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. 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, 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, 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. Greenberg et al 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)**


This immunologic bridging study led
to the FDA approval of QLAIV in pediatrics. Using FDA standards, we found that QLAIV was immunologically non-inferior 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.


This immunologic bridging study led to the FDA approval of QLAIV in adults. Using FDA standards, we found that QLAIV was immunologically non-inferior 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)


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 38% 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**


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 (10^4, 10^5, and 10^6, 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**


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.

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


We compared the immunogenicity of two different IIIV 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-naive 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 IIIV 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 IV (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**


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 “doggly-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**


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.

**CHILDREN’S VACCINE PREFERENCES**


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**


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**


**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%). This approaches flu protection similar to nasal T-LAIV.

**CONCLUSION: A PRODUCTIVE 5 YEARS**

As a springboard from these papers, you should consider the following: 1) use quadrivalent flu vaccines (when supply makes it possible); 2) use QLAIV more frequently for your healthy patients older than 24 months; and 3) use oseltamivir early for suspected or documented flu. These should further reduce flu attack rates, secondary AOM, bacterial resistance, and flu complications. ■

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I wish to thank all of my fellow colleagues who were instrumental in the writing of these important papers. ~ SLB

**REFERENCES**


