Update on Timing of Hepatitis B Vaccination for Premature Infants and for Children With Lapsed Immunization

Committee on Infectious Diseases

The American Academy of Pediatrics (AAP) and the United States Public Health Service have recommended immunization of all infants with hepatitis B vaccine.\(^1\,^2\) Although several immunization schedules have been shown to be effective in infants and children, the AAP recommends that the first dose be administered to newborns before they leave the hospital. Alternative schedules beginning between birth and 2 months of age also are acceptable and have been adopted in many practices. These recommendations were based on studies performed in numerous populations demonstrating high immunogenicity when the vaccines were administered in accordance with the manufacturers’ approved doses and schedules.

In the previous AAP recommendations, similar latitude was given in the initiation of vaccine schedules for premature infants born to women who were hepatitis B surface antigen (HBsAg)-negative. For premature infants and other infants with illnesses in the first few days of life, pediatricians were advised that administration of hepatitis B vaccine could be delayed until hospital discharge, although it was implied that premature infants should receive hepatitis B vaccine at the same chronologic age as recommended for term infants.\(^3\)

HEPATITIS B VACCINE IN PREMATURE INFANTS

Studies have revealed, however, that the percentage of infants that develop protective levels (\(\geq 10\) mIU/mL) of antibody to HBsAg (anti-HBs) and the final anti-HBs concentrations may be lower in premature infants given the recombinant hepatitis B vaccines beginning at birth than if the initial dose is delayed until they are older or weigh more than 2000 g.\(^4\,^5\) In one study,\(^4\) the response rate for premature infants who received their first dose of Engerix-B vaccine at a weight of either 1000 to 1999 g or 2000 g or more was 79% and 91%, respectively; the response rate was 100% for normal term infants. The second dose was given 1 month later, and the third dose was given approximately 5 months after the first dose.

In a study of Thai infants with gestational ages of 28 to 32 weeks, 11 of 14 (78%) developed protective levels of anti-HBs after receiving three 10-µg doses of Engerix-B: at birth, 1 month, and 6 months of age; 11 of 11 infants with gestational ages of 33 to 37 weeks developed protective levels.\(^5\) The overall response rate for premature infants was 22 of 25 (88%).

A third study in Italy revealed that all 37 premature infants (<37 weeks’ gestation) developed anti-HBs levels of 10 mIU/mL or greater after receiving 10-µg doses of Engerix-B vaccine at birth, 1 month, and 3 months, or at birth, 1 month, and 6 months of age.\(^6\) Shorter gestational age but not lower birth weight was associated with lower final antibody concentrations.

Because infants born to HBsAg-negative women are not at immediate risk of exposure to hepatitis B virus (HBV), the first dose of vaccine can be deferred. Infants born to HBsAg-positive women, however, are at immediate risk of contracting HBV infection. Immunization, together with a dose of hepatitis B immune globulin, should be given at birth as previously recommended, and these infants should be tested for anti-HBs antibody (see “Recommendations”).\(^1\,^2\,^7\) Management of infants born to mothers who have not been screened has been described in detail.\(^1\,^7\) These infants should receive the first dose of hepatitis B vaccine at birth with the dose of vaccine recommended for infants born to HBsAg-positive mothers. Subsequent management of these infants is dependent on the results of the serologic screening of the mother.\(^7\)

LAPSED IMMUNIZATION

Physicians have a great deal of flexibility in scheduling the three-dose immunization series for term infants born to HBsAg-negative mothers.\(^8\,^9\) The recommended schedule is initiated during the newborn period or by 2 months of age, the second dose is given 1 to 2 months later, and the third dose is given at 6 to 18 months of age.\(^1\) The vaccines, however, are highly immunogenic in multiple schedules.\(^1\,^8\,^9\) Although the highest titers of anti-HBs are achieved when the last two doses of vaccine are spaced 4 months or longer apart, schedules with 2-month intervals between doses have been demonstrated to produce high rates of seroconversion. Some pediatricians have adopted other three-dose schedules in order to minimize the number of simultaneous injections. Intervals of up to 10 months between the second and third doses have been shown to be highly effective.\(^10\) Intervals of longer than 2 months between the first two doses or more than 1 year between the second and third dose have not been evaluated in controlled trials. On the basis of the immune response to other vaccines\(^7\,^11\) and the limited available

The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.
data for hepatitis B vaccine, however, the AAP currently recommends that children of all ages who have had a longer time elapse than recommended between doses of hepatitis B vaccine can have the series completed without the need to repeat a dose or to start the series over.

**FUTURE DEVELOPMENTS**

Additional studies are in progress to assess further the immune response in premature infants and to evaluate the response in infants vaccinated with longer intervals than recommended between doses.

**RECOMMENDATIONS**

The following interim recommendations are made pending the availability of additional data.

1. Infants born to HBsAg-positive women should be vaccinated at or shortly after birth with the appropriate dose of HBV vaccine and should receive one dose of hepatitis B immune globulin within 12 hours after birth. The second dose of vaccine should be administered at 1 month of age and the third dose at 6 months of age. This recommendation applies to all infants, regardless of gestational age or birth weight, and remains unchanged from previous recommendations. These infants should be tested for anti-HBs 1 to 3 months after the third dose. If the anti-HBs serologic test is negative, refer to the 1994 Red Book: Report of the Committee on Infectious Diseases for guidance.

2. For premature infants with birth weights of less than 2000 g born to HBsAg-negative women, it may be advisable to delay initiation of hepatitis B vaccination until just before hospital discharge, providing the infant weighs 2000 g or more, or until about 2 months of age when other immunizations are given. These infants do not routinely need to have serologic testing performed after the third dose for anti-HBs.

3. For infants with lapsed hepatitis B immunization (longer than the recommended time intervals between doses—see recommendation 2. above), the three-dose series can be completed regardless of the interval from the last dose of vaccine. No need exists to start the series over or to test routinely for anti-HBs unless the child’s mother is HBsAg-positive.

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**REFERENCES**

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