Correspondence

Commentary On Arriola et al. Antivirals and Effect Modification in Influenza Studies

To the Editor—In a recent study, Arriola et al used data from the Influenza Hospitalization Surveillance Network (FluSurv-NET) for the 2012–2013 influenza season to evaluate the effect of influenza vaccination on disease severity in hospitalized patients [1]. Adult patients aged ≥50 years were included in the study, and patients who had uncertain vaccination history, lack of body mass index (BMI) data, or received antiviral treatment 4 or more days before hospitalization were excluded. During the multivariate analysis, patients who did not receive antiviral treatment were also excluded from the analysis. There was no difference in influenza severity by vaccination status in the regression analysis, whereas in a propensity score model, 50–64-year-old adults who were vaccinated against influenza were more likely to be discharged earlier from the intensive care unit (ICU) compared to those not vaccinated (hazard ratio = 1.84, 95% confidence interval, 1.12–3.01). The authors concluded that influenza vaccine has a modest effect on the severity of diseases [1].

A total of 5614 patients were included in their Table 1, but 983 (17.5%) patients who did not receive an antiviral treatment were excluded from the analysis. Exclusion of these cases may have led to significant bias in the results, because the use of antivirals is an effect modifier and may remove the disadvantage of being unvaccinated when it comes to symptom severity. We believe that the impact of vaccine on disease severity cannot be determined if only patients who received antivirals are included in the analysis.

Antiviral treatment reduces the duration of influenza infection and severity of illness, and may also be used for chemoprophylaxis to prevent infections [2]. Untreated patients should not be excluded from the analysis, and should be dealt with using appropriate statistical methods. In fact, the ideal methodology to investigate the effect of vaccine on symptoms is to study only untreated patients. The authors reported substantial differences in the characteristics of the treated versus the untreated cases. Even in the propensity score model, the authors matched for sex, race, state of residence, BMI, underlying medical conditions, presence of any medical condition, alcohol abuse, and smoking status, yet failed to match for antiviral treatment.

Antiviral treatment is generally recommended for severe, complicated, and hospitalized patients with medical comorbidities [2]. The effectiveness of vaccine cannot be determined by including only patients with antiviral treatment, because these patients are also more likely to have severe and complicated forms of disease. Moreover, the risk of hospitalization substantially increases in severe and complicated influenza cases [3], and the risk of hospitalization cannot be determined if the analysis is limited to only those cases who receive antiviral treatment. It would, therefore, be helpful if authors could describe the vaccination status among treated and nontreated groups and the rate of hospitalization in each group. They could have done a separate analysis with only the 983 patients who did not receive an antiviral treatment. This would help examine the independent effect of vaccination on disease severity and hospitalization.

The authors also excluded 1639 (20%) patients who were institutionalized in long-term care facilities before hospitalization. The reason for this was not explained. This group of patients probably would be older than the study group and have a different prognosis. Thus, excluding them from the analysis might have biased the findings.

The authors used a survival analysis method to estimate the hazards ratio for length of ICU stay where the event was release from the ICU. It was mentioned in Table 1 that 118 patients died. We assume that some (or most) of them would have died in the ICU. The authors have not mentioned how they treated the deceased cases in the survival analysis. Death in the ICU would be more likely to be due to the severity of the disease. Therefore, the dead cases could not be simply considered as censored in the survival analysis. The death in the ICU should be considered as a nonindependent competing risk and should be appropriately dealt with in the analysis.

Note

Potential conflicts of interest. C. R. M. has held an Australian Research Council Linkage Grant with 3M as the industry partner, for investigator-driven research. 3M have also contributed supplies of masks and respirators for investigator-driven clinical trials. She has received research grants and laboratory testing as in-kind support from Pfizer, GSK, and Bio-CSL for investigator-driven research. All other authors report no potential conflicts.

All 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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