

Flu Vaccine—Too Much of a Good Thing?

John Treanor

Infectious Diseases Division, Department of Medicine, University of Rochester Medical Center, Rochester, NY

(See the major article by Skowronski et al on pages 1059–69.)

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Control of influenza through vaccination is a particularly difficult task because of the continued antigenic evolution of influenza viruses. Influenza viruses rapidly accumulate mutations in the antibody epitopes of the hemagglutinin (HA) and neuraminidase (NA) proteins that allow them to escape from immunity generated by prior vaccination or infection, a process known as “antigenic drift.” Antigenic drift occurs in unpredictable stops and starts, and at different rates for different types and subtypes of the virus. One consequence of this phenomenon is that for optimal protection, the viruses contained in the vaccine should match the virus(es) causing the outbreaks as closely as possible, requiring comprehensive surveillance for new emerging variants, and continuous updating of the vaccine. Because at least 1 component of the vaccine is almost always updated each year, optimal protection would also require annual vaccination, which is currently recommended for all persons in the United States.

Multiple large networks have been established in the United States, Canada, Europe, and other countries to monitor the effectiveness of influenza vaccine on a yearly basis, using a now well-established

methodology known as the test-negative case-control study. In this approach, individuals with acute respiratory illness are assessed, and the vaccination history of subjects with laboratory-documented influenza (test-positive cases) is compared to that of those whose tests were negative (test-negative controls). Over the last several years, many of these studies have suggested that vaccination in prior seasons can reduce the effectiveness of vaccination in the current season, a phenomenon first identified by Hoskins and colleagues in a British boarding school [1] and referred to as the “Hoskins effect.”

A negative effect of prior vaccination is not a consistent finding of all studies [2, 3], and the mechanisms that might underlie this phenomenon remain unknown. However, it was suggested several years ago that the effect may depend on the antigenic relatedness of the previous vaccine to the current vaccine, and of both to the circulating virus, referred to as the antigenic distance hypothesis (ADH) [4]. According to the ADH, the biggest negative effect would be predicted to occur when the previous and current vaccines are antigenically similar, and the circulating virus is significantly drifted.

In this issue of *The Journal of Infectious Diseases*, an analysis of data over several years from the Canadian Vaccine Effectiveness (VE) network provides support for the ADH as a predictor of the possible inhibitory effect of prior vaccination. Essentially, Skowronski and colleagues [5] found that the greatest negative effect of prior vaccination occurred

in the 2014–2015 season, when the prior and current vaccines were the same, and the circulating virus was a poor antigenic match. In contrast, there was no effect of prior vaccination on VE in 2010–2011, when the prior and current vaccines were distantly related and the circulating virus was also a drift variant, and an intermediate negative effect in 2012–2013, when the current and prior vaccine were similar, but not identical and the circulating virus was again drifted.

The mechanisms that might be responsible for a negative effect of prior vaccination on vaccine effectiveness are not known, but are reviewed in detail in the article. The finding that the magnitude of the negative effect depends on antigenic distance could be consistent with antigenic focusing [6]. In this case, when sequentially exposed to 2 antigenically related viruses, the immune system focuses on the shared epitopes at the expense of novel epitopes on the second virus that might be important for the protection against a third, antigenically drifted virus. In contrast, a person who has not been previously vaccinated might mount a broader response against all of the epitopes in the vaccine. Other potential mechanisms could include interference by prior immunity on antigenic presentation, or the “infection-block hypothesis.” In this case, prior vaccination reduces prior infections with influenza virus, which in turn would have provided more effective protection against subsequent drifted influenza infection than the vaccine does, resulting in lower rates of influenza in subjects with infection-based immunity than in those

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Correspondence: J. Treanor, University of Rochester, Medical Center, Room 3-6209, 601 Elmwood Ave, Rochester, NY, US 14642 (john_treanor@urmc.rochester.edu).

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with vaccine-induced immunity. As the authors point out, there is also the possibility of undetected confounding variables that impact the health-care behavior of multiply vaccinated individuals compared to unvaccinated ones. Multiple factors could all be playing a role, making a complete mechanistic understanding of the phenomenon quite difficult.

The actual measurement of antigenic distance is also challenging, particularly for influenza A subtype H3N2 viruses. Traditionally, the antigenic difference between 2 influenza viruses has been determined by the hemagglutination-inhibition (HAI) assay using ferret antiserum samples. In this test, an influenza-naive ferret is infected by the first influenza virus, and the titer of postinfection serum samples is determined in the HAI assay using 2-fold dilutions of serum samples against the infecting virus and the new virus. If the titer of the serum samples against the infecting virus is 3 or more dilutions higher than it is against the new virus (ie, an antigenic distance of 3 or more), then the 2 viruses are considered antigenically different. In the current study, antigenic distance was calculated from values of the HAI assay for the vaccine and circulating viruses reported by the World Health Organization. However, this would not necessarily be the same result that would be obtained using human sera [7], which might be more relevant to human seasonal outbreaks. In addition, recent H3N2 viruses do not grow well in the laboratory, and may need to be adapted by serial passage to develop high enough hemagglutination titers to use in this type of assay, potentially introducing additional mutations and complicating the assessment of antigenic distance. It will be important in future assessments to include new methodology that is being developed to assess antigenic differences in H3N2 viruses such as sequencing and neutralization assays.

In one year of the study, it appeared that multiply vaccinated subjects were actually more likely to develop influenza than unvaccinated subjects (that is, VE was

statistically significantly less than zero). A similar effect was noted during the 2009 influenza A virus subtype H1N1 pandemic when increased rates of pandemic H1N1 were reported in patients who had previously received seasonal H1N1 vaccine in Canada [8] but not in other countries [9]. The authors speculate that this might be consistent with a disease-enhancing effect of influenza vaccine. Vaccine-enhanced disease has been recognized as a potential problem in other human infectious diseases such as dengue [10] and respiratory syncytial virus [11], and can be a significant obstacle to vaccine development. There is relatively little evidence to support any form of enhanced influenza disease in humans, although disease enhancement by low-avidity antibodies with deposition of immune complexes in the lungs was reported in the 2009 pandemic [12]. Measurements of disease severity were not reported in the current study, so it is not possible to judge whether the disease was more severe in multiply vaccinated individuals. Alternatively, it is possible that the same types of biases that might impact overall estimates could systematically lower estimates of VE in multiply vaccinated subjects, such that the estimates become negative numbers in years when true VE is close to zero.

Continued monitoring of influenza vaccine effectiveness is important in shaping vaccine policy, and it has recently resulted in major changes such as the recommendation against use of quadrivalent live attenuated influenza vaccine in the United States [13]. Because there is no current practical alternative to annual vaccination, the findings in the article by Skowronski and colleagues and others will probably not change public health recommendations. However, they are a call to further research to understand the effects of prior vaccination mechanistically and devise strategies to mitigate any inhibitory effects of prior vaccination. Such approaches might include adjuvants or high-dose vaccines. Ultimately,

the answer may lie in the development of vaccines that provide broad and long-lasting protection against multiple influenza viruses, eliminating the need for annual vaccination altogether.

Notes

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