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Immunogenicity of *Haemophilus influenzae* Type b Protein Conjugate Vaccines in Very Low Birth Weight Infants

Carl T. D'Angio, MD[1], **Theresa E. Murray, MD, MPH**[2], **Lei Li, PhD**[3], **Roy J. Heyne, MD**[4], **T. Michael O'Shea, MD, MPH**[5], **Robert L. Schelonka, MD**[6], **Seetha Shankaran, MD**[7], **Shahnaz Duara, MD**[8], **Ronald N. Goldberg, MD**[9], **Barbara J. Stoll, MD**[10], **David K. Stevenson, MD**[11], **Betty R. Vohr, MD**[12], **Dale L. Phelps, MD**[1], **Waldemar A. Carlo, MD**[13], **Michael E. Pichichero, MD**[14], **Abhik Das, PhD**[15], and **Rosemary D. Higgins, MD**[16] **on behalf of the NICHD Neonatal Research Network**

[1]Department of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, NY

[2]Spotsylvania Regional Medical Center, Fredericksburg, VA

[3]Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC

[4]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX

[5]Wake Forest University School of Medicine, Winston-Salem, NC

[6]Division of Neonatology, Oregon Health Sciences University, Portland, OR

[7]Department of Pediatrics, Wayne State University, Detroit, MI

[8]University of Miami Miller School of Medicine, Miami, FL

[9]Department of Pediatrics, Duke University, Durham, NC

[10]Department of Pediatrics, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, GA

[11]Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA

[12]Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI

[13]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL

[14]Rochester General Hospital, Rochester, NY

[15]Social, Statistical and Environmental Sciences Unit, RTI International, Rockville, MD

[16]*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

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Corresponding Author: Carl T. D'Angio, MD, Box 651, Neonatology, Golisano Children's Hospital at Strong, University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642 Phone: (585) 273-4911 Fax: (585) 461-3614, carl_dangio@urmc.rochester.edu.

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To the Editors

Protection from invasive disease caused by *Haemophilus influenzae* type b (Hib) is due to the production of protective antibody levels against the Hib capsular polysaccharide polyribosylribitol phosphate (PRP). In a case series of Hib vaccine failures, prematurity was the most common clinical risk factor for failure.[1] Several studies in preterm infants suggest that Hib conjugate vaccines, when administered to preterm infants, may elicit anti-PRP antibody titers that are close to those seen among term infants, whereas other studies have identified lower responses.[2]

As part of a study of heptavalent pneumococcal conjugate vaccine immunogenicity among very-low-birth-weight (VLBW) infants,[3] we measured anti-PRP titers among a subset of the infants following a primary series of Hib conjugate vaccinations. We hypothesized that the least mature VLBW infants would have the lowest antibody responses.

Subjects were eligible for the primary study if they were <32 0/7 weeks gestation at birth and had a birth weight 401–1500 grams.[3] At the time of the study, tetanus- (PRP-T), meningococcal- (PRP-OMP) and CRM197-protein-conjugate (HbOC) vaccines were all used for Hib immunization. Subjects were eligible for this secondary analysis if they received 3 doses of any combination of Hib vaccine for their primary series, completed the primary series by 8 months of age, had blood drawn 4–6 weeks after the primary series, and had extra serum available. Subjects were also eligible if they completed a 2-dose primary series (at 2 and 4 months) of PRP-OMP vaccine at one center (Rochester) able to draw blood samples 4–6 weeks thereafter. The primary outcome was geometric mean anti-PRP titer (GMT) 4–6 weeks following the primary Hib series (at 4 or 6 months of age). Anti-capsular PRP antibody was measured by the method of Phipps[4] using PRP oligosaccharide (lower limit of detection = 0.10 μg/mL).

Of 244 infants in the primary study, 161 completed the secondary study. Birth weight was 1041 ± 277 grams (mean ± standard deviation) and gestational age 28.0 ± 2.0 weeks, with 68 infants (42%) being ≤1000 grams. Infants were 6.3 ± 0.4 months at conclusion of the primary series of vaccines, and 5.3 ± 0.5 months and 7.4 ± 0.5 months at blood draw for 2-dose PRP-OMP-only and 3-dose infants, respectively.

Overall, 79% of infants had post-vaccination PRP titers ≥1.0 μg/mL and 96% had titers ≥0.15 μg/mL. PRP GMT were lower among infants ≤1000 grams birth weight (2.5 μg/mL; [95% confidence interval: 1.7, 3.4]) than among those >1000 grams (3.6 μg/mL; [2.7, 4.8]), but this difference did not reach statistical significance (p = 0.25) (Figure). Seventy-four percent of infants ≤1000 grams and 83% of infants >1000 grams achieved titers ≥1.0 μg/mL (p = 0.15). Only 9 infants received a primary series of two doses of PRP-OMP vaccine, limiting the ability to draw conclusions about differing responses to differing vaccine types.

The proportion of VLBW infants achieving the presumed long-term protective PRP antibody titer of ≥ 1.0 μg/mL is lower than the 90–95% reported for full term infants.[5] Timely Hib vaccine boosting may be particularly important among VLBW infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Lei Li (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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NRN Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2001–2006); Michael S. Caplan, MD, Northwestern University (2006–2011).

Duke University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (M01 RR30, U10 HD40492) – C. Michael Cotten, MD; Kathy J. Auten, BS.

Emory University(U10 HD27851, M01 RR39) – Ellen C. Hale, RN BS CCRC.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Stephanie Wilson Archer, MA.

RTI International (U10 HD36790) – W. Kenneth Poole, PhD; Margaret Cunningham, BSCCRP; Jamie E. Newman, PhD MPH; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MSCCRP; Kristin Zaterka-Baxter, RN BSN CCRP.

Stanford University(U10 HD27880, M01 RR70) –Krisa P. Van Meurs, MD; Susan R. Hintz, MD MS Epi; M. Bethany Ball, BS CCRC.

University of Alabama at Birmingham Health System (U10 HD34216, M01 RR32) –Namasivayam Ambalavanan, MD; Myriam Peralta-Carcelen, MD MPH; Monica V. Collins, RN BSN; Shirley S. Cosby, RN BSN; Vivien A.Phillips, RN BSN.

University of Miami Holtz Children's Hospital (U10 HD21397, M01 RR16587) – Ruth Everett-Thomas, RN MSN.

University of Rochester Golisano Children's Hospital at Strong (U10 HD40521, M01 RR44) –GaryJ.Myers,MD; Cassandra A. Horihan, MS; Rosemary L.Jensen; Diane L.Hust, RN PNP; Linda J.Reubens, RN CCRC.

University of Texas Southwestern Medical Center at Dallas (U10 HD40689, M01 RR633) –Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Pablo J. Sánchez, MD; Janet S. Morgan, RN; Jackie F.Hickman, RN; Alicia Guzman; Nancy A. Miller, RN; Gaynelle Hensley, RN; Sally S. Adams, MS RN CPNP; Linda A. Madden, BSN RN CPNP; Elizabeth Heyne, PA-C PsyD. Wake Forest University Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – T. Michael O'Shea, MD MPH; Nancy J. Peters, RN CCRP.

Wayne State University (U10 HD21385)–Rebecca Bara, RN BSN.

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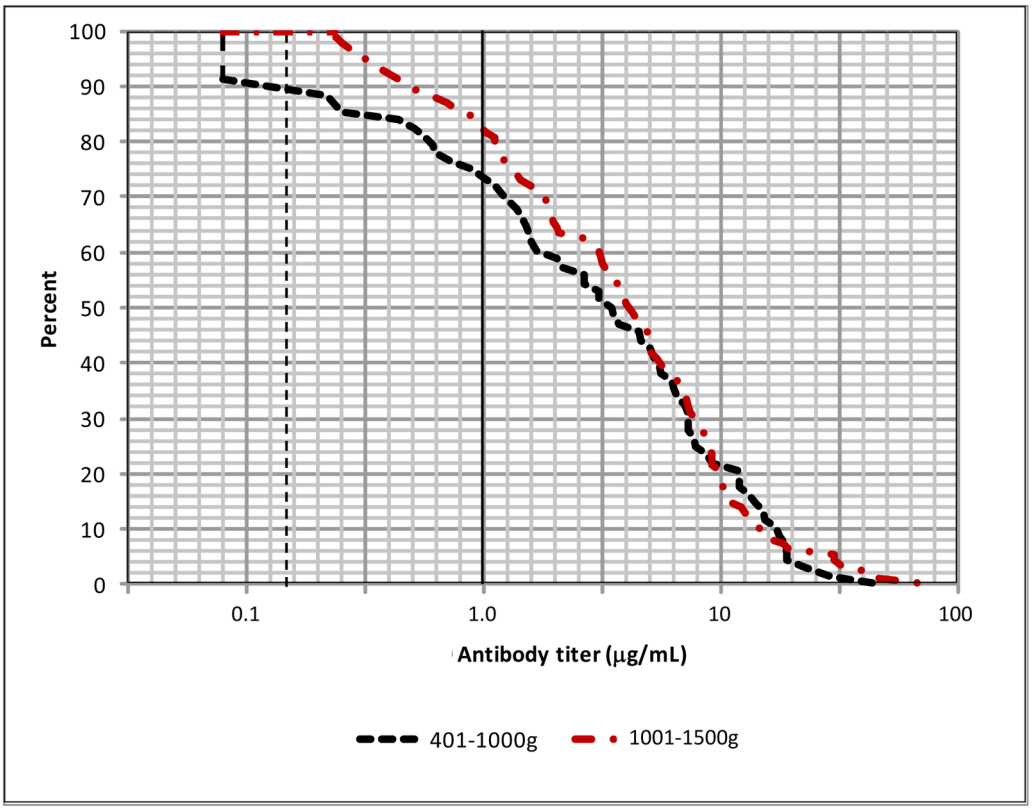

Figure. Reverse distribution curve of antibody responses

Infants with birth weights 401–1000 grams (dashed line) and 1001–1500 grams (dash-dotted line) are shown. Solid vertical line denotes 1.0 μg/mL and dashed vertical line denotes 0.15 μ/mL. Curve allows an assessment of the proportion of children achieving various post-vaccination antibody levels. All infants with titers below the limit of detection were <1000 grams' birth weight.