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EDITORIAL COMMENTARY

Epidemiological Data on the Effectiveness of Influenza Vaccine—Another Piece of the Puzzle

Allen C. Cheng,[1,2] and Kanta Subbarao[3]

[1]School of Public Health and Preventive Medicine, Monash University, [2]Infection Prevention and Healthcare Epidemiology Unit, Alfred Health, and [3]World Health Organization Collaborating Centre for Reference and Research on Influenza, and Department of Microbiology and Immunology, The University of Melbourne, Peter Doherty Institute for Infection and Immunity, Australia

Vaccine effectiveness (VE) is defined as the reduction in risk of an outcome associated with vaccination. To keep pace with ongoing antigenic drift in circulating influenza viruses resulting from immune pressure, the composition of influenza vaccine is reviewed each year and strains are changed as needed. Since the emergence of 2009 pandemic influenza A(H1N1) viruses (A[H1N1]pdm09 viruses), they have gradually evolved into distinct genetic clades; the 6B clade was identified in 2013–2014, and the 6B1 clade was identified in 2015–2016 [1]. Short of conducting controlled clinical trials each year, we are left to rely on methods of monitoring vaccine effectiveness (VE) that are based on observational studies. Since the advent of highly specific influenza diagnostic tests based on nucleic acid detection, the test-negative study, a variant of a case-control study, has become widely used as a simple method to estimate VE [2, 3].

In this issue of *The Journal of Infectious Diseases*, Flannery et al demonstrate the value of epidemiological monitoring of VE. They estimated the effectiveness of inactivated influenza vaccines against medically attended respiratory illness caused by A(H1N1)pdm09 viruses over the course of 5 years in 7 US centers, using results of a test-negative observational study, and found that overall VE in 2010–2013, 2013–2014 (when 6B viruses were identified), and 2015–2016 (when 6B1 viruses predominated) were 69%, 56%, and 47%, respectively. They analyzed the observed reduction in VE in 2015–2016 further in different age cohorts and found that the estimated VE in the birth cohort born between 1958 and 1979 was only 22%.

The proposition of original antigenic sin is that influenza virus strains encountered earliest in life have long-lasting effects and focus the immune response on shared epitopes upon subsequent infection or vaccination later in life [4, 5]. The working hypothesis for this study is that the cohort born between 1958 and 1977, during which A(H1N1) strains did not circulate, was first exposed to the A(H1N1) strain that emerged in 1977 (A/USSR/90/1977). Thus, individuals primed with a pre-1957 A(H1) virus would be expected to respond with antibodies directed against epitopes that were shared with pre-1957 viruses, and individuals primed with post-1977 A(H1) viruses would respond with antibodies directed against epitopes shared with post-1977 viruses. This hypothesis is supported by studies showing that 60% of the serological responses to inactivated influenza vaccines are due to the boosting of preexisting antibodies, rather than new vaccine-induced antibodies [6].

The mechanism for the birth cohort effect was first proposed by Linderman et al, who reported reduced serologic reactivity with the 2013–2014 6B viruses in a large proportion of middle-aged adults, owing to a mutation in the viral hemagglutinin from lysine to glutamate at residue 166 [7]. In a separate study, Huang et al found that a large proportion of monoclonal antibodies isolated from a single adult neutralized A/USSR/90/1977(H1N1) but failed to recognize 6B viruses owing to the same mutation, identified as K163 by their numbering [5]. This residue lies in a patch of conserved residues in the Sa antigenic site common to USSR/77 and A(H1N1) pdm09 viruses. They proposed that antibodies to this site were selectively recalled in 2009 in previously primed individuals, resulting in a focused antibody response that led to selection of mutations at K163. The current study by Flannery et al shows that data at a population level are consistent with highly technical analysis of the antibody response to the viral hemagglutinin in 1 person [5] or a small group of people [7]. It is likely that the population effects were only apparent after the emergence of 6B1 viruses, which the authors point out is likely a result of the addition of a glycosylation site at the adjacent residue (162), which further reduced antibody binding to this site.

The hypothesis is not without flaws, however. A reduction in estimated VE against A(H1N1) viruses has been found in North America [8] but not to the same extent in similar studies conducted elsewhere [9]. Flannery et al also observed reductions in VE in other birth cohorts (eg, from 80% in 2010–2013 to 53% in 2013–2014 in the cohort born between 1982 and 1991 and from 72% in 2010–2013 to 58% in 2013–2014 and 41% in

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Correspondence: A. Cheng, 2nd Fl, Burnet Centre, 85 Commercial Rd, Melbourne VIC 3004 Australia (allen.cheng@monash.edu).

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2015–2016 in the 1947–55 birth cohort) that were not commented on. Given the limits of uncertainty, it is possible that these effects are the result of statistical happenstance, and we should be careful to avoid confirmation bias in accepting only the results that fit our hypothesis. However, based on this accumulated evidence, it seemed prudent to update the vaccine strain from A/California/7/2009 to A/Michigan/45/2015 (a clade 6B1 strain) for the northern hemisphere 2016–2017 and southern hemisphere 2017 influenza seasons.

Epidemiological data have also demonstrated the impact of problems in achieving matches between vaccine strains and circulating A(H3N2) strains. A(H3N2) strains are generally more antigenically diverse and are relatively more difficult to propagate in eggs. The lack of suitable vaccine candidates, combined with the potential for vaccine strains to antigenically change in the egg adaptation process [10], have now been shown to result in impaired protection against this subtype [11].

Similarly, problems with the live attenuated influenza vaccine have surfaced in recent years. This has led to a downgrading in recommendations for this formulation in the United States, from a preferred status for younger children [12], to a neutral recommendation [13], and a nonpreferred status [14], compared with the inactivated vaccine. The reasons for the apparent downward drift in effectiveness over time [15] and the conflicting estimates in other regions are not yet clear but may be related to the effect of revaccination over several seasons [16].

Unfortunately, epidemiological data are a rather blunt measurement device. Confidence intervals around estimates are often imprecise, particularly in smaller subgroups where vaccine coverage is lower, such as children. This has led to the formation of Global Influenza Vaccine Effectiveness collaboration, a loose network of networks that compile available data twice yearly to inform participants in vaccine strain selection meetings. Many systems rely on clinical laboratory testing, where subtyping may not be available, and most systems do not collect data on specific vaccine products, apart from the intranasal vaccine. As with all observational data, estimates are vulnerable to bias and confounding, particularly if the incidence of respiratory illness due to pathogens other than influenza virus varies by vaccination status. Epidemiological data only provide a signal to investigate, although as the study by Flannery et al demonstrates, this signal may provide valuable clues to a mechanism.

Although vaccine strain selection will always be made primarily on the basis of virological factors, epidemiological data are required to measure the overall impact of the program. It took >50 years after the implementation of influenza vaccines to develop systems to routinely monitor their effectiveness. The subsequent 10–15 years of data suggest that, while the vaccines are generally protective, the degree of protection varies from season to season and that, importantly, as highlighted in the current article, it may be lower in certain population groups. These population-level data demonstrate that current vaccines are moderately protective at best, and more effective vaccines are clearly needed.

Notes

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References

1. Broberg E, Melidou A, Prosenc K, et al. Predominance of influenza A(H1N1)pdm09 virus genetic subclade 6B.1 and influenza B/Victoria lineage viruses at the start of the 2015/16 influenza season in Europe. Euro Surveill **2016**; 21.
2. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. Vaccine **2013**; 31:2165–8.
3. Sullivan SG, Feng S, Cowling BJ. Potential of the test-negative design for measuring influenza vaccine effectiveness: a systematic review. Expert Rev Vaccines **2014**; 13:1571–91.
4. Francis T. On the doctrine of original antigenic sin. Proc Am Phil Soc **1950**; 104:572–78.
5. Huang KY, Rijal P, Schimanski L, et al. Focused antibody response to influenza linked to antigenic drift. J Clin Invest **2015**; 125:2631–45.
6. Lee J, Boutz DR, Chromikova V, et al. Molecular-level analysis of the serum antibody repertoire in young adults before and after seasonal influenza vaccination. Nat Med **2016**; 22:1456–64.
7. Linderman SL, Chambers BS, Zost SJ, et al. Potential antigenic explanation for atypical H1N1 infections among middle-aged adults during the 2013–2014 influenza season. Proc Natl Acad Sci U S A **2014**; 111:15798–803.
8. Skowronski DM, Chambers C, Sabaiduc S, et al. Beyond antigenic match: possible agent-host and immuno-epidemiological influences on influenza vaccine effectiveness during the 2015–16 season in Canada. J Infect Dis **2017**.
9. Kissling E, Valenciano M. Early influenza vaccine effectiveness results 2015–16: I-MOVE multicentre case-control study. Euro Surveill **2016**; 21.

10. 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 SA **2017**; 114:12578–83.
11. Skowronski DM, Chambers C, Sabaiduc S, et al. A perfect storm: impact of genomic variation and serial vaccination on low influenza vaccine effectiveness during the 2014–2015 season. Clin Infect Dis **2016**; 63:21–32.
12. Grohskopf LA, Olsen SJ, Sokolow LZ, et al.; Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP) – United States, 2014-15 influenza season. MMWR Morb Mortal Wkly Rep **2014**; 63:691–7.
13. Grohskopf LA, Sokolow LZ, Olsen SJ, Bresee JS, Broder KR, Karron RA. Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2015-16 Influenza Season. MMWR Morb Mortal Wkly Rep **2015**; 64:818–25.
14. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices - United States, 2017-18 influenza season. MMWR Recomm Rep **2017**; 66:1–20.
15. Poehling KA, Caspard H, Peters TR, et al. 2015–2016 vaccine effectiveness of live attenuated and inactivated influenza vaccines in children in the United States. Clin Infect Dis **2017**. doi: 10.1093/cid/cix869.
16. Pebody R, McMenamin J, Nohynek H. Live attenuated influenza vaccine (LAIV): recent effectiveness results from the USA and implications for LAIV programmes elsewhere. Arch Dis Child **2017**. doi: 10.1136/archdischild-2016-312165.