Pertussis immunization during pregnancy:

a review of the evidence and gap analysis

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Abstract

Some countries have experienced marked increases in pertussis incidence, morbidity and mortality, especially among young infants. To protect infants too young to be vaccinated, several countries recommend tetanus-diphtheria-acellular pertussis (Tdap) immunization during pregnancy, preferably during late second or third trimester. Protection is postulated to result from transplacental transfer of enhanced maternal levels of pertussis-specific antibodies. Maternal immunization with Tdap vaccine has been shown to be highly effective in preventing pertussis disease in young infants, but instances of vaccine failure have been reported. Maternally derived antibodies also have the potential to blunt infants' immune responses to primary pertussis immunization, but the clinical relevance of this is unclear. Maternal titers of pertussis antibodies decline rapidly following parturition so re-immunization is likely needed in subsequent pregnancies. While scientific evidence supporting maternal immunization against pertussis is accumulating, there are still important knowledge gaps that should be addressed by future research.

Despite high vaccination coverage against pertussis among children, there have been recent outbreaks of *Bordetella pertussis* with accompanying morbidity and mortality.[1–3] The World Health Organisation estimates the annual worldwide pertussis case total to be in the range of 20-40 million, with an estimated 300,000 deaths annually.[4] In the United States (US), infants during their first months of life have the highest rates of laboratory confirmed pertussis cases and nearly all fatalities occur in infants younger than three months of age.[5,6] In low and middle-income countries (LMICs), accurate estimates of pertussis burden are not available because of inadequate surveillance; however, it is estimated that 90% of global fatalities caused by *B. pertussis* occur in LMICs.[4] In an attempt to protect infants too young to be vaccinated and those who have not yet completed their primary series, a number of public health policies have been implemented. A so called cocooning strategy involving administration of a booster pertussis vaccine to close household contacts of newborn infants, was recommended by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) in 2005.[7,8] Cocooning programs proved to be logistically difficult to implement, restricting their potential.[9]

In 2011, following a surge in incidence rates of pertussis disease among young infants, the ACIP recommended use of tetanus, diphtheria and acellular pertussis (Tdap) vaccine in unvaccinated pregnant women, preferably after 20 weeks gestation.[10] In 2012, this recommendation was expanded to include all pregnant women, preferably at 27-36 weeks gestation, regardless of their previous Tdap vaccination status, and during each pregnancy.[11]Vaccination of pregnant women against pertussis during late pregnancy has also been recommended in the United Kingdom (UK),[12] Israel,[13] Belgium,[14] Australia,[15] and Argentina.[16]

The aim of this article is to review the current data on the safety, immunogenicity, coverage and the effectiveness of immunization against pertussis during pregnancy and to identify gaps in knowledge of the maternal pertussis immunization strategy.

Safety of immunization against pertussis during pregnancy

Safety is an important determinant in a woman's decision whether or not to receive a pertussis containing vaccine during pregnancy. There is a growing literature related to the safety of maternal immunization with Tdap, although the vaccine was not developed or specifically approved for this indication (Table 1). The available evidence does not suggest an increase in adverse events in mothers or infants associated with receipt of Tdap during pregnancy.[10,17-24]

Donegan et al. reported data from a large cohort of women vaccinated with Tdap vaccine during pregnancy in the UK and did not find an association between antenatal vaccination and poor pregnancy outcomes or adverse events among exposed infants.[22] In the US, administration of Tdap vaccine during pregnancy was not linked with an increased risk of various adverse obstetric or birth outcomes but with a modestly higher risk for chorioamnionitis.[18] It should be noted, however, that the reported risk of chorioamnionitis was relatively lower amongst women immunized between 27 and 36 weeks gestation.[18] CDC reviewed the reports from the Vaccine Adverse Event Reporting System for chorioamnionitis following any vaccine administered during pregnancy between the years 1990 and 2014; only 31 cases of chorioamnionitis were reported during this wide time period, 26% of which followed Tdap. The majority of women with chorioamnionitis had a minimum of one risk factor for this complication, thus raising uncertainty regarding the causal relationship between Tdap administration and chorioamnionitis.[23]

Immunogenicity of acellular pertussis vaccine during pregnancy

Immunization with Tdap vaccine during pregnancy is thought to decrease the mother's risk for pertussis infection and the subsequent likelihood of pertussis transmission to the newborn.[25] Moreover, immunization against pertussis during pregnancy boosts maternal pertussis-specific antibodies and increases the transplacental transfer of pertussis-specific immunoglobulin G (IgG) to the newborn .[13,21,26–40] Tdap immunization during pregnancy was also associated with an increase of the avidity of pertussis antibodies in the umbilical cord sera.[41] Moreover, gestational Tdap administration was shown to induce breast milk pertussis-specific antibodies,[42,43] and transiently boosted cellular-mediated immunity (CMI) against *B. pertussis*.[14]

Transplacental transfer of pertussis specific antibodies

Pertussis vaccination during pregnancy increases pertussis-specific antibody levels in the mother; transplacental transfer of pertussis-specific antibodies has been demonstrated for antibodies against pertussis toxin (PT),[26–39] filamentous hemagglutinin (FHA),[29–39] pertactin (PRN),[29,35–39] and fimbriae (FIM).[31,34,37–39] Several studies have shown higher levels of pertussis- specific antibodies in cord sera than maternal sera for women vaccinated with Tdap vaccine before or during pregnancy (Table 2).[13, 21, 36, 38, 40, 44, 45] Different factors might affect the magnitude of the transplacental transfer of pertussis specific IgG to the newborn including the concentration of total and vaccine specific IgG in maternal sera, the integrity of the placenta, the type and timing of vaccine administration during pregnancy, the interval between vaccine administration and delivery, and the gestational age of the newborn at birth .[6,13,46] Transfer of maternal antibodies begins during the second trimester of pregnancy and peaks toward the end of gestation; thus, antibody levels are higher in term than premature infants.[32,33,39]

The duration of protection of the neonate depends on the initial concentration and longevity of passively acquired maternal antibodies. Based on half-lives of PT and FHA IgG of 36 and 40 days, respectively, the duration of passive protection provided to the infant following immunization against pertussis during pregnancy is thought to be in the range of several weeks.[38,47] Infants born to mothers who received Tdap during pregnancy maintained higher pertussis-specific antibody levels at the age of two months compared to infants whose mothers received Tdap postpartum.[21]

The effect of timing of acellular pertussis vaccine administration on pertussis specific antibody levels and avidity at delivery

Timing of Tdap immunization during pregnancy also influences the quantity and function of pertussis-specific antibodies.[13,41] For infants born ≥ 36 weeks gestation, immunization of the mothers with Tdap between 27–30 weeks gestation was associated with the highest umbilical cord levels of IgG to PT and FHA compared with immunization beyond 31 weeks gestation.[13] Although there is no well-established serologic correlate of protection against pertussis infection, higher titers of antibodies against PT, FHA and PRN have correlated with protection from pertussis disease .[6,47–51] Using the same clinical specimens, the avidity of umbilical cord IgG to PT was significantly higher in umbilical cord sera of newborns of women immunized at 27-30 weeks gestation when compared with newborns of women immunized after 31 weeks gestation.[41]

Induction of breast milk pertussis specific antibodies

Pertussis antibodies are also transferred into breast milk, which has been shown to demonstrate an anti-bacterial effect on *B. pertussis* in vitro and in animal models.[42,43,52–55] Pertussis-specific immunoglobulin A (IgA) is detectable in the breast milk of women

vaccinated with Tdap after delivery, declining 14-28 days after vaccination.[55] Pertussis antigen specific IgA antibodies in the breast milk remain detectable up to 8-9 weeks postpartum in women immunized with Tdap during pregnancy or immediately post-partum.[42,43] In addition to IgA antibodies, IgG antibodies to FHA and PRN were detected in the breast milk of Tdap vaccinated women.[42] However, the mechanism by which breastfeeding might potentially augment infants' protection against pertussis needs to be further explored.

Induction of CMI response

Despite increasing understanding of the humoral response to Tdap during pregnancy, little is known about the effect of this strategy on the maternal CMI response. One small study comparing women vaccinated with Tdap during pregnancy and non-pregnant women vaccinated with the same vaccine found T-cell antigen specific proliferative responses to PT and FHA one month after vaccination had increased five to ten times among non-pregnant women but to a lesser extent among pregnant women. [14] One year after vaccination, T-cell proliferative antigen specific responses declined to baseline for PT and FHA for both women vaccinated during pregnancy and the women vaccinated while not pregnant.

The overall CMI response has also shown a similar pattern. The proliferative and interferon (IFN)- γ response following stimulation with polyclonal T and B cell mitogens one month after vaccination was higher among non-pregnant women when compared with pregnant women. However, one year after vaccination, both the proliferative and IFN-γ responses did not differ between the women vaccinated during pregnancy or while not pregnant.[14]These results suggest that vaccination during pregnancy with Tdap might be associated with an attenuated CMI response that appears to be short lived.

Kinetics of maternal pertussis antibodies following acellular pertussis vaccination during pregnancy

While the kinetics of pertussis-specific antibodies following immunization against pertussis during childhood and adulthood is well-described,[56,57] less is known for pregnant women. In postpartum and childbearing age women serially tested to one month after Tdap vaccination, the antibody response to Tdap antigens reached the highest levels by day 14 after vaccination.[55]

Tdap immunization during pregnancy increased maternal pertussis-specific serum antibody levels up to two months after delivery.[21] However, in women immunized with Tdap during late second and third trimester, pertussis-specific IgG levels declined significantly 9-15 months after delivery, but were still higher than those of unimmunized women.[58] Antibody levels against PT, FHA and PRN in women immunized with Tdap during pregnancy decreased significantly one year after vaccination as compared to levels one month after vaccination, but remained higher than pre-vaccination levels.[14] These data suggest that high pertussis antibody titers at the time of delivery may not be sustained through subsequent pregnancies.

Interference with the infant immune response to primary pertussis vaccination

Several studies in the 1990's suggested that high transplacental maternally-derived antibody titers might have a suppressive effect on the infants' response to primary immunization against pertussis, although the clinical significance of this observation has never been evaluated (Table 3).[47,59–64] The potential interference with active immunization against pertussis was not only affected by the levels of maternal antibodies but also by the type of pertussis vaccine administered to the infant. Infants of mothers with high levels of pertussis

antibodies have a lower response to the primary series of whole cell pertussis vaccine than infants whose mothers have low levels of pertussis antibodies;[47,59,60] there was less inhibitory effect on infants' antibody production against pertussis when acellular pertussis vaccine was utilized for the primary infant immunization series.[47,59,61,62]

The effect of maternal immunization with Tdap on infants' responses to the primary pertussis vaccine series has been studied. An observational study by Hardy-Fairbanks et al. found some interference with the immune response to acellular pertussis vaccine; however, this interference was short-lived and did not persist following the booster dose.[40] In a small randomized, controlled trial, maternal immunization with Tdap during pregnancy did not significantly alter the infants' immune response to most pertussis antigens. Infants born to mothers immunized with Tdap during pregnancy had lower FHA antibody concentration following receipt of the third dose of DTaP (age seven months), and there was a non-significant trend to lower antibody levels for the other pertussis antigens. This slight blunting disappeared by the age of 13 months following the receipt of the fourth dose of DTaP.[21] The disappearance of interference following the administration of a booster vaccine might be partially explained by the gradual clearance of maternal antibodies present during the first months of life. In a larger randomized controlled trial of women immunized with Tdap or Td during pregnancy, blunting of antibody responses against PT, FHA, PRN and FIM was observed in infants of the Tdap immunized women (Halperin, unpublished observations). The different mechanisms that are thought to explain the interference between maternal derived antibodies and the infant's response to subsequent immunizations are reviewed elsewhere.[65,66]

Pertussis vaccine coverage among pregnant women

Vaccination against pertussis during pregnancy is thought to afford passive protection to the

newborn via transplacental transfer of pertussis-specific antibodies. Indirect protection may also result from a decrease in the risk of maternal pertussis acquisition and subsequent transmission to the infant. Increasing pertussis vaccine uptake among pregnant women might also facilitate the implementation of the cocooning strategy and further benefit the newborn. Unfortunately, implementation of maternal pertussis vaccination programs in different countries has been challenging (Table 4).[16,67–75] In Michigan, only 14·3% of women who gave birth received Tdap during their pregnancy shortly following the ACIP recommendation.[67] In California, fewer than 30% of pregnant women received Tdap during pregnancy in 2011.[68] More recently, an increase in vaccine uptake during pregnancy has been reported in the US, reaching almost 50%.[70–72] In the UK, Tdap vaccine coverage during pregnancy reached 59·6 % several months following the official recommendations for maternal Tdap administration were issued.[73] In Argentina, a middle-income country, Tdap vaccine coverage during pregnancy increased from 51% in 2012 to greater than 67% in 2013.[16]

Different determinants may explain the variability in vaccine coverage, including financial barriers for the individuals, as well as the accessibility and the availability of pertussis vaccine. The absence of a recommendation by a medical advisor,[74] and women's safety concerns,[76–79] are also crucial factors that might further decrease the uptake of pertussis vaccine among pregnant women.[80]

Several factors might potentially increase women's willingness to receive pertussis vaccine during pregnancy including their perceived risk of being exposed to infection and their knowledge that vaccination against pertussis is effective in preventing the disease in their infant. Moreover, the information given by the healthcare provider, especially the obstetrician, on vaccine effectiveness followed by a recommendation for pertussis

vaccination during pregnancy, may also influence women's decision-making and improve the uptake of pertussis vaccine during pregnancy.[76,77,80,81]

Clinical Effectiveness of acellular pertussis vaccine during pregnancy:

In response to an increase in infant deaths from pertussis, the UK issued a temporary recommendation in September 2012 for vaccination of all women with Tdap between 28 and 38 weeks of pregnancy. One year following the implementation of this strategy, the estimated vaccine effectiveness of Tdap vaccination during pregnancy in the prevention of laboratory confirmed pertussis disease was 91% and 90% for infants younger than three and two months, respectively.[73] A case-control study from England and Wales between October 2012 and July 2013, starting three weeks after gestational pertussis vaccination was recommended by the UK Department of Health, showed that the effectiveness of Tdap administered during pregnancy was 93% in preventing laboratory confirmed pertussis infection among infants younger than eight weeks.[82] However, among the infants who acquired pertussis infection, seventeen percent (10/58) were born to mothers vaccinated with Tdap during pregnancy. Several variables might affect the risk of vaccine failure and therefore have the potential to optimize pertussis control among the young infants: the timing of Tdap administration during pregnancy, the interval between vaccination and delivery, maternal and/or infant pertussis-specific antibodies levels at delivery, and breastfeeding.

Current gaps in knowledge:

Based on the literature review and subsequent broad consultation with experts, as detailed in the companion article by Garand et al, several gaps in knowledge were considered of importance for future studies (Panel).

Although evidence on vaccine effectiveness following acellular pertussis administration during pregnancy is promising, the precise mechanism leading to clinical protection from the disease is not well established. Moreover, the effectiveness of this strategy in LMICs must still be demonstrated. Although transplacental transfer of antibodies against different pertussis antigens has been documented, little is known about which antibodies are essential, how many vaccine antigens are sufficient for clinical protection, whether multiple antigens are better than single antigen, and whether there is a threshold antibody protective level that should be achieved at delivery. While higher antibody levels are presumed to provide better protection against clinical disease, it is not known whether this is the result of achieving a protective threshold (i.e. serologic correlate of protection) or because the duration of protection is prolonged. The potential interference between maternally derived antibodies and the infant's response to active immunization and its underlying mechanism needs to be further investigated to determine if there is an upper antibody threshold that should be avoided.

While antibodies to pertussis antigens are secreted into breast milk after maternal immunization, there is still no evidence in humans that these antibodies contribute to protection from clinical disease. The role of breast milk antibodies as well as cellular components on protection against pertussis in the neonate needs further elucidation. *B. pertussis* establishes infection by attaching to the epithelial cells on the human respiratory tract (nasopharynx) and thus local antibodies might ameliorate or eliminate pertussis disease or carriage, respectively. No data exist regarding the effect of maternal immunization with acellular pertussis vaccine on women's local airway immunity. There is a need to explore whether there is a change in local antibodies against pertussis following maternal Tdap administration and the effect of maternal pertussis immunization on the newborn's local immunity.

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Table 1: Safety of acellular pertussis vaccination during pregnancy

Study setting(s)	No. of women received aP during pregnancy; age (years)	Vaccine's brand name, manufacturer (% of receipt); timing of vaccine administration (%)	Safety outcome	Main results (n, %)	Reference
Pregnant women offered aP vaccine at tertiary medical center during suspected pertussis outbreak, 4-5/2006, US	16; N/P	Adacel, Sanofi Pasteur (100); 1st trimester : (25) 2nd trimester : (50) 3rd trimester : (25)	Mothers' AE [a], Mothers' SAE [b], Infants' AE [c]	Mothers' AE: (3, 18.7) [d] Mothers' SAE: none Infants' AE: none	17
Retrospective review of data from 2 California Vaccine Safety Data link sites, 1/2010-11/2012, US	26, 229; 62.6% of the participating women were between 25-34 years	Adacel, Sanofi Pasteur (the majority, % N/P); 2nd and 3rd trimester: (92%)	Obstetric AE and birth outcome [e]	Vaccination with aP during pregnancy was not associated with increased risk of adverse birth outcome but small increased risk of chorioamnionitis (see text)	18
Review of reports to the VAERS of pregnant women given aP vaccine, 1/2005-6/2010, US	132; Median age (range): 22 (13–42)	Adacel, Sanofi Pasteur (72), Boostrix, GSK (15.2), Unknown (12.9); 1st trimester: (77.3) 2nd trimester: (19.1) 3rd trimester: (3.6)	Pregnancy AE, Non-pregnancy AE, Infant outcomes	Pregnancy AE [f]: 47 (35.6) Non-pregnancy AE [g]: 24 (18.2) Infant outcomes [h]: 6 (4.5)	19
Retrospective review of electronic medical record data, 5/2005-8/2009, US	138; Mean age (range): 27 (14-40)	N/P; 1st trimester: (63) 2nd trimester: (17) 3rd trimester: (20)	Pregnancy outcome [i], Infant's outcome [j]	No increase in pregnancy or infants' AE among pregnant women who received aP during gestation as compared to women who did not receive aP during pregnancy	20
Randomized clinical trial of pregnant women vaccinated with aP antepartum vs. postpartum, 10/2000-8/2012, US	33; Median age (range): 30.5 (18-43)	Adacel, Sanofi Pasteur (100); All participating women were vaccinated between 30-32 weeks gestation	Pregnancy AE and SAE, Infants growth and development	No association between aP administration during pregnancy and increased pregnancy AE, SAE nor impairment of infants' growth and development	21
UK Clinical Practice Research Datalink, 10/2012-3/2013, UK	20074; Median age: 30	Repevax, Sanofi Pasteur (N/P); Median gestational age at aP receipt- 31 weeks (range: 29-35)	Pregnancy AE [k], Infants' AE [l]	No increased risk of pregnancy or infants' AE was associated with gestational aP receipt	22
Retrospective single institution study, Dallas country, 6/2013-7/2014, (US)	7,152; Mean age-28.2	N/P; gestational age at aP receipt was ≥ 32 weeks	Pregnancy outcome[m]	No increase in pregnancy AE was associated with gestational aP administration	24

Abbreviations: aP- acellular pertussis, US: The United States, N/P- not provided, AE: adverse events, SAE: serious adverse events, VAERS: Vaccine Adverse Event Reporting System, GSK -Glaxo Smith-Kline, UK: United Kingdom.

[a] Mothers' adverse events assessed: wheezing, rash, dizziness, fainting, fever/feeling feverish; injection site reactions
[b] Mothers' serious adverse events assessed: death, life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization or a persistent or significant disability/incapacity
[c] Infants' adverse events assessed: prematurity, congenital anomaly
[d] Mothers' adverse events reported: one injection site swelling and 2 feeling feverish
[e] Obstetric adverse events and birth outcome: risks of small-for-gestational-age births (birth weight <10th percentile), chorioamnionitis, preterm birth (<37 weeks' gestation), and hypertensive disorders of pregnancy
[f] The most frequent pregnancy-specific outcome was spontaneous abortion reported in 22 (16.7%) of the pregnancies
[g] The most frequent non-pregnancy specific outcomes were injection site reactions reported for 6 (4.5%) pregnant women
[h] Only 1 of the infants had a major birth defect (gastroschisis)
[i] Pregnancy outcomes assessed: spontaneous or elective abortions, stillbirths, live births and preterm delivery
[j] Infants' outcome assessed: gestational age, birth weight, presence of congenital malformations or adverse perinatal events
[k] Pregnancies' adverse events: stillbirth, maternal death, pre-eclampsia or eclampsia, haemorrhage, fetal distress, uterine rupture, placenta or vasa praevia, caesarean delivery, low birth weight
[l] Infants' adverse events: neonatal death, neonatal renal failure
[m] Pregnancy outcome: still-births, major malformations, chorioamnionitis, 5-minute Apgar score, cord blood pH, neonatal complications including ventilation requirement, sepsis, intraventricular hemorrhage, neonatal death, preterm birth, small for gestational age, length of neonatal hospitalization

Table 2: Trans-placental transfer of pertussis-specific antibodies induced by maternal acellular pertussis immunization

Study setting(s)	Tdap vaccine brand name, manufacturer	Timing of Tdap administration (number of Tdap-vaccinated women*)	Newborn's gestational age	Ratio of Cord sera Antibodies to Maternal sera Antibodies at delivery for different pertussis antigens	Reference
Periparturient women vaccinated with Tdap at > 20 th weeks gestation who delivered at a general hospital, 11/2013-5/2014, Haifa, Israel	Boostrix (GlaxoSmithKline) [a]	Pregnant women received Tdap between: 23–26^{+6} weeks gestation (n=3), at 27–36 weeks gestation (n=51) and at >36 weeks gestation (n=7)	Mean gestational age of newborn infants was 39.3 weeks	PT: 1.3 FHA: 1.08 PRN: 1.03	13
Pregnant women enrolled in 3 National Institutes of Health Vaccine Treatment Evaluation Unit sites (Houston, Durham, Seattle) were randomized to receive Tdap antepartum vs. postpartum during 10/2008- 5/2012, US	Adacel, Sanofi Pasteur [b]	30-32 weeks' gestation (n=33)	Thirty (90.9%) of the pregnant women delivered at gestational age > 37 weeks	PT: 1.23 FHA: 1.27 PRN: 1.19 FIM 2 and 3: 1.26	21
Women who delivered at a tax-supported hospital and immunized with Tdap within 2 years prior to delivery were enrolled during 6/2009-5/2011, Houston, Texas, US	N/P	For women immunized before pregnancy: mean of 13.7 months before pregnancy (n=86) For women immunized during pregnancy: mean gestational age at Tdap administration of 9.3 weeks (n=19)	Mean gestational age of newborn infants was 39.3 weeks	For women immunized before pregnancy: PT: 1.21, FHA: 1.45, PRN: 1.48, FIM: 1.31 For women immunized during pregnancy: PT: 1.65, FHA: 1.78, PRN: 1.73, FIM: 1.86	38
Prospective multicenter study of non-pregnant women who were offered a TdaP booster vaccine between two consecutive pregnancies in Antwerp, Belgium	Boostrix (GlaxoSmithKline) [a]	The mean interval between Tdap vaccination and the next delivery was 12.7 months (n=24)	Mean gestational age of the newborn infants was 38.9 weeks	PT: 1.7 FHA: 1.6 PRN: 1.75	36
Retrospective study of pregnant women vaccinated against pertussis during 2006 respiratory outbreak, US	Adacel (Sanofi Pasteur) [b]	1st trimester: (4) 2nd trimester: (8) 3rd trimester: (4). Of the 16 women followed, 5 women had maternal and cord blood collected at delivery	N/P	PT: 2.3 FHA: 2.1 PRN: 2 FIM 2 and 3: 2.5	40
Randomized controlled study of pregnant women recruited to receive either Tdap or the TT vaccine during routine preventive visits, Vietnam.	Adacel (Sanofi Pasteur) [b]	The mean gestational age at Tdap vaccination was 25.8 weeks (n=52, 51 women had maternal and cord sera collected)	Mean gestational age of the newborn infants was 38.9 weeks	PT: 1.38 FHA: 1.04 PRN: 1.4	44

Prospective study of healthy pregnant women recruited to receive Tdap from 5 hospitals in the province of Antwerp, Belgium.	Boostrix (GlaxoSmithKline) [a]	The mean gestational age at vaccination was 28.6 weeks (n=57)	Mean gestational age of the newborn infants was 39.7 weeks	PT: 3.47 FHA: 1.81 PRN: 1.24	45

Abbreviations: Tdap: Tetanus-diphtheria-acellular pertussis; PT: pertussis toxin; FHA: filamentous hæmagglutinin; PRN: pertactin; US: The United States; FIM: fimbria; N/P: not provided; TT: tetanus toxoid.

* Unless specified otherwise, the number of Tdap-vaccinated women is the number of paired maternal-umbilical cord sera analyzed

[a] Boostrix (GlaxoSmithKline): ≥20IU tetanus toxoid, ≥2IU diphtheria toxoid, 8 µg pertussis toxin, 8 µg filamentous hemagglutinin, 2.5 µg pertactin

[b] Adacel (Sanofi Pasteur): 5 limit of flocculation tetanus, 2 limit of flocculation diphtheria, 2.5 µg pertussis toxin, 5 µg filamentous hemagglutinin, 3 µg pertactin, and 5 µg fimbria 2 and 3

Table 3: The effect of pertussis maternally derived pertussis antibodies on infant's response to primary immunization against pertussis

Study setting(s)	Vaccine's brand name (manufacturer); Timing of vaccine administration (number of vaccinated women)	Type of Vaccine administered to infants for primary immunization series (Brand name- manufacturer)	Main results	Reference
A total of 48 pregnant women enrolled in 3 National Institutes of Health Vaccine Treatment Evaluation Unit sites (Houston, Durham, Seattle) were randomized to receive Tdap antepartum vs. postpartum between 10/2008- 5/2012, US	Adacel (Sanofi Pasteur); at 30 to 32 weeks' gestation (33)	DTaP/IPV/Hib, (Pentacel- Sanofi Pasteur) [a]	At birth and at 2 months [b]: antibody levels against PT, FHA, PRN and FIM 2,3 were higher in infants of mothers vaccinated with Tdap during pregnancy than infants of mothers who received Tdap postpartum At 7 months [c]: antibody levels higher against PT, FHA, PRN and lower against FIM 1,2 in infants of mothers vaccinated with Tdap during pregnancy than infants of women who received Tdap postpartum At 13 months [d]: antibody levels against PT, FHA, PRN, FIM 1,2 were not significantly different between the infants of mothers vaccinated with Tdap during pregnancy versus postpartum	21
Retrospective study of 16 pregnant women vaccinated against pertussis during 2006 respiratory outbreak. Infants of women immunized with Tdap during pregnancy were vaccinated at the age of 2, 4 and 6 months, US	Adacel (Sanofi Pasteur); 1st trimester: (4) 2nd trimester: (8) 3rd trimester: (4)	aP (Pediarix- (GlaxoSmithKline) [e]	At 2 months [b]: Antibody levels against PT, FHA, PRN and FIM 2,3 were higher in infants of mothers vaccinated with Tdap during pregnancy than infants of unvaccinated women. One month following the primary vaccination series- antibody levels against PT, FHA, PRN were modestly lower in infants of mothers vaccinated with aP during pregnancy than in infants of unvaccinated women except for FIM At 12-18 months [f]- Antibody levels against PT, FHA, PRN and FIM were not different between infants of mothers vaccinated with aP during pregnancy than infants of unvaccinated women	40
Randomized controlled study of pregnant women recruited to receive either Tdap or the TT vaccine during routine preventive visits. Infants were offered pertussis immunization at 2, 3 and 4 months of age, Vietnam.	Adacel (Sanofi Pasteur); mean gestational age at Tdap vaccination was 25.8 weeks (52)	DTaP-HBV-IPV/Hib (Infanrix Hexa- GlaxoSmithKline, Belgium)	At month 2 [b], antibody levels against PT, FHA and PRN were higher in in infants of mothers vaccinated with Tdap during pregnancy than infants of mothers who received TT. At month 5 [c], the antibody levels against PRN were significantly lower in in infants of mothers vaccinated with Tdap during pregnancy than infants of mothers who received TT, yet the levels against PT and FHA did not differ significantly between both groups.	44
Prospective study of healthy pregnant women recruited to receive Tdap from 5 hospitals in the province of Antwerp. Pregnant women who did not receive Tdap vaccine were control, Infants were immunized against pertussis,	Boostrix (GlaxoSmithKline); mean gestational age at vaccination was 28.6 weeks	DTaP-HBV-IPV/Hib (Infanrix Hexa- GlaxoSmithKline, Belgium)	At month 2 [b], antibody levels against PT, FHA and PRN were higher in infants born to mothers vaccinated with Tdap during pregnancy compared with infants from unvaccinated mothers.	45

Belgium	(57)		At month 5 [c], the antibody levels against PT were significantly lower in in infants of mothers vaccinated with Tdap during pregnancy than infants of mothers who did not receive received Tdap. yet the levels against PRN and FHA did not differ significantly between both groups	
Retrospective study of 88 infants whose blood samples were prospectively collected during 3 studies in the years 1973 and 1988, US	N/A	wP (N/P-Connaught Laboratories, Swiftwater, PA) or aP (N/P-Institut Merieux)	Higher maternally derived antibody levels to lymphocytosis promoting factor were associated with infants' weaker antibody response to the antigen following primary vaccination with wP vaccine but not with aP primary vaccination	47
A total of 2342 infants recruited from private pediatric offices and vaccine clinics received different aP and wP vaccines at 2, 4 and 6 months of age, US	N/A	Two different wP vaccines and 13 different aP vaccines	Higher maternally derived antibodies against PT were associated with decrease in infants' response at age 7 months following the 3 rd dose of wP vaccine but not when priming was with aP vaccine. Higher maternally derived antibodies against FHA, PRN and FIM modestly affected infants' post-immunization levels at the age of 7 months against the corresponding antigen following vaccination with wP and aP.	59
Prospective study of 201 infants participating in two immunogenicity studies that assessed the use of concurrent Haemophilus influenza type b and wP vaccine during 1988, 1990, UK	N/A	wP (N/P-Wellcome, Beckenhan, Kent, UK)	Infants at age 5 months who had high pre-immunization titers against PT and FIM at 8 weeks (presumed maternally derived) had lower post-immunization levels against the corresponding antigen when compared to infants with low pre-immunization levels	60
Ninety one full-term healthy infants admitted to the neonatal unit randomized to birth, 3, 5, and 11 months or 3, 5, and 11 months immunization schedule between 1-8/1999, Italy	N/A	aP (Acelluvax vaccine-Biocine)	No correlation was demonstrated between the levels of maternal antibodies to PT, FHA and PRN at delivery and the infants' antibody levels for the corresponding antigen at the ages of 3, 5, and 6 months	61
A total of 76 newborns > 36 weeks gestation born in 3 hospitals randomized to aP at birth and 1 month, aP at birth, and not vaccinated neither at birth nor at one month, followed all by routine primary vaccination series at 2, 4, and 6 months; 2/2005-6/2006, Australia	N/A	When applicable, at birth and 1 months age aP (N/P-GlaxoSmithKline); aP Primary vaccine series composed of DTaP-HBV-IPV/Hib (InfanrixHexa-GlaxoSmithKline)	At 8 months: Infants' antibody levels against PT and PRN were similar in the three groups for those born to mothers with detectable antibody levels at delivery as compared to infants whose mothers had no detectable antibody levels at delivery	62
A total of 34 healthy mother–infant pairs were recruited from a maternity unit, London, UK between 3/2011-1/2012 and their paired blood samples were collected from mothers and infants around birth and one month after completion of the primary series (5 months of post-natal age), UK	N/A	DTaP/IPV/Hib (Pediacel-Sanofi Pasteur)	There was a weak inverse correlation between infants' antibody collective response to PT and FHA at birth and post-immunization fold-increase in antibody concentration at 5 months of age. There was no significant correlation between infant antibody collective response to PT and FHA at birth and post-immunization antibody concentration at 5 months of age.	63
Infants born to women who received pertussis vaccine during pregnancy were identified from general practices. Infants in a historical	Repevax (Sanofi Pasteur); the median interval between	DTaP5-IPV-Hib (Pediacel; Sanofi Pasteur)	Three-six weeks after the 3 [rd] immunization, antibody concentrations against PT, FHA and FIM 2/3 were lower in infants born to women immunized with DTaP during	64

cohort whose mothers did not receive a pertussis-containing vaccine during pregnancy were the control. Infants were immunized at 2-3-4 months, UK.	antenatal vaccination and infant birth was 9.9 weeks (141)		pregnancy compared to the historical cohort.	

Abbreviations: Tdap: tetanus-diphtheria-acellular pertussis; US: United States; DTaP-IPV/Hib: Diphtheria and Tetanus Toxoids and Acellular Pertussis-Inactivated poliovirus/*Haemophilus influenza* type b; PT: pertussis toxin; FHA: filamentous hemagglutinin; PRN: pertactin; FIM: fimbria; aP: acellular pertussis; TT- tetanus toxoid; DTaP-HBV-IPV/Hib: diphtheria, tetanus, pertussis, hepatitis B, Inactivated poliovirus and *Haemophilus influenza* type b; N/A: not applicable; wP- whole cell pertussis; N/P: not provided UK: United Kingdom.

[a] Booster dose was accomplished by Pentacel, Sanofi Pasteur

[b] Before the first infant vaccination

[c] Four weeks after the third dose of acellular pertussis vaccine

[d] Four weeks after the fourth dose of acellular pertussis vaccine

[e] The majority of the infants were boosted with Infanrix, GlaxoSmithKline.

[f] One month afteracellular pertussis booster at 12-18 months

Table 4: Uptake of acellular pertussis vaccine during pregnancy

Study setting(s)	Study period	% Coverage	Reference
National data estimates on vaccine coverage in Argentina	Not applicable	Greater than 67% in 2013	16
The pregnant women's publicly funded insurance program (Medicaid) in Michigan, US	11/2011-2/ 2013	14.3%	67
Electronic records of 7 Vaccine Safety Datalink sites located in California, Colorado, Minnesota, Oregon, Washington and Wisconsin, US	2007-2012	7.1% (Peak in 2011- 17.1%)	68
CDC's Pregnancy Risk Assessment Monitoring System survey of 16 states and New York city, US	9-12/2011	9.8%	69
Data of the Defense Medical Surveillance System for all active component service women with a hospitalization for a live birth delivery, US	1/2006-12/2014	1%–3%: (During 2006–2011) 8% in 2012: 54% in 2014	70
Data on women who gave birth at a tertiary referral hospital, Houston, Texas, US	4/2013-6/2014	56%	71
Data obtained from health insurance claims for approximately 49% of Wisconsin births, US	1/2013–3/2014	35% during the study period 13.8% in 1/2013 51% in 3/2014	72
National data on vaccine coverage in England, UK	Not applicable	59.6% peak in 2/2013	73
Questionnaire filled by pregnant women who attended a university hospital for a routine 3 rd trimester ultrasound examination, Belgium	12/2013–2/ 2014	39.2%	74
Retrospective cohort of all women delivered at a university hospital in Boston, US	2/2013- 6/2013	81.6%	75

Abbreviations: US: The United States, CDC- Center for Disease Control and Prevention, UK: United Kingdom

Panel: Current gaps in knowledge in maternal immunization against pertussis

- The exact mechanism of protection provided by acellular pertussis immunization during pregnancy
- The optimal timing of acellular pertussis administration to provide maximal clinical protection for the infant
- Which pertussis specific antibodies are more essential, how many vaccine antigens are sufficient to produce clinical protection and whether multiple antigens are better than single antigen
- A clear serologic correlate of protection to be obtained at delivery
- Immunogenicity and safety of repeated doses of acellular pertussis in subsequent pregnancies
- The possible interference between maternally derived antibodies and infants' responses to active immunization and the clinical relevance of any reduced responses
- The effect of acellular pertussis vaccination during pregnancy on maternal and infant colonization with pertussis bacteria
- Pertussis disease burden among young infants and the applicability of maternal immunization programs against pertussis in low and middle-income countries
- Immunogenicity, efficacy and safety of whole cell pertussis vaccine in pregnancy