EDITORIAL COMMENTARY

Annual Studies of Influenza Vaccine Effectiveness: Evaluating Performance, Informing Policy, and Generating New Questions

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(See the major article by Ohmit et al on pages 319–27.)

Keywords. influenza vaccine; case-control study; vaccine policy; effectiveness.

In the United States and other temperate climates in the Northern Hemisphere, we are waiting and preparing for the 2013–2014 influenza epidemic. We know that it will come but, unfortunately, we don't know when. The epidemic may be upon us by the time this commentary is published or it may still be months away. We don't know where it will strike first, or which strains will predominate, or how long the epidemic will last, or how severe it will be. Dealing with all of these uncertainties is challenging—to the selection and manufacturing processes, as well as to our delivery strategies. Currently, influenza vaccines are manufactured on a biannual basis. Most countries that use influenza vaccines regularly do so on a calendar-based schedule, beginning in September in the Northern Hemisphere when vaccines become available.

Researchers, policy-makers, and clinicians are advocating for better vaccines [1–3]. A better vaccine might be one that allows for easier and more rapid manufacturing, thus allowing strain selection to occur later in the year and closer to vaccine delivery. A better vaccine may be defined as more efficacious against all influenza illness or severe influenza illness when compared with current vaccines. A better vaccine may be more broadly protective against drifted influenza strains or unexpected new strains that may emerge. A better vaccine may induce longer-lasting immunity. A better vaccine would ideally offer all of the aforementioned advantages without compromising safety and without unduly increasing cost. Overall, developing a better influenza vaccine is a formidable challenge.

Currently, we have an unprecedented number and variety of influenza vaccines on the US market that are designed to meet some of the challenges identified above [4]. For the first time, a subset of available influenza vaccines will be quadrivalent formulations and will include 2 type A strains and 2 type B strains. Certainly, the addition of new strains to a vaccine formulation is one approach to broadening protection. The first influenza vaccines contained a single strain; bivalent vaccines became the norm in the 1960s, followed by trivalent vaccines beginning in 1978 and, in 2013, by quadrivalent vaccines [5]. The first recombinant, egg-free influenza vaccine is now approved and available. The rapidly changing landscape of influenza vaccines, coupled with the unpredictable aspects of influenza epidemics, necessitates a nimble system for monitoring and evaluating the impact of individual vaccines and policy decisions.

In this issue of *Clinical Infectious Diseases*, Ohmit et al report on "Influenza vaccine effectiveness in the 2011–2012 season: Protection against each circulating virus and the effect of prior vaccination on estimates" [6]. The study uses the so-called test-negative case-control study design, a modification of the traditional case-control design. Eligible persons with medically attended acute respiratory illness were invited to participate, and illnesses were assessed virologically for influenza infection. Those positive were included as cases and all of those negative were included as controls. The test-negative design can provide valid estimates of vaccine effectiveness but assumes vaccinated and unvaccinated persons to not differ in health care-seeking behavior and likewise that vaccination does not modify the probability of symptomatic illness. The presence of such differences is difficult to measure, and although

Received 28 October 2013; accepted 29 October 2013; electronically published 13 November 2013.

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Clinical Infectious Diseases 2014;58(3):328–9

DOI: 10.1093/cid/cit739

the authors of the current study adjusted vaccine effectiveness estimates during the analysis to control for confounding, they could only rely on strong study design to guard against the aforementioned effects. Fortunately, there are indications that the test-negative design may be valid under a wide range of assumptions [7].

Studies such as that of Ohmit et al will help to guide our decisions on the optimal use of current vaccines and bring into focus questions for further research for development of improved vaccines and their future delivery. For example, the authors demonstrate the continued value of influenza vaccination, showing consistent significant benefit to nearly all age groups in the study for the 2011–2012 season [7]. Likewise, their estimates corroborate the recommendation for 2 doses of influenza vaccine in young children [4, 8]. Interestingly, they found that vaccination provided protection against both circulating B strains, the ones included in the current vaccine, as well as the mismatched strain lineage. Presumably, this observation held for both inactivated and live-attenuated vaccines, given that both B strains circulated equally in all age groups that year. This finding challenges the current view based on serological data—using the traditional measure of antibody assayed by hemagglutination inhibition—that presenting the immune system with antigen from 1 B lineage does not prime for protection against the other lineage [9, 10]. Given the relative lack of clinical data on cross-B lineage protection and the growing body of serologic evidence for lack of cross-protection, even with new adjuvanted influenza vaccines, we should be cautious in overinterpreting this finding. Additional annual studies of the clinical effectiveness of current trivalent influenza vaccines will be critical for addressing this question and for informing the potential public health benefit of quadrivalent vaccines.

Possibly, the most notable finding of the study was that vaccination against influenza in the prior year (2010–2011) was significantly associated with a modestly lower level of clinical protection in the current year. While this finding was likely obtained through a post hoc secondary analysis, the result is consistent with findings from Michigan in a household study that was performed the previous year [11]. In this study, it is difficult to interpret this finding given that exposure to wild-type influenza during the prior season is completely unknown and only partially known in the current season. Nonetheless, the finding raises serious questions regarding the complicated interplay that occurs between our immune systems and repeated annual exposure to influenza antigens in current vaccines and/or potential exposure to wild-type influenza virus.

Annual estimates of influenza vaccine efficacy are critical for guiding policy decisions and should be expanded to allow for more robustly powered investigations of the relative performance of particular vaccines against influenza types or subtypes, across age groups and risk groups, and over multiple years. While the authors conclude that, "it is reassuring to know that annual VE (vaccine effectiveness) studies will give us the ability to assess how well [vaccines] work in large population groups . . ." [6], their findings raise important questions that may not be answered through this case-control design. Larger multiyear prospective studies that include not only measures of the full spectrum of clinical illness caused by influenza but also immunologic measures may be required to allow us to understand the dynamic of the immune system in response to influenza vaccine and natural infection. It is only through careful investigation that we can properly assess current vaccines and guide the development of better vaccines and delivery strategies.

Note

Potential conflicts of interest. K. N. and J. V.: Grant from Bill and Melinda Gates Foundation and a cooperative agreement from the Centers for Disease Control and Prevention for influenza vaccine clinical studies in Senegal.

Both 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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