

# Effect of Influenza Vaccination of Healthcare Personnel on Morbidity and Mortality Among Patients: Systematic Review and Grading of Evidence

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(See the Editorial Commentary by Griffin on pages 58–60.)

**Background.** Influenza vaccination of healthcare personnel (HCP) is recommended in >40 countries. However, there is controversy surrounding the evidence that HCP vaccination reduces morbidity and mortality among patients. Key factors for developing evidence-based recommendations include quality of evidence, balance of benefits and harms, and values and preferences.

**Methods.** We conducted a systematic review of randomized trials, cohort studies, and case-control studies published through June 2012 to evaluate the effect of HCP influenza vaccination on mortality, hospitalization, and influenza cases in patients of healthcare facilities. We pooled trial results using meta-analysis and assessed evidence quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

**Results.** We identified 4 cluster randomized trials and 4 observational studies conducted in long-term care or hospital settings. Pooled risk ratios across trials for all-cause mortality and influenza-like illness were 0.71 (95% confidence interval [CI], .59–.85) and 0.58 (95% CI, .46–.73), respectively; pooled estimates for all-cause hospitalization and laboratory-confirmed influenza were not statistically significant. The cohort and case-control studies indicated significant protective associations for influenza-like illness and laboratory-confirmed influenza. No studies reported harms to patients. Using GRADE, the quality of the evidence for the effect of HCP vaccination on mortality and influenza cases in patients was *moderate* and *low*, respectively. The evidence quality for the effect of HCP vaccination on patient hospitalization was *low*. The overall evidence quality was *moderate*.

**Conclusions.** The quality of evidence is higher for mortality than for other outcomes. HCP influenza vaccination can enhance patient safety.

**Keywords.** decision making; evidence-based medicine; health personnel; influenza vaccines; quality of healthcare.

Influenza vaccination of healthcare personnel (HCP) is recommended in the United States and in >40 other countries [1, 2]. Infected HCP may transmit

influenza to patients, many of whom have serious underlying conditions that increase the risk of complications [3]. There is, however, controversy surrounding the evidence that HCP influenza vaccination reduces morbidity and mortality among patients [4–6]. Of 2 recent systematic reviews, 1 concluded that there is likely a protective effect for patients in long-term care settings [6], and the other concluded that there is a lack of evidence [5]. The main controversies centered on the appropriateness of nonspecific patient outcomes and the quality of the overall body of evidence.

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Our objectives were to conduct a systematic review and to grade the quality of evidence to ascertain the effect of influenza vaccination of HCP on morbidity and mortality in patients of healthcare facilities.

## METHODS

### Search Strategy

We conducted electronic searches of Medline, Embase, CINAHL, Web of Science, and the Cochrane Library for studies published from 1948 through June 2012. Search terms are provided in [Supplementary Table 1](#). We searched for additional studies by scanning references of included studies as well as relevant reviews.

### Study Selection and Data Extraction

We included randomized controlled trials, cohort studies, and case-control studies published in any language that reported the association between vaccination of HCP with inactivated influenza vaccine or live attenuated influenza vaccine (LAIV) and morbidity/mortality in patients of healthcare facilities. Two reviewers (M.C.L. and N.A.) selected studies in 2 stages: review of titles and abstracts, then review of full-text articles. Discrepancies or disagreements were resolved through discussion between the 2 reviewers or with a third reviewer (F.A.). Three reviewers (M.C.L., N.A., F.A.) independently extracted data from eligible full-text articles using standardized forms and graded the quality of evidence; any disagreements were resolved by discussion. We did not contact study authors for additional information.

### Grading Quality of Evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology for grading the quality of evidence [7]. GRADE is used by >60 organizations worldwide, including the US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices, the National Institute of Health and Clinical Excellence (United Kingdom), the Norwegian Directorate of Health, the Robert Koch Institute (Germany), and the World Health Organization [8].

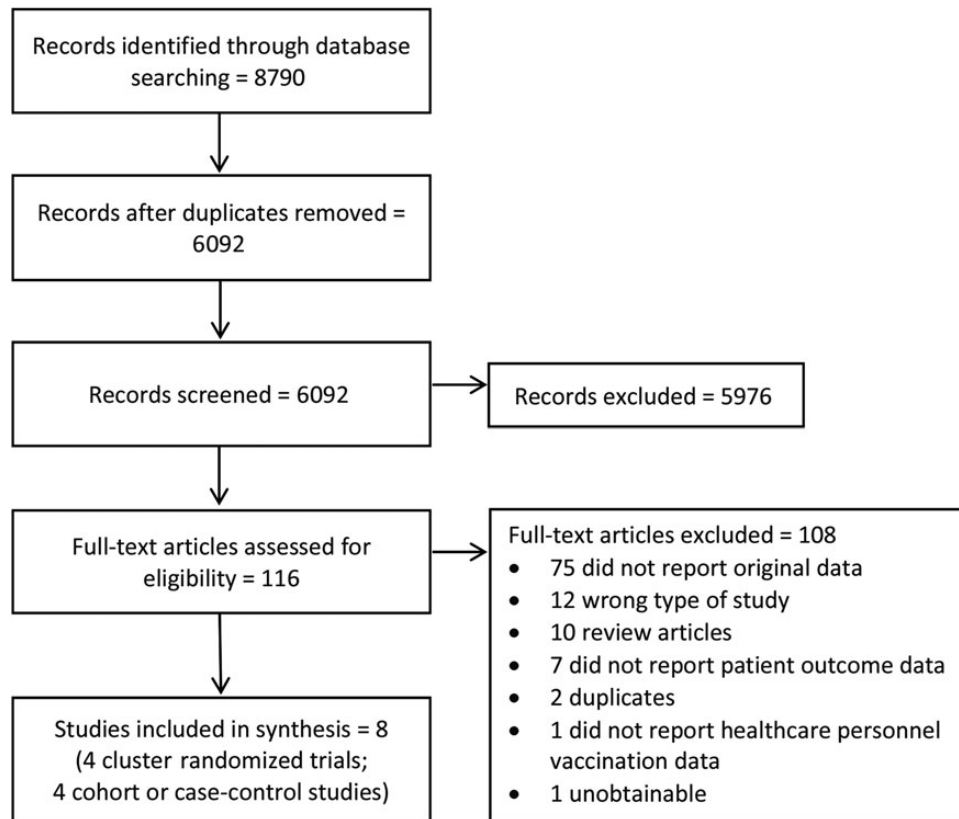
Grading quality of evidence begins with the study design. The initial evidence grade is classified as *high* for randomized controlled trials (RCTs) and *low* for observational studies. There are 5 GRADE criteria for downgrading the evidence grade: risk of bias, inconsistency, indirectness, imprecision, and publication bias. There are 3 GRADE criteria for upgrading the evidence grade: large magnitude of effect, dose-response, and opposing residual confounding or bias. These criteria determine the final classification into 4 evidence grades (*high*, *moderate*, *low*, or *very low*) [9]. The evidence grades reflect confidence in effect estimates.

For assessing risk of bias for cluster randomized trials, we used a tool developed by the Cochrane Collaboration that includes consideration of the following biases: recruitment bias, baseline imbalance, loss of clusters (including missing outcomes for individuals within clusters), and failure to account for clustering in analysis [10]. For assessing risk of bias for cohort and case-control studies, we used the Newcastle-Ottawa Scale [11].

We selected and ranked patient outcomes in terms of their importance for making a recommendation [9]. Using a modified Delphi process, we (F.A., N.A., M.C.L., C.M.W.) ranked outcomes into 3 categories prior to extracting data and grading the evidence: critical to decision making—mortality, hospitalization, cases of influenza; important but not critical to decision making—length of hospital stay, adverse events related to possible transmission of live attenuated influenza virus to immunocompromised patients by HCP vaccinated with LAIV; and low importance—number of days of influenza illness. We present the quality of evidence for outcomes that were considered to be critical to decision making.

### Statistical Analysis

For the cluster randomized trials, we performed meta-analysis using Review Manager software [12]. Because of differences across trials in patient characteristics and HCP influenza vaccination rates, as well as varying outcome definitions and follow-up periods, we used the random effects model (inverse variance method). We computed pooled risk ratios and assessed statistical heterogeneity using the  $\chi^2$  and  $I^2$  statistic. Pooled risk difference estimates may not be meaningful because risk difference is very sensitive to the control group risk, and control group risk may differ substantially between studies [13]. Therefore, we computed risk difference using GRADEPro software for a range of control group risks [8]. Risk difference was calculated by subtracting the assumed control group risk from the corresponding intervention group risk. The corresponding intervention group risk (and its 95% confidence interval [CI]) was derived by multiplying the assumed control group risk by the pooled risk ratio (and its 95% CI). For calculating relative risk reduction, we used the following formula: relative risk reduction =  $(1 - \text{pooled risk ratio}) \times 100$  [14]. We conducted subgroup analysis, which was not prespecified in our study protocol, to assess the effect of potential residual confounding. Our analyses took into account clustering associated with randomization at the facility level: We recalculated the standard error of the effect estimate at the study level ignoring clustering and then multiplied by the square root of the design effect [10]. We used design effects that were cited in a previous systematic review [5]. We did not perform meta-analysis of the cohort and case-control studies because of differing analysis methods and units.



**Figure 1.** Study selection for review of evidence on effect of influenza vaccination of healthcare personnel.

## RESULTS

### Study Selection

Our literature search identified 8790 articles. After removing duplicates, we screened 6092 articles (Figure 1). Four cluster randomized trials [15–18] and 4 observational studies (2 cohort and 2 case-control studies) [19–22] met the inclusion criteria.

The 4 trials presented data on 116 long-term care facilities that were randomized to HCP influenza vaccination and control arms (Supplementary Table 2). The mean age of patients ranged from 77 to 86 years. Reported HCP vaccination rates ranged from 48% to 70% in the intervention arms and 5% to 32% in the control arms. The follow-up period was the entire influenza season for 2 trials [15, 18], and was confined to the period of influenza activity for the remaining 2 trials [16, 17]. Among the 4 observational studies, 3 were conducted in long-term care settings (total of 234 facilities); 1 study was done in a hospital setting.

### Effect Estimate

The pooled risk ratio across the cluster randomized trials for all-cause mortality was 0.71 (95% CI, .59–.85), indicating a 29% (95% CI, 15%–41%) reduction in deaths (Figure 2). For influenza-like illness, the pooled risk ratio and relative risk reduction were 0.58 (95% CI, .46–.73) and 42% (95% CI, 27%–54%),

respectively. The pooled risk ratios for all-cause hospitalization and laboratory-confirmed influenza were not statistically significant. There was low statistical heterogeneity for all outcomes.

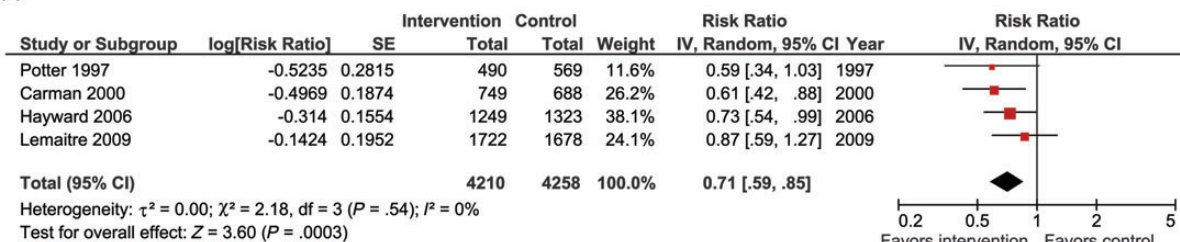
The risk difference (ie, absolute risk reduction) for each outcome associated with the mean control group risk, as well as assumed low and high values of control group risk, is shown in Table 1 and Supplementary Table 3. For example, the risk difference for all-cause mortality was 44 fewer deaths per 1000 patients when the control group risk was 151 deaths per 1000 patients (Table 1); the risk difference was 17 fewer deaths per 1000 when the assumed control group risk was 60 per 1000 (Supplementary Table 3).

The results of observational studies showed that HCP influenza vaccination was associated with a lower risk of influenza-like illness (Table 2). Significant protective associations were also reported for laboratory-confirmed influenza.

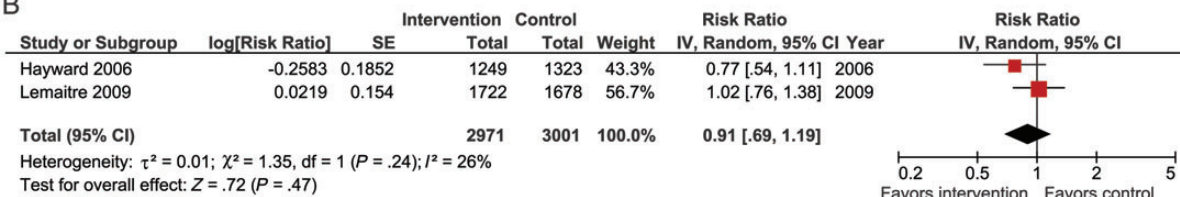
### Subgroup Analysis

Because of concern that residual confounding from other pathogens (eg, respiratory syncytial virus, parainfluenza viruses) could have resulted in overestimation of the effect on reducing patient mortality [5], we conducted subgroup analysis based on the period of follow-up. For the subgroup with follow-up periods comprising the entire influenza season, the pooled risk

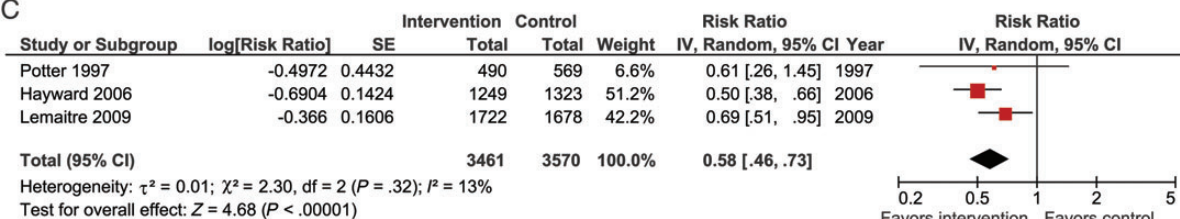
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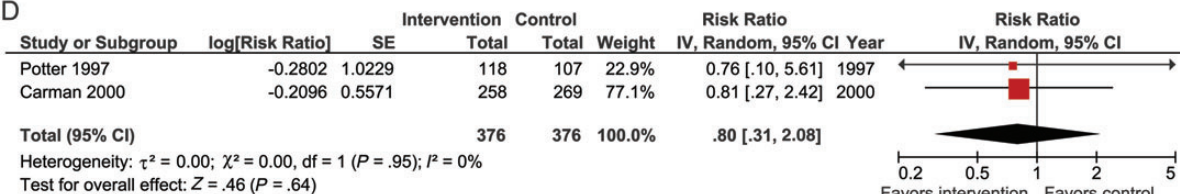
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**Figure 2.** Effect of influenza vaccination of healthcare personnel on patient outcomes: forest plots of cluster randomized trials. A, All-cause mortality. B, All-cause hospitalization. C, Influenza-like illness. D, Laboratory-confirmed influenza A or B. Study-level and pooled risk ratios are adjusted for clustering. Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

**Table 1. Effect of Influenza Vaccination of Healthcare Personnel: Findings of Cluster Randomized Trials<sup>a</sup>**

Outcome Among Patients	No. of Patients (Studies)	Assumed Risk in Control Group per 1000 <sup>b</sup>	Corresponding Risk in Intervention Group per 1000 (95% CI)	Pooled Risk Ratio (95% CI) <sup>c</sup>	Risk Difference per 1000 (95% CI)
All-cause mortality	8468 (4 studies)	151	107 (89–128)	0.71 (.59–.85)	–44 (–23 to –62)
All-cause hospitalization	5972 (2 studies)	95	86 (66–113)	0.91 (.69–1.19)	–9 (–29 to 18)
Influenza-like illness	7031 (3 studies)	162	94 (75–118)	0.58 (.46–.73)	–68 (–44 to –87)
Laboratory-confirmed influenza <sup>d</sup>	752 (2 studies)	64	51 (20–133)	0.80 (.31–2.08)	–13 (–44 to 69)

Abbreviation: CI, confidence interval.

<sup>a</sup> Adjusted for clustering.

<sup>b</sup> Weighted mean control group risk across studies (using weights from meta-analyses).

<sup>c</sup> From meta-analyses (see Figure 2).

<sup>d</sup> Determined using rise in serum antibody titer to influenza A or B among unvaccinated patients [18], or testing of combined nasal and throat swabs by polymerase chain reaction for influenza A and B viruses [15].



**Table 2. Effect of Influenza Vaccination of Healthcare Personnel: Description and Findings of Observational Studies**

Study	Setting	Analysis	Effect Estimate (95% CI)
Oshitani et al [21]	149 LTCFs, Japan	ILI outbreak (ILIs per week exceeded >10% of patients) in facilities with $\geq 10$ vs <10 vaccinated HCP during December 1998 to March 1999	Crude OR = 0.30 (.09–.69)
Enserink et al [20]	18 LTCFs, Netherlands	ILI incidence among patients in facilities with HCP vaccination rates of $\geq 15\%$ vs <15% during December 2008 to April 2009	Adjusted rate ratio = 0.3 (1–1.2)
Wendelboe et al [22]	67 LTCFs, United States	HCP vaccination percentage in facilities with ILI outbreaks ( $\geq 1$ cases of ILI or laboratory-confirmed influenza <sup>a</sup> in patients) vs no outbreaks during 2006–2007 and 2007–2008 influenza seasons (November–April) HCP vaccination percentage in facilities with influenza outbreaks ( $\geq 1$ cases of laboratory-confirmed influenza <sup>a</sup> in patients) vs no outbreaks	Adjusted OR = 0.82 (.68–.99) for 10 percentage point increase in HCP vaccination Adjusted OR = 0.76 (.62–.93) for 10 percentage point increase in HCP vaccination
Benet et al [19]	1 hospital (36 units), France	HCP vaccination percentage in unit for cases (ILI patients with laboratory-confirmed influenza <sup>b</sup> ) vs controls (ILI patients with negative influenza results) during 2004–2005, 2005–2006, and 2006–2007 influenza seasons (October–April)	Adjusted OR = 0.07 (.005–.98) for $\geq 35\%$ vs <35% vaccinated HCP in unit

Abbreviations: CI, confidence interval; HCP, healthcare personnel; ILI, influenza-like illness; LTCF, long-term care facility; OR, odds ratio.

<sup>a</sup> Determined using viral culture and rapid influenza antigen detection test.

<sup>b</sup> Nasal swabs tested for influenza virus by immunocapture enzyme-linked immunosorbent assay, immunostaining, tissue cell culture, and polymerase chain reaction.

ratio and the relative risk reduction were 0.60 (95% CI, .44–.82) and 40% (95% CI, 18%–56%), respectively. For the subgroup with follow-up periods confined to the period of influenza activity, the pooled risk ratio was 0.78 (95% CI, .62–.99) and the relative risk reduction was 22% (95% CI, 1%–38%).

### Quality of Evidence

The quality of evidence from randomized trials for the effect of HCP vaccination on mortality among patients was *moderate* (Table 3, Supplementary Table 4). The quality of evidence was downgraded because of indirectness, as all-cause mortality is a surrogate for influenza-specific mortality. The quality of evidence for the effect on hospitalization was downgraded by 2 levels to *low* because of indirectness and imprecision.

For the effect on influenza cases, evidence was graded for both the surrogate outcome of influenza-like illness and the specific outcome of laboratory-confirmed influenza. For influenza-like illness, the quality of evidence from randomized trials was *low* and that from observational studies was *very low* (downgraded because of risk of bias and indirectness). For laboratory-confirmed influenza, the evidence quality from randomized trials was *very low* (risk of bias and imprecision) and that from observational studies was *low* (none of the criteria for upgrading the initial evidence quality of *low* for observational studies were determined to be applicable).

### Overall Quality of Evidence

Because the body of evidence for the outcomes of influenza-like illness and laboratory-confirmed influenza comprised both

randomized trials and observational studies, the study design that provided higher quality of evidence was selected (Table 4). Therefore, the quality of evidence was *low* for influenza-like illness and *low* for laboratory-confirmed influenza. The quality of evidence for the effect on influenza cases was *low*, regardless of whether influenza-like illness or laboratory-confirmed influenza was used as the basis for grading. The quality of evidence for the effect on hospitalization was *low*, and that for mortality was *moderate*. The overall quality of evidence is determined by the quality of evidence for mortality if reduction in mortality alone is sufficient to support HCP influenza vaccination. Therefore, the overall quality of evidence across outcomes was *moderate* (Table 4), as mortality was considered a critical outcome for decision making.

## DISCUSSION

Our results indicate that the quality of evidence that HCP influenza vaccination reduces mortality and influenza cases in patients of healthcare facilities is *moderate* and *low*, respectively. The quality of evidence for the finding that there is no effect of HCP vaccination on hospitalization is *low*. The overall quality of evidence is *moderate*.

Our study has potential limitations. First, our ranking of outcomes may not represent the views of guideline panels that make vaccination recommendations. However, none of the studies reported data on outcomes we classified as noncritical. We did not consider the outcomes length of hospital stay and

**Table 3. Effect of Influenza Vaccination of Healthcare Personnel: Quality of Evidence**

Outcome Among Patients	Design (No. of Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations <sup>a</sup>	Quality of Evidence (GRADE)
Mortality	RCT (4)	Not serious	No serious	Serious <sup>b</sup>	No serious	None	Moderate
Hospitalization	RCT (2)	Not serious	No serious	Serious <sup>b</sup>	Serious <sup>c</sup>	None	Low
Influenza-like illness	RCT (3)	Serious <sup>d</sup>	No serious	Serious <sup>b</sup>	No serious	None	Low
Influenza-like illness	OBS (3)	Serious <sup>e</sup>	No serious	Serious <sup>b</sup>	No serious	None	Very low
Laboratory-confirmed influenza	RCT (2)	Very serious <sup>f</sup>	No serious	No serious	Serious <sup>g</sup>	None	Very low
Laboratory-confirmed influenza	OBS (2)	No serious	No serious	No serious	No serious	None	Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; OBS, observational study; RCT, randomized controlled trial.

<sup>a</sup> Strength of association, dose response, opposing plausible residual confounding or bias, publication bias.

<sup>b</sup> The study outcomes all-cause mortality, all-cause hospitalization, and influenza-like illness are surrogates for influenza-specific mortality, influenza-specific hospitalization, and influenza cases, respectively.

<sup>c</sup> The 95% confidence interval of the pooled risk ratio includes both no effect and appreciable benefit.

<sup>d</sup> Completeness of assessing influenza-like illness in intervention and control groups was unclear.

<sup>e</sup> Completeness of assessing influenza-like illness and healthcare personnel vaccination was unclear.

<sup>f</sup> Completeness of obtaining patients' samples for laboratory confirmation of influenza was low or differed between intervention and control groups. Intervention and control groups were not well matched for patients' Barthel disability scores in 1 of the 2 studies.

<sup>g</sup> Sample size was small (effective sample size was less than study sample size because of clustering).

number of days of influenza illness to be critical because these are similar in concept to the outcomes hospitalization and cases of influenza, respectively. We are not aware of any studies

**Table 4. Effect of Influenza Vaccination of Healthcare Personnel: Overall Quality of Evidence**

Outcome Among Patients	Study Design (No. of Studies)	Finding	Quality of Evidence (GRADE)	Overall Quality of Evidence <sup>a</sup> (GRADE)
Mortality	RCT (4)	Reduces mortality	Moderate	Moderate
Hospitalization	RCT (2)	No effect on hospitalization	Low	
Influenza <sup>b</sup>				
Influenza-like illness	RCT (3) <sup>c</sup>	Reduces influenza-like illness	Low	
Laboratory-confirmed influenza	OBS (2) <sup>c</sup>	Reduces laboratory-confirmed influenza	Low	

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; OBS, observational study; RCT, randomized controlled trial.

<sup>a</sup> If reduction in mortality alone among patients is sufficient to support influenza vaccination of healthcare professionals, the overall quality of evidence is determined to be moderate.

<sup>b</sup> Quality of evidence for the effect on influenza cases is low, regardless of whether influenza-like illness or laboratory-confirmed influenza is used as the basis for grading.

<sup>c</sup> Body of evidence for outcome includes both RCTs and observational studies; the study design that provides higher quality of evidence was selected.

that reported transmission of vaccine virus from LAIV recipients in healthcare settings. We considered the theoretical harm of transmission to be important but not critical for decision making. Second, pooled risk ratio estimates from the trials indicated a 29% reduction in all-cause mortality among long-term care patients. This finding may be questioned because influenza has been estimated to contribute to <10% of all winter deaths among persons aged 65 years and older [5, 23]. However, no estimates are available on the proportion of winter deaths attributable to influenza among frail elderly patients residing in long-term care settings. Although the facilities were randomized, we cannot rule out the possibility of residual confounding due to different patterns of circulation of pathogens within intervention and control facilities [17]. Our subgroup analysis limited to the period of influenza activity, when the potential for residual confounding due to other pathogens would likely be lower [24–26], showed a 22% reduction in all-cause mortality with very wide confidence intervals. Finally, influenza-specific outcomes provide the most relevant evidence [27, 28]. Use of nonspecific outcomes, assuming adequate control of confounding factors, leads to underestimation of true vaccine effectiveness [28]. The study outcomes of all-cause mortality and all-cause-hospitalization were downgraded for indirectness because these outcomes are surrogates for influenza-specific mortality and influenza-specific hospitalization, respectively. It would have been preferable to have data on influenza-specific mortality and hospitalization, but direct ascertainment of these specific outcomes is problematic because of the difficulty of distinguishing whether hospitalizations

and deaths due to exacerbation of chronic illnesses and other conditions are attributable to the complications of influenza or to other reasons; estimates of influenza-associated mortality and hospitalization are usually computed at the population level using statistical modeling techniques [29, 30]. For influenza cases, study data were available for the surrogate outcome of influenza-like illness and the specific outcome of laboratory-confirmed influenza. However, the quality of evidence was *low* regardless of outcome.

Two cluster randomized trials reported data on laboratory-confirmed influenza, but the quality of the evidence was determined to be *very low*. The real-life challenges and resource intensiveness of obtaining samples, as well as the limitations of laboratory methods, contributed to this determination. The sample size in 1 study was reduced because of the need to exclude vaccinated patients from the analysis (a rise in antibody titer to influenza can be due to either vaccination or infection); furthermore, only 43% of the eligible unvaccinated patients provided paired blood samples [18]. The other study selected a random sample of 50% of patients for conducting nasal and throat swabs taken at 2-week intervals during the peak influenza period; swabs were obtained from 69% of the intervention group and 78% of the control group [15].

Our study differs from previous systematic reviews of the effect of HCP influenza vaccination on protection of patients in 3 main ways: (1) Our assessment of the quality of evidence was based on the GRADE method used by numerous organizations for developing evidence-based recommendations; (2) we present the quality of evidence for each individual outcome; and (3) we used a tool that has been specifically designed by the Cochrane Collaboration to assess risk of bias in cluster randomized studies. The 2 recent systematic reviews included the same 4 cluster randomized trials that we reviewed, but assessed risk of bias using a Cochrane Collaboration tool that was primarily designed to assess risk of bias in trials where individuals rather than facilities are randomized [5, 6]. There were differences in the types and numbers of observational studies reviewed. One review also included cross-sectional and ecologic studies [6], but we decided a priori to exclude such study designs due to their inherent weaknesses. The other review had inclusion criteria similar to ours, but only 1 cohort study was available at the time of their review [5].

Several facts support the biological plausibility of HCP vaccination to reduce influenza among patients: A substantial proportion of HCP become infected with influenza virus during influenza seasons [31–33]; infected persons can shed virus before the onset of symptoms and during subclinical or clinical illness [34]; many HCP with influenza illness continue to work [31, 32, 35]; and influenza vaccination reduces laboratory-confirmed influenza among healthy adults (which includes most HCP) [36]. However, the role of competing sources of transmission, such as visitors and new patients, needs to be

considered. Modeling studies indicate that the relative effect of HCP vaccination on influenza infection among patients is lower in the hospital than in long-term care settings, which may be attributed in part to the relatively greater role of competing sources of transmission in hospitals [37, 38]. Nonetheless, because of higher expected attack rates in hospital patients compared to long-term care patients, the absolute risk reduction in hospital patients may be higher [38]. Such modeling studies are useful when there is a paucity of direct evidence for all parameters of interest. We were not able to assess the effect of HCP vaccination in ambulatory settings as no published studies in these settings met our inclusion criteria.

For any clinical question, the quality of evidence will vary based on the question and the context, and the best available evidence should be used for developing recommendations. An evidence-based approach for developing recommendations requires transparency concerning the evidence and transparency in how judgments regarding the quality of evidence were made. Key factors for developing recommendations include the quality of evidence, balance of benefits and harms, values and preferences, and health economic analyses [7, 39]. The benefits of HCP influenza vaccination, which include likely reduction in morbidity and mortality among patients and reduction in illness among HCP themselves, outweigh possible harms. HCP influenza vaccination can enhance patient safety.

Postscript: A cluster randomized trial published in June 2013 reported that HCP influenza vaccination was associated with decreased influenza and/or pneumonia in hospital patients [40]. However, this study does not change our assessment of the quality of the body of evidence, as its quality is similar to studies on influenza outcomes included in our review.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

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**Potential conflicts of interest.** All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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