Chapter 5

Pertussis Immunization in Pregnancy: A Review

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Abstract

The pregnant woman has an altered immune response and, for some pathologies, is at increased risk of infection and of developing complications and serious outcomes. In addition, maternal infections can result in congenital anomalies, malformations or severe neonatal diseases. Vaccination of pregnant women can therefore have a double goal: to protect the mother from diseases that could have an impact on her health and to avoid infection/disease transmission to the fetus or the newborn. Despite the potential benefits of immunization in pregnant women, it is still evident reluctance and/or refusal of vaccinations by health professionals as well as by pregnant women, who are wary of the real advantages linked to vaccines. Concerning pertussis, immunization is strongly recommended in pregnancy and some data are already available in Europe as well as in other parts of the world. This review describes the rationale for this immunization and summarizes available data around the world.

Keywords: pertussis, whooping cough, maternal immunization, pregnancy

1. Introduction

Pertussis (or whooping cough) is a worldwide endemic-epidemic respiratory infection, caused by *Bordetella pertussis*, a Gram-negative, aerobic, capsulated bacillus.

Since the 1950s, first, the development of whole-cell and subsequently of acellular vaccines, which may be administered in combination with other antigens (e.g., diphtheria and tetanus toxoids), had a huge impact on the incidence of pertussis and on infant mortality, regardless of the type of vaccine and of the immunization schedule used. However, the duration of protection is not long-lasting, but ranges between 4 and 20 years after natural infection and 4 and 12 years after vaccination [1]. This involved, in particular in the presence of high vaccine coverage, a shift

of infection to older age groups, with often unspecific and unrecognized clinical features. Adult subjects with atypical pertussis, often asymptomatic or paucisymptomatic, can become a source of infection for younger children, especially those younger than 2 months of age, who have not yet started the vaccination programs for infants [2] .

A possible solution to limit the likelihood that an infant can be infected during the first months of life is mother's immunization during pregnancy.

Two important results could be achieved through this approach: the first is placental transmission of immunity induced by vaccination; the second is to prevent the mother from being a potential source of infection for the infant.

In the light of the positive experiences of some countries that have recently introduced vaccination in pregnancy, such as USA, Canada, Australia, and UK, vaccination in the third trimester of pregnancy appears to be one of the cornerstones for the prevention of this infection in infants [3].

2. Etiopathogenic and immunological aspects

The transmission of *B. pertussis*, which is an exclusively human and airborne pathogen, occurs through Flügge droplets. The pathogen is characterized by a high basic reproduction number (R0), and for this, it is highly contagious. The infection predominantly affects children and still represents one of the most important causes of death in subjects younger than 1 year of age [4].

Once introduced into the respiratory tract, the pathogen adheres to the ciliary cells of the epithelium by means of adhesins (FHA: filamentous hemagglutinin, FIM1, 2 and 3: fimbriae, PRN: pertactin) and exerts its pathogenic action through the production of some toxins (PT: pertussis toxin PT, AC: adenylated cyclase, DNT: dermonecrotic toxin, TCT: cytotoxin). Adhesins and toxins (TCT excluded) are highly immunogenic [5].

During the incubation period, *B. pertussis* replication, colonization of the respiratory tract, and production of large amounts of toxins occur, causing damage to the epithelium. The toxicity caused by *B. pertussis* stimulates the production of proinflammatory cytokines (IL-1, INF-α, and IL-6) in host cells, responsible for the clinical picture together with the nitric oxide production [5].

Published data show that *B. pertussis* strains evolved over time, with different isolates in pre- and post-immunization ages. Changes in genomic sequences of virulence factors such as PT, FIM, and PRN have been observed in circulating strains. So far, there is no evidence that the effectiveness of whole-cell vaccines decreases due to a continued selection of less susceptible clones to vaccines [6]. In regions where acellular vaccines are in use, the circulation of PRN-negative bacteria, in which the antigen contained in the vaccine is unexpressed, has recently been detected [7]. Very recently, a strain which does not express either PRN or PT has also been described [8].

However, no significant changes in the efficacy of acellular vaccines have been documented, despite the spreading of these new variants of *B. pertussis* [7, 9].

3. Epidemiology

Before the availability of the pertussis vaccine (introduced in the 1950s), about 80% of cases occurred in children <5 years and less than 3% of cases in subjects ≥15 years of age [2].

In 1974, vaccination was included in the "Expanded Programme on immunization" by World Health Organization (WHO), which allowed a gradual increase in vaccine coverage (CV); in 2008, 82% of newborns had received three doses of pertussis vaccine (avoiding 687,000 deaths) and in 2014, the CV was estimated almost equal to 86% [2, 3].

Despite the excellent results related to the worldwide extensive vaccination, WHO data estimated 16 million cases of pertussis in 2010 (95% of which in developing countries), and 195,000 deaths in the pediatric population. In 2013, pertussis caused about 63,000 deaths in children under the age of 5 years [10].

In the USA, the latest CDC estimates reported 15,737 cases in 2016, with a 86% vaccine coverage with three doses. In particular, an incidence rate of 85.5/100,000 and a percentage of hospitalizations of 44% has been registered in children <6 months of age. In children between 6 and 11 months, incidence rate was 27.1/100,000, and 11.9% of them were hospitalized. In the same year, 7 deaths were registered; 6 of them involved <1 year old subjects [11].

With the introduction of vaccination programs, pertussis spreading has shifted to older age groups, thus involving adolescents and adults.

Accordingly to WHO data, this shift may be related to several factors, such as the increased recognition of less frequent manifestations of pathology in older adults, the use of more sensitive lab tests, a more accurate surveillance system that covers the entire life span, and the progressive decay of protective immunity related to a reduction in natural boosters [2].

However, the highest rates of morbidity and mortality attributable to pertussis are reported in children <1 year of age, especially in infants younger than 2 months of age [12]. Infants usually start immunization generally not before 2 months of age and this involves a time frame during which the risk of acquiring pertussis infection transmitted by family members and caregivers (mother, older siblings, grandparents, etc.) is very high [13].

4. Clinical aspects

Clinical presentation is strictly related to the age of acquisition of the infection, the level of immunity, and the use of antibiotic therapy [14].

The disease affects all age groups, especially children, and is one of the most important causes of deaths of <1 year old infants.

The severity of clinical manifestations is inversely related to the age of affected subjects. In children who have not yet been vaccinated, pertussis has a typical course and can lead to

major symptoms with severe complications [15]. The prognosis between the first and second year of life is particularly severe, with a high incidence as well as a high number of hospital admissions and deaths (0.2% and 4% lethality rates in developed and developing countries, respectively) [16].

The pertussis incubation period generally lasts 7–10 days, with a range between 4 and 21 days; rarely, it can last up to 42 days. The typical course of the disease is divided into three phases. The first one, called "catarrhal stage," is characterized by the onset of rhinitis, sneezing, fever, and occasional mild coughing. The cough gradually becomes stiffer, and after 1–2 weeks, the second phase, called "paroxysmal stage" begins. Fever is generally low throughout the duration of the disease. It is during the paroxysmal stage that the diagnosis of pertussis can be suspected. Coughing is typical, generally violent, with sudden and paroxysmal attacks, frequently followed by vomiting. It is generally an expression of the difficulty of ejecting the mucus from the tracheobronchial tract. At the end of the paroxysmal attack, a long high-pitched whoop sound or gasp occurs (except in newborns) [17].

Paroxysmal episodes are often followed by physical prostration. In the period between an episode and the other, the subject does not look ill. Paroxysmal attacks occur more frequently at night, with an average of 15 attacks in 24 hours. During the first 1 or 2 weeks of the paroxysmal phase, the attacks increase in frequency, remain stable for another 2–3 weeks and then gradually decrease. The paroxysmal stage usually lasts from 1 to 6 weeks, but can persist up to 10 weeks. In the third phase, "convalescence stage," there is a gradual recovery; paroxysmal cough attacks are less common and tend to disappear in 2 or 3 weeks. However, paroxysmal attacks can occur again, for many months after the onset of pertussis, in the case of concomitant respiratory infections.

The abovementioned description refers to pertussis in its typical form and without therapeutic intervention. Antibiotics significantly improve the clinical picture. The classic presentation of pertussis occurs less frequently even after vaccination [18].

Adolescents, adults, and partially immunized children may have a milder course of disease than babies and infants; the infection can be asymptomatic or can present with symptoms ranging from mild cough to a classical pertussis with persistent cough. Although the disease may be milder in elderly people, such subjects may transmit the infection to other susceptible subjects, including unimmunized or not completely vaccinated infants [19].

The most common complication and cause of death related to pertussis is secondary bacterial pneumonia (about 10% of cases). Neurological complications, such as seizures and encephalopathy, are more common among newborns and may occur as a result of hypoxia or toxin-induced damage. Other less severe complications include otitis media, anorexia, and dehydration. Complications due to paroxysmal attacks include pneumothorax, epistaxis, conjunctival hemorrhage, subdural hematomas, hernias, and rectal prolapse [17, 20].

5. Immunological aspects

After natural infection, anti-PT antibodies (the only *B. pertussis* specific antigen) are found in 80–85% of patients [2]. Antibodies to different *B. pertussis* antigens are believed to play a

key role in protecting from the disease (as they neutralize bacterial toxins, inhibit the bond between the bacterium and the respiratory tract cells, and allow the capture and destruction of the bacterium by macrophages and neutrophils). Nevertheless, any specific antibody level, against a single antigen or a combination of antigens, which can be related to clinical protection, is currently unknown [21].

Immunity, whether natural or acquired by vaccination, is not long-lasting and tends to decline in a 4–12 years time range. This data is confirmed by the occurrence of epidemics especially in adolescents and adults, even in geographical areas where vaccine coverage is high. Reinfections may occur in adolescents and adults and have been reported in children as well. It is also well known that cell-mediated immunity plays a key role in protecting against infection; the development of this response can be very important in the clearance of the microorganism and in the subsequent protection [22, 23].

Although there is a placental transmission of maternal antibodies, most newborns do not appear to be protected against the disease during the first months of life, probably due to the low and inadequate levels of antibody transferred, unless the mother has been recently vaccinated. Several studies on maternal immunization have evaluated its validity, demonstrating an effective antibody-mediated protection of infants [24].

6. Available vaccines

The WHO, in the "position paper" on pertussis vaccination published in 2015 [2], points out that the primary goal of immunization should be to reduce the risk of severe forms in childhood, when morbidity and mortality are particularly high, and indicates 90% as the minimum level of coverage to be achieved with three doses in infants, starting vaccination at 6 weeks of age.

Historically, vaccination is carried out using two types of vaccine: whole or old generation vaccine and acellular or new generation vaccine. Both are mainly used as components of combined products (along with diphtheria and tetanus toxoid) in a 3-dose vaccine schedule.

The whole cell vaccine, consisting of inactivated bacteria, showed a highly variable efficacy (36–96%) and a relatively high reactogenicity in several clinical trials, and for this reason, its wide-scale use was limited [25–27]. The use of the whole cell vaccine may correlate with relatively frequent adverse reactions (AE) (26–40% of doses) such as fever, irritability, reactions at the inoculation site, or more rare AE, such as hypotonia-hyporesponsiveness (1/1500–2000 doses) [28, 29]. The proportion of local reactions tends to increase with the increase of age and of the number of administered doses; for these reasons, whole cell vaccines are not recommended in adolescents and adults [29].

Acellular vaccines are less reactogenic [30] and, thanks to their better safety and tolerability profile, their introduction has led to a gradual increase in coverage rates in most Western countries and, consequently, to a significant reduction in the incidence of the disease.

However, several studies have shown that the effectiveness of acellular vaccines decreases over time, leading to an increase in pertussis incidence after 8–12 years, even in areas with

high vaccine coverage; this disadvantage has been reduced but not eliminated by using booster doses of reduced antigenic vaccine (ap) [31–33]. The duration of protection, however, tends to decrease, regardless of the administration of whole or acellular vaccine [34].

The introduction of pertussis vaccines, especially acellular ones, has certainly resulted in a strong containment of the incidence of disease, as a result of a gradual increase in vaccine coverage in most Western countries.

However, the illusion of having found a suitable tool to solve a relevant public health problem such as pertussis was short-lived. Since the early 2000s, a rise in pertussis incidence has been observed in several geographic areas, even where high vaccine coverage has been achieved for a long time [35]. This scenario underlines the need to identify a vaccine strategy that prevents the circulation of infection in all age groups and that, above all, helps to prevent illness in infants who have the highest risk of severe and even deadly complications.

7. Cocoon strategy

For several years, the cocoon strategy, which foresees the protection of infants in the first months of life through vaccination of the mother in postpartum and of the family contacts as potential sources of infection, has been considered a promising strategy of vaccination [2].

The rationale of this approach is related to fact that the source of infection for the newborn is represented by parents (5–55% of cases), grandparents (6–8%), and siblings (up to 20%) [36, 37].

However, it is necessary to consider that the maximum immunological response to vaccination does not occur within 14 days after the administration of a booster dose and, for this reason, postpartum immunization does not allow to immediately protect the mother [38].

Anyway, the cocooning was recommended in the early 2000s in some developed countries and since 2005 by ACIP [39, 40].

This strategy has not been completely successful for several reasons [41]: the poor effectiveness, due to the large number of subjects to be vaccinated in order to prevent a single case of pertussis; the inadequate acceptance by family and close contacts of the newborn, especially if there is no pertussis epidemic ongoing (which leads to a perceived low risk); the difficulty in reaching all potential candidates for vaccination, especially if large families are involved; the high economic resources needed to implement such a program in all newborns.

A study conducted in Italy has calculated the number needed to vaccinate (NNV) within the cocoon strategy, that is, the number of people to be vaccinated in order to prevent one hospitalization due to pertussis in 1 year in children <12 months old. The NNV was very high, ranging between 5404 and 9289, depending on the considered variables [42].

The difficulties in implementing the cocoon strategy, its related high costs, and the not completely satisfactory results achieved, lead to the design of a new approach, which is currently considered the main strategy: woman's vaccination during pregnancy.

8. Immunization in pregnancy

Vaccination of pregnant women with dTpa vaccine is nowadays considered the best strategy for the protection of <2 months of age infants, which are a high-risk cohort being too young to be vaccinated.

However, vaccination during pregnancy has been considered for a long time a negligible option because of the difficulty to assess its effectiveness and safety.

The rationale for vaccination in pregnancy with a single dose of dTap is to provide protection against pertussis to the baby in his first months of life through the transplacental passage of maternal antibodies. One of the concerns firstly considered was the possible interference of maternal antibodies on the child's ability to mount an adequate immune response to pediatric DTaP or to other conjugated vaccines containing tetanus or diphtheria toxoids. Other concerns were related to the lack of data on safety and potential teratogenicity. However, now it is well known that there are no potentially serious adverse events in either the mother or the fetus following vaccination during pregnancy [43, 44]. One of the issues for the development of recommendations addressed to immunization of women during pregnancy and lactation is the lack of studies to make evidence-based decisions. Most of the available data on vaccine safety are derived from passive surveillance records. According to the CDC, the risk of a fetus following mother's vaccination during pregnancy is only theoretical. However, when considering vaccination, it is important to distinguish between live and inactivated vaccines. In particular, there is no theoretical reason to suspect that inactivated, bacterial or toxoid vaccines (pertussis one included), are associated with an increased risk of adverse events when given during pregnancy or lactation [45].

As of 2008 [46], the Advisory Committee on Immunization Practices (ACIP) recommended that pregnant women not previously vaccinated with dTap should receive a dose in the immediate postpartum period prior to hospital discharge; could receive dTap even a 2-year interval after a previous dose of dT vaccine; should receive dT during pregnancy as protection against tetanus and diphtheria when indicated; could postpone dT vaccine during pregnancy and replace it with dTap vaccine in the immediate postpartum period, if sufficient protection against tetanus and diphtheria was already available. In conclusion, although there were no contraindications for the administration of dTap vaccine during pregnancy, healthcare professionals had to evaluate risks and benefits before deciding to administer dTap to a pregnant woman.

Subsequently, an analysis was performed comparing immunization in pregnancy to postpartum vaccination in terms of impact, effectiveness, and costs [47]. Vaccination during pregnancy turned out to allow to prevent more cases of disease, hospitalization, and death than the postpartum approach for two reasons: first, because protection is achieved for both the mother and the child at birth; second, because vaccination, when performed during the third trimester of gestation, optimizes the transplacental transfer of maternal antibodies to the fetus, ensuring protection for the newborn during his first months of life.

Based on this evidence, ACIP [48] recommended in 2011 the use of dTpa to all pregnant women who had not previously received the vaccine. The vaccine has to be administered between the

end of the second and the beginning of the third trimester, preferably after the 20th week. If the vaccine has not been given during pregnancy, one dose of dTap should be given immediately after delivery. In 2012, the recommendation was extended to all women at each new pregnancy, regardless of their previous vaccination status [48].

This indication was based on the results of some studies which showed that the production of protective antibodies after vaccination is maximum in the first month and is much lower even after less than 1 year; after 1 year, the antibody protection provided by the mother is no longer sufficient to protect the baby in his first months of life, unless vaccination is made during pregnancy. It has been confirmed that dTap administration should preferably take place during the second trimester of gestation, especially between the 27th and 36th week [49, 50], although a study conducted by Abu Raya et al. has shown that avidity of IgG antibodies against *Bordetella pertussis* is greater if vaccination is performed between the 27th and 30th week of gestation [51, 52].

Recently, an observational perspective study [53] has been conducted in Switzerland to evaluate the best time for maternal vaccination in order to adequately protect preterm infants who, among newborns, are a group even more susceptible and at risk. Antibody levels, expressed as geometric mean titers, were evaluated in preterm children born from two cohorts of women vaccinated with dTap, one in the second and one in the third trimester. The results showed a significantly higher level of antibodies in infants born from mothers vaccinated in the second compared to those vaccinated in the third trimester. One possible explanation is that immunization during the second trimester allows a longer transfer time and a higher accumulation of antibodies in newborns This is the first study showing the benefits of maternal immunization in the second trimester for preterm infants. Noteworthy, these interesting results have to be validated as it is well known that the placental transfer of antibodies is greatly effective during the last trimester of pregnancy.

There is no evidence of adverse effects on the fetus after maternal vaccination with inactivated or toxoid vaccines, and coadministration of dTap and flu vaccines is allowed, and it is safe in pregnancy and can optimize the immune response [54, 55].

A study conducted in New Zealand evaluated the safety of dTap vaccine administered during pregnancy; a cohort of 403 newborns was followed for 6–12 months after birth (84% of whom completed a 12-months follow-up), monitoring over time the onset of possible adverse effects related to vaccination. Several parameters such as gestational age at birth, growth parameters, evidence of congenital abnormalities, immunization status, timeliness of immunization, and possible appearance of pertussis infection after birth were considered. The study showed that there were no significant differences in birth weight, gestational age at birth, congenital anomalies or altered growth parameters, comparing newborns from immunized or unvaccinated mothers. No cases of pertussis occurred in the cohort studied, in spite of the high rates of disease in the community and there were no adverse events related to vaccination. Therefore, these data can be added to the growing pool of evidence that dTap vaccine administration during pregnancy is an adequate and safe strategy to reduce the impact of pertussis in infants [56].

In the United States, the CDC recommends a dose of dTap at each pregnancy, between the 27th and 36th week of gestation (preferably between 28th and 32th). dTap vaccine is also recommended

in the immediate postpartum, before discharge from the hospital, for mothers who have not received dTap in pregnancy or for those with an unknown vaccination status [48].

In Canada, the National Advisory Committee on Immunization (NACI) recommends that all women who have not received a dose of dTpa vaccine after 26 weeks of pregnancy should be encouraged to undergo vaccination. In particular circumstances, such as in an epidemic situation, all women over the 26th gestation week may be offered dTap regardless of their previous immunological condition [57].

Since 2013, in New Zealand, vaccination is recommended for every new pregnancy between the 28th and 38th week of gestation [58]. In Australia, the guidelines in the latest edition of "The Australian Immunization Handbook" recommend a booster dose for all women in the third trimester of each pregnancy (preferably between the 28th and the 32nd week) [59].

In Europe, following the 2012 epidemic, the United Kingdom launched an immunization program for pregnant women offering vaccination between the 16th and 32nd week of gestation [60]. Belgium (week 24–32), Ireland (week 27–36), Czech Republic (week 28–36) [61], and Italy (after the 28th week) [62] recommend vaccination in pregnancy.

9. Conclusions

Although the impact of pertussis has been considerably reduced since the introduction of vaccination programs in the 1950s, the disease continues to be a public health issue, especially in children in their first months of life.

The spread of *B. pertussis* in the cohort of infants is facilitated by the circulation of the pathogen among older age groups (where cases are often atypical and misdiagnosed) that easily become sources of infection for unvaccinated children. The shift of the disease to the older age groups is related to waning immunity occurring after both natural infection and immunization.

It is therefore necessary to implement vaccination strategies taking into account the most vulnerable groups. On one hand, it is recommended to administer booster doses with dTpa vaccine every 10 years to maintain effective immune protection in previously vaccinated population. On the other hand, it is necessary to adopt a preventive strategy addressed to younger babies, already starting immunization in the prenatal age. Women's vaccination in the third trimester of pregnancy appears to be an effective tool as it allows, through the transplacental passage of specific antibodies, newborn's protection in the first few months of life, at least until he reaches the right age to start immunization.

For a more complete protection of the infant, it would be desirable to simultaneously promote the cocoon strategy, immunizing all members of the family and those who will be in close contact with the newborn, to avoid the transmission of the bacterium by these subjects.

Given the new epidemiological situation and on the basis of the scientific evidence, vaccination in the third trimester of pregnancy is currently recommended in several countries such as the United States, Canada, Australia and other European countries (UK, Italy, etc.).

Conflict of interest

Gabutti G received grants from GlaxoSmithKline Biologicals SA, Sanofi Pasteur MSD, Novartis, Crucell/Janssen, Sequirus, Pfizer MSD Italy and Sanofi Pasteur for being consultant or taking part in advisory boards, expert meetings, being a speaker or an organizer of congresses/conferences, and acting as investigator in clinical trials. Gabutti G has no competing interest related to the content of this article. The other authors have no competing interest.

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