

LETTER TO THE EDITOR

In Reply to 'High-Dose Versus Standard-Dose Influenza Vaccine in Hemodialysis Patients'

To the Editor:

We appreciate the letter by Miskulin et al¹ regarding our recent study.² We appreciate the letter by Miskulin et al regarding our recent study and agree with the importance of assessing and accounting for confounding bias in non-experimental studies of preventive interventions. Miskulin et al raise an important concern about potential residual confounding due to the relatively small proportion and potentially highly selected group of high-dose influenza vaccine (HDV) recipients in the national data set that we analyzed in the years following the 2009 introduction of HDV.³ However, we took careful steps to minimize potential confounding by the healthy-user effect and frailty, well-documented challenges in observational studies in older or frail populations.⁴ Variable selection for our propensity score models was informed by prior research, including a predictive model of factors associated with HDV receipt⁵ and a negative control analysis of all-cause mortality in the pre-influenza season.⁶ Additionally, a quantitative bias analysis concluded that the unmeasured confounder-outcome association would have needed to be stronger than any observed confounder-outcome association to mask a true preventive effect of HDV (Tables S11, S12, and S13 of our original article).² The observed confounder-outcome associations (crude risk ratios) ranged from 0.4 to 1.4, from 0.5 to 1.2, and from 0.6 to 1.1 for outcomes of mortality, hospitalization due to influenza or pneumonia, and influenza-like illness, respectively.

We have updated our analyses to include US Renal Data System data from 2016, after uptake of HDV increased substantially among older adults (from 0.6% in 2010 to 20.1% in 2016). Eligible patients included adults 65 years and older with end-stage kidney disease and Medicare as a primary insurance payer who started hemodialysis at least 9 months before influenza vaccination and received continuous hemodialysis for the 3 months immediately before vaccination. Using methods previously described,² we found that HDV does not appear to provide additional protection beyond standard-dose influenza vaccine against all-cause mortality, hospitalization due to influenza or pneumonia, or influenza-like illness for older adults undergoing hemodialysis, consistent with our original results. These findings were replicated in the 2015/2016 season, the 2016/2017 season (through December 31, 2016 only), and overall (2010-2016).

We agree with Miskulin et al that there is convincing evidence suggesting that HDV is more effective than standard-dose influenza vaccine in the general population of older adults. However, our study of national data, using modern epidemiologic study design and analytic methods to rigorously account for potential biases, failed to show a protective

effect in the dialysis population. This finding may be explained by the impaired innate and adaptive immune system, including defects in complement activation and B- and T-cell function, among patients with end-stage kidney disease.⁷

Understanding the effectiveness of influenza vaccine formulations in the dialysis population is vital for patients, clinicians, dialysis practices, and payors. Although HDV continues to be an option, future investigations into other types of vaccines (eg, cell-based and adjuvanted) are warranted to achieve better protection.

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Article Information

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References

- Miskulin D, Weiner D, Manley H. High-dose versus standard-dose influenza vaccine in hemodialysis patients [letter]. *Am J Kidney Dis.* 2019; <https://doi.org/10.1053/j.ajkd.2019.09.019>.
- Butler AM, Layton JB, Dharnidharka VR, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccine among patients receiving maintenance hemodialysis. *Am J Kidney Dis.* 2020;75(1):72-83.
- Schneeweiss S, Gagne JJ, Glynn RJ, Ruhl M, Rassen JA. Assessing the comparative effectiveness of newly marketed medications: methodological challenges and implications for drug development. *Clin Pharmacol Ther.* 2011;90(6):777-790.
- Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. *J Gen Intern Med.* 2011;26(5):546-550.
- McGrath LJ, Layton JB, Krueger WS, Kshirsagar AV, Butler AM. High-dose influenza vaccine use among patients receiving hemodialysis in the United States, 2010-2013. *Vaccine.* 2018;36(41):6087-6094.
- Butler AM, Layton JB, Krueger WS, Kshirsagar AV, McGrath LJ. Assessing residual bias in estimating influenza vaccine effectiveness: comparison of high-dose versus standard-dose vaccines. *Med Care.* 2019;57(1):73-78.
- Kato S, Chmielewski M, Honda H, et al. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol.* 2008;3(5):1526-1533.