# Immunogenic Surprises Limit Combo Vaccines

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WARSAW — Efforts to develop combination vaccines that would streamline immunization schedules have hit some surprising snags, including unpredictable immunogenicity, Jim P. Buttery, M.B., said at an international congress of the World Society for Pediatric Infectious Diseases.

Protein–polysaccharide glycoconjugate vaccines comprise an integral component of immunization efforts against encapsulated bacteria. "Since the staggering success of *Haemophilus influenzae* type b vaccines in reducing invasive Hib disease in many developed countries, different multivalent vaccines have been licensed against up to four meningococcal serogroups and seven pneumococcal serotypes," Dr. Buttery said.

A combination meningococcal/pneumococcal vaccine could eliminate up to four extra injections for U.S. infants by age 18 months, he said. But during development of these vaccines, some important and unexpected interactions have been revealed, including interactions of *H. influenzae* type b (Hib) vaccine when admixed or combined with acellular pertussis–containing vaccines.

Other effects have included possible carrier-induced epitope suppression and unexplained effects upon the immunogenicity of other combination vaccine antigens and even separately coadministered vaccines, said Dr. Buttery of the Murdoch Children's Research Institute, University of Melbourne, and the department of pediatrics, Royal Children's Hospital, Melbourne.

A recent phase II trial evaluating the immunogenicity and safety of a combination vaccine illustrated these observations. In the study, 240 infants received immunizations of diphtheria and tetanus toxoids and whole-cell pertussis (DTwP) vaccine admixed with Hib conjugate, in the right anterolateral thigh at 2, 3, and 4 months. They also received oral polio vaccine and were randomized to receive in the left anterolateral thigh either a combination 9-valent pneumococcal/group C meningococcal polysaccharide protein conjugate (Pnc9-MenC) vaccine or a monovalent serogroup C meningococcal glycoconjugate vaccine (MenC).

The results showed the pneumococcal/meningococcal vaccine was less immunogenic than the monovalent meningococcal vaccine. A smaller proportion of infants who received the Pcn9-MenC vaccine exceeded the protective titer threshold of 1:8, as well as the putative long-term protective threshold titer of 1:128 (JAMA 2005;293:1751-8). Levels of antidiphtheria antibody, as well as Hib antibody concentrations, also were lower in the combination group.

**One lesson learned from the results of the study is that there appears to be a quantitative limit to carrier proteins and 'to how much we can stack into a vaccine.'**

One hypothesis that has been proposed for inadequate immunogenicity in conjugate vaccines is carrier-induced epitope suppression, where the immune response is directed against the carrier protein and the response to the polysaccharide is suppressed. "Not only are these expensive and technically complex vaccines, but they also require increasing amounts of carrier protein," he said. "The increased amount of carrier protein in each Pnc9-MenC dose (38 mcg vs. 10 mcg in MenC) offers some support to this theory," said Dr. Buttery, who was the lead investigator for the trial.

The diminution of antibody response to *H. influenzae* type b also was unexpected. Because the injection site was different from the meningococcal vaccine, physical or chemical interference cannot be blamed. Carrier-induced epitope suppression also is unlikely to be the cause, as there were no shared carrier proteins between the study vaccine and the Hib vaccine, he said.

From this study, one lesson learned is that there appears to be a quantitative limit to carrier proteins and "to how much we can stack into a vaccine," Dr. Buttery said.

These experiences also have underlined the importance of measuring the immunogenicity of all vaccines administered within a vaccine study, including routine, already-licensed, and coadministered vaccines, he said. ■