ELSEVIER

Journal of Clinical Epidemiology 62 (2009) 677−686

Journal of Clinical Epidemiology

Inactivated influenza vaccines: Methods, policies, and politics

T. Jefferson*, C. Di Pietrantonj, M.G. Debalini, A. Rivetti, V. Demicheli

Cochrane Vaccines Field, ASL AL, via Venezia 6—15100 Alessandria, Italy

Accepted 1 July 2008

The critical evaluation of existing policies is necessary, but fraught with difficulties. Perhaps the best example of this statement are policies identifying influenza as a worthwhile target for prevention using trivalent inactivated vaccines (TIVs). At a first glance, influenza vaccines are a global intervention and extensive vaccination policies are in place in many countries [1]. Most policy-makers do not dispute the burden of influenza disease and its complications, nor the effectiveness of TIV in dealing with such a burden. However, a suite of Cochrane reviews of the effects of TIV and detailed methodological work [2−5] have cast doubt on the scientific basis of the current consensus.

The issue is very complicated, but perhaps the starting point is the clinical similarity between influenza-like illness (a syndrome caused by 200-odd known and unknown microorganisms) and influenza (caused by influenza A and B). In any one year, very few cases of influenza-like illness are actually caused by influenza viruses and as such would be amenable of prevention by specific vaccines. The two are not clinically distinguishable and even periods of known higher influenza virus circulation are not predictive, as other organisms (such as rhinoviruses, RSV and parainfluenza viruses) are co-circulating [6,7]. No one knows what the precise burden of influenza morbidity or mortality is as no surveillance system is capable of distinguishing routinely between influenza and influenza-like illness and no one carries out routine autopsies to identify a microbiological cause of death [8,9]. So, guesswork rules. These simple facts are seldom mentioned to physicians and the media, who are instead told that current measures (e.g, vaccination) are sufficient to control the problem, although no one quite knows the size of the problem and few seem to understand its multiagent nature.

Critical evaluation of current evidence of the effects of TIV is also difficult, as Nelson et al. show [10]. Cochrane and other systematic reviews have shown overall poor quality methods of relevant studies, a lack of randomized controlled trials of sufficient duration, and power to detect and effect on serious outcomes (such as hospitalization and death) and over-reliance on nonrandomized studies [11−18].

This triad of problems has different implications for different age groups. In children below 2 years of age, there is no evidence that TIV's effects differ from those of placebo (possibly a reflection of the rarity of the disease and its complications). In older children, adolescents, and healthy adults, better quality randomized studies show an effect against cases of influenza (but not its complications or its transmission). The estimates are very sensitive to the match between circulating antigen and vaccine content and viral circulation levels. This is a logical finding as the better the match and the higher the circulation, the more effective TIVs should be. In people aged 65 years or older, systematic reviews report an implausible sequence of effects, with TIV apparently effective for the prevention of nonspecific outcomes, such as death from all causes, but not for the prevention of influenza or death caused by pneumonia and influenza. As the reviews and the work by Nelson et al. and Simonsen et al. point out [9−18], the most likely explanation for such findings is confounding. This is especially likely because in the general elderly population, the bulk of evidence (hundreds of thousand observations) comes from poor quality, large, retrospective, data-linked cohorts in which data had been collected for other purposes. Twenty-two out of 40 retrospective cohort studies published up to 2006 fail to report either vaccine content, or degree of antigen matching, or both, making generalizing from these large data sets an arduous task. The quoted triad and a myriad of other smaller but linked problems would lead a critical observer to conclude that the effects of TIV are either slight and either do not justify the mammoth yearly efforts to implement vaccination programs or justify urgent evaluation with robust randomized designs.

Strangely, these problems do not seem to be taken into consideration by some policy-makers. This apparently strong statement needs, however, to be justified.

After a brief Web search for up-to-date policy documents and related papers in English or German, we

* Corresponding author. Tom Jefferson, FFPHM, Cochrane Vaccines Field, Via Venezia 6, 15100 Alessandria, Italy; +39-0329-2025051 (mobile).

E-mail address: jefferson.tom@gmail.com (T. Jefferson).

0895-4356/09/$ − see front matter
doi: 10.1016/j.jclinepi.2008.07.001

Table 1
Influenza prevention policy documents and main linked documents—key points summary

Country	Policy Document (reference)	Authorship	Methods	Quality[a]	Competing interest[b]	Bibliography	Notes
Global	WHO Position Paper 2005 [1]	No	No	No	No	No	Linking to evidence contained in other policy documents
UK	Green Book [19]	Yes	No	No	No	Yes (directly linked to the text)	Appears strictly linked to JCVI Annual Report 2005–2006 [25]. Inconsistent referencing
UK	JCVI Annual Report 2005–2006 [20]	Yes	No	No	Yes	No	
Australia	Australian Immunization 2003 (8th edition) [21] and 2008 (9th edition) update [22]	Yes (both 8th and 9th editions)	No in 8th edition, yes in 9th edition	No (both 8th and 9th editions)	No (both 8th and 9th editions)	Yes (directly linked to the text)	Inconsistent referencing and linking to evidence contained in other documents. Several unsupported statements
USA	ACIP 2007 [23]	Yes	Yes	No	No	Yes (directly linked to the text)	
CA	NACI 2007 [24]	Yes	No	No	No	Yes (directly linked to the text)	
Germany	STIKO 2007 [25]	Yes	No	No	No	No	
Germany	Recommendations of Robert Koch Institut (RKI), updated to February 2006 [26]	Yes	No	No	No	No	
Germany	STIKO Adverse Events 2007 [27]	Yes	No	No	No	Yes (without direct link to the text)	The citations remand to other documents
Germany	STIKO MS 2003 [28]	Yes	No	No	No	Yes (directly linked to the text)	
Germany	STIKO ASTHMA-COPD 2003 [29]	Yes	No	No	No	Yes (directly linked to the text)	

[a] Presence of methodological quality assessment of single cited reference.
[b] Presence of authors' competing interest statement in the policy document.

Box 1

Example of confusion between efficacy and effectiveness of the vaccines
WHO [1]

"*In industrialized countries, influenza vaccines offer approximately 70–90% protection against clinical disease in healthy adults*

Page 280

"*However, their respective protective efficacies are believed to be similar and, provided there is a good antigenic match, they will prevent laboratory-confirmed illness in approximately 70–90% of healthy adults*."

Page 284

Comment: the apparent confusion between efficacy (against laboratory-confirmed influenza) and effectiveness (against influenza-like illness) of the vaccines presents an optimistic picture of their performance

Example of inconsistent logic and factual mistakes
Germany (RKI) [26]

The German RKI justified its recommendation for vaccinating in pregnancy as follows:

"Zur Influenza-Impfung in der Schwangerschaft wird seitens der pharmazeutischen Unternehmen darauf verwiesen, dass gezielte Studien zur Sicherheit der Impfung bei Schwangeren fehlen

Schäden aber nicht bekannt sind, die Impfung ist daher nicht kontraindiziert

"*Regarding influenza immunisation during pregnancy, pharmaceutical companies report that there are no studies investigating (vaccine) safety during pregnancy, therefore harms are unknown, therefore there are no contraindications*" [to their use, translator's note].

Comment: This is factually wrong as there is at least one prospective cohort study assessing safety of influenza vaccines in pregnancy (Munoz, 2005).

In addition, the message appears to be: no known harms = benefits

Munoz FM, Greisinger AJ, Wehmanen OA, et al. Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol 2005;192:1098–106.

Example of selective citation within the same study
USA (ACIP) [23]

In the CDC/ACIP policy document (chapter on influenza vaccines in children), the results of the 2-yr placebo-controlled randomized trial by Hoberman et al. are cited only for the year in which the vaccine appeared effective:

"However, a large study conducted among children with a mean age of 14 months did not provide evidence of TIV efficacy against acute otitis media (123, Hoberman et al.), although efficacy was 66% against culture-confirmed influenza illness."

Comment: The Hoberman study, however, considered two seasons, not one. Hoberman et al. write:

"*The efficacy of the vaccine against culture-confirmed influenza was 66% (95% confidence interval [CI], 34%–82%) in 1999–2000 and −7% (95% CI, −247% to 67%) in 2000–2001; however, influenza attack rates differed between these 2 periods (in the placebo group, 15.9% and 3.3%, respectively).*"

Hoberman A, Greenberg DP, Paradise JL, Rockette HE, Lave JR, Kearney DH, et al. Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children: a randomized controlled trial. JAMA 2003;290(12):1608–16.

Example of inappropriate use of evidence to support the recommendation to vaccinate all elderly persons in nursing homes
Australia [22]

The Australian policy document (9th edition, 2008 version, at page 192) justifies the recommendation to vaccinate all elderly nursing homes residents yearly as follows:

"*(v) Residents of nursing homes and other long-term care facilities, due to high rates of transmission and complications during outbreaks* [3,9–13,27]."

Comment: the bibliography refers to two systematic reviews. The review by Gross et al. which is out of date and the overview by Demicheli et al. assessing the effectiveness of influenza vaccines in healthy adults which concluded that do-nothing was the most cost-effective option. Five single studies of different designs are cited, only one of which (Carman) was in nursing homes. The latter concluded that the vaccine was effective even in the absence of influenza circulation.

[3] Carman WF, Elder AG, Wallace LA, et al. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. Lancet 2000;355:93–97. See comment above.

(*Continued on next page*)

Box 1 (*Continued*)

[9] Ruben FL, Jackson GG. A new subunit influenza vaccine: acceptability compared with standard vaccines and effect of dose on antigenicity. J Infect Dis 1972;125:656−64.

[10] Christenson B, Lundbergh P, Hedlund J, Örtqvist A. Effects of a large-scale influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: a prospective study. Lancet 2001;357:1008−1011.

[11] Nichol KL, Wuorenma J, von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. Arch Int Med 1998;158:1769−1776.

[12] Govaert TM, Thijs CT, Masurel N, et al. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. JAMA 1994;272:1661−1665.

[13] Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. Ann Int Med 1995;123:518−527.

[27] Demicheli V, Jefferson T, Rivetti D, Deeks J. Prevention and early treatment of influenza in healthy adults. Vaccine 2000;18:957−1030.

Example of optimistic claims made as to the overall reliability of the policy document
UK [19]

The Introduction to the 2006 edition in the UK's Department of Health Web page to the ''Green Book'' states:

''*All health professionals that give immunisations or provide information and advice on them will find that this edition of the Green Book has been fully updated and gives a comprehensive and invaluable source of current information.*''

Comment: in the absence of a methods section and with only 12 references on influenza vaccines, this claim is misleading.

Example of erroneous attribution of conclusions to a study
UK [19]

From the ''The Green Book'', page 188:

''*Protection afforded by the vaccine lasts for about one year. In the elderly, protection against infection may be less, but immunisation has been shown to reduce the incidence of bronchopneumonia, hospital admissions and mortality (Wright et al., 1977).*

Comment: The study by Wright et al. cited at the end of this sentence is a multicenter trial conducted on 2326 healthy children to evaluate local (e.g, mild local erythema, tenderness) and systemic (e.g, febrile reaction) harms and antigenicity of vaccine. Incidence of bronchopneumonia, hospital admissions, and mortality in the elderly population are not assessed in this study.

Wright PF, Thompson J, Vaughn WK, Folland DS, Sell SH, Karzon DT. Trials of influenza A/New Jersey/76 virus vaccine in normal children: an overview of age-related antigenicity and reactogenicity. J Infect Dis 1977 Dec;136 Suppl:S731−S741.

Example of logic inversion
Canada (NACI) [24]

The NACI document justifies its recommendations to vaccinate pregnant women as follows:

''*There are no randomized controlled trials to assess the efficacy of influenza vaccine in pregnancy. A retrospective review of vaccinated and non-vaccinated pregnant women in a large managed-care organization showed no difference in the occurrence of ILI or hospitalizations with principal diagnoses of influenza or pneumonia, but it was underpowered to do so since only 7% of women had been immunized* ([25], Black 2004).''

Comment: the results of Black 2004 are quoted appropriately (''*Although the immunogenicity of influenza vaccination in pregnancy in mother and infant has been well documented, in this study, we were unable to demonstrate the effectiveness of influenza vaccination with data for hospital admissions and physician visits. One possible interpretation of these findings is that typical influenza surveillance measures based on utilization data are not reliable in distinguishing influenza from other respiratory illness. Hospitalizations for respiratory illness were uncommon in both vaccinees and nonvaccinees*''). However, the policy document text recommends vaccination of pregnant women in the absence of evidence of effectiveness. The concept here seems to be: no apparent effect = benefit.

Black SB, Shinefield HR, France EK, Fireman BH, Platt ST, Shay D. Vaccine Safety Datalink Workgroup. Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants. Am J Perinatol 2004; 21(6):333−339.

(*Continued on next page*)

Box 1 (*Continued*)

Example of a statement not based on any identifiable scientific evidence
WHO [1]

"*Influenza vaccination in pregnancy is considered safe and is recommended for all pregnant women during the influenza season. This recommendation is motivated not only by the potential severe course of influenza during pregnancy, but also in order to protect infants against influenza during their vulnerable first months of life.*"

Comment: the statement is difficult to check as the text of the 2005 WHO policy document has no bibliographical references. In any case, the only study assessing harms in pregnant women (Munoz 2005) is not quoted or was not available at the time of writing.

identified one worldwide (World Health Organization) and five national (United States, Canada, United Kingdom, Germany, and Australia) documents on influenza vaccination. We chose documents in languages known to us, containing sufficient detail to allow appraisal of the sections presenting scientific evidence used in decision making. We concentrated our attention on the paragraphs reporting the absolute (i.e., vs. placebo or no intervention) effects (i.e., effectiveness and safety) of influenza vaccines on which decisions appeared to have been made. Understanding how scientific evidence was identified and used in writing these documents is an impossible task. Of six policy and related documents (Table 1), two did not contain bibliographical references (Germany's STIKO 2007 [25] and the UK's JCVI Annual Report 2005–2006 [20]), a further two present bibliography that are unlinked to the text (Germany's STIKO Adverse Events 2007 [27], WHO Position Paper 2005 [1]) and partly relate to other policy documents rather than original research. Two other policy documents (the UK's Green Book 2006 [19] and the Australian immunization documents 2003 [21] and 2008 [22]) reference in an inconsistent way throughout the assessed paragraphs. For example, the Australian document at times contains statements which were either unreferenced or supported by references to other policy documents [22]. What is most striking, however, is that none of the documents contains a methodological quality assessment of the cited references to studies. Only one supporting document (JCVI Annual Report 2005–2006 [20]) contains a declaration of conflicts of interest of its authors and four of six main policy documents (Germany's STIKO [25], Canadian NACI [24], UK's Green Book [19], WHO [1]) do not contain a Methods section. Two documents have a Methods section (US ACIP [23], Australian immunization document [22]), but these contain statements that do not allow either comprehension or reproduction of pathways used for assembling, assessing, and synthetizing evidence. Within all policy documents there are misquotes, selective citation of pieces of text or results of referenced studies, and factual mistakes in reporting either estimates of effect or the conclusions of authors of the original studies, inconsistent logic, and contradictions (Box 1). All documents show extensive citation bias. For example, the section on evidence efficacy and effectiveness of the vaccines in children of the US ACIP document cites 10 comparative studies and one noncomparative study out of a possible total of 78, and the reasons for the selection are unclear [23]. Precise assessment of the other documents is difficult because of the lack of consistency in citations or their complete absence. In all cases, however, cited evidence is considerably thinner than primary studies included in systematic reviews or identified through a casual PubMed search.

One would expect evidence from systematic reviews to be used to ground policy as in other policy areas. Reviews provide powerful synthesis of all available evidence spread over several seasons (which avoids the trap of interpreting results one season at a time and smooths out the effects of variability in viral circulation and vaccine content). Reviews weigh evidence by its methodological quality, which as we have seen is a major issue in interpreting the results of TIV studies.

Not surprisingly, then, systematic reviews are cited in five of the six policy documents [22–24] and in STIKO-related documents [28,29] (Table 2). Their citation is, however, often incorrect, or haphazard and many of the most up-to-date versions of the reviews are not quoted. In one case, the STIKO document [29] cites a Cochrane review of pneumococcal vaccine as corroboration of the performance of influenza vaccines in Chronic Obstructive Airways Disease. Systematic and descriptive reviews are used interchangeably, although the former have Methods chapters and conduct quality assessment of included studies and the latter do not. In addition, Cochrane reviews are updated every 2 years, whereas one of the most cited reviews by Gross et al. is 15 years out of date [30].

Such startling findings make us wonder why the issue of scientific evidence is not taken seriously by policy-makers at such high levels. The answer may be very complex and involve many actors with different motives and responsibilities. The methodological solutions proposed by Nelson et al. [10] are only a small provisional "patch" on the emperor's large naked body. We wonder whether policymakers seriously intend reducing the burden of acute respiratory infections. If they do, we have effective, acceptable, and cheap interventions (such as handwashing, distancing, and mask wearing) which could be used all together in periods of danger [31].

Table 2
Use of evidence from systematic reviews

Policy document	Review	Context
Australian immunization handbook 2008 (9th edition) [22]	Demicheli 2004 [Demicheli V, Rivetti D, Deeks JJ, Jefferson TO. Vaccines for preventing influenza in healthy adults. [update of Cochrane Database Syst Rev 2001;(4):CD001269]. Cochrane Database Syst Rev 2004;(3):CD001269. doi:10.1002/14651858.CD001269.pub2.]	Cited in general considerations about vaccine effectiveness in adults (page 188):'' In healthy persons <65 yr of age, influenza vaccine is 70% to 90% effective when the antigenic match between vaccine and circulating viruses is close.'' Also cited in recommendations in ''Workers in other industries'': ''…but the overall impact over time is judged to be cost-saving in several settings'' [on page 193, together with Centers for Disease Control and Prevention (CDC)]. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). [Erratum appears in MMWR Morb Mortal Wkly Rep 2006 Jul 28;55(29):800]. MMWR Morb Mortal Wkly Rep 2006;55(RR-10):1–42)]. Comment: The first citation is incomplete because the authors of the Policy Document don't specify outcomes of interest and the high efficacy estimate (90%) is not mentioned in the review. The second citation does not report the second part of the statement from the original text in the Abstract Conclusions the review authors stated that: ''*…However, they are not as effective in reducing cases of clinical influenza and number of working days lost.*''
	Demicheli 2000 [Demicheli V, Jefferson T, Rivetti D, Deeks J. Prevention and early treatment of influenza in healthy adults. Vaccine 2000;18:957–1030].	Cited in Recommendations ''Residents of nursing homes and other long-term care facilities'' at page 192 with another review (Gross 1995) and five studies with different designs and also cited in ''Adverse events'' (page 193). Comment: It is unclear how this review would support recommendations for residents in nursing homes. The authors of this review (which includes studies with participants 14–60 years old) conclude that:'' On current evidence we conclude in healthy adults aged 14–60 the most cost-effective option is not to take any action.'' With regard to citation in ''Adverse events'' together with: Margolis KL, Poland GA, Nichol KL, et al. Frequency of adverse reactions after influenza vaccination. American Journal of Medicine 1990;88:27–30. (no-comparative study). The authors of this review conclude that: ''*However, when safety and quality of life considerations are included, parenteral vaccines have such low effectiveness and high incidence of trivial local adverse effects that the trade-off is unfavourable.*''
	Gross 1995[Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. Ann Int Med 1995;123:518–527]	Cited in specific recommendations for immunization of subjects aged over 65 years (page 190). and cited in the Recommendation ''Residents of nursing homes and other long-term care facilities'' (on page 192).

		Comment: this is a dated meta-analysis carried out on 18 studies in institutionalized and two in non institutionalized elderly and a summary of results of three case-control studies and two cost-effectiveness studies and one randomized placebo-controlled trial. There is a statement in Discussion: "*However if the vaccine is effective in the predominantly institutionalized population studied, it is even more likely to be effective in the healthier elderly persons residing in the community, who are presumably less likely to have immune system defects.*" For citation in residents of nursing homes: The meta-analysis has been conducted on 18 studies carried out on institutionalized elderly and the true causes of hospitalisation and death are unclear. The lack of standard definitions of outcomes, and the possible presence of selection bias indicate the need to interpret the results with caution.
	Poole 2006 [Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. [update of Cochrane Database Syst Rev 2000;(4):CD002733]. Cochrane Database Syst Rev 2006;(1):CD002733. doi:10.1002/14651858.CD002733.pub2.]	Cited twice in recommendation for immunization in subjects ⩾6 months of age affected by chronic respiratory conditions (paragraph iii on page 190): suppurative lung disease, bronchiectasis and cystic fibrosis, and about exacerbations of chronic obstructive pulmonary disease (COPD). Comment: Poole 2006 is a review conducted on patients with COPD.
	Cates 2004 [Cates CJ, Jefferson TO, Bara AI, Rowe BH. Vaccines for preventing influenza in people with asthma. [update of Cochrane Database Syst Rev 2000;(4):CD000364]. Cochrane Database Syst Rev 2004;(2):CD000364. doi:10.1002/14651858.CD000364.pub2.]	Cited in recommendations for subjects affected by asthma (page 191) about the lack of data of RCT *"to define efficacy across the whole spectrum of asthma*." Comment: this review concludes that it is difficult to assess the protective effect of influenza vaccine on asthma exacerbations. However, in the policy document this is stated as a fact. Interpretation of Policy Document recommendations: Influenza vaccine is "*an important part of routine care*" in patients with severe asthma (Policy Document) The degree of protection of influenza vaccine "across the whole spectrum of asthma is uncertain" (In Policy Document quoting the Cates et al. Review)." "…But influenza can cause severe exacerbations of Wheezing" (Policy Document). If the vaccine confers uncertain protection, we do not understand this recommendation. The authors of the policy document seem to be confusing cause with benefit from vaccination.
ACIP 2007 [23]	Thomas 2006 [Thomas RE, Jefferson TO, Demicheli V, Rivetti D. Influenza vaccination for health-care workers who work with elderly people in institutions: a systematic review. Lancet Infect Dis 2006;6:273−279]	Vaccination of HCW and prevention of death cases in institutionalized elderly (page 19, left column, lines 19−22). Comment: even if the authors report evidence about lower incidence of all-causes death and death after pneumonia among vaccinated subjects, they also caution about the likely effects of strong selection bias.

(Continued)

Table 2
Continued

Policy document	Review	Context
NACI 2007 [24]	Rivetti 2006 [Rivetti D, Jefferson T, Thomas R, et al. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev 2006;3:CD004876]	Immunology and efficacy in the elderly (page 14, left column, lines 9 from bottom): "*Systematic reviews have also demonstrated that influenza vaccine decreases the incidence of pneumonia, hospital admission and death in the elderly.*" Comment: again the authors' considerations about possible selection bias are not taken into account. "*The apparent high effectiveness of the vaccines in preventing death from all causes may reflect a baseline imbalance in health status and other systematic differences in the two groups of participants.*"
	Langley 2004 [Langley JM, Faughnan ME. Prevention of influenza in the general population. Can Med Assoc J 2004;171(10):1213–1222]	Paragraph "immunology and efficacy" about efficacy against laboratory-confirmed and clinical influenza (page 14). Comment: The review's authors did not carry out a pooled analysis, but give only the higher and lower observed rate value of all data sets (15 studies on children) for influenza-like illness and serologically confirmed influenza. In a poor quality data set such as this absence of quality assessment is crucial in interpreting results in case of good matching.
	Demicheli 2004 [Demicheli V, Rivetti D, Deeks JJ, Jefferson TO. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 2004;(3):CD001269]	Paragraph "immunology and efficacy": effectiveness (or efficacy) Comment: an update of this review has been published in issue 2 of the 2007 Cochrane Library. However, when we consider "influenza illness" as serologically confirmed influenza (2004 version), vaccine efficacy in presence of good matching in comparison with placebo or other vaccine was estimated to 55% (95%CI from 19% to 76%) for live aerosol vaccine and 76% (95% CI from 59% to 86%) for inactivated parenteral vaccine.
	Poole 2006 [Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2006;(1):CD002733.	Paragraph "immunology and efficacy" about reduction of exacerbations in persons with COPD (page 14, left column, lines 5–6 from the bottom). Comment: Exacerbation episodes were reduced considering the whole and the later follow up period (that includes probably an influenza epidemic). Number of subjects who experienced at least one episode of exacerbation associated with influenza virus isolation was significantly lower among vaccinated (two data sets, $N = 180$).
STIKO MS [28]	Rutschmann 2002 [Rutschmann OT, McCrory DC, Matchar DB. Immunization and MS: a summary of published evidence and recommendations. Neurology 2002;59:1837–1843]	Cited in paragraph 4: "Position and recommendations of other workgroups": "*flu immunisation should be discussed with each MS-patient because of its potential individual advantage.*" Comment: Data presented in this systematic review do not allow to exclude nor to accept an association between influenza vaccine and MS-onset within 6 months after immunization. Incidence of clinical influenza in subjects affected by MS was also not statistically different among placebo and vaccine recipients.
STIKO ASTHMA-COPD [29]	Cates 2004 [Cates CJ, et al. (2004): Vaccines for preventing influenza in people with asthma. Cochrane Database Syst Rev 2004;(2):CD000364]	Cited in the first paragraph "Influenza immunisation for patients with Asthma," in which is reported that safety and effectiveness of flu vaccine in subjects with asthma is "well proved" for children and old subjects. Evidence in other age classes would be provided from observational studies.

Comment: this Cochrane Review is cited together with other studies having different design and investigating different outcomes. The text is very short and does not take into account distinction between safety (short-term asthma exacerbation) and effectiveness (exacerbation in consequence of flu infection). From results of this review there were no significant increases in asthma exacerbation after split-virus immunization but "*Significant benefit in terms of reducing asthma exacerbations caused by influenza virus infection has not been demonstrated.*"

Poole 2000 [Poole PJ, et al. (2000). Influenza vaccine for patients with chronic obstructive pulmonary disease. The Cochrane Library (4)]

Cited in paragraph "Flu immunisation in patients with COPD" as evidence of exacerbation reduction in immunized COPD-patients.
Comment: from two RCTs ($N = 180$) reduction in exacerbation would be demonstrated only if associated with influenza infection.

Sheikh 2003 [Sheikh A, et al. (2003). Pneumococcal Vaccine for Asthma (Cochrane Review). In: The Cochrane Library (1).

Cited in paragraph "Flu immunisation in patients with COPD." This concludes that immunization against influenza in patients with COPD is safe and effective.
Comment: Not pertinent. This is a Cochrane review on safety and effectiveness of pneumococcal vaccine.

Part of their success lies in the absence of specificity: they work against all agents. Whatever policy is chosen, there is an urgent need to replace current practices with accountable policy-making. In this scenario, systematic synthesis of evidence should play a central role in making ethical decisions, in which the influence of lobbies, activism, ideology, and lucre are at least recognized.

Acknowledgments

Peter Gøtzsche, Peter Doshi, and Iain Chalmers commented on sections of previous drafts.

Competing interest statement: T.J. until 2005 owned shares in Glaxo SmithKline and received consultancy fees from Sanofi-Synthelabo (2002) and Roche (1997–1999). All other authors have no conflicts to declare.

References

[1] WHO. Who position paper : influenza vaccines http://www.who.int/wer/2005/wer8033.pdf Accessed January 22, 2008).
[2] Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. Lancet Infect Dis. 2007;7(10):658–66.
[3] Simonsen L, Reichert TA, Viboud C, Blackwelder WC, Taylor RJ, Miller MA. Impact of influenza vaccination on seasonal mortality in the US elderly population. Arch Intern Med 2005;165(3):265–72.
[4] Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. Int J Epidemiol 2006;35(2):337–44.
[5] Jackson LA, Nelson JC, Benson P, Neuzil KM, Reid RJ, Psaty BM, et al. Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. Int J Epidemiol 2006;35(2):345–52.
[6] Pyhala R, Haanpaa M, Kleemola M, Tervahauta R, Visakorpi R, Kinnunen L. Acceptable protective efficacy of influenza vaccination in young military conscripts under circumstances of incomplete antigenic and genetic match. Vaccine 2001;19:3253–60.
[7] Feery BJ, Evered MG, Morrison EI. Different protection rates in various groups of volunteers given subunit influenza virus vaccine in 1976. J Infect Dis 1979;139:237–41.
[8] Doshi P. Are US flu death figures more PR than science? BMJ 2005;331:141210.1136/bmj.331.7529.1412.
[9] Simonsen L, Taylor R, Viboud C, Dushoff J, Miller M. US flu mortality estimates are based on solid science. BMJ 2006;332:177–810.1136/bmj.332.7534.177-a.
[10] Nelson JC, Jackson ML, Weiss NS, Jackson LA. New strategies are needed to improve the accuracy of influenza vaccine effectiveness estimates among seniors. J Clin Epidemiol 2009;62:677–84.
[11] Jefferson T. The prevention of seasonal influenza—policy versus evidence. BMJ 2006;333:912–5.
[12] Jordan R, Connock M, Albon E, Fry-Smith A, Olowokure B, Hawker J, et al. Universal vaccination of children against influenza: are there indirect benefits to the community? A systematic review of the evidence. Vaccine 2006;24:1047–62.
[13] Smith S, Demicheli V, Di Pietrantonj C, Harnden AR, Jefferson T, Matheson NJ, et al. Vaccines for preventing influenza in healthy children. Cochrane Database Syst Rev 2006;(1)10.1002/14651858.CD004879.pub2. CD004879.pub2.
[14] Demicheli V, Rivetti D, Deeks JJ, Jefferson TO. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 2004;(3)10.1002/14651858.CD001269.pub2. CD001269.pub2.
[15] Thomas RE, Jefferson T, Demicheli V, Rivetti D. Influenza vaccination for healthcare workers who work with the elderly. Cochrane

Database Syst Rev 2006;(3)10.1002/14651858.CD005187.pub2. CD005187.pub2.

[16] Rivetti D, Demicheli V, Di Pietrantonj C, Jefferson TO, Thomas R. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev 2006;(3)10.1002/14651858.CD004876. CD004876.

[17] Cates CJ, Jefferson TO, Bara AL, Rowe BH. Vaccines for preventing influenza in people with asthma. Cochrane Database Syst Rev 2003;(4)10.1002/14651858.CD000364.pub2. CD000364.pub2.

[18] Poole PJ, Chacko E, Wood-Baker RWB, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2006;(1)10.1002/14651858.CD002733.pub2. CD002733.pub2.

[19] UK Department of Health. The ''Green Book.'' http://www.dh.gov.uk/en/Policyandguidance/Healthandsocialcaretopics/Greenbook/DH_4097254 Accessed October 20, 2007).

[20] Joint Committee on Vaccination and Immunisation. Annual report (2005/2006). http://www.advisorybodies.doh.gov.uk/JCVI/annualreport2005-06.pdf First accessed October 24, 2007.

[21] Australia Government—Department of Health and Ageing. Australian immunisation handbook. 8th edition. http://www9.health.gov.au/immhandbook/ 2003;. Accessed October 17, 2007.

[22] Australia Government—Department of Health and Ageing. Australian immunisation handbook. 9th edition. http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook-home 2008;. Accessed May 14, 2008.

[23] Centers for Disease Control and Prevention. Prevention and Control of Influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2007;2007:1–54. 56(No. RR-6).

[24] National Advisory Committee on Immunization (NACI). Statement on influenza vaccination for the 2007-2008 season. An Advisory Committee Statement (ACS). Can Commun Dis Rep 2007 Jul 1;33(ACS-7):1–38.

[25] Standing Vaccination Commission (STIKO). Recommendations of the Standing Vaccination Commission (STIKO) to the Robert Koch Institut. Epidemiol Bull 2007;30:267–86.http://www.rki.de/cln_048/nn_195844/DE/Content/Infekt/EpidBull/Archiv/2007/30__07,templateId=raw,property=publicationFile.pdf/30_07.pdf. Accessed November 6, 2007.

[26] Influenza RKI-Ratgeber Infektionskrankheiten—Merkblätter für Ärzte. (Recommendations of Robert Koch Institut (RKI), updated on February 2006). http://www.rki.de/cln_049/nn_200120/DE/Content/Infekt/EpidBull/Merkblaetter/Ratgeber__Mbl__Influenza.html. Accessed November 6, 2007.

[27] Standing Vaccination Commission (STIKO). Updated communication of the STIKO commission to RKI: Informations for physicians about the necessity to inform about unattended reactions following protective immunisations/status. Epidemiol Bull 2007;219.http://www.rki.de/cln_048/nn_195850/DE/Content/Infekt/Impfen/Nebenwirkungen/Anlagen/25__07,templateId=raw,property=publicationFile.pdf/25_07.pdf. Accessed November 6, 2007.

[28] Standing Vaccination Commission (STIKO). Rationale for influenza immunisation recommendations of MS-patients with relapse episodes triggered through infections. http://www.rki.de/cln_048/nn_195848/DE/Content/Infekt/Impfen/STIKO__Empfehlungen/Begruendung/influenza__ms,templateId=raw,property=publicationFile.pdf/influenza_ms.pdf (Accessed November 6, 2007).

[29] Standing Vaccination Commission (STIKO). The indication, ''chronic pulmonary disease'' for STIKO recommendation on influenza vaccination (and pneumococcus) includes also patients affected by bronchial asthma and COPD http://www.rki.de/cln_048/nn_195848/DE/Content/Infekt/Impfen/STIKO__Empfehlungen/Begruendung/influenza__cl,templateId=raw,property=publicationFile.pdf/influenza_cl.pdf. Accessed November 6, 2007.

[30] Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. Ann Intern Med 1995;123:518–27.

[31] Jefferson T, Foxlee R, Del Mar C, Dooley L, Ferroni E, Hewak B, et al. Interventions for the interruption or reduction of the spread of respiratory viruses. Cochrane Database Syst Rev 2007;(4)10.1002/14651858.CD006207.pub2. CD006207.