A Cautionary Tale About Combination Vaccines

Combination meningococcal/pneumococcal vaccine is less effective than meningococcal vaccine alone.

BY ALICIA AULT
Contributing Writer

An experimental vaccine that combines coverage for nine strains of pneumococcus and a single meningococcal strain appears to be less effective than a meningitis vaccine alone, and also decreases the immunogenicity of some other vaccinations given concomitantly, according to a recent report.

The study results provide a cautionary tale for vaccine makers and pediatricians, said John Bradley, M.D., director of the division of infectious disease at Children's Hospital, San Diego, who was asked to comment on the findings.

"It is not easy to put together a vaccine that has all these components," he said. "When you mix them all together you don't get the nice brisk responses you expect when you administer each separately, and we're probably further off from a single vaccine than we were all hoping," added Dr. Bradley, who is a member of the American Academy of Pediatrics Committee on Infectious Diseases.

Lead author Jim P. Buttery, M.D., agreed that the study showed the technical difficulty of building a single-shot package. "Each new antigen is successively more difficult," he said in an interview with this newspaper.

The phase II trial compared Wyeth's Pnc9-MenC vaccine with the company's MenC vaccine alone (JAMA 2005;293:1751-8). MenC (Meningitec) is not used in the United States, and it's not likely that the Pnc9-MenC combination would be sold here, as the strains it covers are not as prevalent.

There is great interest in combination vaccines. Dr. Buttery and his associates noted that if a combination meningococcal/pneumococcal vaccine was adopted, it could spare U.S. infants up to four extra injections by 18 months, and U.K. infants two to three injections at each visit.

Dr. Buttery led the study while at Churchill Hospital in Oxford, England. He is now with Murdoch Children's Research Institute, the University of Melbourne (Australia).

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In the trial, Dr. Buttery and his colleagues enrolled 240 healthy infants aged 7-11 weeks at two United Kingdom hospitals from August 2000 to January 2002.

Children who had known immunosuppression, previous vaccination, or confirmed invasive meningococcal or pneumococcal disease were excluded.

They were divided into two groups: 120 received the Pnc9-MenC vaccine, and 120 received MenC, a monovalent group C meningococcal conjugate vaccine. MenC is the standard in the United Kingdom. There is no separate pneumococcal injection. Both groups also were given diphtheria and tetanus toxoids and whole-cell pertussis, *Haemophilus influenzae* type b (Hib), polyribosylribitol phosphate–tetanus toxoid protein conjugate, and oral polio vaccine.

Vaccinations were given at ages 2, 3 and 4 months—an accelerated schedule, compared with the United States. Home follow-up visits were conducted at 2, 3, 4, and 5 months of age.

At 5 months, serum samples indicated that the combination vaccine was less immunogenic than the MenC vaccine. Antibody concentrations for Hib and diphtheria were lower for infants who received the combination. Dr. Buttery and his colleagues said the effect on diphtheria was unexpected, but he noted that the antibodies were still in the protective range. There was no difference between the groups for tetanus antibodies.

More children in the combination group had to forego second or third vaccinations because of prolonged crying or fever.

The study might not be applicable to U.S. practice because of the accelerated schedule—only a month of separation between each dose—and because of the different vaccinations used. For instance, whole-cell pertussis and oral polio are not usually given in the United States, Dr. Bradley said.

But he said it was important the study was published, especially since it was sponsored by a drug company and was published even though it had negative findings.

Dr. Buttery, who has acted as a consultant for Wyeth and received other assistance from the company, said in an interview that though he is not privy to company decisions, a phase III study "may not occur."

He and his colleagues concluded that, "The reduced immunogenicity of the serogroup C meningococcal component of Pnc9-MenC as well as concomitantly administered Hib and diphtheria may limit its further development." ■

State's Vaccine Financing Affects Children's Odds of Getting Prevnar

BY MIRIAM E. TUCKER
Senior Writer

WASHINGTON — Whether or not a child receives at least three doses of pneumococcal conjugate vaccine depends upon the vaccine financing policy of the state he or she resides in, Shannon Stokley and her associates reported in a poster at the National Immunization Conference sponsored by the Centers for Disease Control and Prevention.

With a price tag of $51.58 per dose for the federal government and $61.65 in the private sector, pneumococcal conjugate vaccine (PCV7 or Prevnar) is the second-most-expensive routine childhood vaccine (after the new meningococcal conjugate vaccine), said Ms. Stokley, an epidemiologist with the national immunization branch of the Centers for Disease Control and Prevention, Atlanta.

All states receive federal funds to purchase vaccine for children eligible for the Vaccines for Children (VFC) program, which covers all routine childhood vaccines for children who are Medicaid eligible, uninsured, Native American or Alaska Native, and those who are underinsured and receive vaccine at a federally qualified health clinic.

States have the ability to use other state and federal funds to purchase additional vaccine for children who aren't VFC eligible. But because PCV7 is so expensive, some states have specifically excluded it from that additional coverage, she said.

Data were analyzed from the 2001-2003 National Immunization Survey for children aged 19-35 months living in 34 states plus one city with the following vaccine financing policies:

► **VFC only (Ala., Colo., Ind., Iowa, La., Miss., Neb., N.J., Ohio, Ore., Pa., Tenn., Wis.).** Supplies only VFC vaccine to all VFC-enrolled providers. Public health clinics may provide all vaccines to all children who present for immunization.

► **VFC and underinsured (Ariz., Fla., Ga., Md., Mich., Minn., N.Y., S.C., San Antonio).** Supplies all vaccines for VFC-eligible and underinsured children to all VFC-enrolled providers.

► **VFC and underinsured-select (Ill.).** Supplies all vaccines for VFC eligible and all vaccines *except* PCV7 for underinsured children to all VFC-enrolled providers.

► **Universal (Ark., Idaho, Mass., Maine, N.H., N.M., R.I., Wash.).** Supplies all vaccines to all providers.

► **Universal-select (Conn., Nev., S.D., Vt.).** Supplies all vaccines *except* PCV7 for children who are underinsured or fully insured, to all providers.

Overall, the proportion of children who received one or more doses of PCV7 rose from 37.3% in 2001 (the year after it was licensed) to 88.5% in 2003. The proportion receiving at least the first three doses rose from 6.7% in 2001 to 69% in 2003.

The likelihood of receiving three or more doses of PCV7 for children living in universal purchase states was 1.73 times greater than for children living in universal-select states, while the odds of receiving three or more doses of PCV7 for children in the VFC and underinsured states (plus San Antonio) were 1.06 times higher than for children in the VFC and underinsured-select states, Ms. Stokley and her associates reported.

After adjustment for child and provider factors, children living in universal-select or VFC and underinsured states had significantly lower odds of receiving three or more doses of PCV7, compared with children living in VFC-only states. ■

Dosing Schedule of 2-Plus-1 May Be Enough for PCV7

A 2-plus-1 dosing schedule of the commonly used pneumococcal conjugate vaccine showed satisfactory antibody responses to all serotypes of the bacteria, comparable with published immunogenicity studies on the usual 3-plus-1 dose schedule.

The descriptive, nonrandomized trial was performed on children at 3, 5, and 12 months of age, and 99 of 101 healthy infants completed the study, wrote Helena Käyhty, Ph.D., of the National Public Health Institute, Helsinki, Finland, and her colleagues.

The investigators compared the geometric mean antibody concentrations for all serotypes with published immunogenicity results, including those from two efficacy trials—the Northern California Kaiser-Permanente study and the Finnish Otitis Media Vaccine Trial—that used the standard 3-plus-1 schedule with different end points—invasive disease or acute otitis media. A similar German trial with a 3-plus-1 schedule was also compared with the present study; it measured a slightly lower incidence of fever, a common, usually mild symptom.

"At 13 months, 1 month after the third dose of [PCV7], antibody concentrations measured in this study were as high as those in the previous Finnish, U.S., and German studies and were distributed similarly with respect to those in the previous Finnish study after four doses, indicating equally good immunologic priming after two to three doses in early infancy," they said (Pediatr. Infect. Dis. J. 2005;24:108-14).

Serious adverse events in four children were lethargy/irritability, gastroenteritis, and scarlatina; one was considered as possibly related to the vaccinations. "All serious adverse symptoms disappeared within 3-6 days," they wrote.

The PCV7, marketed under the trade name Prevnar, is part of the universal vaccination program for U.S. children in a 3-plus-1 schedule, but in other parts of the world, vaccination with PCV7 is still uncommon, according to Dr. Käyhty.

Due to the results of this study, and because "preliminary postmarketing surveillance reports from the United States suggest that two doses in the primary series are sufficient for protection, although additional information on the duration of protection is needed," the authors suggested that the use of fewer than four doses may be a practical option for the administration of PCV7.

—Mark S. Lesney