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EDITORIAL COMMENTARY

Challenges Remain for Influenza Vaccination of Children

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Over the past decades, multiple active surveillance and observational studies have demonstrated the major impact of influenza on children and underscored the need for effective vaccines [1–4]. Since 2009, annual influenza vaccination has been recommended for all children ≥6 months of age in the United States [5]. Extensive studies in children have been conducted over the years with both inactivated influenza vaccines (IIV) and live attenuated influenza vaccines (LAIV). Influenza hemagglutination inhibition (HAI) antibody responses are considered to be the gold standard for assessing IIV immunogenicity and serve as the basis for their licensure. Although achievement of HAI antibody titers of ≥40 (putative protective titer) was associated with a 50% reduction in the occurrence of influenza [6, 7], others have proposed that the protective HAI titer is much higher [8]. Furthermore, there can be variability in HAI assay results among laboratories [9]. Cell-mediated immune (CMI) responses have been less well characterized, and no CMI correlate of protection (COP) has been proposed.

In this issue of *The Journal of Infectious Diseases*, Reber et al report detailed humoral and CMI responses in 50 children ages 9–14 years after receipt of the 2010–2011 seasonal IIV [10]. In the previous year, 38% of the participants had received influenza vaccine (10% received LAIV and 28% received IIV), and 32% had been immunized with monovalent 2009 pandemic influenza A(H1N1) vaccine. Which vaccine(s) the children had received previously was not noted in the article, and their impact on subsequent immune responses was not assessed because of small sample size. HAI antibody responses were assayed against influenza virus antigens included in both the 2009–2010 and 2010–2011 vaccines, as well as the 2008–2009 influenza B vaccine antigen. Most children achieved HAI antibody titers of ≥40 to all of the evaluated antigens; many had titers of ≥160. Elevated antibody titers persisted for 7 months at levels that exceeded the prevaccination titers, although they were approximately 50% lower than peak titers. Subjects previously vaccinated with IIV, LAIV, and/or monovalent 2009 pandemic influenza A (H1N1) had higher baseline HAI titers to all three 2009–2010 vaccine antigens and the 2010–2011 influenza A(H3N2) antigen and developed significantly higher titers to the 2009–2010 influenza A (H1N1) antigen and the 2010–2011 influenza A(H3N2) vaccine antigen 28 days after vaccination with IIV. Interestingly, day 28 postvaccination titers against B/Brisbane/60, the influenza B component for both seasonal influenza vaccines, were significantly lower in the group that received the same component in the 2009–2010 season. This raises the issue of the impact of repeated immunization against influenza, to be discussed below.

CMI responses were also assessed, using live viruses or recombinant hemagglutinin to stimulate peripheral blood mononuclear cells from the vaccinated children. Stimulated cells were then stained for surface markers and intracellular cytokines. After vaccination, significant increases in interferon γ (IFN-γ)–secreting $CD4^+$ T cells and tumor necrosis factor α (TNF-α)–secreting $CD8^+$ T cells were seen with live virus stimulation and, to a lesser degree, with recombinant hemagglutinin stimulation. Children receiving 2009–2010 seasonal influenza vaccine had significantly higher levels of IFN-γ–secreting $CD4^+$ cells before vaccination when stimulated with 2009 pandemic influenza A(H1N1) virus but did not have significantly higher levels of TNF-α–secreting $CD8^+$ T cells after vaccination when stimulated with 2009 pandemic influenza A(H1N1) or A/Perth/16(H1N1) viruses. The significance of these observations is unknown. After immunization with IIV, robust immunoglobulin M and immunoglobulin G production by plasmablasts at 7 days and robust memory B-cell responses at 28 days against H1, H3, and B antigens were observed. These studies demonstrate that prior immunization of young children elicited enhanced humoral and CMI responses to strains encountered in subsequent seasons and to strains previously encountered in earlier seasons. This and many other studies contribute to a growing database regarding the effects of immunization of children against influenza virus; however, a number of unanswered questions and challenges remain.

Since surveillance was not conducted during the subsequent influenza seasons

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in these children, the levels of immunity could not be correlated with protection from influenza. The COP following immunization with IIV has generally been the HAI titer, whereas no accepted COP is available for LAIV. Any serum HAI antibody titer or any nasal wash IgA antibody titer was correlated with protection from LAIV challenge in an earlier study [11]. Recently, Wright et al similarly used an intranasal challenge with LAIV to mimic natural influenza virus infection and found that serum HAI responses after IIV did not correlate with prevention of viral shedding after LAIV challenge [12]. Similarly, levels of mucosal or serum antibodies after LAIV receipt did not predict reduction in viral shedding after LAIV challenge in this study. Unfortunately, immune responses observed after receipt of LAIV or IIV could not be correlated with protection against an LAIV challenge in that study.

Given the concern about immunologic COPs against circulating influenza virus strains, the clinical effectiveness of influenza vaccine has been assessed in an increasing number of studies in real time. In fact, many locales, including Europe, the United States [13], Canada, the Pan American Health Organization, and Australia, have an established infrastructure to conduct yearly studies of influenza vaccine effectiveness (VE). Frequently, these platforms have used a test-negative design, in which VE is calculated on the basis of vaccine receipt by laboratory-confirmed influenza cases versus receipt by test-negative controls who present to the study site for laboratory assessment of influenza, generally by culture or polymerase chain reaction. Such VE studies have shown marked year-to-year variation depending on the season, the match of the vaccine to the circulating strain, and the age and comorbidities of the vaccine recipient. A recent meta-analysis of many of these studies determined that the pooled VE in children against influenza A (H3N2) was 43% (95% confidence interval [CI], 28%–55%), 69% (95% CI, 49%–81%) for influenza A(H1N1), and 56% (95% CI, 38%–69%) for influenza B [14]. These VE estimates were not correlated with antibody responses, and, although providing protection against influenza, licensed influenza vaccines are less efficacious than other currently licensed vaccines, including pneumococcal conjugate vaccines and live attenuated measles vaccines.

Another disappointing turn of events for influenza prevention in children occurred recently when data from the US Influenza Vaccine Effectiveness Network surveillance system for the 2015–2016 influenza season in children aged 2–17 years became available [15]. These data demonstrated that the LAIV VE against any influenza virus was 3% (95% CI, −49%–37%), compared with the IIV VE of 63% (95% CI, 52%–72%). Data from the 2013–2014 and 2014–2015 influenza seasons in children also showed a lower than expected VE for LAIV. Notably, the first quadrivalent LAIV (LAIV4) was introduced in 2013–2014; trivalent LAIV (LAIV3) was used in earlier seasons. Based on these data, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices voted that LAIV should not be used during the 2016–2017 influenza season. This is lamentable, as LAIV is preferred over IIV by many needle-conscious children. Furthermore, earlier head-to-head randomized clinical trials of LAIV3 and IIV in children, using laboratory-confirmed influenza virus infections, demonstrated superior efficacy of the LAIV3 over IIV [16–18]. LAIV was also shown to elicit antibody among young children to an influenza A(H3N2) variant not present in the vaccine in 1997–1998 and to confer significant protection during the subsequent epidemic caused by the variant virus [19].

The reasons for the recent poor performance of LAIV in children are not clear. Potential explanations include interference with the infectivity and/or immunogenicity of LAIV3 with the addition of another strain of influenza B [20], preexisting immunity that impedes the ability of LAIV to infect the nasal mucosa and stimulate an immune response, and/or a change in the actual manufacturing process for LAIV that makes it less immunogenic. The reasons for these changes in LAIV VE must be aggressively explored to develop approaches to improve the existing LAIV vaccines; otherwise, a once promising vaccine may no longer be available for the control of influenza.

Finally, issues related to the impact of repeated vaccination of children against influenza are raised by the data presented in this issue and in earlier studies [21, 22]. Prior immunization with seasonal IIV generally resulted in enhanced immune responses in this trial. The trial participants were 9–14 years of age; therefore, all would be considered to be primed against seasonal H1, H3, and B strains [5]. Thus, it would be expected that their immune response patterns would be similar to those of older children and adults. Observations regarding the effects of prior immunization on serum HAI antibody responses have also been made in numerous clinical trials in children and adults, with the following general conclusions: (1) prior immunization with a seasonal influenza vaccine is associated with higher preimmunization levels of serum antibody in the subsequent season, even when the vaccine antigen changes; (2) immunization boosts antibody levels to earlier and future variants; and (3) variable effects on the postimmunization antibody levels to the current strains may be observed. Most of these data regarding repeated immunization relate to immunization with IIVs; serum HAI antibody responses are generally lower in older children and adults than in young children immunized with LAIV [23]. The frequencies of a ≥4-fold rise in titer according to prior immunization history are not reported in the current article; however, it is predicted that fewer previously vaccinated subjects would experience a significant titer rise than previously unvaccinated subjects.

The effects of prior vaccination on VE have also been reported, and the effect is variable. Beyer et al conducted a meta-

analysis of serologic and field studies assessing the effects of annually repeated vaccination and concluded that there was no consistent evidence for decreasing protection with repeated annual vaccination [24]. These results are very similar to those reported from a randomized, placebo-controlled clinical trial of IIV in middle-aged adults [25]. Smith et al developed a model to test the hypothesis that the antigenic distance between seasonal vaccine antigens in subsequent years, as well as the antigenic distance between epidemic strains, would predict immunogenicity and VE [26]. Using their model, one would predict that the immune response to the 2010–2011 influenza B antigen in the current trial would be lower among previously vaccinated subjects because the vaccine antigen did not change from 2009–2010. The only significantly lower HAI antibody response among previously vaccinated children relative to previously unvaccinated participants was to the B/Brisbane/60 antigen present both years.

The report by Reber et al contributes to the growing body of evidence on the impact of immunization against influenza virus in children, but it also highlights the many questions that remain. What are the differential effects of IIV and LAIV on immune responses? How do we identify new or improved COPs for both IIV and LAIV? What is the impact of repeated yearly influenza vaccinations on VE? Yet, there is little dispute that improved vaccines are needed for influenza control. Universal influenza vaccines that stimulate broadly cross-reactive responses [27], higher HA dose vaccines [28], and adjuvanted vaccines [29] may contribute to this effort. Continued careful assessments of both humoral and cellular responses will be necessary to develop more precise methods for predicting whether a vaccine will confer protection.

Note

Potential conflict of interest. K. M. E. reports receiving grants from Novartis outside the submitted work and membership on a Data Safety Monitoring Committee for an adjuvanted influenza trial funded by Novartis. W. A. K. certifies no potential conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Glezen WP, Couch RB. Interpandemic influenza in the Houston area, 1974–76. N Engl J Med **1978**; 298:587–92.
2. Poehling KA, Edwards KM, Weinberg GA, et al. The underrecognized burden of influenza in young children. N Engl J Med **2006**; 355:31–40.
3. Poehling KA, Edwards KM, Griffin MR, et al. The burden of influenza in young children, 2004–2009. Pediatrics **2013**; 131:207–16.
4. Neuzil KM, Mellen BG, Wright PF, Mitchel EF Jr, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med **2000**; 342:225–31.
5. Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices. MMWR **2009**; 58(RR-8):1–52.
6. Hobson D, Curry RL, Beare AS, Ward-Gardner A. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J Hyg (Lond) **1972**; 70:767–77.
7. Ng S, Fang VJ, Ip DK, et al. Estimation of the association between antibody titers and protection against confirmed influenza virus infection in children. J Infect Dis **2013**; 208:1320–4.
8. Black S, Nicolay U, Vesikari T, et al. Hemagglutination inhibition antibody titers as a correlate of protection for inactivated influenza vaccines in children. Pediatr Infect Dis J **2011**; 30:1081–5.
9. Stephenson I, Das RG, Wood JM, Katz JM. Comparison of neutralising antibody assays for detection of antibody to influenza A/H3N2 viruses: an international collaborative study. Vaccine **2007**; 25:4056–63.
10. Reber AJ, Kim JH, Coleman LA, et al. Seasonal influenza vaccination of children induces humoral and cell-mediated immunity beyond the current season: cross-reactivity with past and future strains. J Infect Dis **2016**; 214:1477–86.
11. Belshe RB, Gruber WC, Mendelman PM, et al. Correlates of immune protection induced by live, attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine. J Infect Dis **2000**; 181:1133–7.
12. Wright PF, Hoen AG, Ilyushina NA, et al. Correlates of immunity to influenza as determined by challenge of children with live, attenuated influenza vaccine. Open Forum Infect Dis **2016**; 3:1–8.
13. Centers for Disease Control and Prevention. Seasonal influenza vaccine effectiveness, 2005–2016. Updated 20 July 2016. http://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm. Accessed 10 August 2016.
14. 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.
15. Centers for Disease Control and Prevention. ACIP votes down use of LAIV for 2016–2017 flu season [media release]. Updated 22 June 2016. http://www.cdc.gov/media/releases/2016/s0622-laiv-flu.html. Accessed 10 August 2016.
16. Belshe RB, Edwards KM, Vesikari T, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. N Engl J Med **2007**; 356:685–96.
17. Fleming DM, Crovari P, Wahn U, et al. Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. Pediatr Infect Dis J **2006**; 25:860–9.
18. Ashkenazi S, Vertruyen A, Arístegui J, et al. Superior relative efficacy of live attenuated influenza vaccine compared with inactivated influenza vaccine in young children with recurrent respiratory tract infections. Pediatr Infect Dis J **2006**; 25:870–9.
19. Belshe RB, Gruber WC, Mendelman PM, et al. Efficacy of vaccination with live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine. J Pediatr **2000**; 136:168–75.
20. Keitel WA, Couch RB, Quarles JM, Cate TR, Baxter B, Maassab HF. Trivalent attenuated cold-adapted influenza virus vaccine: Reduced viral shedding and serum antibody responses in susceptible adults. J Infect Dis **1993**; 167:305–11.
21. Hoskins TW, Davies JR, Smity AJ, Miller CL, Allchin A. Assessment of inactivated influenza-A vaccine after three outbreaks of influenza A at Christ's Hospital. The Lancet **1979**; 1:33–5.
22. Keitel WA. Repeated immunization of children with inactivated and live attenuated influenza virus vaccines: safety, immunogenicity, and protective efficacy. Semin Pediatr Infect Dis **2002**; 13:112–9.
23. Neuzil KM, Dupont WD, Wright PF, Edwards KM. Efficacy of inactivated and cold-adapted vaccines against influenza A infection, 1985 to 1990: the pediatric experience. Pediatr Infect Dis J **2001**; 20:733–40.
24. Beyer WEP, de Bruijn IA, Palache AM, Westendorp RGJ, Osterhaus ADME. Protection against influenza after annually repeated vaccination: a meta-analysis of serologic and field studies. Arch Intern Med **1999**; 159:182–8.
25. Keitel WA, Cate TR, Couch RB, Huggins LL, Hess K. Efficacy of repeated annual immunization with inactivated influenza virus vaccine over a five year period. Vaccine **1997**; 15:1114–22.
26. Smith DJ, Forrest S, Ackley DH, Perelson AS. Variable efficacy of repeated annual influenza vaccination. Proc Nat Acad Sci **1999**; 96:14001–6.
27. Pica N, Palese P. Toward a universal influenza virus vaccine: prospects and challenges. Annu Rev Med **2013**; 64:189–202.
28. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. New Engl J Med **2014**; 371:635–45.
29. Vesikari T, Knuf M, Wutzler P, et al. Oil-in-water emulsion adjuvant with influenza vaccine in young children. N Engl J Med **2011**; 365:1406–16.