Reply to Decker et al

To the Editor—We appreciate the comments from Decker et al regarding our study [1]. There are now 3 studies reporting comparative effectiveness results for high-dose vs standard-dose influenza vaccine. Decker et al’s Sanofi Pasteur randomized trial [2] necessarily focused on symptomatic influenza infection as hospitalization with complications of influenza is less common, and comparisons based on this outcome are more difficult to adequately power in randomized studies, apart from exploratory analyses. The Izurieta observational study [3] examined hospitalization for influenza as an outcome using International Classification of Diseases, Ninth Revision (ICD-9) code 480 (influenza). Our study utilized the broader ICD-9 code group 480–487 for hospitalization with influenza or pneumonia for consistency with prior database studies of influenza-related hospitalizations (see, eg, [4, 5]) and because influenza often presents as other respiratory conditions [6].

Similar to Izurieta et al, we only used subjects from centers offering both vaccines. We are not aware of studies suggesting that increasing the proportion of patients with a new intervention decreases confounding. We agree that confounding by indication is an important consideration of observational studies of interventions. In addition to using propensity score methods to compare outcomes among similar groups of patients to reduce confounding, we also compared the 2 vaccines under a negative control condition (during the noninfluenza season) to confirm that no difference between vaccination groups was detected in the absence of circulating virus. In this way we were able to rule out the potential use of high-dose vaccine preferentially among patients whose rates of hospitalization would be elevated even in the absence of influenza. Decker et al also offer concerns about not accounting for differential time at risk for study outcomes; our Methods section specifies that we did account for time at risk.

Of course, many additional factors can lead to different study outcomes. For example, our study examined data from the year before the Sanofi Pasteur trial began and 2 years before the Izurieta et al study, with different levels of circulating virus and population immunity. The 3 studies had population differences including race (the Izurieta et al and Sanofi Pasteur studies were 95% and 93% white, respectively, vs 74% in our study), which may be associated with factors affecting health outcomes. The studies used 3 different influenza season definitions. In the Izurieta et al study, comparisons were performed using outcomes captured during periods identified with high, moderate, and low influenza activity, with a benefit for high-dose vaccine only seen during the high activity period (see their Figure 2 [3]). Our definition of the influenza season included weeks that would have been classified as both high and moderate by Izurieta et al. These considerations bring into clearer focus the areas of agreement and disagreement between these studies.

These recent studies have advanced our understanding of the clinical outcomes with trivalent, inactivated high-dose vaccine. More studies continue to be needed now and in the future of the effect of high-dose and other vaccines in additional influenza seasons and patient populations, and of the many complications of influenza.

Note

Potential conflict of interest. Both authors: No reported conflicts.

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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