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CLINICAL REPORT
Guidance for the Clinician in Rendering Pediatric Care

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Immunization of Preterm and Low Birth Weight Infants

ABSTRACT. Preterm (PT) infants are at increased risk of experiencing complications of vaccine-preventable diseases but are less likely to receive immunizations on time. Medically stable PT and low birth weight (LBW) infants should receive full doses of diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, hepatitis B, poliovirus, and pneumococcal conjugate vaccines at a chronologic age consistent with the schedule recommended for full-term infants. Infants with birth weight less than 2000 g may require modification of the timing of hepatitis B immunoprophylaxis depending on maternal hepatitis B surface antigen status. All PT and LBW infants benefit from receiving influenza vaccine beginning at 6 months of age before the beginning of and during the influenza season. All vaccines routinely recommended during infancy are safe for use in PT and LBW infants. The occurrence of mild vaccine-attributable adverse events are similar in both full-term and PT vaccine recipients. Although the immunogenicity of some childhood vaccines may be decreased in the smallest PT infants, antibody concentrations achieved usually are protective.

ABBREVIATIONS. PT, preterm; LBW, low birth weight; VLBW, very low birth weight; ELBW, extremely low birth weight; HBV, hepatitis B virus; DTaP, diphtheria and tetanus toxoids and acellular pertussis; IPV, inactivated poliovirus; Hib, *Haemophilus influenzae* type b; FT, full-term; PCV7, heptavalent pneumococcal conjugate vaccine; AAP, American Academy of Pediatrics; HBsAg, hepatitis B surface antigen; anti-HBs, antibody to hepatitis B surface antigen; DTwP, diphtheria and tetanus toxoids and whole-cell pertussis; OPV, oral poliovirus; MCV, meningococcal C conjugate vaccine; CLD, chronic lung disease; HBIG, Hepatitis B Immune Globulin.

INTRODUCTION

Preterm (PT [<37 weeks' gestation]) and low birth weight (LBW [<2500 g]) infants are at greater risk of increased morbidity from vaccine-preventable diseases.[1] PT infants are less likely to receive immunizations in a timely fashion because of high rates of medical complications related to PT birth and practitioner concerns for the PT infant's fragility and ability to develop protective immunity after receiving routinely recommended vaccines.[2–5] Advances in the care of very low birth weight (VLBW [<1500 g]), extremely low birth weight (ELBW [<1000 g]), and critically ill PT infants have increased survival rates substantially, thereby adding challenges in the selection and optimization of appropriate immunization regimens for infants with immature or impaired cellular and humoral immune systems. Several studies have examined the safety, immunogenicity, efficacy, and durability of immune responses to hepatitis B virus (HBV), diphtheria and tetanus toxoids and acellular pertussis (DTaP), inactivated poliovirus (IPV), *Haemophilus influenzae* type b (Hib), influenza, and pneumococcal conjugate vaccines when given to PT and LBW infants.[6–8] Several editions of the *Red Book* (1997,[9] 2000,[10] and 2003[11]) addressed the specific immunization needs of PT and LBW infants and recommended that all PT infants receive, with the qualified exception of hepatitis B vaccine given at birth, full doses of all routinely recommended childhood vaccines at a chronologic age consistent with the schedule used for full-term (FT) infants. This clinical report provides updated information on the immunogenicity, durability, and safety of routinely recommended childhood vaccines given to PT and LBW infants. It also addresses changes in the timing of hepatitis B vaccine given to infants weighing less than 2000 g, introduces heptavalent pneumococcal conjugate vaccine (PCV7) for use in PT and LBW infants, and reinforces the importance of influenza prevention for these at-risk infants.

The conclusions contained in this report are based on the current knowledge of the immune response of PT infants to specific antigens contained in various vaccines. These data, however, are limited by the relatively small number of PT infants studied to date.

HEPATITIS B VACCINE

Hepatitis B vaccine is the only vaccine included in the US childhood and adolescent immunization schedule (www.aap.org, www.cdc.gov/nip, or www.immunize.org) that is recommended for administration at birth. Since inception of the universal hepatitis B infant immunization policy in 1992, the American Academy of Pediatrics (AAP) has expressed a preference that all infants receive hepatitis B vaccine at birth or before discharge home from the hospital.[12,13] An AAP policy statement published in 1994 and reaffirmed in 1998[14] recommended that the first dose of hepatitis B vaccine be deferred in infants weighing

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less than 2000 g and born to hepatitis B surface antigen (HBsAg)-negative mothers until those infants reached 2000 g or 2 months of age. The most compelling data for that recommendation came from a study published in 1992 reporting lower seroconversion rates and hepatitis B antibody concentrations in VLBW and ELBW infants immunized with hepatitis B vaccine when they reached a weight of 1000 g compared with infants immunized at 2000 g.[15] Seven subsequent studies published between 1997 and 1999 in the United States, Europe, the Middle East, and Asia further assessed the effect of the postnatal age on immunogenicity of hepatitis B vaccine in PT and LBW infants born to HBsAg-negative mothers.[16–22] Three studies from the United States concluded that neither low birth weight nor the extremes of early gestational age influenced seroconversion rates in PT infants given hepatitis B vaccine.[16–18] Two of these 3 studies demonstrated that a delay of 7 to 30 days' chronologic age was sufficient to permit VLBW infants to respond satisfactorily to HBV immunization and that a pattern of consistent weight gain during hospitalization was more predictive of immunologic response than was birth weight.[16,18] Studies from Israel,[19] Italy,[20] and Poland[21] confirmed that PT infants seroconverted in response to hepatitis B vaccine by 30 days of age regardless of gestational age and birth weight. Protection derived from HBV immunization comparable to that seen in FT infants could be expected in medically stable* PT, VLBW, and ELBW infants.[20] These studies conclude that prematurity per se, rather than a specific gestational age or birth weight, is more predictive of decreased serum concentrations of antibody to hepatitis B surface antigen (anti-HBs) when compared with those achieved by FT infants. Nonetheless, protective concentrations of anti-HBs are achieved in almost all PT infants by 9 to 12 months of age after receiving the recommended 3 doses of hepatitis B vaccine. The rates of decrease in anti-HBs measured 3 and 7 years after a completed HBV immunization series are similar for PT and FT infants, with protective concentrations maintained throughout in both groups of infants.[7,22,23]

None of the studies reported from 1997 to the present described vaccine-associated adverse events that would preclude offering hepatitis B vaccine to medically stable PT infants at any gestational age or birth weight. Furthermore, the availability of hepatitis B vaccine without thimerosal used as a preservative effectively has removed any theoretic barrier to the use of hepatitis B vaccine in PT infants who had been shown in one study to have a decreased capacity to metabolize and clear mercury-containing compounds when compared with FT infants.[24]

When considering the anatomic limitations of PT and LBW infant muscle mass, the use of needles with lengths of ⅝ inch or less may be appropriate to ensure effective, safe, and deep anterolateral thigh intramuscular administration required for hepatitis B vaccine administration.

The immunization of LBW and VLBW infants born to HBsAg-negative mothers with hepatitis B vaccine as early as 1 month of age allows more latitude when initiating the routine childhood immunization schedule while the PT infant is in the hospital. The number of simultaneous injections can be decreased for tiny infants with limited injection sites. The temporal separation of hepatitis B vaccine from other vaccines given to the hospitalized infant simplifies the assessment of febrile events that may be associated with vaccine administration. Earlier initiation of HBV immunization provides timely protection of vulnerable PT infants who are more likely to receive multiple blood products and undergo surgical interventions. The theoretic risk of horizontal transmission from household members and other hospital visitors with chronic hepatitis B infection also would be minimized. Finally, hepatitis B vaccine given closer to the time of birth increases the likelihood that the hepatitis B vaccine series and other recommended childhood vaccines will be completed on time.[25]

DIPHTHERIA, TETANUS, PERTUSSIS, Hib, AND POLIOVIRUS VACCINES

Several studies conducted in the past decade have confirmed previous findings of acceptable safety, immunogenicity, and efficacy of DTaP,[26] diphtheria and tetanus toxoids and whole-cell pertussis (DTwP),[8,23] Hib,[8,23,27,28] oral poliovirus (OPV),[8,23] and IPV[29,30] vaccines in PT infants (including those of ELBW) beginning at a chronologic age of 2 months. In the absence of major medical complications of prematurity, the magnitude of immune responses in PT infants tends to be directly proportional to gestational age and birth weight. ELBW infants ≤31 weeks' gestation with a complicated postnatal clinical course are more likely to have decreased, although protective, immune responses when completing a primary immunization series. Hib[8,27,28] and poliovirus serotype 3 antibody production may be particularly affected in these tiny infants.[23] The increased severity of vaccine-preventable disease in PT infants precludes delaying the initiation of the first dose of DTaP, Hib, or IPV vaccine beyond a chronologic age of 2 months in the medically stable infant. A DTaP-hepatitis B combination vaccine given to PT infants in Italy demonstrated immune responses similar to those noted after administration of single antigens with diminished but protective antibody concentrations observed in ELBW infants.[31] A combination DTaP-Hib vaccine given in England to PT infants <32 weeks' gestation on a 2-, 3-, and 4-month schedule resulted in substantially decreased responses to the Hib vaccine component and suggested careful assessment of future combination vaccines will be necessary before use in PT and LBW infants.[32]

The safety of DTwP, DTaP, Hib, and IPV vaccines given to PT and LBW infants is comparable to that in FT infants, with no increase in vaccine adverse events noted.[8,23,26] The relative immaturity of the immune system in PT and LBW infants may mute

* Medically stable refers to the condition of PT or LBW infants who do not require significant ventilatory support or ongoing management for debilitating infection, metabolic disease, or renal cardiovascular or respiratory instability and who have demonstrated a clinical course of sustained recovery that allows the maintenance of a pattern of steady growth.

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some forms of vaccine reactogenicity and may be paradoxically protective of mild adverse events from these vaccines. Apnea occurring within 72 hours (peak, 12–24 hours) of administration of DTwP vaccine to ELBW infants <31 weeks' gestation was described in up to 12% of recipients of whole-cell pertussis-containing vaccines in some studies[33–36] but not in others.[8,23,33,37] Apnea has not been reported after administration of acellular pertussis-containing vaccines to ELBW infants.[26]

PNEUMOCOCCAL CONJUGATE VACCINE

Nearly 38 000 infants participated in clinical trials using PCV7.[38] Vaccine recipients were divided evenly between infants receiving PCV7 and those in a control group given meningococcal C conjugate vaccine (MCV). Both groups received either PCV7 or MCV simultaneously with other routinely recommended childhood vaccines given at 2, 4, 6, and 12 to 15 months of age. A total of 1756 LBW infants (including 131 VLBW and 17 ELBW infants) and 4340 infants ≤38 weeks' gestation (2971 born at 36 and 37 weeks, 1180 born at 32–36 weeks, and 167 born at <32 weeks' gestation) were assessed for PCV7 immunogenicity, efficacy, and safety.[39] After the initial 3 doses of PCV7, PT infants demonstrated immune responses to all 7 pneumococcal serotype components of PCV7 that were equivalent to those found in FT infants. PT and LBW infants in this vaccine trial were determined to be at increased risk of invasive pneumococcal disease compared with FT and normal birth weight infants by relative risk ratios of 1.6 ($P = .06$) and 2.6 ($P = .03$), respectively. However, none of the PT and LBW infants receiving PCV7 in the trial contracted invasive pneumococcal disease attributable to vaccine serotypes, compared with 9 cases (sepsis [9] with pneumonia [5] and meningitis [1]) in infants <38 weeks' gestation in the control group. Most local and systemic adverse events from PCV7 were similar in PT and FT vaccine recipients. PT and LBW recipients of PCV7 had more fever, emesis, irritability, and tenderness or swelling at the injection site than did infants in the MCV control group. Urticarial reactions within 48 hours of PCV7 administration were more common in FT and PT infants compared with MCV controls.[38,39] PT infants receiving PCV7 concomitantly with whole-cell DTP and Hib vaccines experienced more febrile seizures compared with FT infants, but this may be reflective of the increased propensity for febrile convulsions of PT infants, immunizations notwithstanding.[39]

INFLUENZA VACCINE

As with all children, PT and LBW infants are at increased risk of excess morbidity from influenza virus infections.[40] Hospitalization rates of infants with chronic cardiopulmonary, renal, and metabolic complications of prematurity are even greater, with mortality rates approaching 10%.[41,42] A 1992 study compared the humoral and cell-mediated responses to trivalent inactivated influenza vaccine by 45 PT infants with various stages of chronic lung disease (CLD) with those of 18 FT infants at 6 and 20 weeks after immunization.[43] Although cell-mediated responses often were depressed in PT infants with more advanced CLD, nearly all PT infants, regardless of their health status and previous influenza immunization history, were able to achieve and sustain protective concentrations of antibody to the 3 strains of influenza virus contained in influenza vaccine. No significant adverse reactions were noted in ill or recovered PT infants who received influenza vaccine.

The 2003 US childhood and adolescent immunization schedule encouraged annual influenza immunization of healthy children between the ages of 6 and 23 months of age because of increased risk of hospitalization of all children in this age group.[44] Future influenza pandemic planning strategy anticipates recommendations for routine yearly influenza immunization of healthy children out of consideration of the role children play in the propagation and spread of influenza virus in the community.[40]

SUMMARY: IMMUNIZING PT AND LBW INFANTS

General

Timing

Medically stable PT and LBW infants should receive all routinely recommended childhood vaccines at the same chronologic age as recommended for FT infants. Under most circumstances, gestational age at birth and birth weight should not be limiting factors when deciding whether a PT or LBW infant is to be immunized on schedule. Infants with birth weight less than 2000 g, however, may require modification of the timing of hepatitis B immunoprophylaxis depending on maternal HBsAg status.

Dosing

Vaccine dosages normally given to FT infants should not be reduced or divided when given to PT and LBW infants. Although studies have shown decreased immune responses to some vaccines given to VLBW, ELBW, and very early gestational age (<29 weeks) neonates, most PT infants produce sufficient vaccine-induced immunity to prevent disease when full doses are given. The severity of vaccine-preventable diseases in PT and LBW infants precludes any delay in initiating the administration of these vaccines.

Vaccine Administration

The anterolateral thigh is the site of choice when administering intramuscular vaccines to PT infants. The choice of needle length used for intramuscular vaccine administration is made on the basis of the available muscle mass of the PT infant and may be less than the standard ⅞-inch to 1-inch length used for FT infants.[45]

Hepatitis B

Infants Born to HBsAg-Negative Mothers

Medically stable PT infants and infants weighing greater than 2000 g at birth should be treated like FT infants and preferentially receive the first dose of monovalent hepatitis B vaccine shortly after birth and no later than hospital discharge. Practitioners

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TABLE 1. Hepatitis B Immunoprophylaxis Scheme for PT and LBW Infants*

Maternal Status	Infant ≥2000 g	Infant <2000 g
HBsAg positive	Hepatitis B vaccine + HBIG (within 12 h of birth)	Hepatitis B vaccine + HBIG (within 12 h of birth)
	Immunize with 3 vaccine doses at 0, 1, and 6 mo of chronologic age	Immunize with 4 vaccine doses at 0, 1, 2–3, and 6–7 mo of chronologic age
	Check anti-HBs and HBsAg at 9–15 mo of age†	Check anti-HBs and HBsAg at 9–15 mo of age†
	If infant is HBsAg and anti-HBs negative, reimmunize with 3 doses at 2-mo intervals and retest	If infant is HBsAg and anti-HBs negative, reimmunize with 3 doses at 2-mo intervals and retest
HBsAg status unknown	Hepatitis B vaccine (by 12 h) + HBIG (within 7 days) if mother tests HBsAg positive	Hepatitis B vaccine + HBIG (by 12 h)
	Test mother for HBsAg immediately	Test mother for HBsAg immediately and if results are unavailable within 12 h, give infant HBIG
HBsAg negative	Hepatitis B vaccine at birth preferred	Hepatitis B vaccine dose 1 at 30 days of chronologic age if medically stable, or at hospital discharge if before 30 days of chronologic age
	Immunize with 3 doses at 0–2, 1–4, and 6–18 mo of chronologic age	Immunize with 3 doses at 1–2, 2–4, and 6–18 mo of chronologic age
	May give hepatitis B-containing combination vaccine beginning at 6–8 wk of chronologic age	May give hepatitis B-containing combination vaccine beginning at 6–8 wk of chronologic age
	Follow-up anti-HBs and HBsAg testing not needed	Follow-up anti-HBs and HBsAg testing not needed

* Extremes of gestational age and birth weight no longer a consideration for timing of HBV doses.
† Some experts prefer to perform serologic testing 1 to 3 months after completion of the primary series.

who are certain of the mother's negative HBsAg status and wish to use a hepatitis B-containing combination vaccine for PT and LBW infants with birth weight greater than 2000 g must delay the first dose of the combination vaccine until the infant is at least 6 weeks of age. There is no contraindication to giving a birth dose of hepatitis B vaccine as the first of 4 doses when a combination vaccine containing hepatitis B vaccine subsequently is used. The final dose of hepatitis B vaccine should not be given earlier than 6 months chronologic age.

Medically stable PT and LBW infants with birth weight less than 2000 g should receive the first dose of hepatitis B vaccine as early as 30 days of chronologic age regardless of gestational age or birth weight. Alternatively, PT and LBW infants weighing less than 2000 g showing consistent weight gain leading to discharge home from the hospital before attaining 30 days of age should receive the first dose of hepatitis B vaccine at the time of hospital discharge.

Infants Born to HBsAg-Positive Mothers

PT and LBW infants born to mothers who are HBsAg positive must receive hepatitis B vaccine and Hepatitis B Immune Globulin (HBIG) within 12 hours after birth, regardless of gestational age or birth weight. Infants weighing less than 2000 g and born to HBsAg-positive mothers should not have the birth dose of hepatitis B vaccine counted as part of the HBV immunization series, and 3 additional doses of hepatitis B vaccine should be given starting at 1 month of age. Combination vaccines containing a hepatitis B component have not been assessed for efficacy when given to infants born to HBsAg-positive mothers. All infants of HBsAg-positive mothers should be tested for the presence of anti-HBs and HBsAg at 9 to 15 months of age, after completion of the HBV immunization series. Some experts prefer to perform serologic testing 1 to 3 months after completion of the primary series.

Infants Born to Mothers Whose HBsAg Status Is Unknown

All PT and LBW infants born to mothers whose HBsAg status is unknown at the time of delivery should receive monovalent hepatitis B vaccine within 12 hours of birth. Because infants weighing less than 2000 g have less predictable responses to hepatitis B vaccine given at birth, they should be given HBIG by 12 hours of life if the mother's HBsAg status cannot be determined within that time period. HBIG may be delayed up to 7 days for PT and LBW infants weighing more than 2000 g at birth while awaiting the mother's HBsAg test results.

Table 1 provides a schematic outline for hepatitis B immunoprophylaxis given to PT and LBW infants.

DTaP, Hib, and IPV Vaccines

All medically stable PT and LBW infants should begin routine childhood immunization with full doses of any DTaP, Hib, and IPV vaccines licensed by the Food and Drug Administration at 2 months of chronologic age regardless of gestational age or birth weight. Although apnea has not been reported in ELBW infants born at less than 31 weeks' gestation after the use of DTaP vaccine alone, in conjunction with other routinely recommended childhood vaccines, or in combination with other vaccine antigens, it is deemed prudent to closely observe hospitalized ELBW infants for significant adverse events for up to 72 hours after immunization until such a time that sufficient data have been collected to firmly establish a pattern of safety.

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Pneumococcal Conjugate Vaccine

All PT and LBW infants are considered at increased risk of invasive pneumococcal disease, and medically stable PT patients should receive full doses of PCV7 beginning at 2 months of chronologic age.

Influenza

All PT infants are considered at high risk of complications of influenza virus infection and should be offered influenza vaccine beginning at 6 months of age and as soon as possible before the beginning and during influenza season. PT and LBW infants receiving influenza vaccine for the first time will require 2 doses of vaccine administered 1 month apart.

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Immunization of Preterm and Low Birth Weight Infants

Thomas N. Saari

Pediatrics 2003;112;193

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