Infant Pertussis: Is Cocooning the Answer?

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(See the article by Halperin et al, on pages 885–92.)

Infants in North America continue to suffer and die of pertussis today, in the 21st century, despite the availability of safe and effective pertussis vaccines for >60 years (Figure 1). A notable resurgence of pertussis has occurred during the past 25 years in the United States, Canada, and other countries where vaccination coverage is high. Since the introduction and widespread use of childhood vaccines, the epidemiological characteristics of pertussis have changed; more cases now occur in adolescents and adults who are susceptible as a result of waning immunity, because protection following vaccination or natural pertussis infection is not lifelong. These older individuals become reservoirs of disease and a potential source of infection to infants too young to be immunized or protected by vaccine [1]. Currently, infants <6 months of age have the highest rate of pertussis infection (143 cases per 100,000 population), compared with the total population (6.9 cases per 100,000 population) [2]. Importantly, ≈90% of pertussis deaths occur in neonates and infants <3 months of age (Figures 2 and 3). During the 2010 California outbreak, 9120 cases of pertussis were reported, and 10 infants who acquired the disease during the first 2 months of life died. The outbreak resulted in the highest number of cases reported in California during the vaccine era, with rates similar to those seen in 1947, and the highest incidence in that state since 1958 [3] (Figure 3). Unfortunately, this situation is not unique, because similar outbreaks have been reported during the past decade throughout the United States in Texas, Michigan, Illinois, and Ohio, and pertussis activity remains high in 2011 [4, 5]. Mothers and fathers but also siblings and adult family contacts are responsible for the transmission of pertussis to young infants [6, 7]. Furthermore, casual community contacts have been estimated to account for up to 34% of cases as a source of pertussis infection in infants [8].

In the United States and Canada, the current pertussis prevention strategy consists of a complicated vaccination schedule including a primary series at 2, 4, and 6 months; boosters at 18 months, 4–6 years, and again around 12 years of age; and later adult vaccination. Immunization of adolescents and adults with a single dose of tetanus–diphtheria–acellular pertussis vaccine (Tdap) has been recommended in Canada since 2003 and in the United States since 2005 [9, 10]. Adults who are in contact with infants or other high-risk groups, such as patients, are strongly encouraged to receive Tdap to prevent transmission of pertussis to these vulnerable populations. However, Tdap vaccination coverage in adults remains low in the United States. In 2008, only 5.9% of adults had received a dose of Tdap; coverage among adults with infant contact was estimated to be 5.0%, and only 15.9% among healthcare workers [11]. As rates of infant pertussis escalate, it is clear that the recommended adolescent and adult vaccination schedules have not affected infant morbidity and mortality. Other proposed strategies to prevent infant pertussis infection include neonatal or maternal immunization, and the so-called cocooning strategy—providing indirect protection of infants who are too young to be vaccinated through immunization of household and close contacts, including postpartum women [12].

In this issue of Clinical Infectious Diseases, Halperin et al report the results of 2 well-executed studies designed to address the basic question of whether antibody responses to Tdap in women are sufficiently rapid to support the cocoon strategy [13]. This information is critical for the prevention of pertussis disease through cocooning, because 2–3-month-old infants are the peak group at risk for serious or fatal disease following exposure during the neonatal period, frequently from their own mothers [6, 7]. For postpartum vaccination of mothers to be effective in
providing indirect protection to infants by preventing maternal infection, mothers should be protected against pertussis shortly after delivery. To determine the rapidity of the immune response, Halperin et al closely followed 30 healthy women of childbearing age and 50 postpartum women after receipt of Tdap (Adacel, Sanofi Pasteur). Pre-vaccination antibody levels (IgG and IgA) to pertussis, tetanus, and diphtheria antigens were compared with levels in serum samples collected frequently after vaccination in women of childbearing age and in postpartum women. Colostrum/breast milk samples were collected from postpartum women at the same times for measurement of breast milk IgA against pertussis antigens. The investigators’ ability to carry out this unique, thorough, and labor-intensive study design is commendable. This study evaluates for the first time the kinetics of the immediate antibody response to Tdap in women and breast milk antibodies to pertussis vaccine antigens in postpartum women.

Tdap elicited an anamnestic response in previously vaccinated women of childbearing age and postpartum women. Although a correlate of immunity is not known for pertussis, a 4-fold increase in serum IgG antibody titers to pertussis antigens (PT, FHA, PRN, FIM), as well as tetanus and diphtheria, was achieved by 83.3%–100% of study participants, and although serum IgA responses to PT were not as robust in healthy women of childbearing age, a 4-fold increase in antibodies to pertussis antigens was achieved by a high percentage of women (43.6%–94.9%). Both studies clearly reveal that serum IgG and IgA antibodies are not detectable until 5–7 days after vaccination and that a maximum response is not achieved until 14 days after vaccination. This critical 2-week gap in “potential protection” is likely to allow maternal infection and exposure of infants to pertussis during a period of maximal vulnerability, reducing the ability of coooning to protect young infants. This period of risk would persist even if postpartum maternal vaccination occurred prior to hospital discharge as in accordance with current recommendations [12]. Although most women with an uncomplicated vaginal delivery are discharged within 48 hours, women undergoing Cesarean section may remain hospitalized for 3–5 days, and in complicated deliveries hospitalization may be prolonged, further delaying the time of Tdap administration. In practice, the cocoon strategy has proven to be challenging to implement as a result of a number of factors, including not only the lack of a platform for postpartum administration of vaccines in general but especially programmatic issues in administering vaccine to fathers and other family members in hospitals and pediatric offices. Complications include the cost of such programs, insurance coverage and reimbursement issues, vaccine acceptance, and the need for education of providers and patients. Given these barriers, it is not surprising that the uptake of postpartum maternal vaccination has been low in the United States and other countries, including Australia, France, Germany, and Austria, where this intervention is recommended [14].
Neonatal vaccination with pertussis-containing vaccines is not currently recommended; results from a small number of clinical trials remain controversial. Early studies of whole-cell combined pertussis vaccine (DTP) suggested that immune tolerance could result from pertussis immunization during the neonatal period [15–17]. More recent studies of distinct monovalent acellular pertussis (aP) vaccines administered at birth revealed that earlier antibody responses could be achieved in newborns [18, 19]. However, 1 study of neonatal vaccination with combined diphtheria–tetanus–acellular pertussis (DTaP) vaccine suggested that such practice could potentially result in interference with active immunization [20]. Yet, a study in Australia suggests that a dose of monovalent aP vaccine at birth and at 1 month of age followed by administration of combined aP-containing vaccine at 2, 4, and 6 months of age induces significantly higher levels of antibodies against pertussis antigens during the first 2 months of life without interference with later responses to routine active immunization [21]. It seems that a monovalent aP vaccine rather than a combined vaccine would be preferable for neonatal vaccination, but additional data on this approach are required.

Vaccination of women during pregnancy with Tdap offers numerous potential advantages over postpartum or neonatal vaccination. Pregnant women are capable of responding adequately to active immunization and can boost their own levels of antibodies to pertussis, resulting in protection against infection and disease before delivery. In addition, immunizing the mother may provide direct protection to the infant by means of the active transport of maternal antibodies across the placenta to the fetus, thus endowing the infant with protection against disease at birth [22]. Infants of vaccinated mothers are born with higher levels of pertussis-specific antibodies than their mothers [23]. Importantly, pregnant women are readily accessible to vaccination through routine prenatal care visits. The safety of maternal immunization with inactivated vaccines during the second to third trimester of gestation has been demonstrated, particularly through the use of tetanus toxoid vaccine in pregnant women worldwide over decades. Similarly, vaccination of pregnant women with inactivated influenza vaccine has been in place in the United States since 1957 and continues to be recommended as a priority in the prevention of influenza. During pertussis outbreaks, such as in California in 2010, pregnant women were offered Tdap vaccination to protect their offspring and no adverse events have been documented in mothers or infants. One concern is that of potential interference of maternal antibodies with active infant immunization; 2 clinical studies addressing maternal immunization and the infant response to active immunization are currently underway in the United States and Canada [24, 25]. Given that this theoretical concern would be unlikely to result in adverse consequences to infants and that the perceived benefits of early protection are great, the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices has now recommended that women who are pregnant and have not previously received Tdap should preferentially be vaccinated with Tdap during pregnancy [26].

The persistence of potentially protective serum antibody levels 14 days after vaccination without significant decline on day 28 reported by Halperin et al, and the presence of pertussis antigen–specific IgA in breast milk are particularly important, because these findings suggest that maternal protection and direct protection derived from maternal immunization may last long enough to protect infants until they receive their own vaccination with DTaP. It would be of interest to measure IgG to vaccine-specific antigens in breast milk, because higher concentrations of antigen-specific IgG, compared with IgA, have been detected in breast milk in other studies following maternal immunization with pneumococcal and respiratory syncytial virus vaccines [27, 28]. Both IgG and IgA may confer mucosal protection to infants who are breastfed.

Cocooning and immunization of women during pregnancy have been found to be cost-effective in reducing the incidence of infant pertussis in modeling studies [29]. However, cocooning is expensive and logistically complicated and does not directly benefit the infant, whereas maternal immunization results in reduction of disease in women and potentially better protection of infants through antibodies directly acquired from the mother. As demonstrated by Halperin et al, cocooning, even if perfectly implemented with prompt postpartum vaccination of mothers, fathers, and...
other close contacts to the newborn, may be insufficient to protect infants from pertussis, given the expected lag in the immune response of healthy adults to achieve optimally protective antibody levels after vaccination. Achieving better population immunity is necessary to control pertussis.

Focusing pertussis prevention in the youngest infants requires more publicity and education of the medical community, the general public, and vaccine-hesitant families to understand that pertussis disease can be deadly. The most effective strategy to prevent the unnecessary hospitalization and death of young children includes a combination of high coverage and on-time infant, childhood, and adolescent immunization; universal adult immunization with repeat booster vaccinations through life; targeted vaccination of all close contacts of infants starting as soon as pregnancy is confirmed; and direct protection of infants through immunization of previously unvaccinated mothers.

Note
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