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Human Immune Responses to Pertussis Vaccines

Clara M. Ausiello, Françoise Mascart, Véronique Corbière, and Giorgio Fedele

Abstract

Pertussis still represents a major cause of morbidity and mortality worldwide. Although vaccination is the most powerful tool in preventing pertussis and despite nearly 70 years of universal childhood vaccination, incidence of the disease has been rising in the last two decades in countries with high vaccination coverage. Two types of vaccines are commercially available against pertussis: whole-cell pertussis vaccines (wPVs) introduced in the 1940s and still in use especially in low and middle-income countries; less reactogenic acellular pertussis vaccines (aPVs), licensed since the mid-1990s.

In the last years, studies on pertussis vaccination have highlighted significant gaps and major differences between the two types of vaccines in the induction of protective anti-pertussis immunity in humans. This chapter will discuss the responses of the immune system to wPVs and aPVs, with the aim to enlighten critical points needing further efforts to reach a good level of protection in vaccinated individuals.

Keywords

Anti-pertussis immunity · Bordetella pertussis (Bp) · Immunization strategies · Mechanisms of protection · Pertussis vaccines

C. M. Ausiello and G. Fedele (✉)
Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy
e-mail: giorgio.fedele@iss.it

F. Mascart
Laboratory of Vaccinology and Mucosal Immunity, Université Libre de Bruxelles, Brussels, Belgium

Immunobiology Clinic, Hôpital Erasme, Université Libre de Bruxelles (U.L.B.), Brussels, Belgium

V. Corbière
Laboratory of Vaccinology and Mucosal Immunity, Université Libre de Bruxelles, Brussels, Belgium

1 Pertussis Vaccination

Historical reports mention a pertussis reminiscent disease as far back as the twelfth century (Weston 2012) but pathogen isolation only occurred in 1906 by Bordet and Gengou (Bordet and Gengou 1906). The first attempts to use whole-cell killed bacteria to develop a pertussis vaccine were made a few years after Bordet and Gengou studies (Lapidot and Gill 2016).

Routine immunization with whole-cell pertussis vaccines (wPVs) started in the late 1940s in the United States, using a wPV combined with diphtheria and tetanus (DTwPV, trivalent). Immunization campaigns were successful, with pertussis cases falling from 115,000–270,000 annually prior to the vaccine era to 1200–4000 annually during the 1980s (Cherry et al. 1988). Despite the high efficacy, DTwPVs showed high reactogenicity and their use was associated with serious systemic reactions, including convulsions and encephalopathies, due to the pertussis

component (Cherry 1996; Jefferson et al. 2003). In 1970s and 1980s safety concerns regarding wPVs raised (Miller et al. 1981; Cody et al. 1981; Gangarosa et al. 1998). For this reason, pertussis vaccination programs were suspended in Japan and Sweden (Sato et al. 1984; Romanus et al. 1987), while in several other countries pertussis vaccine acceptance was greatly reduced (Cherry et al. 1988; Gangarosa et al. 1998; Gonfiantini et al. 2014).

Concerns about the safety of wPVs prompted the development of acellular pertussis vaccines (aPVs). These are subunit vaccines composed of 1–5 purified *B. pertussis* antigens. All aPVs contain the pertussis toxin (PT), believed to be the major virulence factor and target of protective immune responses. Other antigens included in aPVs formulations are the filamentous hemagglutinin (FHA), the pertactin (PRN) and the Fimbriae (Fim2 and Fim3) (Pichichero 1996).

In 1986, the first placebo-controlled trial of an acellular vaccine was carried out in Sweden, selected since at that time it was one of the few countries in Europe that did not administer wPVs routinely to infants (Ad Hoc Group for the Study of Pertussis Vaccines 1988). After this first study, others were performed using aPVs of different formulation and different protocols; a summary is shown in Table 1. The trials that ultimately led to the licensure and adoption of aPVs were those conducted in Sweden and Italy. In both trials, DTaPVs were compared to DTwPV and placebo arms, using a blinded, randomized scheme, with culture or serology confirmed clinical pertussis as the primary endpoint (Gustafsson et al. 1996; Greco et al. 1996). Table 2 summarize a few details of the Italian aPV efficacy trial. The vaccine efficacy study was conduct in about 15,000 infants, humoral response was assayed in about 1,500 infants and T-cell response was tested in about 150 infants. Vaccine efficacy, humoral and T-cell responses were followed in a subgroup of aPV vaccinated children till 33 months of age (Salmaso et al. 1998).

Either the Swedish and the Italian clinical trials showed that, compared with wPVs, aPVs have improved tolerability and safety and induce higher concentrations of antibodies against PT, and proved that the efficacy of aPVs is higher than wPV (Gustaffson et al. 1996; Greco et al. 1996). Unfortunately, the lot of wPV used in the Swedish and the Italian trials, produced by Connaught Laboratories, was less efficacious than expected (Table 2). This probably led to an over-evaluation of aPVs efficacy. In other trials where aPVs were compared to other wPVs preparations, as in the Senegal trial, the wPV showed a better efficacy than the aPV (Simondon et al. 1997).

The vaccine efficacy trials performed in the 1990s marginally investigated crucial parameters of vaccination, such as the duration of protection, the type of immunity evoked or the ability to prevent transmission of infection. These aspects were investigated in depth in follow-up studies. In particular, they were intensified by the observation that the disease was resurging even in countries with high vaccination coverage (Black 1997; Bancroft et al. 2016; van der Lee et al. 2018a, b, c). Most of these studies highlighted straight different responses between wPVs and aPVs, mainly related to the induction of a different type of anti-pertussis immunity.

2 B-cell Immune Responses to Pertussis Vaccination

2.1 Humoral Immune Response after Primary Immunization

Studies on the humoral response to pertussis antigens are crucial in the search of correlates of protection induced by vaccination. In principle, antibodies that can either neutralize the toxic effect of PT and/or prevent the attachment of *B. pertussis* to cells of the upper and lower respiratory tract may provide protection. Primary immunization of children with a pertussis vaccine usually involves a three-dose schedule given in the first 2–11 months of life. In some European countries, a fourth dose is given at 15–18 months of age to complete the primary vaccination schedule (https://ecdc.europa.eu/en/immunisation-vaccines/EU-vaccination-schedules). Figure 1 shows primary vaccination schedules in different

Table 1 Efficacy trials of acellular pertussis vaccine

Study year	Study location	Design and methods	Number of participants	Comments
1985 (Ad Hoc Group for the Study of Pertussis Vaccines 1988)	Sweden	Double blind placebo controlled (compared two Japanese aPV)	3801	No wPV control group 2-dose schedule
1990 (Simondon et al. 1997)	Senegal	Double blind household contact (DTaPV/DTwPV)	4181	No placebo control 3 dose schedule
1991 (Trollfors et al. 1995)	Sweden	Double blind placebo controlled (compared DT/DTaPV)	3450	No wPV control 3-dose schedule
1992 (Gustafsson et al. 1996)	Sweden	Double blind placebo controlled (two-compenent DTaPV/five component DTaPV/DTwPV/DT)	24,336	wPV control (Connaught) 3-dose schedule
1992 (Greco et al. 1996)	Italy	Double blind placebo controlled (DTaPV/DTwPV/DT)	14,751	wPV control (Connaught) 3-dose schedule

Modified from: Lapidot R and Gill CJ (2016)

Table 2 Vaccine efficacy and immunogenicity in the Italian efficacy trials of acellular pertussis vaccine

Vaccine	Nr. of children	Vaccine efficacy (95% CI)	anti-PT IgG 1 month IU/ml (95% CI) N = 1275	anti-PT IgG 15 months IU/ml (95% CI) N = 1275	T-cell proliferation 1 month % of positive response N = 142
aPV (SmithKline and Beecham)	4481	84 (76–89)	51.3 (47.9–57.9)	2.7 (2.4–3.0)	55%
aPV (Chiron Biocine)	4452	84 (76–90)	94.4 (88.8–100.3)	4.5 (4.0–5.0)	83%
wPV (Connaught)	4348	36.1 (14–52)	1.3 (1.1–1.2)	1.1 (1.1–1.2)	46%

From: Greco et al. (1996), Cassone et al. (1997), and Giuliano et al. (1998)

European, Asia-Pacific, African and American countries.

It is known that vaccination with wPV induces specific anti-PT, anti-FHA and anti-PRN immunoglobulin G (IgG) since the first dose (Steinhoff et al. 1995; Pereira et al. 2010), unless in prematurely born infants (Mascart et al. 2018). The induction of higher IgG levels by aPVs compared to wPVs was stated by a study comparing the immunogenicity of 13 different aPVs with a licensed wPV (Edwards et al. 1995). Worth of note, the same study allowed concluding that, particularly for PT, vaccine immunogenicity seems to depend on factors other than antigen concentration, possibly including antigen derivation and formulation. In this regard, it was found that aPVs containing a genetically inactivated PT were responsible of a higher anti-PT IgG response (Edwards et al. 1995;

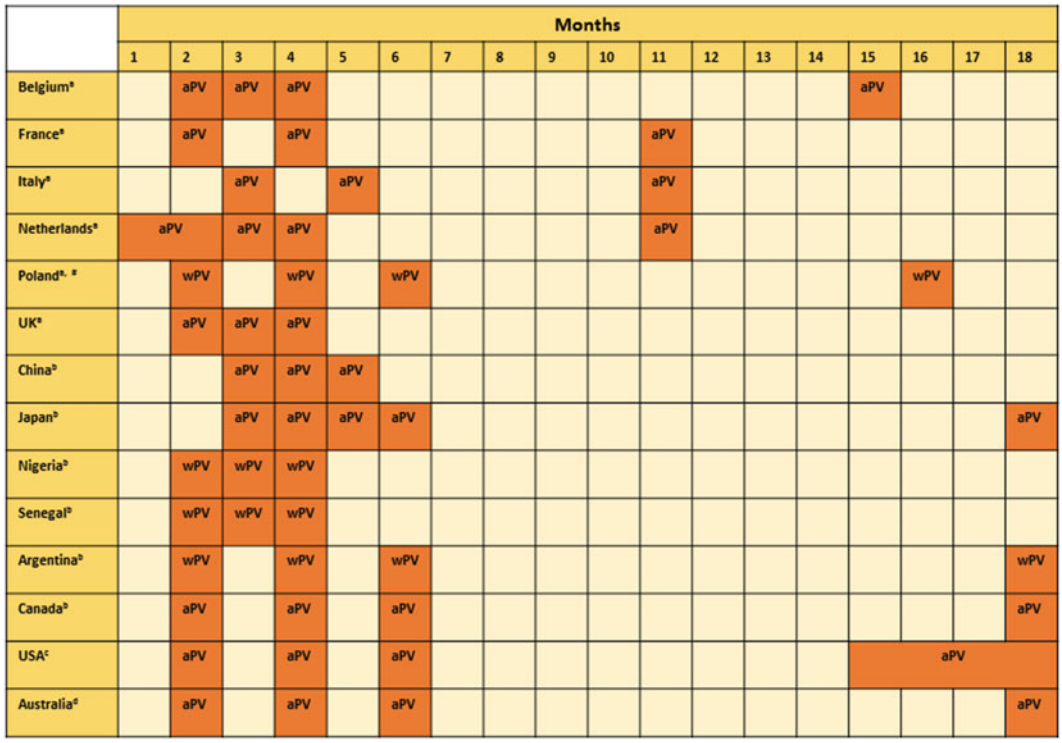

Fig. 1 Examples of primary vaccination schedules reccomemded in different European, Asia-Pacific, African and American countries
Source: [a]ECDC European Vaccine Scheduler; [b]WHO vaccine-preventable diseases: monitoring system. 2018 global summary; [c]CDC's Advisory Committee on Immunization Practices (ACIP); [d]The Melbourne Vaccine Education Centre (MVEC)
[#]aPV are available on the private market; it has been estimated that in 2013 aPV represented 60% of all vaccines used for primary pertussis vaccination in Poland (U. Heininger, et al. PLoS One, 11 (2016), p. e0155949)

Cassone et al. 1997; Giuliano et al. 1998). It should be considered that antigen concentrations are lower in wPVs compared to aPVs, in particular for PT, and that a limited number of purified antigens are present in aPVs. Therefore, the first explanation for lower anti-PT, anti-FHA and anti-PRN antibody titers induced by wPVs compared to aPVs relay to a lower antigen concentration, whereas significant antibody titers were detected in response to a whole-cell *B. pertussis* lysate (Mascart et al. 2018).

The protective implications of humoral responses induced by vaccination are not well understood since clear serological correlates of vaccine-mediated protection are missing. In fact, although some evidences have suggested that antibody response against PT, PRN, and Fimbriae may be associated with protection (Storsaeter et al. 1998; Taranger et al. 2000), the immunogenicity studies performed within the clinical trials did not demonstrate a satisfactory correlation between the levels of antibodies to the vaccine antigens and vaccine efficacy (Ad Hoc Group for the Study of Pertussis Vaccines 1988; Giuliano et al. 1998).

A key point to be considered is that humoral immune responses to pertussis vaccination are of short duration. Follow-up studies on the persistence of the serological response to primary immunization with DTaPV showed a marked decline of IgG level against vaccine antigens approximately after 15–20 months from the last dose (Table 2) (Giuliano et al. 1998; Huang et al. 1996; Hallander et al. 2009).

2.2 Humoral Immune Response after Booster Vaccination

After the introduction of aPVs, infections and disease caused by *B. pertussis* among older children and adults in immunized populations were increasingly recognized (Cromer et al. 1993; He et al. 1994; Black 1997), indicating that the vaccine-induced immunity was waning below the protective level in these age groups. In addition, several household studies and investigations of outbreaks had shown that older family members constitute an important reservoir for spread of infection to susceptible infants (Nelson 1978; Mertsola et al. 1983; Long et al. 1990). These observations suggested the need for booster immunizations of older children and adults, also with the goal of preventing transmission of *B. pertussis* from these age groups to infants. Less reactogenic aPVs seemed to be suitable not only for primary immunization but also for boosting of preschool children. A study by Hallander and colleagues predicted that 65 months after the third dose of a primary vaccination at 2, 4 and 6 months, anti-PT IgG would have been below the detection level in 50% of the vaccinated children (Hallander et al. 2005). Starting from this and similar observations, public health authorities and strategic advisory group of experts started to recommend a pre-school booster immunization at 5–6 years of age in order to maintain an adequate level of immune protection.

Studies on the induction of humoral immunity after vaccine boosters pointed out their importance in restoring antibody levels (Schure et al. 2013; Aase et al. 2014; Carollo et al. 2014). However, it is becoming apparent that, similarly to primary immunization, boost vaccination tends to decline over time. Recently, it was shown that after the booster dose at around 4 years of age, antibodies to PT became undetectable in 49% of children at the 5-year follow-up visit (Voysey et al. 2016). Increasing incidence of the disease in older age-groups, the need to reduce the risk of spreading the infection to unprotected younger infants, and the rapid decline of antibody levels, prompted for the introduction of vaccine booster doses also for adolescents and adults, using vaccines with a reduced antigen content (Tdap) (Halperin 2001; Campins-Martí et al. 2001; Zepp et al. 2011). Studies evaluating the persistence of humoral responses after the booster vaccine dose in adolescents and adults have shown a decline over time of pertussis-specific antibodies that, nevertheless, are usually maintained at greater than pre-immunization levels for several years after the receipt of the last booster dose (Edelman et al. 2004; Edelman et al. 2007; Le et al. 2004).

2.3 B-cell Memory Response to Pertussis Vaccination

In the search of effective correlates of protection, several studies assessed the induction of B-cell memory immune responses to pertussis antigens following vaccination, since these cells can propagate a booster response rapidly enough to outpace pathogenesis of *B. pertussis* (Pichichero 2009). The results obtained indicate that, despite the rapid antibody decay, long-term memory B-cell responses are induced by vaccination and that memory B-cells, in addition to antibodies, may contribute to protection against pertussis. (Hendrikx et al. 2011; Schure et al. 2013; Carollo et al. 2014; Jahnmatz et al. 2014). In particular, in wPV-primed Dutch children the levels of specific memory B-cells increased at 3, 4, 6 and 9 years of age, and could be detected in vaccinated children whose antibody levels had already waned (Hendrikx et al. 2011). In an Italian study, still >80% of aP vaccinated children presented a positive B-cell memory response 5 years after aPV priming (Carollo et al. 2014). The crucial role of memory B-cells response in protection has been demonstrated by a recent study showing that the low levels of pre-formed serum antibodies are insufficient for protection and that memory B cells play a major role in the adult defense (Marcellini et al. 2017).

3 T-Cell Immune Responses to Pertussis Vaccination

3.1 T-Cell Immune Response after Primary Immunization

During the safety and efficacy trials conducted in the 1990s, immunogenicity studies focused on the induction of pertussis-specific antibodies while the interest in studying the T-cell immune response to vaccination was limited. However, during the Italian trial, studies were performed in a small percentage of infants to assess the induction of T-cell responses by pertussis vaccines, measured as pertussis-specific T-cell proliferation and T helper (Th) type cytokines expression (Cassone et al. 1997; Ausiello et al. 1997). The results showed that aPVs were better inducers of T-cell immune responses than the wPVs, (Cassone et al. 1997) (Table 2). However, as underlined previously, the wPV lot used in the trial was less efficacious than expected. Follow-up studies showed that vaccine-induced T-cell proliferation persisted, in contrast to the rapid decline in antibody levels. In fact, 14 months after the last immunization, anti-PT IgG titers fell to low or undetectable values, while T-cell responses substantially persisted (Table 2) (Cassone et al. 1997). The authors proposed that persistence of T-cell immunity against pertussis could be boosted by exposure to natural infection (Cassone et al. 1997; Ausiello et al. 1997, 1999; Cassone et al. 2000).

The profile of Th cells cytokines produced after antigenic stimulation in wPV or aPV vaccinated individuals was evaluated in the same subgroup of infants. A key difference was evidenced, indeed aPV vaccination induced both a Th type 1 and type 2 cytokine profile, marked by the production of Interferon-gamma and Interleukin 5, activating a cell-mediated immune response against intracellular pathogens or a humoral immune response against extracellular pathogens, respectively. On the contrary, the wPV induced a Th type 1 pattern only (Ausiello et al. 1997). Following this first study, many others highlighted the crucial mismatch between aPVs and wPVs induced T-cell immune response. In fact, wP vaccination induces Th1 polarized responses, whereas aP vaccination is followed by a predominant Th2 response, that could change from a mixed Th2/Th1 to a robust Th1 profile following a natural booster or a vaccine booster at 15 months of age (Zepp et al. 1996; Ryan et al. 1998; He et al. 1998; Ausiello et al. 1997, 1999; Mascart et al. 2007; Edwards and Berbers 2014; Mascart et al. 2018).

More recently, in studies performed mainly in animal models, it was shown that both the aPVs and wPVs induce the expansion of another Th subset, Th17 cells, activated to fight extracellular bacteria (Ross et al. 2013; Warfel and Merkel 2013). Overall, it is now clear that natural infection and immunization with wPVs induces a similar pattern of Th1/Th17 response while aPVs induce a Th2/Th17 response (Ross et al. 2013; Warfel et al. 2014). The role of CD4+ T-helper cells in mediating immunity against natural infection is reviewed in depth by Lambert and colleagues in this issue (see chapter 5 of this volume).

3.2 T-Cell Immune Response after Booster Immunization

Several studies have been performed on the persistence of vaccine induced T-cell response and the effect of vaccine booster doses. The results on the importance of booster immunizations in enhancing T-cell responses to pertussis antigens are somewhat contrasting. In some studies, an enhancing effect was recorded. Tran Minh et al. (1999) and Edelman et al. (2004) evaluated pertussis-specific T-cell responses in adolescents. At one month and three years after the aPV boost, T-cell responses were higher than those observed before the boost.

Other studies, on the contrary, did not highlight an enhancing effect. A fourth dose given at 13–16 months of age, to complete the primary vaccination schedule had no major effect on antigen-induced cytokine production neither in full-term born infants nor in preterm infants, but it allowed maintaining significant immune

responses in the same infants tested before and after the fourth dose (Dirix et al. 2009; Vermeulen et al. 2013). According to Schure and colleagues, an increase in cytokine production was missed after a boost vaccination in children primed with aPV, whereas it was not the case for wP-vaccinated children (Schure et al. 2012a). The same research group reported that in 9 years-old children, T-cell responses did not increase after a second aPV booster (Schure et al. 2012b). Poor effect of vaccinal boost was confirmed by another study evaluating T-cell immunity in children 5 years after primary vaccination with two aPVs. A positive T-cell response, evaluated in terms of proliferation and IFN-γ positive CD4+ T cells, was present only in 36.8% of vaccinees (Palazzo et al. 2016a). PT-specific proliferation was higher in children tested before than after the preschool vaccine booster dose (Palazzo et al. 2016a). Similarly, only a marginal effect of a pre-school booster dose on the proportions of FHA- and PT-induced IFN-gamma-containing CD4+ T lymphocytes was observed in Belgium (Mascart et al. 2018). However, the effect in children of a booster dose on T-cell immune responses may also be restricted to Th2-type cytokine production as reported after an aPV booster administrated in aPV primed children (Ryan et al. 2000).

Despite lack of immediate boosting effect on antigen-specific Th1-type responses, pertussis-specific T-cell immunity increases during the 5 year following the booster at 4 years of age (Schure et al. 2012a). The authors conclude that this phenomenon is probably due to natural boosting caused by the high circulation of *B. pertussis*. This might explain, at least in part, the persistence of protection against pertussis in aPV recipients despite a substantial waning of both antibodies and T-cell responses induced by the primary immunization.

All these studies indicated a probable overestimation of the duration of immunity induced by aPVs introduced in the mid-nineties of the last century, due, in part, to an asymptomatic natural booster in countries with high *B. pertussis* circulation. Very few studies investigated the effect of a booster dose administrated in adults in view of the rapid waning of the aPV-induced immune responses. However, preliminary data suggest that booster dose administrated in adults is not associated with an enhancement of specific T-cell immune responses (Mascart et al. 2018). Quite remarkably, review of data from an observational, cross-sectional study performed in the Netherlands, comprising pertussis patients of various ages, suggested that T-cell responsiveness tends to diminish with age (van Twillert et al. 2015).

3.3 T-cell Memory Response to Pertussis Vaccination

In the search of new parameters to assess the level and duration of protection after vaccination or infection, pertussis-specific memory T-cell populations were assessed in humans. Several data showed that pertussis-specific T-cell responses in infants after aPV primary vaccination were mainly restricted to central memory and effector memory T-cell subsets (Sharma and Pichichero 2012; Smits et al. 2013; Palazzo et al. 2016a). However, a vaccine boost had no specific effect on the frequency of memory subsets expansion (Schure et al. 2012b; Smits et al. 2013; Palazzo et al. 2016a). Hence, a correlation between the percentage of the different T memory subsets and duration of protection from pertussis appears to be still elusive.

The induction of CD8+ T-cell response during *B. pertussis* infection was analyzed in details by Mascart's group (Mascart et al. 2003; Dirix et al. 2012). In CD8+ cells, an expansion of effector memory T-cells was observed leading to assume that pertussis-specific CD8+ T memory cells contribute to protection against pertussis (Rieber et al. 2011; Dirix et al. 2012; de Rond et al. 2015).

3.4 T follicular Helper Cells

An important cellular population involved in the development and maintenance of B cell responses, which have not been investigated yet

in pertussis field, is the T follicular helper cells (Tfh). Germinal centers Tfh cells instruct neighboring B lymphocytes to undergo differentiation into memory B cells and plasma cells secreting affinity matured class-switched immunoglobulins (Crotty 2014). Upon recall of the antigen, memory Tfh cells will help part of the B memory cells to differentiate quickly into antibody secreting plasma cells, providing an initial rapid boost of the antibody response (MacLennan et al. 2003). Tfh cells have been initially described in the germinal centers of secondary lymphoid tissues, but circulating Tfh (cTfh) can be detected in the blood and are considered as a memory compartment of germinal center Tfh cells (Morita et al. 2011) with the capacity of rapid and efficient secondary immune responses. cTfh are categorized in distinct subsets which share properties with Th1, Th2 or Th17 cells depending on the combination of surface markers expression (Ueno 2016) and will contribute to the production of different Ig class and subclass (Morita et al. 2011; Locci et al. 2013).

cTfh cells have been associated with protective role in human infectious disease (Locci et al. 2013; Obeng-Adjei et al. 2015; Kumar et al. 2014; Slight et al. 2013; Farooq et al. 2016) and vaccines (Bentebibel et al. 2013; Pallikkuth et al. 2012; Spensieri et al. 2013). Therefore, it is conceivable that Tfh cells play a role also in immunity to pertussis. Long-term specific memory B cells are induced by pertussis vaccines. However, to generate efficient secondary immune responses, Tfh cells are key drivers. The quality of the Tfh cells response induced by pertussis vaccine might influence the type of memory B cell response and the quality of the recall response, and need therefore to be investigated.

4 Different Immune Responses to Different Pertussis Vaccines

There is a rather large consensus for a more rapid waning of protective immunity in aPV than in wPV recipients (Plotkins 2013; Edwards and Berbers 2014; Acosta et al. 2015). Moreover, it is known that teenagers who received wPVs in childhood are more protected than those who received aPVs (Klein et al. 2013; Witt et al. 2013). Rieber and colleagues published a first study focusing on differences in long-term immunity and booster immune response to pertussis antigens between adolescents who previously had received DTaPV or DTwPV. The authors found that subjects who received primary wP vaccination responded with higher IgG-PT titers to the adolescent Tdap booster than those immunized with primary aP vaccination (Rieber et al. 2008). A more recent study, comparing pertussis-specific humoral responses after aP booster vaccination of 4-year-old children who had been vaccinated in the primary series with wPVs or aPVs, showed that the preschool aPV booster at 4 years of age resulted in significantly higher pertussis-specific IgG antibody levels in aPV-primed children than those in wPV-primed children, which remained higher for at least 2 years post-booster (Schure et al. 2013). A follow-up study showed that the pre-adolescent Tdap booster vaccination induced lower vaccine antigen-specific humoral and B memory cell responses in aPV-primed compared with wPV-primed children, suggesting that aPV primed children may experience faster humoral and B memory cells waning (van der Lee et al. 2018a), confirming the result of Rieber et al. (2008). Studies on wPV- or aPV-primed children allowed to demonstrate a different profile of the humoral immune response associated with primary immunization, with high proportions of specific IgG4 in some aPV-primed children, an antibody response associated to a Th2 profile (van der Lee et al. 2018c).

wPV or aPV priming can also determine the outcome of T-cell responses. A study by Smits and colleagues in 9–11 years-old children showed that wPV-primed children have longer lasting Th1-type immune responses than aPV-primed children (Smits et al. 2013). Indeed, even if the time from the last booster vaccine was significantly longer in wPV-compared to aPV-vaccinated children, the T-cell proliferative capacity in response to antigenic stimulation was comparable, and more children had a detectable cytokine response after wPV-compared to aPV-vaccination (Smits et al.

2013). Most interestingly, the influence of pertussis priming vaccines on adult T-cell responses after a Tdap booster vaccination has a key role in skewing the immune profile of vaccine recipients. Indeed, in wPV primed individuals, the T-cell response is Th-1 polarized, while IL-5 is dominant in aPV primed individuals. This differential pattern is maintained after booster vaccination up to several decades after the original aPV/wPV priming (Bancroft et al. 2016). These findings suggest that childhood aPV versus wPV vaccination induces functionally different T-cell responses to pertussis that become fixed and are unchanged even upon boosting. This view was confirmed by a recent study analyzing pertussis-specific memory CD4+ T-cell responses. The authors found a Th2 versus Th1/Th17 differential polarization as a function of childhood vaccination with aPV or wPV, respectively. These differences appeared to be T-cell specific, since equivalent increases of antibody titers and plasmablasts after aPV boost were seen in both groups (da Silva et al. 2018).

Differences in the capacity to induce protective responses by primary or booster vaccination due to differences in aPV components have been reported (Vermeulen et al. 2013; Koepke et al. 2014; Carollo et al. 2014; Palazzo et al. 2016a). Factors causing this differential behavior may include antigenic formulation and concentration, adjuvant content and the PT inactivation process. Specifically, it was conceivable that the milder inactivation of vaccine antigens was responsible for a better T epitope preservation and an induction of a more sustained T-cell proliferative response (Palazzo et al. 2016a). On the contrary, vaccines formulated using antigens adsorbed onto a higher content of aluminum hydroxide better preserved the antibody responses (Carollo et al. 2014).

5 Immune Responses to Pertussis Maternal Immunization

Pertussis-related morbidity and mortality disproportionately affects young infants (Van Hoek et al. 2013), those less than 4 months of age being particularly vulnerable to infection. Vaccination during pregnancy to boost maternal antibody levels and enhance infant passive immunization by IgG placental transfer was therefore considered. This approach was shown to be safe (Campbell et al. 2018; Halperin et al. 2018) and effective to prevent infant pertussis especially during the first 2 months of life (Baxter et al. 2017). Pertussis vaccination during pregnancy was therefore recommended in different countries, the World Health Organization (WHO) considering it as the most cost-effective additional strategy for preventing disease in young infants from birth until protection provided by the first infants immunizations (WHO 2015). The United States were the first to advise in 2011, that pertussis vaccine be administrated to pregnant women in the third trimester, and in 2012, this advice was updated to recommend vaccination in every pregnancy (CDC 2013). A number of countries further introduced maternal Tdap vaccination during pregnancy, starting by Argentina, followed by United Kingdom; Australia, Belgium, Spain (Campbell et al. 2018). There remains however considerable variation between national immunization recommendations. Some countries still recommend the administration of a vaccine booster soon after delivery even if there is now agreement that this cocooning strategy is costly, difficult to implement, and providing uncertain effectiveness (Blain et al. 2016).

The rationale for pertussis vaccination during pregnancy is to provide passive protection for newborn infants by *B. pertussis* antibodies transferred from mother to infant across the placenta, although there is no clear immunological correlate of protection for pertussis. The efficiency of antibody transfer through placenta is dependent on maternal antibody levels, placental function, absence of maternal co-infections that diminish transfer, and IgG subclass induced by vaccine antigens (Kachikis and Englund 2016). As *B. pertussis* antigens present in the acellular vaccines used for booster administration in adults are proteins, they induce IgG1 antibodies which are transported quite efficiently across the placenta, an active transport being mediated by the neonatal receptor for the constant region of immunoglobulin (FcRn) (Roopenian and Akilesh

2007). The concentration of PT-specific antibodies in the cord blood are higher when mothers are immunized during the second trimester or early in the third trimester of gestation as compared to mothers immunized later in the third trimester (Eberhardt et al. 2016; Abu Raya et al. 2015). The highest concentrations of anti-PT antibodies in neonates at birth were observed when the mothers were vaccinated within the window of 27 through 30 weeks of pregnancy whereas the antibody titers declined thereafter (Healy et al. 2018). In these conditions, anti-PT antibody concentrations remained detectable at a substantial level until the initiation of the primary vaccines series in infants, reducing the risk of pertussis-related mortality and morbidity.

The avidity of umbilical cord IgG is reported by some authors to be higher in case of maternal immunization at 27–30 weeks of gestation (Eberhardt et al. 2016), whereas others reported no difference in the pertussis specific antibody avidity when the women are immunized before 27 weeks until at 31–36 weeks of gestation (Maertens et al. 2015).

This recommended strategy has resulted in a 91% reduction in pertussis in infants 3 months or younger in the United Kingdom (Amirthalingam et al. 2014). There is however some concern about the possible impact of the maternal IgG antibodies on the early life immunity. Several studies indicate that high maternally derived pertussis antibody titers can have a suppressive effect on infant responses to primary immunization against pertussis, mostly in case of infant vaccination with the wPV. A smaller and transient inhibitory effect on infant antibody response against pertussis was in contrast observed in case of acellular pertussis vaccination of infants, and globally, the clinical significance of this blunting effect has not yet been assessed (Abu-Raya et al. 2017). The effect of maternally derived antibodies on specific cellular immune responses was only very little investigated in humans but studies performed in animals suggest that T-cell responses would be unaffected.

6 Conclusions

Pertussis outbreaks are recorded even in countries with high vaccination coverage. Resurgence of the disease could be attributed not only to insufficient vaccine uptake, but also to suboptimal protection and waning of vaccine-induced immunity. Data from mathematical modelling (Althouse and Scarpino 2015) and animal experimental models (Warfel et al. 2014) show that even though the aPV is capable of preventing serious symptoms, it does not prevent bacterial colonization (Warfel et al. 2016). Therefore, despite vaccination, people could still transmit the bacteria. This is a possible explanation for the continuing circulation of the pathogen in aPV using countries (Huygen et al. 2014; Palazzo et al. 2016b; Moriuchi et al. 2017).

Maternal immunization has proven safe and effective in limiting severe and deadly pertussis in young infants, thus it should be supported, especially during the outbreak period. Nevertheless, further research efforts are needed to fill knowledge gaps.

It is clear that improvements in aPVs or development of new approaches, like the mucosal administration of an attenuated *B. pertussis* strain, needs an enhanced understanding of the correlates of protection against the disease and of the mechanisms that could induce durable, highly effective immunity.

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