

# Clinical Condition Affects Hearing Loss in Meningitis

BY DENISE NAPOLI

**Serious Adverse Events** In study P3T06, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, 19 of 484 (3.9%) participants who received Pentacel vaccine and 50 of 1,455 (3.4%) participants who received DAPTACEL + IPOL + ActHIB vaccines experienced a serious adverse event. Within 30 days following Dose 4 of Pentacel or Control vaccines, 5 of 431 (1.2%) participants who received Pentacel vaccine and 4 of 418 (1.0%) participants who received DAPTACEL + ActHIB vaccines experienced a serious adverse event. In Study 494-01, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, 23 of 2,506 (0.9%) participants who received Pentacel vaccine and 11 of 1,032 (1.1%) participants who received HCPDT + POLIOVAX + ActHIB vaccines experienced a serious adverse event. Within 30 days following Dose 4 of Pentacel or Control vaccines, 6 of 1,862 (0.3%) participants who received Pentacel vaccine and 2 of 739 (0.3%) participants who received HCPDT + POLIOVAX + ActHIB vaccines experienced a serious adverse event. Across Studies 494-01, 494-03 and P3T06, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, overall, the most frequently reported serious adverse events were bronchiolitis, dehydration, pneumonia and gastroenteritis. Across Studies 494-01, 494-03, 5A9908 and P3T06, within 30 days following Dose 4 of Pentacel or Control vaccines, overall, the most frequently reported serious adverse events were dehydration, gastroenteritis, asthma, and pneumonia. Across Studies 494-01, 494-03, 5A9908 and P3T06, two cases of encephalopathy were reported, both in participants who had received Pentacel vaccine (N = 5,979). One case occurred 30 days post-vaccination and was secondary to cardiac arrest following cardiac surgery. One infant who had onset of neurologic symptoms 8 days post-vaccination was subsequently found to have structural cerebral abnormalities and was diagnosed with congenital encephalopathy. A total of 5 deaths occurred during Studies 494-01, 494-03, 5A9908 and P3T06: 4 in children who had received Pentacel vaccine (N = 5,979) and one in a participant who had received DAPTACEL + IPOL + ActHIB vaccines (N = 1,455). There were no deaths reported in children who received HCPDT + POLIOVAX + ActHIB vaccines (N = 1,032). Causes of death among children who received Pentacel vaccine were asphyxia due to suffocation, head trauma, Sudden Infant Death syndrome, and neuroblastoma (8, 23, 52 and 256 days post-vaccination, respectively). One participant with ependymoma died secondary to aspiration 222 days following DAPTACEL + IPOL + ActHIB vaccines.

**Data From Post-Marketing Experience** The following additional adverse events have been spontaneously reported between 1997 and 2007 during the post-marketing use of Pentacel vaccine outside of the US, primarily in Canada. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. The following adverse events were included based on severity, frequency of reporting, or the strength of causal association to Pentacel vaccine: cardiac disorders (cyanosis); gastrointestinal disorders (vomiting, diarrhea); general disorders and administration site conditions (injection site reactions, including inflammation, mass, abscess and sterile abscess), extensive swelling of the injected limb (including swelling that involved adjacent joints), vaccination failure/therapeutic response decreased (invasive *H influenzae* type b disease); immune system disorders (hypersensitivity, such as rash and urticaria); infections and infestations (meningitis, rhinitis, viral infection); metabolism and nutrition disorders (decreased appetite); nervous system disorders (somnia, HHE, depressed level of consciousness); psychiatric disorders (screaming); respiratory, thoracic and mediastinal disorders (apnea, cough); skin and subcutaneous tissue disorders (erythema, skin discoloration); vascular disorders (pallor).

**Reporting of Adverse Events** The National Childhood Vaccine Injury Act of 1986 requires physicians and other health-care providers who administer vaccines to maintain in the recipient's permanent medical record the manufacturer, lot number, date of administration, and the name, address and title of the person administering the vaccine. The Act further requires the health-care provider to report to the US Department of Health and Human Services the occurrence of certain adverse events following immunization. For Pentacel vaccine, events required to be reported are anaphylaxis or anaphylactic shock within 7 days, brachial neuritis within 2-28 days, encephalopathy or encephalitis within 7 days following vaccination, or any acute complication or sequela (including death) of these events, or any contraindicating event listed in this Pentacel vaccine package insert. (5,6) These events and other suspected adverse reactions should be reported to VAERS at 1-800-822-7967 or <http://www.vaers.hhs.gov> and to Sanofi Pasteur Inc. at 1-800-822-2463.

**DOSAGE AND ADMINISTRATION Vaccination Schedule** Pentacel vaccine is approved for administration as a 4 dose series at 2, 4 and 6, and 15-18 months of age. The first dose may be given as early as 6 weeks of age. Four doses of Pentacel vaccine constitute a primary immunization course against pertussis. Three doses of Pentacel vaccine constitute a primary immunization course against diphtheria, tetanus, *H influenzae* type b invasive disease, and poliomyelitis; the fourth dose constitutes a booster vaccination against diphtheria, tetanus, *H influenzae* type b invasive disease, and poliomyelitis.

**Administration Reconstitution of Freeze-Dried Product and Withdrawal from Stopped Vial** Thoroughly but gently shake the vial of DTaP-IPV component, withdraw the entire liquid content and inject into the vial of the lyophilized ActHIB vaccine component. Shake the vial now containing Pentacel vaccine thoroughly until a cloudy, uniform suspension results. Withdraw and administer a 0.5 mL dose of Pentacel vaccine intramuscularly. Pentacel vaccine should be used immediately after reconstitution.

**Concomitant Administration with Other Vaccines** In clinical trials, Pentacel vaccine was routinely administered, at separate sites, concomitantly with one or more of the following vaccines: hepatitis B vaccine, 7-valent pneumococcal conjugate vaccine, MMR and varicella vaccines. When Pentacel vaccine is given at the same time as another injectable vaccine(s), the vaccines should be given with different syringes.

**STORAGE** Store at 2° to 8°C (35° to 46°F). Do not freeze. Discard product if exposed to freezing. Do not use after expiration date. Pentacel vaccine should be used immediately after reconstitution.

**REFERENCES** 1. CDC. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(RR-15):1-48. 2. Stratton KR, et al. editors. Adverse events associated with childhood vaccines; evidence bearing on causality. Washington, DC: National Academy Press; 1994. p. 67-117. 3. Rothstein EP, et al. Comparison of antigenuria after immunization with three *Haemophilus influenzae* type b conjugate vaccines. *Pediatr Infect Dis J* 1991; 10:311-4. 4. Braun MM. Report of a US Public Health Service workshop on hypotonic-hypoosmotic episode (HHE) after pertussis immunization. *Pediatrics* 1998;102(5):1-5. 5. CDC. Current trends - national vaccine injury act: requirements for permanent vaccination records and for reporting of selected events after vaccination. MMWR 1988;37(13):197-200. 6. [www.hrsa.gov/vaccinecompensation/table.htm](http://www.hrsa.gov/vaccinecompensation/table.htm) (accessed May 28, 2008)

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46 children, and severe impairment (80 dB) was detected in 27 children; 15 children became totally deaf.

Regardless of the threshold level, treatments did not differ from each other or placebo in terms of effect on hearing loss.

Nor did etiology correspond to hearing loss.

"Ineffectiveness of all adjuvant medications remained essentially the same when cases with and without a proven etiology were examined," Dr. Peltola and associates said.

Age, however, did play a role.

"Each increasing month of age decreased the risk of hearing impairment by 2%-6% for any, moderate to severe, and severe impairment," the physicians noted.

"The controversy about dexamethasone therapy for *Streptococcus pneumoniae* is well known, but we all believed that the role of dexamethasone in *Haemophilus influenzae* meningitis had been established," Dr. Ram Yogev and Dr. Stephen Pelton stated in an accompanying editorial.

"Yet, the data ... fail to demonstrate a benefit for dexamethasone in any bacterial meningitis (including *H. influenzae*) and raise questions about past beliefs," they said.

In the editorial, Dr. Yogev of the division of pediatric infectious diseases at the Children's Memorial Hospital, Chicago, and Dr. Stephen Pelton of the division of pediatric infectious diseases at Boston University Hospital pointed to the most recent Cochrane meta-analysis, which states that "data support the use of adjunctive corticosteroids in children in high-income countries" (*Pediatrics* 2010;125:e188-90).

"We suggest that the delay from onset of infection to the start of appropriate therapy (permitting progression of the inflammatory response) is an important contributor to the failure of current adjunctive therapies in resource-limited countries," they wrote, adding, "If adjunctive therapies are only effective before the inflammatory cascade is operational, they will never be fully successful."

They also pointed out that the percentage of patients who experienced hearing loss in this study—roughly one-third—is "higher than in many of the studies in which beneficial outcomes with dexamethasone were observed, possibly suggesting a cohort with more advanced disease or a late diagnosis."

Dr. Yogev and Dr. Pelton concluded with the observation that this study "reminds us that we are still far from preventing many sequelae of childhood bacterial meningitis." ■

Patient age and presenting status—not dexamethasone or glycerol treatment—have the greatest impact on whether a child with bacterial meningitis will develop hearing loss, even in cases due to *Haemophilus influenzae* type b, according to the largest clinical trial yet to tackle the question.

Indeed, "the effect of the clinical condition was so dramatic that each lowering point in the Glasgow Coma Scale increased the risk of hearing impairment by 15%-20%," the study authors wrote.

Dr. Heikki Peltola of the division of pediatric infectious diseases at Helsin-

## VITALS

**Major Finding:** Whether a child with bacterial meningitis had hearing loss depended on patient age and presenting status. Dexamethasone and glycerol treatment did not appear to be helpful.

**Data Source:** A prospective, randomized double-blind trial of 383 children.

**Disclosures:** Dr. Peltola disclosed that he currently serves as a clinical scientific consultant for Serum Institute of India Ltd. GlaxoSmithKline organized the first grant for this study. Dr. Yogev and Dr. Pelton said they had no relevant financial disclosures.

ki University Central Hospital and associates conducted a prospective, randomized double-blind trial of bacterial meningitis patients aged 2 months to 16 years from 10 Latin American institutions (*Pediatrics* 2010; 125:e1-8).

Children included in the study had positive cerebrospinal fluid (CSF) or blood cultures for meningitis, or negative cultures with signs and symptoms of the disease plus three out of four criteria: pleocytosis, a CSF glucose level less than 40 mg/dL, a CSF protein level greater than 40 mg/dL, or a serum C-reactive protein level greater than 40 mg/dL.

Children with a recent head injury, a prior neurologic disease or procedure, immunosuppression, or a known hearing impairment were excluded from the study.

Of the 654 who entered the study, 83 died and 188 were insufficiently tested, leaving 383 children available for analysis.

Most (146) had meningitis due to *H. influenzae* type b (Hib), followed by *S. pneumoniae* (70 cases).

All children received ceftriaxone; then 101 children received adjuvant intravenous dexamethasone, 95 received dexamethasone plus glycerol, 92 received glycerol only, and 95 received placebo only.

Mild hearing impairment (between 41 and 59 dB) was detected in 44 children, moderate to severe impairment (between 60 and 79 dB) was detected in