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Fewer Vaccine Doses Yield Better Immunization

The fewer vaccine doses needed to fully immunize a child, the better the chance that it will happen.

We all understand the importance of ensuring complete immunization in children, and we've all had patients who don't show up for recommended second and third doses of a vaccine series. So it is pertinent to discuss two recent developments—one positive, one worrisome—related to the goal of ensuring that children receive all recommended vaccine doses.

The good news is the accumulating data from three recent studies showing that the efficacy of one dose of the intranasal live attenuated seasonal influenza vaccine (LAIV/Flumist) was 60%, 71%, and 87% compared with placebo in different years with different but vaccine-matched circulating influenza strains. These efficacy rates were only somewhat less than two doses of LAIV. If further testing bears this out, single LAIV dosing could alleviate at least some of the burden as we try to reach the stated Centers for Disease Control and Prevention goal of annually vaccinating every child aged 6 months and older for seasonal influenza.

The concerning news is that Merck & Co. appears to be bending to pressure and has announced that it could begin making separate single-antigen measles, mumps, and rubella vaccines sometime in the next 2 years, a move I consider disappointing and potentially dangerous because it will result in more missed doses, among other negative outcomes.

A recent study involving nearly 3,000 children aged 6-36 months in Brazil, Argentina, and South Africa demonstrated that one intranasal dose of LAIV provided clinically significant protection against influenza in young children previously unvaccinated against influenza (Pediatr. Infect. Dis. J. 2009;28:365-71).

In an older 1998 landmark intranasal LAIV trial by Dr. Robert Belshe and colleagues involving 288 children given one dose and 1,314 who received two doses of vaccine or placebo 60 days apart, efficacy against the 1996-1997 season's influenza A(H3N2) and influenza B was 89% with one dose and 94% with two doses (N. Engl. J. Med. 1998;338:1405-12). Another study produced similar results.

These data were summarized by Dr. Stan Block and his colleagues in a poster at a conference earlier this year, showing the comparative efficacy of a single dose of LAIV in children aged 2-8 years who had never been previously vaccinated was 71.5%, 59.9%, and 87.3%, respectively. In two of the studies, one-dose efficacy was estimated to be approximately 90% of the two-dose efficacy when given in the same season.

The data still show that a second dose provides further protection, yet the finding that one dose may suffice in a majority of patients is important. In influenza seasons past, most children less than 9 years old who are being immunized for the first time have not come back for their second immunization, despite the recommendation to do so. In fact, data show that only 20%-40% actually return for the second dose of flu vaccine. If a single dose of LAIV could provide adequate protection, it could help a great deal. It may be reasonable to consider LAIV for families we think less likely to return for second doses.

Also, I think it would help a great deal if we needed to give only one dose of seasonal influenza and one dose of novel influenza A(H1N1) vaccine this year. Half as many office visits would be needed and vaccine supplies would immunize twice as many people. Studies are underway comparing the antibody response of one vs. two doses of novel H1N1 LAIV vaccine in approximately 300 subjects each, and data should be available by October. MedImmune estimates that by March 2010 it may be able to supply about 200 million bulk doses of 2009 novel H1N1 LAIV and have approximately 40 million doses in nasal sprayers. Establishing this proof of concept for influenza vaccines also would be important in the event that a more severe pandemic influenza strain arises.

And now the not-so-good news, which I hope will not come to pass. Recently, Merck announced plans to manufacture separate measles, mumps and rubella antigen vaccines, apparently in response to pressure from groups whose members wish to delay or spread out selected components of MMR, or to cherry-pick only one or two of the components. This is proposed as a means of giving people "freedom of choice." I am reminded of the campaigns in the 1970's to make fluoride in the water supply a personal choice. Nonscientific fears fueled the fluoride concerns, yet fluoride in water supplies has drastically reduced dental caries in children with no untoward effects.

Splitting MMR vaccine would present a logistical nightmare to providers who are already overburdened with the number of vaccines that need to be stored in precisely temperature-controlled freezers in their offices (http://www2a..gov/vaccines/ed/shtoolkit/pages/storage_practices.htm), not to mention the increase in paperwork and the increased possibility of errors with four different vaccines and up to nine possible permutations of how three individual components might be requested.

And, because patients often don't return for subsequent doses when vaccines are not combined (Pediatr. Infect. Dis. J. 2009;28:98-101), delayed schedules and incomplete immunizations would likely occur at a rate beyond what we see with the combined MMR vaccine.

The MMR is a good vaccine that produces the protective results when administered in the currently Advisory Committee on Immunization Practices–recommended schedule and number of doses. Reduced use in communities leads to ongoing measles circulation (http://www.euro.who.int/vaccine/diseases/20090128_1). There is no credible scientific, immunologic, or safety advantage to splitting MMR into single components in normal children. Studies in many countries have shown that combined MMR does not cause autism. This was reviewed by a special master's panel, which also found no connection of MMR to autism (U.S. Court of Federal Claims, Office of Special Masters, E-Filed: Feb. 12, 2009. No. 03-654V, No. 98-916V, No. 01-162V).

Not only is there no attributable benefit to such a move, but it would end up costing more—in administration fees, paperwork, insurance claims, etc.—at a time when we're trying to contain health costs.

It's a big step backward, and I hope they reconsider this decision, which sends the wrong message at the wrong time. ■

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Number of Novel H1N1 Vaccine Doses Expected to Fall Short

BY JEFF EVANS

Manufacturing issues may limit the number of vaccine doses against novel influenza A(H1N1) that will be available when immunization programs begin around mid-October, officials from the Department of Health and Human Services told members of the National Biodefense Science Board in a public teleconference.

But clinical trial testing of the inactivated and live attenuated virus vaccines already are underway, and programs for distributing the vaccines and conducting surveillance should be in place when the vaccines are ready, the officials said.

Robin Robinson, Ph.D., director of the Biomedical Advanced Research and Development Authority of HHS, reported that, for the most part, vaccine production and testing are on schedule. All five vaccine manufacturers recently received their potency assay reagents so they can know how much vaccine they have produced. But an unanticipated difficulty in bulk production of the live attenuated virus vaccine has slowed its progress.

Although vaccination programs still are slated for mid-October, the number of doses that will be available by then has been lowered from 120 million to 45 million, with 20 million doses coming out each week afterward, Dr. Robinson said. The reduction in doses is a result of lower than expected vaccine yield, compared with previous yields with seasonal flu vaccines. One manufacturer also had obligations to produce vaccine for Australia ahead of other clients. Another manufacturer's difficulty in finishing up its orders of seasonal influenza vaccine has affected the time line for novel H1N1 vaccine production.

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The federal government already has bought 190 million vaccine doses and, if needed, 120 million adjuvant doses. It also has stockpiled 84 million treatment courses of antivirals and another 3 million are expected to arrive soon. In May, states were able to purchase 11 million antiviral treatment courses; another 2 million have been recently purchased, he said.

The National Immunization Survey will be set to begin collecting immunization data as early as Oct. 10 for weekly reports of national coverage estimates. While clinical trials will provide data on reactogenicity to the vaccine, rare adverse events will be monitored through the Vaccine Adverse Event Reporting System and the population-based Vaccine Safety Datalink. Vaccine safety in the military will be collected though the Defense Medical Surveillance System, a collaboration between the Department of Defense and the Food and Drug Administration. A special surveillance program also will be set up for Guillain-Barré syndrome.

Dr. Daniel B. Jernigan, deputy director of the CDC's National Center for Immunization and Respiratory Diseases, noted that public health laboratories will focus their testing more on surveillance than clinical testing capacity. ■