

Vaccination in preterm infants: An Indian prospective

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ABSTRACT

Although available literature on vaccination in preterm infants supports timely vaccination without any correction for birth weight or gestation, a delay is still noted. Unfortunately, this group often suffers from various vaccine-preventable diseases with increased severity, especially in lower-middle-income countries. All this could be attributed to unavailability of robust evidence and clear guidelines related to vaccination. A current review article summarizes the available evidence on the use of these vaccines, their immune response, common myths and facts about vaccination in preterm infants in the Indian context. Authors conclude that the vaccines in preterm infants are equally safe, effective, and immunogenic as compared to full-term infants; hence, they should be vaccinated following the same schedule as of their counterparts who born full term. Only exception to this is hepatitis B vaccine, where additional doses should be administered to infants with weight <2000 g, apart from the birth dose.

Key words: Immunization, Low birth weight, Neonate, Premature, Preterm, Vaccination, Vaccine

Worldwide, every year nearly 15 million babies are born premature and out of them, 3.5 million are born in India, i.e., nearly 1/4th of the global prematurity burden is being handled by India itself [1,2]. Approximately 20% of them are either very low birth weight (LBW) (<1500 g) or very preterm (<33 weeks) who often have prolonged stay in neonatal intensive care unit (NICU) after birth due to prematurity and its associated complications. Epidemiological studies show that premature infants have an increased incidence and severity of vaccine-preventable diseases (VPD) such as pertussis, invasive pneumococcal diseases, and *Haemophilus influenzae* type b (HiB) [3-5]. The exact burden of VPD in lower and middle-income countries is not known.

Although several governing bodies have advised for timely vaccination of premature infants using the same schedule as recommended for full-term infants without any correction for prematurity and LBW, still their vaccination is often delayed [6-11]. Some of the notable reasons for this undue delay could be due to the lack of knowledge among health-care professionals (HCP) as well among parents regarding the safety and efficacy of vaccines in these premature infants. The concern could be due to the occurrence of adverse events such as fever, irritability, seizure, or risk increase in cardiorespiratory instability, e.g., apnea and tachycardia [12,13]. Hence, authors attempted to summarize the several practical issues on preterm vaccination for better understanding among HCP.

SEARCH STRATEGY

Since it is a narrative review, we conducted an informal search in PubMed/Medline using search words (vaccination OR

immunisation OR immunization) AND (preterm OR premature OR “Very low birth weight” or “extreme low birth weight”) AND (infant OR baby OR neonate) with filter human and age of <1 year covering all literature updated until June 2019. From the available results, we included all landmark trials, observational studies (case-control, cohort study and cross-sectional), and excluded the case reports, case series, and review articles. We also searched internationally published guidelines on infant vaccination by various governing bodies for our purpose (e.g., American academy of Pediatrics (AAP), Centers for disease control and prevention (CDC) guideline, National Health Service guideline, and Redbook).

MYTHS AND FACTS ABOUT VACCINATION IN PRETERM INFANTS [6-8,14]

There are several concerns regarding vaccination in preterm NICU graduates among parents as well as HCP which are tabulated as Table 1.

EFFECT OF MATERNAL IMMUNITY ON VACCINATION IN PRETERM INFANTS [15-17]

In the early neonatal period, premature infants are prone to have infection from vaccine-preventable organisms due to their inadequate immunity. This limitation is partially compensated by transfer of maternal antibodies in fetal life. Thus, immunization of pregnant women against pathogens is a method of providing passive immunity to their future child in initial months of life. Transfer of antibodies depends on the various factors such as gestational age (higher toward later period of gestation), maternal

Table 1: Myths and facts about vaccination in preterm infants

Myths	Facts
Vaccination in premature infants needs to be delayed as they are weak and frail	Although prematurity is associated with immunological immaturity, studies have shown that the uptake and immune response of most of the childhood vaccines are similar between preterm and full-term infants. Hence, vaccination should not be delayed and it should be done as per chronological age of the baby
Preterm immune response is inadequate to cause effective protection; hence, multiple extra doses might be required	Evidence has shown that commonly used vaccination schedule by several governing bodies is equally effective in providing adequate protection following primary vaccination series. Hence, apart from the routine booster doses as indicated for term infants, no extra doses of any vaccine are needed
Preterm neonates have more vaccine-related adverse effects	Apart from adverse events related to underlying health conditions (apnea, bradycardia, and desaturations) which are more common in extremely preterm infants (<1000 g), incidence of classic vaccine-related adverse effects is similar to their term counterparts
Preterm neonates have associated comorbidities (BPD, feeding abnormality, and seizure)	Premature infants with associated comorbid conditions are at higher risk from VPD as compared to their healthier counterparts; hence, vaccination should be started in them as early as possible
Vaccines are painful for preterm neonates, and hence painless vaccine should be administered in them	The traditional term “painless vaccine” (combination vaccine containing aP component) is a misnomer created by manufacturers. Classically, aP component of DTaP vaccine is often attributed to less febrile reaction, thus, resulting in less irritability of babies which is interpreted as less pain. However, recent data support in favor of continue using whole-cell pertussis-containing vaccines for primary series in developing world due to acceptability, robust, and long-lasting immune response. Pentavalent vaccine (DTwP + HiB + Hep B) is available free of cost in government health-care facilities. Thus, choice of DPT versus DTaP should be individualized after discussing the facts with parents; choice of DTaP should not be merely due to prematurity
Preterm infants have less muscle mass; hence, it is difficult to give intramuscular vaccines to them	As preterm infants have less muscle mass, thin and shorter needle (5/8 inch) should be used
It is better to avoid vaccination if there is fever	Mild fever alone should not be criteria to delay vaccination if baby is otherwise stable
Preterm infants cannot tolerate multiple vaccines together	To avoid unnecessary delay and multiple hospital visits, it is advisable to give multiple live vaccines in a single setting unless; there is inadequate space for multiple simultaneous intramuscular vaccinations. There should be at least 4 weeks gap between vaccines for optimal response

BPD: Borderline personality disorder, **VPD:** Vaccine-preventable diseases, **DTaP:** Diphtheria, tetanus, and pertussis, **Hep B:** Hepatitis B, **HiB:** *Haemophilus influenzae* type b, **aP:** Acellular pertussis

antibody level, type of immunoglobulin (Ig)G subclass (IgG1 has best permeability and IgG2 least [responsible of the recognition of polysaccharide antigens of encapsulated bacteria]), and placental characteristics (placental infection with malaria and HIV often prevents antibody transfer).

Studies have established the protective role of maternal vaccination for their infants in the initial 6 months due to passive placental transfer of antibodies. Therefore, the Government of India had introduced tetanus vaccine to all pregnant women in universal immunization program, which will soon be replaced by tetanus-diphtheria (Td) vaccine, as per the WHO recommendations. In high-income countries, apart from tetanus vaccine, routinely administered vaccines during pregnancy period include acellular pertussis (aP) (in the form of Tdap) and influenza (trivalent influenza vaccine). Along with placental transfer of protective antibodies in the antenatal period, breast milk is an important source of Igs, immune cells, and immunogenic molecules. Apart from their protective effect against capsulated bacterial infections, maternal antibodies may interfere with antibody response to vaccines (especially measles) in infants younger than 6 months and limit their capacity to develop their own immune response against microorganisms. Hence, some vaccines like measles are administered only after 9 months of age.

NEONATAL IMMUNE SYSTEM [14,16-19]

1. Why NICU graduates are more vulnerable to VPD in infancy?
 - During the intrauterine period, due to low exposure to foreign antigens, the adaptive immunity in the newborn is primarily composed of lymphocytes. The production of antibodies by B cells begins a few months after birth. This limitation is partially compensated by passive transfer of maternal antibodies (IgG) through placenta, particularly in later gestation (3rd trimester). Thus, in premature infants, there is increased susceptibility to capsulated bacterial infection due to reduced transfer of maternal antibodies
 - Among several IgG components, transplacental passage is highest for IgG1 and lowest for IgG2. However, IgG2 is the component, which provides protection against capsulated bacteria
 - Most of the preterm infants due to prematurity itself or due to associated complications often have prolonged NICU stay; thus, there is more exposure to pathogenic organisms in early life
 - Due to suboptimal nutrition and postnatal growth retardation, preterm infants show suboptimal immune response
 - Due to underlying chronic disorders such as bronchopulmonary

dysplasia and gastroesophageal reflux, there is a tendency for repeated respiratory tract infections

- Preterm infants are more prone to have rotaviral diarrhea as compared to term counterparts.

2. What is the difference between vaccine responses between preterm neonates and full-term neonates? [15,16,18]

The preterm neonates who had prolonged NICU stay remain the most vulnerable group to get affected by VPD due to the following reasons:

- Less than adequate secretion of immune peptides such as defensin from skin, lungs, and epithelial cells which can alter host gene expression, act as cytokines, and/or induce less chemokine production and inhibit lipopolysaccharide production
- Premature infants have impaired innate immune system due to less functional antigen-presenting cells, thus, resulting in suboptimal vaccine uptake
- Suboptimal adaptive and cellular immunity including Th1 and Th2 are also less proficient in premature neonates
- Premature infants have predominant IgM response with slower or nil switch IgG response after vaccination
- Maternal antibody levels as well as transfer are lower than term neonates, this is beneficial in the sense it might actually facilitate vaccine responses

CURRENT IMMUNIZATION SCHEDULE

The salient features of the recommendation of vaccination of preterm infants until 2 years of age by National Immunization Schedule (NIS) versus the Indian Academy of Pediatrics (IAP) have been summarized in Table 2 [8,20].

The approximate costs and available brands of various other vaccines for preterm infants until 2 years of age are summarized in Table 3. Wherever parents need to purchase vaccines (which are not been given free by the government), they must be informed about the cost-benefit ratio.

INDIVIDUAL VACCINES FOR PRETERM INFANTS (UNTIL 2 YEARS OF AGE)

Bacillus Calmette Guérin (BCG) Vaccine

BCG can be administered safely and effectively to LBW and preterm infants after stabilization and before discharge as it is found in previous studies that uptake of BCG vaccine is good in premature infants up to 34–35 weeks post-conceptual age [18]. Hence, it is a good practice to inject BCG at the time of discharge for most of the premature infants.

Polio Vaccine (Oral Poliovirus Vaccines [OPV] and Inactivated Polio Vaccine [IPV])

First, oral polio vaccine is to be given before discharge to provide herd immunity and help in gut priming. To prevent enteral

circulation of live poliovirus to other premature sick infants in NICU, it is better to avoid giving polio vaccine to infants still admitted in NICU. These infants should receive all other routine doses of OPV as well as supplementary doses of OPV as per NIS in post-discharge period.

Studies have shown that premature infants are capable of mounting immune response similar to term infants following IPV against all three polio strains [21]. Thus, IPV can be given to preterm infants at recommended chronological age either as part of NIS (two fractional intradermal doses of 0.1 ml at 6 weeks and 14 weeks or a single IM dose of 0.5 ml at 14 weeks) or IAP optional schedule (3 IM doses of 0.5 ml each at 6, 10, and 14 weeks and a booster at 16–24 months) [8,20].

Hepatitis B Vaccine (Hep B)

As hep B remains a major global concern with higher prevalence in South Asian regions, including India, it is of utmost importance to achieve the maximal protection against perinatal transmission by ensuring complete vaccination at birth. Hep B is the only vaccine which has shown a significant lower immunogenicity in preterm infants as compared to term infants (45–85% vs. 90–100%) when administered at birth [22,23]. Although birth dose of Hep B should be administered any time soon after birth in infants >2 kg, due to decreased efficacy in <2 kg weight infants in previous studies, it is generally deferred until the age of 1 month [22].

Recent studies have shown protective levels of anti-HBs antibody after the 3rd month of life even in preterm neonates if they receive the first dose at 30 days of chronological age irrespective of birth weight and gestation [24]. Thus, postnatal age rather than gestational age or birth weight might be a better predictor of vaccine efficacy. Moreover, birth dose can be administered at discharge to all these neonates if consistent weight gain is achieved. In infants < 2 kg, born to hep B positive mother or whose maternal status is unknown, the current practice is to give birth dose Hep B as well as hep B Ig within 12 h of life, followed by 3 more doses at 1, 2, and 6 months of age.

Diphtheria Pertussis Tetanus Combination Vaccine

The similar protective antibody response is seen against diphtheria, pertussis, and tetanus after vaccination both in preterm, LBW and term infants. Much-hyped concern on febrile reactions and apnea following DPT vaccination is primarily due to whole-cell pertussis component, especially when used in extremely LBW (ELBW) infants. In contrast, recent research correlates association of apnea to overall hemodynamic condition of neonate at vaccination time rather LBW. aP vaccine (either in combination or alone) is not associated with apnea and bradypnea even in ELBW infants or <31 weeks of gestation [7]. At present, IAP also recommends the first dose of DPT vaccine alone or in combination in infants

Table 2: Brief summary of recommendation of vaccines for young infants (<24 months) for the year 2018–2019

Postnatal age (in completed weeks/months)	Vaccines as per NIS	Vaccines as per IAP	Comments
Birth	BCG OPV 0 Hep B birth dose	BCG OPV 0 Hep B birth dose	BCG can be given up to 1 year if not given earlier OPV and Hep B birth dose for institutional deliveries to be given within 24 h
6 weeks	Pentavalent 1 (DTwP/HiB/Hep B 1) OPV 1 IPV ^S 1 Rotavirus [#] 1 PCV [#] 1	Pentavalent 1 (DTwP or DTaP/HiB/Hep B) IPV 1 Rotavirus1 PCV1	IPV dose intradermal 0.1 ml at government dispensaries
10 weeks	Pentavalent 2 (DTwP/HiB/Hep B 1) OPV 2 Rotavirus [#] 2	Pentavalent 2 (DTwP or DTaP/HiB/Hep B) IPV 2 Rotavirus2 PCV 2	Bivalent OPV is being used after April 16
14 weeks	Pentavalent 3 (DTwP/HiB/Hep B 1) OPV-3 IPV ^S 2 Rotavirus [#] 3 PCV [#] 2	Pentavalent 3 (DTwP or DTaP/HiB/Hep B) IPV3 Rotavirus3 PCV 3	-
6 months		TCV	-
9 months	Measles/MR [#] 1 JE 1** PCV [#] 3 Vitamin A	MMR1 dose JE 1 Vitamin A	Vitamin A dose 1 lakh per oral
12 months		Hepatitis A ^{&} Influenzae annually [@]	
16–24 months	Measles/MR [#] 2 JE 2** DPT booster OPV booster Vitamin A	MMR2 JE 2 DPT booster HiB booster PCV booster IPV booster Varicella 1 Vitamin A	Vitamin A dose 2 lakhs per oral

[#]Phased introduction of rotavirus, PCV vaccine in selected states. ^STwo doses of fractional intradermal IPV (ID-fIPV) at 6 and 14 weeks. ^{**}Given in JE endemic districts. [&]For live attenuated strain single dose sufficient. [@]Annual influenza (killed vaccine) recommended for age 6 months–5 years. DTaP: Diphtheria, tetanus, and pertussis, BCG: Bacillus calmette guérin, OPV: Oral poliovirus vaccines, Hep B: Hepatitis B, HiB: *Haemophilus influenzae* type b, PCV: Pneumococcal conjugate vaccine, TCV: Typhoid conjugated vaccine, IPV: Inactivated polio vaccine, NIS: National Immunization Schedule, IAP: Indian Academy of Pediatrics

at 6 weeks of chronological age irrespective of birth weight or gestation [8].

HiB Vaccine

Studies on immunogenicity of Hib vaccine have shown variable result. Recent studies show only marginal differences between preterm and term infants and most premature infants are able to mount acceptable immune response after vaccination with primary series followed by booster dose after 32 weeks PMA [25,26]. Optimal safety and immunogenicity of Hib vaccine are seen in preterm infants in various regimens commencing at 6–8 weeks of age. As preterm infants younger than 1 year of age are at increased risk for invasive H. influenzae diseases, IAP/NIS recommends all premature infants to complete the primary series with three doses (from 6 to 14 weeks) followed by one booster dose at 18–24 months [8].

Rotavirus Vaccine (RV)

Premature infants are vulnerable to suffer from severe rotaviral gastroenteritis requiring hospitalization. Therefore, it is recommended to give RV at or after discharge from NICU if infant is clinically stable with minimum chronological age of 6 weeks [6-8]. Studies using Rotarix (Human monovalent live vaccine (RV1) and RotaTeq (Pentavalent human-bovine reassortant rotavirus vaccine RV5) have shown good efficacy and immunogenicity in premature infants [27,28]. The studies are currently lacking for the newly licensed Indian vaccine, Rotavac (Indian neonatal rotavirus live vaccine, 116 E), and Rotasiil, which have been incorporated in NIS.

Pneumococcal Conjugate Vaccine (PCV)

Invasive pneumococcal disease is seen most commonly in young infants (<2 years) and those with chronic diseases.

Table 3: Available brands and approximate costs of available vaccines in market

Vaccines	Commonly used brands	Approximate cost in INR
Conjugated pneumococcal vaccines (PCV 10/13)	Prevenar (PCV-13) by Wyeth	3,800
	Synflorix (PCV-13) by GSK	1,320
Rotavirus vaccine	Rotarix (2 doses) by GSK	1,499
	RotaTeq by MSD	990
	Rotavac by Bharat Biotech	689
	Rotasiil by Sii	500
Injectable polio vaccine	Imovax Polio vaccine by Sanofi Pasteur (Not available)	483
Hepatitis A (formaldehyde inactivated/live attenuated)	Havrix by GSK	960
	Avaxim 80 by Sanofi Pasteur	1,260
	Biovac A (live attenuated) by Wockhardt	1,290
Influenza (inactivated)	FluQuadri by Sanofi Pasteur	1,250
	Fluarix by GSK Biological	599
	Agripal by Panacea Biotech	760
	Vaxiflu by Zydus Cadila	530
TCV	Typbar-TCV by Bharat Biotech	1,799
	Zyvac TCV by Zydus	1,795
MMR (live inactivated)	Trimovax by Aventis Pasteur	150
	Priorix by GSK	545
	Tresivac by Sii	141
MMR+Chickenpox combination	Priorix Tetra by GSK	2,999
Chickenpox	Varilrix by GSK	1,560
	Okavax by Sanofi	1,260
	Biovac V by Wockhardt	1,699
	Varivax by Merck	1,200
Pentavalent/Hexavalent combinations	Pentavac SD (HiB+DTaP+Hep B) from Sii	550
	Pentaxim (DTaP+HiB+IPV) from Sanofi Pasteur	2,495
	Hexaxim (DTaP+HiB+Hep B+IPV) – Sanofi Pasteur	3,300
	Infanrix hexa (DTaP+HiB+Hep B+IPV) by GSK	2,300
	Easy six (DTaP+HiB+Hep B+IPV) by Panacea Biotech	2,100

DTaP: Diphtheria, tetanus, and pertussis, Hep B: Hepatitis B, HiB: *Haemophilus influenzae* type b, PCV: Pneumococcal conjugate vaccine, TCV: Typhoid conjugated vaccine, MMR: Measles mumps rubella, IPV: Inactivated polio vaccine

Hence, preterm neonates with chronic respiratory illnesses like bronchopulmonary dysplasia remain vulnerable. Although preterm infants have lesser antibody levels and immunogenicity to several strains of pneumococcal vaccines following primary immunization series compared to term infants, the differences get nullified after a booster [29-31]. Hence, it is recommended to complete three doses of vaccine schedule from 6 to 14 weeks at 4 weekly intervals followed by a booster at 16–24 months.

Influenza Vaccine

As preterm infants are at increased risk of complicated influenza, two doses of inactivated flu virus vaccine may be considered at the beginning of flu season in preterm infants after 6 months of age after discussion with parents on case to case basis. Along with preterm infants, household contacts as well as hospital personnel caring for these infants (especially in <6 months of age) should be vaccinated as well, with influenza vaccine (cocooning strategy) [32].

Measles Containing Vaccine (Measles Mumps Rubella [MMR]/MR)

Passive transfer of antibodies from immunized mother usually provides sufficient protection until 6 months of age. However,

in preterm NICU graduates, maternal antibodies might be inadequate to provide immunity. A recent study has shown that 60% of preterm and 30% of term infants did not show antibodies against measles in their serum in early infancy [33]. Another study showed that in infants <28 weeks gestation, reduced maternally transferred antibodies against measles by as early as 3 months of age [34]. Hence, it seems rational to immunize all preterm neonates against measles as early as possible. However, vaccination with MMR/MR at 9 months or earlier has resulted in poor seroconversion, and thus booster dose may be required later. Considering these facts, IAP recommends routine immunization of all preterm neonates with measles-containing vaccine starting after 9 months of age which should be followed by two booster doses at 16–24 months and 5 years, respectively [8].

Typhoid Vaccine

Due to the continuous burden of typhoid fever, wide prevalence of antibiotic-resistant strains of *Salmonella typhi* as well as the availability of safe and effective typhoid vaccines, the WHO recommends the use of typhoid vaccines in national programs for the control of typhoid fever [35]. Typhoid conjugate vaccine (TCV) is the preferred vaccine at all ages over typhoid Vi polysaccharide vaccine. Accordingly, IAP endorses a single dose

of TCV for all infants (including preterm infants) and children starting from 6 months of age.

Chickenpox Vaccine

Studies did not show a difference in antibody response to chickenpox vaccine among preterm and term infants when administered after 1 year of age [36]. IAP recommends varicella vaccine to be given between 12 and 23 months of age separately or in combination. At present, it is not included in routine schedule.

Palivizumab/Respiratory Syncytial Virus (RSV) Prophylaxis

Although AAP recommends routine RSV immunoprophylaxis with RSV monoclonal antibodies for all infants born <29 weeks, due to non-availability, high cost, and lack of evidence in Indian scenario, it is not being advised routinely to all preterm infants in India currently [7].

Immunizing Family Members and Close Contacts (Cocooning)

Immunization of family members and other close contacts, including healthcare workers known as cocooning, is an indirect protective strategy for vulnerable preterm infants against diseases such as influenza and pertussis [37]. This can be achieved by active parental involvement and educational counseling.

SOME GENERAL PRECAUTIONS DURING VACCINATION OF PREMATURE/LBW INFANTS

1. Since these infants have low muscle mass, use of shorter and thinner needles (5/8 inch or less) is recommended
2. For infants who were born as extremely preterm (<28 weeks) or very preterm (<32 weeks), it is preferable to give first vaccination at hospital and monitor for 48–72 hours subsequently before discharge as some of them are likely to have apnea or desaturation. However, if such infants have already stayed in NICU for more than 2 months and are hemodynamically stable (apnoea free, not on caffeine) such observations might be omitted [7]. In case of such incident in the first dose, the index case should be monitored vigilantly while receiving booster doses as well.

CONCLUSION

Based on our review, it can be concluded that all vaccines should be administered as per chronological age irrespective of birth weight and gestation in preterm NICU graduates with exception of hep B vaccine. Due to their intrinsic vulnerability to VPD, optional vaccines such as conjugated pneumococcal, rotavirus, and influenza vaccine should be offered after discussion with parents if resources permit. At present, there is no recommendation for using routine RSV prophylaxis in Indian scenario. Apart from direct vaccination of preterm infants, vaccination of pregnant mothers (passive transfer of antibody

in antenatal period), household contacts (cocooning effect), and exclusive breastfeeding are other important strategies to prevent VPD in preterm infants.

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