Flu and You: Research and Me

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As I read the summary article on seasonal influenza vaccination in my August 2013 issue of *The Pediatric Infectious Disease Journal* (of which I am an editorial board member), I realized that, yes, colleagues, this annual chore is imminent.[1] For the next several months, you must now attempt to immunize nearly anybody and everybody who comes through your doors older than age 6 months with an influenza vaccine. And even the families of 2- and 4-month-old infants must be reminded and targeted for future "jabs" of flu vaccine. The Centers for Disease Control and Prevention, the American Academy of Pediatrics, and even the trial lawyers say so. (Yes, litigation might occur for failing to vaccinate!)

So you must beg, cajole, humor, plead, chastise, and castigate about the importance of influenza vaccine for every not-yet-annually-vaccinated pediatric patient. Ironically, you might be held accountable even for patients whom you will not see during the year.

Similar to my earlier discussion about flu vaccines in the December 2009 issue of *Pediatric Annals,*[2] you again are facing the "daunting practicalities" of picking *which* flu vaccine formulation to offer first to each patient. As you learned last month in the August 2013 issue of *Pediatric Annals* from **David P. Greenberg, MD** and colleagues,[3] at least three new pediatric quadrivalent formulations are available now (as of this writing). Note also that two additional important influenza trivalent formulations, Flucelvax (Novartis) produced in canine kidney-cell-culture (see Figure 1, page 356) and Flublok (Protein Sciences) produced in insect virus cells, both of which are egg-free (see Figure 2, page 356) are available for those 18 years and older, but perhaps next year for pediatrics.

For the live intranasal vaccine (FluMist, MedImmune) [see Figure 3, page 358], the transition will be simple, as only a single quadrivalent formulation will be available. By contrast, for the two newest pediatric influenza injectables, an option for either a three- or four-strain formulation will still be available. But aside from the slightly higher cost, insurance coverage issues, and supply issues of quadrivalent vaccine, why would one choose the trivalent anymore?

The two families of B strains (Yamagata and Victoria) together account for up to 25% of circulating influenza strains and cause epidemics every 2 to 4 years. The specific predominant B family "drifts" back and forth. When the trivalent vaccine B strain mismatches, as it has in 6 of the last 12 years, "B" cross-protection is weak to absent.[3] Greenberg et al[3] summarized clearly the possible benefits over a decade of adding an additional B influenza family strain to make a quadrivalent shot formulation: 2.7 million fewer infections, 21,000 fewer hospitalizations, and 1,400 fewer deaths.

Thus, allow me to share several recent reports on influenza and its vaccines, including the newly arrived quadrivalent live attenuated influenza vaccine (QLAIV). In the last 5 years, I happened to be heavily involved (mostly first or second author) in these 14 recent, interesting, and important multicenter, peer-reviewed publications on influenza. I hope they will serve as an important resource for practitioners during the upcoming flu season. As a typical science nerd, I specifically received no compensation for the large quantities of time and energy involved in the writing and crafting of these manuscripts, which I have summarized here for you.

STUDIES OF INTRANASAL QLAIV (WITH 2 B STRAINS)

1. Block SL, Falloon J, Hirschfield JA, et al. The immunogenicity and safety of a quadrivalent live attenuated influenza vaccine in children. *Pediatr Infect Dis J.* 2012;31(7):745-751.

This immunologic bridging study led

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Figure 1. A happy-to-help (non-literal) representation of a potential source for the canine kidney cells to produce one of the two new non-egg version of the influenza vaccine — an important scientific development for the faster mass production of influenza vaccines, and for the improved safety in severely egg-allergic children. This method allows a more precise match to the anticipated circulating strains.

Figure 2. The typical growth medium for nearly every influenza vaccine, except for the new flu vaccines, Flucelvax and Flublok, which are produced in canine kidney cells and insect virus cells, respectively. Vaccine production in eggs may take twice as long, can be erratic for certain more virulent influenza strains, and creates problems for practitioners dealing with egg-allergic children.

to the FDA approval of QLAIV in pediatrics. Using FDA standards, we found that QLAIV was immunologically noninferior to two different trivalent single B formulations (T-LAIV) for geometric mean titers (GMT) and for geometric fold ratios (GMFR). A total of 2,312 healthy patients aged 2 to 17 years were studied: Influenza-vaccine-naïve patients aged 2 to 8 years received two doses; those aged 9 to 17 years received a single dose. As for immunologic interference with QLAIV, the addition of a second B strain yielded only slight reductions in GMT (1.21) and GMFR (1.13) for the B Yamagata strain and in GMFR for the AH1N1 strain (1.07). Individual adverse events were comparable between vaccines except for fever (5.1% vs 3.1%); no vaccine-related serious adverse events were reported.

2. Block SL, Tingting Yi, Sheldon E, Dubovsky F, Falloon J. A randomized, double-blind noninferiority study of quadrivalent live attenuated influenza vaccine in adults. *Vaccine.* 2011;29(50):9391-9397.

This immunologic bridging study led to the FDA approval of QLAIV in adults. Using FDA standards, we found that QLAIV was immunologically noninferior to two different trivalent single B formulations (T-LAIV) for geometric mean titers (GMT) and for geometric fold ratios (GMFR). A total of 1,800 healthy patients aged 18 to 49 years received a single dose of intranasal vaccine. Overall adverse events were similar between vaccines, but one serious adverse event (T-LAIV) of trivalent-vaccine-related asthma was documented.

Pearl for Practice: The new formulation of QLAIV should provide important additional protection because of the 50/50 chance of encountering a mismatched B strain observed with previous trivalent vaccines.

T-LAIV AND ACUTE OTITIS MEDIA (AOM)

3. Heikkinen T, Block SL, Toback SL, Wu X, Ambrose CS. Effectiveness of intranasal live attenuated influenza vaccine against all-cause acute otitis media in children. *Pediatr Infect Dis J.* 2013;32(6):669-674.

4. Block SL, Heikkinen T, Toback SL, Zheng W, Ambrose CS. The efficacy of live attenuated influenza vaccine against influenza-associated acute otitis media in children. *Pediatr Infect Dis J.* 2011;30(3):203-207.

Taken together, these two separate meta-analyses of six double-blind, placebo, randomized controlled trials (RCTs) and two double-blind trivalent IIV (T-IIV) controlled RCTs in 24,046 children aged 6 to 83 months showed the following:

- Among children with influenza *and* AOM, T-LAIV was 85% more effective than placebo and 54% more effective than T-IIV for preventing AOM;
- Among influenza vaccine failures, T-LAIV reduced rates of secondary AOM by 38% compared with placebo; and
- For an entire 12-month period, T-LAIV reduced rates of all causes of AOM by an estimated 7.5% (12.4% in vaccine-naïve children; 6.2% in the second year) when compared with placebo. This reduction in AOM was comparable

to the earliest estimated rates of AOM reduction from PCV7.

Pearl for Practice: If you wish to reduce rates of AOM, administer an annual flu vaccine, with a particular preference for QLAIV in healthy children older than 24 months.

T-LAIV AND POST-VACCINE VIRUS SHEDDING

5. Block SL, Yogev R, Hayden F, Ambrose C, Zeng W, and Walker R. Shedding and immunogenicity of live attenuated influenza vaccine virus in subjects 5 to 49 years of age. *Vaccine.* 2008;26(38):4940-4946.

This elegant and very labor-intensive open-label trial evaluated the frequency and quantity of viral shedding after an intranasal dose of T-LAIV by obtaining nasal swabs for vaccine virus daily on days 1 to 7, every other day on days 9 to 25 and then on day 28. Three age cohorts (n = 344) were studied: 5- to 8-year olds; 9- to 17-year olds; and 18- to 49-year olds. Within these respective cohorts, 44%, 27% and 17% of subjects shed vaccine virus. Maximum shedding occurred on days 2 to 3, but in low quantities (10^5, 10^4, and 10^3 [compared with T-LAIV dose of 10^7]). Virus was undetectable after days 10, 6, and 6, respectively.

Pearl for Practice: These data strongly support the current recommendation that LAIV recipients need to only avoid contact with the severely immunosuppressed, and for only 7 days after vaccination.

EFFICACY OF T-LAIV SINGLE DOSE

6. Block SL, Toback S, Yi T, Ambrose C. Efficacy of a single dose of live attenuated influenza vaccine in previously unvaccinated children 2-6 years of age. *Clin Ther*. 2009;31(10):2140-2147.

This post-hoc analysis of the single-dose efficacy of T-LAIV when compared with placebo in three different RCT studies showed a reduction of influenza attack rates by 60%, 72%, and 87%. During the second year after two doses of T-LAIV in the first year only, vaccine effectiveness still remained at 55%. All of the reactogenicity events were reduced with the second dose when compared with the first dose.

Pearl for Practice: The nearly 70% plus efficacy with a single dose of LAIV should be a vital public health issue. Why? Nearly 50% of vaccine-naïve children never receive their second dose (see article 10 at right), which renders the injectable IIV nearly useless during that first season. Also, most of the mild vaccine reactions with T-LAIV are related to the first dose only in children.

IMMUNOGENECITY OF TRIVALENT IIV (T-IIV) IN CHILDREN 6 TO 36 MONTHS OLD

7. Baxter R, Jeanfreau R, Block SL, et al. A phase III evaluation of immunogenicity and safety of two trivalent inactivated seasonal influenza vaccines in US children. *Pediatr Infect Dis J*. 2010;29(10):924-930.

We compared the immunogenicity of two different IIV shots (Fluarix [GlaxoSmithKline] vs. Fluzone [Sanofi Pasteur]) in a 2:1 ratio for more than 3,000 children and teens aged 6 months to 18 years. All subjects received a single dose of vaccine except for the vaccine-naïve children aged younger than 9 years, who received doses at day 0 and day 28. The new comparator flu vaccine was inferior to the standard vaccine in children aged 6 months to 36 months, but was non-inferior in all other age groups. Reactogenicity and adverse events were comparable.

Pearl for Practice: Once again, for T-IIV vaccines, no other IIV flu shot besides Fluzone is currently approved for children aged 6 to 36 months due to other comparators' inferior immunogenicity in this age group. Afluria IIV (Merck & Co.) was comparable in this age group, but this vaccine became associated with febrile seizures in post-marketing data.

CELL-CULTURE–DERIVED T-IIV FOR CHILDREN AND ADULTS

8. Vesikari T, Block SL, Fernando G, et al. Immunogenicity, safety and reactogenicity of a mammalian cell-culture–derived influenza vaccine in healthy children and adolescents three to seventeen years of age. *Pediatr Infect Dis J*. 2012;31(5):494-500.

9. Reisinger K, Block SL, Izu A, et al. Subunit influenza vaccines produced from cell culture or in embryonated chicken eggs: comparison of safety, reactogenicity, and immunogenicity. *J Infect Dis.* 2009;200(6):849-857.

In a blinded RCT, more than 3,600 children aged 3 to 8 years and 9 to 17 years were given either cell-culture–derived T-IIV (CC-IIV) or T-IIV (single dose in vaccine-naïve children older than 9 years; see Article 8). CC-IIV was non-inferior for both A strains, but had a slightly lower immunologic response for the B strain. For more than 600 adults (18-50 years old), no difference in immunogenicity was observed in the RCT. Overall safety and adverse events were comparable in all age groups (see article 9).

Pearl for Practice: Compared with egg-derived T-IIV, this new "doggy-derived" vaccine (see Figure 1, page 357) formulation can be mass-produced about twice as fast, allows for the use of a better matched flu antigen, and finally (Yes!) avoids problems for egg-allergic patients.

VACCINE LOGISTICS AND BURNOUT

10. Bhatt P, Block SL, Toback SL, Ambrose CS. Timing of the availability and administration of influenza vaccine through the Vaccines for Children Program. *Pediatr Infect Dis J*. 2011;30(2):100-106.

11. Bhatt P, Block SL, Toback SL, Ambrose CS. A prospective observational

study of U.S. in-office pediatric influenza vaccination during the 2007-2009 influenza seasons: use and factors associated with increased vaccination rates. *Clin Pediatr.* 2010;49(10):954-963.

These two studies assessed the effects of office logistics upon flu vaccination in 42 practices during the 2007-2008 season and in 84 practices during the 2008-2009 season. Shipments of influenza vaccine arrived 4 to 5 weeks later for Vaccine for Children (VFC) recipients than for private insurance recipients. Again, only one-half of all vaccine-naïve children received their second dose, and vaccine rates were 17% to 19% lower in VFC children, probably related to their shorter interval to vaccinate. About 80% of all flu vaccine was administered between October and December, suggesting some type of "vaccine burnout" and "saturation-point" after several months of "begging" by clinicians.

Figure 3. Young boy (not crying!) while receiving the intranasal live, attenuated influenza vaccination. Note the plastic stopper on the syringe plunger (see arrow), which allows the delivery of first one-half of the dose to one nostril.

CHILDREN'S VACCINE PREFERENCES

12. Flood EM, Block SL, Hall MC, et al. Children's perceptions of influenza illness and preferences for influenza vaccine. *J Pediatr Health Care*. 2011;25(3):171-179.

A small qualitative survey of 28 children showed that children aged as young as 8 years could understand vaccine rationales and they would prefer a nasal influenza vaccine over a shot. (see Figure 3)

AOM RATES WITH TREATMENT OF INFLUENZA

13. Winther B, Block SL, Reisinger K, Dutkowski R. Impact of oseltamivir treatment on the incidence course of AOM in children with influenza. *Int J Pediatr Otorhinolaryngol.* 2010;74(6):684-688.

Among 695 children aged 1 to 12 years presenting with flu-like illness during this RCT, oseltamivir reduced rates of flu-related AOM by almost half versus placebo recipients (12.4% vs. 21.7%), with the largest effect in 1- to 2-year olds.

NEW ADJUVANTS FOR T-IIV

14. Block SL**,** Ruiz-Palacios GM, Guerrero ML, et al. A dose-range study of MF59-adjuvanted versus non-adjuvanted monovalent A/H1N1 pandemic influenza vaccine in 6 to < 36 month-old children. *Pediatr Infect Dis J.* 2012;31(7):e92-e98.

Pearl for Practice: This new "oil-in-water emulsion" adjuvant for a single-strain IIV showed remarkably good and quite durable immunogenicity even after a single injection in vaccine-naïve children. In another study using a T-IIV formulation, the "oil" version was also twice as protective against influenza than was approved IIV, Fluzone (79% versus 40%).[4] This approaches flu protection similar to nasal T-LAIV.

CONCLUSION: A PRODUCTIVE 5 YEARS

As a springboard from these papers, more effective flu vaccines — including the addition of a second B strain, the wider use of intranasal LAIV, and a new future adjuvant along with early use of oseltamivir in cases of flu should reduce flu attack rates and rates of AOM, possible flu complications, and antibacterial resistance. Flu vaccine distribution for VFC children needs notable improvement. ■

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3. Greenberg DP, Robertson RA, Gordon DM. Prevention and control of influenza and dengue through vaccine development. *Pediatr Ann.* 2013;42(8):325.
4. 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(15):1406-1416.