Challenges of Vaccine Effectiveness and Waning Studies

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(See the Major Article by Ray et al on pages 1623–30.)

There is a growing consensus on the need for better influenza vaccines to improve on the many shortcomings of existing vaccines. Current vaccines' effectiveness is modest in some years and undetectable for some viral (sub)types in others [1]. Antigenic changes in the influenza virus require changes in vaccine strain composition for at least 1 of the 3 viral (sub)types in most years, resulting in further uncertainty about how the new vaccine will perform. Moreover, studies, including that by Ray et al in this issue of *Clinical Infectious Diseases* [2], indicate that the immunity induced by inactivated flu vaccines may wane within months. Thus, those who follow public health advice to get vaccinated well before the winter influenza season may gain less benefit than those who do so later [3, 4]. In the new study, persons who received an influenza vaccination and later received a viral test for an acute respiratory infection were compared, calculating the odds of testing positive for influenza among those who were recently vaccinated at the time of their test to those who had been vaccinated months before. Ray et al found that the odds of testing positive for influenza increased by 16%

per 28-days period between vaccination and testing. From this variant on the test-negative study design (see below) they inferred that vaccine-induced protection waned during 7 influenza seasons from 2010 to 2017.

A truly universal influenza vaccine would be a single immunization that would provide robust, long-lasting protection against multiple subtypes and their antigenic variants, potentially eliminating the need for annual vaccination, offering greater protection than current vaccines, and perhaps even eliminating the need for rapid development of new vaccines when a pandemic comes, because existing universal vaccines would cover even these strains. While complete achievement of this goal is likely far off and will require major research investments, even incremental gains on some of these fronts could produce a considerably better vaccine.

Better ways to evaluate flu vaccines are also urgently needed. Ethical and logistical considerations ordinarily preclude randomized, controlled trials of new seasonal influenza vaccines, because existing manufacturing processes with just a change of strain are presumed to create vaccines that will be efficacious and because delaying the release of annual vaccines until efficacy was proven would mean missing much of the season. Therefore, observational studies, measuring infection, hospitalization, and mortality outcomes in cohorts of vaccinated and unvaccinated persons, or case-control studies, comparing the vaccine status

of influenza-infected persons versus controls, have been used instead to measure the direct impacts of vaccination on the vaccinated persons.

These studies, like all observational studies, suffer from the risk of confounding and other sources of bias. Those who do and do not get vaccinated may differ—for reasons other than the vaccine—in their risks of exposure to influenza infection, their risks of getting clinically ill (or, in mortality studies, dying) if infected, or (in studies requiring laboratory confirmation of infection) their tendency to seek care if ill with a respiratory infection. A study design that combines some features of cohort and case-control studies, called the test-negative design, circumvents some of these biases (confounding associated with health care-seeking behavior) at the expense of potentially creating other forms of bias. These issues have been extensively reviewed [5, 6], and several groups have endeavored to quantify them [7–10].

Another challenge is specific to studies aiming to evaluate whether protection wanes with time since vaccination, especially when evaluating so-called “leaky” vaccines that reduce but do not eliminate a vaccinated person's risk of infection upon exposure to the pathogen. Even if the vaccine effect does not wane over time, then such waning will nonetheless appear to occur in most studies of vaccine protection, including randomized, controlled trials and observational studies, if either or both of 2 conditions occur. These studies will spuriously infer

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waning if (1) there is a heterogeneous risk of becoming infected among those who are vaccinated (even if this heterogeneity is exactly mirrored in the unvaccinated by randomization) [11, 12] or (2) some trial participants during the course of the trial become infected but are not counted as cases (for example, because their mild symptoms do not prompt them to seek testing) [7, 13–15], or both.

Focusing on reason 1 for brevity, if the vaccine is protective, the proportion of high-exposure participants still at risk in the unvaccinated group will fall faster than the proportion in the vaccinated group, because the vaccine is slowing the rate at which vaccinated, high-exposure participants become infected. As time passes during the study, the unvaccinated group still at risk will become increasingly low-exposure, making the rate of new cases in the 2 groups converge or, in extreme cases, even cross, so that the observed incidence is higher in the vaccinated than the unvaccinated group [7]. This false signal may be tiny or large; it grows with the degree of heterogeneity or unobserved infection and with the cumulative incidence in the study.

Ray et al found a large amount of waning: the group with the largest delay from vaccination to testing had over twice the odds of influenza infection compared to those with the shortest delay, adjusting for changing incidence over the season. Peer review was protracted, due to an effort to clarify whether and to what extent the signal of waning may have been artifactual. A reviewer (the author of this editorial) asked the authors to show with simulated data that their effect could not be explained by artifact. In their response, they described simulations they had performed that showed a small (few percent) bias in the estimate of waning, but the bias underestimated the degree of waning rather than exaggerating it. This reviewer undertook some calculations (available as R code [Supplementary Material](#) to this editorial) that agreed with the authors that the bias was expected to be small, but found that it would create a false signal of waning where none existed. Subtle

differences in assumptions between the authors' simulation and the reviewer's calculation probably account for the difference in findings. The reviewer assumed no waning and found spurious evidence of waning, while the authors assumed waning did happen and found the analysis revealed slightly less than the true degree of waning. Moreover, different plausible assumptions were made about the extent to which individuals became infected before vaccination and, thus, were ineligible for study inclusion, which was limited to those who were tested post-vaccination. Neither analysis accounted for unobserved infections post-vaccination that would remove persons from being at risk without the knowledge of the investigators, by making them immune to influenza for the remainder of that season.

This process raised 2 broader issues. The first is the role of simulation, calculations, and causal reasoning (e.g., using causal-directed acyclic graphs) in establishing the validity of study designs, both in those that have been widely used (like the test-negative design) and those containing innovative features, like that used by Ray et al effect estimates calculated in infectious disease intervention studies can have complex interpretations, not obvious even to quantitatively-trained individuals without careful analysis [14, 16–18]. A recent workshop produced a call for greater use of such calculations and simulations in the design of infectious disease intervention studies [19]. While that call referred to randomized trials, there is a similar need to clarify the direction and, especially, the magnitude of bias in observational studies, and to innovate (as Ray et al did) to find new and better ways to measure quantities of interest.

A second issue is how peer review should deal with studies like that by Ray et al.: well-conducted intervention studies using methods that—like all methods—have limitations. Such studies provide important data to inform our scientific understanding of vaccine effects, notwithstanding methodological limitations. It should not be the responsibility of each

study to prove that all potential biases inherent to their method are inconsequential in the study presented; this requirement would hamper scientific progress and suppress many valuable studies. For example, the test-negative design (of which Ray et al. use a novel variant) has been used in over 300 published vaccine papers, and is likely the best observational design we have for such studies, despite many caveats. On the other hand, the mere fact that a particular design has been used repeatedly should not insulate it from criticism.

No simple answer is apparent, but some components of an approach would be to (1) encourage the use of simulation, calculation, and causal reasoning in reports of studies describing results from novel designs, to clarify under what assumptions the interpretation of the data is valid; (2) encourage methodological work to further clarify the features and limitations of existing study designs and to create novel approaches that can circumvent some of the limitations; and (3) encourage studies that take multiple perspectives on important questions. For vaccine waning, these might include, for example, experimental-controlled challenge studies in humans and laboratory animals and longitudinal measurements of immune markers as ways to gain evidence on waning that would have different strengths and limitations from observational effectiveness studies.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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