Pneumococcal Vaccine Schedule Questions Persist

BY MIRIAM E. TUCKER
Senior Writer

ATLANTA — Recommendations regarding use of the 23-valent pneumococcal polysaccharide vaccine in high-risk children aged 24-59 months who previously received the 7-valent pneumococcal conjugate vaccine remain to be finalized after discussion of the issues by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention at its summer meeting.

Current recommendations call for use of 23-valent pneumococcal polysaccharide vaccine (PPV23) at 2 years of age following receipt of the 7-valent pneumococcal conjugate vaccine (PCV7) vaccine series prior to age 2 for children in certain high-risk groups, including those with HIV infection, asplenia, or immunocompromising or chronic conditions. The addition of PPV23 may also be considered among children of Alaska Native or Native American descent. For children aged 10 years or younger, one revaccination should be considered 3-5 years after the previous PPV23 dose.

Although data regarding the safety of PPV23 given after PCV7 are limited, the rationale for the recommendation is to provide additional serotype coverage among children at very high risk (MMWR 2000;49[RR-09]:1-38).

Dr. Pekka Nuorti of the CDC's Respiratory Diseases Branch presented the committee with three possible votes—drafted prior to the meeting by a working group—to clarify language from those recommendations. Of the three issues—use of PPV23 in Alaska Native and American Indian children, the time interval for PPV23 revaccination in high-risk children, and use of the PCV7 in HIV-infected school-age children—the committee ended up voting only on the third item.

That advice, still subject to approval by the CDC, was that providers "may consider" administering two doses of PCV7 followed by PPV23 in HIV-infected children aged 5-17 years on highly active antiretivinal therapy (HAART) who were not previously immunized with PCV7.

The ACIP also agreed with the working group's prior decision not to recommend use of PPV23 in children with asthma who are not on high-dose corticosteroid therapy, despite voting to recommend the vaccine for all adults with asthma. Diagnosis of pediatric asthma is difficult and many children outgrow wheezing, and current rates of invasive pneumococcal disease (IPD) are very low overall in children aged 2 years and older because of both the direct and the indirect impact of routine PCV7 use. Thus, PPV23 is also not recommended even for older adolescents with asthma who did not receive PCV7, Dr. Nuorti said in an interview.


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PPV23 is not recommended even for older adolescents with asthma who did not receive PCV7, said Dr. Pekka Nuorti.

The current American Indian/Alaska Native recommendation was based primarily on expert opinion, and there are few data on use of PPV23 in those populations of children after the PCV7 series. The recommendation also lacks specificity, because not all such groups are at equal risk and the group definitions are not always clear. Moreover, in practice PPV23 typically has not been used among these children except for those with high-risk medical conditions.

Because of concern about potential hyporesponsiveness after PPV23, the working group had prepared a recommendation against routine use of PPV23 in all American Indian/Alaska Native children and to limit its use to only those "living in areas with documented elevated rates of [IPD]." However, several committee members felt this still wasn't clear enough, so the decision was left for the working group to retool. ■

EXPERT COMMENTARY

Patches, Food Among New Vaccine Delivery Methods

New vaccines in the pipeline offer needleless alternatives that will help alleviate the human pincushion problem as well as facilitate immunization in the developing world.

Transdermal patches, oral administration via food or drink, and new intranasal vaccines are three exciting technologies that I foresee becoming available within the next 2-5 years. Such alternative vaccine delivery systems are particularly critical in the developing world, where shortages of needles, contamination problems, and lack of trained personnel often make injections risky or impossible. And of course, injections are uncomfortable.

BY MICHAEL E. PICHICHERO, M.D.

It's logical to assume that one would target an infection that enters the body through the respiratory tract by an intranasal vaccine, while gastrointestinal pathogens would be more amenable to vaccines delivered orally. However, that's not necessarily the case. Intranasal vaccine administration could be used for gastrointestinal pathogens, and oral administration for respiratory ones, because the process proceeds in the same fashion once the antigen gains access to the antigen-presenting cells and is taken to the β cells and T cells in the lymph nodes and spleen. And of course, antigens delivered via patch can go anywhere once they are delivered to the regional lymph nodes draining the skin.

Typically, these new technologies are developed with venture capital by small firms and, if successful, get picked up by the larger vaccine manufacturers.

The latest buzz has come from a phase II randomized, double-blind, placebo-controlled field trial of a traveler's diarrhea vaccine skin patch that contains heat-labile enterotoxin (abbreviated "LT") from *Escherichia coli*. Of 201 healthy adults who were planning trips to either Mexico or Guatemala, 67 were randomized to receive the LT patch and 134 assigned placebo. A total of 59 received a second LT patch and completed in-country surveillance, as did 111 who received a second placebo patch. Patches were worn for about 6 hours and then discarded, at 3 weeks and 1 week prior to travel. The average stay in Mexico or Guatemala was 12.4 days (Lancet 2008;371:2019-25).

The results were promising: The proportion of individuals with diarrhea of any cause—as recorded in diary cards—was 15% with the LT patch, compared with 22% with placebo. Severe diarrhea occurred in 2% vs. 11%. The proportions with diarrhea caused by enterotoxigenic *Escherichia coli* (ETEC) were 5% with the LT vaccine patch vs. 10% with placebo, for a protective efficacy of 49%. For severe diarrhea, those proportions were 5% vs. 2%, translating to 62% protective efficacy.

Moreover, those who did develop diarrhea with the LT patch had a milder course of disease, with a mean stool frequency of 3.7 per episode, compared with 10.5 with placebo. Duration of diarrhea was also much less.

Patches are very attractive delivery systems for vaccines because they introduce the antigens just below the epidermis. This local epidermal delivery appears to produce a more robust immune response than does an intramuscular injection.

On the downside, patches do involve greater potential for local site irritation. In the ETEC patch trial, application of the patch—which involves scraping the skin with a mild abrasive prior to affixing the patch—caused local pruritus in 67% vs. 4% with placebo, rash in 61% vs. 1%, respectively, and pigmentation changes in 7% vs. 0. However, there were no significant differences in systemic events such as fever, malaise, or headache.

Patch technology also is being studied for the prevention of disease caused by a variety of other pathogens, including tetanus and *Helicobacter pylori*.

I'm also excited about the use of transgenic plants such as potatoes and corn as another alternative vaccine delivery method. Thus far in early human trials of diarrheal diseases, transgenic plant-derived vaccines appear to be safe and immunogenic without the need for a buffer or vehicle other than the plant cell.

Among these are transgenic potatoes and corn that express the B subunit of the ETEC toxin, another transgenic potato that expresses the hepatitis B surface antigen, and a third, the capsid protein of norovirus (NV). In a study of the latter, 24 healthy adult volunteers were randomly assigned to one of three regimens: Three doses of transgenic potato expressing NV capsid protein on days 0, 7, and 21, two doses of the transgenic potato on days 0 and 21 plus a dose of wild-type potato on day 7, or three doses of wild-type potato on days 0, 7, and 21.

Blood was collected before and at 7, 14, 21, 28, and 60 days after the first dose of transgenic plant for measurement of serum antibodies to LT or NV capsid protein. Whole blood was collected for antibody-secreting cell assays on days 0, 7, 14, 21, and 28 (J. Infect. Dis. 2000;182:302-5).

Nineteen of the 20 subjects who ingested transgenic potatoes developed significant increases in the numbers of specific IgA antibody-secreting cells, 4 developed specific serum IgG, and 6 developed specific stool IgA. Overall, 19 of 20 subjects developed an immune response of some kind, although the level of serum antibody increases was modest.

As for the intranasal route, my lab under National Institutes of Health–funded grants is working on anthrax, botulism, and tularemia in the bioterrorism arena. Others are investigating intranasal vaccines against respiratory syncytial virus.

I think that much of this work will apply to the prevention of diseases that we currently are unable to prevent, both here and in the developing world.

I have no financial relationships with any of the companies developing these alternative vaccines. ■

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