H influenzae Vaccines Gain Favor

IN THE RACE to get a vaccine against *Haemophilus influenzae* type b that will protect the very youngest infants, two leading candidates have emerged. Although they are made by different manufacturers and have significantly different characteristics, they appear to complement each other.

One vaccine raises antibody levels almost immediately after the first injection at 2 months of age; the second takes longer to induce protective antibody levels but, once having reached a protective level, stays there for at least 2 years in more than 80% of subjects.

After hearing the reports of studies showing the efficacy and immunogenicity of these vaccines in preventing disease in infants younger than 6 months, presented at a Food and Drug Administration (FDA) committee meeting, Floyd Denny, MD, University of North Carolina School of Medicine, Chapel Hill, chair of the Vaccine and Related Biological Products Advisory Committee, said it appears that the ideal way to immunize infants against *H influenzae* is to use both vaccines, one as a first dose and the other as a second and possibly third dose.

The vaccines are made by Praxis Biologics, Rochester, NY, and Merck Sharp & Dohme, West Point, Pa. Both are made from a fraction of the bacterial capsule coupled to a protein that enhances its immunogenicity. Both are now on the market but are not recommended for use in children younger than 15 months. There the similarity ends.

In the Praxis product, the capsule is linked to a nontoxic variant of diphtheria toxin. In the Merck product, the capsular polysaccharide of the bacterium is covalently linked to an outer membrane protein from *Neisseria meningitidis*.

What makes the Merck vaccine unique among all the *H influenzae* vaccines is that the field trials show that a single dose protects against disease in infants 2 months of age. By comparison, the Praxis agent takes at least two doses to achieve antibody levels of 1 mg/L—the figure generally cited as sufficient to provide adequate protection against disease, although the precise protective level is not known.

The Praxis agent, known as HbOC, has been extensively tested in the field in Finland and in a field trial in California by two investigators from the Kaiser Permanente Medical Group, Steven Black, MD, and Henry R. Shinefield, MD. The findings from this study were presented to the committee by Black. The vaccine is given in three doses at 2, 4, and 6 months of age. Much of the data from this trial have been reported (*JAMA*. 1990;264:164).

The Merck vaccine, known as PRP-OMP, has been undergoing a field trial among Navajo Indian children, a group that has an attack rate of *H influenzae* four to five times higher than the US general population. In these children, too, 40% of the disease occurs before 6 months of age compared with only 15% among US infants in general, says Mathuram Santosham, MD, The Johns Hopkins University School of Medicine, Baltimore, Md, the trial's principal investigator.

The double-blind, placebo-controlled trial started in July 1988. It was stopped August 2, 1990, when its safety and data monitoring committee stated that clear evidence of vaccine efficacy had been obtained. Subjects were randomized to receive either vaccine or placebo in two doses at 2 and 4 months of age. The two groups were comparable in age, sex, and demographic characteristics.

Overall, 2229 subjects received the first dose of the vaccine and 2230 the placebo. There were 1725 infants who received both doses of the vaccine and 1759 subjects who received the placebo. Approximately 800 infants in each group received complete follow-up for 14 months.

In those infants who received the two doses of vaccine, there was one case of bacteriologically proven *H influenzae*. In those who received the placebo, there were 14 cases. In the period between the first and second doses there were no cases of *H influenzae* disease in the 2229 vaccinated subjects but eight cases in the 2230 subjects in the placebo group. "A vaccine efficacy rate of 100%," comments Santosham.

Not all subjects were eligible to receive the second dose under the protocol at the time the trial was stopped, Santosham notes. But an estimated 86% of those eligible for the second dose actually received it.

Serum samples were taken during the course of the study for antibody determinations. Half the vaccinees reached antibody levels of 1 mg/L after the first dose and 60% did so after the second dose. Geometric mean titers of antibody rose to above 1 mg/L after the first dose and to 1.32 mg/L after the second. But by 1 year of age the titers had dropped to 0.43 mg/L.

Reviewing the data, biostatistician Paul Meier, PhD, of the University of Chicago, a consultant to the committee, described the Navajo study as a model that meets all the standards. "The results are truly impressive. As an efficacy study it seems to have answered all the questions."

But Meier was more dubious about the way the Kaiser Permanente study on the Praxis vaccine was conducted. He says he found the study's design "troubling." This was not a randomized study; children were assigned to receive vaccination or not according to date of birth. To try to correct for this the investigators did a number of different analyses to check on possible bias.

"We found no bias that would lead us to conclude other than the vaccine was highly efficacious," says Peter Paradiso, PhD, of Praxis. Black adds, "Our advisory group concurs in this, and because of ethical concerns we have discontinued excluding children from vaccination on the basis of birth date."

Collectively the committee were impressed with the efficacy of both vaccines in reducing *H influenzae*, but made no recommendation that either vaccine be used in 2-month-old infants.

The group had reservations regarding the immunogenic aspects of the vaccines. It was concerned about the duration of immunity conferred by Merck's vaccine, and about the onset of protection with the Praxis product. Members indicated they would like to see much more data on immunogenicity, perhaps through a post-marketing surveillance plan.

But, says Samuel Katz, MD, of Duke University School of Medicine, Durham, NC, "I don't think there's been a single vaccine from which we haven't learned a lot of things after it had been licensed, and I don't think *H influenzae* type b is going to be any different. Get the vaccines out there so we can use them and then you'll get your surveillance study."—by Charles Marwick

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