1. Introduction

*Bordetella pertussis* is a Gram-negative coccobacillus that causes whooping cough, also known as pertussis, in humans [1]. Historical reports mention the disease as far back as the XIIth century [2], but pathogen isolation only occurred in the XXth century [3]. Since then, much has been learned about the pathogenesis and prevention of the disease, but infection is still a concern in several countries [4].

Respiratory infection is especially aggressive in young children, who are more likely to experience the classical manifestation of the disease [5], divided into three phases: the first phase is characterized by unspecific symptoms, such as coryza, fever, and occasional cough. After two weeks, the cough is aggravated and becomes constant and uncontrollable, followed by forced inspiration producing a whooping sound. Symptoms can decrease progressively into the convalescence phase; however, complications such as pneumonia are frequent and are responsible for over 90% of the deaths attributable to the disease in children younger than 3 years of age [6, 7].

Until 2003, 50 million cases and 300,000 deaths were estimated every year around the world, mostly in children younger than 5 years of age [8].

Between 2010 and 2014, however, a rise in cases has been seen worldwide. In the US, the incidence before the 1980s was 1 case for each 100,000 inhabitants; in 2012, the incidence increased to 9 : 100,000, with more than 42,000 cases [6]. In the UK, over 9,000 children younger than 3 years old were infected in 2011 [9], and in Brazil, there were 22,426 confirmed cases, mostly in children younger than 1 year of age; in São Paulo, the largest state in the country, the incidence increased from 2.20 per 100,000 in 2011 to 5.06 per 100,000 in 2014 [10]. Other countries such as Argentina, Chile, Canada, and Australia also reported an increase in the number of cases [11, 12].

Treatment with macrolide antibiotics can be effective in eliminating the pathogen if administered at the beginning
of the symptoms; but as these antibiotics are unspecific and the disease is usually diagnosed due to the paroxysmal cough, treatment is often delayed, and by the time it is prescribed, the symptoms are already more severe, making prevention vital, especially for young children [13].

2. Immunopathogenesis of Pertussis

When the bacteria enter the human body, they adhere to the respiratory epithelium and produce a number of pathogenic toxins [4] to break natural barriers, such as cilia and mucus, to evade the innate immune system [14]. Then, bacteria can reach epithelial cells and replicate intracellularly [1], leading to the recruitment of different arms of the immune system [15–18].

Briefly, the regular immune response against pertussis infection recruits both innate and adaptive immune responses. After recognition of bacterial patterns by Toll-like receptors (TLRs), resident macrophages and neutrophils phagocytize and destroy bacteria at the infection site while dendritic cells (DCs) present and activate T CD4+ lymphocytes, which in turn mainly differentiate into IFN-γ-producing T helper (Th) 1 cells. Natural killer (NK) cells can also be recruited to produce IFN-γ to help polarize T cells. These molecules are especially important for activating macrophages through the production of IFN-γ to destroy bacteria that can survive phagocytosis and escape into the cell cytoplasm [18].

Pertussis can, however, use toxins to stimulate DCs to produce IL-10, instead leading to the differentiation of T regulatory cells and a predominance of an anti-inflammatory response, which is more favourable to the survival of the bacteria in the host [18].

In addition, antibodies, especially IgG and IgA, may have a role in bacterial clearance, even though there have been no previously defined correlates of protection [1, 19]. Antibodies can act by neutralizing bacterial toxins or as opsonins to prevent cell infection [1, 19], and maternal anti-pertussis antibodies are transmitted via the placenta to the foetus, contributing to newborn protection [18]. Nevertheless, more studies show that Th1 and Th17 responses are more efficient in rapidly clearing the bacteria [17, 20–22].

3. Neonatal Immunity

In children, several qualitative and quantitative differences in the immune response contribute to the severity of disease [23]. For a long time, neonates were considered most susceptible to disease due to a deficient and immature immune system [24]; however, it is currently known that the newborn immune system is only less responsive than that of the adult due to the regulatory effects of foetal-maternal tolerance that are imposed during development in the uterus and that remain active soon after birth [25].

Healthy newborns express TLRs in a stable way similar to that expression manner in adults and are capable of enhancing the expression of TLR on mononuclear cells in case of bacterial sepsis [26]. However, cells such as neutrophils, monocytes, and macrophages have more difficulty in expressing costimulatory molecules such as CD80 and CD86, secreting cytokines such as tumor necrosis factor α, IL-12p70, and IFN-γ and responding to chemokines until approximately 2 years of age [27–29]. They also have less capacity for antigen processing and less major histocompatibility complex II molecules, which participate in the activation of naïve T CD4+ cells and the differentiation of these cells to the Th1 profile, leading to anergy [25, 27–29].

Neutrophils are present in a lower number in the bone marrow in neonates and are more immature compared to those in adults, having fewer preformed antimicrobial peptides and a lower capacity for Gram-negative bacterial elimination, justifying their higher susceptibility to infection and sepsis [27, 30]. NK cell counts are elevated in newborns’ peripheral blood, but these cells secrete small amounts of IFN-γ [29]. Impaired innate immunity can be partly explained by the immunomodulation by CD71+ erythroid suppressor cells. These cells are present in high numbers in neonates and human cord blood and are capable of inhibiting innate response to B. pertussis infection in neonatal mice by the expression of arginase II [31]. Similarly, the presence of erythroid suppressor cells decreases TNF-α production and B. pertussis phagocytosis by human CD11b+ cells in vitro.

These differences in the innate immune response are reflected especially in the development and in the profile of the newborn’s adaptive immune response to B. pertussis [32]. Alongside not having a fully developed anatomical microenvironment that is suited to the interaction between DCs and T and B lymphocytes (there is no defined demarcation between different lymphoid zones and T CD4+ zones in neonates [28]), neonate cells have a lower capacity to generate memory cells and Th1 effector responses, also due to the lower IL-12 production by DCs [25]. Thus, there is lower subsequent production of IL-12 and IFN-γ [33] and a lower CD40L expression [27], which also lead to a lower production of IgG, IgA, and IgE [28], making the bacterial clearance compromised.

However, the production of IL-10, IL-6, IL-23, and IL-1β, cytokines that contribute to Th17 cell polarization, is higher in neonates than in adults [25, 26]. Additionally, elevated IL-10 production in early life was shown to be predominant in B. pertussis-infection cases [25, 34, 35].

While there is less Th1 polarization, there is higher IL-4 detection in neonate cells, both in unstimulated and in stimulated cells, compared to that in adult cells. The Th2 locus is hypomethylated in neonates and methylated in adults, while transcription of the subunit p35 of IL-12p70 in DCs derived from monocytes, when stimulated with lipopolysaccharide, is limited by epigenetic regulation [25, 36]. This makes Th2 cells more predominant in neonates, even after vaccination. However, it is known that the bacillus Calmette-Guérin vaccine can induce Th1 cells [37], so perhaps Th2 predominance is not a characteristic that is biased towards the newborn period, but is derived from the difficulty in polarizing cells to the Th1 profile during this period [25].

Th2, Th17, and regulatory lymphocyte predominance, allied to the absence of memory, favours the higher susceptibility of newborns to infection and intracellular or capsulated pathogens [38]. In addition, antibodies produced by newborns have a shorter duration, are initially produced later,
and show lower affinity, reduced heterogeneity, and deficient response to bacterial polysaccharides [27]. Further limiting vaccination after birth, plasma cells show low induction and less migration to the bone marrow, which contributes to limited humoral response and rapid decline of vaccine antibodies [28, 29, 39].

4. Vaccination

The introduction of a combined diphtheria/tetanus/whole cell pertussis vaccine (DTwP) in the 1940s and 1990s has been effective in the large decrease in pertussis morbidity and mortality in young children. Between 1999 and 2014, the World Health Organization (WHO) records suggest that more than 100,000 infant deaths could have been prevented mainly by increased coverage of pertussis vaccination [40].

The appearance of adverse reactions such as convulsions and encephalopathies [41] led the development of an acellular pertussis vaccine (aP) based on purified B. pertussis antigens, which were less reactogenic than the whole-cell vaccine [42, 43].

Acellular vaccines are presented in two formulations: DTaP, for vaccination of children, and Tdap, for vaccination of adults, with higher or lower concentrations of diphtheria toxoid and pertussis antigens [44]. For the immunization of individuals older than 7 months of age, Tdap is recommended rather than DTaP due to adverse reactions increasing with age and number of doses [45]. Many countries replaced DTwP for acellular vaccines, but countries such as Brazil and Argentina still use the whole-cell formulation since acellular formulations have a much higher cost [45].

Despite the differences between adult and children immune systems, it is known that DTwP in children can prime their immune system for a Th1 response, while acellular vaccines induce a mixed Th1/Th2 response, with production of both IFN-γ and IL-4 [46, 47]. There are studies showing that children vaccinated with DTaP in the first year of life produced more IFN-γ than IL-5 [47, 48]. However, this relationship shifted after boost doses [47] or natural asymptomatic infections [4].

Regarding antibodies, primary immunization of children with DTwP showed induction of specific anti-PT, anti-FHA, and anti-pertactin IgG, since the first dose at 2 months of age and lasting until 2 years of age [49] or longer [50, 51]. Anti-PT IgG was also positively correlated with protection of children after aP administration [52].

The WHO recommends the administration of three doses in the first year of life to decrease the incidence of pertussis. Vaccination is recommended at six weeks of age with the other two doses administered at 4- and 8-week intervals, respectively, until the child’s sixth month of life [45].

The organization states that both cellular and acellular vaccines are safe and effective in disease prevention in the first year of life [45]. However, it recommends that low- and middle-income countries that use DTwP should not replace the vaccine since the whole-cell formulation is low-cost (US$ 0.38 per DTwP dose compared with US$ 9.15 per DTaP dose) and highly effective, without directly related, important adverse events reported [53, 54].

Nevertheless, data from mathematical modelling [55] and baboon experiments [56] show that even though the acellular vaccine is capable of preventing serious symptoms, it does not prevent bacterial colonization. Since DTwP consists of whole bacteria, this vaccine elicits antibodies and cytokines against a wider range of antigens, which may affect attachment to the respiratory tract and bacterial opsonization [57]. Therefore, despite vaccination, animals and people could still transmit the bacteria. This could be a possible explanation for the pathogen permanence in aP-vaccinated countries, as well as occasional mutations that can lead to immune response evasion by the bacteria [58].

It is well known that immunity after natural infection is not permanent, decaying after 4-20 years after infection [59]. Therefore, immunity after vaccination is also not long lasting, but immunity after DTwP lasts from 4 to 12 years, and immunity after aP lasts an even shorter period, even after booster doses [53, 59–61].

Thus, the WHO alerts to the possibility of pertussis reemergence, especially in countries using aP vaccines alone. The WHO suggests the use of booster doses at two years of age, during pregnancy and in people directly in touch with young children to avoid serious pertussis cases in at-risk groups [62], as newborn and infants are the most susceptible groups to disease [45] and infection in these groups results in a higher lethality rate [63]. The main contagious sources are siblings and parents [64–66], and countries such as Australia, Germany, and the US recommend booster doses in these groups [67].

The vaccination scheme against pertussis needs to undergo a reevaluation, especially since there has been a resurgence of this disease. Recent vaccine candidate studies explored live-attenuated formulations that cause lower adverse reactions than DTwP and include possible mutations of the wild-type bacteria with the goal of also reducing transmission of the pathogen [68–70]. One example is a whole-cell vaccine produced with lower endotoxin levels developed by the Butantan Institute, Brazil, aimed at reducing severe reactogenicity caused by the bacteria’s lipooligosaccharide [70].

Nevertheless, while new vaccines were in trials, different vaccination strategies were implemented, such as neonatal immunization (from birth to 1 month of age), cocooning, postpartum vaccination, and maternal immunization, to increase protection levels and prevent further pertussis cases [71, 72].

5. Prevention Strategies

5.1. Vaccination at Birth. The viability of immunizing children soon after birth with DTwP has been studied for more than 40 years but has been discontinued because it results in immunological tolerance, where the levels of antibodies to B. pertussis antigens are reduced compared to those in children who were vaccinated later [73].

However, while aP vaccination in neonate mice induced low antibody responses [74], recent studies show that acellular vaccine after birth can elicit specific antibody responses during the neonate phase [72, 75]. Supporting the results found in humans, the study conducted by Warfel and
coworkers [76] using a baboon model showed protection of newborns against pathogen challenge.

5.2. Cocooning. Cocooning has been recommended since the early 2000s in the US, France, Australia, and Germany to prevent pertussis in newborns [45, 77, 78]. This strategy consists of vaccinating all the close relatives when a child is born [79]; this population should receive Tdap at least two weeks before initiating close contact with the child [80]. Cocooning is mainly directed to reduce disease-associated morbidity and transmission to young, unvaccinated children [81]. Recently, cocooning was recommended in Latin America in Brazil, Chile, and Costa Rica [45]. In Chile, in 2012-2013, it is estimated that 84% of potential pertussis deaths in infants were prevented [82], but in other countries around the world, current data found a minor or no impact of this approach [83]. Therefore, the efficacy of cocooning is limited because the child has no specific protection, and the approach demands the vaccination of several adults, making cocooning both costly and difficult to implement [79]. Cocooning is, however, still practiced and studied in several countries (reviewed by Forsyth et al. [84]).

5.3. Postpartum Vaccination. In countries such as Brazil and the US, postpartum vaccination or partial cocooning is recommended as early as possible for women not vaccinated during pregnancy to prevent the mother from transmitting pertussis to the newborn [85, 86], but this strategy is not ideal because it offers protection only to the mother. After vaccination, it takes two weeks to generate a maximal immune response to the vaccine antigens, during which time the mother is vulnerable to contracting and disseminating the disease to the child [86]. It is possible that the postpartum immunization of mothers can be administered too late to protect newborns if the mother is already infected during childbirth or is exposed to pertussis soon after [87].

5.4. Maternal Immunization. The most recent strategy is aimed at inducing higher anti-pertussis antibody levels in pregnant women and higher placental transfer rates to the foetus [77], since pertussis has no protection conferred by natural maternal antibodies (MatAbs) [88], and children are most vulnerable to infection during the first months of life because they are not fully vaccinated [77].

Countries such as the US, UK, and Australia have recommended maternal immunization since 2012 for both the protection of children and mothers [89]. Efficacy and security studies have been published in these countries, indicating decreased hospitalization and disease severity [90–94]. In Brazil, the incidence dropped from 4.2/100,000 to 0.9/100,000 cases/inhabitants after introduction of the vaccine [95].

Maternal antibodies are transferred especially during the third trimester of pregnancy, with a half-life in the newborn of approximately six weeks [13]. Before the 16th gestational week (GW), fetal IgG serum levels correspond to 8% of the maternal levels, but the fetal levels increase until they reach maternal levels at 26 GW, especially for IgG1. Neonates reach adult levels of self-produced IgG at 3 years of age [96].

Several studies estimated the best period for vaccination, which was found to be between 27 and 31 weeks of gestation [97–99] when anti-PT IgG has higher affinity. However, other studies show that earlier immunization promotes higher antibody transference to the newborn, most likely due to a cumulative effect, which can be especially important regarding preterm neonate protection [100, 101].

In the US, vaccination is still recommended at the 27th GW and onwards [102]. However, in the UK, women are vaccinated starting in the 16th GW [103], and in Brazil, even though the vaccine was initially administered from the 27th to the 36th GWs, initial administration recently changed to start at the 20th GW to reach a higher number of women [104], and this timing has been proven to be cost-effective [105].

However, since the 1950s, it is known that maternal antibodies can interfere in the child’s own immune response to vaccination [106]. There are many studies on this subject, especially in vaccination models of tetanus and measles [107–110].

The interval between immunization and birth can determine the behaviour of antibodies when they contact vaccine antigens in infancy; this behaviour may depend on the vaccine formulation (acellular or whole-cell vaccine) given to the child [27, 107].

High antibody concentrations can suppress the child’s immune response by not completely elucidated mechanisms. The most accepted theories state that maternal antibodies can form immune complexes with vaccine antigens, either inhibiting neonatal B lymphocyte activation or eliminating the antigen via antibody-dependent phagocytosis, and can mask antigenic epitopes, preventing antigens from bonding with neonatal B lymphocytes [27, 110]. However, this lack of B-cell stimulation may be compensated by the noninterference in the induction of the T-cell response in the neonate; the complexes formed by MatAbs and bacterial peptides are captured by phagocytes and presented to naïve T cells, allowing them to be activated and to differentiate [33].

Recent humoral studies show lower antibody levels in children born from vaccinated mothers [111, 112], but preliminary studies show that the T cell remains unchanged (Argondizo et al., unpublished data); however, larger and more representative studies must be developed to evaluate possible interactions.

6. Discussion and Conclusion

Globally, pertussis reemergence is a challenge in developed and developing countries, with high morbidity and mortality rates in young children [71]. Several strategies (reviewed in Table 1) have been recommended to compensate for incomplete immunization until the sixth month of age [45], but during the first year of life, children are exposed to an environment full of antigenic stimuli and are highly susceptible to infections.

Even though children ultimately develop an immune system that is able to respond to infection, there is a need to initially balance between hypoinflammation and hyperinflammation once the transition from the partially sterile
| Strategy                        | Objective                                      | Number of doses          | Advantages                                                    | Disadvantages                                                    | References                        |
|--------------------------------|-----------------------------------------------|--------------------------|---------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------|
| Child vaccination with DTwP    | Induce specific protection in children        | 3 doses in the first year of life and 2 boost doses | (i) Th1 response induction (ii) Antibody response (iii) Prevent pertussis symptoms | (i) Higher risk of local and systemic adverse reactions (ii) Immunity lasts for 4-12 years | [41, 46–49, 53, 59–61]            |
| Child vaccination with DTaP    | Induce specific protection in children with less side effects | 3 doses in the first year of life and 2 boost doses | (i) Less reatogenic than DTwP (ii) Primes a Th1/Th2 response (iii) Antibody response (iv) Prevent pertussis symptoms | (i) Do not prevent bacterial colonization and transmission (ii) Immunity lasts for a shorter period of time than DTwP | [41–43, 46–49, 52, 53, 55, 56, 59–61] |
| Mother post-partum vaccination with Tdap | Confer protection to mothers and prevent child contamination | 1 dose after labour | (i) Protect the mother to transmit the disease | (i) Confers protection only to the mother, and after two weeks from vaccination | [85–87] |
| Newborn vaccination            | Induce protection in children as soon as they are born avoiding the first two months of age being unprotected | 1 dose just after birth | (i) First dose still in the hospital | (i) (wP) Immunological tolerance; lower antibody production (ii) (aP) Antibody production and protection against experimental challenge | [72, 73, 75, 76] |
| Cocooning                      | Create a protected environment for unvaccinated children | 1 dose for every relative, every time a child is born | (i) Prevent contamination of the unprotected child | (i) Costly (ii) Difficult to implement (iii) Child remains without specific protection | [79, 81, 84] |
| Vaccination with Tdap during pregnancy | Induce protection in mothers and transmit specific passive protection to the foetus and newborn, until the child’s vaccination | 1 dose from the 20th to the 36th gestational week, in every pregnancy | (i) Induces specific protection in children (ii) Just one dose for every pregnancy (iii) Cost-effective (iv) T cell responses remains unaffected by maternal antibodies inhibition | (i) High maternal antibody concentration can interfere in the child’s immune response | [77, 104–106] |
placental environment to the external environment is complete [25]. As pathogen recognition is mediated by the same receptors that recognize commensal organisms that colonize the neonate from birth, these receptors must be regulated to avoid harmful inflammation [25]. Therefore, neonates’ immune responses are usually lower and less effective when compared to those in adults. Regular pertussis vaccination in early life can induce protection, but protection only starts at 2 months of age [113]. Some studies have shown that newborn vaccination is well tolerated [73, 114], but there is no direct evidence currently available, and it remains controversial whether newborn vaccination can interfere with future vaccinations.

Vaccinating mothers just after labour and/or close relatives in the cocooning strategy can prevent disease spread, but there are difficulties for large-scale implementation of these approaches because they are costly and require vaccination of multiple people in addition to leaving the children born with no specific protection [79].

Maternal vaccination, on the other hand, provides protection for both the mother and the newborn, and a study on the safety and immunogenicity of vaccination in the third trimester of pregnancy revealed that babies born to vaccinated mothers have higher concentrations of antibodies against pertussis at birth and at two months of age compared to babies born to postpartum, immunized mothers [115]. Nevertheless, maternal antibodies can have inhibitory effects on the child’s immune response, and these effects should be further investigated [110].

Despite all existing strategies, no vaccine prevents the silent transmission of the pathogen, so new formulations are needed. Several options are being explored and have been investigated [110]. The authors declare that there is no conflict of interest regarding the publication of this article.

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References

[1] K. H. G. Mills, “Immunity to Bordetella pertussis,” Microbes and Infection, vol. 3, no. 8, pp. 655–677, 2001.
[2] R. Weston, “Whooping cough: a brief history to the 19th century,” Canadian Bulletin of Medical History, vol. 29, no. 2, pp. 329–349, 2012.
[3] J. Bordet and O. Gengou, “Le microbe de la coqueluche,” Annales de l’Institut Pasteur, vol. 2, pp. 731–741, 1906.
[4] M. Zlamy, “Rediscovering pertussis,” Frontiers in Pediatrics, vol. 4, p. 52, 2016.
[5] J. A. Melvin, E. V. Scheller, J. F. Miller, and P. A. Cotter, “Bordetella pertussis pathogenesis: current and future challenges,” Nature Reviews Microbiology, vol. 12, no. 4, pp. 274–288, 2014.
[6] Centers for Disease Control and Prevention, “Pertussis cases by year (1922-2015),” Pertussis (Whooping Cough) 2017, https://www.cdc.gov/pertussis/surv-reporting/cases-by-year.html.
[7] Centers for Disease Control, “Pertussis (Whooping Cough) | Signs and Symptoms | CDC 2017,” December 2018, https://www.cdc.gov/pertussis/about/signs-symptoms.html.
[8] World Health Organization, WHO–Recommended Standards for Surveillance of Selected Vaccine-Preventable Diseases, Geneva, Switzerland, 2003.
[9] Public Health England, “Laboratory confirmed cases of pertussis reported to the enhanced pertussis surveillance programme in England: annual report for 2013,” Health Protection Report 2014, 2017, https://www.gov.uk/government/publications/pertussis-enhanced-surveillance-laboratory-confirmed-cases-in-england-in-2013/laboratory-confirmed-cases-of-pertussis-reported-to-the-enhanced-pertussis-surveillance-programme-in-england-annual-report-for-2013.
[10] E. G. Fernandes, A. M. C. Sartori, P. C. de Soárez, T. R. M. P. Carvalhanas, M. Rodrigues, and H. M. D. Novaes, “Challenges of interpreting epidemiologic surveillance pertussis data with changing diagnostic and immunization practices: the case of the state of São Paulo, Brazil,” BMC Infectious Diseases, vol. 18, no. 1, p. 126, 2018.
[11] Pan American Health Organization, Epidemiological Alert Pertussis (Whooping Cough), PAHO, 2012.
[12] P. M. Luz, C. T. CdeCodoce, and G. L. Werneck, “A reemergência da coqueluche em países desenvolvidos: um problema também para o Brasil,” Cadernos de Saúde Pública, vol. 19, no. 4, pp. 1209–1213, 2003.
[13] Public Health England, Guidelines for the Public Health Management of Pertussis in England, London, UK, 2016.
[14] D. de Gouw, D. A. Diavatopoulos, H. J. Bootsma, P. W. M. Hermans, and F. R. Mooi, “Pertussis: a matter of immune modulation,” FEMS Microbiology Reviews, vol. 35, no. 3, pp. 441–474, 2011.
[15] C. M. Ausiello, F. Urbani, A. La Sala, R. Lande, and A. Cassone, “Vaccine- and antigen-dependent type 1 and type 2 cytokine induction after primary vaccination of infants

Disclosure

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Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.
with whole-cell or acellular pertussis vaccines,” *Infection and Immunity*, vol. 65, no. 6, pp. 2168–2174, 1997.

[16] F. B. Hickey, C. F. Brereton, and K. H. G. Mills, “Adenylate cyclase toxin of Bordetella pertussis inhibits TLR-induced IRF-1 and IRF-8 activation and IL-12 production and enhances IL-10 through MAPK activation in dendritic cells,” *Journal of Leukocyte Biology*, vol. 84, no. 1, pp. 234–243, 2008.

[17] P. J. Ross, C. E. Sutton, S. Higgins et al., “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*, vol. 9, no. 4, article e1003264, 2013.

[18] R. Higgs, S. C. Higgins, P. J. Ross, and K. H. G. Mills, “Immunity to the respiratory pathogen *Bordetella pertussis*,” *Mucosal Immunology*, vol. 5, no. 5, pp. 485–500, 2012.

[19] L. H. Hendriksen, K. Öztürk, L. G. H. de Rond et al., “Serum IgA responses against pertussis proteins in infected and Dutch wP or aP vaccinated children: an additional role in pertussis diagnostics,” *PLoS One*, vol. 6, no. 11, article e27681, 2011.

[20] R. P. Mahon, R. J. Sheahan, F. Griffin, G. Murphy, and K. H. G. Mills, “Atypical disease after *Bordetella pertussis* respiratory infection of mice with targeted disruptions of interferon-γ receptor or immunoglobulin μ chain genes,” *The Journal of Experimental Medicine*, vol. 186, no. 11, pp. 1843–1851, 1997.

[21] J. Barbic, M. F. Leef, D. L. Burns, and R. D. Shahin, “Role of gamma interferon in natural clearance of *Bordetella pertussis* infection,” *Infection and Immunity*, vol. 65, no. 12, pp. 4904–4908, 1997.

[22] M. Ryan, G. Murphy, L. Gotheofers, L. Nilsson, J. Storsaeter, and K. H. G. Mills, “*Bordetella pertussis* respiratory infection in children is associated with preferential activation of type I T helper cells,” *The Journal of Infectious Diseases*, vol. 175, no. 5, pp. 1246–1250, 1997.

[23] A. Marchant and T. R. Kollmann, “Understanding the ontogeny of the immune system to promote immune-mediated health for life,” *Frontiers in Immunology*, vol. 6, p. 77, 2015.

[24] B. Adkins, C. Leclerc, and S. Marshall-Clarke, “Neonatal adaptive immunity comes of age,” *Nature Reviews Immunology*, vol. 4, no. 7, pp. 553–564, 2004.

[25] X. Zhang, D. Zhivaki, and R. Lo-Man, “Unique aspects of the perinatal immune system,” *Nature Reviews Immunology*, vol. 17, no. 8, pp. 495–507, 2017.

[26] T. R. Kollmann, O. Levy, R. R. Montgomery, and S. Gorilej, “Innate immune function by toll-like receptors: distinct responses in newborns and the elderly,” *Immunity*, vol. 37, no. 5, pp. 771–783, 2012.

[27] C. A. de Brito, A. L. Goldoni, and M. N. Sato, “Immune adjuvants in early life: targeting the innate immune system to overcome impaired adaptive response,” *Immunotherapy*, vol. 1, no. 5, pp. 883–895, 2009.

[28] C. A. Siegrist, P. H. Lambert, and WHO Collaborating Center for Neonatal Vaccinology, “Immunization with DNA vaccines in early life: advantages and limitations as compared to conventional vaccines,” *Springer Seminars in Immunopathology*, vol. 19, no. 2, pp. 233–243, 1997.

[29] O. Levy, S. Martin, E. Eichenwald et al., “Impaired innate immunity in the newborn: newborn neutrophils are deficient in bactericidal/permeability-increasing protein,” *Pediatrics*, vol. 104, no. 6, pp. 1327–1333, 1999.

[30] G. Dunsmore, N. Bozorgmehr, C. Delyea, P. Koleva, A. Namdar, and S. Elahi, “Erythroid suppressor cells compromise neonatal immune response against *Bordetella pertussis*,” *Journal of Immunology*, vol. 199, no. 6, pp. 2081–2095, 2017.

[31] A. Namdar, P. Koleva, S. Shahbaz, S. Strom, V. Gerds, and S. Elahi, “CD71* erythroid suppressor cells impair adaptive immunity against *Bordetella pertussis*,” *Scientific Reports*, vol. 7, no. 1, p. 7728, 2017.

[32] P.-H. Lambert, M. Liu, and C. A. Siegrist, “Can successful vaccines teach us how to induce effective protective immune responses?,” *Nature Medicine*, vol. 11, pp. S54–S62, 2005.

[33] V. Dirix, V. Verschueren, T. Goetghbeuer et al., “Monoocyte-derived interleukin-10 depresses the *Bordetella pertussis*-specific gamma interferon response in vaccinated infants,” *Clinical and Vaccine Immunology*, vol. 16, no. 12, pp. 1816–1821, 2009.

[34] M. E. Belderbos, G. M. van Bleek, O. Levy et al., “Skewed pattern of Toll-like receptor 4-mediated cytokine production in human neonatal blood: low LPS-induced IL-12p70 and high IL-10 persist throughout the first month of life,” *Clinical Immunology*, vol. 133, no. 2, pp. 228–237, 2009.

[35] B. Adkins and M. Yoshimoto, “Epigenetic regulation of the Th2 locus in fetal and neonatal T cells,” *Advances in Neuroimmunology*, vol. 5, pp. 69–73, 2014.

[36] M. O. C. Ota, J. Vekemans, S. E. Schlegel-Haeter et al., “Influence of *Mycobacterium bovis* bacillus Calmette-Guérin on antibody and cytokine responses to human neonatal vaccination,” *Journal of Immunology*, vol. 168, no. 2, pp. 919–925, 2002.

[37] A. B. Maddux and I. S. Douglas, “Is the developmentally immature immune response in paediatric sepsis a recapitulation of immune tolerance?,” *Immunology*, vol. 145, no. 1, pp. 1–10, 2015.

[38] M. Pihlgren, N. Schallert, C. Tougue et al., “Delayed and deficient establishment of the long-term bone marrow plasma cell pool during early life,” *European Journal of Immunology*, vol. 31, no. 3, pp. 939–946, 2001.

[39] C. H. W. von König, “Acellular pertussis vaccines: where to go to?,” *The Lancet Infectious Diseases*, vol. 18, no. 1, pp. 5–6, 2018.

[40] J. D. Cherry, “Historical review of pertussis and the classical vaccine,” *The Journal of Infectious Diseases*, vol. 174, Supplement 3, pp. S259–S263, 1996.

[41] S. A. Plotkin, W. A. Orenstein, and P. A. Offit, *Vaccines*, Elsevier Inc., 6th edition, 2012.

[42] G. R. G. R. Noble, R. H. R. H. Bernier, E. C. E. C. Esber et al., “Acellular and whole-cell pertussis vaccines in Japan. Report of a visit by US scientists,” *JAMA*, vol. 257, no. 10, pp. 1351–1356, 1987.

[43] M. V. Rigo-Medrano, J. L. Mendoza-García, A. Gimeno-Gascón et al., “Vacunas acelulares (DTPa/dTpa) contra la tos ferina: duración de la protección,” *Enfermedades Infecciosas y Microbiología Clínica*, vol. 34, no. 1, pp. 23–28, 2016.

[44] World Health Organization, “Pertussis vaccines: WHO position paper - August 2015,” *Weekly Epidemiological Record*, vol. 90, pp. 433–460, 2015.
[46] M. Ryan, G. Murphy, E. Ryan et al., “Distinct T-cell subtypes induced with whole cell and acellular pertussis vaccines in children,” Immunology, vol. 93, no. 1, pp. 1–10, 1998.

[47] E. J. Ryan, L. Nilsson, N. I. M. Kjellman, L. Gothefors, and K. H. G. Mills, "Booster immunization of children with an acellular pertussis vaccine enhances Th2 cytokine production and serum IgE responses against pertussis toxin but not against common allergens," Clinical and Experimental Immunology, vol. 121, no. 2, pp. 193–200, 2000.

[48] C. Ausiello, R. Lande, F. Urbani et al., “Cell-mediated immune responses in four-year-old children after primary immunization with acellular pertussis vaccines,” Infection and Immunity, vol. 67, no. 8, pp. 4064–4071, 1999.

[49] A. Pereira, A. S. P. Pereira, C. L. Silva et al., “Antibody response from whole-cell pertussis vaccine immunized Brazilian children against different strains of Bordetella pertussis,” The American Journal of Tropical Medicine and Hygiene, vol. 82, no. 4, pp. 678–682, 2010.

[50] R.-M. Schure, L. H. Hendriks, L. G. H. de Rond et al., “Differential T- and B-cell responses to pertussis in acellular vaccine-primed versus whole-cell vaccine-primed children 2 years after preschool acellular booster vaccination,” Clinical and Vaccine Immunology, vol. 20, no. 9, pp. 1388–1395, 2013.

[51] L. H. Hendriks, R.-M. Schure, K. Öztürk et al., “Different IgG-subclass distributions after whole-cell and acellular pertussis infant primary vaccinations in healthy and pertussis infected children,” Vaccine, vol. 29, no. 40, pp. 6874–6880, 2011.

[52] J. Taranger, B. Trollfors, T. Lagergård et al., “Correlation between pertussis toxin IgG antibodies in postvaccination sera and subsequent protection against pertussis,” The Journal of Infectious Diseases, vol. 181, no. 3, pp. 1010–1013, 2000.

[53] World Health Organization, Pertussis Vaccines: WHO Position Paper - August 2015. Table III: Pertussis Vaccine Evidence to Recommendations Table, 2015.

[54] World Health Organization, Review of Vaccine Price Data, Geneva, Switzerland, 2013.

[55] B. M. Althouse and S. V. Scarpino, “Asymptomatic transmission and the resurgence of Bordetella pertussis,” BMC Medicine, vol. 13, no. 1, p. 146, 2015.

[56] J. M. Warfel, L. I. Zimmerman, and T. J. Merkel, “Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model,” Proceedings of the National Academy of Sciences of the United States of America, vol. 111, no. 2, pp. 787–792, 2014.

[57] J. M. Warfel, L. I. Zimmerman, and T. J. Merkel, “Comparison of three whole-cell pertussis vaccines in the baboon model of pertussis,” Clinical and Vaccine Immunology, vol. 23, no. 1, pp. 47–54, 2016.

[58] N. Hegerle and N. Guiso, “Bordetella pertussis and pertactin-deficient clinical isolates: lessons for pertussis vaccines,” Expert Review of Vaccines, vol. 13, no. 9, pp. 1135–1146, 2014.

[59] A. M. Wendelboe, A. Van Sic, S. Salmaso, and J. A. Englund, “Duration of immunity against pertussis after natural infection or vaccination,” The Pediatric Infectious Disease Journal, vol. 24, Supplement, pp. S58–S61, 2005.

[60] S. L. Sheridan, K. Frith, T. L. Snelling, K. Grimwood, P. B. McIntyre, and S. B. Lambert, “Waning vaccine immunity in teenagers primed with whole cell and acellular pertussis vaccine: recent epidemiology,” Expert Review of Vaccines, vol. 13, no. 9, pp. 1081–1106, 2014.

[61] N. Burdin, L. K. Handy, and S. A. Plotkin, “What is wrong with pertussis vaccine immunity? The problem of waning effectiveness of pertussis vaccines,” Cold Spring Harbor Perspectives in Biology, vol. 9, no. 12, 2017.

[62] World Health Organization, “Table 1: Summary of WHO Position Papers—Recommendations for Routine Immunization 2017,” October 2017, https://www.who.int/immunization/policy/Immunization_routine_table1.pdf?ua=1.

[63] U. Heininger, M. Riffelmann, B. Leineweber, and C. H. Wissing von Koenig, “Maternally derived antibodies against Bordetella pertussis antigens pertussis toxin and filamentous hemagglutinin in preterm and full term newborns,” The Pediatric Infectious Disease Journal, vol. 28, no. 5, pp. 443–445, 2009.

[64] T. H. Skooff, C. Kenyon, N. Cocoros et al., “Sources of infant pertussis infection in the United States,” Pediatrics, vol. 136, no. 4, pp. 635–641, 2015.

[65] G. Fedele, M. Carollo, R. Palazzo et al., “Parents as source of pertussis transmission in hospitalized young infants,” Infection, vol. 45, no. 2, pp. 171–178, 2017.

[66] E. N. Berezin, J. C. de Moraes, D. Leite et al., “Sources of pertussis infection in young babies from São Paulo state, Brazil,” The Pediatric Infectious Disease Journal, vol. 33, no. 12, pp. 1289–1291, 2014.

[67] World Health Organization, WHO SAGE Pertussis Working Group: Background Paper, 2014.

[68] C. Locht, “Will we have new pertussis vaccines?,” Vaccine, vol. 36, no. 36, pp. 5460–5469, 2018.

[69] A.-S. Debrie, L. Coutte, D. Raze et al., “Construction and evaluation of Bordetella pertussis live attenuated vaccine strain BPZE1 producing Fim3,” Vaccine, vol. 36, no. 11, pp. 1345–1352, 2018.

[70] W. O. Dias, A. A. J. van der Ark, M. A. Sakauchi et al., “An improved whole cell pertussis vaccine with reduced content of endotoxin,” Human Vaccines & Immunotherapeutics, vol. 9, no. 2, pp. 339–348, 2013.

[71] N. Wood and P. McIntyre, “Pertussis: review of epidemiology, diagnosis, management and prevention,” Paediatric Respiratory Reviews, vol. 9, no. 3, pp. 201–212, 2008.

[72] N. Wood, T. Nolan, H. Marshall et al., “Immunogenicity and safety of monovalent acellular pertussis vaccine at birth,” JAMA Pediatrics, vol. 172, no. 11, pp. 1045–1052, 2018.

[73] M. Knuf, H. J. Schmitt, J. Wolter et al., “Maternal and neonatal vaccination protects pertussis antibodies in infants,” The Journal of Pediatrics, vol. 152, no. 5, pp. 655–660.e1, 2008.

[74] C. Roduit, P. Bozotti, N. Mielcarek et al., “Immunogenicity and protective efficacy of neonatal vaccination against Bordetella pertussis in a murine model: evidence for early control of pertussis,” Infection and Immunity, vol. 70, no. 7, pp. 3521–3528, 2002.

[75] N. Wood, P. McIntyre, H. Marshall, and D. Robertson, “Acellular pertussis vaccine at birth and one month induces antibody responses by two months of age,” The Pediatric Infectious Disease Journal, vol. 29, no. 3, pp. 209–215, 2010.

[76] J. M. Warfel, J. F. Papin, R. F. Wolf, L. I. Zimmerman, and T. J. Merkel, “Maternal and neonatal vaccination protects
newborn baboons from pertussis infection,” *The Journal of Infectious Diseases*, vol. 210, no. 4, pp. 604–610, 2014.

[77] C. Locht and N. Mielcarek, “New pertussis vaccination approaches: en route to protect newborns?”, *FEMS Immunology and Medical Microbiology*, vol. 66, no. 2, pp. 121–133, 2012.

[78] R. Cohen, J. Gaudelus, F. Denis et al., “Pertussis vaccination coverage among French parents of infants after 10 years of cocoon strategy,” *Médecine et Maladies Infectieuses*, vol. 46, no. 4, pp. 188–193, 2016.

[79] A. Terranella, G. R. B. Asay, M. L. Messonnier, T. A. Clark, and J. L. Liang, “Pregnancy dose Tdap and postpartum cocooning to prevent infant pertussis: a decision analysis,” *Pediatrics*, vol. 131, no. 6, pp. e1748–e1756, 2013.

[80] H.-J. Lee and J.-H. Choi, “Tetanus–diphtheria–acellular pertussis vaccination for adults: an update,” *Clinical and Experimental Vaccine Research*, vol. 6, no. 1, pp. 22–30, 2017.

[81] M. Suryadevara and J. B. Domachowske, “Prevention of pertussis through adult vaccination,” *Human Vaccines & Immunotherapeutics*, vol. 11, no. 7, pp. 1744–1747, 2015.

[82] R. Villena, P. Vidal, F. Carrillo, and M. Salinas, “Pertussis vaccination in pregnancy: security and effectiveness in the protection of the infant,” *Revista Chilena de Pediatria*, vol. 88, no. 3, pp. 318–323, 2017.

[83] G. DiMattia, A. Nicolai, A. Frassanito, L. Petrarca, R. Nenna, and F. Midulla, “Pertussis: new preventive strategies for an old disease,” *Paediatric Respiratory Reviews*, 2018.

[84] K. Forsyth, S. Plotkin, T. Tan, and C. J. Baker, “Strategies to decrease pertussis transmission to infants,” *Pediatrics*, vol. 135, no. 6, pp. e1475–e1482, 2015.

[85] Ministério da Saúde, “Calendário Nacional de Vacinação, 2017,” October 2017, http://portalsaudes.gov.br/secretaria-svs/13600-calendario-nacional-de-vacinacao.

[86] Centers for Disease Control and Prevention, “Pertussis | Pregnancy | Vaccinating Pregnant Patients | CDC 2018,” June 2018, https://www.cdc.gov/pertussis/pregnant/hcp/pregnant-patients.html.

[87] L. A. Castagnini, C. M. Healy, M. A. Rench, S. H. Wootton, F. M. Munoz, and C. J. Baker, “Impact of maternal postpartum tetanus and diphtheria toxoids and acellular pertussis immunization on infant pertussis infection,” *Clinical Infectious Diseases*, vol. 54, no. 1, pp. 78–84, 2012.

[88] P. McIntyre, “Vaccines for other neonatal infections: vaccination strategies for the prevention of neonatal pertussis,” *Expert Review of Vaccines*, vol. 5, no. 4, pp. 375–378, 2004.

[89] 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,” *Morbidity and Mortality Weekly Report*, vol. 62, no. 7, pp. 131–135, 2013.

[90] G. Amirthalingam, N. Andrews, H. Campbell et al., “Effectiveness of maternal pertussis vaccination in England: an observational study,” *The Lancet*, vol. 384, no. 9953, pp. 1521–1528, 2014.

[91] G. Dabrera, G. Amirthalingam, N. Andrews 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*, vol. 60, no. 3, pp. 333–337, 2015.

[92] G. Amirthalingam, H. Campbell, S. Ribeiro et al., “Sustained effectiveness of the maternal pertussis immunization program in England 3 years following introduction,” *Clinical Infectious Diseases*, vol. 63, Supplement 4, pp. S236–S243, 2016.

[93] K. Winter, J. D. Cherry, and K. Harriman, “Effectiveness of prenatal tetanus, diphtheria, and acellular pertussis vaccination on pertussis severity in infants,” *Clinical Infectious Diseases*, vol. 64, no. 1, pp. 9–14, 2017.

[94] H. Petousis-Harris, T. Walls, D. Watson, J. Paynter, P. Graham, and N. Turner, “Safety of Tdap vaccine in pregnant women: an observational study,” *BMJ Open*, vol. 6, no. 4, article e010911, 2016.

[95] Ministério da Saúde, “Situação Epidemiológica-Dados 2018,” September 2018, http://порталs.saudes.gov.br/saudes-de-a-z/Coqueluche/11196-situacaos-epidemiologicas-dados.

[96] F. Saij, Y. Samejima, S. Kamiura, and M. Koyama, “Dynamics of immunoglobulins at the fetomaternal interface,” *Reviews of Reproduction*, vol. 4, no. 2, pp. 81–89, 1999.

[97] C. M. Healy, M. A. Rench, and C. J. Baker, “Importance of timing of maternal combined tetanus, diphtheria, and acellular pertussis (Tdap) immunization and protection of young infants,” *Clinical Infectious Diseases*, vol. 56, no. 4, pp. 539–544, 2013.

[98] B. Abu Raya, E. Bamberger, M. Almog, R. Peri, I. Srugo, and A. Kessel, “Immunization of pregnant women against pertussis: the effect of timing on antibody avidity,” *Vaccine*, vol. 33, no. 16, pp. 1948–1952, 2015.

[99] B. Abu Raya, I. Srugo, A. Kessel 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*, vol. 32, no. 44, pp. 5787–5793, 2014.

[100] C. S. Eberhardt, G. Blanchard-Rohner, B. Lemaître et al., “Maternal immunization earlier in pregnancy maximizes antibody transfer and expected infant seropositivity against pertussis,” *Clinical Infectious Diseases*, vol. 62, no. 7, pp. 829–836, 2016.

[101] C. S. Eberhardt, G. Blanchard-Rohner, B. Lemaître et al., “Pertussis antibody transfer to preterm neonates after second-versus third-trimester maternal immunization,” *Clinical Infectious Diseases*, vol. 64, no. 8, pp. 1129–1132, 2017.

[102] Centers for Disease Control and Prevention, “Get the whooping cough vaccine while you are pregnant. Pregnancy and Whooping Cough 2017,” September 2018, https://www.cdc.gov/pertussis/pregnant/mom/get-vaccinated.html.

[103] Oxford Vaccine Group, “Pertussis (whooping cough) vaccine in pregnancy 2018,” September 2018, http://vk.ovg.ox.ac.uk/pertussis-vaccine-in-pregnancy.

[104] Ministério da Saúde, *Nota informativa sobre mudanças no calendário nacional de vacinação para o ano de 2017*, Brasilia, Brazil, 2016.

[105] A. M. C. Sartori, P. C. de Soárez, E. G. Fernandes, L. C. F. Gryninger, J. Y. K. Viscondi, and H. M. D. Novaes, “Cost-effectiveness analysis of universal maternal immunization with tetanus-diphtheria-acellular pertussis (Tdap) vaccine in Brazil,” *Vaccine*, vol. 34, no. 13, pp. 1531–1539, 2016.

[106] J. J. Osborn, J. Dancis, and J. F. Julia, “Studies of the immunology of the newborn infant,” *Pediatrics*, vol. 10, pp. 339–345, 1952.
C. A. Siegrist, M. Córdova, C. Brandt et al., “Determinants of infant responses to vaccines in presence of maternal antibodies,” *Vaccine*, vol. 16, no. 14-15, pp. 1409–1414, 1998.

M. Premenko-Lanier, G. Hodge, P. Rota, A. Tamin, W. Bellini, and M. McChesney, “Maternal antibody inhibits both cellular and humoral immunity in response to measles vaccination at birth,” *Virology*, vol. 350, no. 2, pp. 429–432, 2006.

S. A. Gall, J. Myers, and M. Pichichero, “Maternal immunization with tetanus–diphtheria–pertussis vaccine: effect on maternal and neonatal serum antibody levels,” *American Journal of Obstetrics and Gynecology*, vol. 204, no. 4, pp. 334.e1–334.e5, 2011.

C. A. Siegrist, “Mechanisms by which maternal antibodies influence infant vaccine responses: review of hypotheses and definition of main determinants,” *Vaccine*, vol. 21, no. 24, pp. 3406–3412, 2003.

S. A. Halperin, J. M. Langley, L. Ye et al., “A randomized controlled trial of the safety and immunogenicity of tetanus, diphtheria, and acellular pertussis vaccine immunization during pregnancy and subsequent infant immune response,” *Clinical Infectious Diseases*, vol. 67, no. 7, pp. 1063–1071, 2018.

K. Maertens, T. T. H. Hoang, T. D. Nguyen et al., “The effect of maternal pertussis immunization on infant vaccine responses to a booster pertussis-containing vaccine in Vietnam,” *Clinical Infectious Diseases*, vol. 63, Supplement 4, pp. S197–S204, 2016.

World Health Organization, “Pertussis. Immunization, vaccines and biologicals 2017,” October 2017, https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/pertussis/en/.

M. Knuf, H.-J. Schmitt, J.-M. Jacquet et al., “Booster vaccination after neonatal priming with acellular pertussis vaccine,” *The Journal of Pediatrics*, vol. 156, no. 4, pp. 675–678, 2010.

E. Souder and S. S. Long, “Pertussis in the era of new strains of *Bordetella pertussis*,” *Infectious Disease Clinics of North America*, vol. 29, no. 4, pp. 699–713, 2015.

C. Locht and N. Mielcarek, “Live attenuated vaccines against pertussis,” *Expert Review of Vaccines*, vol. 13, no. 9, pp. 1147–1158, 2014.