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Clinical Experiences in Pertussis in a Population with High Vaccination Rate

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Abstract

Infection caused by *Bordetella pertussis* in young infants can lead to severe illness and death. Several countries with good pertussis vaccine coverage, above 90%, had outbreaks of this disease from 2010, including Brazil. One of the strategies to reduce the transmission of pertussis to young infants, especially below 6 months of age, is the introduction of Tdap vaccination in pregnant women between 27 and 36 weeks of gestation. Vaccination of pregnant women with Tdap is an emergency measure to reduce hospitalizations and deaths from pertussis in young infants, especially those younger than 3 months of age, which is the population group where the most frequent serious illness occurs. Passive immunity to pertussis in these newborns is temporary, lasting less than 6 months, and there is discussion in the literature of its interference with maternal immunity and immunity of young infants to other vaccines. The acquired immunity to pertussis, both by natural disease and by vaccines, is temporary, and it is known that the immune response to the acellular vaccine is smaller and less durable than the whole-cell vaccine. New strategies for pertussis control should be developed to better cope with this disease overall.

Keywords: pertussis, *Bordetella pertussis*, whole-cell pertussis vaccines, acellular pertussis vaccines, maternal pertussis vaccination, passive protection, infants, vaccine effectiveness, whooping cough

1. Introduction

Whooping cough is mentioned in medical literature since 1540, in the pre-vaccine era, when the incidence of the disease ranged from 100 to 200 cases per 100,000 people [1, 2].

This same incidence is observed nowadays in many developing countries and also in some high-income countries among children under 1 year of age. The vaccine age begins in the 1940s with the whole-cell pertussis vaccines (wP vaccines) and in 1992 with acellular pertussis vaccines (aP vaccines) in developed countries, with a marked decrease in the number of sick individuals as well as in the number of hospitalizations. Despite this, there has been an increase in the incidence and deaths due to pertussis in infants fewer than 6 months of age between 1980 and 2010 in the USA, in Europe, and in many other countries [1–5]. Whooping cough is a highly infectious disease caused by *Bordetella pertussis* and, more rarely, by *Bordetella parapertussis*, *B. bronchiseptica*, or *B. holmesii*. It is the most ill-controlled vaccine-preventable bacterial disease in countries with high vaccination coverage, in which disease peaks occur every 3–5 years. Although routine childhood vaccination has produced a substantial reduction in the number of cases, it continues to cause high morbidity and mortality in children in countries across the globe [6–8]. In developed countries with pertussis vaccination coverage above 90–95%, such as the USA, the UK, several European countries, and Australia, pertussis has manifested in children under 6 months of age when they have not yet completed their primary series and in adolescents and adults who lost their immunity induced by the vaccine (the last booster is given at the age of 5 years). Young infants present atypical and potentially serious conditions, with about 50% of the cases leading to hospitalizations and often even to death, while adolescents and adults also present atypical but mild symptomatology, and as a result, the individual is often mistakenly diagnosed with other infections of the upper respiratory tract [2, 3, 9, 10]. The causes of the decreasing immunity to pertussis are varied: from the primary vaccine failure due to bacterial adaptations to the failure of the vaccine to eliminate the bacteria from the carriers' organism and thereby prevent transmission to the dropping of protective antibodies. The duration of protection of the acellular vaccines is approximately 3 years, with 85% efficacy, and the risk of contracting the disease increases by 1.33 times each year after the last dose of the vaccine. Therefore, the vaccine protects against the disease, but not against bacterial colonization and its consequent transmission. Loss of vaccine-derived protection over time and increased circulation of *B. pertussis* lead to increased susceptibility of adolescents and adults. As a result, whooping cough is often reported as a cause of persistent cough in adolescents and adults [6, 11–14]. The variation in the notification of the age group affected by pertussis can be explained in part by a growing recognition of the less typical manifestations of the disease in adolescents and adults and by severe cases in young infants. It can also be explained by the development of more sensitive laboratory tests and by a more sensitive and extended healthcare surveillance to cover all life periods [15–17]. Outbreaks in areas of high vaccination coverage demand a review of vaccination strategies. It is necessary to take into account adolescent and adult transmitters, as well as health professionals and pregnant women. In order to better assess changes in epidemiology over time and to optimize disease control, it is important to improve whooping cough surveillance, from clinical recognition of the disease to laboratory diagnosis [18]. In 2013, according to the WHO estimates, pertussis caused about 63,000 deaths in children under 5 years of age, although there is considerable uncertainty about these estimates in view of the scarcity of reliable

surveillance data, especially in developing countries [16, 19]. In 2014, pertussis global vaccination coverage was estimated at 86%, considering adherence to the vaccine primary series of three doses. A change in age distribution of the disease for older children and certain age groups (adolescents and young adults) has been reported in recent years in some high-income countries, in particular where aP vaccines have replaced wP vaccines in primary series and booster doses [15, 16]. High vaccination coverage needs to be maintained in order to ensure protection of newborns and young infants, the two groups most likely to show the most severe symptoms and who have not yet started or did not complete their primary series of vaccines. The recent shortage of pertussis vaccine in Europe and elsewhere represents a considerable challenge for maintaining such coverage [18]. It is estimated that the incidence of whooping cough is actually 6–9 times higher than the reported cases, which in 2016, according to the WHO, were 139,535 cases. The unfamiliarity with the disease and its incorrect diagnosis seem to be particularly common among adolescents and adults, due to its atypical clinical presentation. Persistent cough is often the only sign of the disease, and this signal can be attributed to many other conditions and is generally not correlated to whooping cough; so, diagnostic is not performed. On the other hand, the search for specific antibodies in respiratory secretions of patients with chronic cough usually comes as negative. Only serology will identify the cases, and, in turn, serology may not be able to differentiate current active cases from recent cases. The actual incidence of pertussis remains unknown, because data collection varies greatly between countries, which affect the interpretation of trends. There are also variations in the diagnostic methods for laboratory confirmation, in the definition of a case of pertussis and the clinical diagnosis itself [18, 20, 21]. In addition to all the difficulties of data collection, there is still the issue of high contagiousness of the disease, even among vaccinated individuals. A study carried out on vaccinated children, aged 1–5 years, in a preschool class, who had contact with a pertussis case, observed attack rates approaching 50%. This shows the importance of diagnostic investigations even in vaccinated children. The clinical condition will also highly depend on the history of each child, which emphasizes the seriousness of the matter [22].

2. Whooping cough: current situation

There is no consensus as to why the number of pertussis cases has increased in countries with high vaccination coverage. The reasons range from improvements in diagnosis, earlier diagnosis, and more accurate surveillance. These changes have led to an increase in the number of reported cases, but there is also evidence of increased circulation of the bacteria in the population. There are several other explanations for increased epidemics: changes in circulating pertussis virulence, vaccine failure against new bacteria, vaccine failure to block transmission of infection, decreased adherence to vaccination, rapid loss of immunity in adolescents and adults due to the vaccine or due to the disease itself over time, making the vaccinated individuals susceptible, and also the increase of susceptible individuals in the population [10, 17, 23–25].

2.1. Loss of immunity

Neither vaccination nor disease induces long-term protection against pertussis. Loss of protection occurs from 4 to 12 years after the last dose of vaccine and from 7 to 20 years after an episode of disease. The duration of protection of the whole-cell vaccine corresponds to that of the natural infection [3, 25].

The protection evoked by the vaccine tends to get lost over time. Predicted time of the drop of antibody protective levels after vaccination to pre-vaccine levels varies according to different antigens: 15.3 years for pertactin, 11 years for fimbria types 2 and 3, 5 years for pertussis toxin (PT), and 9.5 years for filamentous hemagglutinin. Adolescent vaccination has a good cost-benefit, since it leads to a significant reduction in costs with the disease, but yet not all developed countries provide the booster dose for individuals aged between 10 and 17 years. There is evidence that immunization of adolescents also does not provide long-term protection, which may lead to the risk of adults and elderly people being more affected by infection. This raises the issue that adults should also receive booster doses, since adolescents and adults only have protection for a few years, and should receive booster doses every 10 years [20].

The antibodies to pertactin are correlated to the protection of the disease, but nowadays there is an increase of non-pertactin producing *B. pertussis* strains. In developed countries that use the acellular vaccine (which has pertactin as one of its components), loss of immunity may occur, as well as failure to prevent colonization by pertussis. However, other components of the vaccine (pertussis toxin, filamentous hemagglutinin, or fimbriae) also seem to prevent symptomatic pertussis [26].

2.2. Pertussis genetic changes

Genetic changes in *B. pertussis* may be one of the factors that have contributed to the recent reappearance of whooping cough. In the USA, isolated cases of *Bordetella pertussis* without pertactin have increased from 14% in 2010 to 85% in 2012. The effectiveness of the acellular vaccine appears to remain the same, but surveillance for the adaptations and mutations of the bacteria must be enhanced, as new genotypes have been reported [26, 27].

2.3. Current situation around the world

In the USA, notable increases in pertussis disease occurred in 2004 (25,827 cases, 27 deaths), in 2010 (27,550 cases, 27 deaths), and, more recently, in 2012, when more than 41,000 cases and 18 deaths have been reported, the largest number of cases in the USA since 1959. In addition, the epidemiological characteristics of whooping cough have changed in recent years with an increased load of disease among fully vaccinated children and adolescents [28].

In 2012 when whooping cough was epidemic in the USA, there was an incidence of 103 cases per 100,000 inhabitants in Vermont. These evidences suggest a resurgence of pertussis in the USA [3, 26].

According to the WHO SAGE pertussis working group report in April 2014 [3], the data from the USA suggest a decrease in immunity after aP vaccine replaced wP, but no impact was

observed on overall infant mortality. It also indicates the limited duration of the protection for pertussis in adolescents, pointing to the need for booster vaccination in adolescents who received the aP vaccine compared to those who had at least one dose of wP. There was no resurgence of the disease in Canada, but the periodic cycle had a higher peak in 2012 than in the previous two cycles. An increase in reported cases was limited to certain regions and happened over short periods. In general, the situation in the country is very heterogeneous with multiple causes for increase in pertussis cases (low vaccine coverage, decreasing immunity, previous wP vaccine with low efficacy), but there is no evidence that aP has contributed to the most recent increase in cases. The data suggest that the immunity induced by aP vaccines decreases before the booster dose of adolescence. Therefore, it can be concluded that the timing of adolescent's vaccination is important and that the age in which the third booster is commonly ministered (14–16 years old) may be too late.

In Brazil, a country that still uses wP vaccines, national vaccination coverage in infants under 1 year of age with DTP3 (diphtheria-tetanus-pertussis) vaccine was high (>95%) between 2001 and 2011. From 2006 to 2012, the number of municipalities with coverage above 95% decreased from 83 to 55%, resulting in a heterogeneous coverage throughout the country. The causes for the decline were mainly operational issues due to supply and social problems. In Brazil, the number of pertussis cases increased from 2001 to 2012, with a large increase in morbidity and mortality among infants under 1 year old. This increase was attributed in part to improvements in surveillance sensitivity. Between 2007 and 2012, 51% of reported cases of whooping cough in children under 6 months of age did not receive any dose of vaccine, 37% received only one dose against whooping cough, and 12% received 2 or more doses. The majority of deaths, 342 (97%), occurred in children younger than 1 year of age. The increase in fatal cases among children under 6 months of age led the country to introduce the aP vaccine in pregnant women and also to recommend a cocooning strategy. The recurrence of the natural cycle, the drop in vaccination coverage, and the increase in laboratory tests may be responsible for the increase in the number of cases. There is no evidence of diminishing immunity, as cases are predominant in young infants not yet immunized, supported by the fact that the increase is not observed in older age groups, and the change in disease activity does not exceed what would normally be expected in epidemic cycles [3, 29].

In Chile, the quality of data was improved in 2012, since the laboratory methods were previously not ideal. The resurgence of whooping cough observed in 2011 and 2012 was preceded by a drop in vaccine coverage and thus may be partly linked to this fall [3]. In Cuba, the notification is based only on the clinical definition, without laboratory confirmation. The country's data is therefore not comparable with data from other countries, thereby limiting its usefulness [3]. In Mexico, the data quality has serious limitations, and the sensitivity of the surveillance system is low. The increase in cases may be related to the low and heterogeneous vaccination coverage. The use of a more sensitive laboratory method (PCR) may explain the recent increase in cases, an idea supported by the dissociation of the total infant cases from whooping cough and infant mortality in 2012 [3]. In the European Union (EU), 40,727 cases of whooping cough were notified in 29 countries in 2014. The reporting rate was 9.1 cases per 100,000 inhabitants, higher than in 2013 but lower than in the epidemic year of 2012 [18]. Germany reported 12,339 cases (15.3 cases per 100,000 inhabitants) in 2014. Rates

were highest among children under 1 year of age (51.6 cases per 100,000 individuals), followed by 10–14 years (24.4 per 100,000) and 15–19 years (19.7 per 100,000). The German data is of good quality; therefore, the hypothesis of resurgence of the disease can be discarded. A low overall incidence and low numbers of hospitalizations are observed despite the years of recurrent outbreaks. The increase in incidence may be due to the greater number of serological tests in adolescents [3, 18]. Spain has had a higher mortality rate and hospitalization for whooping cough in children under 3 months of age in 2010 (142.55/100,000) [30–32]. The situation in Denmark is stable, with an observed increase in cases occurring by natural recurrent cycles of the disease and by the use of serological diagnosis. Denmark is the only country with the exclusive use of monovalent aP vaccine: primary immunization begins at 3 months of age, followed by doses at 5 and 12 months. Since 2004, the total number of reported cases has remained relatively stable since the introduction of the aP vaccine, contrary to what has been reported by other countries that have used long-term aP vaccines [3, 5]. The observed epidemiology of Finland is explained by naturally occurring cycles. The situation is stable; no statistically significant change in trends is identified after 2003–2004. Since the aP vaccine was introduced in 2005, the time elapsed is still short to allow observation of possible resurgence of the disease due to the decrease in aP-related immunity. In France, there was no resurgence of the disease, with the aP vaccine being used in the past 10 years with a high coverage. Available data suggest a recent increase in incidence in the age range between 5 and 10, which may reflect an increasing decrease in protection in cohorts exclusively vaccinated with aP. New strategies, such as adult reinforcement and cocooning, have not had a major impact, and their level of implementation remains low [3]. The incidence of pertussis in Belgium at all ages was estimated from 24.2 to 30.8 per 100,000 individuals in 2014. In a study with identification of *B. pertussis* with real-time PCR, the culture of these cases was positive in 30%. In this same study, 60% of the cases were positive in serology with anti-PT antibodies, two serology samples were required, and rare cases were positive for both methods, with which it was demonstrated that diagnosis may require both microbiological and immunological methods [3, 25, 33]. In Portugal, there was a significant increase in incidence in infants under 1 year of age, suggesting a true resurgence of the disease, although the increased incidence may also be associated with the increased use of the PCR test. Pertussis infant mortality was very high in 2012, while mortality from the period 2000 to 2011 was similar to that of other countries. There is likely underreporting in the older age groups. The whole-cell vaccine was replaced by acellular vaccine in 2006. In Sweden there has been no resurgence of pertussis to date, and there have been no major outbreaks since 2004. There has been a successive reduction in the overall incidence of whooping cough since the reintroduction of the vaccine against pertussis after a 17-year period without the vaccine [3]. In the UK, evidence suggests a resurgence of whooping cough. Although the incidence has declined in the last 20 years, there has been no interruption of the natural epidemic cycle, which happens every 3–4 years. A real increase over the natural cycle was observed in infants younger than 3 months of age in 2011 and 2012. An increase in reported cases, hospitalizations, and the number of deaths in young infants was observed. The actual resurgence of pertussis was recorded 7 years after the introduction of the aP vaccine, coinciding with the peak of the natural epidemic cycle [3]. In Eastern European countries, there have been several outbreaks, whose incidence varied from 0.01 to as high as 96 per 100,000 inhabitants. The highest index was found in Estonia [34]. The data available in Israel do not provide clear evidence of the resurgence of pertussis.

Possible explanations for the increase in child cases include greater awareness of whooping cough and the availability of better laboratory tests. Vaccination coverage is high in Israel, which has been using aP (ranging from 3 to 5 components) for the past 7 years [3]. Incidence data for children under 6 years of age in Japan were highest in 2000. The most recent data (2010) show an increase in cases of adults over 20 years. This increase was surprisingly not reflected in young infants, and only a small increase can be observed among older children. No data were obtained concerning hospitalizations and deaths related to whooping cough in Japan. There is no evidence of resurgence, although data are limited [35]. The quality of the data is good in Singapore, and there is no evidence of the resurgence of whooping cough [3]. The data does not allow drawing conclusions about the sudden increase in pertussis in 2007 among those unimmunized or with incomplete immunization, which may be due to the introduction of PCR or whether it was a real increase with case duplication in 2007. Despite the two peaks in 2007 and 2011, the overall incidence was low. The recent rise in whooping cough began shortly after moving from wP to aP vaccine in 2006. Data quality is limited in Thailand, since cases are underreported and there is a low sensitivity of the surveillance system. There is no evidence of a resurgence of whooping cough: incidence remained low between 2009 and 2014. Thailand uses only wP vaccination [3, 36]. In Australia, there was a resurgence of whooping cough between 2008 and 2012 in children under 10 years of age, in particular at 2–4 and 7–9 age ranges. Pertussis is an important public health issue in Australia, with continuous increases observed over a long period of time. The increase was observed at first in adults, related to the availability of serological tests, and then in adolescents, which was related to a history of low coverage of vaccines. More recently, increase of pertussis was observed in younger children, consistent with declining immunity in the context of increased availability and use of tests. Withdrawal of the booster dose in early childhood (at 18 months of age) appears to have made an important contribution to the resurgence of the disease in children aged 2–4 years, with decreasing immunity after the last dose of acellular vaccine at 6 months. The 18-month vaccine was reintroduced in 2015. As in the USA, Australia had large increases of the disease in children over 6 years of age [3, 37, 38].

There are few publications on pertussis in Africa, and most of them do not contain surveillance data and epidemiological trends. In addition we have lack of laboratories capable of adequate diagnosis [39]. Based on the WHO data, the number of cases of pertussis in Africa decreased from 2000 to 2010, except in 2011, when an increase occurred [40]. The WHO in 2016 reported 139,535 cases of pertussis in the world, and in Africa we had only 1425 reported cases [21]. Nigeria, on the other hand, had a peak in whooping cough activity in 2009, reporting the second largest number of cases worldwide, and the diagnosis was made primarily clinical as there are few laboratories for the research [40]. In some African countries, wP vaccine coverage is very low, as measured in Chad (22%), Equatorial Guinea (33%), Gabon (45%), Nigeria (47%), Liberia 49%), Ethiopia (51%), Central African Republic (54%), Guinea (59%), Cote d'Ivoire (62%), and Cameroon (68%) [40]. The WHO African Regional Office (AFRO) is working on reducing missed opportunities for vaccination in 20 priority countries representing 30% (5.9 million) of the unvaccinated or partially vaccinated global birth cohort [41].

Country-specific data provided no evidence of a widespread resurgence of whooping cough globally. The increase in the number of pertussis cases observed in recent years has been attributed to cyclical patterns in most countries, probably amplified by increased disease

awareness, increased global laboratory tests, and increased sensitivity of diagnostic methods, as well as by the use of PCR amplification. Recurrent natural cycles may be more visible in countries where surveillance is more sensitive and where disease control in recent years has generally been good.

Data from only five of these countries (Australia, Chile, Portugal, the USA, and the UK) supported the hypothesis of a real resurgence in pertussis-related morbidity in recent years compared to previous periods of time. Only one country that used wP vaccine against pertussis, Chile, reported a resurgence. For the time being, the increase in cases can be attributed to a sustained decrease in vaccine coverage, to variable coverage at the district level, to changes in surveillance practices, as well as to problems with the specificity of diagnostic tests. The increase in infant cases was noteworthy and associated with increased disease mortality. However, since this was based on fluorescent antibody test data alone (which is known to have problems with specificity), more data will be needed for a better characterization of the problem [3, 39].

3. Vaccination and control strategies

There is a wide variety of vaccine calendars in the world. By 2015, 86% of children worldwide (116.1 million) received three doses of diphtheria, tetanus, and pertussis (DTP) vaccines. However, to reach coverage of 95% or more, 13.5 million unvaccinated children should be vaccinated annually, and an additional 6 million children with incomplete vaccination should complete the timeline. Restricted access and missed opportunities for vaccination remain a challenge worldwide, as well as for middle- and upper-income countries [41].

3.1. Newborns

The increased incidence of whooping cough in countries with high vaccine coverage is alarming, with rates only previously seen in 1950. The protection of newborns is urgently needed, especially during the period between birth and the first dose of the vaccine [10].

Vaccination in newborns is not an option at the present time, both due to the immaturity of the immune system of the newborn and its weak response to the vaccine. Besides these factors, the vaccine against pertussis may also interfere with the newborn's response to the hepatitis B vaccine. For the protection of the newborn, we currently can resort to three related strategies: cocooning, booster schedule, and vaccination of pregnant women [10, 42].

3.2. Children: primary vaccination and booster schedule

The WHO recommends three doses of vaccine in the primary series, the first dose being given at 6 weeks of age (at the latest at 8 weeks of age). The second dose should be given 4–8 weeks after the first one. The last dose should be given at 6 months of age or at any opportunity after. Delaying the third dose may reduce protection against severe illness in the first year of life. A booster dose is recommended after 1 year of age, preferably in the second year of life, 6 months after the primary vaccination scheme. In countries that use aP vaccine, protection

diminishes before the age of 6 years old, whereas those who use wP offer a protection that lasts for 6 years or more. A second booster dose should be given from 4 to 6 years of age for both vaccines [16, 43].

National programs currently administering wP vaccination should continue to use wP vaccines for the primary vaccination series. National programs currently using the aP vaccine may continue to use this vaccine but should consider the need for additional booster doses and additional strategies, such as maternal immunization in case of pertussis resurgence. Only the aP vaccine can be administered in individuals from the age of 7 onward. Vaccination at this age must be based on cost-effectiveness mindset, since the priority is always to maintain high vaccination coverage in the first years of life [16].

3.3. Adolescents and adults: booster schedule

The acellular vaccine was introduced in 1992 in the American calendar, and in 1997 it was already part of the entire childhood calendar (2, 4, 6, and 15 months and 4–6 years). In 2006, a booster dose was introduced at 11–12 years old. Despite this, there was a large outbreak in 2012 in children vaccinated with the acellular vaccine, probably due to the loss of immunity, lower immune response induced by the aP, increased awareness and notification, as well as improved diagnostic techniques, and possibly genetic alterations of the bacteria [26].

One of the reasons for the increase in pertussis is the loss of immunity induced by the vaccine or by infection among adolescents and adults. This leads to the discussion about the need for changes in the vaccine calendars of adolescents and adults. In countries with high vaccination coverage, there has also been an increase in pertussis cases in adolescents and adults in recent years, which is one of the causes of the onset of diseases in young infants, so a vaccine booster in adolescence and adulthood is recommended in order to reduce the spread of the disease among young infants [20].

The duration of immunity of the wP vaccine is 4–12 years, and the aP protection begins to diminish after 4–5 years. This led to the need of a booster dose in the adolescence (from 8 to 11 years), because adolescents present low levels of antibodies, which increase later in life (from 12 to 15 years) due to natural infection [44].

Although a booster dose in adolescence has been shown to decrease the disease in adolescents, this is generally not recommended as a means of controlling disease in infants. Introduction of reinforcements in adolescents and/or in adults should only be done after evaluation of local epidemiology [16, 43]. Adult vaccination in most countries with high vaccination coverage is done with dT, and even when done with dTap, as in the USA, this occurs in only 14.2% of adults who have done so in the last 7 years [45].

One of the risk factors associated with pertussis in young infants is the presence of a household contact, usually parents, siblings, or caregivers, with a cough for 5 days or more [46].

3.4. Pregnant women: booster doses

One of the strategies to reduce the transmission of pertussis to young infants, especially less than 6 months of age, is the introduction of Tdap vaccination in pregnant women between 27

and 36 weeks of gestation in all pregnancies (not just the first one). Vaccination of the pregnant woman is most effective when administered 28 days or more before delivery, when a greater number of antibodies are transferred to the fetus. No adverse events were reported for the mother or the newborn with this measure, except for a small significant increase in chorioamnionitis seen by Kharbanda in 2014 [47–50]. The transplacental transfer of vaccine-induced antibodies from the pregnant woman to the fetus before birth and through maternal breastfeeding after birth is the basis of the prenatal immunization [19]. If the mother is vaccinated with the aP vaccine during pregnancy, her maternal antibodies against pertussis will also be transferred to the newborn through breast milk [46].

In 2012, vaccination of pregnant women in the third trimester of pregnancy was instituted by the American Centers for Disease Control and Prevention (CDC), regardless of their vaccination status, due to the loss of immunity a few months after booster vaccination. Several studies have attested the safety of dTap use in pregnant women [51, 52]. These studies showed that women vaccinated before pregnancy had less than 50% detectable antibodies against pertussis during gestation, which led to the adoption of the measure of vaccinating the woman at each gestation, regardless of her previous vaccination status [10, 53]. Vaccination in pregnant women between 27 and 36 weeks is more effective for the prevention of pertussis in young infants than vaccination in the second trimester of pregnancy. On the other hand, it is known that the vaccine given at the beginning of this period of 27–31 weeks is more effective in reducing pertussis in young infants. Efforts should be made for adequate vaccination schedule during prenatal consultations. Vaccination of 27–36 weeks is 85% more effective than Tdap postpartum vaccination [12, 51].

In the UK, vaccination was introduced in 2012 for pregnant woman between 28 and 32 weeks. In 2016, the country began recommending vaccination between 16 and 32 weeks, in order to improve the chance of vaccination to protect preterm infants, as well as to improve the level of maternal antibodies at birth. Later, vaccination during pregnancy protects the mother from developing the disease, giving some degree of protection to the newborn. Some studies have shown that women who were vaccinated after 32 weeks of pregnancy did not have the best level of passive protection for the newborn. In Belgium, the orientation for pregnant women is from 24 to 32 weeks of gestation [19, 25, 54, 55].

The timing of pregnant women vaccination is still controversial, with recent studies recommending it in the second trimester of pregnancy, while previous studies advocated for the third trimester [10, 52].

The recommendation of vaccination in pregnant women has expanded to several countries, such as Argentina, Belgium, Brazil, Colombia, El Salvador, Mexico, New Zealand, Australia, Switzerland, Ireland, the Czech Republic, Israel, Spain, and Greece [19].

It is known that the transfer of maternal antibodies to the newborn can interfere with the response of young infants to their own vaccination [56, 57], a phenomenon called blunting. This phenomenon depends on the type of vaccine antibody: the PT antibody increases after primary immunization, but the FHA antibody decreases in infants born from mothers vaccinated during pregnancy [19, 58, 59]. A study showed that the level of antibodies in the newborn

and infants of mothers vaccinated for pertussis was adequate and protective, although their levels were slightly lower after the first three doses of the vaccine, and there was no difference in antibody levels after the first booster in the second year of life [10]. Monitoring the immunity of children vaccinated or not should be done regardless of age, in order to understand the long-term impact and the real significance of these immunological findings [19].

Prenatal vaccination induces protection against pertussis by producing high levels of antibodies, which are transferred to the fetus. This strategy will protect newborns when they are vulnerable to the disease, which happens mainly in the period before they complete their primary vaccination schedule with all three doses of the vaccine [19].

Vaccination in pregnant women is the most cost-effective strategy for disease prevention in young infants and unvaccinated newborns. It is more effective to vaccinate the pregnant mother than to vaccinate those interacting with the baby. The vaccine should be given in the second or third trimester of pregnancy, at least 15 days before delivery. This strategy should be adopted in countries with high or increasing morbidity and mortality of young infants due to pertussis [16, 60].

3.5. Caregivers: cocooning strategy

The cocooning strategy consists of vaccinating the whole family and intimate contacts of the newborn, in addition to vaccination of the pregnant woman. It is important to remember that the vaccine takes 2 weeks to raise the antibodies to protective levels; therefore, the newborn is exposed to the transmission of the pertussis during this critical period [20]. Vaccination of household members is effectively provided as it is performed in a timely manner [16]. All caregivers of young infants (who feed, dress, and bathe them regularly) should also be considered for vaccination [46]. It is necessary to achieve adherence by all of those in contact with the newborn or young infant, in order to obtain the effectiveness of the cocooning strategy. It is important to note that the mother accepts this initiative better than the father of the child and other relatives tend to accept it even more rarely [20].

In an American study of 115 young infants with severe pertussis, 72% had previously had contact with adults or children over 11 years of age who showed acute cough for 5 days or more, referred to in the last month. This contact was often with the mother. The fact that infants received a dose of aP did not protect them from the disease [46]. The route of contamination was usually through a member of the family [6].

It has been observed that infants and young infants with older siblings are also at increased risk for pertussis. Each older sibling of the young infant increases the chance of having pertussis 1.5 times more, speaking in favor of the hypothesis that the source of contamination is the older sibling [12].

The American CDC recommends vaccination with a dose of Tdap for every adult and adolescent who have contact or who live with infants younger than 12 months of age [50]. Chile also adopted this strategy in 2011 with a significant impact: there was an 84% reduction in infant mortality when comparing cocooning strategy with no action taken [3].

Cocooning doses may reduce the serious morbidity of the infant, but timing is crucial, and the overall impact and cost-effectiveness may vary between countries and situations. The advantages of cocooning are better acceptance of vaccination in the postpartum period than during pregnancy, accessibility to the whole family, and the opportunity for health education. Disadvantages are the slow response to produce immunity to protect the newborn and logistical and economic issues. In addition, the challenges to implementing cocooning strategies include parental refusal, political hardship, logistical issues, and cultural issues. The cost-benefit ratio of cocooning is lower than maternal immunization, since it requires only one dose, whereas the cocooning strategy requires at least two doses for both parents [3, 61].

Vaccination of pregnant women is likely to be the most cost-effective additional strategy to prevent pertussis disease in young infants and appears to be more effective and favorable than the cocooning strategy.

3.6. Healthcare professionals: booster schedule

In countries that have implemented pertussis vaccination for adults, vaccination of healthcare workers should be given priority, but there is no evidence that this decreases the acquisition or transmission of the disease but otherwise avoids nosocomial disease transmitted to newborns and young infants. Health professionals in contact with pregnant women, parturients, newborns, and young infants should also be prioritized. New studies are needed to assess the real impact of this measure [16, 44, 62].

4. Conclusions

Health education programs are needed to improve adherence to the pertussis immunization programs. Scientific divulgation of the disease and its prevention strategies are fundamental. Vaccination, especially for pregnant women and young infants, must also be publicized, as well as the discussion for incorporation of the vaccine against pertussis into the vaccination programs for adolescents, adults, and the elderly.

Vaccination for pertussis has had a major impact in reducing the overall burden of the disease, with a general reduction in its incidence and, in particular, a reduction in infant mortality. Nevertheless, the cyclic and recurrent patterns of whooping cough are still observed in countries with high vaccine coverage. New vaccination schemes against pertussis have been developed to reduce the risk of serious illness in young infants and young children. It is necessary that all children worldwide, including HIV-positive individuals, be immunized against pertussis, and every country should seek to reach the entire population with anti-pertussis vaccination and also maintain high coverage ($\geq 90\%$) at all levels (national and district).

Both the wP and aP vaccines are effective in reducing infant mortality, highlighting the importance of timely vaccination and the need to maintain high coverage, as current data point to a decrease in aP-related immunity. One future challenge may be the improvement of new vaccines considering all these factors, as well as the importance of the production of vaccines against parapertussis, which seems to be more frequent than originally imagined.

Determining the true incidence of pertussis in each country is vital in order for health authorities to devise the best vaccine strategies to control the disease and its consequences.

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