HUMAN VACCINES & IMMUNOTHERAPEUTICS
2016, VOL. 12, NO. 8, 1972–1981
http://dx.doi.org/10.1080/21645515.2016.1171948

Taylor & Francis
Taylor & Francis Group

REVIEW

Pertussis vaccination in pregnancy

C. Mary Healy

Department of Pediatrics, Section of Infectious Diseases, Baylor College of Medicine, Center for Vaccine Awareness and Research, Texas Children's Hospital, Houston, TX, USA

ABSTRACT

Pertussis has had a resurgence with the highest incidence and complication rates in young infants, and deaths occurring mainly at < age 3 months. Infants are infected by older individuals whose immunity has waned. Strategies such as targeted immunization of infant caregivers have had limited success. Pertussis vaccination in pregnancy may protect infants through passive and active transfer of maternal antibodies that protect the infant until the primary immunization series. Studies show vaccinating pregnant women with acellular pertussis vaccine is safe for mother and infant, immunogenic with efficient transfer of antibodies to infants, and effective in preventing pertussis in young infants. Vaccine uptake in pregnant women is sub-optimal, but provider recommendation is the most important factor in improving vaccination rates. Studies are ongoing to determine the best timing of vaccination to protect infants, and into other strategies. Vaccinating pregnant women offers hope to prevent pertussis-related morbidity and mortality in infants worldwide.

ARTICLE HISTORY
Received 3 February 2016
Revised 10 March 2016
Accepted 24 March 2016

KEYWORDS
disease burden; maternal immunization; pertussis; safety and immunogenicity

Despite the advent of effective infant immunization programs throughout the world, pertussis, also called whooping cough, remains a significant cause of infant morbidity and mortality. The World Health Organization (WHO) estimates that approximately 50 million cases and 300,000 deaths are attributable to pertussis each year.[1] The highest burden of disease and largest number of fatal cases occur in resource-poor nations, where vaccination coverage with 3 doses of whole cell pertussis-containing vaccine in infancy is suboptimal.[1] The true burden of pertussis in these nations is likely underestimated as surveillance systems may be less robust. However, even in resource-rich nations where infant immunization rates exceed 95%, pertussis is widely acknowledged as a very poorly controlled vaccine-preventable disease.[2-5]

A resurgence of pertussis has been documented in resource-rich nations during the last 30 years and regular outbreaks are reported. The reason behind this resurgence is multifactorial. Under-diagnosis of atypical or subclinical cases in adolescents and adults who then spread the infection widely in their communities, improved detection secondary to increasing use of polymerase-chain reactions (PCR) based tests rather than the more difficult to perform culture for diagnosis, and possible variations in *Bordetella pertussis* may all contribute. Waning immunity to pertussis, acquired from natural disease or induced after vaccination, is a significant factor.[2-5] Significant waning of pertussis immunity occurs within 5 to 10 years after infection or vaccination with whole cell pertussis vaccines. Further, data from the 2010 pertussis epidemic in California demonstrate that waning of immunity occurs more rapidly after receipt of acellular pertussis vaccines compared to whole cell vaccines, rendering significant numbers of individuals susceptible to repeated infection as soon as one to 3 years after their most recent vaccine dose.[6-8]

Disease burden of pertussis

Pertussis infection, regardless of whether disease is endemic or epidemic, carries a substantial disease burden for all age groups, such as chronic cough, the associated complications (post-tussive emesis, weight loss, urinary incontinence, rib fractures etc), and time lost from education or employment. These effects, while unpleasant, are rarely life threatening, except in young infants who are the age group infected disproportionately by this illness. In resource poor countries, pertussis-associated case fatality rates as high as 4% are reported.[1] In resource rich countries infant case fatality rates are lower, but infants who are too young to have completed their primary infant immunization series with diphtheria, tetanus and acellular pertussis vaccine (DTaP), consistently have approximately a 20-fold increased incidence of pertussis infection compared with other age groups and suffer significantly higher morbidity and mortality.[9-14] For example, of pertussis-infected infants in the United States, where diphtheria, pertussis and acellular pertussis (DTaP) vaccine is given at 2, 4 and 6 months of age in the primary immunization series, approximately 2 thirds of pertussis-infected infants under one year of age will be hospitalized, 61% will have apnea, 23% will develop pneumonia, 1% will develop seizures, 0.3 % encephalopathy and 1% will die.[15] During the 2010 pertussis epidemic in California, the attack rate for pertussis in infants under 6 months of age reached 435 per 100,000 population and 10 infants died, all but one of

CONTACT C. Mary Healy, MD chealy@bcm.edu 1102 Bates St., Suite 1120, Houston, TX 77030, USA.

whom was too young to have started the DTaP series at 2 months of age.[13] This epidemiological pattern of disproportionately high incidence of infection and pertussis-associated complications in young infants is repeated in other resource-rich countries. Pertussis-associated deaths occur almost exclusively in infants less than 3 months of age, 76% in those less than 2 months of age.[16]

Control strategies

Pertussis (the 100 day cough) is characterized by 3 stages of illness, the catarrhal stage which resembles any upper respiratory infection, paroxysmal stage characterized by spasms of coughing, and the convalescent stage where coughing spasms become less frequent and less severe. Individuals become susceptible to pertussis infection multiple times during their lifetime due to waning immunity. A major difficulty in controlling pertussis is late diagnosis, particularly in adolescents and adults who often have atypical disease or are asymptomatic. Despite this atypical, non-specific illness, they are capable of transmitting infection, especially to vulnerable young infants. Antibiotic prophylaxis is of limited value since it is most effective in ameliorating disease during the catarrhal phase of infection, and most individuals are diagnosed later, or their infection may go unrecognized.[17]

The mainstay of pertussis control has been immunization, predominantly through infant and childhood immunization programs. While countries differ in their infant and childhood immunization schedules, all recommend pertussis-containing vaccine as a 2 or 3 dose primary course in infancy followed by booster dose(s) for toddlers or in later childhood. Such programs have reduced pertussis-associated morbidity and mortality by over 90%.[18] Reports of adverse events associated with whole cell pertussis vaccines, led to the development of less reactogenic acellular pertussis vaccines with comparable short term immunogenicity, and acellular pertussis vaccines have been routinely used in resource-rich countries since the 1990s and early 2000s.[19] Increased recognition of adolescent and adult pertussis infection led to the development of acellular pertussis vaccines for use in adolescents and adults (Tdap). Acellular pertussis vaccines are given in combination with tetanus and diphtheria toxoids (which contribute to their reactogenicity) and contain different numbers and concentrations of pertussis antigens, depending on the manufacturer. Acellular pertussis vaccines available in resource rich nations contain pertussis toxin (PT), filamentous hemagglutinin (FHA), and pertactin (PRN), with fimbrial proteins 2 and 3 (FIM) also being components in some. Regardless of manufacturer, adolescent and adult formulations contain lower amounts of pertussis antigen than the corresponding infant formulation.[20]

The most common source of pertussis infection in infants is typically a household contact. Most often this was mothers followed by fathers and other family members or caregivers,[21-23] however, recent studies indicate that other siblings now surpass parents as the infecting source.[24] This change in source of infant infection is likely a combination of increased circulation of pertussis in older children who received their last dose of acellular pertussis vaccine 3 to 5 y previously and in whom immunity has waned, with possible contributions from other control strategies specifically targeted to prevent infant infection.[6-8]

Targeted immunization of parents and adult caregivers of young infants, the primary sources of infant infection at the time, seemed an attractive strategy to control infant pertussis once tetanus, diphtheria and acellular pertussis booster vaccine (Tdap) was licensed. This strategy, known as "cocooning," was recommended by the Centers for Disease Control and Prevention (CDC) in the US in 2005 and focused on providing Tdap to postpartum women prior to their being discharged from hospital, and young infant caregivers ideally a minimum of 2 weeks before infant contact was anticipated, thus providing indirect protection to infants by protecting those most likely to infect them.[11,20,25] Although effectiveness data were lacking the Global Pertussis Initiative (GPI) recommended cocooning, estimating that it could have a strong indirect effect on infection and potentially reduce pertussis cases by 70% in infants under 3 months of age.[25] Despite the lack of data, the GPI considered cocooning "worthy of implementation because even protecting some infants would be considered a success." Cocooning was also recommended in some European countries and in Australia. On a practical level however, cocooning proved extremely difficult to implement on a widespread scale. In the US, single centers reported successful cocooning programs with uptake rates varying from 40% (parents in pediatric office settings) to between 70% and 95% (postpartum and family immunization programs in birthing hospitals and neonatal intensive care units),[26-30] but financial and logistical issues limited implementation of cocooning at a national level.[31] Moderate uptake rates were also reported in select programs in Europe.[32,33] However, a study in Canada noted poor cost –effectiveness for cocooning when pertussis incidence was low,[34] and outcome studies performed in the US and Australia demonstrated little or modest clinical effectiveness of cocooning.[35-37] These studies demonstrate the inherent limitations of cocooning as a stand-alone pertussis prevention strategy for infants, although it remains a recommended component of a multi-faceted approach to decrease pertussis disease burden.[38]

Rationale for pertussis immunization in pregnancy

There are reasons to be confident that maternal pertussis vaccination will effectively reduce infant pertussis infection, at least in the first few months of life when the risk of mortality and morbidity are highest.[5,39-41] First, maternal immunization offers an ideal "2-for one" strategy because it offers direct protection of the infant through the induction of maternal antibodies that can be transported across the placenta to protect the infant from birth, while also indirectly protecting the infant through preventing infection in and thus transmission from their mother.[21,24] Second, Tdap is an inactivated vaccine so there are no theoretical concerns regarding safety in pregnant women. Third, unlike influenza, pertussis is not known to increase morbidity in pregnant women (although contemporary data are lacking), therefore Tdap administration can be delayed until later in pregnancy, thereby avoiding concerns about interference with fetal development or mistaken association with pregnancy loss which is most common in the first trimester. Vaccination later in pregnancy also has the advantage

that maternal antibodies are highest when placental transport is most efficient (from approximately 34 weeks gestation).[39,41] This timing theoretically optimizes levels of maternally-derived antibodies in the newborn infant leading to more sustained protection. Fourth, unlike antibodies induced by polysaccharide antigens (IgG_2) where placental transport is less efficient, Tdap induces antibodies of the immunoglobulin G_1 subclass; these IgG_1 antibodies are both actively and passively transported across the placenta leading to increased infant levels. Fifth, because the first dose of the primary immunization series is given early in life (2 months of age in resource rich nations, 6 weeks of age in resource poor), it is likely that antibody levels need to persist for relatively short periods of time to protect against severe and fatal infant disease.

Safety of pertussis immunization in pregnancy

Numerous studies have assessed the safety and immunogenicity of acellular pertussis vaccines in infants and children, adolescents and adults.[20,31] These studies invariably demonstrated that acellular pertussis vaccines are well-tolerated with lower rates of adverse events than whole cell pertussis vaccines. Although, pregnant women were excluded from pre-licensure studies of Tdap, because it is an inactivated vaccine no theoretical safety concern existed. Further, there were extensive data on the safety of tetanus and diphtheria toxoid vaccines in pregnancy as this was the cornerstone of efforts to eliminate neonatal tetanus worldwide.[31] Post-licensure, both manufacturers of Tdap set up registries to collect information on pregnant women who received Tdap during pregnancy, either inadvertently or deliberately as part of outbreak control measures.[42-45] Available data prior to recommendations to immunize pregnant women with Tdap did not show any pattern of increased adverse events, including pregnancy loss or poor neonatal outcomes, from either registry data or small studies in pregnant women. In 2011, these data were sufficient for the US to become the first country to recommend Tdap immunization of pregnant women who had not previously received Tdap, regardless of the interval from prior tetanus-containing vaccine.[31] This was later updated to recommend Tdap during the third trimester of every pregnancy.[10] The United Kingdom recommended Tdap in pregnancy in 2012 in response to a pertussis epidemic causing many infant deaths,[46] and this policy has since been adopted by other countries.[47,48]

A number of studies have been published evaluating the safety of Tdap immunization during pregnancy since the original 2011 US recommendation. The first US phase 1–2 randomized, double-blind, placebo-controlled study recruited 48 Tdap-naïve pregnant women who received Tdap ($N = 33$) or placebo ($N = 15$) during weeks 30 to 32 gestation with crossover immunization postpartum.[49] A group of non-pregnant women also received Tdap for comparison. There were no Tdap-associated serious adverse events (SAE) in mothers or infants, and no difference in the proportion of participants reporting any injection-site reaction following Tdap immunization between pregnant, postpartum or non-pregnant women (78.8%, 80% and 78.1%, respectively, $P > 0.99$). Systemic symptoms (mostly mild and self-limited) post-vaccination were less frequent in pregnant women (36.4%) than in either postpartum (73.3%) or non-pregnant recipients (53.1%), respectively (P 0.055). A recent randomized controlled trial reported from Vietnam comparing 52 women who received Tdap with 51 receiving TT in pregnancy found that while approximately 50% of women reported an adverse event post-vaccination, these occurred in similar proportions of Tdap and TT recipients and were predominantly short lived, and no Tdap-associated SAEs occurred.[50] Donegan et al reported an observational cohort study of 20,074 pregnant women who received Tdap in the first 6 months of the UK pregnancy campaign and matched them with a historical unvaccinated cohort.[51] There was no evidence of increased risk of early or late stillbirth post Tdap in pregnancy compared with national historical rates. There was no increased risk of earlier delivery or increased risk of serious antenatal or neonatal events. In addition, although congenital malformation was not a pre-specified adverse event of interest in this study because Tdap is given in the third trimester of pregnancy after organogenesis, this outcome is monitored continuously through pharmacovigilance and no signals for increased risks were raised.

In the US, Tdap safety is monitored through the manufacturer registries and several national surveillance systems such as vaccine adverse event reporting system (VAERS), vaccine safety datalink (VSD) and clinical immunization safety assessment (CISA) project.[52] Some single center or managed care organizations have also reported their experience.[53-55] All but one report found no difference in risk of any adverse pregnancy or neonatal adverse event.[52] One single center study of more than 7,000 women actually found that the rate of preterm birth, small for gestational age and neonatal hospitalization was increased in the unvaccinated group although the small numbers of unvaccinated women in this study preclude a definitive answer that Tdap is protective for these outcomes.[54] A small but statistically significant increased risk of a recorded diagnosis of chorioamnionitis was found in a retrospective cohort study of pregnant women from 2 VSD sites between 2010 to 2012, although the magnitude of this risk was lower in those immunized during the third trimester.[56] However, it was not possible to adjust for other chorioamnionitis risk factors in the cohort and there was no increased risk of preterm birth, a major sequela of chorioamnionitis. This finding should therefore be interpreted with caution due to residual confounders and the fact that only there was only a 50% positive predictive value for having a clinical presentation consistent with chorioamnionitis in those given the diagnosis, reflecting the difficulty in reliably diagnosing chorioamnionitis. It is noteworthy that no other study has found a similar signal to date.[52]

Acellular pertussis vaccine is currently available only in combination with tetanus and diphtheria toxoids. Concerns were therefore expressed that administering Tdap soon after a previous dose of tetanus and diphtheria containing vaccine (TT or Td) would increase the rate of local and systemic reactions. This led to initial recommendations that a 2 y interval since either TT or Td be observed before giving Tdap to postpartum women.[11] This minimum interval was removed from US pertussis recommendations in 2011 and 2012,[10,31] however, concerns persisted that repeated doses of tetanus containing vaccines may lead to increased adverse events. Sukumaran et al. addressed this concern in a retrospective cohort study of

29,155 women across 7 VSD sites who received Tdap in pregnancy following a tetanus containing vaccine less than 2 (N = 4,812), 2 to 5 (N = 9,999) and more than 5 y (N = 14,344) previously.[57] No significant differences in rates of medically-attended adverse events or adverse birth outcomes (preterm delivery, low birth weight, small for gestational age) were found. It is possible that this tolerance of short tetanus vaccination intervals in pregnant women may be related to the natural immunosuppression of pregnancy, with differences in humoral and cell-mediated responses and natural killer cells that occur to protect the fetus, compared with the non-pregnant population. There was no increase in adverse events or poor birth outcomes when Tdap was given concomitantly with influenza vaccine during pregnancy.[58] Although continued surveillance is prudent, the conclusions from all the available data support the safety of Tdap immunization in pregnancy, even when repeated doses are given at short intervals.

Immune response following pertussis immunization in pregnancy

Prior to implementation, there was indirect evidence that pertussis immunization in pregnancy was likely to be immunogenic and effective. Anecdotal evidence from the pre-vaccine era when peak incidence of infant infection was older than age 2 months suggested that high levels of passively acquired maternal antibodies in infants, presumably boosted by natural infection in mothers prior to delivery, may have protected them in early life.[41] During the 1940s and 1950s small numbers of women received whole cell pertussis vaccine during the third trimester of pregnancy.[59-62] No adverse events were documented and increased antibody levels in mother and baby with enhanced *in vitro* killing of *B. pertussis* were reported. Concerns that high maternal antibody levels would suppress infant immune response to pertussis vaccines in infancy were lessened when Englund et al. demonstrated that no significant interference occurred with DTaP vaccines.[63] Further studies since 2000 demonstrated that both naturally and vaccine-induced pertussis-specific IgG in mothers was efficiently transported across the placenta, resulting in higher infant than maternal antibody levels for tested pertussis antigens.[64-68] Van Savage et al. had calculated the half-life ($t_{1/2}$) of naturally-induced maternal antibody to PT and FHA to be 36 and 40 days, respectively.[69] Serological correlates of protection from pertussis are not known. However, if it is assumed that the $t_{1/2}$ of Tdap-induced antibodies is similar to that of natural antibody, it is reasonable to expect that high maternal antibody levels in infants following immunization in pregnancy would persist at "sufficient" levels to protect infants from acquiring infection in the early months of life.

The US Phase 1–2 study demonstrated that Tdap in pregnancy was immunogenic resulting in geometric mean concentrations (GMC) of pertussis toxin (PT) antibodies in mothers and infants at delivery that were 5.6-fold (51 ELISA units [EU]/ml [95% C.I. 37.1–70.1] versus 9.1 EU/ml [95% C.I. 4.6–17.8]) and 4.9-fold (68.8 EU/ml [95% CI 52.1–90.8] vs. 14 EU/ml [95% C.I. 7.3–26.9]) greater, respectively, in women who received Tdap in pregnancy than those who received placebo ($P < 0.001$).[49] Significant, although slightly lower magnitude, differences in response to PT were seen at delivery in women receiving Tdap versus TT during pregnancy in the RCT in Vietnam, with approximately 3-fold higher concentrations in Tdap-vaccinated women ($P < 0.001$).[50] Similar findings were reported in studies from Belgium, Israel and Spain, when delivery samples from infants of 57, 61 and 132 Tdap immunized women, respectively, were tested.[70-72] The largest reported delivery cohort to date compared infant cord delivery samples from 312 pregnancies where women received Tdap during the third trimester as per CDC recommendations in the US (Tdap+) with those from 314 pregnancies where Tdap was not given (Tdap-).[73] The GMC to PT was 47.3 international units (IU)/ml (95% CI 42.1–53.15) in samples from Tdap+ pregnancies vs. 12.93 IU/ml (95% CI 11.8–14.17) in Tdap- pregnancies ($P<0.001$).

The effectiveness of a pregnancy immunization strategy in preventing infant pertussis relies on maintaining antibody levels in infants at a "protective" level through the period of highest risk of death or serious illness (age 3 months). A generally accepted serological correlate for protection against pertussis is not defined, but it is likely to be higher in infants than in older children or adults primed through natural infection or immunization. Young infants rely solely on passively acquired antibodies for protection and lack the ability to mount cell-mediated responses for recovery. Although contemporary data on the $t_{1/2}$ of Tdap-induced maternally derived antibodies are lacking, they would be expected to wane quickly as do antibodies induced following natural infection. This rapid waning was confirmed by both RCTs and by the prospective cohort study in Belgium where, although still significantly higher than in infants of mothers not immunized with Tdap or from historical unimmunized cohorts, the GMCs of PT antibodies were significantly lower (approximately 3-fold in RCTs; 6-fold in cohort study) in infants of immunized mothers prior to starting the primary immunization series compared to those at delivery.[49,50, 71] Despite this rapid waning, it is reasonable to assume that should "high" levels of antibodies be present at delivery, these will be "sufficient" for protection through the start of the primary immunization series. It is therefore reassuring that data from the larger delivery cohorts estimate that infants of approximately 2 thirds of women receiving Tdap in late pregnancy (≥20 weeks gestation [Spain]; ≥27 weeks gestation [US]) would have PT ≥ 10 IU/ml at 2 months of age.[72,73]

The need for high levels of pertussis antibodies at delivery is important because it influences recommendations on the need for repeated doses of Tdap during subsequent pregnancies and timing of immunization during pregnancy to give maximum immunological benefit to the infant. Recommendations for immunization during every pregnancy in the US were driven by continued high morbidity and mortality in infants, but also by data suggesting that immunization during one pregnancy would be unlikely to protect infants of subsequent pregnancies.[10,74] One study evaluated 105 mother-newborn infant pairs where the mother had received Tdap at a median of 13.4 months (all within 24 months) prior to the birth of the infant.[72] Most mothers had received Tdap postpartum after the birth of a prior infant but 19 received Tdap during pregnancy, 16 in early pregnancy. Although the GMC of pertussis antibodies in maternal and infant cord samples at delivery was higher

than that reported in the pre-Tdap era, it was estimated that the GMC of PT-specific IgG would be less than 5 EU/ml in infants by the time of the first DTaP dose and that only 40% of infants would have detectable antibody through age 2 months. This suggests that most infants whose mothers were immunized prior to the third trimester of pregnancy would have little immunological benefit as a consequence of maternal vaccination, although some indirect benefit likely could be expected as a consequence of preventing maternal infection and transmission to the infant (that is, through partial cocooning).

The specific timing of maternal Tdap during the third trimester of pregnancy to maximize infant antibody levels is not well-defined. Biological data suggest that 28 through 32 weeks would be optimal.[39] A single study suggests that 27 through 30 weeks may be better but this was limited by small numbers of mother-infant pairs studied.[70] Further, data on whether the gestation at immunization versus interval between immunization and delivery is more important for immunological protection of infants are lacking. These and other questions, including tailoring recommendations to protect infants at high risk of being born preterm, remain high priority for investigation.

The possibility that maternal immunization will interfere with the induction of antibodies in infants in response to their immunization series is another factor to consider. The extent and duration of immune interference when present appears to be dependent on maternal antibody and declines with postnatal age as maternal antibodies wane. This phenomenon has been observed for measles, oral poliovirus and hepatitis A vaccines.[39] There is some insight into immune responses in infants following maternal Tdap from the RCTs and prospective cohort studies. Munoz et al. (US) reported equivalent concentrations of antibodies to PT, PRN and FIM but significantly lower concentrations of antibodies to FHA at 7 months of age, after infants received DTaP at 2, 4 and 6 months, in infants of mothers immunized in pregnancy vs. postpartum.[49] However, at age 13 months after a fourth dose of DTaP, concentrations of antibodies were not statistically different. Hoang et al. (Vietnam) reported significantly lower concentrations of antibodies to PRN, but not PT or FHA after 3 doses of DTaP given at 2, 3 and 4 months; no booster dose was given.[50] Maertens et al. (Belgium), in a study where pregnant women received a Tdap vaccine with higher quantities of PT antigen than either of the RCTs, showed blunting of PT response only, after a 2, 3 and 4 month infant schedule.[71] In the UK, Ladhani et al. compared 127 infants of Tdap immunized mothers, immunized with DTaP at 2,3 and 4 months, with a historical cohort to 246 infants born to non-immunized mothers.[75] They found that only antibodies to PT rose after completion of the immunization series and antibodies to PT, FHA and FIM were all lower after the series in infants of immunized mothers.

It is difficult to interpret the significance of the variable immune interference demonstrated in these studies. First, different acellular vaccine products were used in the studies (for both mothers and infants) possibly resulting in different antibody responses in infants. Second, the degree of interference may be affected by different infant vaccination schedules with possibly accelerated infant schedules resulting in more immune interference. Third, it is unclear if the degree of interference seen in any of the studies is likely to have any clinical significance, especially if booster doses are given in the second year of life.[76] In summary, critical evaluation of the immunological data available to date suggests that inducing high antibodies in infants at birth to sustain them through the critical first months of life is of greater benefit in preventing infant pertussis-associated mortality than possible mild interference with infant immune response that may be overcome by giving a booster dose after age 12 months.[76]

Effectiveness of maternal immunization in preventing infant disease

The best evidence that maternal pertussis immunization will protect very young infants comes from observational and case-control studies performed in the UK.[77,78] In September 2012 the UK responded to a resurgence of pertussis during the previous 2 y with accompanying pertussis-attributable deaths in very young infants, by recommending pertussis immunization for pregnant women at weeks 28 to 38 gestation. After introduction, vaccine uptake in pregnant women was high, peaking at 78% and then leveling out at approximately 60%. Amirthalingam et al. analyzed laboratory confirmed pertussis cases and hospital admissions for pertussis in infants between January 2008 through September 2013.[77] Vaccine effectiveness was calculated by comparing vaccination status for mothers in confirmed cases of pertussis with estimates of vaccine coverage in pregnant women in England. One month after the introduction of maternal immunization, the monthly total of confirmed cases peaked and then fell in all age groups. There was a decrease of 78% (95% CI 72% to 93%) in confirmed pertussis cases and 68% (95% CI 61% to 74%) in pertussis-associated hospitalizations in infants aged less than 3 months between 2012 and 2013, the only age group in whom fewer cases were seen in 2013. There were 3 infant pertussis-related deaths in 2013, all in infants of unvaccinated mothers, compared to 14 in 2012 all of which occurred prior to the introduction of maternal immunization. Vaccine effectiveness was 91% (95% CI 84% to 95%) in preventing pertussis in infants less than age 3 months if mother was vaccinated at least 7 d before infant delivery. Similar results were found in a case control study of pertussis infected infants in England and Wales.[78] These studies, coupled with emerging immunological data, strongly support maternal immunization as a strategy to prevent severe disease in young infants although ongoing studies of effectiveness are necessary.

Implementation of maternal immunization

There are many challenges in implementing a successful maternal immunization program, even when the strategy has proven safety and efficacy. Maternal immunization programs against influenza in the US for example, had been recommended for many decades, yet uptake prior to the H1N1 influenza pandemic in 2009 was 15%.[39] This increased to approximately 50% after the pandemic, but has since shown minimal improvement since then.[16] The same is true of pertussis immunization which although slowly increasing had estimated national uptake less than 20%.[79] There a number of barriers to be overcome. First, although maternal immunization is an established strategy in

many resource-poor nations through efforts to eliminate maternal and neonatal tetanus, it is a relatively new concept in resource-rich countries. Second, the target population is healthy adults who may be unaware of the need for immunizations throughout their lifetime. Third, there is a perceived reluctance of pregnant women to take any medications, including vaccines, during pregnancy. Fourth, there is concern that adverse events may be erroneously associated with vaccination, a particular concern given the natural rate of pregnancy loss. Fifth, obstetrical care providers have not previously been vaccinators. Finally, there are substantial logistical and financial barriers.

The responsibility for educating and informing pregnant women about recommendations for vaccination in pregnancy has not been left to providers alone. National immunization bodies, professional and not-for-profit organizations have a prominent role in raising awareness about the danger of pertussis in infants and the recommendations to immunize pregnant women for the general public, and pregnant women in particular.[80-82] This is particularly important given the increasing use of online resources. Many organizations have developed online information that may be downloaded, are exploring using social media platforms as education tools, or are developing smartphone applications that send out reminders, to improve vaccine uptake. Such organizations, coupled with print resources such as magazines specializing in pregnancy and childbirth, are valuable resources in raising awareness.

Receiving a strong provider recommendation, however, is the single most important factor in a pregnant woman's ultimate vaccination decision. Studies show that 78% to 93% of pregnant or postpartum women say they would receive a vaccine recommended by their provider, regardless of influence from other sources such as family, friends or online resources.[83-89] Numerous studies have evaluated the attitudes of pregnant and postpartum women toward maternal immunization. Although some cultural differences exist, themes are emerging. Maternal attitudes are remarkably consistent; their primary concern is that the vaccine is safe both for them and their baby, and they desire sufficient discussion with their provider to explain the rationale behind immunization.[83,84, 86-89] The benefits of and likely acceptance by pregnant women of pertussis vaccination has resulted in strong statements in support from organizations such as the American College of Obstetricians and Gynecologists, along with resources such as the Tdap toolkit, which provides literature and talking points for providers.[90,91] While these interventions have not as yet been translated into robust uptake rates, at least at a national level in the US, they address some of the provider level barriers.

Logistical and financial barriers also need to be considered when developing a maternal immunization program. In the US, pregnant women whose providers stock and administer influenza vaccine on site are up to 5 times more likely to receive it than other pregnant women.[16] This has also been shown in reports from hospital–based clinics and managed care organizations in the US, where Tdap uptake rates of 61% to 95% have been attained.[92-94] These reports describe the use of proven effective strategies such as provider education initiatives, standing order protocols and best practice alerts in electronic medical records to attain these rates, but these settings benefit from being part of large organizations with more resources in terms of ordering and storing vaccines compared to smaller, standalone practices. The latter may require different strategies to provide immunizations for their patients, such as partnering with local pharmacies to administer vaccine to their patients. Familiarity with the practical aspects of vaccination also may explain some of the disparity between the national uptake of maternal pertussis immunization in the US compared to the UK, even though this strategy was recommended a year earlier in the US. In the UK, pregnant women receive care predominantly from community-based general practitioners who work in cooperation with hospital-based obstetricians. The former, who also function as primary care providers for children, are not only more personally aware of the consequences of pertussis in young infants, but also routinely vaccinate against other diseases on-site. This ability to stock, store, and administer vaccines, may be an unfamiliar paradigm to obstetrical providers in other countries or with different models of healthcare delivery, such as the US. Providers and public health officials need to therefore be aware of the challenges and resources available in their particular country or region and plan accordingly to best protect mother and infants.

Other strategies

Cocooning is recommended in the US in addition to immunization in pregnancy. Quinn et al. demonstrated a modest decrease (51%) in the risk of pertussis in infants 4 months of age or younger if both parents were immunized a minimum of 4 weeks prior to illness onset in the infant; to date this is the only study to demonstrate effectiveness.[37] While potentially a tool to reduce the reservoir of infection in infant contacts, cocooning is difficult to implement and not particularly cost effective, thus it is probably best viewed as an important adjunct strategy to maternal immunization. However, cocooning remains the only potential protection for infants born preterm, infants over 3 months of age or infants whose mothers were not offered, declined, or did not respond to Tdap in pregnancy.

Neonatal immunization is another strategy under investigation and studies to date have shown variable and sometimes conflicting results. Studies in Italy, Germany and Australia demonstrated that giving a monovalent aP vaccine at birth, or at birth and one month of age led to increases of pertussis antibodies during and after the primary infant series.[95-97] Halasa et al. showed lower pertussis responses after the primary series in infants given an additional dose of DTaP at birth.[98] There was also evidence of interference to a variable degree with infant response to *Haemophilus influenza type b* (Hib), hepatitis B (HBV) and diphtheria vaccines in 3 of the 4 studies, and in one cohort this interference appeared to persist 4 y later.[96-99] More recently, Wood et al. compared 221 infants who received aP within 5 d of birth with 219 infants who did not; all infants subsequently received a hexavalent DTaP-Hib-HBV-inactivated polio vaccine at 6 weeks, 4 and 6 months.[100] Monovalent aP vaccine at birth induced significantly higher antibodies against PT and PRN by 10 weeks of age without reducing subsequent pertussis antibody responses to routine primary immunization; response to other antibodies was not reported.

Although concerns about the acceptability of adding another dose to the infant schedule and potential immune interference will need to be addressed, and neonatal immunization will not protect an infant from the time of birth, these data suggest that neonatal immunization is worthy of study as another strategy to prevent pertussis,

Conclusions

Pertussis remains a serious public health problem and an extremely serious life-threatening problem for young infants who become infected. Currently available vaccines do not give life-long immunity and acellular pertussis vaccines used in resource-rich countries have less durable immunity than previously thought. There is likely no single paradigm to effectively control pertussis, which will likely require a combination of efforts. Pertussis vaccination in pregnancy offers the best opportunity to prevent pertussis-related deaths in young infants. This approach has proven safety, immunogenicity and effectiveness in preventing pertussis in young infants in countries where acellular pertussis vaccines are used, although questions remain as to the optimal gestation to administer vaccine and whether observed immune interference in infants has any clinical significance. While research continues to answer these questions, and to determine the value and effectiveness of adjunct strategies, it is imperative that efforts are made to optimize uptake of pertussis vaccine by pregnant women. This requires continued efforts to educate providers and pregnant women, and novel thinking to help obstetrical care providers overcome logistical and financial barriers to vaccination. Examples include adopting strategies that have successfully impacted vaccination rates in pregnant women and other populations such as standing order protocols, automatic prompts and "hard stops" in electronic medical records, or partnering with pharmacies to administer vaccines. Above all, it requires a strong recommendation in favor of vaccination by obstetrical care providers. It is only through these efforts and the development of robust maternal immunization programs, that infant pertussis-related deaths will be eradicated.

Disclosure of potential conflicts of interest

The author reported no conflicts of interest.

Funding

Dr. Healy has received research grants from Sanofi Pasteur and Novartis Vaccines and has served on an Advisory Board for Novartis Vaccines and Pfizer Inc.

References

[1] World Health Organization. WHO-recommended surveillance standard of pertussis. Available at: http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/pertussis_standards/en/. Accessed January 31, 2016.

[2] Cherry JD. Epidemic pertussis in 2012–the resurgence of a vaccine-preventable disease. N Engl J Med 2012; 367:785-7; PMID:22894554; http://dx.doi.org/10.1056/NEJMp1209051

[3] Chiappini E, Stival A, Galli L, de Martino M. Pertussis re-emergence in the post-vaccination era. BMC Infect Dis 2013; 13:151; PMID:23530907; http://dx.doi.org/10.1186/1471-2334-13-151

[4] Guiso N, Wirsing von Konig CH, Forsyth K, Tan T, Plotkin SA. The Global Pertussis Initiative: report from a round table meeting to discuss the epidemiology and detection of pertussis, Paris, France, 11–12 January 2010. Vaccine 2011; 29:1115-21; PMID:21168525; http://dx.doi.org/10.1016/j.vaccine.2010.12.010

[5] Mooi FR, de Greeff SC. The case for maternal vaccination against pertussis. Lancet Infect Dis 2007; 7:614-24; PMID:17537674; http://dx.doi.org/10.1016/S1473-3099(07)70113-5

[6] Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med 2012; 367:1012-9; PMID:22970945; http://dx.doi.org/10.1056/NEJMoa1200850

[7] Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med 2012; 367:1012–9; PMID:22970945; http://dx.doi: 10.1056/NEJMoa1200850

[8] Misegades LK, Winter K, Harriman K, Talarico J, Messonnier NE, Clark TA, Martin SW. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. JAMA 2012; 308:2126-32; PMID:23188029; http://dx.doi.org/10.1001/jama.2012.14939

[9] Centers for Disease Control and Prevention. Pertussis–United States, 1997–2000. MMWR 2002; 51:73-6; PMID:11837909

[10] Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women–Advisory Committee on Immunization Practices (ACIP), 2012. MMWR 2013; 62:131-5; PMID:23425962

[11] Murphy TV, Slade BA, Broder KR, Kretsinger K, Tiwari T, Joyce PM, Iskander JK, Brown K, Moran JS; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). Prevention of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2008; 57:1-51; PMID:18509304

[12] Vitek CR, Pascual FB, Baughman AL, Murphy TV. Increase in deaths from pertussis among young infants in the United States in the 1990s. Pediatr Infect Dis J 2003; 22:628-34; PMID:12867839

[13] Winter K, Harriman K, Zipprich J, Schechter R, Talarico J, Watt J, Chavez G. California pertussis epidemic, 2010. J Pediatr 2012; 161:1091-6; PMID:22819634; http://dx.doi.org/10.1016/j.jpeds.2012.05.041

[14] Tanaka M, Vitek CR, Pascual FB, Bisgard KM, Tate JE, Murphy TV. Trends in pertussis among infants in the United States, 1980–1999. JAMA 2003; 290:2968-75; PMID:14665658; http://dx.doi.org/10.1001/jama.290.22.2968

[15] Centers for Disease Control and Prevention. Pertussis (whooping cough): Clinical Complications. Available at http://www.cdc.gov/pertussis/clinical/complications.html. Accessed January 31, 2016

[16] The National Vaccine Advisory Committee: reducing patient and provider barriers to maternal immunizations: approved by the National Vaccine Advisory Committee on June 11, 2014. Public Health Reports 2015; 130:10-42; PMID:25552752

[17] American Academy of Pediatrics. Pertussis. In: Kimberlin DW, Brady M, Jackson M, Long SS, eds. Red Book:2015 Report of the Committee on Infectious Diseases 29th Ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2015:608-621

[18] Roush SW, Murphy TV, Vaccine-Preventable Disease Table Working Group. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. JAMA 2007; 298:2155-63; PMID:18000199; http://dx.doi.org/10.1001/jama.298.18.2155

[19] Decker MD, Edwards KM, Steinhoff MC, Rennels MB, Pichichero ME, Englund JA, Anderson EL, Deloria MA, Reed GF. Comparison of 13 acellular pertussis vaccines: adverse reactions. Pediatrics 1995; 96:557-66; PMID:7659476

[20] Kretsinger K, Broder KR, Cortese MM, Joyce MP, Ortega-Sanchez I, Lee GM, Tiwari T, Cohn AC, Slade BA, Iskander JK, et al. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. MMWR 2006; 55:1-37; PMID:17167397

[21] Bisgard KM, Pascual FB, Ehresmann KR, Miller CA, Cianfrini C, Jennings CE, Rebmann CA, Gabel J, Schauer SL, Lett SM. Infant pertussis: who was the source? Pediatr Infect Dis J 2004; 23:985-9; PMID:15545851; http://dx.doi.org/10.1097/01.inf.0000145263.37198.2b

[22] de Greeff SC, de Melker HE, Westerhof A, Schellekens JF, Mooi FR, van Boven M. Estimation of household transmission rates of pertussis and the effect of cocooning vaccination strategies on infant pertussis. Epidemiology 2012; 23:852-60; PMID:23018969; http://dx.doi.org/10.1097/EDE.0b013e31826c2b9e

[23] Wiley KE, Zuo Y, Macartney KK, McIntyre PB. Sources of pertussis infection in young infants: a review of key evidence informing targeting of the cocoon strategy. Vaccine 2013; 31:618-25; PMID:23200883; http://dx.doi.org/10.1016/j.vaccine.2012.11.052

[24] Skoff TH, Kenyon C, Cocoros N, Liko J, Miller L, Kudish K, Baumbach J, Zansky S, Faulkner A, Martin SW. Sources of Infant Pertussis Infection in the United States. Pediatrics 2015; 136:635-41; PMID:26347437; http://dx.doi.org/10.1542/peds.2015-1120

[25] Forsyth KD, Wirsing von Konig CH, Tan T, Caro J, Plotkin S. Prevention of pertussis: recommendations derived from the second Global Pertussis Initiative roundtable meeting. Vaccine 2007; 25:2634-42; PMID:17280745; http://dx.doi.org/10.1016/j.vaccine.2006.12.017

[26] Dylag AM, Shah SI. Administration of tetanus, diphtheria, and acellular pertussis vaccine to parents of high-risk infants in the neonatal intensive care unit. Pediatrics 2008; 122:e550-5; PMID:18762489; http://dx.doi.org/10.1542/peds.2008-0813

[27] Healy CM, Rench MA, Baker CJ. Implementation of cocooning against pertussis in a high-risk population. Clin Infect Dis 2011; 52:157-62; PMID:21288837; http://dx.doi.org/10.1093/cid/ciq001

[28] Healy CM, Rench MA, Castagnini LA, Baker CJ. Pertussis immunization in a high-risk postpartum population. Vaccine 2009; 27:5599-602; PMID:19647062; http://dx.doi.org/10.1016/j.vaccine.2009.07.030

[29] Tan TQ, Gerbie MV. Pertussis and patient safety: implementing Tdap vaccine recommendations in hospitals. Jt Comm J Qual Patient Saf 2010; 36:173-8; PMID:20402374

[30] Walter EB, Allred N, Rowe-West B, Chmielewski K, Kretsinger K, Dolor RJ. Cocooning infants: Tdap immunization for new parents in the pediatric office. Acad Pediatr 2009; 9:344-7; PMID:19596219; http://dx.doi.org/10.1016/j.acap.2009.05.027

[31] Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine from the Advisory Committee on Immunization Practices, 2010. MMWR 2011; 60:13-5; PMID:21228763

[32] Durand C, Flament E. Pertussis vaccination for parents: proposal and evaluation of two professional practices in a maternity hospital. Arch Pediatr 2011; 18:362-9; PMID:21353770; http://dx.doi.org/10.1016/j.arcped.2011.01.013

[33] Simonetti A, Martini I, Bonomo G, D'Avino R, Puggina P, Vairo U, Piscopo P, Marchetti F. Improving adherence rates to a cocooning program: a pilot experience in Italy. Hum Vaccin Immunother 2013; 9:1142-5; PMID:23370334; http://dx.doi.org/10.4161/hv.23795

[34] Skowronski DM, Janjua NZ, Tsafack EP, Ouakki M, Hoang L, De Serres G. The number needed to vaccinate to prevent infant pertussis hospitalization and death through parent cocoon immunization. Clin Infect Dis 2012; 54:318-27; PMID:22156850; http://dx.doi.org/10.1093/cid/cir836

[35] Castagnini LA, Healy CM, Rench MA, Wootton SH, Munoz FM, Baker CJ. Impact of maternal postpartum tetanus and diphtheria toxoids and acellular pertussis immunization on infant pertussis infection. Clin Infect Dis 2012; 54:78-84; PMID:22075790; http://dx.doi.org/10.1093/cid/cir765

[36] Healy CM, Rench MA, Wootton SH, Castagnini LA. Evaluation of the impact of a pertussis cocooning program on infant pertussis infection. Pediatr Infect Dis J 2015; 34:22-6; PMID:24992123; http://dx.doi.org/10.1097/INF.0000000000000486

[37] Quinn HE, Snelling TL, Habig A, Chiu C, Spokes PJ, McIntyre PB. Parental Tdap boosters and infant pertussis: a case-control study. Pediatrics 2014; 134:713-20; PMID:25225136; http://dx.doi.org/10.1542/peds.2014-1105

[38] Healy CM, Baker CJ. Infant pertussis: what to do next? Clin Infect Dis 2012; 54:328-30; PMID:22156848; http://dx.doi.org/10.1093/cid/cir846

[39] Healy CM. Vaccines in pregnant women and research initiatives. Clin Obstet Gynecol 2012; 55:474-86; PMID:22510631; http://dx.doi.org/10.1097/GRF.0b013e31824f3acb

[40] Healy CM, Baker CJ. Maternal immunization. Pediatr Infect Dis J 2007; 26:945-8; PMID:17901801; http://dx.doi.org/10.1097/INF.0b013e318156c18c

[41] Van Rie A, Wendelboe AM, Englund JA. Role of maternal pertussis antibodies in infants. Pediatr Infect Dis J 2005; 24:S62-5; PMID:15876928; http://dx.doi.org/10.1097/01.inf.0000160915.93979.8f

[42] Moro PL. Enhanced surveillance of Tdap safety in pregnancy in the vaccine adverse events reporting system (VAERS). Presented ACIP Feb Meet 2014. Available at http:http://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-2014-02.pdf.

[43] Pichichero ME, Rennels MB, Edwards KM, Blatter MM, Marshall GS, Bologa M, Wang E, Mills E. Combined tetanus, diphtheria, and 5-component pertussis vaccine for use in adolescents and adults. JAMA 2005; 293:3003-11; PMID:15933223; http://dx.doi.org/10.1001/jama.293.24.3003

[44] Talbot EA, Brown KH, Kirkland KB, Baughman AL, Halperin SA, Broder KR. The safety of immunizing with tetanus-diphtheria-acellular pertussis vaccine (Tdap) less than 2 years following previous tetanus vaccination: Experience during a mass vaccination campaign of healthcare personnel during a respiratory illness outbreak. Vaccine 2010; 28:8001-7; PMID:20875487; http://dx.doi.org/10.1016/j.vaccine.2010.09.034

[45] Wang MKA, Mahmood A, Dickinson N. Pregnant women receiving tetanus, diphtheria-acellular pertussis (Tdap(vaccine: 6 years of Adacel vaccine pregnancy registry data. Pharmacoepidemiol Drug Saf 2011; 20:S1-364; PMID:21837638; http://dx.doi.org/10.1002/pds.2161

[46] Vaccine Knowledge Project. Vaccine in Pregnant: Pertussis (whooping cough). Available at http://www.ovg.ox.ac.uk/pertussis-vaccine-in-pregnancy. Accessed January 31, 2016

[47] Immunisation Advisory Centre. The University of Auckland. Available at: http://www.immune.org.nz/sites/default/files/resources/ProgrammePregnancyImac20150228V01Final_0.pdf (accessed 31 January 2016)

[48] Superior Health Council Belgium. Pertussis Vaccination. Update 2013. Available at http://www.health.belgium.be/filestore/13036470_FR/vaccination%20contre%20coqueluche%20%2030082013.pdf. Accessed January 31, 2016

[49] Munoz FM, Bond NH, Maccato M, Pinell P, Hammill HA, Swamy GK, Walter EB, Jackson LA, Englund JA, Edwards MS, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. JAMA 2014; 311:1760-9; PMID:24794369; http://dx.doi.org/10.1001/jama.2014.3633

[50] Hoang HT, Leuridan E, Maertens K, Nguyen TD, Hens N, Vu NH, Caboré RN, Duong HT, Huygen K, Van Damme P, et al. Pertussis vaccination during pregnancy in Vietnam: Results of a randomized controlled trial. Vaccine 2016; 34:151-9; PMID:26529073; http://dx.doi.org/10.1016/j.vaccine.2015.10.098

[51] Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. BMJ 2014; 349:g4219; PMID:25015137; http://dx.doi.org/10.1136/bmj.g4219

[52] Moro PL, McNeil MM, Sukumaran L, Broder KR. The Centers for Disease Control and Prevention's public health response to monitoring Tdap safety in pregnant women in the United States. Hum

Vaccin Immunother 2015; 11:2872-9; PMID:26378718; http://dx.doi.org/10.1080/21645515.2015.1072664

[53] Kharbanda EO, Vazquez-Benitez G, Lipkind HS, Klein NP, Cheetham TC, Naleway A, Omer SB, Hambidge SJ, Lee GM, Jackson ML, et al. Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. JAMA 2014; 312:1897-904; PMID:25387187; http://dx.doi.org/10.1001/jama.2014.14825

[54] Morgan JL, Baggari SR, McIntire DD, Sheffield JS. Pregnancy outcomes after antepartum tetanus, diphtheria, and acellular pertussis vaccination. Obstet Gynecol 2015; 125:1433-8; PMID:26000515; http://dx.doi.org/10.1097/AOG.0000000000000862

[55] Shakib JH, Korgenski K, Sheng X, Varner MW, Pavia AT, Byington CL. Tetanus, diphtheria, acellular pertussis vaccine during pregnancy: pregnancy and infant health outcomes. J Pediatr 2013; 163:1422-6-e1-4; PMID:23896191; http://dx.doi.org/10.1016/j.jpeds.2013.06.021

[56] Kharbanda EO, Vazquez-Benitez G, Lipkind H, Naleway AL, Klein NP, Cheetham TC, Hambidge SJ, Vellozzi C, Nordin JD. Receipt of pertussis vaccine during pregnancy across 7 Vaccine Safety Datalink sites. Prev Med 2014; 67:316-9; PMID:24952094; http://dx.doi.org/10.1016/j.ypmed.2014.05.025

[57] Sukumaran L, McCarthy NL, Kharbanda EO, McNeil MM, Naleway AL, Klein NP, Jackson ML, Hambidge SJ, Lugg MM, Li R, et al. Association of Tdap Vaccination With Acute Events and Adverse Birth Outcomes Among Pregnant Women With Prior Tetanus-Containing Immunizations. JAMA 2015; 314:1581-7; PMID:26501534; http://dx.doi.org/10.1001/jama.2015.12790

[58] Sukumaran L, McCarthy NL, Kharbanda EO, Weintraub ES, Vazquez-Benitez G, McNeil MM, Li R, Klein NP, Hambidge SJ, Naleway AL, et al. Safety of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis and Influenza Vaccinations in Pregnancy. Obstet Gynecol 2015; 126:1069-74; PMID:26444109; http://dx.doi.org/10.1097/AOG.0000000000001066

[59] Cohen P, Scandron SJ. Placental transmission of protective antibodies against whooping cough by inoculation of the pregnant mother. JAMA 1943; 121:656-662; http://dx.doi.org/10.1001/jama.1943.02840090026008

[60] Mishulow L, Leifer L, Sherwood C, Schlesinger AL, Berkey SR. Pertussis antibodies in pregnant women: protective, agglutinating, and complement-fixing antibodies before and after vaccination. Am J Dis Child 1942; 64:608-617; http://dx.doi.org/10.1001/archpedi.1942.02010100034003

[61] Lichty JR, Slavin B, Bradford WL. Attempt to increase resistance to pertussis in newborn infants by immunizing their mothers during pregnancy. J Clin Invest 1938; 17:613-621; PMID:16694606; http://dx.doi.org/10.1172/JCI100987

[62] Kendrick P, Thompson M, Elderling G. Immunity response of mothers and babies to injections of pertussis vaccine during pregnancy. Am J Dis Child 1945; 70:25-28

[63] Englund JA, Anderson EL, Reed GF, Decker MD, Edwards KM, Pichichero ME, Steinhoff MC, Rennels MB, Deforest A, Meade BD. The effect of maternal antibody on the serologic response and the incidence of adverse reactions after primary immunization with acellular and whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids. Pediatrics 1995; 96:580-4; PMID:7659480

[64] Shakib JH, Ralston S, Raissy HH, Stoddard GJ, Edwards KM, Byington CL. Pertussis antibodies in postpartum women and their newborns. J Perinatol 2010; 30:93-7; PMID:19812588; http://dx.doi.org/10.1038/jp.2009.138

[65] Healy CM, Munoz FM, Rench MA, Halasa NB, Edwards KM, Baker CJ. Prevalence of pertussis antibodies in maternal delivery, cord, and infant serum. J Infect Dis 2004; 190:335-40; PMID:15216470; http://dx.doi.org/10.1086/421033

[66] Healy CM, Rench MA, Edwards KM, Baker CJ. Pertussis serostatus among neonates born to Hispanic women. Clin Infect Dis 2006; 42:1439-42; PMID:16619157; http://dx.doi.org/10.1086/503567

[67] Gall SA, Myers J, Pichichero M. Maternal immunization with tetanus-diphtheria-pertussis vaccine: effect on maternal and neonatal serum antibody levels. Am J Obstet Gynecol 2011; 204:334e1-5; PMID:21272845; http://dx.doi.org/10.1016/j.ajog.2010.11.024

[68] Gonik B, Puder KS, Gonik N, Kruger M. Seroprevalence of Bordetella pertussis antibodies in mothers and their newborn infants. Infect Dis Obstet Gynecol 2005; 13:59-61; PMID:16011994; http://dx.doi.org/10.1080/10647440500068289

[69] Van Savage J, Decker MD, Edwards KM, Sell SH, Karzon DT. Natural history of pertussis antibody in the infant and effect on vaccine response. J Infect Dis 1990; 161:487-92; PMID:2313127; http://dx.doi.org/10.1093/infdis/161.3.487

[70] Abu Raya B, Srugo I, Kessel A, Peterman M, Bader D, Gonen R, Bamberger E. The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels - a prospective study. Vaccine 2014; 32:5787-93; PMID:25173476; http://dx.doi.org/10.1016/j.vaccine.2014.08.038

[71] Maertens K, Cabore RN, Huygen K, Hens N, Van Damme P, Leuridan E. Pertussis vaccination during pregnancy in Belgium: Results of a prospective controlled cohort study. Vaccine 2016; 34:142-50; PMID:26592142; http://dx.doi.org/10.1016/j.vaccine.2015.10.100

[72] Vilajeliu A, Gonce A, Lopez M, Costa J, Rocamora L, Rios J, Teixidó I, Bayas JM, PERTU Working Group. Combined tetanus-diphtheria and pertussis vaccine during pregnancy: transfer of maternal pertussis antibodies to the newborn. Vaccine 2015; 33:1056-62; PMID:25573035; http://dx.doi.org/10.1016/j.vaccine.2014.12.062

[73] Healy CM, Swaim LS, Rench MA, Harrison M, Martin M, Baker CJ. Third-Trimester Tdap Immunization Elicits Substantial Pertussis Toxin Immunoglobulin G in Neonates. Open Forum Infect Dis (Fall 2015) 2 (suppl 1): S517

[74] Healy CM, Rench MA, Baker CJ. Importance of timing of maternal combined tetanus, diphtheria, and acellular pertussis (Tdap) immunization and protection of young infants. Clin Infect Dis 2013; 56:539-44; PMID:23097585; http://dx.doi.org/10.1093/cid/cis923

[75] Ladhani SN, Andrews NJ, Southern J, Jones CE, Amirthalingam G, Waight PA, England A, Matheson M, Bai X, Findlow H, et al. Antibody Responses After Primary Immunization in Infants Born to Women Receiving a Pertussis-containing Vaccine During Pregnancy: Single Arm Observational Study With a Historical Comparator. Clin Infect Dis 2015; 61:1637-44; PMID:26374816; http://dx.doi.org/10.1093/cid/civ695

[76] Cherry JD. Editorial Commentary: The Effect of Tdap Vaccination of Pregnant Women on the Subsequent Antibody Responses of Their Infants. Clin Infect Dis 2015; 61:1645-7; PMID:26374815

[77] Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, Fry NK, Miller E, Ramsay M. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet 2014; 384:1521-8; PMID:25037990; http://dx.doi.org/10.1016/S0140-6736(14)60686-3

[78] Dabrera G, Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Fry NK, Ramsay M. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012–2013. Clin Infect Dis 2015; 60:333-7; PMID:25332078; http://dx.doi.org/10.1093/cid/ciu821

[79] Kharbanda EO, Vazquez-Benitez G, Lipkind HS, Klein NP, Cheetham TC, Naleway AL, Lee GM, Hambidge S, Jackson ML, Omer SB, et al. Maternal Tdap vaccination: Coverage and acute safety outcomes in the vaccine safety datalink, 2007–2013. Vaccine 2016; 34:968-73; PMID:26765288; http://dx.doi.org/10.1016/j.vaccine.2015.12.046

[80] Centers for Disease Control and Prevention. Pregnancy and Whooping Cough. Available at:http://www.cdc.gov/pertussis/pregnant/mom/index.html. Accessed January 31, 2016

[81] National Foundation for Infectious Diseases. Tdap Immunization Recommendations for Pregnant Women. Available at http://www.family-vaccines.org/families/pregnant-women/tdap-recs. Accessed January 31, 2016.

[82] American College of Obstetricians and Gynecologists. Immunization for Women. Available at http://immunizationforwomen.org/patients/diseases-vaccines/tetanus-diphtheria-pertussis/vaccine-recommendations-safety.php. Accessed January 31, 2016

[83] Dempsey AF, Brewer SE, Sevick C, Pyrzanowski J, Mazzoni S, O'Leary ST. Tdap vaccine attitudes and utilization among pregnant women from a high-risk population. Hum Vaccin Immunother 2015; 12: 872–8; PMID:26430729; http://dx.doi.org/10.1080/21645515.2015.1094594

[84] Beel ER, Rench MA, Montesinos DP, Mayes B, Healy CM. Knowledge and attitudes of postpartum women toward immunization during pregnancy and the peripartum period. Hum Vaccin Immunother 2013; 9:1926-31; PMID:23782490; http://dx.doi.org/10.4161/hv.25096

[85] Varan AK, Esteves-Jaramillo A, Richardson V, Esparza-Aguilar M, Cervantes-Powell P, Omer SB. Intention to accept Bordetella pertussis booster vaccine during pregnancy in Mexico City. Vaccine 2014; 32:785-92; PMID:24394441; http://dx.doi.org/10.1016/j.vaccine.2013.12.054

[86] Healy CM, Rench MA, Montesinos DP, Ng N, Swaim LS. Knowledge and attitiudes of pregnant women and their providers towards recommendations for immunization during pregnancy. Vaccine 2015; 33:5445-51; PMID:26307234; http://dx.doi.org/10.1016/j.vaccine.2015.08.028

[87] Maher L, Dawson A, Wiley K, Hope K, Torvaldsen S, Lawrence G, Conaty S. Influenza vaccination during pregnancy: a qualitative study of the knowledge, attitudes, beliefs, and practices of general practitioners in Central and South-Western Sydney. BMC Fam Pract 2014; 15:102; PMID:24884996; http://dx.doi.org/10.1186/1471-2296-15-102

[88] Wiley KE, Cooper SC, Wood N, Leask J. Understanding pregnant women's attitudes and behavior toward influenza and pertussis vaccination. Qual Health Res 2015; 25:360-70; PMID:25246330; http://dx.doi.org/10.1177/1049732314551061

[89] Wiley KE, Massey PD, Cooper SC, Wood N, Quinn HE, Leask J. Pregnant women's intention to take up a post-partum pertussis vaccine, and their willingness to take up the vaccine while pregnant: a cross sectional survey. Vaccine 2013; 31:3972-8; PMID:23777954; http://dx.doi.org/10.1016/j.vaccine.2013.06.015

[90] American College of Obstetricians and Gynecologists. Update on immunization and pregnancy: tetanus diphtheria and pertussis vaccination. Committee Opinion Number 566. June 2013. Available at http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Update-on-Immunization-and-Pregnancy-Tetanus-Diphtheria-and-Pertussis-Vaccination. Accessed January 31, 2016

[91] American College of Obstetricians and Gynecologists. Tdap Immunization, Fall 2013. Available at http://www.acog.org/-/media/Departments/Immunization/2013TdapMailingSmall.pdf. Accessed January 31, 2016

[92] Goldfarb IT, Little S, Brown J, Riley LE. Use of the combined tetanus-diphtheria and pertussis vaccine during pregnancy. Am J Obstet Gynecol 2014; 211:299 e1-5; PMID:24858200; http://dx.doi.org/10.1016/j.ajog.2014.05.029

[93] Healy CM, Ng N, Taylor RS, Rench MA, Swaim LS. Tetanus and diphtheria toxoids and acellular pertussis vaccine uptake during pregnancy in a metropolitan tertiary care center. Vaccine 2015; 33:4983-7; PMID:26192356; http://dx.doi.org/10.1016/j.vaccine.2015.07.018

[94] Morgan JL, Baggari SR, Chung W, Ritch J, McIntire DD, Sheffield JS. Association of a Best-Practice Alert and Prenatal Administration With Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccination Rates. Obstet Gynecol 2015; 126:333-7; PMID:26241423; http://dx.doi.org/10.1097/AOG.0000000000000975

[95] Belloni C, De Silvestri A, Tinelli C, Avanzini MA, Marconi M, Strano F, Rondini G, Chirico G. Immunogenicity of a three-component acellular pertussis vaccine administered at birth. Pediatrics 2003; 111:1042-5; PMID:12728086; http://dx.doi.org/10.1542/peds.111.5.1042

[96] Wood N, McIntyre P, Marshall H, Roberton D. Acellular pertussis vaccine at birth and one month induces antibody responses by two months of age. Pediatr Infect Dis J 2010; 29:209-15; PMID:20009964; http://dx.doi.org/10.1097/INF.0b013e3181bc98d5

[97] Knuf M, Schmitt HJ, Wolter J, Schuerman L, Jacquet JM, Kieninger D, Siegrist CA, Zepp F. Neonatal vaccination with an acellular pertussis vaccine accelerates the acquisition of pertussis antibodies in infants. J Pediatr 2008; 152:655-60, 60 e1; PMID:18410769; http://dx.doi.org/10.1016/j.jpeds.2007.09.034

[98] Halasa NB, O'Shea A, Shi JR, LaFleur BJ, Edwards KM. Poor immune responses to a birth dose of diphtheria, tetanus, and acellular pertussis vaccine. J Pediatr 2008; 153:327-32; PMID:18534242; http://dx.doi.org/10.1016/j.jpeds.2008.03.011

[99] Wood N, Marshall H, White OJ, Holt PG, McIntyre P. Antibody and cell-mediated immunity to pertussis 4 years after monovalent acellular pertussis vaccine at birth. Pediatr Infect Dis J 2014; 33:511-7; PMID:24445839; http://dx.doi.org/10.1097/INF.0000000000000246

[100] Wood N, Nolan T, Marshall H, Richmond P, Gibbs E, Gebski V, McIntyre P. High and Persistent Antibody Responses to Monovalent Acellular Pertussis Vaccine at Birth: A Large Randomised Controlled Trial. Open Forum Infect Dis (Fall 2015) 2 (suppl 1): S58