Pertussis Serostatus among Neonates Born to Hispanic Women

C. Mary Healy,1,2 Marcia A. Rench,1 Kathryn M. Edwards,4 and Carol J. Baker1,2

Departments of 1Pediatrics and 2Molecular Virology and Microbiology, Section of Infectious Diseases, Baylor College of Medicine, and 3Ben Taub General Hospital, Houston, Texas; and 4Division of Infectious Diseases, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee

The reasons for the higher pertussis incidence among Hispanic infants, compared with among infants of other ethnicities, are unknown. The geometric mean concentration of pertussis toxin–specific immunoglobulin G in serum samples from 220 Hispanic neonates was 8.45 EU/mL, as determined by enzyme-linked immunosorbent assay, and it was significantly lower if mothers were adolescents (4.63 EU/mL; P = .001). A lack of maternal immunity is one explanation for pertussis susceptibility in very young Hispanic infants.

The highest incidence of pertussis occurs among infants too young to have completed their primary diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine series (i.e., among infants who are <6 months old) [1–4]. This is especially evident among Hispanic infants: in the 1990s, the mean annual incidence of pertussis was 74% higher among Hispanic infants (68 cases per 100,000 population) than among non-Hispanic infants (39 cases per 100,000 population). Hispanic infants also accounted for 36%–41% of pertussis-related deaths [2–4] but only 17% of the US birth cohort [5]. Reasons for this ethnic disparity are unclear, but this disparity is not related to lower immunization rates [1].

Acellular pertussis antigen–containing (Tdap) vaccines for use in adolescents and adults recently were licensed on the basis of serologic correlates bridging pertussis toxin (PT)–specific IgG concentrations in serum samples from infants in an efficacy trial; concentrations in serum samples from adolescents and adults were not inferior to concentrations in serum samples from infants [6, 7]. Although serological correlates of pertussis protection are uncertain, a large trial of a monovalent PT vaccine in infants demonstrated efficacy [8, 9].

Because new Tdap vaccines theoretically could prevent pertussis in very young infants through passive immunization with maternal PT-specific IgG, we measured serum concentrations in a cohort of term neonates born to Hispanic mothers to determine whether low concentrations of PT-specific IgG might partially explain the elevated risk of pertussis in young Hispanic infants. We also evaluated the role of maternal age on cord serum concentrations, because in previous studies, young maternal age was a risk factor for infant pertussis [10]. Finally, placental transfer of maternal PT-specific IgG was measured.

Patients and methods. Eligible neonates were single children born consecutively at ≥37 weeks of gestation to self-identified Hispanic mothers at Ben Taub General Hospital in Houston, Texas, during July and August 2004. Enrollment required availability of cord serum samples, data on maternal age, and an incomplete predesignated maternal age cohort. Maternal age cohorts reflected proportions of Hispanic mothers in Texas. Twenty (10%) of the subjects were ≤19 years old, 60 (30%) were 20–24 years old, 60 (30%) were 25–29 years old, and 60 (30%) were ≥30 years old, for a total of 200 subjects. Because more pertussis cases are reported among adolescents than among other age groups [3, 10, 11], 20 additional neonates of adolescent mothers were enrolled to allow a more robust comparison of adolescents with older age cohorts. To assess placental transfer of maternal PT-specific IgG, a subset of 55 matched maternal delivery samples (obtained routinely from mothers for typing and cross-matching) were collected in an age distribution identical to that of the entire cohort. Demographic and clinical data were obtained from delivery register and birth certificates. The study was approved by the institutional review boards of Baylor College of Medicine (Houston, TX) and Ben Taub General Hospital. Informed consent was waived.

Blood samples were transported from Ben Taub General Hospital to the Baylor laboratory for processing. The 100-μL serum aliquots were coded (maternal delivery–cord pairs had linked codes) and shipped to Vanderbilt University School of Medicine (Nashville, TN). PT-specific IgG was quantified by ELISA, as described elsewhere [12], using US Food and Drug Administration–provided reference serum samples from the
same lot, as previously reported [11, 13, 14]. The lower limit of detection of the assay was 2 EU/mL.

A sample size of 220 samples had power to detect a correlation between PT-specific IgG in cord serum samples (the dependent variable) and maternal age (the independent variable) of \( r = 0.2 \) by regression analysis, and 80% power to detect a \( \geq 0.6 \) SD difference between age groups. Dichotomous outcomes were compared by \( \chi^2 \) test or Fisher’s exact test. PT-specific IgG was reported as geometric mean concentration with 95% CIs. Maternal age groups were compared for PT-specific IgG in cord serum samples using analysis of variance and Tukey’s post hoc testing procedure on log-transformed data.

**Results.** Of 473 eligible newborn infants born to Hispanic mothers, 253 were excluded from the study because the maternal age group was complete (225 neonates) or cord serum samples were unavailable (28). Among the 220 enrolled neonates, 55 had paired maternal delivery serum samples collected, distributed among the 4 previously determined age groups (maternal age range, 13.6–42.3 years; table 1). There were no statistically significant differences in neonatal or maternal demographic or clinical characteristics between subsets of maternal-infant pairs who had or did not have maternal delivery serum samples collected. Most mothers were of Mexican origin (76%) and had prenatal care. Each country of maternal origin administers the final pertussis vaccine dose at \( \approx 6 \) years of age [15].

The geometric mean concentration of PT-specific IgG in cord serum samples from the 220 neonates born to Hispanic mothers was 8.45 EU/mL (table 1). Cord serum samples from infants born to adolescent mothers had a significantly lower geometric mean concentration (4.63 EU/mL) than did cord serum samples from other maternal age groups, whether analyzed individually (\( P \leq 0.05 \)) or collectively (\( P = 0.001 \)) (table 1 and figure 1). A similar (but not significant) lower geometric mean concentration of PT-specific IgG in adolescents also was noted in the 55 maternal delivery serum samples (\( P = 0.07 \)). By regression analysis, maternal age and PT-specific IgG concentration were determined to be nonlinear. Placental transfer expressed as ratio of PT-specific IgG in cord serum samples to maternal delivery samples was 1.08, indicating efficient transport of maternal antibodies (table 1).

**Discussion.** Our study provides the first insight into an important pertussis risk factor in Hispanic infants, especially those \( \leq 4 \) months of age—namely, serostatus at birth. Although “protective” levels of antibodies to pertussis antigens are uncertain, protection of infants given monovalent PT vaccine has been established [8, 9]. Furthermore, unlike other pertussis antigens, PT is specific for *Bordetella pertussis*, and all licensed pertussis vaccines contain PT. In cord serum samples from our cohort of term neonates born to Hispanic mothers, maternally acquired PT-specific IgG concentrations were too low to be associated with protection. Thus, Hispanic pregnant women (especially adolescents who, as an age cohort, comprise a large portion of the contemporary pertussis disease burden) are unlikely to have pertussis immunity, as is the case with women of other ethnicities [13, 14]. Population-based studies will be required to fully elucidate why Hispanic infants are over-represented in pertussis case rates.

Our data also demonstrate efficient placental transfer of maternal PT-specific IgG, and concentrations in cord serum samples obtained from term neonates predictably reflect maternal PT-specific IgG levels at delivery. The high PT-specific IgG concentrations (>100 EU/mL) observed in a few of our Hispanic neonates are likely to have reflected immune response following recent natural pertussis in their mothers, because...
Vaccine-induced antibodies wane by early adolescence [7, 11]. Furthermore, our finding that PT-specific IgG levels are at their nadir during adolescence (figure 1) supports observations made during pertussis outbreaks in Chicago, Illinois, where infants born to adolescent mothers had 6.4 times the risk of pertussis infection, compared with infants of older mothers [10]. The peak age of pertussis infection in our population appears to be older than the 13–17 years of age described during the late 1980s [11]. Even though pregnant Hispanic adolescents and their neonates appear to be particularly susceptible to pertussis, the low PT-specific IgG in serum samples from Hispanic women aged ≥20 years and their neonates indicates that these patients also are vulnerable.

Our study has some limitations. First, we did not have a non-Hispanic control group. Second, demographic and clinical data were derived without patient contact; thus, history of prolonged cough (possibly representing pertussis) in contacts was unavailable. Third, because PT-specific IgG was almost uniformly low, we could not assess whether placental transfer is influenced by higher maternal PT-specific IgG being available at delivery or by other maternal or infant factors. Fourth, we evaluated immunity to PT only, and other pertussis antigens, such as pertactin, may be important in protection against mild or atypical disease [16]. However, our prior study of serum samples obtained from predominantly non-Hispanic mother-infant pairs found similarly low concentrations of IgG to PT, filamentous hemagglutinin antigen, and fimbriae [14], and antibodies to PT are accepted indicators of recent infection or vaccination [6–9].

In 2004, the incidence of reported pertussis cases exceeded that in all years since 1964 and reached 136.5 cases per 100,000 infants ≤6 months of age (Centers for Disease Control and Prevention, unpublished data). This incidence certainly reflects nonprotective levels of maternal PT-specific IgG, increased exposure of young infants to pertussis, or both [13, 14]. Although universal or selected adolescent and adult Tdap vaccination should reduce pertussis among these infants prior to their own active immunization at 2, 4, and 6 months of age, it likely will require years for a high proportion of women to be protected during their pregnancies. Although the high incidence of pertussis in Hispanic neonates and young infants is probably multifactorial, lack of maternal antibodies is likely to be a risk factor. Maternal susceptibility is important, because neonates and young infants are likely to acquire pertussis from infected household contacts, especially their mothers [10, 17].

One immediate method of achieving sufficient pertussis-specific IgG concentrations in neonates and young infants is to administer Tdap in pregnant women reaching the third trimester [18]. In efficacy trials, subjects who received Tdap vaccines demonstrated pertussis antibody levels 2–5 times greater than levels found in infants who received DTaP [6]. Even allowing for the rapid decay of maternal antibodies (maternal PT-specific IgG half life, 36 days [13]), such boosting of maternal immunity could result in protection of infants until 4 months of age, when 2 doses of DTaP have been given. Studies have demonstrated that high maternal PT-specific antibody levels do not suppress infant responses to DTaP antigens [13, 19], but limited data suggest that they did interfere with immune responses in infants given whole-cell pertussis vaccines [19]. Further investigation should define the role of maternal Tdap immunization (if any) in infant DTaP vaccine responses and explore its usefulness as a strategy to prevent life-threatening pertussis in very young infants.

Acknowledgments

We thank Carolyn Fairchild (Coordinator of Data Informatics for Women and Infants, Ben Taub General Hospital) for assistance in data collection, Charity Moore and Kristen Ewing (Baylor College of Medicine) for collection and processing of serum samples, E. O’Brian Smith (Baylor College of Medicine) for advice on statistical analysis, Jody Peters (Vanderbilt University Laboratory, Nashville, TN) for performing the serological assays, Morven S. Edwards (Baylor College of Medicine, Houston, TX) for...
helpful comments, and Robin Schroeder (Baylor College of Medicine, Houston, TX) for assistance in preparing this manuscript.

Financial support. National Institutes of Health-National Institute of Allergy and Infectious Diseases (NO1 AI-25462-04 and NO1 AI-25465-04).

Potential conflicts of interest. K.M.E. has received a grant from sanofi-pasteur to assess the use of acellular pertussis vaccine in neonates; has received grant support from sanofi, Vaxgen, Medimmune, the National Institutes of Health, and the Centers for Disease Control and Prevention; and is a consultant for Nabi and Wyeth. C.J.B. is a consultant to Glaxo-SmithKline for adolescent acellular pertussis vaccine education and has received grant support from the National Institutes of Health. All other authors: no conflicts.

References