Universal Hepatitis B Immunization

Committee on Infectious Diseases

HEPATITIS B DISEASE AND EPIDEMIOLOGY

In the United States 200 000 to 300 000 acute infections with hepatitis B virus (HBV) occur each year. More than one million persons in the United States have chronic HBV infection, and approximately 4000 to 5000 persons die each year from HBV-induced chronic liver disease and hepatocellular carcinoma. Although HBV infections occur during childhood and adolescence, the full impact of these infections is not recognized until many years later when chronic liver disease and hepatocellular carcinoma may develop. The incidence of HBV infection increases rapidly during adolescence, with higher rates among blacks than among whites (Fig 1). Although rates vary by region, sex, and race, between 3.3% and 25% of all persons have had HBV infection by 25 to 34 years of age. The likelihood of becoming chronically infected with HBV varies inversely with the age at which infection occurs. HBV transmitted from hepatitis B surface antigen (HBsAg)-positive mothers to their newborns results in HBV carriage for up to 90% of infants. Between 25% and 50% of children infected before 5 years of age become carriers, whereas only 6% to 10% of acutely infected adults become carriers. It is estimated that more than 25% of carrier infants will die from primary hepatocellular carcinoma or cirrhosis of the liver, with most of these deaths occurring during adult life.

HBV infection occurs more commonly in certain populations, including Pacific Islanders, Alaskan Natives, immigrants from countries in which infection is highly endemic, persons who require multiple transfusions of blood or blood products, and persons with high-risk lifestyles, including intravenous drug abuse and contact with multiple sexual partners. However, approximately 30% to 40% of acute HBV infections in the United States occur in persons with no identifiable risk factors.

HBV is transmitted through exposure to blood and blood products, through sexual contact, and from mothers to infants primarily at the time of birth. It also can be acquired by close contact within families, from person to person through contact between open skin lesions, and possibly by exposure of mucous membranes to other infected body fluids, such as saliva.

VACCINES AND PREVIOUS RECOMMENDATIONS

The first HBV vaccine in the United States was licensed in 1982. Although both plasma-derived and recombinant vaccines are licensed in the United States, only recombinant vaccines are produced currently. Both plasma-derived and recombinant vaccines induce more than 90% protection against HBV infection and are highly immunogenic in infants when given in a variety of immunization schedules. More than 95% of infants have developed a satisfactory serologic response (antibody to HBsAg (anti-HBs)) concentration of ≥10 mIU/mL) after administration of three doses of vaccine. Intervals of 4 or more months between the second and third doses resulted in higher geometric mean titers than intervals of 1 or 2 months. These vaccines have been shown to be highly effective in preventing HBV infection in infants whose mothers are chronic HBV carriers.

The recommended doses and volumes of HBV vaccines differ by manufacturer, age of the individual to be immunized, maternal HBsAg serologic status, and presence of underlying disease (Table 1). The two vaccines currently being marketed appear equally immunogenic and may be used interchangeably in their respective, recommended doses. Adverse effects are minimal, consisting primarily of soreness at the injection site. Hypersensitivity to yeast or preservative in the recombinant vaccines has been reported rarely, and no serious adverse effects in children have been linked definitively to HBV vaccines.

Previously, both the American Academy of Pediatrics (AAP) and the US Public Health Service Immunization Practices Advisory Committee (ACIP) recommended a two-part strategy for control of HBV infection, which consisted of selective vaccination of high-risk populations and serologic screening of all pregnant women for HBsAg. Unfortunately, selectivvaccination strategies have had little impact on the control of HBV infections or their sequelae (Fig 2). Individuals in high-risk groups are not identified readily, and they often undergo preventive health care services. Universal screening of pregnant women for HBsAg with active and passive immunization of their infants will prevent only about 6000 of the more than 200 000 HBV infections that occur in the United States each year. A change in strategy for vaccine use in this country is required to control HBV infections.

UNIVERSAL IMMUNIZATION

The Academy's Committee on Infectious Diseases considered several possible strategies to improve the...
hepatitis B vaccine

TABLE 1. Recommended Doses of Licensed Hepatitis B Vaccines*

<table>
<thead>
<tr>
<th>Vaccine†</th>
<th>Recombivax HB (MSD‡)</th>
<th>Engerix-B§ (SKB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants of HBsAg-negative mothers and children &lt;11 y</td>
<td>2.5 (0.25)</td>
<td>5 (0.5)</td>
</tr>
<tr>
<td>Infants of HBsAg-positive mothers (HBIG 0.5 mL should also be given)</td>
<td>5 (0.5)</td>
<td>10 (0.5)</td>
</tr>
<tr>
<td>Children and adolescents 11 to 19 y</td>
<td>5 (0.5)</td>
<td>20 (1.0)</td>
</tr>
<tr>
<td>Adults ≥20 y</td>
<td>10 (1.0)</td>
<td>20 (1.0)</td>
</tr>
<tr>
<td>Dialysis patients and other immunosuppressed persons</td>
<td>40 (1.0††)</td>
<td>40 (2.0)**</td>
</tr>
</tbody>
</table>

*Heptavax B (MSD), a plasma-derived vaccine, is also licensed, but no longer produced in the US.
† Vaccines should be stored at 2°C to 8°C. Freezing destroys effectiveness.
‡ Merck, Sharp & Dohme.
§ The Food and Drug Administration has approved this vaccine for use in an optional schedule: four doses at 0, 1, 2, and 12 months (see 1991 Report of the Committee on Infectious Diseases††). || Smith Kline Biologicals.
† Special formulation for dialysis patients.
** Four-dose schedule recommended at 0, 1, 2, and 12 months.

Adapted from the 1991 Report of the Committee on Infectious Diseases.10,p244

cost of HBV infections including immunizing in infancy, at adolescence, or a combination approach. Infant immunization offers the most feasible approach to protecting all persons and eventual elimination of disease, but the complete effect of this strategy will not be noted for 25 or more years. Universal immunization of adolescents alone has the advantage of a more immediate effect, but this strategy is problematic. Adolescents at the highest risk would most likely be the least compliant, and asking adolescents to participate in a three-dose immunization series over a 6-month period is likely to result in high drop out rates.

Therefore, the Academy recommends a combination strategy, including universal immunization of all infants. Immunization of all infants has been shown to be cost-saving in controlling HBV infections (Centers for Disease Control, 1991).1,2 A major factor in the cost-effectiveness is the lower dose of vaccine given infants (Table 1). In Alaska the universal HBV
immunization program has resulted in interruption of HBV transmission among Native American children.\textsuperscript{14} Universal infant immunization has been implemented in several of the Pacific Islands under the jurisdiction of the United States, and Hawaii recently has initiated universal immunization of infants for HBV. At least 20 other countries now recommend HBV vaccine for all infants.\textsuperscript{15}

Routine serologic screening of all pregnant women for HBsAg continues to be recommended. Screening should be performed during a prenatal visit for each pregnancy. The dose and schedule of the vaccine to be given to the infant, as well as the use of hepatitis B immune globulin (HBIG), are based on the HBsAg status of the mother (Table 1).

Routine Immunization of Infants Born to HBsAg-Negative Mothers

The Academy recommends administering the first dose of HBV vaccine to newborns before hospital discharge, the second dose at 1 to 2 months of age, and the third dose at 6 to 18 months of age (Table 2). The dose recommended for newborns of HBsAg-negative mothers is different for the two vaccines (Table 1). An alternative schedule of the three doses administered at 2, 4, and 6 to 18 months during regularly scheduled visits and concurrently with other routine vaccines, may be used for HBsAg-negative infants not vaccinated at birth.

These recommendations are based on the need for flexible scheduling of HBV vaccination in the first 18 months of life to integrate this vaccine into routine preventive health care. Since HBV vaccine is highly immunogenic in a variety of schedules, extra visits should not be required to incorporate it into a child’s routine health care. A schedule of immunization at birth, 1 month, and 6 to 18 months may avoid the need to administer three injections of different vaccines at the same visit. Administration of the first dose in the hospital also reduces the need for extra office visits and helps to emphasize to parents and hospital-based personnel the importance of immunizations and preventive services. For premature and other infants with illnesses in the first few days of life, HBV vaccine may be delayed until hospital discharge, provided the mother is not HBsAg-positive.

Immunization of Infants Born to HBsAg-Positive Mothers

Infants born to HBsAg-positive women should receive HBIG at or shortly after birth and should be immunized at birth (within 7 days, preferably with 12 hours). The second and third doses of vaccine should be administered at 1 and 6 months of age, according to current recommendations (Table 2). The dose of Recombivax HB vaccine (Merck, Sharp & Dohme) for infants of carrier mothers is twice (0.5 mL) that given to infants of HBsAg-negative mothers. The dose of Engerix B vaccine (Smith Kline Biologicals) is the same (0.5 mL) for infants of both HBsAg-positive and HBsAg-negative mothers (Table 1).

For infants born to HBsAg-positive women, immunization starting at birth is highly effective in preventing HBV transmission from mother to infant.\textsuperscript{6–9,16}\textsuperscript{17} In infants who have received three doses of HBV vaccine with administration of the first dose by 7 days of age, the risk of chronic HBsAg carriage was reduced by 65% to 90%. The additional administration of HBIG at or shortly after birth has further reduced the risk by 5% to 20%, according to some studies.\textsuperscript{16,17}

Infants of HBsAg-positive mothers should be tested for HBsAg and anti-HBs at 9 months of age or later (at least 1 month after the third dose of vaccine). A fourth dose of HBV vaccine should be administered to infants who are HBsAg-negative and have titers of anti-HBs < 10 mIU/mL. These children should be retested 1 month later for anti-HBs (see The Report of the Committee on Infectious Diseases\textsuperscript{10,12,25}). Additional doses (up to two more) may be considered for those who fail to respond.

Immunization of Infants Whose Mothers Have Unknown HBsAg Status

An infant whose mother’s HBsAg status is unknown and cannot be determined before delivery should be immunized at birth with the dose of vaccine recommended for infants of HBsAg-positive mothers (Table 1). The additional administration of HBIG should depend on the results of the serologic screening of the mother. The mother should be screened for HBsAg as soon as possible, since the efficacy of HBIG has been proven only when given within 12 hours of birth. If the mother is HBsAg-positive, HBIG should be administered immediately to the infant, provided that the infant is less than 1 week old. Efficacy of HBIG given 12 to 48 hours after birth and 7 days of age is not known. The HBsAg status of the mother also determines the subsequent vaccine dose and schedule, as previously described.

**TABLE 2.** Recommended Routine Hepatitis B Immunization Schedules

<table>
<thead>
<tr>
<th>Maternal Hepatitis B Surface Antigen Status</th>
<th>Dose</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative*</td>
<td>1</td>
<td>0–2 d</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1–2 mo</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6–18 mo</td>
</tr>
<tr>
<td>Positive</td>
<td>1†</td>
<td>0 d</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1 mo</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6 mo</td>
</tr>
</tbody>
</table>

*Alternative schedule: dose one at 1 to 2 months of age, dose two at 4 months, and dose three at 6 to 18 months.
†Hepatitis B immune globulin should also be administered.

**ADMINISTRATION OF HEPATITIS B VACCINE**

**Concurrent Administration With Other Vaccines**

Hepatitis B virus vaccine can be given simultaneously with diphtheria-tetanus toxoids-pertussis (DTP), *Haemophilus influenzae* type b, polio, and/or measles-mumps-rubella vaccines without interference.\textsuperscript{6,18} Hepatitis B virus vaccine should not be mixed in the same syringe with any other vaccine or medication because compatibility between products has not been demonstrated. Combined products are likely to become available in the future (see "Future Developments").
IMMUNIZATION OF ADOLESCENTS AND OLDER CHILDREN

Older children and adolescents at increased risk of exposure to HBV infection (see Table 3) should be immunized. Major risk factors for acquisition of HBV infection in adolescents include multiple sexual partners (defined as more than one in 6 months) and intravenous drug abuse. In addition, immunization should be emphasized for adolescents living in areas where increased rates of perinatal drug abuse, teenage pregnancy, and/or sexually transmitted diseases occur.

The AAP recommends that universal immunization of all adolescents should be implemented when resources permit. The current policy of selective immunization of teenagers at high risk for acquisition of HBV infection requires prospective assessment of behavioral risk factors, which is often difficult and inadequate. Although the costs would be higher than for infant immunization due to the larger dose of vaccine administered, the additional strategy of universal adolescent immunization will result in a more rapid reduction of HBV transmission and infection, particularly among adolescents, the age group of children currently most at risk for acquiring HBV infection.

Universal infant immunization will have an immediate impact on reducing vertical transmission of HBV infection from mothers to infants and will diminish or eliminate horizontal transmission between preschool-age children within 5 years. Transmission among teenagers, however, would remain unaffected for the next one to two decades.

Other groups who should receive HBV vaccine are listed in Table 3. Children who are not in these groups will be immunized at adolescence. Although it may be ideal to immunize such children at this time, this recommendation is not being made currently because of limited resources.

The usual schedule of immunization for older children, adolescents, and adults is 0, 1, and 6 months. The dose, according to vaccine and age, is listed in Table 1.

FUTURE DEVELOPMENTS

Manufacturers are developing products combining HBV vaccine with DTP and/or *H influenzae* type b vaccines. If and when these products become available, integration of HBV vaccine into the routine immunization schedule for infants of HBsAg-negative mothers at 2, 4, and 6 months of age will be simplified.

The need for booster doses of HBV vaccine in older children and adolescents and for those immunized in infancy will be assessed as individuals are followed for 10 or more years after primary immunization. Routine serologic testing for HBV immunity is not indicated for these persons.
SUMMARY OF RECOMMENDATIONS

The highest priority should be for immunization of high-risk children and all infants, followed by immunization of adolescents living in high-risk areas, and then all adolescents. A summary of recommendations is as follows:

1. Routine serologic screening of all pregnant women for HBsAg should continue.
2. All infants should be immunized with HBV vaccine. The appropriate doses and schedules are detailed in Tables 1 and 2.
   A. For infants born to HBsAg-negative mothers:
      • The recommended schedule is administration of the first dose to newborns before discharge from the hospital; the second dose should be administered at 1 to 2 months of age, followed by the third dose at 6 to 18 months of age (Table 3).
      • Infants who did not receive a dose of vaccine at birth should receive three doses by 18 months of age. The minimal interval between the first two doses is 1 month and between the second and third doses is 2 months, but 4 months or more may be preferable.
      • The alternative schedule of immunization at 2, 4, and 6 to 18 months of age, although not preferred, is acceptable, provided the infant's mother is HBsAg-negative.
   B. Infants born to HBsAg-positive women must be immunized at or shortly after birth with the appropriate dose of vaccine (Table 1) and should receive one dose of HBIG as soon as possible after birth. The second dose of vaccine should be administered at 1 month and the third dose at 6 months. These infants should be followed up and their serologic status checked at 9 months of age, as recommended in the 1991 Report of the Committee on Infectious Diseases.10,1249
   C. If the mother's HBsAg status is unknown at the time of delivery, the infant should be immunized at birth with the dose of vaccine recommended for infants born to HBsAg-positive mothers. The mother should be screened for HBsAg as soon as possible to determine the subsequent management of the infant, including the need to administer HBIG.
3. Older children, adolescents, and adults at increased risk of HBV infection (Table 3) should be immunized with HBV vaccine (Table 1).
4. Routine immunization of all adolescents against HBV should be encouraged and implemented when feasible.
5. The dose of vaccine depends on the manufacturer, the patient's age, the maternal HBsAg status, and the presence of underlying disease (Table 1).

REFERENCES

Universal Hepatitis B Immunization

Pediatrics 1992;89;795

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ERRATUM

In the statement, “Universal Hepatitis B Immunization,” by the Committee on Infectious Diseases (Pediatrics. 1992;89:795–800), the paragraph following the heading “Immunization of Infants Whose Mothers Have Unknown HBsAg Status” on page 797 should read:

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*Pediatrics* 1992;89;795

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