EDITORIAL COMMENTARY

Influenza Vaccination of Healthcare Workers: Making the Grade for Action

Marie R. Griffin

Department of Health Policy, Vanderbilt University Medical Center, Nashville, Tennessee

(See the Major Article by Ahmed et al on pages 50–7.)

Keywords. influenza vaccination; healthcare workers.

It is reasonable to ask what type of evidence is needed to recommend or require annual influenza vaccination of healthcare workers to help prevent transmission of influenza to vulnerable hospitalized patients and to residents of long-term care facilities. To make such a recommendation, one would want to know the risks and consequences of influenza in such patients, the safety of the vaccine and its efficacy in preventing influenza in healthcare workers, and the likelihood that vaccinating such workers could prevent the spread of influenza within these facilities in addition to costs and feasibility.

There is little disagreement about the burden of influenza and the disproportionate share of severe morbidity and mortality suffered by older persons and those with chronic health conditions [1–3]. Such individuals are especially vulnerable to influenza infection and its complications when they are hospitalized or institutionalized. There is also little disagreement that influenza vaccine provides protection to healthy adults, preventing an estimated 59% of laboratory-confirmed influenza-associated illness [4]. Although imperfect, influenza vaccination has a good safety record and is the most effective existing strategy for prevention of influenza disease.

Prior to instituting a program for healthcare worker vaccination, it would be desirable to have clinical trial evidence that such a program is effective in protecting vulnerable patients and long-term care residents. In this issue of *Clinical Infectious Diseases*, the meta-analysis by Ahmed et al summarized 4 cluster randomized controlled trials conducted in long-term care facilities that have addressed this important question [5].

Ahmed et al found evidence that healthcare worker vaccination prevented all cause death and influenza-like illness. Using the pooled results, they estimated that all-cause death was reduced by approximately 29%. Death rates in the 4 studies varied by 2- to 3-fold, and the intervention to increase influenza vaccination of healthcare workers compared to no intervention was associated with absolute reductions in deaths ranging from a low of 0.8% to a high of 8% among facility residents. They also estimated a 42% reduction in influenza-like illness; however, the reduction in the more specific outcome, laboratory-confirmed influenza, was lower and not statistically significant [5]. This seems counterintuitive, because if the association between the intervention and outcome were causal, one would expect the strongest relationship with the most specific outcome, laboratory-confirmed influenza. Another concern is that the risk reduction in death was greater (40%) when the analysis included a broader time period than when the analysis was confined to only the period when influenza was circulating (22%). If homes were appropriately balanced through the randomization process, and vaccination provided protection, one would expect to find the greatest effects during the time influenza was circulating, unless a large proportion of deaths were delayed, occurring days or weeks after illness onset, which is possible.

Appraisal of the 4 trials led Ahmed et al to assign an evidence grade of "moderate," based primarily on the consistent reduction in all-cause deaths in the intervention compared to control groups. However, it is important to note that the trials included in Ahmed et al's review faced a number of challenges, including years with low influenza activity, baseline differences in facilities despite randomization, and failure to achieve large differences in vaccination rates between control and intervention homes in some studies. Moreover, laboratory confirmation of

Received 23 August 2013; accepted 5 September 2013; electronically published 17 September 2013.

Correspondence: Marie R. Griffin, MD, MPH, Department of Preventive Medicine, Vanderbilt University Medical Center, 1500 21st Ave S, Nashville, TN 37212 (marie.griffin@vanderbilt.edu).

Clinical Infectious Diseases 2014;58(1):58–60

DOI: 10.1093/cid/cit590

influenza was often lacking, or methods such as rapid tests and cultures known to be insensitive in older patients were used [6]. In one of the studies included in this meta-analysis, Carman et al [7] collected combined nose and throat swabs from a 50% sample of residents every 2 weeks in both intervention and control homes. Influenza was detected by reverse transcription polymerase chain reaction in about 6% of residents in both intervention and control homes. Despite an inability to demonstrate a difference in influenza prevalence in the homes, postmortem samples obtained from about 18% of residents who died yielded intriguing results. Influenza was detected in 0 of 17 versus 6 of 30 samples taken from residents who died in intervention and control homes, respectively. This lent credibility to the conclusion that the difference observed in mortality was influenza related. To obtain accurate information on influenza-associated illness, it is likely that more frequent and systematic testing in persons experiencing illness, hospitalization, or death would be needed.

When looking at the 4 trials individually, the 2 early trials done in the 1990s as pilot and follow-up studies [7, 8] were important and provocative, but had some methodological weaknesses. The most recent of the 4 studies [9] was severely underpowered, in part, because there was little difference in vaccination rates between intervention and control homes. The other included trial, the 2-year study of Hayward et al [10], was methodologically strong, achieved significant separation of vaccination rates among healthcare workers between intervention and control sites, and encompassed 1 moderately severe influenza season. However, this study did not evaluate specific laboratory-confirmed influenza outcomes. In this study, differences in death rates were achieved only when influenza was circulating, whereas mortality was similar at other times. Other endpoints also favored an effect of healthcare worker vaccination.

Since Ahmed et al's meta-analysis was submitted, the Cochrane meta-analysis on this same topic was updated and concluded that there was no evidence to mandate compulsory vaccination of healthcare workers [11]. It is disconcerting when meta-analyses come to different conclusions. Unlike the previous iteration of this Cochrane meta-analysis [12] and that of Ahmed et al discussed above, the recent one [11] eliminated influenza-like illness and all-cause mortality as outcomes of interest because they are nonspecific and thus excluded the study of Hayward et al. Nevertheless, for the more specific outcomes, prevention of laboratory-confirmed influenza illness and acute respiratory hospitalizations, there was agreement between these 2 meta-analyses on the lack of evidence for protection.

Given that the evidence from these studies may not be as strong as one might like, and the challenges with performing such studies, it is important to consider whether there is other evidence supporting indirect (herd) protection from influenza vaccination. An important and compelling cluster randomized trial in Canadian Hutterite communities reported by Loeb et al [13] demonstrated that vaccination of 83% of 3- to 15-year-olds in intervention communities not only protected vaccinated children but also reduced influenza-confirmed illness by 61% in nonvaccinated community members compared to nonvaccinated members of communities randomized to a control vaccine. This study serves as a strong proof of concept. That is, under some situations influenza vaccination can protect unvaccinated persons. In addition to the study of Loeb et al, several prior studies with less robust designs also strongly suggested herd protection when high vaccination of children was achieved [14, 15].

In his 1965 Presidential Address to the Royal Society of Medicine [16], Sir Austin Bradford Hill detailed some thoughts about causation and wondered if the scientific community had gone too far in its respect for "statistical significance." He invoked an old proverb likening the χ^2 test to fire—it makes a good servant, but a bad master. At the end of a powerful exposition about causation, he made "the case for action," saying, "All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or postpone the action that it appears to demand at a given time."

Given the dire consequences that outbreaks of influenza can have in institutional settings, the known safety and efficacy of current influenza vaccines, and the strong evidence that vaccinating a segment of the population can protect unvaccinated persons who are in contact with vaccinees, the meta-analysis by Ahmed et al offers additional reassurance that the threshold for action has been reached or surpassed. Vaccination of healthcare workers to protect vulnerable patients and residents of long-term care facilities should be viewed as an evidence-based recommendation.

Notes

Acknowledgments. The author thanks Carlos G. Grijalva, MD, MPH, and Kathryn M. Edwards, MD, for their insightful and helpful comments on an earlier version of this editorial.

Potential conflicts of interest. M. R. G. reports receiving grant support from Medimmune.

The author has 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.

References

1. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA **2004**; 292: 1333–40.
2. Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993–2008. Clin Infect Dis **2012**; 54: 1427–36.
3. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the united states. JAMA **2003**; 289:179–86.

4. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis **2012**; 12:36–44.
5. Ahmed F, Lindley MC, Allred N, Weinbaum CM, Grohskopf L. Effect of influenza vaccination of healthcare personnel on morbidity and mortality among patients: systematic review and grading of evidence. Clin Infect Dis **2014**; 58:50–7.
6. Talbot HK, Williams JV, Zhu Y, Poehling KA, Griffin MR, Edwards KM. Failure of routine diagnostic methods to detect influenza in hospitalized older adults. Infect Control Hosp Epidemiol **2010**; 31:683–8.
7. Carman WF, Elder AG, Wallace LA, et al. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. Lancet **2000**; 355:93–7.
8. Potter J, Stott DJ, Roberts MA, et al. Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. J Infect Dis **1997**; 175:1–6.
9. Lemaitre M, Meret T, Rothan-Tondeur M, et al. Effect of influenza vaccination of nursing home staff on mortality of residents: a cluster-randomized trial. J Am Geriatr Soc **2009**; 57:1580–6.
10. Hayward AC, Harling R, Wetten S, et al. Effectiveness of an influenza vaccine programme for care home staff to prevent death, morbidity, and health service use among residents: cluster randomised controlled trial. BMJ **2006**; 333:1241.
11. Thomas RE, Jefferson T, Lasserson TJ. Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions. Cochrane Database Syst Rev **2013**; 7:CD005187.
12. Thomas RE, Jefferson T, Lasserson TJ. Influenza vaccination for healthcare workers who work with the elderly. Cochrane Database Syst Rev **2010**; CD005187.
13. Loeb M, Russell ML, Moss L, et al. Effect of influenza vaccination of children on infection rates in Hutterite communities: a randomized trial. JAMA **2010**; 303:943–50.
14. Monto AS, Davenport FM, Napier JA, Francis T Jr. Effect of vaccination of a school-age population upon the course of an A2-Hong Kong influenza epidemic. Bull World Health Organ **1969**; 41:537–42.
15. Reichert TA, Sugaya N, Fedson DS, Glezen WP, Simonsen L, Tashiro M. The Japanese experience with vaccinating schoolchildren against influenza. N Engl J Med **2001**; 344:889–96.
16. Hill AB. The environment and disease: association or causation? J R Soc Med **1965**; 58: 295–300.