Increasing Protection of Dialysis Patients against Influenza

Megan C. Lindley and David K. Kim

Clin J Am Soc Nephrol 13: 1624–1626, 2018. doi: https://doi.org/10.2215/CJN.11670918

Adults with CKD or ESKD have impaired immune systems and are at high risk of infectious disease–related illness, including significantly increased risk of serious complications from influenza infection (1,2). The Advisory Committee on Immunization Practices recommends routine influenza vaccination for persons with CKD and ESKD (2,3). Studies suggest that standard-dose influenza vaccines provoke a lesser immune response among persons with CKD and ESKD, although whether this translates to lower protection against influenza disease is unclear (1).

Despite this possible limitation, annual seasonal influenza vaccination remains the best way to protect all persons, including adults with CKD and ESKD, against serious complications of influenza infection (2,4). For this reason, research has focused on ways to improve influenza vaccines to increase immune response and, ultimately, protection against infection and disease. Similar to adults with ESKD, older adults have altered immunocompetence and immunogenicity of influenza vaccine may be lower in this population, although this does not necessarily indicate lower vaccine effectiveness. On the basis of superior efficacy against laboratory-confirmed influenza of high-dose trivalent inactivated influenza vaccine (4), which contains four times as much antigen as standard-dose inactivated influenza vaccine, Miskulin *et al.* (5) compared protective effects of high-dose trivalent and standard-dose quadrivalent inactivated influenza vaccines among adults with ESKD on dialysis over two influenza seasons.

Miskulin *et al.* offer a well designed study that, although falling short of the rigor of a randomized, controlled trial, provides an important contribution to the literature on the impact of influenza vaccination among adults with ESKD. The authors analyzed data from two consecutive influenza seasons for a large cohort of adults with ESKD who underwent dialysis and received influenza vaccination from clinics belonging to a not-for-profit dialysis organization in the United States; decisions about which vaccine to use were made at the clinic level. They found that during the 2016–2017 influenza season, after adjustment for demographic and disease-related factors and dialysis treatment modality, adults in the study population who had received high-dose trivalent inactivated influenza vaccine had a statistically significant lower rate of hospitalizations from all causes compared with those who had received standard-dose quadrivalent inactivated influenza vaccine. When examined by age group, a statistically significant protective effect of high-dose trivalent inactivated influenza vaccine was seemingly larger among adults aged ≥65 years, although an interaction term for age and vaccine type was nonsignificant in analysis. Lower risk of hospitalizations among adults who received high-dose trivalent inactivated influenza vaccine was not observed for the 2015–2016 influenza season, and no effect of vaccine type on all-cause mortality was noted in either season (5).

It is not surprising that no differences in effectiveness between high-dose trivalent inactivated influenza vaccine and standard-dose inactivated influenza vaccine were found during the 2015–2016 influenza season because, as the investigators note, only 8% of the study population received high-dose trivalent inactivated influenza vaccine in that period. In addition, the substantial variability in the timing and severity of seasonal influenza epidemics and the types of influenza viruses that predominate commonly poses limitations for influenza vaccination research and underscores the need for studies that gather data in multiple locations over multiple influenza seasons. The 2015–2016 influenza season started and peaked late, and was milder than the three previous seasons, whereas the 2016–2017 season was moderately severe (6). These factors may partially explain why vaccine type effects were observed in 2016–2017 but not in 2015–2016.

Miskulin *et al.* note that as a strength of their study, the capture rate for hospitalizations exceeding 24 hours was high because of their ability to track the data in the dialysis provider's information system. Although the study used the nonspecific outcome of all-cause hospitalization, the ability to capture most hospitalizations among the study population should have reduced the potential for bias. As the investigators point out, the ability to discern and analyze cause-specific hospitalizations would have significantly strengthened the findings of this study and may have resulted in stronger observed effects of high-dose trivalent inactivated influenza vaccine compared with standard-dose quadrivalent inactivated influenza vaccine, especially during the 2016–2017 influenza season. Despite the lower risk of hospitalizations observed in 2016–2017, no effect of high-dose influenza vaccination on all-cause

Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases, Atlanta, Georgia

Correspondence:
Ms. Megan Lindley, Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases, 1600 Clifton Road N.E., Mailstop A-19, Atlanta, GA 30329. Email: MLindley@cdc.gov

mortality was seen in the study population in either study year. Although all-cause mortality is a nonspecific outcome, overall estimates of excess mortality attributable to influenza suggest a significant annual burden of influenza disease in the United States, and presumably many of the >900 deaths in the study population each season were influenza-related (7). Given that patients on dialysis, particularly those aged ≥65 years, are at significantly increased risk of influenza complications including death, further studies to examine the effect of high-dose trivalent inactivated influenza vaccine on influenza-associated mortality among patients on dialysis are needed.

Although high-dose trivalent inactivated influenza vaccine is licensed and recommended for use among adults aged ≥65 years, there is interest in using high-dose influenza vaccine for other populations in whom standard-dose inactivated influenza vaccine is thought to potentially be insufficiently immunogenic. Several small studies have examined the use of high-dose trivalent inactivated influenza vaccine in populations whose immune systems are compromised because of disease rather than age, *e.g.*, persons with HIV infection, bone marrow or solid organ transplant recipients, or patients with cancer. These studies generally found increased immunogenicity of high-dose trivalent inactivated influenza vaccine over standard-dose inactivated influenza vaccine, although not all differences were significant and no study examined the clinical effectiveness of high-dose trivalent inactivated influenza vaccine in prevention of influenza disease. The current literature, although sparse, suggests that additional protection from high-dose trivalent inactivated influenza vaccine use in immunocompromised adults aged <65 years is possible. Miskulin *et al.* estimate that if the association between vaccine type and reduced risk of hospitalizations observed in the 2016–2017 influenza season were causal, 5.3 additional hospitalizations per 100 patients on dialysis could be prevented each year with the use of high-dose trivalent inactivated influenza vaccine instead of standard-dose quadrivalent inactivated influenza vaccine. The investigators note that this effect size is consistent with other studies of high-dose trivalent inactivated influenza vaccine versus standard-dose inactivated influenza vaccine in adults aged ≥65 years (4); it is also consistent with the literature on patients aged <65 years who are immunocompromised. Given the substantial disease burden of influenza (7), including hundreds of thousands of hospitalizations each year, the potential impact on clinical outcomes associated with even modest improvements in vaccine efficacy is significant in this medically vulnerable population.

In addition to increasing the immunogenicity of influenza vaccines in adults with CKD and ESKD, increasing annual influenza vaccination coverage, both among these patients and the health care providers who treat them, is an important strategy to increase their protection against influenza disease and its complications. A recent analysis of Medicare Part B claims data by Shen *et al.* (8) indicated that among adult patients with ESKD, approximately 70% received an influenza vaccine during the 2015–2016 influenza season, although <10% of those aged ≥65 years had received high-dose trivalent inactivated influenza vaccine. The patient population in Miskulin *et al.*'s analysis was even more highly vaccinated, with 87% influenza vaccination coverage for each season when vaccines given outside the dialysis centers were included (in-center influenza vaccination coverage was similar to that noted by Shen *et al.*, at 73% and 70% for the two study years). Dialysis centers routinely administer recommended vaccines (2,3) to patients and record these vaccinations in the Consolidated Renal Operations in a Web-enabled Network (CROWNWeb). CROWNWeb is a web-based data management system designed to improve quality of care for Medicare ESKD beneficiaries; one of its functions is to allow Medicare-certified dialysis facilities to securely submit administrative and clinical data to the Centers for Medicare and Medicaid Services in fulfillment of quality reporting requirements for dialysis facilities, including data on influenza, pneumococcal, and hepatitis B vaccination (9). CROWNWeb functionalities can support dialysis clinic–based providers in following the recommended standards for adult immunization practice: assess patient vaccination status, strongly recommend needed vaccines, offer vaccines to patients, and document vaccines administered in the state or local immunization information system (also known as an immunization registry) (10). Providers at clinics that do not stock vaccines should refer patients to alternate locations such as pharmacies or health departments for needed vaccines. In addition to following recommended practice standards, all health care providers should "walk the walk" by being up to date on their own immunizations and receiving an influenza vaccination every year (2,10).

The study by Miskulin *et al.* suggests patients on dialysis may benefit from use of high-dose trivalent inactivated influenza vaccine. To further quantify the potential benefits of high-dose trivalent inactivated influenza vaccine in adults with CKD or ESKD, controlled trials including random assignment of vaccine types, analysis of influenza-specific end points, more complete data capture on vaccinations received in alternate locations, and follow-up over multiple influenza seasons would be needed. Additional studies of other strategies to increase influenza vaccine effectiveness in patients on dialysis and other immunocompromised populations, including the use of adjuvants and booster doses, could also be beneficial. Even in the absence of increased vaccine effectiveness, improvements in influenza vaccination coverage among medically vulnerable populations such as patients on dialysis could increase protection against influenza. In groups where the burden of influenza disease and its complications are disproportionately felt, small improvements in vaccine effectiveness and vaccination coverage may have large effects.

Acknowledgments

The findings and conclusions of this report are those of the authors and do not represent an official position of the Centers for Disease Control and Prevention.

Disclosures

None.

References

1. Mastalerz-Migas A, Gwiazda E, Brydak LB: Effectiveness of influenza vaccine in patients on hemodialysis–a review. *Med Sci Monit* 19: 1013–1018, 2013

2. Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Fry AM, Jernigan DB: Prevention and control of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2018–19 influenza season. *MMWR Recomm Rep* 67: 1–20, 2018
3. Kim DK, Riley LE, Hunter P; Advisory Committee on Immunization Practices: Recommended immunization schedule for adults aged 19 years or older, United States, 2018. *Ann Intern Med* 168: 210–220, 2018
4. DiazGranados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, Pollak R, Christoff J, Earl J, Landolfi V, Martin E, Gurunathan S, Nathan R, Greenberg DP, Tornieporth NG, Decker MD, Talbot HK: Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med* 371: 635–645, 2014
5. Miskulin DC, Weiner DE, Tighiouart H, Lacson EK Jr., Meyer KB, Dad T, Manley HJ: High-dose seasonal influenza vaccine in patients undergoing dialysis. *Clin J Am Soc Nephrol* 13: 1703–1711, 2018
6. Centers for Disease Control and Prevention: Past Flu Seasons, Updated 2018. Available at: www.cdc.gov/flu/pastseasons/index.htm. Accessed September 19, 2018
7. Rolfes MA, Foppa IM, Garg S, Flannery B, Brammer L, Singleton JA, Burns E, Jernigan D, Olsen SJ, Bresee J, Reed C: Annual estimates of the burden of seasonal influenza in the United States: A tool for strengthening influenza surveillance and preparedness. *Influenza Other Respir Viruses* 12: 132–137, 2018
8. Shen AK, Kelman JA, Warnock R, Zhang W, Brereton S, McKean S, Wernecke M, Chu S, Gellin BG: Beneficiary characteristics and vaccinations in the end-stage renal disease Medicare beneficiary population, an analysis of claims data 2006-2015. *Vaccine* 35: 7302–7308, 2017
9. Centers for Medicare & Medicaid Services: CROWNWeb: The ESRD National Patient Registry & Quality Measure Reporting System, Updated 2018. Available at: http://mycrownweb.org/. Accessed September 19, 2018
10. National Vaccine Advisory Committee: Recommendations from the National Vaccine Advisory Committee: Standards for adult immunization practice. *Public Health Rep* 129: 115–123, 2014

Published online ahead of print. Publication date available at www.cjasn.org.

See related article, "High-Dose Seasonal Influenza Vaccine in Patients Undergoing Dialysis," on pages 1703–1711.