MAJOR ARTICLE

Impact of Maternal Postpartum Tetanus and Diphtheria Toxoids and Acellular Pertussis Immunization on Infant Pertussis Infection

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(See the Editorial Commentary by Libster and Edwards, on pages 85–7.)

Background. Mothers often are the source of pertussis illness in young infants. The Centers for Disease Control and Prevention recommend tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine for postpartum women before hospital discharge. In January 2008, this recommendation was implemented in a predominantly Hispanic, medically underserved population at Ben Taub General Hospital (BTGH) in Houston (hereafter the intervention population).

Methods. A cross-sectional study compared preintervention (July 2000 through December 2007) and postintervention (January 2008 through May 2009) periods. Pertussis diagnosis was determined using *International Classification of Diseases, Ninth Revision* (ICD-9) codes and microbiology reports from 4 major children's hospitals in Houston. Only those infants ≤6 months of age with laboratory-confirmed pertussis illness were included. The proportions of pertussis-infected infants born at BTGH in the pre- and postintervention periods were compared.

Results. Of 514 infants with pertussis, 378 (73.5%) were identified during preintervention and 136 (26.5%) during postintervention years. These groups were similar in age (mean, 79.3 vs 72 days; $P = .08$), sex (males, 55% vs 52%; $P = .48$), length of hospitalization (mean, 9.7 vs 10.7 days; $P = .62$), mortality (2 deaths each; $P = .29$) and hospital of pertussis diagnosis. After adjustment for age, sex, and ethnicity, the proportions of pertussis-infected infants born at BTGH and potentially protected through maternal postpartum Tdap immunization were similar for the 2 periods (6.9% vs 8.8%; odds ratio, 1.06; 95% confidence interval, 0.5–2.2; $P = .87$).

Conclusions. Immunizing only postpartum mothers with Tdap vaccine did not reduce pertussis illness in infants ≤6 months of age. Efforts should be directed at immunizing all household and key contacts of newborns with Tdap, not just mothers.

Despite high infant immunizations rates, pertussis is the only vaccine-preventable disease in the United States for which the incidence reached a nadir in the late 1970s, subsequently increased, and remains high. Although the greatest number of pertussis cases reported to the Centers for Disease Control and Prevention (CDC) annually occur in adolescents and young adults, the highest age-specific attack rate is among infants aged <6 months, in whom rates are up to 20-fold higher than in other age groups [1, 2]. The highest rate of pertussis-associated complications, hospitalizations, and deaths also occurs in young infants who have not yet completed their 3-dose pertussis immunization series at 6 months of age [2–6]. For reasons that are poorly understood, Hispanic infants have substantially higher rates of pertussis-associated complications and death than infants of other ethnicities [2, 5]. The 2010 pertussis epidemic in California, which afflicted more persons than in the previous 65 years, powerfully illustrates the vulnerability of young infants and the disparity in pertussis rates for Hispanic infants [7].

Received 30 March 2011; accepted 17 August 2011; electronically published 10 November 2011.

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Clinical Infectious Diseases 2012;54(1):78–84

DOI: 10.1093/cid/cir765

The increase in pertussis cases in the United States in the latter 20th and early 21st centuries is probably multifactorial. Increased physician awareness, improved surveillance, more accurate reporting of cases, and greater use of more sensitive diagnostic methods, such as polymerase chain reaction (PCR), each probably contributes. One important explanation for the increase in pertussis cases is waning immunity 5–8 years after children receive their final diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine dose at age 4–6 years, rendering adolescents and adults susceptible to pertussis [8–11]. Once infected, adolescents and adults become important transmitters of infection to young infants. In up to 75% of infant pertussis cases, the source of infection is another household member, who may have no or only mild pertussis symptoms. Most often the source is a mother with undiagnosed pertussis infection (an estimated 33% of cases) [12–18].

In 2006 the Advisory Committee on Immunization Practices to the CDC recommended that postpartum women and adolescent and adult household contacts of newborn infants receive immunization with tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap) before hospital discharge (''cocooning'') [8]. The aim of cocooning is to interrupt transmission to young infants before they are able to complete the primary DTaP vaccine series, with the hope of reducing their pertussis-associated morbidity and mortality. However, apart from reports from 1 birthing center, 1 neonatal intensive care unit, and some pediatric office settings, cocooning has not been widely implemented [19–21].

Computer simulation models predict a strong indirect effect of cocooning, estimating that immunizing mothers and household members could result in a 70% reduction in the incidence of pertussis in infants 0–3 months of age [22], but no studies have directly evaluated the impact of cocooning on infant pertussis illness. Moreover, no models have addressed the impact of immunizing only postpartum mothers as a single intervention. The objective of our study was to evaluate the impact of routine maternal postpartum Tdap immunization in preventing pertussis illness in infants ≤6 months of age.

METHODS

Study Design and Subjects

We performed a cross-sectional study comparing 2 time intervals: preintervention (July 2000 through December 2007) and postintervention (January 2008 through May 2009). The intervention was a routine standing order for maternal postpartum Tdap immunization at Ben Taub General Hospital (BTGH), Houston, Texas. The majority of pertussis cases in infants in Houston (and a substantial proportion of cases in infants who are not hospitalized) are diagnosed and treated in 1 of 4 Texas Medical Center hospitals: Texas Children's Hospital, Children's Memorial Hermann Hospital and 2 Harris County Hospital District Hospitals, BTGH, and Lyndon B. Johnson Hospital. We identified infants ≤6 months of age with pertussis as a primary or secondary diagnosis at 1 of these 4 hospitals using *International Classification of Diseases, Ninth Revision* (ICD-9) codes (033.0, 033.1, 033.8, 033.9, and 484.3) and hospital microbiology laboratory reports. We included only laboratory-confirmed pertussis cases in whom *Bordetella pertussis* was detected by culture, direct fluorescence assay, or PCR. PCR was performed using standard techniques to amplify the insertion sequence IS481 in *B. pertussis* (GenBank accession No., M28220). PCR testing employed the same methods and reagents from Roche Diagnostics in each of the participating hospital laboratories. The electronic medical record system was used to identify which of these pertussis-infected infants had been born at BTGH, the likely beneficiaries of the maternal postpartum Tdap vaccine intervention program. The study was approved by the institutional review boards of all participating institutions and hospitals.

Intervention

Beginning in January 2008, postpartum Tdap immunization was implemented at BTGH as a standing order [23]. Briefly, physicians and nursing personnel caring for women in the peripartum period were educated about the severity of pertussis in very young infants, the need for pertussis booster immunization (Tdap) in adolescents and adults, and the rationale behind cocooning. This was achieved through obstetrical grand rounds and multiple small group in-service sessions. Pertussis education was incorporated into childcare and breastfeeding classes. Mothers were provided with packets containing bilingual information about pertussis and Tdap vaccine. Nursing personnel and physician directors of the cocooning program were available to answer any questions that arose. All women were offered Tdap vaccine before hospital discharge unless there was a medical contraindication (history of anaphylaxis or current unstable neurological condition) or the woman had received a tetanus-containing vaccine within the previous 2 years [24, 25].

From January 2008 through May 2009, 5223 of 7782 (67%) postpartum women received Tdap. Acceptance rates of >95% were reported in women who believed themselves eligible for postpartum vaccination on direct questioning. Approximately 60% of Tdap refusals were due to Td receipt within the previous 2 years [23]. The program was supported through foundation grants from the Baylor-Methodist Community Health Fund and Harris County Hospital District Foundation (estimated cost, $106 000, not including faculty effort), and through donated Tdap vaccine from Sanofi Pasteur (estimated value, $149 065).

Data Collection

Pertussis-infected infants from each of the 4 participating hospitals were identified from 2 sources; microbiology laboratory

records reporting *B. pertussis* or *Bordetella parapertussis*, or ICD-9 codes recording pertussis or whooping cough as a primary or secondary diagnosis. The electronic medical record of each identified infant was reviewed to verify that the pertussis diagnosis was laboratory confirmed. Infants excluded from further analysis were those >6 months of age, those with a birth date outside the study periods, or those with only a *B. parapertussis* diagnosis. We recorded infant age at diagnosis, sex, ethnicity, hospital of diagnosis, hospital setting (emergency department visit vs hospitalization), length of hospitalization, and need for intensive care.

We next determined whether any of the pertussis-infected infants had been born at BTGH, using the electronic database and infant's date of birth. Pertussis-infected infants born at BTGH during the postintervention period were cross-referenced with our postpartum immunization database to determine whether their mothers had received postpartum Tdap vaccine. The proportions of infants with laboratory-confirmed pertussis who were born at BTGH in the pre- and postintervention periods were then calculated.

Sample Size Calculation

The projected indirect impact of cocooning in reducing pertussis in infants age ≤3 months is estimated to be as high as 70% if *all* household members of a newborn infant are immunized [22]. For our study we hypothesized that a 6% reduction (from 10% to 4%) in the proportion of pertussis-infected infants ≤6 months of age born at BTGH would represent an adequate impact of postpartum Tdap vaccination. The number of infants needed to measure this reduction was feasible, given that the mean annual numbers of births at BTGH during the pre- and postintervention periods were 5719 and 5416, respectively. Assuming a power of 80%, a significance level of .05 and ratio of 2:1 between the pre- and postintervention samples, we calculated that 368 and 184 infant pertussis cases were required in the pre- and postintervention periods, respectively, (STATA software, version IC10; StataCorp).

Statistical Analysis

Variables were analyzed using STATA software (version IC10). Means and medians were calculated for continuous variables. Student *t* test and Wilcoxon rank sum test were used to compare pre- and postinterventions years. A χ^2 test was used for categorical variables. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to compare the pre- and postintervention proportions of pertussis-infected infants born at BTGH. A logistic regression model that adjusted for age, sex, and Hispanic ethnicity was used to compare the proportions of pertussis-infected infants born at BTGH before and after the intervention with routine maternal Tdap postpartum immunization.

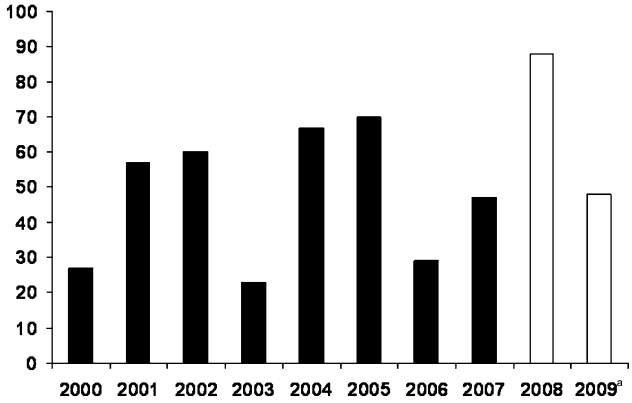

Figure 1. Numbers of pertussis-infected infants by year, in preintervention (closed bars) and postintervention (open bars) periods. [a]Through 31 May 2009.

RESULTS

During the entire study period, 664 infants ≤6 months of age had a *B. pertussis/B. parapertussis* ICD-9 code recorded as their primary or secondary diagnosis at 1 of 4 participating hospitals. After exclusion of 8 infants in whom only *B. parapertussis* was identified and infants who did not have laboratory-confirmed infection, 519 (78%) infants were eligible. Five patients were evaluated at >1 of the 4 hospitals during their pertussis illness and were counted only once. The number of pertussis-infected infants annually varied over the study period, reflecting the known temporal trends in pertussis cases (Figure 1).

Overall, 514 infants had laboratory-confirmed pertussis during the study period, 378 (73.5%) in the pre-and 136 (26.5%) in the postintervention period. Two were coinfected with *B. parapertussis*. The mean age at pertussis diagnosis for all infants was 77 days (median, 69 days; range, 14–210). Pertussis-infected infants identified during the pre- and postintervention periods were similar in age at diagnosis, sex, hospital of diagnosis, severity of illness, and outcome (Table 1). Infants ≤3 months of age, the age group in which the majority of pertussis-related deaths occur nationally, accounted for 70% (264 of 378) and 76% (103 of 136) of pertussis-infected infants in the pre- and postintervention periods, respectively (Figure 2). Infants of Hispanic ethnicity, another group overrepresented in national pertussis incidence and mortality rates, accounted for 62% (318) of infants with pertussis infections detected during the entire study period. The proportion of pertussis-infected infants of Hispanic ethnicity was higher in the postintervention than in the preintervention interval (71.3% vs 58.5%; $P = .01$).

There was a slight increase between the pre- and postintervention periods in the proportion of pertussis-infected infants born at BTGH (the intervention hospital) (Table 1). This difference was not significant when tested in a univariate model

Table 1. Characteristics of Pertussis-Infected Infants[a]

	Preintervention (n = 378)	Postintervention (n = 136)
Age at diagnosis, days		
0–62	153 (40.5)	70 (51.5)
63–123	168 (44.4)	48 (35.3)
≥124	57 (15.1)	18 (13.2)
Age, mean (range), days	79.3 (14–210)	72 (16–181)
Male sex	208 (55)	70 (52)
Race/ethnicity		
Hispanic	221 (58.4)	97 (71.3)
White	73 (19.3)	20 (14.7)
Black	64 (17)	16 (11.8)
Asian	3 (0.8)	0
Other	6 (1.6)	1 (0.7)
Unknown	11 (2.9)	2 (1.5)
Hospital of diagnosis[b]		
TCH	326 (86.2)	122 (89.7)
CMHH	31 (8.2)	7 (5.1)
BTGH	17 (4.5)	5 (3.7)
LBJH	4 (1.1)	2 (1.5)
Hospital setting		
ER visit only	102 (27)	38 (28)
Inpatient	276 (73)	98 (72)
Diagnostic test[b]		
PCR	341 (90.2)	132 (97)
Culture	32 (8.5)	3 (2.2)
DFA	5 (1.3)	1 (0.8)
Duration of hospitalization,[c] mean (range), days	9.7 (1–191)	10.7 (1–77)
Hospital floor[c]		
General	190 (69)	67 (68.4)
PICU	46 (16.8)	18 (18.4)
NICU	39 (14.2)	13 (13.2)
Deaths	2 (0.5)	2 (1.5)
Born at BTGH	26 (6.9)	12 (8.8)

Abbreviations: BTGH, Ben Taub General Hospital; CMHH, Children's Memorial Hermann Hospital; DFA, direct fluorescence assay; ER, emergency room; LBJH, Lyndon B. Johnson Hospital; NICU, neonatal intensive care unit; PCR, polymerase chain reaction; PICU, Pediatric intensive care unit; TCH, Texas Children's Hospital.

[a] Data represent No. (%) of infants, unless otherwise indicated.

[b] $P < .05$.

[c] In the pre- and postintervention periods, 275 and 98 patients were hospitalized, respectively.

($P = .45$) or when included in a logistic regression model that also accounted for age, sex, and Hispanic ethnicity ($P = .87$; OR, 1.06; 95% CI, 0.5–2.2). More pertussis-infected infants born at BTGH were Hispanic, compared with the proportion of pertussis-infected infants who were Hispanic and born at other hospitals, (89.5% vs 60%; $P < .001$), but this ethnic difference persisted during both pre- and postintervention periods. There were no differences by hospital of birth in infant demographics, age at diagnosis, length of hospitalization, or outcome. Similarly, no differences in any parameters were noted when subanalysis was performed for infants with pertussis diagnosed by means of PCR in the pre- and postintervention periods.

The mothers of the 12 pertussis-infected infants born at BTGH in the postintervention period had all received postpartum Tdap vaccine. These infants were all of Hispanic ethnicity, and 7 (58%) were <2 months of age at diagnosis (age range, 31–132 days). Nine (75%) were hospitalized (2 required intensive care), but all recovered.

DISCUSSION

This study describes, to our knowledge, the first critical evaluation of a recommended public health strategy that is specifically targeted toward preventing pertussis among infants too young

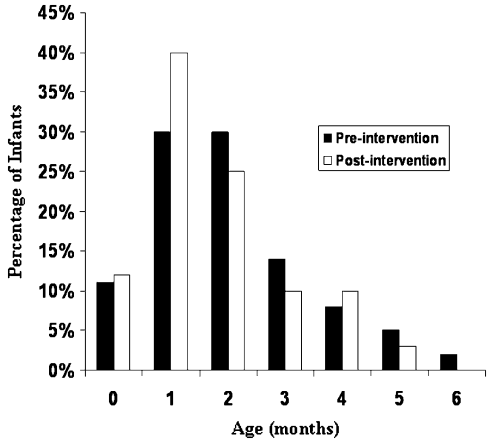

Figure 2. Pertussis-infected infants by age (in months) and intervention period.

to have completed their primary DTaP immunization series. Administration of Tdap vaccine to postpartum women theoretically is a promising new immunization platform, given how frequently mothers are the source of infant pertussis [13, 17, 26]. This recommended intervention was well accepted in a cohort of women at high risk of acquiring and transmitting pertussis to their infants, by reason of Hispanic ethnicity and medically underserved status [2, 5, 23]. It was disappointing—but not surprising, given the likelihood of contact with other pertussis-infected individuals—that we were unable to demonstrate any impact of this program on the occurrence of pertussis in infants.

Our finding has a number of plausible explanations. First, it is possible that postpartum immunization of mothers could be too late to protect newborn infants if the mother is already infected at delivery or is exposed to pertussis shortly after delivery [12, 16, 18, 27]. Pertussis-specific antibodies require ~2 weeks after Tdap administration to develop, leaving a window of opportunity for maternal infection and transmission to the infant [25]. Second, maternal postpartum immunization, though undoubtedly targeting the most important source of infant infection, is limited. Targeting only mothers creates an incomplete cocoon of protection around the infant, who is vulnerable to pertussis infection from other unimmunized and susceptible contacts within and outside of the household for several months [18, 28]. Finally, although this is not an explanation for our findings because mothers of infected infants born at BTGH *had* received Tdap, observing any minimum interval since prior tetanus-containing vaccines (no longer recommended by the CDC), or relying on personal recall of immunization history which may be inaccurate, leads to fewer mothers receiving postpartum Tdap vaccine. These factors negatively affect the ability of this strategy to reduce infant pertussis.

Although cocooning has been recommended by the CDC to prevent pertussis and influenza in young infants, it has yet to be proved effective. Several other interventions are under investigation. Neonatal vaccination has been studied in a variety of settings and using different vaccines and administration schedules [29–31], but inconsistent results preclude this approach from being recommended in the United States. Some studies demonstrated good immunogenicity after neonatal immunization with monovalent acellular pertussis vaccine, but others noted varying degrees of immune interference with response to other recommended infant vaccines [30, 32]. In one study this interference persisted through 18 months of age. Neonatal DTaP vaccine resulted in poor immunogenicity [33].

Another potential pertussis immunization strategy that has recently been recommended by the CDC is administration of Tdap vaccine during pregnancy [34]. It is theoretically possible that achieving high maternal pertussis-specific immunoglobulin G would passively protect the infant for the first few months of life. Studies immunizing pregnant women with whole-cell pertussis vaccine several decades ago demonstrated safety for mothers and infants and good transplacental pertussis-specific antibody transfer [35, 36]. Contemporary studies confirm that active placental transfer of naturally acquired pertussis-specific antibodies occurs [37–39], and the durability of such passively acquired antibody has been calculated [39]. Concerns remain that high concentrations of maternal antibodies could interfere with the infant's immune response to active immunization with DTaP vaccine. However, Englund et al [40] reported little or no interference of naturally acquired maternal pertussis-specific antibodies with the infant's immune response to active immunization with acellular pertussis vaccines. These observations make maternal immunization in the early third trimester of pregnancy a promising intervention, and further research should focus on the effectiveness of this strategy.

Our study has several limitations. First, it is possible that some pertussis infections in infants were diagnosed at a hospital other than the 4 included in our study. However, community hospitals in our area typically transfer pertussis-infected infants with moderate to severe illness to 1 of the 4 tertiary care pediatric hospitals, where intensive care is available if needed. It is also unlikely that parents changed their healthcare-seeking behavior between the pre- and postintervention periods. Second, it is possible that maternal postpartum Tdap vaccine was administered in hospitals other than BTGH and that infants born at these other hospitals were "cocooned" in a different setting, thereby limiting our ability to detect a reduction in pertussis attributable to our program. However, to our knowledge no medical facility in the Texas Medical Center or surrounding areas provided this intervention routinely during our postintervention period, and public awareness of the need for and implementation of cocooning was uncommon during the study period. Third, we included only laboratory-confirmed cases to avoid including infants with medical conditions similar to

pertussis, thereby excluding infants in whom the clinician failed to order a pertussis diagnostic test. Fourth, the most sensitive diagnostic test (PCR) was used consistently in only 1 hospital (Texas Children's Hospital) throughout the study period, but this hospital had the most confirmed cases. Fifth, although we did not detect an impact of maternal postpartum Tdap immunization in protecting young infants, the number of infants in whom confirmed pertussis developed after birth at BTGH could have been too small to detect minimal differences between the pre- and postintervention years. It is unlikely that infant immunization rates in our cohort had any impact on our observation, because the majority of infants with pertussis were <4 months of age, too young to be protected by 1 or 2 doses of DTaP. Finally, we did not reach the predicted sample size for pertussis-infected infants in the postintervention period (n = 184), because funding to provide Tdap immunizations to additional contacts of newborn infants was secured late in the intervention period, thus biasing our ability to examine the effects of immunizing only postpartum women on infant infection.

Cocooning and immunization of pregnant women with Tdap in the late second or third trimester are currently recommended strategies in the United States to protect young infants against pertussis. However, it is likely that, as happened with influenza, Tdap immunization during pregnancy will need time to become widely accepted and established as the standard of care; to date, Tdap immunization rates in adolescent and adults fall far short of those necessary to attain adequate herd immunity and significantly reduce rates of disease in infants. An incomplete cocoon lacks an adequate protective effect. Our experience, coupled with other reports [19, 20], indicates that logistical, financial, and other barriers are limiting the widespread implementation of cocooning. Ideally, pregnant women and close contacts of newborn infants should be immunized before the infant's birth. When this does not occur, targeting mothers during the postpartum period presents an invaluable opportunity for healthcare professionals to reach the entire household before the infant is discharged from the hospital, thus creating a protective barrier around vulnerable infants during the period of highest risk. Further studies are needed to assess the impact of immunizing other family members and close contacts of newborn infants in addition to postpartum women. The data gained from such studies will provide the necessary information to guide public health policy to effectively reduce infant pertussis-associated morbidity and mortality in the future.

Notes

Acknowledgments. The authors gratefully acknowledge the Baylor Methodist Community Health Fund and Children's Health Fund of the Harris County Hospital District Foundation for the funding to establish and run this program and Sanofi Pasteur for donated Tdap vaccine. We thank Kenneth Mattox MD, Harold Miller MD, Amy Young MD, Joseph Garcia-Prats MD, Lori Sielski MD, Rachelle Nurse BSN, RN, and Frances Kelly BSN, RN (Ben Taub General Hospital [BTGH]) for their assistance in establishing and ongoing support for this program; Betsy H. Mayes BSN, RN (Center for Vaccine Awareness and Research, Texas Children's Hospital, Houston), Carolyn Fairchild BSN, RN (Coordinator of Data Informatics for Women and Infants, BTGH), and Elizabeth Aguilera MD (Clinical Research Coordinator, University of Texas Health Science Center at Houston) for assistance in data collection; and Robin Schroeder (Baylor College of Medicine, Houston, Texas) for assistance in preparing the manuscript.

Financial support. This work was supported in part by foundation grants from the Baylor Methodist Community Health Fund and the Harris County Hospital District Foundation. Tdap vaccine was donated by Sanofi Pasteur.

Potential conflicts of interest. C. M. H. is the recipient of a research grant from Sanofi Pasteur and has served on an advisory board for Novartis Vaccines. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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