Common Queries About Immunizations in Preterm Infants

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ABSTRACT

Preterm infants are at an increased risk of morbidity and mortality from vaccine-preventable diseases. Despite this, delays in routine immunization of preterm infants are common. Available guidelines clearly state that they should be immunized according to chronological age, irrespective of gestational age and birth weight or current weight. In this article, we try to assuage parental and provider doubts by reviewing data about immunogenicity, safety, and responses to routine immunizations in preterm infants with and without comorbidities. We also look at evidence for other strategies to help protect this fragile population. **[*Pediatr Ann*. 2018;47(4):e147-e153.]**

Preterm births, defined as births prior to 37 weeks, account for 10% to 12% of births in the United States.[1] Improvements in neonatal care have resulted in an increased number of children who survive into childhood and into the care of general pediatricians. As the composition of these survivors changes from predominantly late preterm infants (PTI; gestational age [GA] 34-36 weeks) to an increasing number of extreme PTI (GA <28 weeks) with very low birth weights (<1,500 g) and comorbid conditions (eg, bronchopulmonary dysplasia [BPD], seizures), questions regarding the recommended immunization schedules are common and understandable.

Since 1982, the American Academy of Pediatrics (AAP) and numerous national and international bodies have recommended that PTI be immunized at the same chronological age as their full-term (FT) counterparts.[2] Low birth weight (LBW) and PTI are more susceptible to an increased frequency, severity, and need for hospitalization from vaccine-preventable diseases.[3] Despite this understanding, PTI continue to have inadequate immunization coverage at discharge from the neonatal intensive care unit (NICU) and in the outpatient setting, with delays persisting until age 3 years.[2,3]

PARENTAL FEAR: MY PREEMIE IS TOO SMALL FOR MULTIPLE VACCINES SO THEY WON'T WORK

Prematurity is associated with immunologic immaturity of multifactorial etiology. First is the innate immaturity of the infant's system, with decreased T and B cells, antibodies, and ability to mount an adequate response to antigens. Humoral immunity is also impaired, and PTI are dependent on maternal antibodies for initial defense. This transfer of immunoglobulin (Ig) G predominantly occurs in the last 4 weeks of the third trimester. Thus, even late PTI (34-36 weeks) lack adequate maternal protective IgG. This fear of immaturity is a major factor in practitioner and parent hesitancy about immunizations, but actually these are the factors that should convince parents and providers to immunize earlier, due to their child's inadequate innate defenses.[4]

HEALTH CARE QUESTION: IS THE PRETERM IMMUNE RESPONSE ADEQUATE ENOUGH TO RESULT IN EFFECTIVE PROTECTION?

It is logical to assume that immunogenicity of vaccines could be suboptimal because immune response is directly proportional to GA and birth weight (BW). Factors such as comorbid conditions, vaccine composition, medications, and vaccine schedules also influence response. In all these conditions, the evidence shows that protective immune response has been attained in all ranges of PTI.[5] All of the commonly used schedules, such as the AAP recommended 2, 4, and 6 months, an accelerated trial of 2, 3, and 4 months commonly used in Europe, and even a reduced 2- and 4-month schedule, have all produced adequate protection in PTI. As anticipat-

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ed, the titers are sometimes less than in term infants but still enough to provide a protective response. Importantly, vaccination produces a subgroup of memory cells that result in an enhanced response to the booster doses in PTI.[6]

VACCINE-PREVENTABLE DISEASES AND IMMUNIZATION STRATEGIES

The following is a review of vaccine-preventable diseases and their respective immunization strategies.

Diphtheria

Prior to the implementation of childhood immunizations, diphtheria was a major cause of mortality. Since the end of World War II, use of the diphtheria toxoid has restricted the disease to sporadic outbreaks. The current accepted US schedule of 2, 4, and 6 months, as well as the accelerated schedule from the United Kingdom at 2, 3, and 4 months, is as effective in PTI as in FT infants.[7-9]

The quadrivalent vaccine DTaP–Hib (Diphtheria, Tetanus, acellular Pertussis–*Haemophilus influenzae* type b) has shown protective levels of diphtherial antibodies in PTI, despite a drop in absolute levels of antibodies compared to FT infants.[10] The currently used combinations—the pentavalent (DTaP-IPV [Inactivated Polio Vaccine]-Hib) and hexavalent (DTaP-IPV-Hib/HepB [Hepatitis B])—have been shown to achieve almost 98% protective geometric mean titer (GMT) against diphtheria in PTI with no significant difference in titers.[8,9]

Diphtheria-toxoid combination vaccines are equally effective in PTI following standard schedules.

Tetanus

Neonatal tetanus, although rare in the developed world, continues to be a cause of morbidity and mortality in the developing world. The tetanus toxoid is an adjuvant vaccine that generates neutralizing antibodies. Optimal antibody titers were achieved in both PTI and FT infants immunized on a routine or on an accelerated 2, 3, 4-month schedule.[6,7] The pentavalent and hexavalent vaccines with tetanus toxoid can also maintain immunogenicity in a combined format.[7,9]

Evidence supports the effectiveness in PTI of tetanus-toxoid combination vaccines given on standard schedules.

Pertussis

Pertussis, also known as whooping cough, is an endemic infection that has seen a resurgence recently. Waning immunity has been implicated, triggering a re-emphasis on booster doses. PTI have repeatedly been shown to have a higher risk of mortality and pertussis-related hospitalization than FT infants. Riise et al.[11] showed that this risk of pertussis and related hospitalization remained higher until age 2 years, even when vaccine effectiveness was similar.

The pertussis vaccine can be given in either a whole cell or an acellular format, with the latter containing two to five different antigens (eg, pertussis toxin [PT], filamentous hemagglutinin [FHA], pertactin [PRN]). Currently, most countries are using the acellular format for which immunogenicity is shown but difficult to quantify as the correlates for protection are not well established. Antibodies to the specific antigens are accepted as surrogate markers for immunity even though levels have no specific consensus. The antigenicity to PT, FHA, and PRN is established by showing a 4-fold rise in titers in PTI despite actual levels being lower than that of FT infants.[12]

Of all antigens, PT has the most variability in response, with some studies showing a significant difference in PTI.[6,9] When combavalent vaccines are studied, these differences remain, with FHA and PRN showing a term-like response and PT being lower. This effect is exaggerated in LBW infants and those born younger than age 31 weeks, even after a booster dose.[9,10] Overall, use of the hexavalent vaccine resulted in a 98.9% response after primary immunizations.[13] Nonspecific protection with interferon gamma was shown in infants born younger than age 31weeks when immunized with the quadrivalent vaccine.[14]

Pertussis vaccine has a lower immunogenicity in PTI but the antibody levels are adequate enough to provide immunity.[13,14] Vaccination also provides nonspecific disease protection.

Polio

Since widespread immunization with inactivated polio vaccine (IPV) in the 1950s, endemic polio has been eradicated in the Western world.[15] In countries where polio is still endemic, the live oral polio vaccine (OPV) is still used, but in the developed countries, IPV is preferred to avoid the rare side effect of vaccine-associated paralysis. The commonly used vaccines are trivalent against serotypes I, II, and III and their efficacy is established in PTI.[16] Even though adequate protection levels are reached in both FT infants and PTI with mixed IPV/OPV combinations, response differs based on serotypes. Serotype III showed a lower response in PTI.[7] Both hexavalent and pentavalent combinations produced protective titers even when GMT were lower in PTI.[17]

IPV or combination vaccination should be used on a regular schedule. In areas where outbreaks continue, a combination of OPV/IPV may help with immediate protection.

Haemophilus Influenzae Type B

Haemophilus influenzae type B (Hib) results in invasive disease in infants

younger than age 1 year. The immunogenicity of the Hib vaccine is more variable than others. This is related to the polyribositol coat (a polysaccharide antigen) eliciting a poor response from infants and toddlers. Efficacy data have been mixed with Hib vaccine. D'Angio et al.[7] and Kirmani et al.[18] showed no difference in protective titers in PTI (<29 weeks) and FT infants after primary immunization with the 2, 4, and 6-month schedule and similar levels of protection at age 3 and 7 years. However, these data were contradicted with the combined format in which antibodies were significantly lower in PTI for both short- and long-term protection.[19] The latter studies used an accelerated 2, 3, and 4-month schedule. An observational study attributed this conjugate vaccine failure to prematurity in the absence of booster dose.[20] This risk of vaccine failure in PTI, although high, did not reach statistical significance. Antibody levels in PTI, measured after two doses, were lower than in FT infants. After the third dose, the antibodies were comparable in extended schedules but remained lower in infants with an accelerated schedule.[19] Vaccination with Hib is also supported by demonstrated increase in avidity maturation after vaccination in PTI.[6]

Immunogenicity of Hib vaccines in PTI varies with schedules and combination of other antigens. A series of three vaccines on an extended schedule followed by a booster provides the best coverage.[6]

Pneumococcus

Invasive pneumococcal disease is most commonly seen in children younger than age 2 years and in those with chronic illness. Since the addition of the heptavalent vaccine, a 50% reduction in pneumococcal meningitis has been noted in the US.[15] The heptavalent vaccine showed no difference in antibodies, but depending on serotypes, PTI had lower antibodies and protection than FT infants. This difference was eliminated after the booster dose when both groups achieved equivalent protection.[21] The now commonly used 10- or 13-valent vaccines have similar results. Omenaca et al.[22] showed adequate and comparable immunogenicity of infants age 27 to 31, 31 to 37, and more than 37 weeks given 10-valent vaccine. The booster dose further increased its coverage.[22] The pneumococcal conjugate 13-valent vaccine given at 2, 3, 4, and 12 months showed lower IgG titers in PTI but achieved level of protection. The booster dose is considered essential in PTI to achieve adequate protection.[23]

PTI show lower antibody levels to pneumococcal vaccine after a primary dose but are adequate for protection. The booster dose is strongly advised in PTI to help maintain protection.[22,23]

Hepatitis B

Hepatitis B (HepB) is a major global health burden, with a particularly high prevalence in Africa and southeast Asia. Prevention through immunization at birth provides maximal protection from perinatal infection.[24]

In PTI, this is a dilemma as hepatitis B virus (HBV) is the only vaccine known to have a significantly lower response in PTI compared to FT infants (45%-85% vs 90%-100% when given at birth).[25-27] Further stratification showed that lower BW and earlier GA are contributing factors.[25] A study that looked at BW categories showed in PTI who weighed more than 2,000 g the response was the same as in FT infants.[26] In PTI with GA of 23 to 26 weeks, when immunization was delayed until 30 days or hospital discharge, it was found that PTI seroconverted in rates comparable to FT infants after the primary series and maintained their protection to age 7 years.[18] It appears that prematurity, not GA/BW, is the risk factor that is predictive of a decreased serum HBV surface antibody titer level.[5]

Currently, if maternal status is unknown or seropositive, the recommendation is to give HBV at birth, regardless of GA or BW, along with hepatitis B Ig but not count it as part of the primary series.[24]

If maternal status is negative it is advisable to delay giving HBV until 30 days after birth or discharge to ensure maximum protection.[28] For infants who get HBV before they weigh at least 2 kg, the first dose is discounted and they should get the usual three-dose schedule afterwards, which is necessary to maintain long-term protection.[26]

Measles-Mumps-Rubella/Varicella

Prior to vaccination for measles, mumps, and rubella (MMR), immunity is dependent on the transfer of maternal antibody to the infant. As most mothers are currently immunized and not naturally immune, the number of antibodies available for transfer is lower. In PTI, this is compounded by a reduced duration of transfer of antibodies. Data show that in infants younger than GA 28 weeks, most had lost their immunity as early as age 3 months, and in another group was absent from birth.[5] Presently, the decision to not vaccinate PTI at 6 to 9 months has been made due to relative immunological immaturity concerns.[29] Even in FT infants, seroconversion rates to MMR are low at 9 months, potentially due to interaction with maternal antibodies; thus, currently, the recommendation remains at 1 year.[30] A link between the MMR vaccine and autism spectrum disorder, although completely disproven,[31] is still raised by many parents. It continues to be our responsibility to assuage those fears, especially for PTI (who are inherently at a higher risk for sensory disorders).

The MMR vaccine should be given after age 1 year in all infants.[32] In the case of an outbreak, earlier immunization for PTI should be considered.

Varicella vaccine, like the MMR one, is a live attenuated vaccine and considered highly immunogenic. It is also recommended at a later age to ensure an adequate and persistent immune response. Comparison data between FT and PTI do not show any difference in antibody responses when given after 1 year.[33] At this time the combination MMR/varicella vaccine can be given for both doses too, while recognizing that a small group of infants vaccinated between ages 12 and 23 months have a slightly increased risk of febrile seizures after the first dose.[34] In lieu of this, it might be prudent to give these vaccines separately in PTI initially.

Rotavirus

Rotavirus gastroenteritis results in severe dehydration and hospitalization in children between ages 6 and 24 months. LBW infants are at an increased risk of hospitalization from rotavirus disease and it is a significant burden on the preterm population. Both formats of the vaccine (rotavirus 5 and rotavirus 1) have shown similar seroconversion rates in PTI and FT infants.[35] Comparisons between early and late PTI showed the infants with lower GA had significantly lower titers and seroconversion rates. Use of the vaccine in PTI (25-36 weeks GA) has been shown to decrease hospitalization and emergency department visits for rotavirus gastroenteritis by 100% and cases by 73%.[36] Protection from the vaccine extends up to three epidemic seasons after immunization.[36]

NICUs often delay initiating this vaccine during hospitalization due to a theoretical risk of horizontal transmission. It is up to the pediatrician to be alert to the small window for immunization (age 6-32 weeks) on initial visits with NICU graduates.

Evidence supports immunization per routine schedule of the PTI prior to 32 weeks post-conceptual age.[35]

Meningitis C

Invasive meningococcal disease has a primary incidence in children younger than age 5 years, followed by a second spike in teenagers. Its immunogenicity is established and shown to be comparable in PTI and FT infants, despite lower titers, with similar antibody persistence at a year.[17]

Presently, there is no US recommendation for vaccine in children younger than age 10 years, but response is comparable in PTI.

PARENTAL FEAR: MY BABY WILL REACT BADLY AND GET SICK FROM THE SHOTS

It is understandable to be concerned about the adverse reactions of vaccines in PTI. This is the most common reason given for delayed immunizations.[3] Data are mixed but there are some differences in adverse events such as apneas and bradycardias after immunization with vaccines, especially combination vaccines; however, these are not predicted by GA, BW, or the infant's clinical condition at the time of immunization.[5] Close monitoring is ideal and thus the recommendation is to immunize the infant in the hospital prior to discharge. Fever risk is higher when all shots are administered together, so premedication is prudent.[37] The whole cell pertussis vaccine was associated more with severe hospital-based symptoms, but the current acellular version showed no difference between FT infants and extreme PTI.[36] Consequently, premedication and possibly staggering vaccines may be the best way to minimize side effects.

HEALTHCARE QUESTION: WITH A SMALL BUT REAL RISK OF ADVERSE EVENTS, WHY EXPOSE MY INFANT TO EVEN MORE CONTROVERSIAL VACCINES LIKE INFLUENZA VACCINE AND PALIVIZUMAB?

The concern about adverse events and questions of effectiveness are justified at this time regarding both the influenza vaccine and palivizumab. What is clear is that both these diseases (ie, influenza and respiratory syncytial virus) cause a disproportionate burden in PTI. Rates of hospitalization, pediatric intensive care unit stays, and even intubations are significantly higher in infants discharged from the NICU, particularly those with a history of BPD.[39] The mortality rates are also higher for this age group. In such a scenario, it becomes imperative that we provide all available protection.

Maternal influenza has been implicated as an etiology for prematurity, particularly during the historical pandemics of 1915 and 2009.[39] No vaccine has been shown to be effective in producing a protective antibody response in infants younger than age 6 months, so the focus should be on maternal and caregiver immunization. The trivalent vaccine is safe for breast-feeding mothers and can be given during those critical first 6 months of life.[40] The attenuated live vaccine is no longer recommended. Once the infant is age 6 months, the vaccine should be given to PTI too regardless of maternal immunization. As it is shown that vaccine response is somewhat lower in PTI than in FT infants, even after repeat doses, herd immunity is critical for their protection.[41]

Palivizumab has been shown to have a significant effect on the mortality and morbidity in the preterm population.[42] Annual changes in the recommendations have been made to limit administration to the most vulnerable populations; however, economic costs have also crept into this decision-making. For the 2017-2018

season, criteria were limited to <29 weeks GA, BPD on oxygen, or hemodynamically significant congenital heart disease. Cost efficacy data have been inconsistent, hence the narrowing of administration criteria.[43] Regardless, lack of administration has led to increased rehospitalization, particularly in those younger than age 28 weeks with chronic lung disease.[42] Until there is more conclusive evidence, we should continue to immunize seasonally.

PARENTAL FEAR: MY BABIES ARE NOT JUST PRETERM, THEY ALSO HAVE OTHER DISEASES

PTI often leave the NICU with associated diagnoses, BPD, feeding abnormalities, seizures, severe combined immunodeficiency (SCID), and a need for steroids or other medications. It is exactly this fragility that puts them at even more risk from vaccine-preventable diseases, making it imperative to immunize them as soon as possible.

HEALTHCARE QUESTION: SHOULD COMORBIDITIES AND MEDICATIONS INFLUENCE MY DECISION ABOUT TIMING OF IMMUNIZATION?

The presence of comorbidities is another roadblock for on-time immunization of PTI. BPD (defined as requiring oxygen at 28 days after birth and/or 36 weeks corrected GA is an independent risk factor for susceptibility to respiratory illness (eg, pertussis, respiratory syncytial virus).[11] Despite a perception of increased respiratory events with immunizations, there is no difference in respiratory decompensation in infants with or without BPD. Infants who have cardiovascular instability are more likely to be those that were unstable at baseline. Close monitoring is prudent but delayed vaccination is not justified. It must be reiterated that if events happen, they are temporary, whereas an actual case of pertussis and/or respiratory syncytial virus can lead to hospitalization, intubation, and further lung damage in this most vulnerable of populations.

Antenatal steroid use has shown no effect on vaccines but there is a small difference in titers after the use of postnatal steroids. These differences in titers, although significant, still attain a level sufficient to provide protection against disease.[6,44] Dexamethasone use affected both pertussis and HiB titers, but none of these drops in titer rendered the vaccine completely ineffective or justified need for further doses.[44] After a short course of medium potency, or even inhaled steroids, immunization, even with live vaccines, is still able to elicit a response.[45] If steroid dose of >2 mg/kg of BW/day is given for more than 2 weeks, then a delay in live vaccines should be considered. Maternal steroids showed no effect on response to vaccines even though initial IgG levels were lower than FT infants.[4]

A history of seizures is commonly found in extreme PTI, especially with a history of intraventricular hemorrhage (IVH). Seizures that are controlled and unrelated to a previous dose of vaccination are not a contradiction for delay in immunizations. The only time DTaP or Tdap (tetanus, diphtheria, and pertussis) are contraindicated in infants is in those with a history of an encephalopathic event within 7 days of the vaccine that is not attributable to any other cause. Seizures present within 3 days of immunization are not absolute contradictions but warrant some caution. Stable neurological conditions, such as cerebral palsy, developmental delays, or even history of high fevers (but not >105°F), are not barriers for immunization.[46]

Many states are now including SCID in their newborn screening checklist. This is a condition in which consulting an immunologist for the vaccine schedule is recommended. Live vaccines like MMR, OPV, and varicella are contraindicated in this condition. Rotavirus vaccine has also been associated with increased risk of intussusception in cases of SCID, so it is contraindicated. For the inactivated vaccines, the recommendation is to continue to give them at the appropriate age. In primary immune deficiency, the whole cell pertussis vaccine is associated with seizures, and so the acellular pertussis vaccine is recommended. The comparison between both types has been complicated to study as different components are used.

PARENTAL FEAR: I'M PREGNANT AND DON'T WANT TO HARM THE FETUS—ISN'T THERE SOMETHING ELSE I CAN DO?

The safety of the Tdap vaccine in pregnancy has been well established, and thus the recommendation is that all pregnant women be vaccinated. Immunizing in pregnancy has a 2-fold effect: (1) in FT infants, maternal antibodies produced and transferred to infants protect them until their primary immunization; and (2) in PTI, who may not achieve complete immunity util after completion of all 3 doses, there is a cocooning safety net in place. Updates in antenatal vaccine recommendations have come as data emerge about effectiveness and effect on disease burden, particularly in the face of rising pertussis cases. Cocooning, in which postpartum women and caregivers were immunized to provide a protective environment, was ineffective, so the target group now includes all women with fetus(es) between GA 27 and 36 weeks, regardless of previous vaccine status. This policy helps to protect all but the most extreme of premature babies with some maternal antibodies.

The inactivated flu vaccine is now also a universal recommendation based on data that pregnancy by itself is a risk

factor for hospitalization for influenza, and results in more LBW and preterm deliveries.[39] The inactivated vaccine is safe in any trimester of pregnancy and during breast-feeding. Maternal antibodies are a major defense for all infants younger than age 6 months, particularly infants with chronic respiratory problems.

HEALTH CARE QUESTION: WHO SHOULD BE PART OF THIS ROUTINE IMMUNIZATION, AND WON'T MATERNAL VACCINES AFFECT THE INFANT'S RESPONSE?

Strong advocacy for antenatal vaccination of pregnant women is a useful protective mechanism to provide protection to both FT infants and PTI while primary immunizations are completed and protective titers achieved, usually after age 6 months. As the burden for these preventable diseases continues to rise, particularly in the vulnerable preterm population, it is imperative that we try to enhance the cocoon effect by not just vaccinating mothers but also ensuring that all caregivers, including health professionals, are part of the immune protection team. The timing of vaccines is still being debated, but currently the second trimester (27-36 weeks) is ideal because it gives enough time for IgG to form and transfer to the baby in a full-term gestation. As most transfer occurs within the third trimester, most PTI will have a limited but still significant benefit.[4] For practitioners, it is important to remember that the presence of maternal vaccination just prior to delivery may result in some effect to vaccine response in the PTI. In such cases, it's ideal to give vaccines on the 8-week schedule and not earlier.

Flu vaccine coverage has increased in pregnancy but there is still room for improvement. Flu vaccination during pregnancy and in the first 6 months postpartum helps to decrease hospitalizations from flu-like illnesses in FT infants.[37] A recent meta-analysis has shown a decreased risk of LBW or preterm birth in mothers who received the vaccine during pregnancy.[47] All family members should be encouraged to get the flu vaccine, particularly with PTI whose birth and course leaves them unimmunized over the course of two flu seasons.

CONCLUSION

Primary care givers need to be more aggressive with encouraging these vaccinations to benefit infants. Premature infants have clearly shown adequate immunogenicity and tolerance to immunizations. It is imperative that the primary caregivers continue be strong advocates for timely vaccinations, particularly in this fragile population.

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