EDITORIAL

Influenza Vaccination in 2013-2014
Achieving 100% Participation

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Every year, the public and health care system experience clinical and financial consequences of influenza epidemics. Influenza infection leads to hospitalizations, deaths, excess medication usage, and days missed from work and school. Influenza is a preventable disease, and advisory bodies in the United States recommend influenza vaccine for everyone 6 months and older, with particular emphasis on the need to vaccinate young children, older adults, and persons of all ages with high-risk conditions, including cardiovascular disease.[1] In 2013, an unprecedented number of influenza vaccines are available in the US market, including quadrivalent vaccines, live, attenuated vaccines, high-dose vaccines, and vaccines manufactured in cell culture.[1] Comparative trials in certain pediatric age groups have shown the relative benefits of live, attenuated influenza vaccine and as yet unlicensed adjuvanted vaccines.[2,3] Likewise, studies evaluating the comparative benefits of high-dose vs standard-dose influenza vaccines in older adults are nearing completion.[4]

Individually randomized, placebo-controlled clinical trials with laboratory-confirmed clinical end points are generally considered to be the strongest study design to assess vaccine efficacy. While such trials are certainly vital to establish the level of protection of a vaccine, from a public health perspective, they have limitations. Randomized clinical trials (RCTs) are generally not adequately powered to detect less common, more severe outcomes of influenza. Further, RCTs focused on laboratory-confirmed end points may underestimate the absolute disease reduction attributable to influenza vaccine if influenza infection leads to clinical illness at a point in time beyond when the virus is detectable by routine diagnostic methods (polymerase chain reaction or culture). For example, if influenza virus infection predisposes a patient to a secondary bacterial pneumonia, or an exacerbation of chronic illness, the influenza virus may no longer be detectable by the time the patient presents for medical care. Thus, to estimate the overall value of a vaccine, other study designs also can be helpful. For instance, observational studies are useful to assess multiple outcomes in large populations throughout many years at a reasonable cost but are subject to bias.[5]

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There are additional ways to overcome the limitations of traditional, relatively small RCTs. Vaccine probe studies are one such approach; they seek to identify a comprehensive burden of disease prevented by comparing disease outcomes between vaccinated and nonvaccinated (either alternative vaccine or placebo) groups, assuming that differences are causally attributed to the disease.[6] The advantage of probe studies is that they generally involve larger numbers of participants and focus resources on identifying serious clinical outcomes, rather than on surveillance for less severe outcomes or laboratory diagnostic testing. Probe studies have been used to assess the association of *Haemophilus influenzae* type b and *Streptococcus pneumoniae* vaccines with clinically important outcomes including pneumonia, meningitis, and even all-cause mortality.[7,8]

Meta-analyses also can be useful to assess the relationship between vaccine administration and outcomes that may be too rare to address in single RCTs. In this issue of *JAMA*, Udell and coauthors[9] report findings from a meta-analysis to investigate the association between influenza vaccine and risk of cardiac complications. It is biologically plausible that influenza vaccine could prevent serious cardiovascular outcomes, and this is supported by animal models and epidemiological studies examining the relationship of cardiovascular disease and influenza virus circulation.[10,11] The primary conclusion of Udell et al was that influenza vaccine was associated with a reduced risk of major adverse cardiovascular events. In 5 studies that included 6469 patients, influenza vaccine, compared with placebo or no vaccine, was associated with a lower risk of composite cardiovascular events (2.9% for intervention vs 4.7% for placebo or control).[9]

For any meta-analysis, it is important to understand the criteria and quality of the trials included. The primary analysis by Udell et al was based on 5 clinical trials, 2 of which were randomized but not placebo-controlled. Of the 3 high-quality, randomized, double-blind, placebo-controlled trials, 1 showed the benefit of influenza vaccine on cardiovascular events and 2 did not.[12-14] The single high-quality, randomized, placebo-controlled trial that showed benefit of influenza vaccine included patients with known coronary artery disease; thus, cardiovascular events were relatively common. However, because the trial only included 658 participants, statistical significance was achieved only for the secondary composite end point of coronary ischemic events.[14] The 2 high-quality trials that did not demonstrate benefit included participants enrolled based on age criteria, and there were relatively few cardiac events overall.[12,13] The 2 trials that did not have placebo or active controls and were ranked lower in regard to quality showed benefit of influenza vaccine.[15,16]

It is also important to examine the absolute effects reported in this study. Assuming that attack rates for influenza infection vary between 5% and 20%, and the efficacy in middle-aged and older adults varies between 40% and 70%, then for every 100 persons vaccinated, 2 to 14 cases of influenza would be prevented.[1,12,13,17] Presumably, prevention of influenza illness would be required to prevent the subsequent secondary cardiovascular complications. Thus, in the study by Udell et al,

the estimate of 1.7 major cardiovascular events prevented for every 100 persons with cardiovascular disease vaccinated is plausible and would represent a significant public health benefit of influenza vaccination in addition to the prevention of primary influenza illness. In contrast, in a subset analysis that included only the 3 clinical trials that enrolled participants with known coronary artery disease (only 1 of these trials was rated as high quality),[13-15] the estimate of 12.9 major cardiovascular events prevented for every 100 persons vaccinated would require a high attack rate, high vaccine efficacy, and nearly every episode of clinical influenza leading to a major cardiovascular event. This scenario seems unlikely, and suggests possible design flaws and residual bias in at least some of the individual studies that contributed to the meta-analysis. Alternatively, subclinical infection may trigger a cascade of inflammatory events leading to cardiovascular outcomes, although, based on what is known about influenza attack rates, this explanation seems insufficient to account for the magnitude of this estimated effect.

Although the results of the study by Udell et al suggest that influenza vaccine may be associated with a reduced risk of cardiovascular events, as with all meta-analyses, the findings are limited by the quality of the underlying studies and do not imply causation. Regardless of whether influenza vaccine reduces cardiovascular disease, the known morbidity of influenza in older adults with and without high-risk conditions and the known efficacy of the vaccine warrant its use.

Research and development efforts are under way to improve the immunogenicity and cross-protection of influenza vaccines, including adding adjuvants or targeting more conserved regions of the influenza virus. However, it may be many years before these vaccines reach the public. What can be done in the meantime? Today, less than 50% of persons younger than age 65 years with high-risk conditions, including cardiovascular disease, receive influenza vaccine annually.[18] The coverage rates of influenza vaccine among adults aged 65 years and older are somewhat better, yet up to one-third remain unvaccinated.[18] While ideally the clinical and research communities should strive for better vaccines and better coverage, from the public health perspective, as much can be gained by increasing coverage as from increasing vaccine efficacy. If the currently available moderately efficacious vaccines can reach 100% of the population, as much disease will be prevented as with more highly efficacious vaccines reaching half of the population.

There are proven ways to increase vaccination coverage, including expanding access through nontraditional settings (eg, pharmacy, workplace, school venues), improving the use of evidence-based practices at medical sites (eg, standing orders, reminder or recall notification), and using immunization registries.[18] One of the most consistent and relevant findings of operational research is that recommendation for vaccination from physicians and other health care professionals is a strong predictor of vaccine acceptance and receipt among patients. While few are in a position to develop new influenza vaccines, all health care practitioners can recommend influenza vaccine to their patients. Doing so will help achieve the goal of 100% vaccination for the 2013-2014 influenza season.

ARTICLE INFORMATION

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REFERENCES

1. Centers for Disease Control and Prevention. Prevention and control of seasonal influenza vaccines. *MMWR Recomm Rep*. 2013;62(RR07):1-43.

2. Vesikari T, Knuf M, Wutzler P, et al. Oil-in-water emulsion adjuvant with influenza vaccine in young children. *N Engl J Med*. 2011;365(15):1406-1416.

3. Ambrose CS, Levin MJ, Belshe RB. The relative efficacy of trivalent live attenuated and inactivated influenza vaccines in children and adults. *Influenza Other Respi Viruses*. 2011;5(2):67-75.

4. ClinicalTrials.gov. Study of Fluzone high-dose vaccine compared with Fluzone vaccine in elderly adults. http://www.clinicaltrials.gov/ct2/show/NCT01427309?term=sanofi+and+influenza+vaccine&rank=38. Accessed September 26, 2013.

5. Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. *Int J Epidemiol*. 2006;35(2):337-344.

6. Gessner BD, Brooks WA, Neuzil KM, et al. Vaccines as a tool to estimate the burden of severe influenza in children of low-resourced areas (November 30-December 1, 2012, Les Pensieres, Veyrier-du-Lac, France). *Vaccine*. 2013;31(32):3222-3228.

7. Cutts FT, Zaman SM, Enwere G, et al; Gambian Pneumococcal Vaccine Trial Group. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia. *Lancet*. 2005;365(9465):1139-1146.

8. Gessner BD, Sutanto A, Linehan M, et al. Incidences of vaccine-preventable *Haemophilus influenzae* type B pneumonia and meningitis in Indonesian children. *Lancet*. 2005;365(9453):43-52.

9. Udell JA, Zawi R, Bhatt DL, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. *JAMA*. 2013. doi:10.1001/jama.2013.279206.

10. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med*. 2004;351(25):2611-2618.

11. Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease. *Lancet Infect Dis*. 2009;9(10):601-610.

12. Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. *JAMA*. 1994;272(21):1661-1665.

13. De Villiers PJ, Steele AD, Hiemstra LA, et al; LAIV Elderly Study Trial Network. Efficacy and safety of a live, attenuated influenza vaccine in adults 60 years of age and older. *Vaccine*. 2009;28(1):228-234.

14. Ciszewski A, Bilinska ZT, Brydak LB, et al. Influenza vaccination in secondary prevention from coronary ischaemic events in coronary artery disease. *Eur Heart J*. 2008;29(11):1350-1358.

15. Phrommintikul A, Kuanprasert S, Wongcharoen W, Kanjanavanit R, Chaiwarith R, Sukonthasarn A. Influenza vaccination reduces cardiovascular events in patients with acute coronary syndrome. *Eur Heart J*. 2011;32(14):1730-1735.

16. Gurfinkel EP, Leon de la Fuente R, Mendiz O, Mautner B. Flu vaccination in acute coronary syndromes and planned percutaneous coronary interventions (FLUVACS) study. *Eur Heart J*. 2004;25(1):25-31.

17. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines. *Lancet Infect Dis*. 2012;12(1):36-44.

18. Centers for Disease Control and Prevention. Flu vaccination coverage, United States, 2012-2013 influenza season. http://www.cdc.gov/flu/fluvaxview/coverage-1213estimates.htm. Accessed September 30, 2013.