Influenza Vaccine: Glass Half Full or Half Empty?

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In this issue of *Clinical Infectious Diseases*, Ohmit and colleagues report the results of an assessment of influenza vaccine effectiveness during the 2010–2011 influenza season, using a nonrandomized, prospectively followed cohort [1]. This intriguing study had 2 surprising findings. Remarkably, the rate of polymerase chain reaction–documented influenza illness was not substantially different between those subjects who received influenza vaccine and those who did not, and the study was unable to demonstrate statistically significant vaccine effectiveness even after adjustment for age and the presence of high-risk conditions. The second surprising finding is that receipt of influenza vaccination in a previous season may have impacted the effectiveness of the vaccine in the current season. The population under study was predominantly young healthy adults and children with a low frequency of chronic health conditions, the types of subjects that typically mount the best immune responses to vaccine. In addition, there was a close antigenic match between the vaccine and circulating viruses. As we are currently struggling through one of the most vigorous influenza seasons in

recent memory, the apparent failure of influenza vaccine under optimal conditions seen in this study is indeed troubling.

Influenza vaccines are unique among currently licensed vaccines in that the continuous antigenic evolution of the virus requires frequent updating, reformulation, and annual administration of the vaccine. Thus, each year's influenza season essentially represents a test of a new vaccine against a new virus. Partly for this reason, there has been substantial interest for developing systems to monitor the performance of influenza vaccines on an annual basis. Prospective, randomized controlled trials are the method that is least susceptible to bias as the assignment of vaccinated or unvaccinated groups is made randomly. Organizing such trials on an annual basis would be quite challenging, however. Alternatively, several large networks have been developed that monitor vaccine effectiveness using a test-negative case-control design. In these studies, selected persons seeking care for acute respiratory illness are tested using a sensitive and specific test for influenza, and the vaccination histories of those testing positive are compared to those testing negative. The selection of cases based on a prespecified case definition and diagnostic testing without knowledge of vaccine history may eliminate some of the biases inherent in other observational studies [2], but the assessment is typically limited to medically attended outcomes. Because the majority of influenza infections do

not result in a medical visit, this provides a somewhat incomplete assessment of the impact of vaccination.

The innovative prospective surveillance approach used by Ohmit and colleagues allowed the investigators to assess effectiveness against both medically attended and nonmedically attended illnesses, similar to the outcomes typically assessed in randomized trials. However, the result of this study was strikingly different than that reported in recent randomized trials conducted by the same investigators in which inactivated vaccine efficacies of 68%–75% were reported, even though the vaccine and circulating viruses were antigenically mismatched [3, 4]. The Michigan group was also a major contributor to the recent assessment of effectiveness against medically attended illness performed during the same 2010–2011 influenza season as the current report, but showing substantial vaccine effectiveness of 60% [5]. Understanding the reasons for these widely varying results is a critically important component of the effort to improve our control of influenza.

Inactivated influenza vaccines are generally believed to provide "nonsterilizing" immunity—that is, vaccination does not necessarily prevent infection, but it reduces the likelihood that infection will result in illness, and reduces the severity of the illness caused by infection. Thus, it would be conceivable that in a given year, vaccination might have a substantially greater effect at reducing relatively

severe illness resulting in a medical visit (the endpoint used in the parallel, case-control study [5]) than in reducing less severe illnesses detected in prospective surveillance. A minority of the cases in this study were medically attended, and probably even fewer were seen in emergency departments or involved hospitalizations. However, the crude rate of medically attended visits in the vaccinated subjects (25/866 [2.9%]) was not different from that in the unvaccinated subjects (15/575 [2.6%]).

Additional factors may have contributed to the surprising lack of vaccine effectiveness in the Ohmit study versus analogous studies of medically attended visits. In the Ohmit study design, the choice to receive influenza vaccine is up to the individual participant, and the reasons why some people decide for or against vaccination are not always well understood. Confounding from self-selection is therefore another possible factor contributing to the findings. For example, persons who chose to be vaccinated might be more interested in their health generally, and might be more inclined to report illnesses to the investigators or to make clinic visits for specimen collection than unvaccinated participants who are not as health conscious. Or, possibly persons who chose vaccination might have done so because they were aware of other factors that increased their risk of influenza, such as workplace exposures or other contacts. Adjustment for known risk factors can partially correct for this, but is obviously limited to those factors that the investigators are able to ascertain. These types of undetected biases are clearly possible in any study, and improved approaches to detect and control these factors remain an important methodologic issue. Future community-based studies should measure additional demographic and behavioral characteristics, and make statistical adjustments (such as propensity scoring) that might help account for potential sampling/selection biases and confounding

that could impede estimations of vaccine effectiveness.

In addition, it is possible that the subjects enrolled in the study are different from the general population. Only 328 of 4511 targeted households actually enrolled in the study for an enrollment rate of 7%. Inherent differences between the families who enrolled in the study and families in general could also theoretically impact the results of the study. Of course, this difficulty is true for randomized trials and case-control studies as well.

An additional intriguing issue raised by a secondary analysis of this study is that receipt of influenza vaccination in a previous season may have reduced the effectiveness of the vaccine in the current season. Because our current practice is to immunize each year, this observation has substantial implications. As the authors point out, repeated vaccination may be a surrogate for other health factors, and it is notable that while 72% of those who chose to be vaccinated had also received vaccine in the previous year, only 20% of the unvaccinated cohort had a history of prior seasonal vaccine. However, concerns regarding the potential impact of prior vaccination on influenza vaccine efficacy have been raised repeatedly, beginning with observations among children and adolescents in British boarding schools [6]. Subsequent randomized trials (using whole virus vaccine in healthy adults) have not shown a consistent effect [7]. It has been suggested that the possible negative effects of prior vaccination may be related to the antigenic distance between the prior vaccine, the current vaccine, and the circulating virus, with interference seen when sequential vaccines were closely related [8]. Because some of the vaccine components between seasons in this study were identical and some were changed, it is of interest to assess the effect of prior vaccination separately for H1, H3, and B, although clearly the statistical power is low for such comparisons.

After more than 50 years of routine use, there are still many unanswered questions about influenza vaccine. The early report of approximately 60% effectiveness for this year's vaccine [9] is encouraging, but clearly much more needs to be done. It is frequently stated that evaluation of influenza vaccines in randomized controlled trials is "unethical," but given that the effectiveness of the vaccine is unclear, the subjects in such studies are typically at extremely low risk of serious disease, and effective antiviral therapy is available, perhaps this statement should be reconsidered. There is general agreement that the current vaccine is suboptimal [10], but it is very safe and at least partially effective. Introduction of new vaccines will need to balance the potential benefits and risks, some of which are unpredictable [11]. In the meantime, our task is to optimize the use of the tools we currently have in hand while we vigorously pursue new opportunities to develop and deploy new approaches to influenza control.

Note

References

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