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Vaccination strategies in preterm infants.

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Abstract

The fetal immune system is highly specialized which is to generate both tolerogenic and protective immune responses to tolerate both self and maternal- antigens. For a number of antigens, the antibody response to initial doses of vaccines may be lower than that of term infants, but protective concentrations are often achieved and memory successfully induced. Vaccines are immunogenic, safe and well tolerated in preterm infants. Preterm infants should be vaccinated using the same schedules as those usually recommended for full-term infants, with the exception of the hepatitis B vaccine. This review aims to discuss the recent advances in immunization through vaccines in preterm infants.

Keywords: Neonatal, Preterm infants, Infectious disease, Vaccination.

Abbreviations

GMT: Geometric Mean Titer; PCV: Pneumococcal Conjugate Vaccine; MMR: Measles Mumps Rubella; HepB: Hepatitis B; VLBW: Very Low Birth Weight.

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Introduction

Preterm infants are at a higher risk of infections and death compared to full-term infants. The major risk factors are perinatal infections, prolonged hospitalization after birth, iatrogenic complications of lifesaving therapies, low levels of circulating maternal antibodies, and an immature immune system [1]. The lower gestational age and birth weight are the main causes of the immature immune system [2-4]. Over the period, numbers of international and national bodies have suggested preterm infants to be immunized at the similar chronological age as their full-term counterparts [5]. Preterm infants are more vulnerable and under severe risks, therefore, increasing needs for hospitalization from vaccine preventable diseases [6]. Despite these facts, insufficient immunization coverage is the risk of vaccine preventable diseases for the preterm infants [5,6]. This review focuses the immunization strategies through vaccination in the preterm infants.

Immunization Strategies with Vaccine in Preterm Infants

Gestation age, birth weight, clinical conditions, prescribed therapies and vaccination schedules are the important factors of immune response in preterm infants [7]. In preterm infants, vaccines persuade a protective immune response in the majority of cases. The diseases, symptoms of diseases and age of vaccination are illustrated in Table 1. The following vaccines are disease preventive and their respective antibody producer.

Vaccines	Diseases	Symptoms	Age of vaccination
Diphtheria, tetanus, and whooping cough (pertussis; DTaP)	Diphtheria	Diphtheria infects the throat and tonsils, making it hard for children to breathe and swallow. Severe cases can cause heart, kidney and/or nerve damage.	Infant needs 5 doses of DTaP vaccine. The first dose is given at 2 months, the second at 4 months, the third at 6 months, the fourth at 15–18 months, and the fifth at 4–6 years [8-17].
	Tetanus	Tetanus causes very painful muscle contractions. It can cause children's neck and jaw muscles to lock (lockjaw), making it hard for them to open their mouth, swallow (breastfeed) or breathe. Even with treatment, tetanus is often fatal.	
	Pertussis	Pertussis (whooping cough) causes coughing spells that can last for weeks. In some cases, it can lead to trouble breathing, pneumonia, and death.	
Polio (IPV)	Poliovirus	Polio is a virus that paralyzes 1 in 200 people who get infected. Among those cases, 5 to 10 per cent die when their breathing muscles are paralyzed. There is no cure for polio once the paralysis sets in –only treatment to alleviate the symptoms.	Infant needs 4 doses of polio vaccine (IPV). The first dose is given at 2 months, the second at 4 months, the third at 6–18 months, and the fourth at 4–6 years [18,19].
Haemophilus influenzae type b (Hib)	Haemophilus influenza type b (Hib)	Hib is a bacterium that causes pneumonia, meningitis and other severe infections almost exclusively in children under 5 years old.	Infant needs 3–4 doses of Hib vaccine, depending on the brand of vaccine. The first dose is given at 2 months, the second at 4 months, the third at 6 months (if needed), and the last at 12–15 months [20-22].
Pneumococcal (Prevnar (conjugate, PCV13), Pneumovax (polysaccharide, PPSV23))	Pneumococcal diseases	Pneumococcal diseases range from serious diseases such as meningitis and pneumonia to milder but more common infections like sinusitis and ear infections.	Infant needs 4 doses of Prevnar (PCV13). The first dose is given at 2 months, the second at 4 months, the third at 6 months, and the fourth at 12–15 months. Some children also need a dose of Pneumovax (PPSV23) [23-28].
		Pneumococcal diseases are a common cause of sickness and death worldwide, especially among young children under 2 years old.	
Hepatitis B (HepB)	Hepatitis B	Hepatitis B virus is a dangerous liver infection that, when caught as an infant, often shows no symptoms for decades. It can develop into cirrhosis and liver cancer later in life.	Infant needs 3–4 doses of hepatitis B vaccine, depending on the brand of vaccine. The first dose is given at birth, the second at 1–2 months, the third at 4 months (if needed), and the last at 6–18 months [29-34].
Measles, Mumps, Rubella (MMR)	Measles	Measles is a highly contagious disease with symptoms that include fever, runny nose, white spots in the back of the mouth and a rash. Serious cases can cause blindness, brain swelling and death.	Infant needs 2 doses of MMR vaccine. The first dose is given at 12–15 months and the second at 4–6 years [35-41].
	Mumps	Mumps can cause headache, malaise, fever, and swollen salivary glands. Complications can include meningitis, swollen testicles and deafness.	
	Rubella	Rubella infection in children and adults is usually mild, but in pregnant women it can cause miscarriage, stillbirth, infant death or birth defects.	
Chickenpox (varicella; Var)	Varicella		Child needs 2 doses of chickenpox vaccine. The first dose is given at 12–15 months and the second at 4–6 years [42].
Meningococcal (MenACWY (MCV4), MenB)	Meningitis	Meningitis can cause sudden illness with symptoms that include high fever, headache, rash, a stiff neck, drowsiness, seizures etc.	Infants and children age 0–10 years with certain health conditions (such as a non-functioning spleen) need one or both meningococcal vaccines [43,44].

Rotavirus (RV)	Rotavirus	Rotaviruses cause severe diarrhoea and vomiting, which can lead to dehydration, electrolyte imbalance and shock in young children. This can lead to death if treatment, especially fluid replacement, is not immediately started.	Infant needs 2–3 doses of rotavirus vaccine (RV), depending on the brand of vaccine. The first dose is given at 2 months, the second at 4 months, and the third (if needed) at 6 months [45,47].
Influenza (Flu)	Influenza	Influenza can cause mild to severe illness with symptoms that include fever, cough, sore throat, runny or stuffy nose, body aches, headaches, fatigue, vomiting.	Everyone age 6 months and older needs influenza vaccination every fall or winter and for the rest of their lives. Some children younger than age 9 years need 2 doses [48-51].

Table 1. Vaccines, diseases, symptoms of diseases and age of vaccination.

Diphtheria

Diphtheria toxoid is a vaccine that generates neutralizing antibodies. It is equally effective in preterm and full term infants. The acceptable schedule of 2,4, and 6 or 2,3, and 4 months are used most parts of the world as effective in preterm and full term infants. The pentavalent (DTaP-IPV-Hib) and hexavalent (DTaPIPV-Hib/HepB) vaccines have been widely used and achieved almost 98% protective against diphtheria in preterm infants [8,9].

Tetanus

The morbidity and mortality due to neonatal tetanus in the developing countries is alarming even it is rare in developed countries. The application of tetanus toxoid to both preterm and full term infants on 2,4, and 6 month schedule or on an accelerated 2-4 months schedule has been produced optimal antibody titers [10,11]. Several studies have showed that the preterm infants of 24-36 weeks of gestation with a birth weight <1000-2000 g was administered DTwP or DTwPIPV/Hib or DTaPHBVIPV/Hib vaccines at 2,4 and 6 months developed protective Geometric Mean Titer (GMT) [8,12,13]. This result suggests the use of tetanus toxoid combination vaccines in preterm infants on standard schedules.

Pertussis

Pertussis-related hospitalization and mortality in preterm infants are at higher risk than full term infants until 2 years of age, even when vaccine efficacy is comparable [14]. The antigenicity to pertussis is a 4-fold higher in titers in preterm infants despite actual levels being lower than full term infants [15]. The hexavalent (DTaP-HBV-IPV/Hib) vaccine administered to the preterm infants on a 2,4 and 6 months schedule showed in a 98.9% response [16]. The preterm infants 31 weeks less of gestation when immunized with the quadrivalent vaccine showed nonspecific protection with interferon gamma [17]. Pertussis vaccine has produced adequate levels to provide immunity in preterm infants even immunogenicity is lower [16,17].

Polio

The trivalent polio vaccines are effective in preterm infants against serotypes I, II, and III. The mixed inactivated polio vaccine/oral polio vaccine combinations have provided adequate levels of protection in both preterm and full term infants, response differs based on serotypes. Preterm infants attained a level 1:8 for serotypes I, II and III [18]. The combinations of both the hexavalent and pentavalent were formed protective titers even when GMT was lower in preterm infants [19].

Haemophilus influenzae type B

Haemophilus influenzae type B (Hib) vaccine has provided the protective titers in preterm and full term infants with the 2,4, and 6 month schedule [13,20]. A poor response from infants and toddlers was found since it is a polysaccharide antigen producing vaccine, while the immunogenicity of Hib vaccine is more variable than others. After two doses, the antibody levels in preterm infants were lower than in full term infants, after the third dose, the antibodies were similar in preterm and full term infants extended schedules [21]. The main cause of the failure of the Hib conjugate vaccine was identified as prematurity in the absence of booster dose [22].

Pneumococcal conjugate vaccine

The antibody production through administering booster dose of heptavalent Pneumococcal Conjugate Vaccine (PCV) in preterm and full term infants is similar [23-25]. The adequate and comparable immunogenicity of preterm infants at 27-37 weeks of gestation was shown after administered 10-valent vaccine with booster dose [26]. The immune response to all PCV7 serotypes was higher in preterm infants compared to full term infants while the efficacy of PCV7 was equivalent to both of the preterm and full term infants [27]. The 13-valent PCV administered at 2,3,4, and 12 months showed adequate protection with booster dose in preterm [28]. The booster dose is strongly recommended in preterm infants to maintain higher protection.

Hepatitis B virus

Hepatitis B (Hep B) is a preventable health burden particularly in Africa and Southeast Asia, Hep B vaccination at birth provides utmost protection from perinatal infection [29]. Hep B vaccine has a significantly lower response to preterm infants compared to full term infants [29-31]. The birth weight of preterm infants is a factor of vaccine effectiveness, it has been shown 2,000 g> in preterm infants the response was the same as in full term infants [32]. The HepB vaccine is recommended

at birth, regardless of gestation age or birth weight when maternal status is unknown or seropositive [18]. Additionally, the HepB vaccine is recommended to delay until 30 days after birth to ensure maximum protection when maternal status is negative [33]. After administration of 3 recommended vaccine doses, preterm infants showed the protective concentrations of HepB antibodies by 9-12 months of age [34]. Protective antibody levels were found 93.4% and 95.2% in preterm infants and full term infants, respectively after administration of a hexavalent DTaP-HBV-IPV/Hib at 2,4 and 6 months [16].

Measles, Mumps, Rubella-(MMR)

The immunity of Measles, Mumps, and Rubella (MMR) is dependent on the transfer of maternal antibody to the infant. The mothers are now vaccinated for covering shortage of antibody, fewer antibodies transfer to their offspring compared to naturally immune mother [35,36]. Modification of measles vaccination program is needed of maternal antibodies is lost early, which is a critical risk for measles infection. In the context of an epidemic, several studies suggested that the MMR immunization at an earlier age for preterm infants is needed [37-40]. In general, the MMR vaccine should be administered after 1 year of age in all infants [41].

Varicella

Varicella vaccine is a live attenuated and highly immunogenic which is recommended at a later age to ensure an adequate and persistent immune response. The antibody responses when given after 1 year in preterm and full term infants were found comparable [42].

Meningitis C

The immunogenicity of meningitis C in preterm and full term infants is comparable while GMTs were lower in preterm compared to full term infants during primary vaccination. The primary incidence of invasive meningococcal disease was found in children younger than age 5 years, followed by a second spike in teenagers [43,44].

Rotavirus

The symptom of rotavirus gastroenteritis is severe dehydration in children between ages 6 and 24 months. It also occurs in the preterm infants. Rotavirus vaccines were shown similar seroconversion rates in preterm and full term infants [45] while VLBW preterm infants had significantly lower titers and seroconversion rates [46]. After administering 3 doses of the pentavalent human-bovine reassortant rotavirus vaccine, preterm infants with 25-36 weeks of gestation age showed 73.0% prevention of rotavirus gastroenteritis cases [47]. In addition, it is reported that the rotavirus vaccines decreased the incidence of diarrhea [46].

Influenza

A very few data are available on influenza vaccination in both preterm and full term infants considering safety, immunogenicity, and efficacy. The development of immune responses to influenza vaccine has been shown significantly lower in the preterm infants compared to full term infants. Nevertheless, almost all infants developed GMTs of >1:32, independent of gestation [48]. Additionally, immunogenicity of trivalent influenza vaccine in preterm infants and full term infants was almost similar [49]. The vaccine protects preterm infants of <6 months of age with a cocooning strategy in which all family members receive influenza immunization [50,51] while new born preterm infants is currently not recommended this vaccine.

Safety of vaccines in preterm infants

The different adverse events of preterm infants associated with prematurity puzzles physicians on safety of vaccine. The safety of pentavalent or hexavalent vaccines (DTaP-IPV-Hib) in preterm infants was observed, immunization generated temporary cardiorespiratory events (apnea, bradycardia, desaturations) in 13%-47% of infants and a 5-8 folds increase in risk who have pre-existing [52,53]. The clinical condition of preterm infants has the impact on the risk of adverse events rather gestation age or birth weight at the time of immunization [52]. There was no significant difference between preterm and full term infants on safety of vaccinations. Immunization of preterm infants is like healthy term infants regardless of their birth weight or gestational age is supported even with some adverse events [54].

Conclusion

The human immune system matures over several years; the adaptive immune system confers major protection while being carried by the innate immune system. During gestation, insightful developmental changes occur which is essential to survive the neonates. At early stage, the immune deficiencies with impaired response to pathogen challenge may be influenced by developmental signals and changes. The stem cell transplantation, tissue engineering for immunotherapy and regenerative medicine in the near future will revolution of developing immune system in preterm infants. After born of preterm infants, vaccination should be scheduled as term infants with the exception of the HBV vaccine. However, the routine immunization of preterm infants is often delayed due to the health condition of preterm infants despite this recommendation. The universal guidelines should be followed during application of any efforts on preterm infants and during vaccination, pediatricians and parents should be convinced that vaccines are immunogenic, safe and well tolSSSSerated in preterm infants.

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