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Pertussis seroepidemiology in women and their infants in Sarlahi District, Nepal

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ABSTRACT

Background: Infants are at greatest risk for pertussis morbidity and mortality. Maternal vaccination during pregnancy has been shown to prevent pertussis in young infants in high- and middle-income countries. However, data on the levels of maternal pertussis antibodies and the efficiency of transplacental transfer in low-income South Asian settings are limited.

Objective: To estimate the prevalence of maternal pertussis antibodies and the efficiency of transplacental transfer in rural southern Nepal.

Design/methods: Paired maternal-infant blood samples were collected from a subsample of participants in a randomized, controlled trial of maternal influenza immunization (n = 291 pairs). Sera were tested by enzyme-linked immunosorbent assays for pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae. Maternal and infant pertussis antibody levels and transplacental transfer efficiency were determined and potential factors associated with both were assessed.

Results: Elevated maternal antibodies to pertussis toxin, suggesting recent pertussis infection, were rarely detected (4%, tested n = 305). However, paired maternal-cord sera were highly correlated across all antibodies; transplacental antibody transfer ratios for pertussis toxin were 1.14 (n = 291, 95% CI 1.07–1.20); filamentous hemagglutinin 1.10 (n = 120, 95% CI: 1.01–1.20); fimbriae 2/3 1.05 (n = 120, 95% CI: 0.96–1.15) and pertactin 0.96 (n = 289, 95% CI: 0.91–1.00). Older gestational age was associated with increased pertussis toxin and decreased fimbriae 2/3 antibody transport.

Conclusions: A low prevalence of maternal antibody to all four pertussis antigens was noted in Nepal, but transplacental antibody transfer was efficient. No consistent demographic factors were associated with elevated maternal antibody levels or efficiency of transplacental transfer. If an increase in infant pertussis disease burden was detected in this population, maternal immunization could be an effective intervention to prevent disease in early infancy.

1. Introduction

Epidemic levels of pertussis have been reported recently, mainly in high-income countries where acellular vaccines are exclusively used [1–3]. Age groups particularly affected include infants and adolescents [4,5]. The resurgence of infant pertussis is of greatest concern as infants are at highest risk for severe morbidity and mortality, particularly before they begin their primary pertussis vaccination series [1,6].

Although adolescent and adult boosters [7] and "cocooning" of infant caregivers by vaccination have been attempted, these approaches have not effectively decreased infant pertussis burden [1,8]. The most promising strategy that has recently been implemented in several high- and middle-income countries has been the vaccination of women during pregnancy [9–11]. This approach boosts maternal antibodies, providing protection to both mothers

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and infants, through transplacental antibody transport and potential augmentation of breastmilk antibody [12–14].

While several studies have examined the level of maternal and cord blood pertussis antibodies and the efficiency of transplacental antibody transfer [15–27], few studies have been conducted in low-income country settings where whole cell diphtheria-tetanus-pertussis vaccine is exclusively used in infants and rates of maternal and infant malnutrition and prematurity are high [14]. Thus, we sought to determine maternal and cord blood antibody levels to four pertussis antigens, the efficiency of transplacental antibody transfer, and those factors that modify these levels.

2. Methods

2.1. Settings and population

The study was nested within a randomized controlled trial of maternal influenza vaccination during pregnancy conducted within a population of about 98,000 individuals in 9 administrative Village Development Communities in Sarlahi District, Nepal [28–30]. In brief, pregnancies were identified through a pregnancy surveillance system (women 15–40 years) where field workers visited all households at 5 week intervals and performed urine pregnancy tests. Between April 25, 2011 and September 9, 2013, 3,693 women, between 17 and 34 weeks gestation, who consented to participate, were enrolled and randomized to receive either influenza vaccine or placebo in two consecutive cohorts. A substudy of pertussis antibody prevalence was conducted in a convenience sample of women and their liveborn infants from whom blood samples were collected, starting approximately 10 months after the main trial began. Study approval was obtained from Institutional Review Boards at the Johns Hopkins Bloomberg School of Public Health, Cincinnati Children's Medical Center, Institute of Medicine at Tribhuvan University, Kathmandu, and the Nepal Health Research Council. The trial is registered at Clinicaltrials.gov (NCT01034254).

2.2. Data collection

Baseline demographic and household data were collected at enrollment. Household size was dichotomized at the median ($\leq$4 versus > 4 people). Responses to twenty-five questions were used to develop a household socioeconomic (SES) construct [31]. Results were averaged and divided into SES quartiles for analysis. Once a pregnancy was identified, women reported their literacy status (binary), number of pregnancies, and date of last menstrual period. For parity analysis, women were categorized as nulliparous or parous. Field workers identified maternal ethnicity (Pahadi or Madeshi).

Mothers were requested to collect between 2 and 5 cubic centimeters of umbilical cord blood either in the home or at the local delivery center as soon as the placenta was delivered. The woman or her representative contacted the local study team and they collected birth information, retrieved the cord blood samples, and measured infant weight. For mothers who delivered in a health facility, cord blood was collected by facility staff, who notified the study team. Maternal blood was collected approximately 1 week post-partum in the home setting. All blood was transported on ice to the central field-processing laboratory for centrifugation. Sera were removed, aliquoted into cryovials and stored in liquid nitrogen.

Gestational age was determined using date of last menstrual period recorded during pregnancy surveillance. Those infants who delivered at <37 weeks were categorized as preterm, but were not excluded from the antibody study. Birthweight was obtained at home after birth using a digital scale; those children with weights collected >72 hours after birth were excluded from the analysis. Infants were categorized as low birthweight if <2500 g. Small for gestational age (SGA) was calculated using INTERGROWTH-21 sex-specific 10th percentile cut-off standards [32].

2.3. Laboratory assays

Immunoglobulin G (IgG) anti-pertussis toxin (PT), pertactin (PRN), filamentous hemagglutinin (FHA), and fimbriae 2/3 (FIM) enzyme-linked immunosorbent assays (ELISA) were performed at Vanderbilt University School of Medicine according to previously described methods [33]. ELISA units were assigned based on the US Food and Drug Administration human reference pertussis antisera lot 3 for PT and FHA and lot 4 for PRN. An internal Vanderbilt standard was used to calibrate FIM. The lower level of quantification (LOQ) for each antigen was 10 ELISA units (EU)/mL.

2.4. Analytic dataset

Mother-infant pairs were included in the initial testing list if both delivery cord and maternal post-partum blood samples were collected (Supplemental Fig. 1). Samples with inadequate quantity of sera for analysis were excluded; this resulted in some women not having paired infant sera due to insufficient infant sera volume. Due to sample availability and funding constraints, PT and PRN testing were prioritized, resulting in different sample sizes for the different pertussis antibodies. More details on the full sample selection process may be found in Supplemental Fig. 1.

2.5. Statistical analysis

Maternal and infant antibody levels below the LOQ were assigned one-half of the assay LOQ (5 EU/mL) and geometric mean concentrations (GMC) and the percent below the LOQ were determined. Reverse cumulative distribution curves compared the distribution of log transformed antibody titers [34]. Differences in maternal pertussis antibody levels by maternal, infant, and household characteristics were compared using non-parametric testing for binary (Wilcoxon rank sum test with continuity correction) and nominal (Kruskal-Wallis rank sum test) variables. Maternal antibody titers that met or exceeded 94 EU/mL for PT were defined as recently infected [35]; PT is the only antigen seen with pertussis infection and none of the mothers had been recently immunized with pertussis containing vaccines.

The ratio of infant to maternal pertussis antibody GMC was calculated and correlated using the Spearman's rank correlation. A multivariable linear regression model was developed to examine the association of the log ratio of infant to maternal pertussis antibody levels with infant, maternal, and household characteristics. We did not use a specific p-value cut-off for inclusion and excluded some covariates that were closely associated in the final model (for example, low birth weight and SGA).

The cutoff for statistical significance in all testing was $p < .05$. Statistical analyses were conducted in R version 3.3.2 (2016-10-31) and Stata 14.2.

3. Results

305 mother and 291 infant blood samples collected between March 1, 2012 and October 30, 2013 were analyzed (Supplemental Fig. 1). The 305 maternal blood samples were collected from 4-38 days post-partum (median = 10 days). Average maternal age was 24 years compared to 23 years in the overall study population. The 291 infant cord blood samples were collected from

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