed case.

Six studies in adults and children reported adverse events. No statistical differences were found for number of asthma attacks in the two weeks after vaccination (two studies, n = 2306), pulmonary function and the use of airway dilators (4 studies, n = 4924), medical consultations (3 studies, n = 5092), or the use of corticosteroids (2 studies, n = 4419).

3.2.9. Individuals with bronchiectasis

Up to July 2010 no studies could be retrieved by a Cochrane systematic review of Chang et al. [41] evaluating the effectiveness of influenza vaccination on exacerbations in individuals suffering from bronchiectasis.

3.2.10. Individuals with cystic fibrosis

A Cochrane systematic review conducted by Dharmaraj et al. [42] evaluated studies of influenza vaccination in children and adults with cystic fibrosis and found no RCTs that estimated the effectiveness or efficacy of influenza vaccination compared with placebo or no intervention. Only comparisons between two different vaccine types were found, from which no meaningful conclusions could be drawn.
3.2.11. *Individuals with cardiovascular disease*

In a Cochrane systematic review by Keller et al. [43] on the effect of influenza vaccination in adults with cardiovascular disease, the pooled results of two RCTs (FLUVACS and FLUCAD study) showed an effect of influenza vaccination on cardiovascular mortality (combined primary and secondary prevention) of 61% (95%CI: 23–78%) (3 studies, n = 858). No effect of influenza vaccination on the primary prevention of cardiovascular mortality or acute myocardial infarction could be shown, but this evidence is very limited (one study, n = 102). With respect to secondary prevention, there was an effect on cardiovascular mortality (2 studies, n = 858) of 74% (95%CI: 37–89%) but not on the prevention of acute myocardial infarction (Grade B).

After January 2008, one additional study of moderate quality by Prommintikul et al. [32] was conducted among 439 patients suffering from an acute coronary syndrome. These authors found that vaccination was effective against combined major cardiovascular events (adjusted hazard ratio = 0.67 (95%CI: 0.51–0.86)) but not against cardiovascular or total mortality.

3.2.12. *Individuals with diabetes or kidney diseases*

For patients with diabetes or kidney diseases, no systematic reviews or randomised controlled trials on the effect of influenza vaccine versus a placebo or no intervention could be retrieved.

3.2.13. *Individuals with liver diseases*

No systematic reviews of influenza vaccination in individuals with liver disease could be found. One RCT (vaccine versus no vaccine) by Song et al. [33] among 311 patients with liver cirrhosis showed an efficacy of 76% (18–93%) against proven influenza, but no significant effectiveness against ILL. Fewer episodes of liver failure were noticed in the vaccinated group, but this observation needs to be confirmed by larger studies (Grade B).

3.2.14. *Individuals with HIV*

The efficacy of influenza vaccination in individuals with HIV was investigated in a systematic review by Anema et al. [19]. Data from three studies (two cohort studies (n = 473) and one RCT (n = 102)) were pooled. The efficacy was calculated to be 66% (95%CI: 36–82%), and significant heterogeneity was found. When only the data from the RCT were considered, the efficacy was 41% (95%CI: 2–55%). No adverse event data were reported. After the inclusion date of the previous review, one additional study by Madhi et al. [23] evaluated 506 HIV infected adults. The efficacy was 76% (95%CI: 9–96%), but no effectiveness could be shown. No statistical difference was found in the reporting of adverse events.

3.2.15. *Individuals suffering from immune suppression*

In a Cochrane systematic review by Goossen et al. [44] studying the effect of influenza vaccination in children treated with chemotherapy for cancer, one RCT and eight CCTs (n = 708) were included. Only immune response and side effects were reported. The immune response was weaker in children receiving chemotherapy. Only mild local reactions and mild fever were reported. No life-threatening or permanent effects occurred.

Two RCTs (n = 332) of low quality were included in a Cochrane systematic review by Cheuk et al. [18] that evaluated the effect of vaccines for prophylaxis of viral infections in patients with haematological malignancies. Efficacy was not measured, and the effectiveness was 44% (95%CI: 28–56%). Effectiveness rates of 61% on pneumonia (95%CI: 22–81%) and 83% on hospitalisation (95%CI: 69–91%) were shown. A significantly higher frequency of irritability was observed in the intervention group (RR 19, 95%CI: 1.12–321.07, P = 0.04).

No RCTs on the clinical benefit of influenza vaccine versus placebo and no intervention could be found for adults with immune suppression (e.g., auto-immune disease, transplant patients).

4. *Discussion*

4.1. *Summary of the evidence*

In this update, we show that the quality of the available evidence regarding the efficacy and effectiveness of influenza vaccination remains moderate to poor for those at risk of serious influenza complications, such as individuals with co-morbidities and the elderly. Although the number of publications, trials and participants is enormous and has only increased since the review of van der Wouden et al. [45], the evidence base for worldwide guidelines for the yearly administration of trivalent inactivated influenza vaccines in different target groups can still be challenged. Table 6 provides a comprehensive summary of our findings. Consistent Grade A evidence is only available for healthy adults.

The inactivated influenza vaccine is effective in preventing proven influenza among healthy adults and older children, who do not need as much protection. No efficacy has been shown in young children (less than 2 years) and institutionalised elderly. Although strong evidence for these conclusions is missing, some immunological explanations can be given. In young children, the immune system is immature, and the humoral immune response elicited by the inactivated vaccine may be insufficient and might also decline rapidly [46,47]. The live attenuated [48] and adjuvanted vaccines [49] are more promising for use in this age group, although the live attenuated vaccine has more side effects. In elderly individuals (older than 75 years), the incidence of influenza is lower and their failing immune system may not react adequately to the vaccination [7,47].

The most important finding in this study is that there is a striking lack of high-quality evidence for the effect of vaccination on complications of influenza such as pneumonia, hospitalisation and mortality among individuals with co-morbidities such as diabetes, COPD, bronchiectasis, cystic fibrosis, asthma and cardiovascular, kidney and liver disease. Inconsistent results were also found in studies of children younger than 6 years, elderly in nursing homes and individuals with COPD (where an effect on ILL was found and no effect on proven influenza was demonstrated).

In contrast with the RCT evidence, the apparently high effectiveness of the vaccines in preventing death from all causes in cohort studies among institutionalised elderly and elderly with co-morbidities may reflect a baseline imbalance in health status (frailty selection bias) and other systematic differences in the two groups of participants, making this evidence unreliable (Grade C). Indeed, in most studies, healthy elderly were vaccinated, and those severely ill (pre-terminal patients) were not, creating a direct effect on total mortality (47% reduction, while an excess mortality of only about 5–10% may be due to influenza) [7,50,51]. This phenomenon is called the “healthy user effect” and remains controversial among vaccination supporters [7,51–53] and opponents [54,55] despite the overwhelming arguments and proof provided by Simonsen et al. [7,51,56] and Baxter et al. [57].

The evidence that vaccinating healthcare workers prevents influenza in elderly residents of long-term care facilities is contradictory. No effect was shown for specific outcomes such as proven influenza rates, pneumonia and death from pneumonia, but favourable effects were demonstrated for non-specific outcomes such as ILL. GP consultations for ILL and overall mortality in elderly individuals. This suggests that these results may be due to some unexplained bias, such as a cluster difference in hand-washing habits or other precautions taken by caregivers.
Table 6
Summary of the evidence of the effect of inactivated influenza vaccine versus a placebo on different outcomes and in different target groups using the GRADE classification method.

<table>
<thead>
<tr>
<th>Target groups</th>
<th>Influenza-like illness</th>
<th>Influenza</th>
<th>Pneumonia</th>
<th>Hospitalisation</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy adults (16–65 years)</td>
<td>++ (A)</td>
<td>++ (A)</td>
<td>– (A)</td>
<td>– (A)</td>
<td>NE</td>
</tr>
<tr>
<td>Healthy children &lt;2 years</td>
<td>– (B)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Healthy children ≥6 years</td>
<td>+ (A)</td>
<td>++ (B)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Pregnant women/newborn</td>
<td>– (B)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>All elderly (≥65 years)</td>
<td>+ (A)</td>
<td>++ (B)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Elderly without co-morbidity</td>
<td>NE</td>
<td>– (B)</td>
<td>– (B)</td>
<td>– (B)</td>
<td>– (B)</td>
</tr>
<tr>
<td>Elderly in homes</td>
<td>– (B)</td>
<td>– (B)</td>
<td>– (B)</td>
<td>– (B)</td>
<td>– (B)</td>
</tr>
<tr>
<td>Health care workers/elderly in homes</td>
<td>– (B)</td>
<td>– (B)</td>
<td>– (B)</td>
<td>– (B)</td>
<td>– (B)</td>
</tr>
<tr>
<td>COPD</td>
<td>++ (B)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Bronchiectasis/mucoviscidose</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>++ (B)♯</td>
</tr>
<tr>
<td>Diabetes/renal disease</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Liver disease</td>
<td>– (B)</td>
<td>++ (B)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>HIV</td>
<td>NE</td>
<td>++ (B)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Hematological malignancies</td>
<td>– (B)</td>
<td>++ (B)</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Chemo, lupus, RA, transplant</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
</tbody>
</table>

++, Significant effect ≥50%; +, significant effect ≤50%; +/−, conflicting evidence; −, no effect; NE, no evidence, not estimated.
(A), (B), (C): grade qualification.
♯ In secondary prevention.

Because most of the studies in pregnant women were in subtropical and less developed countries, high-quality studies to confirm these effects in temperate regions are urgently needed.

One study [29] investigated the effectiveness of influenza vaccination among the non-recipients of the vaccine living in the same community as vaccinated children; these data demonstrated a protective effect on transmission.

4.2. Limitations of our review

There are some limitations inherent to the strategies used in this project. Our own search focused only on published, peer-reviewed data. Studies that were published in languages other than English and French were excluded, but several studies in Spanish (N = 16), Russian (N = 9) and Chinese (N = 8) have been conducted. Most of these did not fulfil our inclusion criteria, with the exception of one Chinese publication [58], which was a meta-analysis of studies published between March 1998 and May 2008 in Chinese journals about the effectiveness of TIV in all age groups. The exclusion of unpublished trials and language restrictions might bias our final conclusions.

Other limitations were inherent to the original studies included in our review. First, investigators in the studies that we reviewed used vaccines with different immune properties. Originally, these were inactivated whole virus vaccines grown in chicken eggs and insufficiently purified, which had many side effects. The recent development of subunit, split-virion, purified whole virus, with or without adjuvant (MF59, Al, virosomes, AS03) or DNA-inactivated vaccines have produced better immune inducing properties and fewer side effects [5]. This may change the effect sizes and affect the comparability of the studies (both in the systematic reviews and primary studies) in this review.

Second, vaccines are administered with different schedules (1–2 administrations) according to age, different quantities of antigen per dose (7.5–30 µg) and different routes of administration (intranasal, intramuscular or intradermal), which all may cause different immune responses and consequently different efficacies. It is impossible to generalise the results of studies of old vaccine types to these new vaccine types. The results of trials with new vaccines may change our overall conclusions.

Third, influenza vaccines contain at least three strains (two influenza A and one B), which are updated each year according to surveillance of A/H1N1, A/H5N1, A/H3N2 and B strains by the World Health Organization (WHO) [1]. These strains receive the label of seasonal (recurring) or pandemic (occurring for the first time). The prediction of the WHO does not always correspond to the circulating wild type strains, and the match level has a significant influence on vaccine efficacy. Furthermore, different circulating influenza viruses may exhibit different attack rates and virulence in different age and risk groups annually.

Fourth, outcomes such as proven influenza incidence are measured in different ways with different sensitivities. The laboratory evidence of influenza infection has changed over time. Initially, infection was confirmed by a four-fold increase in influenza antibody titre compared to viral culture; more recently, PCR confirmation has been used. A titre increase is induced by vaccination alone, making the chance of finding a four-fold titre increase higher in the control group, and efficacy might therefore be over-estimated [59]. However, viral culture is less sensitive than PCR. In addition, the clinical case definition of IILI differs from study to study and shows a wide variety in sensitivity.

Fifth, the design, conduct and reporting of the influenza studies on which guideline recommendations are based have differed over the years in several respects (RCTs versus cohort studies, blinded versus unblinded, comparison with placebo or no intervention, clinical outcome versus immune response), and different clinical outcomes and unclear diagnostic definitions of complications have also been common [3]. This mix of study designs makes comparisons between studies difficult. More specific limitations are observed in the studies of influenza vaccination in the different target groups with specific co-morbidities, including poor reporting, small numbers of participants, unclear outcome definitions and high drop-out rates, which makes the validity of these results questionable.

Finally, Jefferson et al. [2] did not retrieve the studies of Monto et al. [20] and O'Neill et al. [21,22] in their systematic review of healthy adults, although they fulfill their inclusion criteria and should have been found by applying their search strategy. A special, and troublesome, warning was included in their review regarding the better results found in industry-funded trials compared to
publicly funded trials, which makes it even more challenging to draw sound conclusions.

4.3. Results in perspective

Despite the shortcomings in the existing evidence, current guidelines recommend annual influenza vaccination among several target groups. They differ in the specification of these groups and in age category delineation. For example, there are differences between the American and European guidelines and even between European and Belgian guidelines.

Almost all countries support the vaccination of individuals 65 or older, specifically including residents of nursing homes and other long-term care facilities. Some countries even lowered this age range, to 60 years in Germany, Poland, Ireland and the Netherlands and to 50 years in the USA, Austria, Poland and Belgium [8,9,60]. A wide consensus suggests that a threshold of 65 years is a reasonable minimum recommendation for policy decisions [8,61].

People (other than 6 months) with chronic medical conditions that indicate a greater risk of influenza-related complications are generally considered to be an important target group, although specifications regarding who belongs to certain risk groups differ from one country to another. Children between 6 months and 18 years who receive chronic ASA therapy should be included [8,60,61]. Exceptions for mild chronic conditions such as asymptomatic HIV infection, chronic respiratory disease due to isolated mild asthma (not resulting in hospitalisation over the last five years) and chronic cardiovascular disease due to isolated mild hypertension have been proposed [8]. Pregnant women are at higher risk and became a target group for immunisation, especially during the A/H1N1 pandemic: Austria, Belgium, Cyprus, Denmark, Estonia, Italy, Portugal, Slovakia, Spain in Europe and the USA specifically recommend vaccination for pregnant women [8,9,60]. There is no EU or WHO consensus on the influenza vaccination of children. Some countries (such as Austria, Estonia, Finland, Latvia, Slovakia, Slovenia) recommend vaccination between 6 months and 2 years of age. Others expand the range to 18 years (Austria), which is also the recommendation in the USA. In Austria, and in the USA as of 2010, the immunisation of the entire population (over the age of 6 months) is recommended [8,9].

The immunisation of individuals who share a household with people at a higher risk for influenza complications is recommended in a few countries (Belgium [60], USA [9], WHO [61]), but there is little evidence of its effectiveness. The immunisation of health care and other care workers is recommended in many EU countries and in the USA [8,9,60], but again, there is little evidence that such immunisation is effective in protecting patients.

Immunisation of special groups such as essential service workers, veterinarians and individuals who work with poultry and pigs is recommended in a few countries. These recommendations aim to avoid productivity losses among important service workers and prevent reassortment between human and animal influenza strains [60].

Jefferson et al. highlighted the lack of solid evidence of the effectiveness of influenza vaccination on the prevention of pneumonia, hospitalisation and mortality in all age groups [2,37,38]. Recently, an excess mortality of 7.8% during flu virus circulation and a corresponding vaccine effectiveness of 4.6% (95%CI: 0.7–8.3) on total mortality averaged over nine years was estimated by Fireman et al. among 273,000 elderly individuals (65 years and older) in CA, USA [62]. This corresponds to 4000 individuals vaccinated to prevent one death (i.e., number needed to treat). When the cause of death was cardiovascular or respiratory disease, the effectiveness increased to 8.5% (95%CI: 3.3–13.4), but among individuals 80 and older, the effectiveness dropped to a statistically insignificant 3.9% (95%CI: −1.6 to 9.0) [62]. In the same population of elderly individuals (65 years and older), Baxter et al. estimated an adjusted effectiveness of 8.5% (95%CI: 3.3–13.5) in preventing hospitalisation for pneumonia or influenza, which corresponds to approximately 2900 elderly vaccinated to avoid one hospitalisation. Effectiveness dropped to 5% (95%CI: −1% to 11%) among those 75 years old or older [63]. No effectiveness of influenza vaccination on the prevention of pneumonia in immune-competent elderly people could be found in a nested case-control study by Jackson et al. after adjusting for frailty and co-morbidities [64]. These numbers seem to better reflect reality and are very important when adjusting cost-effectiveness studies and guidelines [65].

This evidence suffers from a variety of gaps and limitations, making practical interpretation difficult. Policymakers have to weigh many parameters such as the validity of the evidence, the clinical relevance of the outcomes, the effect size expressed as number needed to treat and the possibility and validity of extrapolating the results, before they can begin to formulate valuable recommendations [66,67]. Especially when evidence regarding important outcomes such as hospitalisation and mortality is scarce and conflicting, two ways to deal with it emerge. First, if no reliable evidence can be found, no recommendation should be made. Alternatively, recommendations could be made based on indirect evidence. If efficacy against influenza has been proven, then a theoretical profit based on hospitalisation or mortality could be assumed, as these outcomes occur as a direct consequence of influenza cases. In this case, estimating effect sizes remains guesswork. As a consequence, the cost benefit studies that underpin final decision making will be based on several assumptions, which make them volatile and manipulable [68]. In contrast, the low cost and the lack of serious harm of the vaccine favour their continued use. Only weak recommendations can be made based on these decision processes, along with strong advice to invest in further research, consider quality of life issues and respect the preferences of the patients [67,69].

4.4. Recommendations for the future

In many European countries, the existing guidelines might not fully appreciate the best current evidence. As we have shown, the grades of the evidence upon which guidelines are based need to be reconsidered. A modest effect on hospitalisation and mortality in all elderly between 65 and 80 years might support yearly vaccination in this age group. As no significant effect on hospitalisations and mortality has been shown among individuals 80 and older in epidemiological studies with adequate correction for confounding variable [7,62], yearly influenza vaccination (with the current inactivated vaccines) could probably be questioned in this age group. New strategies should be explored, such as vaccinating school-aged children to diminish the burden of influenza in the entire community [29] or the introduction of new vaccines that might enhance the immune response, the efficacy and the effectiveness in this older age group. Pregnant women and their newborns might benefit from influenza vaccination, but large studies in temperate climate zones are still needed. The benefit of vaccinating healthcare workers to protect their patients remains highly questionable and should not be mandatory at present. The benefit of influenza vaccination in individuals with co-morbidities or predisposition to severe complications has not yet been demonstrated, and many doubts about its utility remain. In this case, indirect evidence could support a weak recommendation.

Despite the weak evidence for these guidelines, they might obstruct future placebo-controlled studies by introducing ethical objections [38,45]. When inactivated influenza vaccines try to enter the market (e.g., vaccines for new influenza strains such as H5N1 or H1N1, vaccines including adjuvants and/or vaccines administered by new injection methods), they are only required to
prove their equivalency to existing vaccines in terms of humoral immune response. Placebo-controlled trials or non-inferiority trials among clinical outcomes have not been required, although regulatory agencies recently changed this policy by requiring placebo-controlled efficacy studies post-approval. Thus, inactivated influenza vaccines might be improved in several ways. Future studies must focus on other production methods to shorten the vaccine production cycle by avoiding the use of eggs [26,70]. New vaccine formulae, for example, the inclusion of adjuvants, might enhance immune responses. Searching for vaccines that could broaden immune targeting to secretory IgAs, anti-neuraminidase antibodies, cellular-mediated immune systems and anti-M2 antibodies might improve the efficacy and the duration of the immune response to influenza vaccination [70]. Administration routes other than intramuscular injection, such as intraderal injection, intranasal and sublingual administration and aerosol application, all have the potential to improve the current vaccines [4] but presently lack Grade A evidence.

There remains an urgent need for good quality, randomised, placebo-controlled trials run over several seasons and rigorously reviewed and audited by regulatory agencies [45]. Future influenza efficacy/effectiveness studies need to fulfil the following criteria: enough participants from specific target groups; focus on important clinical outcomes such as influenza, pneumonia, hospitalisation, mortality and adverse events; and rigorous study design with extra attention paid to avoiding selection bias [71]. Special studies are needed to evaluate the effect of influenza vaccination on the transmission of influenza and concomitant infections such as pneumococcal pneumonia.

5. Conclusion

Despite the large number of reviews and RCTs addressing value of influenza vaccination, many limitations make the conclusions in present guidelines for different target groups questionable. The inactivated influenza vaccine shows efficacy in healthy adults and children (>6 years, Grade A evidence). No efficacy has been shown in young children (less than 2 years) or institutionalised elderly. Inconsistent results are found in studies among children younger than 6 years, individuals with COPD, institutionalised elderly, elderly with co-morbidities and healthcare workers in elderly homes, which might be explained by unknown biases. There is a striking lack of sound evidence for the effect of vaccination on influenza complications such as pneumonia, hospitalisation and mortality among individuals with co-morbidities. The vaccination of pregnant women might be beneficial for their newborns. Vaccination of children might be protective in non-recipients of all ages living in the same community. There remains an urgent need for good quality, publicly funded, randomised, placebo-controlled trials that run over several seasons. The existing guidelines might not fully incorporate the best available current evidence and should be adapted accordingly.

Role of the funding source

This systematic literature search was funded by the government- al organization NIHDI (National Institute for Health and Disability Insurance) in Belgium. The sponsor only played a role in study design; but had no influence on the collection, analysis, and interpretation of data; on the writing of the report or on the decision to submit the paper for publication.

Acknowledgements

We are grateful for the valuable suggestions made by Prof. Pierre Van Damme, head of the Vaccine and Infectious Disease Institute (VAXINFECTIO) of the University of Antwerp.

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