Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis

Michael T Osterholm, Nicholas S Kelley, Alfred Sommer, Edward A Belongia

Summary

Background No published meta-analyses have assessed efficacy and effectiveness of licensed influenza vaccines in the USA with sensitive and highly specific diagnostic tests to confirm influenza.

Methods We searched Medline for randomised controlled trials assessing a relative reduction in influenza risk of all circulating influenza viruses during individual seasons after vaccination (efficacy) and observational studies meeting inclusion criteria (effectiveness). Eligible articles were published between Jan 1, 1967, and Feb 15, 2011, and used RT-PCR or culture for confirmation of influenza. We excluded some studies on the basis of study design and vaccine characteristics. We estimated random-effects pooled efficacy for trivalent inactivated vaccine (TIV) and live attenuated influenza vaccine (LAIV) when data were available for statistical analysis (eg, at least three studies that assessed comparable age groups).

Findings We screened 5707 articles and identified 31 eligible studies (17 randomised controlled trials and 14 observational studies). Efficacy of TIV was shown in eight (67%) of the 12 seasons analysed in ten randomised controlled trials (pooled efficacy 59% [95% CI 51–67] in adults aged 18–65 years). No such trials met inclusion criteria for children aged 2–17 years or adults aged 65 years or older. Efficacy of LAIV was shown in nine (75%) of the 12 seasons analysed in ten randomised controlled trials (pooled efficacy 83% [69–91]) in children aged 6 months to 7 years. No such trials met inclusion criteria for children aged 8–17 years. Vaccine effectiveness was variable for seasonal influenza: six (35%) of 17 analyses in nine studies showed significant protection against medically attended influenza in the outpatient or inpatient setting. Median monovalent pandemic H1N1 vaccine effectiveness in five observational studies was 69% (range 60–93).

Interpretation Influenza vaccines can provide moderate protection against virologically confirmed influenza, but such protection is greatly reduced or absent in some seasons. Evidence for protection in adults aged 65 years or older is lacking. LAIVs consistently show highest efficacy in young children (aged 6 months to 7 years). New vaccines with improved clinical efficacy and effectiveness are needed to further reduce influenza-related morbidity and mortality.

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Center for Infectious Disease Research and Policy, University of Minnesota, MN, USA (Prof M T Osterholm PhD, N S Kelley PhD); **Department of International Health, and the Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA** (Prof A Sommer MD); **and Epidemiology Research Center, Marshfield Clinic Research Foundation, Marshfield, WI, USA** (E A Belongia MD)

Correspondence to: Prof Michael Osterholm, Center for Infectious Disease Research and Policy, University of Minnesota, MN 55455, USA **mto@umn.edu**

Introduction

The main strategy for prevention and control of seasonal and pandemic influenza for the past 60 years has been vaccination.[1,2] The first population-scale use of an inactivated influenza vaccine was in US military personnel in 1945.[3] In 1960, the US Surgeon General, in response to substantial morbidity and mortality during the 1957–58 pandemic, recommended annual influenza vaccination for individuals with chronic debilitating disease, people aged 65 years or older, and pregnant women.[4] This recommendation was made without data for vaccine efficacy or effectiveness for these high-risk populations. Instead, it was made on the basis of studies showing efficacy in young, healthy military recruits with clinical illness or seroconversion as primary measures of infection. In 1964, the Advisory Committee on Immunization Practices (ACIP) reaffirmed this recommendation but noted the absence of efficacy data.[5] Because of the longstanding public health recommendation of annual vaccination in the elderly and other high-risk groups, such patients have been excluded from placebo-controlled randomised clinical trials in the USA for the past 50 years. The ACIP supports the widely held view that inclusion of individuals at high-risk of influenza in placebo-controlled trials would be unethical.[2]

In 2010, the ACIP established the first recommendation of national universal seasonal influenza vaccination.[2] Vaccination every year is now recommended with trivalent inactivated vaccine (TIV) for all individuals aged 6 months or older, or live attenuated influenza vaccine (LAIV) for healthy non-pregnant people aged 2–49 years.[2] In the USA, TIV has been used since 1978 and accounts for approximately 90% of influenza vaccine given at present.[6] The LAIV was first approved for use in the USA in 2003 and accounts for approximately 9% of the vaccine given.[7,8] The universal influenza vaccination recommendation came after a decade of incremental changes during which the ACIP expanded recommendations to include an ever-increasing proportion of the US population.

Previous meta-analyses of TIV or LAIV efficacy and effectiveness have included studies that used diagnostic

Panel: **Inclusion criteria for studies of trivalent inactivated vaccine and live attenuated influenza vaccine published in 1967–2011**

Efficacy studies

- A published, masked, randomised controlled trial indexed by Medline
- Study reported overall vaccine efficacy against all circulating influenza strains irrespective of match or number of strains identified in surveillance
- Outcome defined as RT-PCR or viral culture confirmation of influenza infection of wild strains
- Comparison group received placebo or vaccine other than influenza
- Study assessed inactivated influenza vaccines that were licensed at the time of study or eventually licensed in the USA and antigen concentrations reported as μg of haemagglutinin, or live attenuated influenza vaccines licensed at the time of study or eventually licensed in the USA and active virus reported as tissue-culture infective doses of $10^{6.5}$–$10^{7.5}$

Effectiveness studies

- A published case test-negative control, case cohort, or prospective cohort study design indexed by Medline
- Vaccine effectiveness reported for individual seasons and adjusted (as necessary on the basis of study design) for age and calendar time (week or month of enrolment); interim or partial season estimates were excluded as were studies assessing the effectiveness of seasonal influenza vaccines for the prevention of pandemic H1N1
- Eligible patients were tested on the basis of systematic sampling with defined clinical criteria irrespective of vaccination status; studies allowing enrolment of patients based on clinical judgment were excluded to reduce selection bias
- Vaccination status established by self-report, medical record review, or immunisation registry
- Cases had influenza confirmed by RT-PCR or viral culture
- Controls had a negative RT-PCR or viral culture for influenza (test-negative control design) or had no influenza-like illness (cohort design)

See Online for webappendix

endpoints with little sensitivity or specificity to confirm influenza infection in recipients of vaccine and placebo.[9–12] For example, the use of serology to confirm influenza infection in participants who were vaccinated with an inactivated vaccine had been recognised as problematic since the 1940s and 1950s.[13–16] Investigators noted that the increased antibody titres after vaccination in individuals given an inactivated vaccine made it difficult to document a four-fold rise in hemagglutinin antibodies necessary to confirm an influenza infection. Studies into the efficacy and effectiveness of TIV continue to use serology as a primary endpoint for confirmation of influenza infection in study participants, without addressing concerns raised by the studies done in the 1940s and 1950s. Petrie and colleagues[17] showed that, in participants who had received TIV, only 23% who had RT-PCR-confirmed H3N2 influenza had serological evidence of infection. By contrast, 90% of cases confirmed by RT-PCR in the placebo group had serologically confirmed infection. This biased case detection contributes to overestimation of the effect of vaccines in studies of TIV that rely on serological confirmation of influenza infection.

To assess the highest quality evidence about the efficacy and effectiveness of licensed influenza vaccines in the USA, we did a meta-analysis of randomised controlled trials and observational studies that used RT-PCR or viral culture to confirm influenza infections.

Methods

Definitions and outcomes

We defined influenza vaccine efficacy as the relative reduction in influenza risk after vaccination as established by a randomised placebo-controlled clinical trial. We defined influenza vaccine effectiveness as relative reduction in influenza risk in vaccinated individuals in observational studies that used medically attended, laboratory-confirmed influenza as the primary outcome of interest.[18] Observational study designs included case-control (with test-negative controls), case-cohort, and prospective cohort. We defined laboratory-confirmed influenza as RT-PCR-confirmed or culture-confirmed influenza. RT-PCR is the preferred diagnostic test for influenza because of its high sensitivity and low likelihood of false positives.[19] TIV efficacy and effectiveness studies that used serology endpoints to diagnose influenza were excluded because of biased case detection in vaccinated individuals as already described.[13,17] We assessed published randomised controlled trials and observational studies with the criteria defined in the panel. For all studies, efficacy and effectiveness were regarded as statistically significant if the 95% CI for efficacy or effectiveness did not cross 0.

Search strategy and selection criteria

We searched Medline (PubMed database) for articles on influenza vaccine efficacy and effectiveness published in English between Jan 1, 1967, and Feb 15, 2011 (for the full search strategy see webappendix p 2). Studies were included if efficacy or effectiveness was reported against all circulating influenza viruses during individual seasons and influenza was confirmed by RT-PCR or viral culture, or both. The panel lists additional inclusion criteria. NSK assessed studies for potential eligibility and studies needing adjudication of methods or results were reviewed by EAB and MTO.

Influenza vaccine challenge studies were excluded from review because they might not be directly comparable with natural infection. Nearly all challenge studies have used homologous strains[20] and challenge virus tissue deposition might not be analogous to natural infection. We also excluded studies that employed only non-specific outcomes, such as mortality, influenza-like illness, or reduction in sick days. Efficacy studies that used non-specific clinical outcomes are not directly comparable with those that used virological endpoints, and use of non-specific outcomes complicates interpretation of observational studies because of unmeasured confounding.

We excluded studies if efficacy or effectiveness estimates were not reported (or calculable) for individual seasons, or if estimates were only reported for specific influenza types or subtypes rather than all influenza infections occurring in study participants. We included this

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restriction because efficacy or effectiveness against all circulating influenza viruses is the most relevant endpoint from a clinical and public health perspective. Effectiveness studies had to have employed systematic sampling of participants on the basis of well-defined symptom criteria; we excluded studies that allowed enrolment and testing based on clinical judgment. Finally, we excluded studies that reported effectiveness of seasonal influenza vaccines (before the 2009 pandemic) for prevention of illness caused by pandemic H1N1 (pH1N1). We calculated vaccine efficacy by season for one study using the raw data provided in the report.[21]

Statistical analysis

We calculated Mantel-Haenszel fixed effect and random effect pooled odds ratios and corresponding 95% CI for influenza vaccine recipients versus placebo when there were three or more randomised controlled studies with equivalent age ranges and vaccine characteristics.[22] We assessed homogeneity of the odds ratios by calculating the Breslow-Day statistic. We report the vaccine efficacy with the random-effects odds ratio; the point estimates were the same for the fixed and random effect calculations. The pooled odds ratios were used to establish pooled vaccine efficacy with the following formula: (1−odds ratio)×100.

We interpreted vaccine efficacy point estimates and CIs that included a negative estimate as zero efficacy. With presently accepted statistical methods for calculating vaccine efficacy, negative estimates are possible. A negative point estimate or CI does not necessarily imply that the vaccine is associated with an increased risk of influenza.

All analyses were done with SAS version 9.2.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 5707 studies on influenza vaccines in human beings with our PubMed search (figure 1). Of these, 992 were identified as cohort studies, case-control studies, clinical trials, randomised controlled trials, or did not have MeSH terms. A review of the abstracts of these studies suggested 176 (18%) potentially eligible studies; 73 (41%) were randomised controlled trials estimating vaccine efficacy and 103 (59%) were observational studies estimating vaccine effectiveness. 31 of these studies were eligible; webappendix pp 3–17 lists excluded studies and reasons for their exclusion.

17 (23%) of 73 randomised controlled trials met inclusion criteria. These trials had data for 24 influenza seasons and 53 983 participants from 23 countries. Three studies assessed TIV and LAIV. 17 (71%) of the 24 influenza seasons covered by the 17 trials suggested significant overall efficacy, but data were incomplete for specific age groups (table 1).

Ten randomised controlled trials assessed TIV efficacy during 12 influenza seasons; eight (67%) analyses for these seasons showed significant efficacy and four (33%) did not (table 2). None of these trials exclusively assessed adults aged 65 years or older or children aged 2–17 years;

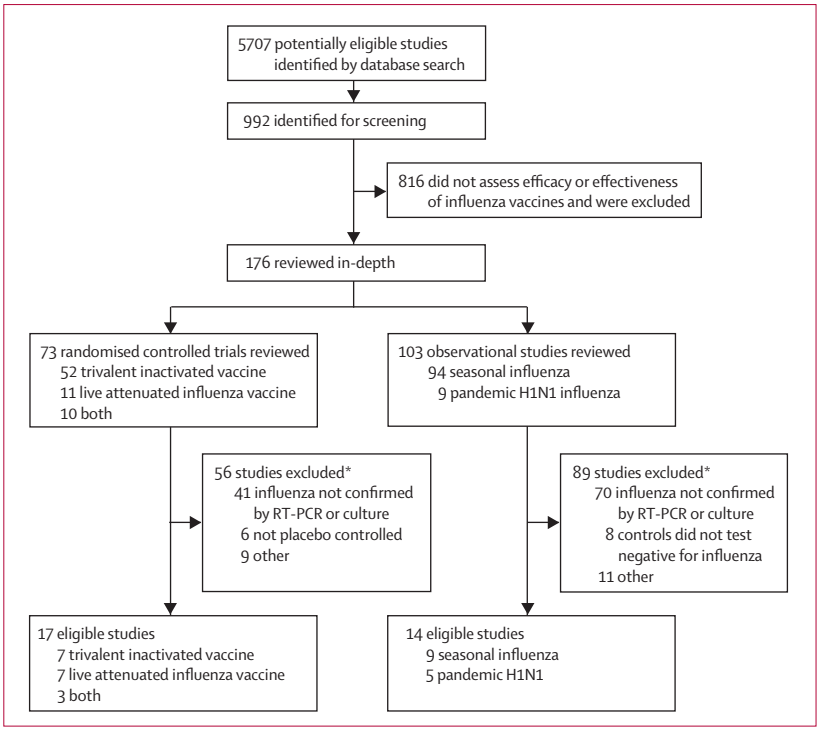

Figure 1: **Study selection**
*See webappendix pp 3–17 for more details.

	Number of trials
Trivalent inactivated vaccine	
6–23 months	1
2–17 years	0
18–64 years	6
≥65 years	0
Overall	8*
Live attenuated influenza vaccine	
6 months–7 years	8
8–17 years	0
18–49 years	0
50–59 years	0
≥60 years	1
Overall	9

*One study[23] included all age groups and showed combined significant efficacy.

Table 1: **Number of randomised controlled trials showing significant vaccine efficacy (lower 95% CI >0%) by age, 1967–2011**

	Population (dates)	Patients randomly allocated to receive TIV and placebo	Vaccine efficacy (95% CI)	Reported antigenic match
Adults (18–64 years)				
Ohmit et al (2006)[24]	Healthy adults aged 18–46 years (2004–05)	728	75% (42 to 90)	Type A: drifted H3N2; type B: mixed lineage
Ohmit et al (2008)[25]	Healthy adults aged 18–48 years (2005–06)	1205	16% (–171 to 70)	Type A: drifted H3N2; type B: lineage mismatch (1 isolate)
Beran et al (2009)[26]	Healthy adults aged 18–64 years (2005–06)	6203	22% (–49 to 59)	Type A: similar H3N2 and H1N1; type B: lineage mismatch
Beran et al (2009)[27]	Healthy adults aged 18–64 years (2006–07)	7652	62% (46 to 73)	Type A: similar H3N2; type B: lineage mismatch
Monto et al (2009)[28]	Healthy adults aged 18–49 years (2007–08)	1139	68% (46 to 81)	Type A: drifted H3N2; type B: lineage mismatch
Jackson et al (2010)[21]	Healthy adults aged 18–49 years (2005–06)	3514	50%† (14 to 71)	Type A: similar H3N2; type B: lineage mismatch
Jackson et al (2010)[21]	Healthy adults aged 18–49 years (2006–07)	4144	50%† (–3 to 75)	Type A: similar H3N2; type B: mixed lineage
Frey et al (2010)[29]	Healthy adults aged 18–49 years (2007–08)	7576	63% (one-sided 97·5% lower limit of 47%)	Type A: mixed strains; type B: lineage mismatch
Madhi et al (2011)[30]	Adults aged 18–55 years with HIV infection (2008–09)	506	76% (9 to 96)	Type A: drifted H1N1; type B: not reported
Children (6–24 months)				
Hoberman et al (2003)[31]	Healthy children aged 6–24 months (1999–2000)	411	66% (34 to 82)	Type A: similar H3N2 and H1N1; type B: not reported
Hoberman et al (2003)[31]	Healthy children aged 6–24 months (2000–01)	375	–7% (–247 to 67)	Type A: similar H3N2 and H1N1; type B: lineage match

No studies were available for adults aged 65 years or older or children aged 2–17 years. *One other study by Loeb and colleagues[23] met inclusion criteria and contained data for all age groups. †Our calculation.

Table 2*: Randomised controlled trials of trivalent inactivated vaccine (TIV) meeting inclusion criteria

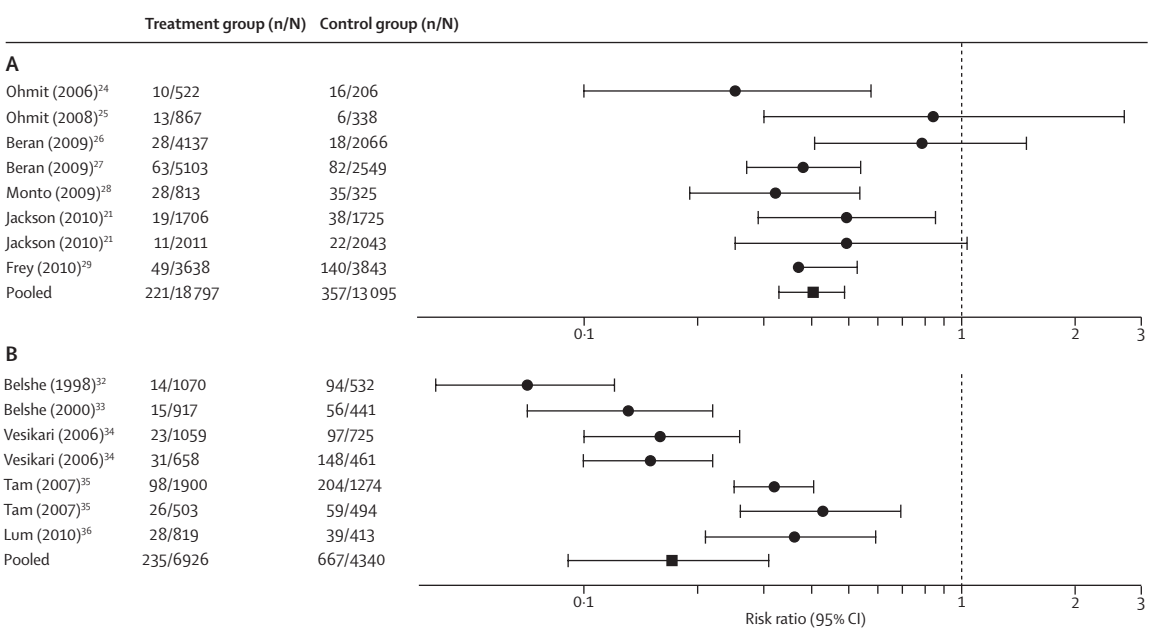

***Figure 2*: Vaccine efficacy compared with placebo (Mantel-Haenszel random-effects model)**
(A) Trivalent inactivated influenza vaccine in adults aged 18–64 years. (B) Live attenuated influenza vaccine in children aged 6 months to 7 years. Studies were prospective (risk ratio) which are equivalent to case-control (odds ratio). n=cases of influenza. N=group size.

and nine of ten studies were done in healthy individuals. Eight studies were done in adults aged 18–64 years, covering nine influenza seasons. The random-effects pooled vaccine efficacy was 59% (95% CI 51–67; figure 2) and the median vaccine efficacy was 62% (range 16–76).[21,24–30] One study[31] assessing efficacy in children aged 6–24 months was done over two seasons with good matches between vaccine and circulating strains in both years. In the first year vaccine efficacy was 66% and in the second year it was –7%.[31] A cluster-randomised trial in children aged 6 months to 15 years reported combined direct and indirect vaccine efficacy in members of Hutterite communities (aged 6 months to >65 years), which is not directly comparable with the other randomised trials.[23] In this study, the combined vaccine efficacy was 59% (95% CI 4–82).

	Population (dates)	Patients randomly allocated to receive LAIV and placebo	Vaccine efficacy (95% CI)	Reported antigenic match
Adults (≥60 years)				
De Villiers et al (2010)[37]	Community-dwelling ambulatory adults aged ≥60 years (2001–02)	3242	Overall 42% (21 to 57); 31% (–3 to 53) for patients aged 60–69 years; 57% (29 to 75) for patients aged ≥70 years	Type A: similar H3N2; type B: lineage match
Adults (18–49 years)				
Ohmit et al (2006)[24]	Healthy adults aged 18–46 years (2004–05)	725	48% (–7 to 74)	Type A: drifted H3N2; type B: mixed lineage
Ohmit et al (2008)[25]	Healthy adults aged 18–48 years (2005–06)	1191	8% (–194 to 67)	Type A: drifted H3N2; type B: lineage mismatch (1 isolate)
Monto et al (2009)[28]*	Healthy adults aged 18–49 years (2007–08)	1138	36% (0 to 59)	Type A: drifted H3N2; type B: lineage mismatch
Children (6 months–7 years)				
Belshe et al (1998)[32]	Healthy children aged 15–71 months (1996–97)	1602	93% (88 to 96)	Type A: similar H3N2; type B: lineage match
Belshe et al (2000)[33]	Healthy children aged 26–85 months (1997–98)	1358	87% (78 to 93)	Type A: drifted H3N2; type B: not reported (1 isolate)
Vesikari et al (2006)[34]	Healthy children aged 6–<36 months attending day care (2000–01)	1784	84% (74 to 90)	Type A: similar H3N2 and H1N1; type B: lineage match
Vesikari et al (2006)[34]	Healthy children aged 6–<36 months attending day care (2001–02)	1119	85% (78 to 90)	Type A: similar H3N2 and H1N1; type B: mixed lineage
Bracco Neto et al (2009)[38]	Healthy children aged 6–<36 months (2000–01)	1886	72% (62 to 80)	Majority of strains were similar (not reported by type)
Tam et al (2007)[35]	Healthy children aged 12–<36 months (2000–01)	3174	68% (59 to 75)	Type A: similar H3N2 and H1N1; type B: lineage match
Tam et al (2007)[35]	Healthy children aged 12–<36 months (2001–02)	2947	57% (30 to 74)	Type A: similar H3N2 and H1N1; type B: mixed lineage
Lum et al (2010)[36]	Healthy children aged 11–<24 months (2002–03)	1233	64% (40 to 79)	Type A: similar H1N1 and mixed H3N2; type B: mixed lineage

No studies were available for adults aged 50–59 years or children aged 8–17 years. *Authors reported culture, RT-PCR, and RT-PCR/culture; we report RT-PCR/culture results.

Table 3: **Randomised controlled trials of live attenuated influenza vaccine (LAIV) meeting inclusion criteria**

Ten randomised controlled trials assessed LAIV efficacy during 12 influenza seasons; nine (75%) analyses for these seasons showed significant efficacy (table 3). All these trials were undertaken in healthy individuals. The one study[37] done in adults aged 60 years or older reported significant overall efficacy (42%, 95% CI 21–57), but efficacy seemed to be lower in individuals aged 60–69 years (31%) and higher in those aged 70 years or older (57%). There were three randomised controlled trials of LAIV in adults aged 18–49 years; none showed significant protection.[24,25,28] In children aged 6 months to 7 years, there were six studies covering eight influenza seasons. In all eight seasons, the vaccine provided significant protection against infection; the random-effects pooled vaccine efficacy was 83% (95% CI 69–91; figure 2) and median vaccine efficacy was 78% (range 57–93).[32–36,38] The pooled vaccine efficacy estimate excluded one study[38] because of a lack of sufficient data.

14 (14%) of 103 observational studies about effectiveness of influenza vaccines met the inclusion criteria. Nine studies reported effectiveness for seasonal influenza vaccine, and five did for monovalent pH1N1 vaccine.

The nine published reports of seasonal influenza vaccine effectiveness included 17 embedded seasonal or cohort analyses (table 4). The percentage of participants receiving TIV or LAIV in these studies was not explicitly stated, but based on the age of individuals in the study and the licensed use of the specific influenza vaccines, vaccine effectiveness estimates were mainly for TIV. Six (35%) of 17 analyses showed significant effectiveness (lower 95% CI >0%) against medically attended, laboratory-confirmed influenza in the outpatient or inpatient setting. In children aged 6–59 months, significant vaccine effectiveness was reported in three (38%) of eight seasons.[39,40,43,46] Vaccine effectiveness against medically attended influenza was noted in one (33%) of three seasons in individuals in a community cohort who were recommended to receive influenza vaccine based on ACIP criteria for age group or high-risk medical status during each season.[41] Vaccine effectiveness was shown in one of two studies in adults aged 65 years or older.[44,45] In one study of adults aged 50 years or older, vaccine effectiveness for prevention of hospital admission due to influenza was 56–73% in each of three seasons, but the CI crossed 0 for each season.[47]

Five studies assessed the effectiveness of the monovalent pH1N1 vaccine for prevention of medically attended, RT-PCR confirmed pH1N1 infection (webappendix p 18). These studies were done in Europe or Canada, and four of the studies[48–51] enrolled and obtained samples from participants with influenza-like illness. Median vaccine effectiveness for prevention of medically attended influenza was 69% (range 60–93%), but comparatively few cases of influenza occurred in individuals aged 65 years or older.[48–51] The fifth study[52] reported vaccine effectiveness of 90% (95% CI 48–100%) for prevention of hospital admission with RT-PCR confirmed pH1N1 infection. The mean age of 145 patients admitted to hospital with influenza was 37·9 years (SD 22·0; range 9 to 91 years).[52] Monovalent vaccines containing adjuvant were used in all five studies,

	Population (dates)	Patients randomly allocated	Vaccine effectiveness against medically attended influenza (95% CI)
Eisenberg et al (2008)[39]	All patients aged 6–59 months admitted to hospital, seen in emergency department or by primary-care doctors for acute respiratory illness (2003–05)	2003–04 (927 patients); 2004–05 (1502 patients)	44% (–42 to 78); 57% (28 to 74)
Szilagyi et al (2008)[40]	All patients aged 6–59 months admitted to hospital, seen in emergency department (inpatient) or by primary-care doctors (outpatient) for acute respiratory illness (2003–05)	2003–04 (4760 inpatients); 2003–04 (696 outpatients); 2004–05 (4708 inpatients); 2004–05 (742outpatients)	12% (–120 to 60); 52% (–100 to 90); 37% (–50 to 70); 7% (–80 to 50)
Belongia et al (2009)[41]	Residents recommended for vaccination by ACIP with acute respiratory illness: <24 months, ≥65 years, or high-risk (2004–05); <24 months, ≥50 years, or high-risk (2005–06); <59 months, ≥50 years, or high risk (2006–07)	 2004–05 (818 patients); 2005–06 (356 patients); 2006–07 (932 patients)	 10% (–36 to 40); 21% (–52 to 59); 52% (22 to 70)
Skowronski et al (2009)[42]	All patients aged ≥9 years presenting with ILI to sentinel primary-care practitioners	841	47% (18 to 65)
Heinonen et al (2011)[43]	Cohort of patients aged 6–35 months presenting with ILI enrolled in a randomised controlled trial for antivirals (2007–08)	340	72% (35 to 88)
Savulescu et al (2010)[44]	All patients ≥65 years old presenting with ILI (2008–09)	103	79% (–26 to 96)
Kissling et al (2009)[45]	All patients ≥65 years old presenting with ILI (2008–09)	292	59% (15 to 80)
Kelly et al (2011)[46]	All patients aged 6–59 months presenting with ILI (2008)	289	68%* (26 to 86)
Talbot et al (2011)[47]	Adults aged >50 years admitted to hospital with respiratory symptoms or non-localising fever (2006–09)	2006–07 (168 patients); 2007–08 (68 patients); 2008–09 (181 patients)	57% (–44 to 87)†; 56% (–63 to 88)†; 73% (–15 to 94)†

*Controls tested negative for influenza but positive for other respiratory viruses. †Vaccine effectiveness against hospitalisation. ACIP=Advisory Committee on Immunization Practices. ILI=influenza-like illness.

Table 4: **Vaccine effectiveness of seasonal influenza vaccine in studies meeting inclusion criteria**

and most vaccinated participants received a vaccine containing an adjuvant.

Discussion

Our analysis differs from previous reviews of influenza vaccine efficacy and effectiveness because of our use of restrictive study inclusion criteria to minimise bias and confounding. Our approach uses only very specific outcome endpoint data for virologically confirmed influenza. When these more stringent criteria were applied, we noted substantial gaps in the evidence base for some age groups with regard to efficacy data for TIV and LAIV.

There are no randomised controlled trials showing efficacy of TIV in people aged 2–17 years or adults aged 65 years or older. For LAIV, there are no randomised controlled trials showing efficacy for people aged 8–59 years. The evidence from trials and observational studies suggests that presently available influenza vaccines can provide moderate overall protection against infection and illness, with LAIV providing a consistently higher level of protection in children aged 7 years or younger. The studies included in our review—excluding LAIV in young children—also show substantial variability by season and age group that cannot be attributed to differences in study design or outcome measures. In some influenza seasons, and especially in some age groups, the level of protection was low or not evident. Interpretation of age-stratified estimates is difficult when there were few cases and wide CIs. Seasonal influenza vaccines have been reported to be 70–90% effective in prevention of laboratory-confirmed influenza in healthy adults when the vaccines are well matched to the circulating strains.[2,53] We noted this magnitude of effectiveness only for LAIV use in children aged 7 years or younger. The ACIP has not preferentially recommended LAIV over TIV in children aged 2–7 years. However, we found consistent evidence for moderate to high efficacy of LAIV in this age group.

Studies with few participants or few cases of influenza had low statistical power to detect a difference between groups. The incidence of influenza in a specific season is very variable and unpredictable, and thus the precision of vaccine effectiveness measures was reduced during mild seasons with fewer than expected cases. As a result, interpretation of estimates of efficacy or effectiveness that are based on few cases with a wide CI is difficult.

Although many studies failed to meet our inclusion criteria, we believe that the results of this meta-analysis provide the most accurate estimates of the efficacy and effectiveness of influenza vaccines that are licensed at present in the USA. This information is particularly useful for efforts to estimate the potential public health benefits of influenza vaccination.

Our meta-analysis differs from previously published meta-analyses in two key ways. First, eligible studies of both vaccines were restricted to those that used direct virus detection methods as primary endpoints. Although less specific endpoints can provide useful information when assessed in a randomised and adequately masked clinical trial, the efficacy estimates are not directly comparable with efficacy on the basis of virus-confirmed infections. Second, we excluded randomised controlled trials in which the comparison group did not receive either placebo or a vaccine other than for influenza.

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Reviews by the Cochrane Collaboration use a different standard for assessment of influenza vaccine efficacy and effectiveness.[9–11] Many studies included in the Cochrane meta-analysis reviews had a serology-based endpoint, which resulted in overestimation of efficacy or effectiveness of TIV. An often-cited randomised controlled trial[54] included in the Cochrane analysis of adults aged 65 years or older, but not in our meta-analysis (because they did not use RT-PCR or viral culture only), reported an efficacy of 58% for clinically defined influenza that was confirmed by serology. Our meta-analysis also identified studies that were not referenced in the Cochrane analyses despite the use of similar search strategies (see webappendix p 19).

Our review did not include studies of mortality after influenza vaccination, but this topic has received much attention in recent years, especially for individuals aged 65 years or older.[55,56] A series of observational studies undertaken between 1980 and 2001 attempted to estimate the effect of seasonal influenza vaccine on rates of hospital admission and mortality in such adults.[57–59] Reduction in all-cause mortality after vaccination in these studies ranged from 27% to 75%. In 2005, these results were questioned after reports[60] that increasing vaccination in people aged 65 years or older did not result in a significant decline in mortality. Five different research groups in three countries have shown that these early observational studies had substantially overestimated the mortality benefits in this age group because of unrecognised confounding.[55,61–68] This error has been attributed to a healthy vaccine recipient effect: reasonably healthy older adults are more likely to be vaccinated, and a small group of frail, undervaccinated elderly people contribute disproportionately to deaths, including during periods when influenza activity is low or absent. Recent studies in a northern Californian population addressed this confounding and noted that influenza vaccination decreased all-cause mortality in people aged 65 years or older by 4·6% (95% CI 0·7–8·3) and hospital admissions for pneumonia and influenza by 8·5% (3·3–13·5).[62,68] These findings suggest that presently licensed vaccines might prevent some serious complications of influenza in the elderly, but not as many as would be predicted based on results of earlier cohort studies that failed to control for confounding.

Every year, large-scale campaigns in many developed countries are undertaken to vaccinate all people aged 65 years or older to prevent serious illness and mortality. With an estimated 90% of all seasonal influenza-related mortality occurring in this group, an effective intervention is an important public health priority.[69] However, this is the age group for which we have the least data supporting the efficacy or effectiveness of influenza vaccines to reduce morbidity or mortality. Only LAIV has been noted to have a significant efficacy in this age group, and only in one study;[38] this vaccine is not approved for use in adults aged 50 years or older in the USA.

The effectiveness of the pH1N1 pandemic vaccines might be regarded as our best estimate of vaccine effectiveness because the vaccine strain was a very close match to the circulating strain. The vaccine strain was highly effective for prevention of hospitalisation in one study.[52] However, these vaccines, which were mostly adjuvanted, were only 60–93% effective (median 69%) for prevention of medically attended influenza in individuals younger than 65 years. This amount of protection is not adequate for a pandemic setting where the antigenic match is ideal and antigenic drift has not occurred. The difference between 69% effectiveness and 90% effectiveness (or greater) will have a major public health effect in any pandemic that causes serious morbidity or increased mortality.

Routine field studies of the effectiveness of presently licensed influenza vaccines that use virus-confirmed endpoints are needed for all age groups. Because placebo-controlled efficacy studies are not feasible for licensed vaccines, innovative approaches to measurement of vaccine effectiveness will be important. Moreover, studies of new technology vaccines, if undertaken in countries with universal vaccination recommendations, will probably need comparison groups that receive licensed vaccines and are powered to show superiority rather than non-inferiority.

Seasonal influenza is an important public health and medical challenge. Pandemic influenza would cause a substantial burden of disease and seriously threaten the global economy. Based on a track record of substantial safety and moderate efficacy in many seasons, we believe the current influenza vaccines will continue to have a role in reduction of influenza morbidity until more effective interventions are available. However, evidence for consistent high-level protection is elusive for the present generation of vaccines, especially in individuals at risk of medical complications or those aged 65 years or older. The ongoing public health burden caused by seasonal influenza and the potential global effect of a severe pandemic suggests an urgent need for a new generation of more highly effective and cross-protective vaccines that can be manufactured rapidly.[70,71] New vaccines based on novel antigens that differ from the presently licensed vaccines are in development. Active partnerships between industry and government are needed to accelerate research, reduce regulatory barriers to licensure, and support financial models that favour the purchase of vaccines that provide improved protection. Active pursuit of this goal now will save lives every year and when the next influenza pandemic occurs. In the meantime, we should maintain public support for present vaccines that are the best intervention available for seasonal influenza.

Contributors

MTO, NSK, and AS designed the study. NSK, EAB, and MTO reviewed potentially eligible studies. All authors wrote and reviewed the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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Estimating the effect of influenza vaccines

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In *The Lancet Infectious Diseases*, Michael Osterholm and colleagues report a meta-analysis[1] on the efficacy and effectiveness of influenza vaccines licensed in the USA. Although not confined to country of licensure, similar analyses have been published by the Cochrane collaboration.[2] However, this new study[1] differs in several ways from the Cochrane analyses.

Osterholm and colleagues' meta-analysis[1] uses the classic epidemiological definitions of efficacy and effectiveness, in which efficacy refers to the relative risk reduction attributed to vaccination as estimated from a randomised controlled trial, and effectiveness refers to the same measure of effect from an observational study.[3] The Cochrane reviews use efficacy to refer to the relative-risk reduction in which symptomatic laboratory confirmed influenza is the outcome, whereas effectiveness is used for influenza-like illness.[2] Such illness is a non-specific clinical outcome associated with a wide range of respiratory viruses. Influenza vaccination is a specific intervention and assessment against a specific outcome is appropriate. Evaluation of influenza vaccines against non-specific outcomes, such as influenza-like illness, hospital admission due to pneumonia, or all-cause mortality, potentially confuses the understanding of the true burden of influenza and the effect of influenza vaccines.[4]

Thus, Osterholm and colleagues included only studies whose endpoints were laboratory-confirmed influenza on RT-PCR or viral-culture. These endpoints are effectively 100% specific but sensitivity (especially for culture) might be lower.[5] Notably, the same outcomes were used in the vaccine effectiveness studies undertaken within the I-MOVE network, which is a collaboration of European researchers supported by the European Centre for Disease Prevention and Control.[6]

Unlike the previous Cochrane analyses, the new meta-analysis[1] excluded studies whose endpoint was a serological diagnosis of influenza. This exclusion criterion is the main reason for the difference in the number of studies included in the respective meta-analyses, but is not without merit. Differentiation between rises on antibody titres due to vaccination from those due to infection it is often difficult, unless the rise attributable to infection is large.

Serological studies from the community would be expected to capture influenza infections that did not result in clinical presentation and subsequent laboratory testing, and should therefore be a more sensitive marker of infection.[7] However a study[8] during the influenza pandemic of 2009 showed that about 10% of people whose influenza diagnosis was confirmed by RT-PCR had a neutralising antibody titre of less than 40 and would not have been classified as infected. Although serology is a useful diagnostic assay, it is not a perfectly sensitive marker of infection. Importantly, serology is differentially less sensitive in people who have received inactivated vaccines,[5] and is non-specific, with a substantial proportion of haemagglutination inhibiting (HI) antibodies to one influenza virus strain crossreacting with influenza virus strains of the same subtype. This effect was noted in a study[7] that identified antibodies that were crossreactive with the pandemic influenza A H1N1 2009 (pH1N1), mainly in elderly people.

The more restrictive selection criteria for study inclusion used by Osterholm and colleagues[1] led to some differences in results from the most recent Cochrane review.[2] The new meta-analysis[1] estimated a pooled inactivated vaccine efficacy against influenza infection in adults of 59% (95% CI 51–67), compared with estimated efficacy in healthy adults of 73% (54–84) in the Cochrane review[2] for years when circulating and vaccine strains were well-matched and 44% (23–59) in years when they were not.

The median vaccine effectiveness of the monovalent pandemic vaccine against medically attended pH1N1 influenza was 69%, whereas in another study[9] effectiveness was estimated to be 90% (95% CI 48–100) against hospital admission due to laboratory-confirmed pH1N1 infection. However, other studies have reported lower vaccine effectiveness for the same outcome. In Australia in 2010, when pH1N1 influenza made up 79% of documented infections, vaccine effectiveness against hospital admission was 49% (13–70).[10] A study undertaken in the Navarra region of Spain in 2010–11 estimated vaccine effectiveness against hospital admission to be 58% (16–79) with a cohort analysis and 59% (4–83) with a test-negative design (J Castilla, Public Health Institute Navarra, Spain; personal communication).

Because of these estimates of seasonal and pandemic vaccine effectiveness, Osterholm and his coauthors have understandably joined the call for improved influenza

vaccines. Acknowledging the burden of influenza, they also support the use of current vaccines while improved vaccines are developed. In the interim, they emphasise the need for routine effectiveness studies of presently licensed influenza vaccines with virus-confirmed endpoints. For inactivated vaccines, these endpoints should be RT-PCR diagnosed infection, because culture will miss cases and serology alone will overestimate vaccine efficacy and effectiveness.[5]

Now might also be an appropriate time to use revised estimates of the most probable effectiveness of influenza vaccines to re-examine the effectiveness and cost-effectiveness of some policy options. This re-examination would need to be done in conjunction with studies that, similar to the new meta-analysis of the effect of influenza vaccines, use highly specific laboratory-confirmed outcomes to assess influenza burden.

Heath Kelly, Marta Valenciano
Victorian Infectious Diseases Reference Laboratory, Melbourne, VIC, Australia (HK); and EpiConcept, Paris, France (MV)
heath.kelly@mh.org.au

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