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Reply to Chughtai et al

Carmen S. Arriola[1,2] and **Sandra S. Chaves**[2]

[1]Epidemic Intelligence Service Program, Atlanta, Georgia

[2]Influenza Division, Centers for Disease, Control and Prevention, Atlanta, Georgia

To the Editor

We thank Dr Chughtai et al for providing feedback on our article entitled "Does Influenza Vaccination Modify Influenza Severity? Data on Older Adults Hospitalized With Influenza During the 2012–2013 Season in the United States." They point out three main issues with our analysis: (1) exclusion of hospitalized cases who were not treated with antivirals, (2) exclusion of hospitalized cases who were institutionalized in long-term care facilities, and (3) death in the intensive care unit (ICU) as a nonindependent competing risk.

We have carefully reviewed their comments and suggestions, reanalyzed the data, and prepared our responses. We will address the three issues separately:

1. Exclusion of hospitalized cases who were not treated with antivirals

   As mentioned in the article [1], we excluded cases who were not treated with antivirals for two main reasons: (1) most hospitalized cases received antiviral treatment, thus limiting our ability to look at those who were not treated as a separate group; and (2) there were substantial differences between characteristics of treated cases and those untreated. By restricting the analysis to those treated, we avoided selection bias, as we did not have a way to ascertain why some patients were treated while others were not (decision was made at the discretion of the clinician providing care). We acknowledged in our article that antiviral treatment could indeed dilute the effect of vaccination, explaining, perhaps, why we found very modest effects from influenza vaccination. We agree that analyzing the data of untreated patients may be helpful in understanding the effect of influenza vaccination on disease severity. Therefore, we analyzed the data for those untreated without propensity score matching and found no effect in most categories (Table 1). However, in the 50–64-year age group, vaccine did have significantly beneficial effects on severe disease (odds ratio, 0.4) and length of stay (relative hazard of discharge, 1.23). Unfortunately, our sample size was

Correspondence: Carmen S. Arriola, DVM, PhD, Influenza Division, National Center for Immunization and Respiratory Diseases Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS A-32, Atlanta, GA 30329 (wus3@cdc.gov).

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too small to further investigate with propensity score matching. We plan to further explore the effect of influenza vaccination on disease severity among treated and untreated cases using different seasons (with varying matches between circulating influenza viruses and vaccine-selected strains and age groups).

2. Exclusion of hospitalized cases who were institutionalized in long-term care.

   For our current study, we aimed to present results regarding the effect of influenza vaccination in disease severity in adults ≥50 years living in the community. Thus, we excluded hospitalized cases with laboratory-confirmed influenza who came from institutionalized long-term care facilities because this is a different population that should be studied separately, as they present significant differences compared to people living in the community [2, 3].

3. Death in the ICU as a nonindependent competing risk.

   Finally, we reanalyzed the data using death as a nonindependent competing risk (see Table 2) and found that the probability of being discharged earlier from the ICU accounting for death was 1.6 times higher (95% confidence interval, 1.04–2.46) among vaccinated cases aged 65–74 years compared to those who were unvaccinated, after propensity score matching. The results of this analysis were similar to our previous results; therefore, we reaffirm that our findings show a modest effect of influenza vaccination on disease severity for the influenza season 2012–2013. Analysis of data from seasons with a better match between vaccine strains and circulating viruses and, thus, better vaccine effectiveness against influenza infection are needed.

In addition to the three issues mentioned above, Chughtai et al suggested presenting hospitalization rates by vaccination status among treated and untreated groups. However, even though FluSurv-NET is a population-based surveillance system, we do not have denominator information on influenza vaccination coverage by treatment.

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Table 1

Influenza Vaccination and Severity of Influenza Disease Analysis for Cases Untreated With Antivirals by Age Category, Before Propensity Score Matching (n = 966)[a]

	Influenza Vaccine 2012–13 Season					
	50–64 y (n = 328)		**65–74 y (n = 232)**		**≥75 y (n = 406)**	
Clinical Outcomes	**Point Estimate (95% CI)**	***P* Value**	**Point Estimate (95% CI)**	***P* Value**	**Point Estimate (95% CI)**	***P* Value**
Severe disease[b] (OR)	**0.4 (.17; .98)**	**.04**	0.9 (.35; 2.32)	.83	0.76 (.37; 1.54)	.45
Diagnosis of pneumonia[c] (OR)	0.83 (.47; 1.47)	.53	0.91 (.45; 1.83)	.79	0.85 (.54; 1.33)	.47
Length of hospital stay (RH)[d]	**1.23 (1.02; 1.49)**	**.03**	0.95 (.74; 1.20)	.65	1.20 (1.00; 1.45)	.05

Data excluded: untreated, FluA&B, FluA/B.

Analysis for ICU length of stay was not performed due to small numbers (36, 27, and 37, observations in age groups 50–64, 65–74, and ≥75 years, respectively).

Abbreviations: BMI, body mass index; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; RH, relative hazard.

[a] Adjusted for sex, race, BMI, medical condition (asthma, chronic lung disease, cardiovascular disease, chronic metabolic disease, neurologic disease, immunosuppression, renal disease), alcohol abuse, smoking, and influenza virus type.

[b] Admitted to ICU or deceased.

[c] Among those who had a chest X-ray taken *within 3 days* of admission (n = 932).

[d] RH represents hospital discharge accounting for death as a nonindependent competing risk.

Table 2

Influenza Vaccination and Severity of Influenza Disease Analysis for Cases Treated With Antivirals by Age Category, After Propensity Score Matching (n = 1509)[a]

	Influenza Vaccine 2012–13 Season					
	50–64 y (n = 494)		65–74 y (n = 495)		≥75 y (n = 520)	
Clinical Outcomes	**Point Estimate (95% CI)**	***P* Value**	**Point Estimate (95% CI)**	***P* Value**	**Point Estimate (95% CI)**	***P* Value**
Severe disease[b] (OR)	0.97 (.62; 1.52)	.89	1.27 (.81; 1.99)	.29	0.99[c] (.59; 1.66)	.97
Diagnosis of pneumonia[d] (OR)	0.79 (.54; 1.18)	.25	0.86[c] (.59; 1.26)	.44	0.94[c] (.65; 1.35)	.72
ICU length of stay (RH)[e]	1.25 (.82; 1.91)	.3	**1.60 (1.04; 2.46)**	**.03**	0.94 (.50; 1.77)	.85
Length of hospital stay (RH)[e]	1.03 (.88; 1.21)	.69	1.03 (.88; 1.21)	.68	1.02 (.87; 1.19)	.80

Abbreviations: BMI, body mass index; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; RH, relative hazard.

[a]Variables used for propensity score matching: sex, race, BMI, medical condition (asthma, chronic lung disease, cardiovascular disease, chronic metabolic disease, neurologic disease, immunosuppression, hemoglobinopathy/blood disorders, renal disease, liver disease), alcohol abuse, and smoking.

[b]Admitted to ICU or deceased.

[c]Adjusted for the Charlson score.

[d]Among those who had a chest X-ray taken *within 3 days* of admission (n = 1,460).

[e]RH represents ICU or hospital discharge accounting for death as a nonindependent competing risk.