How Can We Solve the Enigma of Influenza Vaccine–Induced Protection?

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(See the major article by Ohmit et al on pages 1519–28.)

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For the past decade, on an annual basis, multiple sites across the United States have estimated the effectiveness of seasonal influenza vaccine to prevent influenza-associated, medically attended acute respiratory illness [1]. The standard design involves selecting persons who present to medical facilities with acute respiratory infection and are laboratory-test positive for influenza virus (defined as cases) and comparing their odds of having been vaccinated to those of persons who are laboratory-test negative for influenza virus (controls). Such studies are now done routinely in the United States, Canada, and several other countries [1–4]. This design has been validated using data sets from the gold standard, randomized, placebo-controlled clinical trials of influenza vaccines [4].

Beginning in the 2010–2011 influenza season, Ohmit et al assessed annual influenza vaccine effectiveness by using a prospective household cohort study design [5, 6]. While consuming more time and resources than the case-control approach, this method has the advantage of capturing multiple outcomes (including less severe illness), establishing denominator-based attack rates, and allowing for collection of influenza serology prior to the influenza season. In this issue of The Journal of Infectious Diseases, Ohmit et al provide effectiveness estimates from this Michigan household cohort for the 2012–2013 influenza season [7]. As previously demonstrated in this cohort, there was a detrimental effect of prior vaccination on current vaccine performance. The authors appropriately highlight that comparisons are complex, since vaccination during the prior year may provide some residual disease protection, particularly if the vaccine strain does not change between seasons. Therefore, the use of “neither year” vaccination status as the reference group, in this and other studies, is appropriate.

This phenomenon that vaccination against influenza in the prior year is significantly associated with a modestly lower level of clinical protection in the current year has now been reported from multiple populations during multiple influenza seasons, using both the prospective household design, as well as the test-negative case-control design. In addition to the single season effect, McLean et al recently reported on a cohort in Wisconsin with 5 years of historical vaccination data. They found that vaccine effectiveness was significantly higher among individuals with no prior vaccination history, compared with individuals with a frequent vaccination history [8].

Understanding influenza vaccine–induced immunity and protection is complex. In these cohorts, it is not possible to fully account for the interaction between past exposure to naturally circulating influenza virus, past exposure to influenza vaccines, strain match, and age and immunocompetence of each individual. Further, unmeasured confounding remains a concern for any observational study. However, one might postulate that individuals who are not vaccinated in the prior year, or years, would be more likely to have an influenza virus infection and that natural immunity resulting from this infection would be superior to vaccine-induced immunity in preventing influenza. In the study by McLean et al, for example, cases of influenza were less likely to have been vaccinated but also less likely to have received a previous diagnosis of influenza, compared to controls [8]. Further, in a landmark study by Hoskins et al, in a boys’ boarding school in England in the 1970s, attack rates during influenza outbreaks were lowest in boys with documented prior influenza virus infection [9].

Understanding the immunologic mechanisms underlying this clinical observation of attenuation of influenza
vaccine effectiveness with prior vaccination is important. Vaccine-induced and naturally induced serum antibody responses correlate with protection against influenza. Because of the repeated exposure to influenza virus infection and influenza vaccination, the B-cell response to influenza vaccination is an antigen-recall response in most older children and adults [10]. The emergence of the 2009 pandemic influenza A(H1N1) strain (A[H1N1]pdm09) in 2009 provided an opportunity to compare B-cell responses induced by natural infection and vaccine in naive adults, without the confounder of previous exposure. Infection with A(H1N1)pdm09, as compared to vaccination with inactivated A(H1N1)pdm09 vaccines, resulted in an increased breadth and magnitude of B-cell responses in adults. Wild-type A(H1N1)pdm09 infection did not affect the antigen-recall response to subsequent inactivated vaccines with the same strain, whereas receipt of A(H1N1)pdm09 inactivated vaccines reduced the B-cell response to repeated vaccination [11]. Ideally, such measures of immunologic responses would be incorporated into multiyear, prospective studies of vaccine effectiveness.

In the meantime, what do these observations tell us about the value of repeated vaccinations? Table 1 uses estimates from the Michigan household cohort to highlight the current findings from a disease-prevention standpoint [7]. Based on this scenario, over a 2-year period, the highest number of influenza cases will occur in the population that does not receive any influenza vaccine. Likewise, a single vaccination is better than no vaccination. In support of the current influenza vaccine policy, vaccination in both years prevents more disease than vaccination in a single year, although depending on the assumptions, that benefit may be minimal. While looking at vaccination in a single year may illustrate an apparent negative effect, compared with either year alone, the overall public health impact must be considered over all years, not just the current year. The hypothetical scenario in Table 1 assumes that at entry into the first year of the cohort, all individuals are vaccine naive, which is likely not a reasonable assumption. The lifetime history of influenza virus infection and influenza vaccination will be unique for each person in the cohort. Only through multiyear prospective studies, with evaluation of subclinical infections, will we be able to solve the enigma of vaccine-induced influenza virus immunity. In the meantime, the current policy to administer influenza vaccine every year should be maintained.

**Note**

**Potential conflict of interest.** Author certifies no potential conflicts of interest.

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Table 1. Cases of Influenza Prevented in a Hypothetical Cohort in Which the Influenza Attack Rate for Symptomatic Acute Respiratory Illness Is Held Constant at 10% Each Year and Using Point Estimates of Effectiveness in Table 4 From the Associated Article by Ohmit et al [7]

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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.

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**References**