



REVIEW ARTICLE

# An update on vaccination in preterm infants

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## Abstract

**Objective:** The objective of this article is to review the most current literature on vaccines, focusing on their safety, immunogenicity, and efficacy in preterm newborns, aiming to improve vaccine coverage in this population.

**Data source:** Most recent scientific publications addressing the immunization of preterm newborns.

**Data synthesis:** Despite its immunological immaturity, vaccination is well tolerated by preterm infants, and protective immune responses are observed, but some studies have shown that preterm infants undergo unjustified delays in their vaccination schedule.

**Conclusions:** Despite being widely recommended, the routine immunization of preterm infants is often delayed, putting this vulnerable population at risk for several diseases, many of which are preventable by immunization. Every effort should be made to develop universal guidelines that define the immunization of preterm infants.

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## Introduction

In recent decades, the prevalence of prematurity has progressively increased and, currently, almost 11% of births per year in the world occur before 37 weeks of gestational

age.<sup>1</sup> This trend has been observed in Brazil, with an increase of 40% in the last decade, from 8.0% in 2010 to 11.2% in 2019, according to data from DataSUS. In addition, advances in intensive care for preterm newborns (PTNBs), especially the extremely preterm ones, have substantially increased survival rates in the neonatal period. However, many of these children will die during the first year of life, in part due to vaccine-preventable infections, as they are less likely to receive the immunizations at the appropriate time. Part of

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the vaccine delay is due to the high rates of medical complications related to prematurity, but it is often due to concerns about their fragility, their ability to develop protective immunity, and the safety of routinely recommended vaccines.<sup>1</sup>

The timely vaccination of preterm infants is still a challenge that must be addressed by the multidisciplinary team responsible for their follow-up, including the selection and optimization of appropriate immunization schedules for these infants, who have an immature immune systems. According to the current recommendations, PTNB vaccination should be based on chronological age, following the same schedule as those born at term, without correction for gestational age or birth weight, with few exceptions.<sup>2,3</sup> Given the fact that vaccine safety, efficacy, and immunogenicity in PTNBs are comparable to those born at term, there is no reason to delay vaccination in this vulnerable group.<sup>4-6</sup>

The objective of this article is to review the most current literature on vaccines, focusing on safety, immunogenicity, and efficacy in preterm newborns, aiming to improve vaccine coverage in this population, ideally at an appropriate age.

### Vaccine-preventable diseases and risk for preterm infants

PTNBs are at greater risk for morbidity and mortality from vaccine-preventable diseases than full-term infants. The risk of severe infection is inversely proportional to gestational age and birth weight.<sup>4,7</sup> The greater vulnerability of these children is mainly attributed to their immature immune system, which shows incomplete development and functional immaturity.<sup>7,8</sup>

Other important points to be considered are plasma levels of antibodies, the frequent lack of maternal breastfeeding, and birth by cesarean section. The transfer of maternal antibodies through the placenta starts from the 17th to the 18th week of gestation, progressively increasing, reaching higher titers the higher the gestational age at birth. Consequently, in preterm infants, antibody titers are lower than those born at term, rendering them more unprotected. PTNBs who do not receive an enteral diet have less passive protection present in breast milk, in addition to interfering with the intestinal flora, with reduced colonization of the gastrointestinal tract by symbiotic bacteria. Births by cesarean section also lead to changes in the colonization of the gastrointestinal tract and the nasopharynx, resulting in more pathogenic bacterial flora.<sup>7,8</sup>

Prolonged hospitalization in the Neonatal Intensive Care Unit (NICU), frequent in PTNBs, is another risk factor for this population group. During hospitalization, the risk is greater of being exposed to factors that reduce the ability of the immune system to fight infections, such as resistant pathogens, administration of broad-spectrum antibiotics or steroids, lack of breastfeeding, and disruption of protective barriers (skin, respiratory), due to invasive medical procedures associated with comorbidities.<sup>7,8</sup>

It is important to point out that preterm infants can experience diseases that are preventable by vaccines with greater frequency and severity in the first months of life,<sup>4,6</sup> such as pertussis, pneumococcal infections, and influenza. More than 50% of the reported cases of pertussis occur in

infants, especially those born with low birth weight (birth weight < 2500g), with a relative risk of 1.86 (95% CI: 1.33 to 2.38) when compared to those with birth weight  $\geq$  2500 g.<sup>9</sup> In another prospective study carried out in Australia, prematurity was independently associated with severe infections caused by pertussis (OR 5.00, CI: 1.27–19.71).<sup>10</sup> Invasive pneumococcal diseases account for up to 11% of cases of bacteremia and sepsis in infants.<sup>4</sup> Preterm infants and/or those born with low birth weight have an increased risk of developing the pneumococcal disease compared to those born at term. Shinefield et al.<sup>11</sup> found an odds ratio (OR) of 2.6 and 9.1 for invasive pneumococcal disease in infants with low birth weight and preterm infants with less than 32 weeks of gestation, respectively, when compared with infants who were born weighing more than 2500 g or at term. PTNBs also have a higher risk of complications and hospitalization rates for rotavirus that is two-fold higher when compared to full-term infants.<sup>4</sup> Higher morbidity from the influenza virus is also associated with prematurity.<sup>4</sup>

### Preterm infants' immune response

Immune response mechanisms are characterized by two major defense systems: the non-specific innate immune mechanism and the adaptive immune system. Innate immunity includes defense mechanisms that operate effectively without prior exposure to an antigen. These mechanisms include physical barriers, such as intact skin and mucous membranes. Mononuclear inflammatory cells, particularly mast cells and tissue macrophages, are the sentinels of host defense against any agents that breach the physical barriers. Mast cells, for instance, operate in part by releasing tumor necrosis factor-alpha (TNF-alpha), which together recruit other innate defense cells, such as polymorphonuclear leukocytes, monocytes, and dendritic cells, with an important role in guiding the defense cells to process and to present the microbial antigenic material to T lymphocytes, a crucial starting step in generating a specific immune response. Thus, mast cells are important components of both the innate and acquired immune systems and are necessary for an effective immune response.<sup>8</sup>

The immune system of newborns, especially preterm ones, is under development and has an immature function, so these children are more unprotected from infectious diseases<sup>1</sup>. Their antibody response is also different from that of adults, as the maturation of their adaptive immunity and antibody production mechanism occurs gradually during the first two years of life. At two months of age, when the first vaccines are administered, PTNBs have lower absolute counts of lymphocytes, T cells, B cells and T helper cells and a lower CD4/CD8 ratio than full-term infants. At seven months of age, B-cell counts are comparable between preterm and full-term infants, but absolute lymphocyte, T-cell, and T-helper cell counts remain lower in preterm infants. Additionally, the number of antigens that the B cells recognize is lower, as the differentiation of these cell receptors was not completed before the 3<sup>rd</sup> trimester of pregnancy. However, this differentiation of B cell receptors can be accelerated by exposure to vaccine antigens<sup>1</sup>. The inadequate transfer of maternal antibodies through the placenta is a factor that leads to a better immune response after the vaccination of preterm infants. The presence of the

maternal antibody binds to the antigen epitope and prevents lymphocyte adhesion, preventing the production of antibodies by the newborn. As preterm newborns have low or absent maternal antibody titers, in some cases, there may be a higher vaccine immune response in PTNBs than in full-term newborns.<sup>8</sup>

Several studies have shown that preterm infants are generally capable of producing an adequate immune response, indicating the need for timely vaccination of preterm infants according to their chronological age, as recommended, for instance, by the German Standing Committee on Vaccination (STIKO) and by the American Academy of Pediatrics Committee on Infectious Diseases.<sup>6,12,13</sup> Recent data confirm that preterm infants should be vaccinated following the same schedule as full-term infants, with rare exceptions. Although the absolute primary antibody responses may be lower in preterm infants when compared to full-term ones, when vaccinated according to chronological age, most of them achieve antibody concentrations above the levels considered to be protective.<sup>4</sup>

Therefore, despite their immunological immaturity, preterm infants generally respond well to vaccines. As long as they are clinically stable and there are no contraindications to vaccination, they should receive the vaccines, according to the schedule recommended for full-term infants and their chronological age.<sup>14</sup>

### Vaccine delay in preterm infants

Vaccination is well tolerated and protective immune responses are observed, but some studies have shown that preterm infants experience unjustified delays in their vaccination schedule. An integrative review of the empirical literature,<sup>15</sup> which evaluated studies published in Medline, Academic Search Premier, Cochrane Database of Systematic Reviews, among others, identified fourteen studies, which demonstrated that infants born with lower gestational ages and lower birth weight show the greatest delays.<sup>15</sup> The most important factor explaining the delay in administering routine vaccines is probably the lack of knowledge about the safety and efficacy of vaccines in PTNB among health professionals and parents, with fear of adverse events being one of the main reasons for delaying the administration of vaccines in this group of infants.<sup>4</sup> Magoon et al.<sup>16</sup> reported immunization delays in 30 to 70% of infants when evaluated at two to 10 months of chronological age. Langkamp et al.<sup>17</sup> demonstrated that infants with low birth weight were less likely to be fully immunized at 12, 24, and 36 months than those with higher birth weights. This delay in starting the vaccination was confirmed in a prospective French study that analyzed 87 preterm newborns and observed that immunization started late and was started mainly with DTP-Hib (63%), usually after the fourth month of life. Fewer than one in two babies (45%) received three doses at six months of chronological age.<sup>18</sup>

A recent Italian population-based cohort study confirmed that the start of immunization for all vaccines was considerably delayed in many infants born at less than 32 weeks of gestational age.<sup>19</sup> A study carried out in Israel was the first to evaluate routine vaccination and timeliness in an annual national cohort of 181,543 live births, comparing preterm and full-term infants. The study showed that those born with low birth weight were significantly more likely to

receive the first dose of inactivated poliovirus (IPV), diphtheria, tetanus, acellular pertussis, and *Haemophilus influenzae* type b (DTPa-Hib) with delay, the latter being greater the lower the birth weight (21.9% in very low birth weight infants and 53.7% in extremely low birth weight infants, with delays of more than one month from the recommended schedule), compared to 90% of full-term infants who received the first dose at the appropriate age. In addition to this initial delay, all subsequent doses were subsequently delayed. The same pattern of delay is evident in the other indicated vaccines, such as the pneumococcal, rotavirus, and hepatitis B vaccines. The vaccination coverage rates become equal between the two groups when analyzed at 12 and 24 months of age.<sup>20</sup>

Several factors contribute to delayed vaccination in preterm infants, the most common being concern about adverse events, followed by issues of limited understanding of vaccine efficacy and safety.<sup>21</sup> Both parents and physicians may hesitate to administer vaccines to infants born prematurely, even after their stabilization.<sup>21</sup> Although they may have higher rates of post-vaccination fever and cardiorespiratory events compared to full-term infants, most do not experience clinical alterations, and if they do, they are usually transient and mild.<sup>6,21</sup> A better understanding of the efficacy, safety and potential adverse events of immunization in this group of children allow parents and health professionals to be adequately informed, giving them peace of mind and guiding them toward possible post-immunization changes in the clinical status.<sup>21</sup>

### Vaccination in the neonatal unit

Vaccines should be routinely administered to patients admitted to the NICU, except oral vaccines with live attenuated components, according to the chronological age and clinical stability. Several publications have highlighted the importance of starting the vaccination schedule during hospitalization, when indicated, before hospital discharge to achieve better vaccination rates.<sup>4,16–21</sup>

Some studies, aimed at improving the quality of preterm care, have reported success in increasing immunization rates in infants admitted to NICUs, particularly in tertiary and quaternary units.<sup>19,21</sup> It is important to highlight that multiple actions must be integrated to improve the implementation of the existing recommendations. Positive strategies comprise evidence-based education of health professionals; wide dissemination in a format that is adequate for the lay public, especially parents and caregivers; better access to immunization services; immunization before discharge from the Neonatal ICU. Information and education programs should focus on the importance of chronological age as the only parameter that, together with clinical conditions, guides the start of the immunization.<sup>19,21</sup>

### Particularities of immunization in preterm infants

#### BCG vaccine

The BCG vaccine mainly protects against severe forms of tuberculosis (tuberculous meningitis and disseminated

tuberculosis). In Brazil, the vaccine is administered intradermally at a dose of 0.1mL, preferably in the right arm, at the level of the lower insertion of the deltoid muscle.<sup>22</sup>

The Ministry of Health recommends the application of the intradermal vaccine against tuberculosis (BCG-ID) only in newborns weighing more than 2000 g.<sup>22</sup> In newborns born to mothers who used immunosuppressants during pregnancy, or with a family history of immunosuppression, the vaccination may be postponed or contraindicated.<sup>23</sup>

## Hepatitis B vaccine

The Hepatitis B virus (HBV) is the most common hepatitis virus that causes chronic liver infections in humans and constitutes a major public health problem. The probability of an individual developing a chronic infection depends on the age at which they are infected. More than 90% of infected newborns, 25% to 50% of infected children between one and five years of age, and 6% to 10% of older children and acutely infected adults will develop chronic infection, justifying the neonatal vaccination, regardless of the weight and gestational age at birth.<sup>24</sup>

The application of this vaccine at birth, in preterm newborns weighing less than 2000g, leads to a lower rate of seroconversion, with lower levels of protective antibodies. After 30 days of life, all newborns, regardless of their weight and gestational age at birth, respond adequately to immunization with the hepatitis B vaccine.<sup>25</sup> Thus, it is recommended to apply a fourth dose to all newborns weighing less than 2000 g or having less than 33 weeks of gestational age at birth, who received the vaccine immediately after birth, that is, the vaccination schedule must be administered at 0, 1, 2 and 6 months of life. Newborns whose mothers are chronic carriers of the hepatitis B virus (HBsAg positive), in addition to vaccination within the first 12 hours of life, should also receive specific hyperimmune immunoglobulin against hepatitis B (HBIG) during the first days of life.<sup>26</sup>

## Prophylaxis of Infections caused by the Respiratory Syncytial Virus (RSV)

RSV is the main agent of acute respiratory infections that affect the lower respiratory tract in children younger than one year of age. The RSV has, in general, a defined seasonality, causing annual epidemics during the autumn and winter months.<sup>27</sup>

The RSV assumes crucial importance when it affects PTNBs, with a risk of more severe evolution. The frequency of hospitalization in this group is up to 10 to 16 times greater than that of full-term newborns, and the morbidity of RSV infection in preterm infants is higher, associated with a longer hospital length of stay. Other risk groups are those with chronic lung disease, heart disease, and immunodeficiencies.<sup>27</sup>

There are no licensed vaccines against RSV and the prophylaxis is performed through passive immunization, with the use of a humanized monoclonal antibody (palivizumab), directed against the RSV glycoprotein F. Palivizumab is able to reduce RSV hospitalizations by up to 70% in immunized preterm infants, with a reduction in the number of days of oxygen therapy and admissions and length of stay in Intensive Care Units (ICUs). It was also shown that children who received palivizumab had less recurrence of wheezing in the

first years of life when compared to those who were not immunized.<sup>28</sup>

Palivizumab should be administered intramuscularly in up to five consecutive monthly doses of 15mg/kg during the period of greater RSV circulation. The use of this product for the treatment of RSV infections is not recommended.

Recently, the use of a new monoclonal antibody with a long half-life, nirsevimab, was approved, with safety and efficacy data, sustained for five months, demonstrated in preterm newborns and also in infants born at term after the administration of a single dose.<sup>29</sup>

## Pneumococcal conjugate vaccine

*Streptococcus pneumoniae* or *pneumococcus* is a frequent cause of infections in all age groups, but the highest incidence of the invasive pneumococcal disease occurs at the extremes of age: children in their first years of life and the elderly. PTNBs are at greater risk of developing the invasive form of the disease compared to children born at term. The risk increases the lower the gestational age and the lower the birth weight.<sup>30</sup>

Although PTNBs are more likely to develop inferior responses to conjugate vaccines, these have proven to be safe, well tolerated, with few local and systemic adverse events, and are indicated for all children, even preterm ones, from six weeks of life, as long as the clinical conditions of the newborn allow its application.<sup>31</sup>

## Rotavirus vaccine

Rotavirus infection is the leading cause of severe acute diarrhea in infants worldwide. The great majority of cases occur before the age of five years. PTNBs have a higher risk of complications and hospitalization in cases of rotavirus diarrhea than children born at term. Among these children, those with low birth weight (< 2500 g) or very low birth weight (< 1500 g) have the highest risk of complications (OR 2.6 and 95% CI: 1.6 to 4.1 and OR of 1.6 and 95% CI: 1.3 to 2.1, respectively), mainly gastrointestinal hemorrhage and necrotizing enterocolitis.<sup>32</sup> The greater severity of these infections in preterm infants can be explained by the relative immaturity of their immune systems and the lower levels of maternal antibodies transferred transplacentally before birth when compared to full-term newborns. The efficacy and safety of rotavirus vaccines in premature infants have been demonstrated.<sup>33</sup> Due to the possible risk of dissemination of the vaccine virus inside the NICU, the rotavirus vaccine has been contraindicated in hospitalized newborns in several countries, although several more recent studies have not demonstrated this risk. As there is a maximum age limit for applying the first dose of the rotavirus vaccine, this restriction often ends up being a limiting factor in its administration.<sup>34</sup>

## Influenza vaccine

Premature newborns are at greater risk of hospitalization due to influenza compared to full-term newborns, particularly those with chronic lung disease.<sup>35</sup> Vaccination is recommended as of six months of chronological age, since the immunogenicity is reduced at a younger age, due to the

interference of maternal antibodies.<sup>36</sup> The immune response of premature infants aged six to 17 months to flu vaccines is comparable to that of full-term infants, with no records of a higher incidence of adverse events in this population.<sup>37</sup>

### Combination vaccines with the pertussis component

Pertussis is an acute respiratory disease caused by *Bordetella pertussis*. Preterm newborns are especially susceptible to the disease in its most severe form and in this age group, lethality is high. The vaccination of pregnant women significantly reduces the risk of developing the disease in newborns and infants in the first months of life; however, preterm children may not be protected due to the fact that the pregnant woman did not have the opportunity to be vaccinated or because of the low transfer of antibodies due to the occurrence of the preterm birth.<sup>38</sup>

The vaccination of premature infants should be carried out according to their chronological age, using acellular formulations, which are less reactogenic, and in association with the components of polio, diphtheria, tetanus, *Haemophilus influenzae* type b, and hepatitis B.<sup>39</sup>

### Covid-19 pandemic

Covid-19 is an important risk factor for miscarriages and early termination of pregnancy, leading to an increase in the number of births of preterm newborns.<sup>40</sup> The vaccination of women of childbearing age and pregnant women is a crucial strategy to reduce this risk. Messenger RNA platform Covid-19 vaccines have been licensed in several countries and in Brazil, for use in infants from six months of age, with no contraindications for their use in preterm infants.<sup>41</sup>

### Conclusion

Despite being widely recommended, the routine immunization of preterm infants is frequently delayed, putting this vulnerable population at risk for several diseases, many of which are preventable by immunization. The most important factor that explains the delay in the administration of routine vaccines is the lack of knowledge about the safety and efficacy of vaccines in preterm infants. Every effort should be made to develop universal guidelines that define immunization in preterm infants, with clarifications on its benefits. The vaccination strategy of those who live with preterm infants should be encouraged, especially for pertussis and influenza, aiming to prevent the transmission of diseases through their contacts<sup>4</sup>

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### Conflicts of interest

The authors declare no conflicts of interest.

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