# Poor Immune Responses to a Birth Dose of Diphtheria, Tetanus, and Acellular Pertussis Vaccine

Natasha B. Halasa, MD, MPH, Alice O'Shea, RN, Jian R. Shi, MD, Bonnie J. LaFleur, PhD, MPH, and Kathryn M. Edwards, MD

**Objectives** To evaluate the safety and immunogenicity of an additional birth dose of diphtheria, tetanus, and acellular pertussis vaccine (DTaP).

**Study design** Fifty infants between 2 to 14 days of age were randomly assigned to receive either DTaP and hepatitis B vaccines (experimental) or hepatitis B alone (control) at birth. At 2, 4, 6, and 17 months of age, DTaP and routine vaccines were administered to both groups. Safety data were collected after each dose, and sera were obtained at birth, 6, 7, 17, and 18 months. Immune responses to pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae were measured by enzyme-linked immunosorbent assay; responses to other vaccines were assessed.

**Results** No differences were seen between the 2 groups in either local or systemic reactions; all vaccines were well tolerated. Compared with the control group, infants in the experimental group demonstrated significantly lower geometric mean antibody concentrations for pertussis toxin and pertactin 6, 7, and 18 months, for fimbrae at 6, 7, 17, and 18 months, and for FHA at 18 months, and lower geometric mean antibody concentrations for diphtheria at 7 months. Immune responses to all other vaccine antigens were comparable.

**Conclusion** Administration of an additional dose of DTaP at birth was safe but was associated with a significantly lower response to diphtheria and 3 of 4 pertussis antigens compared with controls. *(J Pediatr 2008;153:327-32)*

Pertussis (whooping cough) is a respiratory tract infection caused by *Bordetella pertussis*, a gram-negative bacillus. The disease is most severe in infants and young children, with hospitalization and complication rates highest in this age group.[1] Most deaths associated with confirmed pertussis occur in infants <6 months of age, too young to have received the primary series of diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP).[2] Additional reports of increasing rates of infant pertussis in Canada and Europe also have appeared.[3-7] Given these observations, we hypothesized that an additional dose of acellular pertussis vaccine might enhance protection. Therefore we evaluated the safety and immunogenicity of administering an additional dose of DTaP at birth and compared it with the standard DTaP vaccination schedule alone.

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From the Departments of Pediatrics, Division of Infectious Diseases (N.H., A.O., J.S., K.E.), Vanderbilt University School of Medicine, Nashville, TN, and the Section of Biostatistics, Department of Pediatrics, University of Utah, Salt Lake City, UT (B.L.).

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Reprint requests: Natasha Halasa, MD, MPH, D7232 Medical Center N., 1161 21st Ave. S., Nashville, TN 37232. E-mail: Natasha.Halasa@vanderbilt.edu.

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## METHODS

### Study Design

This was a prospective, randomized, controlled pilot study conducted in healthy full-term infants between 2 and 14 days of age who were available for the entire study period and whose parents or guardians provided written informed consent. Subjects were randomly assigned to either the experimental group that concomitantly received DTaP in the left thigh and hepatitis B vaccine in the right thigh or to the control group that received hepatitis B vaccine in the right thigh alone. Subjects in both groups received

| | | | |
|---|---|---|---|
| DTaP | Diphtheria and tetanus toxoids and acellular pertussis vaccine | Hib | *Haemophilus influenzae* type b conjugate vaccine |
| DTP | Diphtheria and tetanus toxoids | IgG | Immunoglobulin G |
| ELISA | Enzyme-linked immunosorbent assay | IPV | Inactivated trivalent poliovirus vaccine |
| FDA | Food and Drug Administration | MMR | Measles mumps rubella |
| FHA | Filamentous hemagglutinin | PCV7 | Pneumococcal conjugate vaccine 7-valent |
| FIM | Fimbriae 2 and 3 | PRN | Pertactin |
| GMC | Geometric mean concentration | PRP | Polyribosylribitol phosphate |
| HBS | Hepatitis B surface | PT | Pertussis toxoid |
| HepB | Hepatitis B vaccine | V | Varicella virus vaccine live |

**Table I. Vaccination and phlebotomy schedule for experimental and control groups**

| Group | Age at vaccination | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2-14 Days | 2 Mos | 4 Mos | 6 Mos | 12 Mos | 17 Mos | 18 Mos |
| Experimental group (25 subjects) | Hep B (LLAT)<br>DTaP (RAT) | DTaP (RAT)<br>IPV (LLT)<br>PCV (LUT)<br>Hep B (LLAT)<br>Hib (RLT) | DTaP (RAT)<br>IPV (LLT)<br>PCV (LUT)<br>Hib (RLT) | DTaP (RAT)<br>PCV (LUT)<br>Hep B (LLAT)<br>Hib (RLT) | MMR (RUAT)<br>Varicella (LLT)<br>PCV (LUT) | DTaP (RAT)<br>IPV (LLT)<br>Hib (RLT) | |
| Control group (25 subjects) | Hep B (LLAT) | DTaP (RAT)<br>IPV (LLT)<br>PCV (LUT)<br>Hep B (LLAT)<br>Hib (RLT) | DTaP (RAT)<br>IPV (LLT)<br>PCV (LUT)<br>Hib (RLT) | DTaP (RAT)<br>PCV (LUT)<br>Hep B (LLAT)<br>Hib (RLT) | MMR (RUAT)<br>Varicella (LLT)<br>PCV (LUT) | DTaP (RAT)<br>IPV (LLT)<br>Hib (RLT) | |
| Blood Draws | x | | x | x | | x | x |

Location of injections: *RAT*, right anterolateral thigh; *RUAT*, right upper anterolateral thigh; *RLT*, right lower thigh; *LLAT*, left lower anterolateral thigh; *LLT*, left lower thigh; *LUT*, left upper thigh.

DTaP at 2, 4, 6, and 17 months of age concomitantly with the other vaccines recommended routinely by the American Academy of Pediatrics (Table I). The study was approved by the Vanderbilt University Institutional Review Board and conducted at the Vanderbilt University Hospital and Vanderbilt Children's Hospital.

## Study Objectives

The 2 main objectives of the trial were to assess the safety and immunogenicity of an additional birth dose of DTaP given with the standard DTaP schedule at 2, 4, 6, and 17 months of age compared with the standard schedule alone.

## Vaccines

All of the vaccines were administered according to the schedule outlined in Table I. A single lot of Daptacel DTaP (sanofi pasteur, Swiftwater, Pennsylvania) was provided by the manufacturer and used throughout the study. Each standard 0.5-mL dose of Daptacel contained diphtheria toxoid 15 Lf, tetanus toxoid 5 Lf, pertussis toxoid (PT) 10 $\mu$g, filamentous hemagglutinin (FHA) 5 $\mu$g, pertactin (PRN) 3 $\mu$g, and fimbriae 2 and 3 (FIM) 5 $\mu$g. The other vaccines included the following: hepatitis B vaccine (HepB) (Recombivax HB, Merck, Whitehouse Station, New Jersey), inactivated trivalent poliovirus vaccine (IPV) (IPOL, sanofi pasteur), *Haemophilus influenzae* type b conjugate vaccine (Hib) (ActHIB, sanofi pasteur); pneumococcal conjugate vaccine 7-valent (PCV7) (Prevnar, Wyeth, Madison, New Jersey), varicella virus vaccine live (V) (Varivax, Merck); and measles mumps rubella (MMR), (M-M-R, Merck). The components of each of these licensed vaccines are provided in the Appendix (available at www.jpeds.com).

## Safety Evaluation

After each injection with DTaP, the infant was observed for 30 minutes for any immediate reactions. Parents/guardians, unaware of which vaccines were injected into which thigh, were given a digital thermometer, instructed in its use, and taught how to record local site reactions (pain, erythema, or thigh swelling by measuring thigh diameter), fever (rectal temperatures), systemic adverse events (crying for >3 hours, irritability/fussiness, drowsiness, and loss of appetite), and antipyretic use in a diary for 7 days after the birth vaccinations and for 3 days with the subsequent immunizations.

Phone calls were made by the study nurse on days 1 to 3 and day 8 after vaccination to review the diary cards. Illnesses or events that required physician intervention or concomitant medication use within 30 days of immunization were recorded. Serious adverse events were assessed for the entire 18-month study duration.

## Immunogenicity Evaluation

Venous blood samples were obtained just before administration of the birth doses at 2 to 14 days of life, and again at 6, 7, 17, and 18 months of age. In 1 subject the parents requested that a cord blood sample be substituted for the prevaccination birth sample. Immunoglobulin G (IgG) antibodies to PT, FHA, PRN, and fimbriae 2/3 (FIM) were assayed using standardized enzyme-linked immunosorbent assay (ELISA) as previously described[8-12] and were performed in the Pediatric Research Laboratories at Vanderbilt University.

ELISA units were assigned based on the U.S. Food and Drug Administration (FDA) human reference pertussis antisera (Lots 3 and 4). The minimum level of detection for each IgG antibody was established at 2 ELISA Units (EU)/mL. The limit of quantification was 2 EU/mL, 3 EU/mL, and 5 EU/mL for IgG PT, IgG FHA, and IgG FIM, respectively. Sequential serum samples from each subject were run simultaneously in the same assay.

To evaluate the possibility of interference with the other standard approved vaccines, the FDA required that serum specimens collected at 7 and 18 months also be analyzed for responses to polyribosylribitol phosphate (PRP) Hib capsule