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Comparing Influenza Vaccine Types: The Path Toward Improved Influenza Vaccine Strategies

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The 2017–2018 influenza season was a reminder that seasonal influenza can be associated with a large burden of severe disease and that adults aged ≥ 65 years are disproportionately affected; 660 000 hospitalizations and 68 000 deaths were estimated to be associated with influenza virus infection in this age group [1]. Older adults are a priority group for annual influenza vaccination. The 2017–2018 season, notable for the predominance of A(H3N2) viruses, also was a reminder that the H3N2 vaccine component is not as effective as other vaccine components. Vaccines reduced the risk of laboratory-confirmed influenza A and B–associated outpatient visits by 40%, but vaccine effectiveness (VE) estimates against A(H3N2) viruses were 24% [2]. Since 2004–2005, VE point estimates against A(H3N2) viruses have been lower than against 2009 pandemic influenza A(H1N1) virus (A[H1N1]pdm09) or influenza B viruses, and VE estimates against A(H3N2) viruses are usually lowest among older adults [2–4]. Thus, understanding why influenza vaccines are less effective against A(H3N2) viruses and identifying new strategies to improve VE are critical, especially during A(H3N2)-predominant seasons, such as 2017–2018.

In this issue of *the Journal of Infectious Diseases*, Izurieta et al used data from Medicare beneficiaries aged ≥ 65 years to compare *International Classification of Diseases, 10th Revision* (ICD-10)–coded influenza-associated hospital visits among recipients of different influenza vaccines during the 2017–2018 influenza season [5]. The large population of Medicare recipients allowed the authors to compare not just 2 vaccine types, as reported previously [6, 7], but to compare multiple vaccine types during 1 influenza season. Comparisons among multiple vaccines aid understanding of current issues related to influenza vaccines and also offer insight into potential strategies to improve vaccine effectiveness.

For the 2018–2019 influenza season, there are 9 licensed vaccines recommended for people aged ≥ 65 years in the United States. The Advisory Committee on Immunization Practices indicates no preference for one type of influenza vaccine [8]. Most influenza

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vaccines contain vaccine viruses that are initially isolated and propagated in chicken eggs (ie, egg-based vaccines). Inactivated egg-based influenza vaccines are available in trivalent and quadrivalent formulations. Two vaccines designed to result in an enhanced immune responses are available for older adults [8]. High-dose vaccine is a trivalent inactivated egg-based vaccine with 4 times the antigen dose, compared with standard vaccines. A randomized clinical trial [9] during 2011–2012 and 2012–2013 and several observational studies [6, 7] reported a higher relative effectiveness of high-dose as compared to standard-dose egg-based vaccines, although results from observational studies vary. An MF59-adjuvanted egg-based vaccine is also licensed for use in older adults [8]. One observational study reported a higher relative effectiveness of adjuvanted as compared to nonadjuvanted vaccines in this age group [10]. The effectiveness of high-dose and adjuvanted vaccines has not been compared previously. Finally, 2 licensed vaccines for older adults are not egg based: the cell-culture vaccine and a vaccine based on a recombinant influenza virus hemagglutinin (HA) protein that is produced in insect cells. In addition to several potential production advantages of non-egg based vaccines, the recent issues with A(H3N2) viruses have further increased interest in these vaccines.

Human influenza viruses grown in eggs may acquire mutations that facilitate propagation in eggs but inadvertently change antigenic properties of vaccine viruses; this is especially true for recent A(H3N2) viruses [11]. While these changes from egg propagation could result in less effective vaccines, the contribution of these changes toward lower VE estimates has not been quantified. Few studies are available to shed light on this issue. A randomized trial among adults aged ≥ 50 years during 2014–2015, an A(H3N2)-predominant season, reported a higher relative effectiveness of recombinant vaccine as compared to standard egg-based vaccines [12]. Unfortunately, there was too little use of the recombinant vaccine among Medicare beneficiaries to include this vaccine in the analysis by Izurieta et al [5]. Until 2017–2018, the cell-culture vaccine used viruses initially isolated in eggs followed by propagation in a mammalian cell line. For the first time, in 2017–2018, the A(H3N2) vaccine virus in the cell-culture vaccine was completely cell derived from initial isolation through vaccine production [13]. The remaining 3 vaccine components of the 2017–2018 cell-culture vaccine were produced from egg-adapted A(H1N1) pdm09 and B viruses but, in future years, will also be completely cell derived. Since A(H3N2) viruses predominated during the 2017–2018 season, this was the first season that a completely cell-derived vaccine virus could be evaluated. Despite limited commercial uptake, the large Medicare population allowed evaluation of recipients of this vaccine by Izurieta et al [5].

For their primary outcome of ICD-10-coded influenza-associated hospital visits, Izurieta et al reported an 11% and 9% relative effectiveness among recipients of the cell-culture vaccine and high-dose egg-based vaccines as compared to standard egg-based trivalent or quadrivalent vaccines, respectively. In addition, they demonstrated no statistically significant relative effectiveness of cell-culture vaccine as compared to high-dose vaccine among beneficiaries during the 2017–2018 influenza season. The superior relative effectiveness of the cell-culture vaccine, with the same amount of HA antigen as the standard-dose egg-based comparator and one fourth as much H3N2 antigen as the high-dose vaccine, was likely due to the cell-derived A(H3N2) component. However, the small relative increase suggests that egg-adaptation changes do not entirely explain the lower VE reported for

A(H3N2) viruses as compared to the other vaccine components, A(H1N1)pdm09 and B viruses. In addition, despite changes in the HA during egg propagation, high-dose vaccine offered superior effectiveness (similar to that of cell-culture vaccine) as compared to standard-dose egg-based vaccines. One wonders how a vaccine with a higher dose and an absence of egg-adaptation changes would have compared in this study. Finally, cell-culture vaccine and high-dose egg-based vaccine had a 5%–7% higher relative effectiveness as compared to adjuvanted egg-based vaccine, which was 4% more effective than standard (ie, nonadjuvanted) egg-based vaccines. This suggests that adjuvant worked less well than an increased antigen dose at improving effectiveness against A(H3N2) viruses. In the future, we need to understand whether adjuvanted vaccines offer benefits against antigenically drifted viruses, as well as A(H1N1)pdm09 and B viruses, and, potentially, what role an adjuvanted cell-culture vaccine may have.

The measure used to compare vaccine types in the study by Izurieta et al is relative VE. In their cohort analysis, it represents the decrease in rates of ICD-10-coded influenza-associated hospitalization visits among beneficiaries who received a selected vaccine type as compared to those who received a comparator vaccine. It is analogous to the relative efficacy measured as the difference in attack rates in a clinical trial. An advantage of this approach is that it does not require an unvaccinated cohort. Medicare records may not capture all influenza vaccinations, leading to misclassification of some vaccinated individuals as unvaccinated. In addition, unvaccinated cohorts may introduce additional biases related to who gets vaccinated [6]. A disadvantage of this approach is that it does not permit estimation of the absolute VE for any vaccine; that is, the decrease in rates of outcomes in each vaccinated cohort as compared to an unvaccinated cohort. To put the relative effectiveness estimate in context, the authors derive estimates of absolute VE for each vaccine, based on several possible values for the 2017–2018 comparator vaccine. It is clear from this example that the relative effectiveness of cell-culture and high-dose vaccine resulted in modest improvements in protection against influenza-associated hospitalizations.

Since most postlicensure evaluations of different vaccine types will be observational studies, it is important to monitor and account for changes in the use of different vaccine types over time. In 2012–2013, 19% of vaccinated Medicare beneficiaries received high-dose vaccine, and 81% received trivalent standard-dose vaccine [6]. In 2017–2018, 63% received high-dose vaccine, and only 7% received trivalent standard-dose vaccine [5]. This may have played a role in the differences between the findings for hospital outcomes versus outpatient visit outcomes, as reported by Izurieta et al [5]. It is plausible that the small group of beneficiaries who received trivalent standard-dose vaccine in 2017–2018 may have differed from the majority of vaccinees in care-seeking behavior or likelihood of influenza testing in ways that affected influenza-related office visits differently than influenza-associated hospitalizations. In addition, commercial uptake will influence the ability to evaluate new vaccines and understand their role in vaccination strategies.

A limitation of using Medicare data is the absence of laboratory-confirmed influenza outcomes. Because A(H3N2) viruses predominated, we can only assume the cell-culture vaccine effects were related to the A(H3N2) vaccine virus. Therefore, replication of these findings with studies using laboratory-confirmed influenza virus infection outcomes will

be needed to determine absolute and relative effectiveness of different influenza vaccines, by specific influenza virus types and subtypes. Several networks report annual absolute VE estimates against all vaccine viruses and by vaccine type in the United States [2]. Thus, evidence to inform future policy decisions will be dependent on multiple studies with different but complementary methods that can report annual results over several seasons, as well as statistical models to evaluate potential impact of changes in vaccine uptake. The lessons we learn from these studies will help improve influenza vaccines and vaccine strategies so that we optimize the protection provided by seasonal influenza vaccines.

References

1. Centers for Disease Control and Prevention. Estimated influenza illnesses, medical visits, hospitalizations, and deaths in the United States—2017–2018 influenza season. <https://www.cdc.gov/flu/about/burden/estimates.htm>. Accessed 6 December 2018.
2. Flannery B, Chung JR, Ferdinands JM. Preliminary estimates of 2017–18 seasonal influenza vaccine effectiveness against laboratory-confirmed influenza from the US flu VE and HAIVEN networks. Atlanta, GA: Advisory Committee on Immunization Practices, 2018.
3. Belongia EA, Simpson MD, King JP, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. *Lancet Infect Dis* 2016; 16:942–51. [PubMed: 27061888]
4. Rondy M, El Omeiri N, Thompson MG, Levêque A, Moren A, Sullivan SG. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: a systematic review and meta-analysis of test-negative design case-control studies. *J Infect* 2017; 75:381–94. [PubMed: 28935236]
5. Izurieta HS, Chillarige Y, Kelman J, et al. Relative effectiveness of cell-cultured and egg-based influenza vaccines among the U.S. elderly, 2017–18. *J Infect Dis* 2018. In this issue.
6. Izurieta HS, Thadani N, Shay DK, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. *Lancet Infect Dis* 2015; 15:293–300. [PubMed: 25672568]
7. Shay DK, Chillarige Y, Kelman J, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines among US medicare beneficiaries in preventing postinfluenza deaths during 2012–2013 and 2013–2014. *J Infect Dis* 2017; 215:510–7. [PubMed: 28329311]
8. Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Jernigan Fry AMDB. 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* 2018; 67:1–20.
9. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med* 2014; 371:635–45. [PubMed: 25119609]
10. Van Buynder PG, Konrad S, Van Buynder JL, et al. The comparative effectiveness of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly. *Vaccine* 2013; 31:6122–8. [PubMed: 23933368]
11. Zost SJ, Parkhouse K, Gumina ME, et al. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. *Proc Natl Acad Sci U S A* 2017; 114:12578–83. [PubMed: 29109276]
12. Dunkle LM, Izikson R, Patriarca P, et al. ; PSC12 Study Team. Efficacy of recombinant influenza vaccine in adults 50 years of age or older. *N Engl J Med* 2017; 376:2427–36. [PubMed: 28636855]
13. Barr IG, Donis RO, Katz JM, et al. Cell culture-derived influenza vaccines in the severe 2017–2018 epidemic season: a step towards improved influenza vaccine effectiveness. *NPJ Vaccines* 2018; 3:44. [PubMed: 30323955]