Maternal Pertussis Vaccination: Protecting Neonates From Infection

Laura E. Riley¹ and Richard H. Beigi²,³

¹Department of Obstetrics, Gynecology and Reproductive Biology, Massachusetts General Hospital, Harvard Medical School, Boston; and Divisions of ²Reproductive Infectious Diseases and ³Obstetric Specialties, Department of Obstetrics, Gynecology and Reproductive Sciences, Magee-Womens Hospital of the University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

Pertussis (“whooping cough”) remains endemic in the United States with disease outbreaks generally occurring every 3–5 years. There has been a steady rise in the total number of cases in the United States since historically low rates were recorded in the 1970s, making it a poorly controlled vaccine-preventable disease. In the first half of 2012, many states reported increased pertussis cases, including but not limited to the ongoing epidemic in Washington State [1]. Importantly, the overwhelming majority of pertussis-associated hospitalizations and deaths occur in infants <3 months of age [2]. This is primarily due to the inability of the neonate’s immature immune system to mount an effective response to pathogen and/or immunization challenge for a variety of infectious conditions. The Advisory Committee on Immunization Practices (ACIP) currently recommends infant pertussis immunization with diphtheria, tetanus, and pertussis vaccine (DTaP) starting at age 2 months, followed by repeat immunizations at 4, 6, 15–18 months, and 4–6 years of age. Thus, the first 3 months of an infant’s life are a uniquely susceptible period for pertussis infection.

Since 2006 the ACIP has endorsed an approach to early neonatal disease prevention known as cocooning. This strategy strives to immunize all adults (with tetanus, diphtheria, and pertussis vaccine [Tdap]) who currently have or anticipate having close contact with neonates to form a protective “cocoon” of pertussis immunity around the newborn. This approach was based in part on data suggesting that the majority (>75%) of neonatal pertussis cases were transmitted to the infant by close family members, including parents and grandparents [3]. In addition, there is recognition that immunity to pertussis after both infection and immunization wanes over time, thus providing ongoing population susceptibility. Correspondingly, the ACIP currently recommends that (1) all adolescents and adults receive the Tdap vaccine to replace the scheduled tetanus and diphtheria toxoids vaccine (Td) booster, (2) all people who have or anticipate having close contact with infants <12 months of age receive a single dose of Tdap, and (3) all immediately postpartum women who have not previously received a Tdap vaccine receive a dose prior to leaving the hospital. Despite these guidelines, cases of neonatal disease persist, largely because of challenges with implementation of effective cocooning programs.

In recognition of these real-life challenges with cocooning programs as well as ongoing cases of severe neonatal pertussis, the ACIP reconsidered this topic. In June 2011, the ACIP issued a new recommendation that all pregnant women who have not previously received a Tdap vaccine should be immunized after 20 weeks’ gestation, preferably in the third or late second trimester [4]. This recommendation was based in part on the demonstrated prevention of neonatal tetanus and influenza infection(s) via maternal immunization by passive antibody transfer to the fetus/newborn via transplacental passage of maternally derived immunoglobulin G (IgG) [5, 6]. Accordingly, maternal Tdap immunization programs have begun in earnest across the United States. Because immunity to pertussis is known to wane over time and neonatal protection is likely correlated to level of antibody present at birth through 3 months of life, much attention is focused on determining the appropriate interval for Tdap boosters in this population.

In this issue of Clinical Infectious Diseases, Healy et al provide important new data contributing to our understanding...
of the rate of decline of pertussis-specific immunity in neonates after maternal Tdap immunization [7]. The investigators prospectively enrolled a cohort of 105 predominantly Hispanic mothers who had received Tdap within 2 years of a term delivery and quantified pertussis-specific IgG in maternal–umbilical cord serum pairs. The authors compare geometric mean concentrations of pertussis-specific IgG (to 4 known pertussis antigens: pertussis toxin [PT], filamentous hemagglutinin [FHA], fimbrial protein [FIM], and pertactin [PRN]) in maternal serum and umbilical cord blood of 19 women who received Tdap during pregnancy (3 after 20 weeks’ gestation) vs 86 who received Tdap prior to the index pregnancy. The study demonstrates that infants born to mothers who were vaccinated preconception or in early pregnancy had similarly low levels of pertussis-specific IgG present in cord blood specimens at birth. They also note that active placental transport of maternally derived pertussis-specific IgG was efficient and results in higher cord blood concentrations compared with maternal serum for all 4 antibodies, as previously demonstrated by their group [8].

The investigators then perform modeling estimations based on previously published half-life values of maternally acquired PT-specific IgG and project that IgG levels rapidly decline in neonates. In fact, only 40% of infants appear to have IgG concentrations at birth that would persist to detectable levels at the lower limit of quantification (4 ELISA units/mL) by 2 months of age (time of first infant DTaP). Although not statistically significant, it appears that neonates of mothers immunized during pregnancy (especially those immunized after 20 weeks of gestation) are more likely to have quantifiable IgG levels (although low) at 2 months of age compared with those immunized prior to conception. The authors conclude that based on the rapid decline after birth and the relatively low predicted levels at 2 months of age, maternal immunization in the third trimester of each pregnancy may be necessary to provide adequate neonatal protection against pertussis infection. This is an intriguing hypothesis that warrants future study to enable more definitive conclusions.

Previous investigations have studied pertussis antibody levels in maternal serum and cord blood [8, 9]. These earlier studies have also demonstrated that pertussis antibodies appear to be actively transported across the placenta and can be detected in higher concentrations in the neonate than the mother. What the recent work by Healy et al uniquely demonstrates is the concentration of antibodies attained in the neonatal system after maternal Tdap immunization (with attention to timing of vaccination) and how rapidly these antibodies likely decline to marginally detectable levels.

The serologic correlates of protection against pertussis are currently unknown, making assessment of vaccine efficacy challenging. It is not certain that antibodies to PT, FHA, FIM, or PRN are more or less protective against disease, but it is assumed that the vaccine protects by providing antibody to the pertussis antitoxin, as well as antibody to attachment factors which are critical to preventing mucosal infection. Healy et al only model the rate of antibody decay in pertussis-specific antibody to PT; the rate of decay for antibody to other antigens is unknown. Still, this study provides the initial step in adding to our knowledge about the protective capacity of maternal Tdap for neonates. It may be that higher pertussis-specific IgG antibody levels to antitoxin and/or attachment factors are needed in neonates whose relatively naive immune systems have not been primed.

The results of this study do address much-needed biologic data concerning potential maternal immunization vaccine efficacy for neonates. Subsequent larger studies with ethnically diverse populations encompassing different gestational age timing of vaccine administration and antibody quantification in neonatal blood at 2–3 months of life are urgently needed to fill this knowledge gap. Future prospective studies will allow investigation of the possible booster effect of pertussis illness in previously vaccinated mothers. Information gathered will provide evidence to guide recommendations concerning the ideal reimmunization schedule for new and experienced mothers. Additionally, studies of disease prevalence that correlate cord blood antibody levels in neonates who are breastfed vs those who are bottlefed may address questions concerning the impact of additional breast milk–derived antibodies in providing disease protection. This investigation by Healy et al certainly underscores the need for more work on the efficacy of this vaccine in pregnancy as we strive to protect the most vulnerable population of newborns. Our current strategy involves a 2-pronged approach, first by providing protective antibodies to newborns through placental transport in the latter half of pregnancy, and second, by coothing the infant from disease by vaccinating those in closest contact. To maximize the benefits of maternal immunization, it is critically important to establish the specific vaccine schedule that will optimize transport and persistence of protective antibodies in the early neonatal period.

Note
Potential conflicts of interest. Both authors: No reported conflicts.
Both 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.

References