Effectiveness and harms of seasonal and pandemic influenza vaccines in children, adults and elderly

A critical review and re-analysis of 15 meta-analyses

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Meta-analyses have been published between 1995 and 2011 to evaluate the benefits and harms of influenza vaccines,1-15 which are considered the most important tool to control influenza pandemics.16 Such meta-analyses have evaluated diverse influenza vaccines (seasonal, pre-pandemic H5N1, and H1N1) and in different age-classes (healthy children, adults or elderly). Even meta-analyses on the same vaccination and age-class have often used different stratified analyses and study selection criteria. It is therefore difficult to have a clear picture of vaccine benefits and harms examining single systematic reviews, we compiled the main findings and evaluated which could be the most reasonable explanations for some differences in findings (or their interpretation) across previously published meta-analyses. For each age group, we performed analyses that included all trials that had been included in at least one relevant meta-analysis, also exploring whether effect sizes changed over time. Although we identified several discrepancies among the meta-analyses on seasonal vaccines for children and elderly, overall most seasonal influenza vaccines showed statistically significant efficacy/effectiveness, which was acceptable or high for laboratory-confirmed cases and of modest magnitude for clinically-confirmed cases. The available evidence on parenteral inactivated vaccines for children aged < 2 y remains scarce. Pre-pandemic “avian” H5N1 and pandemic 2009 (H1N1) vaccines can achieve satisfactory immunogenicity, but no meta-analysis has addressed H1N1 vaccination impact on clinical outcomes. Data on harms are overall reassuring, but their value is diminished by inconsistent reporting.

Introduction

A large body of evidence has been generated on influenza vaccines for different types of virus strains and different populations and settings. As an effort to integrate this evidence, several...
### Table 1. Meta-analyses on influenza vaccines for healthy children/adolescents

| Study       | End date of the search (mm/yy) | Participant's age-range (years) | Included study designs | Funding source | Laboratory-confirmed cases | Clinically-confirmed cases | Acute otitis media |
|-------------|---------------------------------|---------------------------------|------------------------|----------------|---------------------------|---------------------------|-------------------|
|             |                                 |                                 | RCTs                  | NR             | `- Overall ψ`              | `- Overall ψ`              | `- Overall ψ`     |
| Negri         | 12/2003                         | ≤ 18                            | RCTs                  | None           | N. data sets (sample): 11 (2,711) | N. data sets (sample): 17 (148,738) | N. data sets (sample): 33 (22; 42) |
| Manzoli       | 05/2005                         | ≤ 18                            | Obs.: 10 (7,629)       | Public institutions | N. data sets (sample): 11 (2,711) | N. data sets (sample): 17 (148,738) | N. data sets (sample): 33 (22; 42) |
| Jefferson     | 09/2007                         | ≤ 16                            | Obs.: 6 (1,956)        | MedImmune      | N. data sets (sample): 11 (2,711) | N. data sets (sample): 17 (148,738) | N. data sets (sample): 33 (22; 42) |
| Rhorer *       | Not reported                    | ≤ 17                            | N. data sets (sample): 11 (2,711) | Not-for-profit foundation | N. data sets (sample): 11 (2,711) | N. data sets (sample): 17 (148,738) | N. data sets (sample): 33 (22; 42) |
| Resnikov **   | 02/2011                         | All ages §                       | RCTs                  | RCTs: 10 (12,052) | N. data sets (sample): 11 (2,711) | N. data sets (sample): 17 (148,738) | N. data sets (sample): 33 (22; 42) |
| H Moss        |                                 |                                  | Obs.: 6 (2,067)        |                |                           |                           |                   |
| Laboratory-confirmed cases |

| Vaccine efficacy, % (95% CI) | N. data sets (sample) | Vaccine efficacy, % (95% CI) | N. data sets (sample) | Vaccine efficacy, % (95% CI) | N. data sets (sample) | Vaccine efficacy, % (95% CI) | N. data sets (sample) |
|------------------------------|-----------------------|------------------------------|-----------------------|------------------------------|-----------------------|------------------------------|-----------------------|
| `- Overall ψ`               | N. data sets (sample) | Vaccine efficacy, % (95% CI) | N. data sets (sample) | Vaccine efficacy, % (95% CI) | N. data sets (sample) | Vaccine efficacy, % (95% CI) | N. data sets (sample) |
| `- Live-attenuated`          | N. data sets (sample) | Vaccine efficacy, % (95% CI) | N. data sets (sample) | Vaccine efficacy, % (95% CI) | N. data sets (sample) | Vaccine efficacy, % (95% CI) | N. data sets (sample) |
| `- Parenteral-inactivated`   | N. data sets (sample) | Vaccine efficacy, % (95% CI) | N. data sets (sample) | Vaccine efficacy, % (95% CI) | N. data sets (sample) | Vaccine efficacy, % (95% CI) | N. data sets (sample) |

**Notes:**
- ψ: Not reported
- RCTs: Randomized controlled trials
- Obs.: Observational studies
- *: Pooled analysis
- **: Meta-regression

**References:**
- Negri BM, Manzoli E, Jefferson T, Rhorer *, Osterholm M. (2021). Human Vaccines & Immunotherapeutics, 8(7), 852-862.
of LCC, which typically also include cases assessed serologically). Finally, Osterholm et al. also evaluated only vaccines licensed in USA to prevent RT-PCR or culture-confirmed influenza infections in all ages, including both RCTs and observational studies. RCTs were included in all meta-analyses, two of which also included observational studies. The funding source was not declared in one meta-analysis; a manufacturing company funded the work by Rhorer et al. and the other three meta-analyses were either funded by not-for-profit institutions or had received no funding.

For LCC, despite some diversities in outcome definition, study inclusion criteria (and discrepancies in their application), and the dates of search end (which have been detailed in the Table S1), the overall vaccine efficacy coming from RCTs (considering all vaccine types) was relatively high, ranging from 59% to 75% across all meta-analyses. Stratifying by type of vaccine, small differences could be noted for parenteral inactivated vaccines (PIV), the efficacy of which ranged from 59% to 65%, with the exception of US vaccines (46%). The latter estimate, however, was based upon a relatively small sample (n = 786). Some more variability was observed for LAV, but with the exception of the serologically-confirmed outcome, vaccine efficacy ranged from 72% to 83%. Except for PIV licensed in US, both PIV and LAV were always able to confer substantial protection against LCC. Notably, when only observational studies were considered, vaccine efficacy was lower than that from RCTs in most cases, and it fell below 50% in one analysis, which was based on one small study on LAV.

The results derived from an overarching meta-analysis considering all studies that were included in at least one meta-analysis appear in Figures S1 and S2. PIV efficacy remained around 60%, with small or any change over time and adopting various inclusion criteria (data not shown). LAV efficacy did not substantially change, being around 68%, with small variation over time. Only the choice of more stringent criteria for LCC increased the efficacy to 78%.

Table 1. Meta-analyses on influenza vaccines for healthy children / adolescents

| Vaccine efficacy, % (95% CI) | NA | 32 (-15; 60) |
|-----------------------------|----|-------------|
| N. data sets (sample)       | NA | 12 (96)     |
| RCTs: 4 (1228) **           | NA | 19 (1)      |
| Obs.: 1 (159)               | NA | 62 (3; 78)  |
| Vaccine efficacy, % (95% CI) | NA | 32 (-15; 60) |
| N. data sets (sample)       | NA | 32 (-15; 60) |
| RCTs: 14 (-39; 6)           | NA | 52 (3; 78)  |
| Obs.: 2 (5)                 | NA | NA         |

Cr, confidence interval; NA, not assessed; NR, not reported; RCT, randomized clinical trial; Obs., observational studies; q, some meta-analyses only reported separated estimates for PIV or LAV in these cases, the overall estimate of efficacy was derived combining PIV and LAV summary estimates using a generic inverse variance approach, with a random-effect method; α, The total sample of the overall meta-analysis (which includes both LAV and PIV) has been recomputed because authors repeated placebo data for each sub-trial (see Table S1 for more details); β, The values in the first line are referred to serologically-confirmed influenza cases, those in the second line to culture-confirmed influenza cases (the definition of which, however, differed from the meta-analyses by Rhorer et al. and Osterholm et al.; see Table S1); γ, authors included only studies on FluMist® live-attenuated vaccine, assessing only culture-confirmed symptomatic influenza cases; δ, authors included only studies on vaccines licensed in USA, assessing RT-PCR or culture-confirmed influenza cases. Estimates on PIV from RCTs were re-elaborated from Osterholm et al., Table 2. Estimates on PIV from observational studies were re-elaborated (to compare results with other meta-analyses, we included only outpatient subjects). All estimates in the table are referred to children only; **to be comparable, analyses were re-elaborated from analyses 8.6 and 9.6 (Colombo 2001 study was added to the meta-analysis and Vesikari 2006 data were only included once; after two doses—see Table S3 for details and references). It was not possible to report data on safety outcomes for children/adolescents because of the heterogeneity in their presentation in the included studies (see text for details).
out meta-analysis for any outcome because of the heterogeneity in the presentation of outcomes in the included studies. As for other influenza vaccines or other medical interventions (i.e., antibiotics), evidence of reporting bias was reported for LAV, and authors highlighted the need for a complete safety outcomes disclosure, into a standardized format. Although no quantitative estimates are available, however, some brief comments on the safety of influenza immunization for children could be attempted. Vaccination seems to be associated with higher rates of serious adverse events. We also extracted all data on serious vaccine-related adverse events from both RCTs and observational studies (Table S3). No deaths were observed, and in the few studies in which some serious adverse events were reported, the number of events among vaccinated and unvaccinated participants were 23 (among 20,289 participants) vs. 7 (among 8,451 participants), respectively, a difference that is not beyond chance. Importantly, one recent study (sponsored by MedImmune) used no meta-analytic technique but pooled the results of 20 RCTs to evaluate the safety of Ann Arbor strain LAV in children aged 2–17 y, finding no evidence of an increase in any potential vaccine-related serious adverse event in LAV recipients.

With regard to the interpretation of the results or specific stratified analyses or outcomes, besides AOM, no author outlined a substantial improvement or worsening of vaccine efficacy over time, and there was agreement across meta-analyses on a significant efficacy of influenza vaccination, on a higher efficacy of LAV vs. PIV, and on the scarcity of data on children aged < 2 y. In particular, only two data sets from one study (including 786 subjects) were available on PIV efficacy to prevent LAV for children under 2 y (overall efficacy 49%), while six data sets from four studies evaluated LAV efficacy in young children (6–36 mo), with a summary efficacy of 74%, based upon 10,001 subjects (Fig. S5). However, LAV is not recommended for children aged < 2 y, while PIV is recommended in several countries. In addition, very limited data are available on the safety profile of both vaccines. Therefore, although there may be few reasons to believe that data from older children cannot be transferred to younger children, more evidence is strongly needed on children aged < 2 y.

As a final remark, Manzoli et al. reported that vaccination efficacy in preventing CCC substantially improved (from 36% to 61%) when former USSR studies were excluded. The authors suggested that the larger average sample size of USSR studies (20,470 vs. 478 of non-USSR trials) might be a potential explanation for the observed finding, because careful and standardized criteria are needed to diagnose CCC and diagnoses may have been more specific in the smaller non-USSR studies. Jefferson et al. also highlighted methodological flaws of the included Russian studies (Table S4), and performed several sensitivity analyses excluding Russian studies. When these were not included, both meta-analyses of RCTs and cohort studies showed substantial increases in the overall efficacy of PIV in preventing CCC (from 36% to 60% and from 4% to 74%, respectively). Such an issue was no more noticeable in the overarching meta-analysis for LAV, while it was still apparent for PIV (Figs. S3 and S4): when Russian studies were excluded, vaccine efficacy to prevent CCC rose to 58% (95% CI: 15–79%). The sample, however, was reduced to 2087 individuals (data not shown).

Meta-analyses on seasonal vaccination for healthy adults. Three published meta-analyses evaluated the efficacy of influenza vaccines for healthy adults, while only one of them also assessed harms (Table 2). As mentioned before, the most recent meta-analysis, by Osterholm et al., evaluated only vaccines licensed in USA to prevent RT-PCR or culture-confirmed influenza infections. All meta-analyses included RCTs only and compared vaccines vs. placebo or no intervention. All meta-analyses were either funded by not-for-profit institutions or had received no funding. The detailed list of included studies and inclusion criteria for each meta-analysis is reported in the Table S5. As noted also by Osterholm et al., in the meta-analysis by Jefferson et al. we observed some major discrepancies between inclusion criteria and their application: besides minor “physiological” issues, five large data sets from four RCTs published from 2006 to March 2010 into highly-reputed journals were not included not mentioned in the review. The potential impact of study inclusions/exclusions is discussed separately for each outcome.

For LCC, the summary estimates of efficacy for PIV were comparable among the three meta-analyses, ranging from 59% to 67%. In contrast, the efficacy of LAV differed between the two meta-analyses by Villari et al. (53%; 95% CI: 35% to 66%) and Jefferson et al. (62%; 95% CI: 45% to 73%), and that by Osterholm et al. (52%; 95% CI: 2% to 55%). In a comment on Osterholm et al. results, Kerry and Valenciano acknowledged that such a difference is most probably caused by the more restrictive selection criteria for study inclusion used by Osterholm et al. In fact, the latter authors emphasized the need for routine effectiveness studies of presently licensed influenza vaccines with virus-confirmed endpoints, especially RT-PCR diagnosed infections, because culture could miss cases and serology alone would overestimate vaccine efficacy and effectiveness. As shown in the Table S5, even some supposedly minor differences in study inclusion criteria resulted in large discrepancies among meta-analyses in the number of included studies. In example, eight data sets on PIV that used control groups receiving influenza B or other vaccines were included by Villari et al. and excluded by Jefferson et al. When we investigated the potential role of study inclusion/exclusion criteria/outcome definition, and time through an overarching meta-analysis (in which we included all studies that were considered in at least one meta-analysis—Figs. S6, S7A, B and C), PIV and LAV efficacy did not substantially vary, remaining around 60% and 50%, respectively, with small or any change over time. For both vaccines, stratification by outcome showed that, as compared with cases with cultural and/or serological confirmation (LCC-C), the use of culture-confirmed cases only (LCC-G) lead to lower summary estimates of vaccine efficacy. However, the differences were not significant in all analyses, and when estimates from the same studies providing both LCC-C and LCC-G data were considered, the summary risk ratios did not substantially differ (Fig. S7C). Finally, when we re-computed the results by Jefferson et al., adding the five large data sets that were apparently missed in the search, both PIV
### Table 2. Meta-analyses on influenza vaccines for healthy adults

|                     | Villari13 | Jefferson2 | Osterholm9 |
|---------------------|-----------|------------|------------|
| End date of the search (mm/yy) | 12/2002   | 06/2010    | 02/2011    |
| Participant’s age-range (years) | 15–65     | 16–65     | All ages § |
| Included study designs | RCTs      | RCTs       | RCTs (Obs.) § |
| Funding source        | Public institutions | None | Not-for-profit foundation |

#### Laboratory-confirmed cases

- **Overall**
  - N. data sets (sample) | 25 (18,920) | 23 (37,748) | 11 (35,215) § |
  - Vaccine efficacy, % (95% CI) | 63 (13; 71) | 61 (52; 69) | 49 (16; 69) § |

- **Live-attenuated (LAV)**
  - N. data sets (sample) | 7 (6,661) Ω | 6 (8,524) | 3 (3,054) § |
  - Vaccine efficacy, % (95% CI) | 53 (35; 66) | 62 (45; 73) | 32 (12; 55) § |

- **Parenteral inactivated (PIV)**
  - N. data sets (sample) | 18 (12,259) Ω | 17 (31,265) | 8 (32,161) § |
  - Vaccine efficacy, % (95% CI) | 67 (55; 76) | 61 (48, 70) | 59 (31; 67) § |

- **Aerosol inactivated (AIV)**
  - N. data sets (sample) | 0 (0) | 0 (0) | 0 (0) |
  - Vaccine efficacy, % (95% CI) | – | – | – |

#### Clinically-confirmed cases

- **Overall**
  - N. data sets (sample) | 49 (46,622) | 35 (34,819) | NA |
  - Vaccine efficacy, % (95% CI) | 22 (16; 28) | 19 (6; 30) | NA |

- **Live-attenuated**
  - N. data sets (sample) | 8 (13,964) Ω | 6 (12,688) | NA |
  - Vaccine efficacy, % (95% CI) | 15 (8; 23) | 10 (6; 16) | NA |

- **Parenteral inactivated**
  - N. data sets (sample) | 35 (30,121) Ω | 25 (25,065) | NA |
  - Vaccine efficacy, % (95% CI) | 23 (15; 30) | 20 (15; 29) | NA |

- **Aerosol inactivated**
  - N. data sets (sample) | 6 (1,937) Ω | 4 (1,674) | NA |
  - Vaccine efficacy, % (95% CI) | 55 (27; 72) | 42 (17; 60) | NA |

#### Mild/moderate adverse events

- **Local harm**
  - N. data sets (sample) | NA | LAV: 3 (4,921); PIV: 14 (6,833); AIV: 3 (565) | NA |
  - Increase in Risk, % (95% CI) | NA | LAV: 3 (15; 30); PIV: 16 (6; 30) | NA |

- **Fever**
  - N. data sets (sample) | NA | LAV: 3 (713); PIV: 8 (2775); AIV: 0 (0) | NA |
  - Increase in risk, % (95% CI) | NA | LAV: 28 (7; 279); PIV: 17 (10; 2); AIV: – | NA |

- **Systemic, any**
  - N. data sets (sample) | NA | LAV: 5 (1,018); PIV: 8 (2,603); AIV: 3 (565) | NA |
  - Increase in risk, % (95% CI) | NA | LAV: 40 (18; 138); PIV: 29 (1; 64); AIV: -17 (-46; 27) | NA |
The authors discussed the results of three observational studies on Guillain-Barré syndrome with contrasting results, but focused on the results of one study, which estimated the incidence of vaccine-related Guillain-Barré syndrome as 1.6 extra cases per million vaccinations.9

Jefferson et al. expressed some concerns on publication bias (which was also reported for CCC by Villari et al.), and warned against a potential reporting bias of privately sponsored studies.

Meta-analyses on seasonal vaccination for the elderly. We found six meta-analyses which evaluated the efficacy/effectiveness of influenza vaccination in people older than 64 years.1,3,9,11,14,41 and only one of them also assessed harms (Table 3).1 Meta-analysis focused on hospitalizations only and included a subset of studies (n = 8) already considered in the Gross et al. meta-analysis.1 It is therefore not discussed. Another meta-analysis was excluded because only subjects with underlying chronic diseases were included.44 All remaining reviews did not consider (or treated separately) studies which included only selected groups of elderly (i.e., affected by a specific disease such as diabetes etc.), as they were interested in the whole population of elderly.43-45 One meta-analysis, however, included only community-living elderly.44 The

| Table 2. Meta-analyses on influenza vaccines for healthy adults |
|---------------------------------------------------------------|
| **Serious adverse events**                                    |
| Villari3,13 Jefferson3 Osterholm9                              |
| N. studies (sample)                                          |
| NA                                                            |
| Increase in risk, % (95% CI)                                  |
| NA                                                            |
| Table 3. Meta-analyses on influenza vaccines for the elderly |
|---------------------------------------------------------------|
| **Laboratory-confirmed cases**                                |
| - Parenteral inactivated                                      |
| N. data sets (sample)                                        |
| NA                                                            |
| RCTs: 3 (2,217)                                              |
| Obs.: 10 (20,190)                                            |
| Osterholm4                                                   |
| Public institution                                           |
| Not-for-profit foundation                                    |
| NA                                                            |
| RCTs: Obs.                                                   |
| NA                                                            |
| Increase in risk, % (95% CI)                                  |
| NA                                                            |
| RCTs: 3 (2,217)                                              |
| Obs.: 10 (20,190)                                            |
Table 3. Meta-analyses on influenza vaccines for the elderly (continued)

| Vaccine efficacy, % (95% CI) | Gross\(^1\) | Vu\(^2\) | Jefferson\(^3\) | Osterholm\(^9\) |
|-----------------------------|------------|--------|----------------|----------------|
| Clinically-confirmed cases  |            |        | RCTs: 58 (54; 73) | Obs.: 63 (28; 81) |
| - Parenteral inactivated     | RCTs: 4 (9;894) | Obs.: 37 (66;239) | NA | |
| N. data sets (sample)       | 23 (9;043) | RCTs and Obs.: 3 (8;271) | NA | |
| Vaccine efficacy, % (95% CI) | 56 (19;68) | RCTs and Obs.: 35 (19;47) | NA | |
| Hospitalization for influenza or pneumonia |            |        | RCTs: 1 (699) | Obs.: 7 (742;575) |
| - Parenteral inactivated     | RCTs: 4 (6;894) | Obs.: 37 (66;239) | NA | |
| N. data sets (sample)       | 9 (24;324) | Obs.: 9 (> 446;336) | NA | |
| Vaccine efficacy, % (95% CI) | 48 (28;65) | Obs.: 33 (27;38) | NA | |
| Mortality for any cause      |            |        | RCTs: -2 (-872; 89) | Obs.: 47 (39; 54) |
| - Parenteral inactivated     | RCTs: 1 (699) | Obs.: 7 (742;575) | NA | |
| N. data sets (sample)       | 30 (10;028) | Obs.: 4 (163;087) | NA | |
| Vaccine efficacy, % (95% CI) | 68 (56;76) | Obs.: 50 (45;56) | NA | |
| Mild/moderate adverse events |            |        | RCTs: 2 (672; 89) | Obs.: 47 (39; 54) |
| - Local pain                 | RCTs: -2 (-872; 89) | Obs.: 47 (39; 54) | NA | |
| N. data sets (sample)       | NA | NA | 4 (2;564) | NA |
| Increase in risk, % (95% CI) | NA | NA | 256 (19;387) | NA |
| - Fever                     | RCTs: -2 (-872; 89) | Obs.: 47 (39; 54) | NA | |
| N. data sets (sample)       | NA | NA | 3 (2;519) | NA |
| Increase in risk, % (95% CI) | NA | NA | 57 (8; 171) | NA |
| - Systemic, any             | RCTs: -2 (-872; 89) | Obs.: 47 (39; 54) | NA | |
| N. data sets (sample)       | NA | NA | 1 (8;72) | NA |
| Increase in risk, % (95% CI) | NA | NA | 75 (26; 312) | NA |
| Serious adverse events      |            |        | RCTs: 2 (672; 89) | Obs.: 47 (39; 54) |
| (Guillain-Barré syndrome)   | RCTs: -2 (-872; 89) | Obs.: 47 (39; 54) | NA | |
| N. data sets (sample)       | NA | NA | 4 (> 100 millions) | NA |
| Increase in risk, % (95% CI) | NA | NA | 60 (53; 444) | NA |

RCT, randomized clinical trial; Obs., observational studies; CI, confidence Interval; NA, not assessed; NR, not reported. \(^1\) RCTs were searched but none was found including only elderly. Only two out of four studies reported outcome stratified by age, allowing data extraction for subjects aged 64 and over; the other two studies included subjects aged 18 and over, with no stratification. \(^2\) Authors included solely the studies enrolling community-living elderly only, with samples larger than 30; in which the influenza vaccine strain matched the circulating strain. It was not possible to extract the total number of subjects enrolled in the studies evaluating hospitalizations. Cohort and case-control studies were pooled together. \(^3\) Authors included only studies on vaccines licensed in US, assessing RT-PCR or culture-confirmed influenza cases. Estimates on LAV from RCTs were re-elaborated from Osterholm et al., Table 3. All estimates reported in the table are referred to elderly only. \(^4\) Results have been re-elaborated combining studies on community-dwelling elderly (analyses 2.1) and elderly from nursing homes, with (analysis 1.1) or without (analysis 1.2) a clear definition of the outcome. Only meta-analyses on cohort studies have been used. \(^5\) Adjusted rates of community-dwellers only. \(^6\) Re-elaborated from Jefferson et al., Table 1; the samples were the entire US population in different seasons plus 21 million subjects from another study.

Most recent meta-analysis also adopted restrictive inclusion criteria, as authors evaluated only vaccines licensed in US to prevent RT-PCR or culture-confirmed influenza infections. All reviews also considered RCTs in addition to observational studies, but only one provided summary estimates for RCTs-RCTs are uncommon because most ethics committees reject experimental study designs for interventions that are recommended, such as influenza vaccination for the elderly. Also, overall only one study was found on LAV showing a significant 62% vaccine efficacy in preventing RT-PCR/culture confirmed influenza cases, and one study on AIV (which failed to show a significant protection by vaccination), thus all estimates and our discussion only refer to PIV. The
with those from other reviews. Gross et al. used unadjusted estimates, mostly included elderly from nursing homes and also included one RCT. In fact, when the Gross et al. results are compared with those of the stratified meta-analysis of cohort studies in nursing homes by Jefferson et al., using unadjusted estimates, the summary estimates are practically identical (respectively, 48% and 49%, with similar confidence limits). However, eight community cohort studies that were published after the Gross et al. meta-analysis provided adjusted rates of hospitalizations due to influenza and pneumonia—and protection (63%; 28% to 81%) was found when we combined the results of the only two studies included in Osterholm et al. meta-analysis that evaluated vaccine effectiveness through a more specific outcome (RT-PCR or culture-confirmed influenza infections only). These studies were both published after the end of the search by Jefferson et al., and thus no meaningful comparison is possible. Notably, the inclusion of LCC based on serology alone (as made in Jefferson et al. review), if any, should have lead to an over-rather than under-estimation of vaccine effectiveness. Therefore, no firm conclusions can be drawn and some uncertainty remains on this important issue. Given that vaccination was found to be significantly effective in preventing the other traditional outcome—CCC (as discussed below)—which is typically characterized by lower efficacy estimates, the LCC finding in Jefferson et al. is to some extent paradoxical.

Concerning CCC, all reviews showed a significant protection conferred by vaccination. The four RCTs showed a summary efficacy estimate of 41%, while the overall effectiveness from meta-analyses of cohort studies ranged from 56% to 24%. Eleven data sets (some of which with large samples) were published after the meta-analysis by Gross et al., and only three of them showed a significant effectiveness by vaccination. Thus, the Jefferson et al. results could simply be more updated, and no discrepancy really exists. As regards Vu et al., effectiveness was relatively low (35%), due to restrictive inclusion criteria (studies enrolling community-living elderly only; with samples larger than 30; in which the influenza vaccine strain matched the circulating strain), such an estimate was based on three studies only with different designs: one RCT, one non randomized clinical trial, and one cohort study. Moreover, when we performed a meta-analysis restricted to the seven data sets that were published after 2000 (the year of the search end by Vu et al.), the summary vaccine efficacy was similar to the overall one reported by Jefferson et al. (31%; 95% CI: -1%; 53%—Fig. S10). Therefore, overall, the summary estimate by Jefferson et al. could be considered the most reliable one. Although the effectiveness of vaccine in preventing CCC in the elderly is modest (24%), it matches quite well that of the adults (19–22%) and there are no reasons to believe that it should be relevantly higher. Three meta-analyses evaluated other outcomes than CCC and LCC. With regard to hospitalizations due to influenza or pneumonia, PIV was significantly better than placebo in all meta-analyses, whereas the summary estimates varied, ranging from 48% to 27%. Besides the more selective inclusion criteria discussed above, both case-control and cohort studies were included by Vu et al., thus their results could not be compared...
three surveillance studies on the association between vaccination and mortality. Osterholm et al. concluded that “the 47% reduction in risk of all-cause mortality in elderly community-dwellers observed in this review, exceeds by far the estimated possible impact of influenza on winter-seasonal mortality of 5% in an average season.” It is very likely that observational studies are extremely difficult to prove beyond doubt with observational studies and would require the conduct of very large pragmatic RCTs.

Meta-analyses on pre-pandemic vaccines (H5N1) and pandemic 2009 (H1N1) vaccines. One meta-analysis and one systematic review evaluated the immunogenicity and harms of “Avian” influenza H5N1 vaccines. Manzoli et al. included only RCTs evaluating all vaccines (including a total of 58 data sets with more than 10,000 subjects), while Prieto-Lara et al. considered also non-randomized studies, however evaluating only licensed vaccines (including a total of 17 data sets with 6476 subjects).

Both stopped their search during 2009 and tried to identify the best formulation among several doses of vaccines containing either no adjuvant, adjuvants based on aluminum or oil-in-water emulsion-based adjuvants. In addition to traditional head-to-head comparisons, Manzoli et al. also synthesized the evidence using multiple treatments meta-analysis that can incorporate the evidence from all comparisons of different treatments within a single analysis, allowing a better appreciation of the relative merits of each treatment within a common analytical framework. Despite such differences, the conclusions were in agreement: the best available option in a pandemic is currently represented by emulsion-based adjuvants. In addition to traditional head-to-head comparisons, Manzoli et al. also synthesized the evidence using multiple treatments meta-analysis that can incorporate the evidence from all comparisons of different treatments within a single analysis, allowing a better appreciation of the relative merits of each treatment within a common analytical framework.

Despite such differences, the conclusions were in agreement: the best available option in a pandemic is currently represented by oil-in-water adjuvanted vaccines, administered in two doses containing each 3.8–6 μg of hemagglutinin antigen. These formulations were more prone to cause adverse reactions, but they were the only preparations showing acceptable immunogenicity rates (a 70%), so the trade-off may be considered acceptable. Finally, both reviews found no serious vaccine-related adverse events, and concluded that all tested vaccines had an acceptable safety profile. In the absence of studies on clinical outcomes, however, the efficacy/effectiveness of the vaccine cannot be taken for granted.

Also the two meta-analyses on pandemic influenza 2009 (H1N1) vaccines come to substantially similar conclusions: after two doses, all split/subunit inactivated vaccines were able to confer adequate seroprotection (a 70%); after one dose only, all split/subunit vaccines were highly immunogenic in adults and adolescents, while only high doses of non-adjuvanted vaccines or oil-in-water adjuvanted formulations (even at doses as low as 1.8 μg of hemagglutinin antigen) showed acceptable results in elderly and children. The latter preparations (oil-in-water...
emulsion-based) were also more immunogenic at any dose. As regards harms, the findings were similar to those on H5N1 vacci-
nation: both meta-analyses found a higher (and high) frequency
of mild or moderate adverse events by oil-in-water adjuvants,
although they concluded that such a lower tolerability could be
acceptable in a pandemic, and a low rate of serious adverse events
(three, all solved in 10 d, out of 22,826 vaccinated subjects).15 Such
conclusions were based upon a large set of meta-analyses
including a total of 52 data sets from 17 clinical trials (17,921
subjects),15 or 76 data sets from 18 RCTs (enrolling 16,725 sub-
jects) and 18 data sets from 14 clinical trials (2,495 subjects).5 No
formal meta-analysis has addressed clinical efficacy/effectiveness.
However, scattered large observational studies evaluating clinical
outcomes seem to confirm the favorable results on immuno-
genicity and tolerability.53-56 Also, one recently published computer
simulation model concluded that 2009 (H1N1) vaccination for
children and adults is cost-effective compared with other preven-
tive health interventions under a wide range of scenarios.57 The
lack of formal clinical efficacy/effectiveness meta-analyses, how-
ever, is a concern that cannot be dismissed.

For both H5N1 and 2009 pandemic (H1N1) vaccines, Mantzolou et al. highlighted the need for more RCTs (especially if publicly sponsored, given than most trials were sponsored by manufacturing companies) comparing vaccines including different adjuvants, and reported a high potential for publication bias, in particular for the meta-analysis on H1N1 vaccination.54 In fact, after 2.5 y from the pandemic start, only 21 RCTs evaluating influenza 2009 (H1N1) vaccines were published out of 73 RCTs that were registered in trial registries (68 of them had also been completed by June 30, 2011).55

Methods

Aims and search strategy. The main purpose of this umbrella
review is to systematically compile the main findings, including
estimates of effects for major outcomes for all age-classes and
influenza vaccines from published meta-analyses. We aimed to
juxtapose these results for an overall comparative evaluation of
the data. Furthermore, we have tried to evaluate whether any
substantial differences in meta-analyses findings (or their inter-
pretation) exist, and, if so, which could be the most reasonable
explanations, e.g., inclusion or exclusion of specific studies, or
evolution of the effects over time with differences in earlier vs.
more recent studies. We focused on healthy participants derived
from the general population of different age-groups, excluding
meta-analyses that focused on people with specific diseases or
comorbidities.

Meta-analyses or systematic reviews evaluating influenza vac-
cine safety and/or efficacy/effectiveness in humans were retrieved
through searches in MEDLINE, EMBASE, and the Cochrane
Database of Systematic Reviews with no language restriction
(last update December 1, 2011). Search terms were “influenza,”
“vaccine,” “vaccination,” and “meta-analysis or pooled analy-
sis or systematic review” in all fields. The bibliographies of all
relevant articles including reviews were reviewed for further eli-
gible references. We included meta-analyses of either randomized
controlled trial (RCTs) and observational studies, on any type
of influenza vaccine, assessing protection vs. naturally occurring
infection.

Eligible meta-analyses and outcomes. We focused on meta-
analyses evaluating clinical outcomes and/or harms. When infor-
ma tion on clinical outcomes was not available (as in the case of
H5N1 and 2009 H1N1 vaccines), meta-analyses on immuno-
genicity outcomes were also examined. We considered consistently
the two traditional clinical outcomes—laboratory confirmed
cases (LCC) and clinically confirmed cases (CCC)—that have
been sometimes also defined as “efficacy” and “effectiveness,”
respectively, based upon their different specificity (much lower
for CCC). One should be aware that this distinction has recently
been challenged58 because both outcomes are extracted from
RCTs, while in classic epidemiology efficacy refers to the rela-
tive risk reduction attributed to vaccination as estimated from a
RCT, and effectiveness refers to the same measure of effect from
an observational study.59 Additional outcomes considered were:
effect on acute otitis media (for children), hospitalizations (for
adults and elderly), and mortality (for elderly). We excluded meta-
analyses that focused on specific topics or hypotheses related to
influenza vaccine efficacy/effectiveness or safety (e.g., gender dif-
f erences, or other postulated effect modifiers) without providing
overall estimates of vaccine impact on any eligible outcomes.60-62

Funding, potential biases and interpretation. For each meta-
analysis, we also reported whether it stated sources of funding (in
particular public/governmental and industry). We also recorded
potential biases identified by the authors of each meta-analysis
(including confounding, selection and information biases in the
included studies, as well as sponsorship, publication, and selective
reporting biases in the accumulated available evidence). Finally,
we recorded the interpretation of the authors for the overall
results and juxtaposed these final interpretations and conclusions
across meta-analyses on the same age group.

Comparative evaluation of included/excluded studies and
overarching meta-analyses. Different published meta-analyses
on the same age group and type of vaccine may reach differ-
ent conclusions, because they vary on which trials they include
or exclude. This may be due to differences in eligibility crite-
rion, non-sensitive literature searches, differences in timing of the
meta-analyses (more recent papers would include more trials), or
other reasons. In order to probe these possibilities for each major
age group and type of vaccine, we juxtaposed the included stud-
ies in each published meta-analysis and recorded the apparent
reasons for the non-inclusion/exclusion of each trial from each
meta-analysis where it had not been used in the summary effect
calculations. We also performed overarching meta-analyses: these
are re-analyses for each age group and vaccine that included all
the trials that had been included in at least one published
meta-analysis of the same age group and vaccine type. Data were
synthesized using the risk ratio metric and using a random effects
model.63 Heterogeneity metrics are also provided (chi-square
based Q test and I-squared metric), but should be interpreted
cautiously in the presence of few studies per meta-analysis.64 All
calculations were made in RevMan 5.0 (Copenhagen: The
Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Studies were ordered chronologically in the forest plots, so as to discern any strong evidence for changes in effect sizes over time. Formal cumulative meta-analyses are also available from the corresponding author. Any obvious data errors in the previous meta-analyses were also corrected in the re-analysis process.

Conclusions

Most influenza vaccines have been shown to confer some protection against naturally acquired infection and no evidence for major harms has emerged. In adults and children, the efficacy/current effectiveness of current seasonal vaccines was generally high for laboratory-confirmed cases (especially for LAV in children aged 2–17 y), and modest for clinically-confirmed cases and for the elderly. For children aged < 2 y, while several studies support LAV efficacy, the evidence on PV efficacy and safety data remains scarce. Some of the outcomes have results that seem incongruent when juxtaposed, e.g., the huge impact on all-cause mortality in the elderly as opposed to far more modest effects against CCC. Data on harms are reassuring, and there is no selective evidence that Guillain-Barré syndrome should be a concern. However, the overall quality of the harms data are suboptimal, and this information seems to suffer from lack of standardized definitions and data collection and inconsistent and potentially selective reporting. Pre-pandemic H1N1 and 2009 pandemic H1N1 vaccines in particular can achieve satisfactory immunogenicity, when given at proper doses and formulations, but no meta-analysis has addressed H1N1 vaccination impact on clinical outcomes. Although we identified several discrepancies among meta-analyses on seasonal vaccines for children and elderly, it is possible to conclude that most seasonal influenza vaccines showed statistically significant efficacy/effectiveness, the magnitude of which, however, largely varied. The use of influenza vaccines is recommended worldwide, and this makes the conduct of pragmatic RCTs with hard clinical outcomes difficult in some settings. Cost-effectiveness issues have to be properly re-assessed in times of economic recession.

We certainly embrace the request by Osterholm et al for a new generation of more highly effective seasonal vaccines. There is also still an unmet need for adequately powered publicly-funded RCTs on both young children and elderly. Ethics committees should acknowledge this need and allow the conduct of well-planned experimental studies in particular in children and in people aged 65 y and older. Finally, these RCTs should not only be registered in public trial registries, but also promptly published without selective analysis and reporting biases affecting the results or their interpretation.

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Supplemental Materials

Supplementary materials may be found at:

www.landesbioscience.com/journals/vaccines/article/19917

References

1. Goon MA, Harrington ARE, Sooth HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly people. A meta-analysis and review of the literature. Ann Intern Med 1995; 123:518-27. PMID:7746477
2. Jefferson T, Di Pietrantonj C, Borell A, Hassan GM, Al-Ansary LA, Torelli P. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 2010; CD006120. PMID:20064924
3. Jefferson T, Di Pietrantonj C, Al-Ansary LA, Torelli P, Thersing S, Thomas RE. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev 2010; CD006120. PMID:20064924
4. Jefferson T, Borell A, Harkin A, Di Pietrantonj C, Daneshzadeh V. Vaccines for preventing influenza in healthy children. Cochrane Database Syst Rev 2008; CD003457. PMID:18373055
5. Macken L, De Vries C, Salton G, Al-Ansary M, Villari P, Ioannidis JP. Meta-analysis of the immunogenicity and safety of the pandemic pandemic A/H1N1 influenza vaccine. Flued. 2011; 6:4-9.406.http://dx.doi.org/10.1177/1650632610382253; PMID:21175319
6. Macken L, Salton G, De Vries C, Bocca A, Ioannidis JP, Villari P. Immunogenicity and adverse events of a trivalent influenza A (H1N1) vaccine in healthy adults: a multiple-treatments meta-analysis. Lancet Infect Dis 2009; 9:442-52. PMID:19910743
7. Macken L, Salton G, De Vries C, Bocca A, Ioannidis JP, Villari P. A multivariate analysis of the risks of a trivalent influenza A (H1N1) vaccine in healthy adults: a multiple-treatments meta-analysis. Lancet Infect Dis 2009; 9:442-52. PMID:19910743
8. Nigri E, Colombo C, Gismondo L, Greot N, Apolloni G, La Vecchia C. Influenza vaccine in healthy children: a meta-analysis. Vaccine 2009; 27:3417-21. http://dx.doi.org/10.1016/j.vaccine.2009.02.059; PMID:19275783
9. Osterholm MT, Kuller LL, Cinti S, Bologna EA. Efficacy and effectiveness of influenza vaccine: a systematic review and meta-analysis. Lancet Infect Dis 2011; 11:22-34. PMID:21160566
10. Porter-Law E, Hanno-Müller A. Safety and immunogenicity of pandemic H1N1 influenza vaccine: a systematic review of the literature. Vaccine 2010; 28:6326-36.http://dx.doi.org/10.1016/j.vaccine.2010.05.068; PMID:20693350
11. Peng Barbetti J, Marques Galindo S. Efficacy of influenza vaccine in the elderly: a critical review of the evidence. Med Clin (Barc) 1995; 105:645-8; PMID:798184
12. Gross PA, Hermogenes AW, Sacks HS, Lau J, Jefferson T, Di Pietrantonj C, Al-Ansary LA, Ferroni E, Thersing S, Thomas RE. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 2010; CD004876; PMID:20166072.
13. van der Heijden GA, Al-Ansary LA, Ferroni E. Vaccines for preventing influenza in elderly persons. A meta-analysis and review of the literature. Vaccine 2010; 28:6326-36.http://dx.doi.org/10.1016/j.vaccine.2010.03.068; PMID:20693350
14. Petrie RB, Järvinen S. Gender differences in local and systemic reactions to annually repeated vaccination: a meta-analysis of serologic and immunologic data. Vaccine 2006; 24:4875-86. http://dx.doi.org/10.1016/j.vaccine.2006.04.006; PMID:16885197
15. Tappenden K, Mactier R, Maitland M. Estimating the effect of influenza vaccine. Lancet Infect Dis 2011; 11:2-5. PMID:21361645
16. Lau J, ed. A dictionary of epidemiology, 4th edn. New York: Oxford University Press, 2001.
17. Broz WE, de Rougemont P, Rüegg AM, Werdan KG, Osterholm MT. Precaution against influenza after annually repeated vaccination: a meta-analysis of serologic and field studies. Arch Intern Med 1999; 159:182-8. http://dx.doi.org/10.1001/archinte.159.2.182; PMID:9927024
18. Broz WE, Rüegg AM, Kurrer B, Ruedi N. Gender differences in local and systemic reactions to inactivated influenza vaccine, established by a meta-analysis of fourteen independent studies. Eur J Clin Microbiol Infect Dis 1994; 13:180-6. http://dx.doi.org/10.1007/BF01586187; PMID:819960
attenuated influenza vaccine in children aged 2-17.

study analysis of the safety of Ann Arbor strain live influenza vaccine. J Infect Dis 2002; 185:1137-42. http://dx.doi.org/10.1086/339885; PMID:12027719

Osterhaus AD. Immunogenicity and safety of inactivated influenza vaccine in children. Pediatr Infect Dis J 2011; 30:203-7. PMID:21301216

CS. The efficacy of live attenuated influenza vaccine in children and youth for the 2011/2012 season. Pediatr Infect Dis J 2012; 31:235-42. http://dx.doi.org/10.1097/Inf.0b013e31825905f5; PMID:22275555

Osterhaus AD, Fauquet C, Haagmans B, Heeres J, Bergeron J, Wertzova V, Honegr K, Kaliskova E, Schief RR. Evaluation of monovalent influenza vaccine in a simian community during the epidemic of 2009-2010 (I-MOVE). PLoS ONE 2011; 6:e19458. http://dx.doi.org/10.1371/journal.pone.0019458; PMID:21921200

Lin NM, van der Zuil BA, Boon CJ, Osterhaus AD. Impact of influenza vaccination on household contacts. Vaccine 2011; 29:7975-81. http://dx.doi.org/10.1016/j.vaccine.2011.08.068; PMID:21884747

Rossiter LA, Lavelle TA, Fiore AE, Bridges CB, Reed C, Jain S, et al. Cost-effectiveness of 2009 pandemic influenza A(H1N1) vaccination in the United States. Vaccine 2011; 29:4163-75. http://dx.doi.org/10.1016/j.vaccine.2011.05.005; PMID:21523194

Villari P. Publication delay of randomized trials on influenza A(H1N1) vaccination in the United States. BMJ 2011; 342:cbd1512. http://dx.doi.org/10.1136/bmj.cbd1512; PMID:21824956

Iavazzino MA, Mannucci L, Di Vito C, D’Addario M, Villar P. Publication delay of randomized trials on 2009 H1N1 influenza vaccination. JAMA 2011; e28:1-10. http://dx.doi.org/10.1001/jama.2011.13716; PMID:21805298

Chiatti C, Barchiesi B, Lammara G, Di Santantonio E, Fughi P. Improving the delivery of the vaccine for the older people in times of economic recession: what social epidemiology tells us, and what else we need to know. Eur J Public Health 2011; 21:986-90. http://dx.doi.org/10.1093/eurpub/cqr036; PMID:21727853

Dearth AS, Moffett CR, Bowdell A, Dreyer DE, Lindley BI, Boru R, et al. Inapparently matched influenza vaccine will provide protection in frail elderly. Vaccine 2010; 28:664-7. http://dx.doi.org/10.1016/j.vaccine.2010.04.002; PMID:20359352

Jackson LA, Jackson RL, Nelson JC, Lonial KM, Winstead MJ. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. J Epidemiol Community Health 2006; 60:44-9. http://dx.doi.org/10.1136/jech.2005.036736; PMID:16467875

Steyn CG, Steyn MS. Risk factors and interventions with statistically significant effects. Int J Epidemiol 2011; 40:832-37. http://dx.doi.org/10.1093/ije/dyr097; PMID:21776969

Sahni G, Higgins JP, Adis AE, Ioannidis JP. Evaluation of network of randomized trials. Stat Methods Med Res 2008; 17:179-301. http://dx.doi.org/10.1177/0962280208087643; PMID:17972835

Valenzuela M, Kosting F, Cohen JM, Ornski L, Barrett AS, Rice C, et al. Estimation of pandemic influenza vaccine effectiveness in Europe, 2009-2010: results of Influenza Monitoring Vaccine Effectiveness in Europe (IMoVE) multicentre case-control study. PLoS Med 2011; 8:e1001088. http://dx.doi.org/10.1371/journal.pmed.1001088; PMID:21937310

Wu Y, Xu X, Li J, Li M, Xiao J, Gao Y, et al. Safety and effectiveness of a 2009 H1N1 vaccine in Beijing. N Engl J Med 2010; 363:266-75. http://dx.doi.org/10.1056/NEJMoa0909396; PMID:20056658

Mehner S, Henselmann R, Elliott L, Holsmann T, Krabbe C, Casadevall A, et al. The effectiveness of the pandemic H1N1 influenza vaccine against laboratory-confirmed H1N1: subgroups population-based case-control study. Vaccine 2011; 29:477-83. http://dx.doi.org/10.1016/j.vaccine.2011.02.008; PMID:21288687

Pozner LS, Landau TH, Bros AE, Bridges CB, Rod C, Jan A, et al. Effectiveness of 2009 pandemic influenza A H1N1 vaccine in the United States. N Engl J Med 2010; 363:557-64. http://dx.doi.org/10.1056/NEJMoa0909396; PMID:20056658

Iranmanesh R, Schrag AS, Cohen JM, Ornski L, Barrett AS, Rice C, et al. Estimation of pandemic influenza vaccine effectiveness in Europe, 2009-2010: results of Influenza Monitoring Vaccine Effectiveness in Europe (IMoVE) multicentre case-control study. PLoS Med 2011; 8:e1001088. http://dx.doi.org/10.1371/journal.pmed.1001088; PMID:21937310

Saira G, Higgins JP, Adis AE, Ioannidis JP. Evaluation of network of randomized trials. Stat Methods Med Res 2008; 17:179-301. http://dx.doi.org/10.1177/0962280208087643; PMID:17972835

Valenzuela M, Kosting F, Cohen JM, Ornski L, Barrett AS, Rice C, et al. Estimation of pandemic influenza vaccine effectiveness in Europe, 2009-2010: results of Influenza Monitoring Vaccine Effectiveness in Europe (IMoVE) multicentre case-control study. PLoS Med 2011; 8:e1001088. http://dx.doi.org/10.1371/journal.pmed.1001088; PMID:21937310