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Preventive and Protective Properties of Pertussis Vaccines: Current Situation and Future Challenges

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Abstract

Pertussis, more commonly known as whooping cough, is a potentially fatal respiratory disease caused by *Bordetella pertussis*. Two different types of vaccines provide effective protection: killed whole-cell vaccines (wPV) and more recently available acellular vaccines (aPVs) formulated with specific components. Disturbingly, while the vaccines are widely used, the incidence of disease is increasing in several developed countries that have switched from wPV to an aPV. It is suggested that the single most important underlying cause suggested for the resurgence is transmission through asymptomatic infections. While both vaccines protect against disease, a newly developed baboon model has shown that they do not prevent infection. Importantly, wPV-vaccinated animals appeared to clear an infection more rapidly than those vaccinated with aPV, which can relate to the period of possible disease transmission. To ultimately control whooping cough, it is clear that a more effective vaccine is needed that can prevent both disease and transmission. Modifications underway include the elimination of LPS from wPVs to improve their safety profiles and augmentation of aPVs with other bacterium proteins to increase immunogenicity and the longevity of protection. In the interim, vaccinations with aPV during pregnancy appear to protect newborns, the most susceptible to deadly pertussis.

Keywords: pertussis, whooping cough, whole-cell vaccine, acellular vaccine, herd protection

1. Introduction

Pertussis or whooping cough, caused by *Bordetella pertussis*, is a severe respiratory childhood disease that can be fatal, particularly in very young infants. However, it also represents a significant disease burden in older children, adolescents, and adults [1]. The first pertussis vaccine was developed in 1926 [2] but has only been available for large-scale administration

since the middle of the last century. Today, more efficacious vaccines based on key antigens of pertussis have been developed and are available for providing global coverage in vaccination programs [3]. These vaccines are included on the World Health Organization (WHO) Model List of Essential Medicines, as one of the most effective and safe medicines needed in a healthcare system [4]. Nevertheless, the disease is still not under control and today is considered one of the most prevalent vaccine-preventable childhood diseases. The World Health Organization (WHO) records close to 160,700 pertussis-related deaths in children younger than 5 years in 2014 and more than 24.1 million yearly pertussis cases worldwide [5]. Since the 1950s, the incidence and the numbers of pertussis-linked deaths have declined dramatically and reached its lowest point in several countries in the late 1970s, which showed the effectiveness of mass vaccination programs against pertussis. Prior to their implementation, the reported incidence of the disease was as high as 150 cases per 100,000 persons, which was most likely a vast underestimation even in countries like the USA [6]. More recently, the number of cases and associated deaths has again increased in several industrialized countries, reflecting a shortcoming in current vaccination strategies.

Two types of pertussis vaccines (PVs) are currently available: the first-generation whole-cell vaccines (wPV) and the more recent acellular vaccines (aPVs). While the efficacy of wPV (Table 1) has been demonstrated to be $\geq 94\%$ after three administrations [7], the occurrence of adverse local and systemic events along with difficulties in production consistency leads to the development of aPVs in the 1980s, currently composed of one to five purified key antigens (Table 2). All available aPVs are combined with tetanus and diphtheria toxoids. Several are also formulated with hepatitis B, inactivated polio, and *Haemophilus influenza* B polysaccharide [8]. The aPVs clearly have an improved safety profile over wPV, and their short-term efficacy after three administrations was estimated to be 67–70% up to 84%, even those containing three or five *B. pertussis* components [8]. This value was recently confirmed in a systematic review of meta-analysis data focusing on the short-term protective effect of currently available childhood pertussis vaccines [9]. Because of their improved safety profiles and similar efficacies, most

Manufacturer or Distributor	Country
Behringwerke	Germany
CSL Limited	Australia
Institute of Technology in Immunobiology (Bio-Manguinhos) / Butantan Institut	Brazil
Merck Sharp @ Dohme	USA
Pasteur/Mérieux	France
SmithKline Beecham	USA
Wyeth-LederleVaccines and Pediatrics (Wyeth-Ayerst Laboratories)	Germany/Austria

Table 1. List of whole cell pertussis vaccine manufacturers or distributors.

Name of aPVs	Composition ¹	Manufacturers/Distributor
² Acel-Imune	(PT, FHA, PRN, FIM) +DT+TT	Wyeth Pharmaceuticals (USA)
² Acelluvax (Triacelluvax)	(PT, FHA, PRN) +DT+TT	Chiron Vaccines (USA)
³ Adacel	(PT, FHA, PRN, FIM) +DT+TT	Sanofi Pasteur
⁴ Boostrix-3	(PT, FHA, PRN) +DT+TT	Sanofi Pasteur
BSc-1	(PT)	Biocine Sclavo
CLL-3F2	(PT, FHA, FIM)	Sanofi Pasteur (Canada)
Certiva	(PT)+DT+TT	Baxter Laboratory
Daptacel (Tripacel)	(PT, FHA, PRN, FIM) +DT+TT	Sanofi Pasteur
⁵ DTaP-HB-IPV-Hib	PT, FHA, PRN, FIM) +DT+TT + HB + IPV + Hib	MGM Vaccines Co (Merck/Sanofi)
⁶ 2HCPDT	(PT, FHA, PRN, FIM) +DT+TT	Sanofi Pasteur (Canada)
Infanrix	(PT, FHA, PRN) + DT+TT	Glaxo Smith Klein (Rixensant, Belgium)
⁷ JNIM-7	(PT)	Japan Nat Inst of Healthy
LPB-3P	(PT, FHA, PRN)	Wyeth Lederle Vaccines and Pediatric (Germany)
MIch-2	(PT, FHA)	Michigan Department of Public Health
⁸ NIH-6	(PT, FHA)	Japan Nat Inst of Healthy
⁹ Pentavac	(PT, FHA, PRN, FIM) +DT+TT + HB + IPV + Hib	Sanofi Pasteur (France)
Por-3F2	(PT, FHA, FIM)	Speywood (Porton) Pharmaceuticals
¹⁰ Repevax	(PT, FHA, PRN, FIM) +DT+TT + IPV	Sanofi Pasteur
SSVI-1	(PT)	Swiss Serum and Vaccine Institute
¹¹ SKB-2	PT, FHA) +DT+TT	SmithKline Beecham Biologicals
Triavax	(PT, FHA) +DT+TT	Sanofi Pasteur (France)
Tripedia	(PT, FHA) +DT+TT	Sanofi Pasteur (USA)

¹Quantitative difference can be found in the aPV compounds formulations.

²No longer available (as of 2013).

³A 3-in-1 vaccine, differ from Infanrix by containing reduced quantities of PT (8 µg) + FHA (8 µg) + PRN (2,5 µg) + DT (2,5 lf) + TT (5lf). Licensed for use in person with 4 yr age or older. In the USA 10-60 yr older.

⁴A 3-in-1 vaccine approved for individuals aged ≥10 yr including those aged ≥65 yr.

⁵The 6-in-1 vaccine is given to babies as a series of 3 doses. The first dose is given at 2 months of age, the second at 4 months, and the third at 6 months. The vaccine is given at the same time as other childhood immunizations.

⁶Used in Pentacel and Pediacel.

⁷HCPDT is the "hybrid" formulation of Tripacel, evaluated in 1993 Stockholm trial.

⁸JNIH-6 and 7 were the aPV used in the 1986 Swedish trial.

⁹The 5-in-1 vaccine was used in the UK for many years. In late September 2017 the UK replaced it with a 6-in-1 vaccine for all babies born on or after 1st August 2017. Both vaccines give protection against diphtheria, tetanus, whooping cough (pertussis), polio and Hib disease (*Haemophilus influenzae* type b).

¹⁰A 3-in1 vaccine indicated for persons from 3 years of age as a booster following primary immunizations.

¹¹SKB-2 was an experimental two-company DTaP evaluated in the 1992 Stockholm trial.

Abbreviations: PT, pertussis toxin; FHA, phytohemagglutinin; PRN, pertactin; FIM, fimbriae (mixture of FIM-2 and FIM-3); TT, tetanus toxoid; DT, diphtheria toxoid, HB, Hepatitis B; IPV, Inactivated Polio; Hib, *Haemophilus influenzae* type b.

Table 2. Source and composition of acellular pertussis vaccines studied and producers.

developed countries have replaced wPV with an aPV. Globally, wPVs are still the most used vaccines due the higher cost of aPVs, which are difficult to afford in resource-poor countries.

Although the vaccines together have saved millions of people since its introduction, it has been estimated that their effectiveness appears to decrease between 2 and 10% per year [1, 10]. This rate of decrease has been observed in countries that continue to administer wPV. Yet, it has become apparent that the immunity induced by aPV declines substantially faster than that induced by wPV [11, 12], which led the WHO to recommend that countries considering a switch from wPV to aPV should expect further guidance [4]. Multiple studies, both epidemiological and serological, have confirmed that immunity wanes rapidly after the aPV booster at age 4–6 years and the preadolescent dose at age 10–12 years [13–18]. Nonetheless, it appears that the waning immunity induced by aPV, or wPV, is not the only reason for the observed resurgence in pertussis infections.

Another possible mechanism is asymptomatic transmission. Mathematical modeling of the incidence rates of pertussis in the USA and UK supports a role for undetectable transmission in the recent increase cases [19]. The potential for an essentially silent transmission is also supported by observations in a baboon model recently developed for studying *B. pertussis* infections. Vaccinations with aPV did not prevent transmission of *B. pertussis*. Virulent *B. pertussis* continued to establish infections in animals vaccinated with either aPV or wPV, even though both vaccines protected against disease. A major difference observed between the two vaccines was that infections cleared more rapidly in wPV-vaccinated baboons [20]. All vaccinated animals showed a lower total bacterial load compared to naïve animals suggesting that both vaccines have a positive impact to limit the progression of an infection. Yet, it appears that this impact may not be sufficient to control the circulation of *B. pertussis* within a population and could lead to the generation of vaccine escape mutants, which have indeed been observed in several countries where aPV is in use. A likely explanation is the observed increase in the isolation of strains not producing pertactin, due to selective pressure [21]. Conversely, there is no apparent major difference in the pathogenesis of whooping cough in children infected with pertactin-deficient strains compared to pertactin-producing strains. This indicates that pertactin is not required for infection by *B. pertussis* or for the development of the disease, suggesting a role of pertactin in the immune response following vaccination.

In contrast to vaccination with either aPV or wPV, a natural infection by *B. pertussis* is able to induce sterilizing immunity in baboons [20]. This fact is intriguing since studies in human have shown that infection-induced immunity is longer lived than vaccine-induced immunity [22], although probably not lifelong as reinfections have been reported to occur. While the second attacks are very rare, they are usually much milder than the primary infections [23]. Since *B. pertussis* is strictly a mucosal pathogen, it is conceivable that its restricted localization could influence the immunity induced from a natural infection. Although the protective role of mucosal immunity has so far attracted little attention, it may contribute to the differences observed between the protection obtained by a vaccine and a natural infection. These observations suggest that a vaccination approach that more closely mimics a natural infection without resulting in disease may be more successful to ultimately control pertussis.

Such a vaccine is currently under development based on a live attenuated *B. pertussis* strain. Named BPZE1, it has been genetically modified to affect the activity of three different toxins such that they are absent, inactive, or minimally active [24]. This strain has been documented to be safe in preclinical models and genetically stable over at least 1 year of continuous passaging in vitro and in vivo in mice [25]. It can induce a strong protection against challenge infections after a single intranasal administration, which lasted at least for up to 1 year. This contrasts with the protection conferred by aPV that can begin to wane after only 6 months. The strain BPZE1 has successfully completed a Phase I clinical trial that showed its safety profile in young male volunteers with a single intranasal dose of up to 10^7 colony-forming units suspended in 100 μ l. This trial also showed that BPZE1 can transiently colonize the human nasopharynx and induce *B. pertussis*-specific antibody responses in all colonized individuals. At 6 months, follow-up studies measured antibody titers against all antigens tested to be at least at the same level as detected at 1 month postvaccination. One concern with the trial was the observation that not all subjects showed colonization by BPZE1, even at the highest dose tested, since colonization was found to be essential for the induction of an immune response. A possible reason of the absence of colonization in some individuals may have been their prior contact with wild-type *B. pertussis*, which could have prevented a response to the vaccine. Consistent with this hypothesis is the detection of preexisting antibody titers in the non-colonized individuals that were significantly higher than the pre-vaccination titers of individuals that displayed colonization, especially against pertactin. Additional studies are needed to test the influence of a prior exposure to wild-type *B. pertussis* on BPZE1 colonization and to eliminate the possibility for a previously imperceptible subclinical disease. New clinical trials are in progress to test the hypothesis that the presence of preexisting antibodies prevents colonization by the vaccine strain and to determine if their activity can be neutralized by increasing the vaccine dosage.

Realistically, it would require many more years of research and regulatory approval before a new pertussis vaccine could be available for general use. In the interim, efforts are being made to optimize the application of current vaccines. A promising observation is the protection afforded to newborns, less than 2 months of age, from the immunization of their mothers with aPV during the 28–38th week of gestation. In a recent pertussis outbreak in the UK, the effectiveness of this vaccination schedule was shown to be greater than 90% [26]. Several countries have now made recommendations for providing aPV during pregnancy. However, many issues remain unresolved. For example, the impact of maternal immunization on the immune responses in infants following their primary vaccination is unclear. Several studies have observed a reduction in the primary antibody response to *B. pertussis* antigens following a maternal vaccination [27]. Another issue is the observation that the adoptive caring immunity is effective to prevent disease but does not prevent pertussis infections in neonates [28]. This suggests that the maternal levels of preexisting pertussis-specific antibodies cannot transfer complete protection against infection. The maternal immune system can be activated in response to pertussis and generates a recall response from memory B cells that increases the levels of milk IgA, but the clinical relevance remains to be determined. Lastly, in a mouse model, challenge studies also have shown that antibodies resulting from maternal vaccinations interfere with the functionality of antibodies induced from a subsequent vaccination [29].

2. Resurgence, vaccine design, and new targets

In 2008, there was an estimated incidence of 16 million cases of pertussis infection worldwide that resulted in approximately 195,000 children deaths, making pertussis one of the leading causes of vaccine-preventable deaths in children under 5 years of age [30, 31]. Most of pertussis deaths occur in developing countries. However, pertussis has not only persisted in countries with high vaccination coverage but has resurged with a number of epidemic episodes being recorded [32–34]. The resurgence of pertussis as a deadly childhood disease is a major public health concern that reflects changes in its epidemiology but is also affected by a growing attitude among parents to delay or even refuse vaccination of their children, which highlights the urgent need for new integrated approaches to control the spread and impact of whooping cough. Several explanations have been presented to enlighten the resurgence of pertussis disease over the past few decades in which most of them is associated with the aPVs currently in use: (i) the decrease of vaccine effectiveness over time (declining immunity) [35, 36], (ii) the selection of mutants that can escape the immunity induced by a vaccine [37, 38], and/or (iii) failure of the vaccine to induce sterilizing immunity to the pathogen that avoids transmission [20]. However, perhaps the most significant contributing factor is our relative lack of understanding the basics of pertussis infection, immunity, and disease. We are still unsure of which specific immune responses are protective against *B. pertussis* infection and disease in humans and how to elicit protective responses through vaccination.

To address the resurgence, new vaccination strategies have been explored such as the “cocooning strategy” and maternal immunization. Cocooning refers to the vaccination of mothers and others with direct contact to newborns and infants. Cost-effective cocooning would be difficult to implement since a successful program requires a very high number of contacts be vaccinated to attain a significant impact on the incidence of severe infant pertussis [39]. Currently, there is a growing evidence for effectiveness of immunization of women during pregnancy rather than during the immediate postpartum period. This approach has been found to be more cost-effective than cocooning with a level of vaccine effectiveness against infant deaths that reach an estimated 95% [27]. Alongside the vaccination of contacts, an alternative option under consideration is to advance the vaccination schedule for newborns to 6–8 weeks of age. However, this approach still does not provide protection to infants during their most susceptible period for potentially deadly pertussis infections. A missing element to refinements in the application of available vaccines is an improved surveillance for pertussis. Improvements in the detection of infections and the immune response can positively contribute to evaluations on vaccine efficacy that will help advance our understanding of performance and duration of a pertussis vaccine to provide protection in the field.

Since the 1950s, the toxicity of traditional wPV has been associated with the presence of lipopolysaccharides (LPS), the major constituents of the bacterial outer membranes. To improve on traditional wPVs, the Butantan Institute in Brazil recently produced a wPV with reduced quantities of LPS that removed $\geq 80\%$ of the endotoxin-related toxicity in comparison to traditional wPV production methods using a chemical extraction of lipo-oligosaccharide (LOS) from the outer membrane. The process maintained the main protective immunogens as well as the

integrity of the bacteria in the vaccine [40]. A major challenge over the next few years will be the implementation of a reproducible process that can produce consistent lots under good manufacturing practice conditions.

In recent years, extensive research efforts have elucidated that natural infections and immunizations with wPVs predominantly induce IFN- γ -secreting T-helper 1 cells (Th1) and IL-17-secreting Th17 cells [41–44]. By contrast, it has been shown that aPVs induce a qualitatively different immune response, characterized by the induction of Th2 immunity [39, 43–45]. This difference in the immune response, along with the chemical inactivation of the pertussis toxin antigen in aPVs, may account for the apparent lack of aPV protection against colonization by subsequent *B. pertussis* infections and suboptimal T-cell priming that has been observed as a reduction in the efficiency for the generation of an immune memory repertoire.

Since current aPVs mainly elicit a Th2 response, several solutions have been proposed to improve the Th1/Th17 responses. One possibility is to combine these vaccines with Th1-driving adjuvants, at least for the priming doses [46, 51]. The development of such a candidate vaccine based on a single-immunization platform consisting of three immune stimulators is in progress [47], namely, (i) host defense peptides, (ii) polyphosphazenes (a family of inorganic molecular hybrid polymers based on a phosphorus-nitrogen backbone substituted with organic side groups with very diverse properties), and (iii) the synthetic oligonucleotides containing CpG-ODN (oligodeoxynucleotides) combined with poly(I:C), (polyinosinic-polycytidylic acid) an agonists of Toll-like receptor 9 (TLR9). This last immune stimulatory compound associated with dacarbazine, a therapeutic agent, has been successfully used to promote antitumor immunity [48].

In the case of pertussis, the inclusion of these immune stimulators resulted in a humoral immune response from a single application in neonatal mice and pigs that was 100- to 1000-fold stronger than a licensed aPV [47]. The onset of immunity occurred more quickly with a predominantly Th1 response. Importantly, immunity persisted for more than 2 years and appeared to be highly effective even in the presence of maternal antibodies. To address the contribution of chemically inactivating pertussis toxin to vaccine performance, a strain of *B. pertussis* was engineered as a source for genetically detoxified Ptx for the formulation of a new aPV. In Thai adolescents, its safety was like Adacel, a trivalent aPV combined with diphtheria and tetanus compounds produced by Sanofi Pasteur (see **Table 2**) with an improved induction of neutralizing antibodies against PTx [47].

Substantial evidence has been accumulated in the last 2 years that immunity induced by aPVs is much shorter lived than immunity induced by wPV [10]. Additionally, using refined techniques of peptide microarray, it has been demonstrated that qualitative differences within the humoral response of individuals vaccinated with wPV and aPVs exist. Using a microarray technique, it was shown that animals immunized with wPV recognize qualitatively a major number of B epitopes in the PTx than mice immunized with aPV [49]. Another study using a similar approach compared the recognition pattern of sera from children immunized with different pertussis vaccines (17 *B. pertussis* proteins) and concluded that 11% of the individuals displayed a private humoral response [50]. All these studies are important to guide the rational development of new vaccines.

3. Difficulties with vaccine reformulation

While adults and adolescents normally only experience mild symptoms from a pertussis infection, they are the usual source of infection for neonates, and adoptive maternal immunity does not appear to prevent pertussis in neonates. In a study that compared the specific immune response in mothers of neonates diagnosed with pertussis and mothers of control children [28], preexisting pertussis-specific antibodies were insufficient for protection suggesting that memory B cells play a major role in the adult defense, which is not transferred to neonates. To provide newborns with protection, a new approach would be required, but to change the vaccine given to infants in the first 2 years of life is a discouraging proposition. It would involve a large data set for safety evaluation. Also, the pertussis vaccine is often combined into a multivalent formula with components against other pathogens. Any change directed at improving effectiveness against pertussis would require a recertification process that would impact a wide spectrum of vaccines currently on the market.

More importantly, it would be unethical to conduct formal efficacy studies for new vaccines/formulations that included a non-vaccinated control group. Considering the epidemiological and serological studies that show a rapid decline in immunity after the recommended aPV boosters at ages 4–6 and 10–12 years [13, 15, 16, 18], an intensive focus is being given on the booster vaccines given to preschool-age children and adolescents. However, even for a new booster vaccine, the regulatory pathway is unclear. A classical efficacy study would have to compare a new vaccine with a currently accepted one to show non-inferiority or superiority. Such studies would be expensive and require a long evaluation period considering that the current vaccines are effective for the first couple of years after administration.

Ideally, licensing authorities could present new approaches to evaluate the efficacy of a new vaccine. Alternatives include a greater reliance on the use of protection data obtained from animal studies [52]. The newly developed baboon model could provide in-depth serological data on the levels and duration of antibody titers, which can be verified in smaller human challenge studies using circulating strains of *B. pertussis*. Safety profiles could also be generated from fewer participants if modifications simply involve an update in the components with newer inactivation methods, such as genetic modifications. However, the greatest obstacle is most likely to recruit manufacturers to participate in the development of a new pertussis vaccine or booster. After the tremendous effort and expenditure invested to launch the aPVs along with shifting priorities to new pathogens, major manufacturers are resistant to shouldering multiple and simultaneous clinical development programs [52]. Physicians and government health agencies will be critical to creating a new demand. Assistance from academia and science funding agencies could assist vaccine development by conducting basic research on the pathogenesis and immunology of pertussis along with preliminary clinical trials [52]. All of this implies an enormous effort, but a new pertussis vaccine is needed. It is unethical to continue to allow a vaccine-preventable disease to be incompletely controlled, especially one that prejudices the very young people and disproportionately in less developed countries.

4. Protecting versus vaccination during pregnancy

Since the resurgence of pertussis infection, several studies have shown that the main source of infections in newborns and infants involved close-contact persons, mostly family members [53, 54]. In the first attempt to reduce the incidence of pertussis infections, indirect protection for the reduction of transmission rates was favored, the so-called cocooning strategy. In response, some countries adapted their national immunization guidelines [53–55]. Another study focused on the influence of vaccination rates among siblings and vaccination rates among mothers showed that the provided protection rates are comparable [56, 57]. In contrast, a recent study on the effect of cocooning infants younger than 6 months of age did not detect any reduction in pertussis cases [57]. Besides that, it is not yet clear and has created some controversy if cocoon strategies are cost-effective or even prevent infections [38, 58]. Even in the absence of definitive proof, it is still advisable for recent mothers to know their immunization status as well as those of all potentially close-contact individuals, all of whom can play a critical role in the potential transmission of pertussis to a newborn.

Another means to reduce the rate of pertussis transmission to neonates and young infants is the practice of providing pertussis vaccinations during pregnancy. This has become an important strategy in many countries in the absence of vaccines licensed for use before the age of 6 weeks and unknown effectiveness of cocooning strategies [53, 59–61]. The observation of the transplacental transfer of maternal anti-pertussis antibodies to the fetus led health authorities to first recommend the use of pertussis vaccinations during pregnancy in 2011 [62–64]. In the USA, a maternal vaccination was first recommended after gestational week 20 that was later shifted to a window between weeks 27 and 36 [65]. This recommendation has been adopted by both Switzerland and the UK [64].

Early studies showed that vaccination with Tdap vaccines during gestational week 27–30 + 6 was associated with the highest levels of IgG in umbilical cord blood when compared to vaccination beyond gestational week 31 [59], according to one of the most potent virulence factors of pertussis PTx. A recent study supports these data by showing that the maternal vaccination with Tdap early in the second trimester significantly increased neonatal antibodies at birth in comparison with neonates born from mothers vaccinated in the third trimester [61]. All in all, the antenatal vaccination campaign in the UK achieved a vaccine coverage of 60% with >90% effectiveness [66, 67]. A UK study conducted after initiating maternal vaccinations identified a large reduction in the number of confirmed cases of pertussis infection reported as the cause for a hospital admission that was especially notable for infants younger than 3 months of age [66].

From this campaign, the question arose as to whether a vaccination early in pregnancy might adversely affect the immune response in an infant to vaccinations after birth. Some studies showed that antibody concentrations at birth did not interfere with the immune response to further immunizations after birth [68]. However, it is known that maternally derived antibodies can interfere with the immune response in an infant vaccinated with the same vaccine [68],

which was detected after DTaP¹ (administered to children under 7 years of age) vaccination [69]. Maternal antibodies were also shown to interfere with the antibody response to the primary vaccination administered during infancy to children born to Tdap¹ (administered to older children and adults)-vaccinated mothers [62, 70]. Interestingly, a mouse model showed that the vaccination of infant mice reduced the protective functions of maternally derived antibodies in vitro and in vivo [29]. A study that focused on vaccinations with Repevax, a five component aPV combined with tetanus, low-dose diphtheria, and inactivated polio vaccine (Sanofi Pasteur), detected a significant attenuation of pertussis antibodies in infants whose mothers were vaccinated with Repevax during pregnancy [71]. Together with the diminished protection afforded by aPVs, recent findings suggest that the efficacy of current vaccines should be maximized by prenatal vaccination followed by boosting. It is important to continue studies to determine the functionality of maternal antibodies resulting from vaccinations during pregnancy and infant antibodies generated from subsequent vaccinations to better understand the potential for cross interference to design alternative vaccination strategies.

5. Conclusion

It is irrefutable that the worldwide incidence of severe pertussis cases is rising. Nearly 90% of all instances of deaths caused by pertussis occur in infants younger than 4 months of age and are caused by fatal pertussis pneumonia due to PTx activity [72], which highlights the need to inhibit PTx during an acute infection. Over the past few years, the scientific community has responded by initiating studies focused on a better understanding of virulence factors, like PTx, transmission dynamics, and host immune reactions, which can provide a foundation for the generation of a new vaccine but can also guide improvements in the use of current vaccines. It is clear that a control of pertussis requires a durable protection against disease and disruption of transmission. The two types of vaccines available, wPV and aPV, are effective in preventing the disease, but the immunity developed by each wane over time, even more rapidly with aPV, which should encourage countries in which wPV is still in use, not to switch to aPV. Further, transmission from vaccinated individuals is possible since *B. pertussis* can still colonize their respiratory tracts. Improvements to both types are in development, but it will be several years before their widespread use. In the interim, expansions in the use of the current vaccines have been proposed. Cocoon vaccination programs, which are controversial in their effectiveness, rely on generating herd immunity to protect young infants by vaccinating individuals with close contact. In contrast, immunization with aPV during pregnancy can reduce the incidence of severe and deadly pertussis in neonates. However, there are concerns that the antibodies raised from the maternal immunization can interfere with the immune response in the child to their primary vaccination. All approaches under development would benefit from

¹DTaP, Tdap, and Td are all similar vaccines, given for the same diseases at different times of life. Depending on the age, certain amounts of vaccine components are administered. Typing uppercase and lowercase letters denotes the component of the vaccine and the quantities in it. Uppercase letters in abbreviations denote undiluted doses of diphtheria (D), tetanus (T), and pertussis (P) toxoids. The lowercase letters d and p denote reduced doses of diphtheria and pertussis toxoids used in formulations for adolescents and adults. The letter a in the DTaP and Tdap vaccines means acellular.

a more detailed surveillance program to determine the rates of symptomatic and asymptomatic infections as well as an examination of the genetic diversity of *B. pertussis* strains in circulation to better understand methods to prevent the impacts of infection.

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Conflict of interest

The authors declare no conflict of interest.

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References

- [1] Hewlett EL, Edwards KM. Clinical practice. Pertussis-not just for kids. The New England Journal of Medicine. 2005;**352**:1215-1222. DOI: 10.1056/NEJMcp041025
- [2] Macera CA, Shaffer R, Shaffer PM. Introduction to Epidemiology: Distribution and Determinants of Disease in Humans. 1st ed. Boston, MA, USA: Cengage Learning; 2013. p 251
- [3] de Gouw D, Diavatopoulos DA, Bootsma HJ, Hermans PW, Mooi FR. Pertussis: A matter of immune modulation. FEMS Microbiology Reviews. 2011;**35**:441-474. DOI: 10.1111/j.1574-6976.2010.00257.x

- [4] WHO. Meeting of the strategic advisory group of experts on immunization, April 2014—Conclusions and recommendations. *Weekly Epidemiological Record*. 2014;**89**:221-236
- [5] Yeung KHT, Duclos P, Nelson EAS, Hutubessy RCW. An update of the global burden of pertussis in children younger than 5 years: A modelling study. *The Lancet Infectious Diseases*. 2017;**17**:974-980. DOI: 10.1016/S1473-3099(17)30390-0
- [6] Mooi FR, van Loo IH, van Gent M, He Q, Bart MJ, Heuvelman KJ, et al. *Bordetella pertussis* strains with increased toxin production associated with pertussis resurgence. *Emerging Infectious Diseases*. 2009;**15**:1206-12213. DOI: 10.3201/eid1508.08151
- [7] Guiso N, Hegerle N. Other Bordetellas, lessons for and from pertussis vaccines. *Expert Review of Vaccines*. 2014;**13**:1125-1133. DOI: 10.1586/14760584.2014.942221
- [8] SmithKline Beecham Biologicals. Synopsis of Final Study Report 217744/025 (DTPa-HBV-IPV-025); 1999
- [9] Fulton TR, Phadke VK, Orenstein WA, Hinman AR, Johnson WD, et al. Protective effect of contemporary Pertussis vaccines: A systematic review and meta-analysis. *Clinical Infectious Diseases*. 2016;**62**:100-110. DOI: 10.1093/cid/ciw051
- [10] Koepke R, Eickhoff JC, Ayele RA, Petit AB, Schauer SL, et al. Estimating the effectiveness of tetanus-diphtheria-acellular pertussis vaccine (TDaP) for preventing pertussis: Evidence of rapidly waning immunity and difference in effectiveness by TDaP brand. *The Journal of Infectious Diseases*. 2014;**210**:942-953. DOI: 10.1093/infdis/jiu322
- [11] Witt MA, Katz PH, Witt DJ. Unexpectedly limited durability of immunity following acellular pertussis vaccination in preadolescents in a North American outbreak. *Clinical Infectious Diseases*. 2012;**54**:1730-1735. DOI: 10.1093/cid/cis287
- [12] Gambhir M, Clark TA, Cauchemez S, Tartof SY, Swerdlow DL, et al. A change in vaccine efficacy and duration of protection explains recent rises in pertussis incidence in the United States. *PLoS Computational Biology*. 2015;**11**:e1004138. DOI: 10.1371/journal.pcbi.1004138
- [13] Misegades LK, Winter K, Harriman K, Talarico J, Messonnier NE, et al. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. *JAMA*. 2012;**308**:2126-2132. DOI: 10.1001/jama.2012.14939
- [14] Sheridan SL, Ware RS, Grimwood K, Lambert SB. Number and order of whole cell pertussis vaccines in infancy and disease protection. *JAMA*. 2012;**308**:454-456. DOI: 10.1001/jama.2012.6364
- [15] Baxter R, Bartlett J, Rowhani-Rahbar A, Fireman B, Klein NP. Effectiveness of pertussis vaccines for adolescents and adults: Case-control study. *BMJ*. 2013;**347**:f4249. DOI: 10.1136/bmj.f4249
- [16] Klein NP, Bartlett J, Fireman B, Rowhani-Rahbar A, Baxter R. Comparative effectiveness of acellular versus whole-cell pertussis vaccines in teenagers. *Pediatrics*. 2013;**131**:e1716-e1722. DOI: 10.1542/peds.2012-3836

- [17] Liko J, Robison SG, Cieslak PR. Priming with whole-cell versus acellular pertussis vaccine. *The New England Journal of Medicine*. 2013;**368**:581-582. DOI: 10.1056/NEJMc1212006
- [18] Tartof SY, Lewis M, Kenyon C, White K, Osborn A, et al. Waning immunity to pertussis following 5 doses of DTaP. *Pediatrics*. 2013;**131**:e1047-e1052. DOI: 10.1542/peds.2012-1928
- [19] Althouse BM, Scarpino SV. Asymptomatic transmission and the resurgence of *Bordetella pertussis*. *BMC Medicine*. 2015;**13**:146. DOI: 10.1186/s12916-015-0382-8
- [20] Warfel JM, Zimmerman LI, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. *PNAS*. 2014;**111**:787-792. DOI: 10.1073/pnas.1314688110
- [21] Martin SW, Pawloski L, Williams M, Weening K, DeBolt C, Qin X, et al. Pertactin negative *Bordetella pertussis* strains: Evidence for a possible selective advantage. *Clinical Infectious Diseases*. 2015;**60**:223-227. DOI: 10.1093/cid/ciu788
- [22] Le Coustumier A, Njamkepo E, Cattoir V, Guillot S, Guiso N. *Bordetella petrii* infection with long-lasting persistence in human. *Emerging Infectious Diseases*. 2011;**17**:612-618. DOI: 10.3201/eid1704.101480
- [23] Cherry JD, Grimprel E, Guiso N, Heininger U, Mertsola J. Defining pertussis epidemiology: Clinical, microbiologic and serologic perspectives. *The Pediatric Infectious Disease Journal*. 2005;**24**:S25-S34. DOI: 10.1097/01.inf.0000160926.89577.3b
- [24] Kliegman R, Stanton B, St Geme J, Schor N, editors. *Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2015; 197p
- [25] Thorstensson R, Trollfors B, Al-Tawil N, Jahnmatz M, Bergström J, Ljungman M, et al. A Phase I clinical study of a live attenuated *Bordetella pertussis* vaccine—BPZE1; a single centre, double-blind, placebo-controlled, dose escalating study of bpze1 given intranasally to healthy adult male volunteers. *PLoS One*; **9**:e83449. DOI: 10.1371/journal.pone.0083449
- [26] Amirthalingam G, Campbell H, Ribeiro S, Fry NK, Ramsay M, Miller E, Andrews N. Sustained effectiveness of the maternal pertussis immunization program in England 3 years. *Clinical Infectious Diseases*. 2016;**63**:S236-S243. DOI: 10.1093/cid/ciw559
- [27] Chiappini E, Stival A, Galli L, de Martino M. Pertussis re-emergence in the post-vaccination era. *BMC Infectious Diseases*. 2013;**26**, **13**:151. DOI: 10.1186/1471-2334-13-151
- [28] Marcellini V, Piano-Mortari E, Fedele G, Gesualdo F, Pandolfi E, et al. Protection against Pertussis in humans correlates to elevated serum antibodies and memory B cells. *Frontiers in Immunology*. 2017;**8**:1158. DOI: 10.3389/fimmu.2017.01158
- [29] Feunou PF, Mielcareck N, Locht C. Reciprocal interference of maternal and infant immunization in protection against pertussis. *Vaccine*. 2016;**34**:1062-1069. DOI: 10.1016/j.vaccine.2016.01.011
- [30] Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, et al. Global, regional, and national causes of child mortality in 2008: A systematic analysis. *Lancet*. 2010;**375**:1969. DOI: 10.1016/S0140-6736(10)60549-1

- [31] Gall SA. Prevention of pertussis, tetanus, and diphtheria among pregnant, postpartum women, and infants. *Clinical Obstetrics and Gynecology*. 2012;**55**:498-509. DOI: 10.1097/GRF.0b013e.31824f3b38
- [32] Cherry JD. Epidemic pertussis in 2012—The resurgence of a vaccine-preventable disease. *The New England Journal of Medicine*. 2012;**367**:785. DOI: 10.1056/NEJMp1209051
- [33] Winter K, Glaser C, Watt J, Harriman K. Centers for Disease Control and Prevention (CDC). Pertussis epidemic—California. *MMWR. Morbidity and Mortality Weekly Report*. 2014;**63**:1129-1132
- [34] Tan T, Dalby T, Forsyth K, Halperin SA, Heininger U, et al. Pertussis across the globe: Recent epidemiologic trends from 2000-2013. *The Pediatric Infectious Disease Journal*. 2015;**34**:e222-ee32. DOI: 10.1097/INF.0000000000000795
- [35] Wendelboe AM, Van Rie A, Salmaso S, Englund JA. Duration of immunity against pertussis after natural infection or vaccination. *The Pediatric Infectious Disease Journal*. 2005;**4**:S58-S61. DOI: 10.1097/01.inf.0000160914.59160.41
- [36] McGirr A, Fisman DN. Duration of pertussis immunity after DTaP immunization: A meta-analysis. *Pediatrics*. 2015;**135**:331-343. DOI: 10.1542/peds.2014-1729
- [37] Mooi FR, van Loo IH, King AJ. Adaptation of *Bordetella pertussis* to vaccination: A cause for its reemergence? *Emerging Infectious Diseases*. 2001;**7**:526-528. DOI: 10.3201/eid0707.010708
- [38] Bart MJ, Harris SR, Advani A, Arakawa Y, Bottero D, et al. Global population structure and evolution of *Bordetella pertussis* and their relationship with vaccination. *mBio*. 2014;**5**:e01074. DOI: 10.1128/mBio.01074-14
- [39] Swamy GK, Wheeler SM. Neonatal pertussis, cocooning and maternal immunization. *Expert Review of Vaccines*. 2014;**13**:1107-1114. DOI: 10.1586/14760584.2014.944509
- [40] Dias WO, van der Ark AAJ, Sakaushi MA, Kubrusly FS, Prestes AFRO, et al. An improved whole cell pertussis with reduced content of endotoxin. *Human Vaccines & Immunotherapeutics*. 2013;**9**:339-348. DOI: 10.4161/hv.22847
- [41] Rieber N, Graf A, Belohradsky BH, Hartl D, Urschel S, et al. Differences of humoral and cellular immune response to an acellular pertussis booster in adolescents with a whole cell or acellular primary vaccination. *Vaccine*. 2008;**26**:6929-6235. DOI: 10.1016/j.vaccine.2008.09.064
- [42] Fedele G, Spensieri F, Palazzo R, Nasso M, Cheung GY, et al. *Bordetella pertussis* commits human dendritic cells to promote a Th1/Th17 response through the activity of adenylate cyclase toxin and MAPK-pathways. *PLoS One*. 2010;**5**:e8734. DOI: 10.1371/journal.pone.0008734
- [43] Ross PJ, Sutton CE, Higgins S, Allen AC, Walsh K, Misiak A, Lavelle EC, McLoughlin RM, Mills KH. Relative contribution of Th1 and Th17 cells in adaptive immunity to *Bordetella*

- pertussis*: Towards the rational design of an improved acellular pertussis vaccine. PLoS Pathogens. 2013;**9**:e1003264. DOI: 10.1371/journal.ppat.1003264
- [44] Warfel JM, Merkel TJ. *Bordetella pertussis* infection induces a mucosal IL-17 response and long-lived Th17 and Th1 immune memory cells in nonhuman primates. Mucosal Immunology. 2013;**6**:787-796. DOI: 10.1038/mi.2012.117
- [45] Ausiello CM, Lande R, Urbani F, Di Carlo B, Stefanelli P, et al. Cell-mediated immunity and antibody responses to *Bordetella pertussis* antigens in children with a history of pertussis infection and in recipients of an acellular pertussis vaccine. The Journal of Infectious Diseases. 2000;**181**:1989-1995. DOI: 10.1086/315509
- [46] Allen AC, Mills KH. Improved pertussis vaccines based on adjuvants that induce cell-mediated immunity. Expert Review of Vaccines. 2014;**13**:1253-1264. DOI: 10.1586/14760584.2014.936391
- [47] Carbonetti NH, von König CHW, Lan R, Jacob-Dubuisson F, Cotter PA, et al. Highlights of the 11th International Bordetella symposium: From basic biology to vaccine development. Clinical and Vaccine Immunology. 2016;**23**:842-850. DOI: 10.1128/IAI.01578-06
- [48] Noci V, Tortoreto M, Gulino A, Storti C, Bianchi F, Zaffaroni N, Tripodo C, Tagliabue E, Balsari A, Sfondrini L. Poly(I:C) and CpG-ODN combined aerosolization to treat lung metastases and counter the immunosuppressive microenvironment. Oncoimmunology. 2015;**4**:e1040214. DOI: 10.1080/2162402X.2015.1040214
- [49] Silva FR, Napoleão-Pego P, De-Simone SG. Identification of linear B epitopes of pertactin of *Bordetella pertussis* induced by immunization with whole and acellular vaccine. Vaccine. 2014;**32**:6251-6258. DOI: 10.1016/j.vaccine.2014.09.019
- [50] Valentini D, Ferrara G, Advani R, Hallander HO, Maeurer MJ. Serum reactome induced by *Bordetella pertussis* infection and Pertussis vaccines: Qualitative differences in serum antibody recognition patterns revealed by peptide microarray analysis. BMC Immunology. 2015;**16**:40. DOI: 10.1186/s12865-015-0090-3
- [51] Locht C. Pertussis: Acellular, whole-cell, new vaccines, what to choose? Expert Review of Vaccines. 2016;**15**:671-673. DOI: 10.1586/14760584.2016.1161511
- [52] Zlamy M. Rediscovering pertussis. Frontiers in Pediatrics. 2016;**4**:52. DOI: 10.3389/fped.2016.00052
- [53] McGuirk P, Heininger U. Protecting newborns from pertussis—The challenge of complete cocooning. BMC Infectious Diseases. 2014;**14**:397. DOI: 10.1186/1471-2334-14-397
- [54] Healy CM, Rench MA, Wootton SH, Sastagnini LA. Evaluation of the impact of a pertussis cocooning program on infant pertussis infection. The Pediatric Infectious Disease Journal. 2015;**34**:22-26. DOI: 10.1097/INF.0000000000000486
- [55] Frère J, De Wals P, Ovetchkine P, Coïc L, Audibert F, et al. Evaluation of several approaches to immunize parents of neonates against *B. pertussis*. Vaccine. 2013;**31**:6087-6091. DOI: 10.1016/j.vaccine.2013.09.043

- [56] De Greeff SC, de Melker HE, Westerhof A, Schellekens JF, Mooi FR, et al. Estimation of household transmission rates of pertussis and the effect of cocooning vaccination strategies on infant pertussis. *Epidemiology*. 2012;**23**:852-860. DOI: 10.1097/EDE.0b013e31826c2b9e
- [57] Marchant A, Sadarangani M, Garand M, Dauby N, Verhasselt V, et al. Maternal immunization: Collaborating with mother nature. *The Lancet Infectious Diseases*. 2017;**17**:e197-e208
- [58] Rivero-Santana A, Cuéllar-Pompa L, Sánchez-Gómez LM, Perestelo-Pérez L, Serrano-Aguilar P. Effectiveness and cost-effectiveness of different immunization strategies against whooping cough to reduce child morbidity and mortality. *Health Policy*. 2014;**115**:82-91. DOI: 10.1016/j.healthpol.2013.12.007
- [59] Tiwari TS, Baughman AL, Clark TA. First pertussis vaccine dose and prevention of infant mortality. *Pediatrics*. 2015;**135**:990-999. DOI: 10.1542/peds.2014-2291
- [60] Abu-Raya B, Srugo I, Kessel A, Peterman M, Bader D, et al. The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels—A prospective study. *Vaccine*. 2014;**32**:5787-5793. DOI: 10.1016/j.vaccine.2014.08.038
- [61] Eberhardt CS, Blanchard-Rohner G, Lemaître B, Boukrid M, Combescure C, et al. Maternal immunization earlier in pregnancy maximizes antibody transfer and expected infant seropositivity against pertussis. *Clinical Infectious Diseases*. 2016;**62**:829-836. DOI: 10.1093/cid/ciw027
- [62] Gall SA, Myers J, Pichichero M. Maternal immunization with tetanus—Diphtheria pertussis vaccine: Effect on maternal and neonatal serum antibody levels. *American Journal of Obstetrics and Gynecology*. 2011;**204**:e1-e5. DOI: 10.1016/j.ajog.2010.11.024
- [63] Hardy-Fairbanks AJ, Pan SJ, Decker MD, Johnson DR, Greenberg DP, et al. Immune responses in infants whose mothers received Tdap vaccine during pregnancy. *The Pediatric Infectious Disease Journal*. 2013;**32**:1257-1260. DOI: 10.1097/INF.0b013e3182a09b6a
- [64] UK Department of Health. Pregnant Women to be Offered Whooping Cough Vaccination. 2015. Available from: <http://www.dh.gov.uk/health/2012/09/whooping-cough/> [Accessed: 2017.07.16]
- [65] Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women—Advisory Committee on Immunization Practices (ACIP), 2012. *MMWR. Morbidity and Mortality Weekly Report*. 2013;**62**:131-135
- [66] Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, et al. Effectiveness of maternal pertussis vaccination in England: An observational study. *Lancet*. 2014;**384**:1521-1528. DOI: 10.1016/S0140-6736(14)60686-3
- [67] Dabrera G, Amirthalingam G, Andrews N, Campbell H, Ribeiro S, et al. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012–2013. *Clinical Infectious Diseases*. 2015;**60**:333-337. DOI: 10.1093/cid/ciu821

- [68] Heininger U. Pertussis: What the pediatric infectious disease specialist should know. *The Pediatric Infectious Disease Journal*. 2012;**31**:78-79. DOI: 10.1097/INF.0b013e31823b034e
- [69] Niewiesk S. Maternal antibodies: Clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. *Frontiers in Immunology*. 2014;**5**: 446. DOI: 10.3389/fimmu.2014.00446
- [70] Eberhardt CS, Blanchard-Rohner G, Lemaître B, Combescure C, Othenin GV, et al. Pertussis antibody transfer to preterm neonates after second-versus third-trimester maternal immunization. *Clinical Infectious Diseases*. 2017;**64**:1129-1132. DOI: 10.1093/cid/cix046
- [71] Ladhani SN, Andrews NJ, Southern J, Jones CE, Amirthalingam G, et al. Antibody responses after primary immunization in infants born to women receiving a pertussis-containing vaccine during pregnancy: Single arm observational study with a historical comparator. *Clinical Infectious Diseases*. 2015;**61**:1637-1644. DOI: 10.1093/cid/civ695
- [72] Melvin JA, Scheller EV, Miller JF, Cotter PA. *Bordetella pertussis* pathogenesis: Current and future challenges. *Nature Reviews. Microbiology*. 2014;**12**:274-288. DOI: 10.1038/nrmicro3235

