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A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States

Recommendations of the Advisory Committee on Immunization Practices (ACIP) Part 1: Immunization of Infants, Children, and Adolescents

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
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A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States

Recommendations of the Advisory Committee on Immunization Practices (ACIP) Part 1: Immunization of Infants, Children, and Adolescents

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Summary

This report is the first of a two-part statement from the Advisory Committee on Immunization Practices (ACIP) that updates the strategy to eliminate hepatitis B virus (HBV) transmission in the United States. The report provides updated recommendations to improve prevention of perinatal and early childhood HBV transmission, including implementation of universal infant vaccination beginning at birth, and to increase vaccine coverage among previously unvaccinated children and adolescents. Strategies to enhance implementation of the recommendations include 1) establishing standing orders for administration of hepatitis B vaccination beginning at birth; 2) instituting delivery hospital policies and procedures and case management programs to improve identification of and administration of immunoprophylaxis to infants born to mothers who are hepatitis B surface antigen (HBsAg) positive and to mothers with unknown HBsAg status at the time of delivery; and 3) implementing vaccination record reviews for all children aged 11–12 years and children and adolescents aged <19 years who were born in countries with intermediate and high levels of HBV endemicity, adopting hepatitis B vaccine requirements for school entry, and integrating hepatitis B vaccination services into settings that serve adolescents. The second part of the ACIP statement, which will include updated recommendations and strategies to increase hepatitis B vaccination of adults, will be published separately.

Strategy to Eliminate Hepatitis B Virus Transmission

Hepatitis B virus (HBV) is a bloodborne and sexually transmitted virus. Rates of new infection and acute disease are highest among adults, but chronic infection is more likely to occur in persons infected as infants or young children. Before hepatitis B vaccination programs became routine in the United States, an estimated 30%–40% of chronic infections are believed to have resulted from perinatal or early childhood transmission, even though <10% of reported cases of hepatitis B occurred in children aged <10 years (*1*). Chronically infected persons are at increased lifetime risk for cirrhosis and hepatocellular carcinoma (HCC) and also serve as the main reservoir for continued HBV transmission.

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Hepatitis B vaccination is the most effective measure to prevent HBV infection and its consequences. Since they were first issued in 1982, recommendations for hepatitis B vaccination have evolved into a comprehensive strategy to eliminate HBV transmission in the United States (*2–6*) (Box 1). A primary focus of this strategy is universal vaccination of infants to prevent early childhood HBV infection and to eventually protect adolescents and adults from infection. Other components include routine screening of all pregnant women for hepatitis B surface antigen (HBsAg) and postexposure immunoprophylaxis of infants born to HBsAg-positive women, vaccination of children and adolescents who were not previously vaccinated, and vaccination of unvaccinated adults at increased risk for infection.

To date, the immunization strategy has been implemented with considerable success. Recent estimates indicate that >95% of pregnant women are tested for HBsAg, and case management has been effective in ensuring high levels of initiation and completion of postexposure immunoprophylaxis among identified infants born to HBsAg-positive women (*7*). Hepatitis B vaccine has been successfully integrated into the childhood vaccine schedule, and infant vaccine coverage levels are now equivalent to those of other vaccines in the childhood schedule. During 1990–2004, incidence of acute hepatitis B

BOX 1. Immunization strategy to eliminate transmission of hepatitis B virus (HBV) infection in the United States

- Universal vaccination of infants beginning at birth
- Prevention of perinatal HBV infection through
  - routine screening of all pregnant women for hepatitis B surface antigen (HBsAg), and
  - immunoprophylaxis of infants born to HBsAg-positive women and infants born to women with unknown HBsAg status
- Routine vaccination of previously unvaccinated children and adolescents
- Vaccination of previously unvaccinated adults at increased risk for infection

in the United States declined 75%. The greatest decline (94%) occurred among children and adolescents, coincident with an increase in hepatitis B vaccine coverage. As of 2004, among U.S. children aged 19–35 months, >92% had been fully vaccinated with 3 doses of hepatitis B vaccine (*8*). This success can be attributed in part to the established infrastructure for vaccine delivery to children and to federal support for perinatal hepatitis B prevention programs.

Vaccine coverage among adolescents has also increased substantially. Preliminary data demonstrate that 50%–60% of adolescents aged 13–15 years have records indicating vaccination (with 3 doses) against hepatitis B (CDC, unpublished data, 2003). As of November 2005, a total of 34 states require vaccination for middle-school entry (*9*). Certain programs provide hepatitis B vaccine to youth who engage in behaviors that place them at high risk for HBV infection (i.e., injection-drug use, having more than one sex partner, and male sexual activity with other males), and adolescent hepatitis B vaccination is included as a Health Plan Employer Data Information Set (HEDIS) measure (*10*).

Despite these successes, challenges remain. Even with improvements in the management of pregnant women, only approximately 50% of expected births to HBsAg-positive women are identified (on the basis of application of racial/ethnic-specific HBsAg prevalence estimates to U.S. natality data) for case management, which maximizes timely delivery of postexposure immunoprophylaxis (*11*; CDC, unpublished data, 2004). The need for proper management of women without prenatal care, including HBsAg testing at the time of admission for delivery and administration of the first dose of vaccine to infants <12 hours of birth, is underscored by the higher prevalence of HBsAg seropositivity among these women than among women who are screened prenatally (*12*). Even when maternal HBsAg testing does occur, certain infants of HBsAg-positive mothers do not receive postexposure immunoprophylaxis because of testing errors and lapses in reporting of test results (*13*), and infants of women with unknown HBsAg status at the time of delivery often do not receive a birth dose of vaccine (*14*). Birth dose coverage in 2004 was only 46% (National Immunization Survey, unpublished data, 2004), and coverage has not returned to levels from before July 1999 (54%), when recommendations were made to temporarily suspend administration of hepatitis B vaccines at birth until vaccines that do not contain thimerosal as a preservative became available (*15*). Among adolescents, efforts to prevent HBV transmission are hampered by the low rate of health-care visits in this age group compared with that of young children and the frequency of initiation of high-risk behaviors.

To address these remaining challenges and accelerate progress toward elimination of HBV transmission in the United States, the ACIP has updated the hepatitis B immunization recommendations for infants, children, and adolescents and supplemented the recommendations with strategies for implementation. The recommendations and implementation strategies address prevention of perinatal and early childhood transmission and routine vaccination of children and adolescents. A main focus is on universal infant vaccination beginning at birth, which provides a "safety net" for prevention of perinatal infection, prevents early childhood infections, facilitates implementation of universal vaccination recommendations, and prevents infections in adolescents and adults. The second part of the ACIP statement, which includes updated recommendations and implementation strategies to increase hepatitis B vaccination among unvaccinated adults, will be published separately (*16*).

Major Updates to the Recommendations

This report provides updated recommendations and approaches to address challenges in implementing the strategy to eliminate HBV transmission in the United States. These include the following measures:

- **Improve prevention of perinatal and early childhood HBV transmission.** Implement delivery hospital policies and procedures, case-management programs, and laws and regulations to improve identification of infants born to HBsAg-positive mothers and to mothers with unknown HBsAg status at the time of delivery, ensure administration of appropriate postexposure immunoprophylaxis to these infants beginning at birth, and administer a birth dose of hepatitis B vaccine to medically stable infants who weigh ≥2,000 g and who are born to HBsAg-negative mothers.

- **Improve vaccine coverage of children and adolescents who were not previously vaccinated.** Implement immunization record reviews for all children aged 11–12 years and children and adolescents aged <19 years who were born in countries in which HBV endemicity is high or intermediate (Figure 1 and Box 2); adopt hepatitis B vaccine requirements for school entry; and vaccinate all unvaccinated adolescents in settings that provide health-care services to persons in this age group.

Background

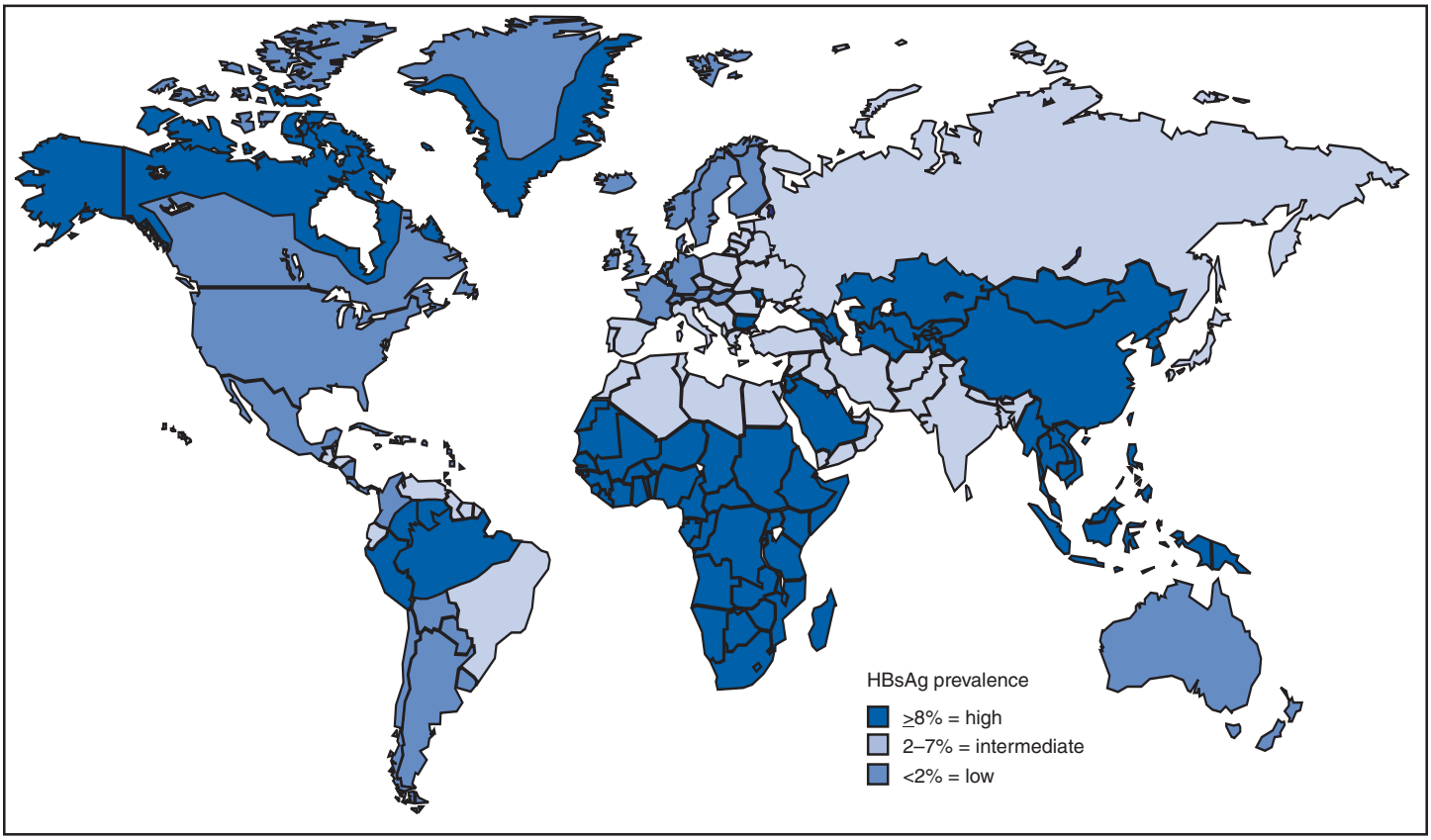
Clinical Features and Natural History of HBV Infection

HBV is a 42-nm DNA virus classified in the *Hepadnaviridae* family. The liver is the primary site of HBV replication. After a susceptible person is exposed, the virus enters the liver via the bloodstream; no evidence exists indicating that the virus replicates at mucosal surfaces. HBV infection can produce either asymptomatic or symptomatic infection. The average incubation period is 90 days (range: 60–150 days) from exposure to onset of jaundice and 60 days (range: 40–90 days) from exposure to onset of abnormal serum alanine aminotransferase (ALT) levels (*17,18*).

The onset of acute disease is usually insidious. Infants and young children (aged <10 years) are typically asymptomatic (*19*). When present, clinical symptoms and signs might include anorexia, malaise, nausea, vomiting, abdominal pain, and jaundice. Extrahepatic manifestations of disease (e.g., skin rashes, arthralgias, and arthritis) also can occur (*20*). The fatality rate among persons with reported acute hepatitis B is 0.5%–1.5%, with highest rates in adults aged >60 years (*21*).

Although the consequences of acute hepatitis B can be severe, the majority of serious sequelae associated with HBV disease occur in persons who are chronically infected. Persons with chronic infection also serve as the major reservoir for continued HBV transmission. Chronic infection occurs in approximately 90% of infected infants, 30% of infected children aged <5 years, and <5% of infected persons aged ≥5 years, with continuing viral replication in the liver and persistent viremia (*19,22–24*). Primary infections also become chronic more fre-

FIGURE 1. Geographic distribution of chronic hepatitis B virus (HBV) infection, 2005*



* For multiple countries, estimates of prevalence of hepatitis B surface antigen (HBsAg), a marker of chronic HBV infection, are based on limited data and might not reflect current prevalence in countries that have implemented routine childhood hepatitis B vaccination. In addition, HBsAg prevalence rates might vary within countries by subpopulation and locality.

BOX 2. Geographic areas with intermediate* and high† hepatitis B virus endemicity

Africa: all countries
South Asia: all countries except Sri Lanka
Western Pacific: all countries and territories except Australia and New Zealand
Middle East: all countries except Cyprus
Eastern Europe: all countries except Hungary
Newly Independent States of the former Soviet Union: all countries
Western Europe: Greece, Italy, Malta, Portugal, and Spain
North America: Alaska Natives and indigenous populations of Northern Canada and Greenland
Central America: Belize, Guatemala, Honduras, and Panama
South America: Argentina, Bolivia, Brazil, Ecuador, Guyana, Suriname, Venezuela, and the Amazonian areas of Colombia and Peru
Caribbean: Antigua and Barbuda, Dominica, Dominican Republic, Grenada, Haiti, Jamaica, Puerto Rico, St. Kitts and Nevis, St. Lucia, St. Vincent and Grenadines, Trinidad and Tobago, and Turcs and Caicos

* Hepatitis B surface antigen (HBsAg) prevalence of 2%–7%.
† HBsAg prevalence of ≥8%.

quently in immunosuppressed persons (e.g., hemodialysis patients and persons with human immunodeficiency virus [HIV] infection) (*23,25,26*). On the basis of data from follow-up studies of persons infected with HBV as infants or young children, approximately 25% of those with chronic infection die prematurely from cirrhosis or liver cancer; the majority remain asymptomatic until onset of cirrhosis or end-stage liver disease (*27–29*).

No specific treatment exists for acute hepatitis B. Persons who have chronic HBV infection require medical evaluation and regular monitoring (*30,31*). Therapeutic agents approved by the Food and Drug Administration (FDA) for treatment of chronic hepatitis B can achieve sustained suppression of HBV replication and remission of liver disease in certain persons (*31*). Periodic screening with alfa fetoprotein or imaging studies has been demonstrated to enhance early detection of HCC (*31*). Chronically infected persons with HCC have been reported to have experienced long-term survival after resection or ablation of small HCCs, and persons who were screened had a substantial survival advantage compared with historic controls (*31*).

Reinfection or reactivation of latent HBV infection has been reported among certain groups of immunosuppressed persons, including renal transplant recipients, HIV-infected patients, bone marrow transplant recipients, and patients receiving chemotherapy (*32–35*). The frequency with which this phenomenon occurs is unknown.

Interpretation of Serologic Markers of HBV Infection

The antigens and antibodies associated with HBV infection include HBsAg and antibody to HBsAg (anti-HBs), hepatitis B core antigen (HBcAg) and antibody to HBcAg (anti-HBc), and hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe). At least one serologic marker is present during the different phases of HBV infection (Table 1) (*18,36*). Serologic assays are commercially available for all markers except HBcAg because no free HBcAg circulates in blood.

The presence of a confirmed HBsAg result is indicative of ongoing HBV infection. All HBsAg-positive persons should be considered infectious. In newly infected persons, HBsAg is the only serologic marker detected during the first 3–5 weeks after infection, and it persists for variable periods at very low levels. The average time from exposure to detection of HBsAg is 30 days (range: 6–60 days) (*17,18*). Highly sensitive single-

TABLE 1. Typical interpretation of serologic test results for hepatitis B virus infection

Serologic marker				
HBsAg*	Total anti-HBc†	IgM§ anti-HBc	Anti-HBs¶	Interpretation
–**	–	–	–	Never infected
+††§§	–	–	–	Early acute infection; transient (up to 18 days) after vaccination
+	+	+	–	Acute infection
–	+	+	–	Acute resolving infection
–	+	–	+	Recovered from past infection and immune
+	+	–	–	Chronic infection
–	+	–	–	False positive (i.e., susceptible); past infection; "low-level" chronic infection;¶¶ passive transfer to infant born to HBsAg-positive mother
–	–	–	+	Immune if concentration is ≥10 mIU/mL,*** passive transfer after hepatitis B immune globulin administration

* Hepatitis B surface antigen.
† Antibody to hepatitis B core antigen.
§ Immunoglobulin M.
¶ Antibody to HBsAg.
** Negative test result.
†† Positive test result.
§§ To ensure that an HBsAg-positive test result is not a false positive, samples with repeatedly reactive HBsAg results should be tested with a licensed (and, if appropriate, neutralizing confirmatory) test.
¶¶ Persons positive for only anti-HBc are unlikely to be infectious except under circumstances in which they are the source for direct percutaneous exposure of susceptible recipients to large quantities of virus (e.g., blood transfusion or organ transplant).
*** Milli-International Units per milliliter.

sample nucleic acid tests can detect HBV DNA in the serum of an infected person 10–20 days before detection of HBsAg (*37*). Transient HBsAg positivity has been reported for up to 18 days after vaccination and is clinically insignificant (*38,39*).

Anti-HBc appears at the onset of symptoms or liver test abnormalities in acute HBV infection and persists for life. Acute or recently acquired infection can be distinguished by the presence of the IgM class of anti-HBc, which is detected at the onset of acute hepatitis B and persists for up to 6 months if the disease resolves. In patients who develop chronic hepatitis B, IgM anti-HBc can persist at low levels during viral replication and can result in positive tests for IgM anti-HBc (*40*). In addition, false-positive IgM anti-HBc test results can occur. Because the positive predictive value is low in asymptomatic persons, for diagnosis of acute hepatitis B, testing for IgM anti-HBc should be limited to persons with clinical evidence of acute hepatitis or an epidemiologic link to a case.

In persons who recover from HBV infection, HBsAg is eliminated from the blood, usually within 3–4 months, and anti-HBs develops during convalescence. The presence of anti-HBs typically indicates immunity from HBV infection. Infection or immunization with one genotype of HBV confers immunity to all genotypes. In addition, anti-HBs can be detected for several months after hepatitis B immune globulin (HBIG) administration. The majority of persons who recover from natural infection will be positive for both anti-HBs and anti-HBc, whereas persons who respond to hepatitis B vaccine have only anti-HBs. In persons who become chronically infected, HBsAg and anti-HBc persist, typically for life. HBsAg will become undetectable in approximately 0.5%–2% of chronically infected persons yearly, and anti-HBs will occur in the majority of these persons (*41–44*).

In certain persons, the only HBV serologic marker detected in serum is anti-HBc. Isolated anti-HBc can occur after HBV infection among persons who have recovered but whose anti-HBs levels have waned or among persons in whom anti-HBs failed to occur. Persons in the latter category include those with circulating HBsAg levels not detectable by commercial assays. These persons are unlikely to be infectious except under circumstances in which they are the source for direct percutaneous exposure of susceptible recipients to substantial quantities of virus (e.g., through blood transfusion or following liver transplantation) (*45*). HBV DNA has been detected in the blood of <5% of persons with isolated anti-HBc (*46*). Typically, the frequency of isolated anti-HBc relates directly to the prevalence of HBV infection in the population. In populations with a high prevalence of HBV infection, isolated anti-HBc likely indicates previous infection, with loss of anti-HBs. For persons in populations with a low prevalence of HBV infection, an isolated anti-HBc result often represents a false-positive reaction. The majority of these persons have a primary anti-HBs response after a 3-dose series of hepatitis B vaccine (*47,48*). Infants who are born to HBsAg-positive mothers and who do not become infected might have detectable anti-HBc for ≤24 months after birth from passively transferred maternal antibody.

HBeAg can be detected in the serum of persons with acute or chronic HBV infection. The presence of HBeAg correlates with viral replication and high levels of virus (i.e., high infectivity) (*49,50*). Anti-HBe correlates with the loss of replicating virus and with lower levels of virus, although reversion to HBeAg positivity has been observed (*44*).

Epidemiology of HBV Infection

Transmission

HBV is transmitted by percutaneous (i.e., puncture through the skin) or mucosal (i.e., direct contact with mucous membranes) exposure to infectious blood or to body fluids that contain blood. All HBsAg-positive persons are infectious, but those who are also HBeAg positive are more infectious because their blood contains high titers of HBV (typically 10^7–10^9 virions/mL) (*49,50*). Although HBsAg has been detected in multiple body fluids, only serum, semen, and saliva have been demonstrated to be infectious (*51,52*). HBV is comparatively stable in the environment and remains viable for ≥7 days on environmental surfaces at room temperature (*53*). HBV at concentrations of $10^{2–3}$ virions/mL can be present on environmental surfaces in the absence of any visible blood and still cause transmission (*53,54*).

For infants and children, the two primary sources of HBV infection are perinatal transmission from infected mothers and horizontal transmission from infected household contacts. Adolescents are at risk for HBV infection primarily through high-risk sexual activity (i.e., sex with more than one partner and male sexual activity with other males) and injection-drug use (*21*). Transmission of HBV via transfusion of blood and plasma-derived products is rare because of donor screening for HBsAg and viral inactivation procedures.

For a newborn infant whose mother is positive for both HBsAg and HBeAg, the risk for chronic HBV infection is 70%–90% by age 6 months in the absence of postexposure immunoprophylaxis (*55–57*). For infants of women who are HBsAg positive but HBeAg negative, the risk for chronic infection is <10% in the absence of postexposure immunoprophylaxis (*58–60*). Rare cases of fulminant hepatitis B among perinatally infected infants also have been reported (*61,62*). Studies suggest that breastfeeding by an HBsAg-

positive mother does not increase the risk for acquisition of HBV infection in the infant (*63*).

Children who are not infected at birth remain at risk from long-term interpersonal contact with their infected mothers. In one study, 38% of infants who were born to HBsAg-positive mothers and who were not infected perinatally became infected by age 4 years (*64*). In addition, children living with any chronically infected persons are at risk for becoming infected through percutaneous or mucosal exposures to blood or infectious body fluids (e.g., sharing a toothbrush, contact with exudates from dermatologic lesions, contact with HBsAg-contaminated surfaces). HBV transmission rates to susceptible household contacts of chronically infected persons have varied (range: 14%–60%) (*65,66*). High rates of infection also have been reported among unvaccinated long-term residents of institutions for the mentally handicapped (*67,68*), and, in rare instances, person-to-person transmission has been reported in child care settings (*69,70*).

Incidence

During 1990–2004, overall incidence of reported acute hepatitis B declined 75%, from 8.5 to 2.1 per 100,000 population. The most dramatic declines occurred in the cohort of children to whom recommendations for routine infant and adolescent vaccination have applied. Incidence among children aged <12 years and adolescents aged 12–19 years declined 94%, from 1.1 to 0.36 and 6.1 to 2.8 per 100,000 population, respectively (Figure 2). Since implementation of routine childhood immunization, an estimated 6,800 perinatal infections and an additional 18,700 infections during the first 10 years of life have been prevented annually in the United States (*71*).

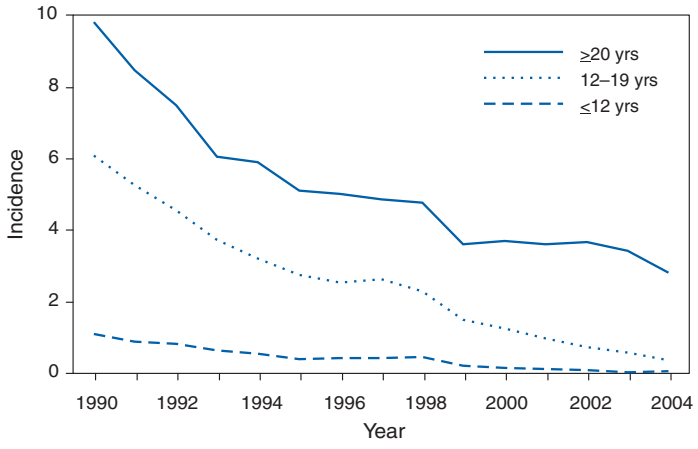
Although infections in infants and children aged <10 years represented <10% of all HBV infections before implementation of childhood immunization programs, childhood infections resulted in an estimated 30%–40% of the chronic HBV infections among persons who acquired their infections in the United States (*1*). In two population-based studies conducted among Asian/Pacific Islander children who were born in the United States before perinatal hepatitis B prevention programs were widely implemented, 61%–66% of the chronic HBV infections occurred in children born to HBsAg-negative mothers (*72,73*). A substantial proportion of these chronic infections would not have been prevented by a selective program of identification and immunization of only infants born to HBsAg-positive mothers.

In addition to declines in incidence among all age groups, racial disparities in hepatitis B incidence among children have been substantially reduced (Figure 3). The reduction of the disparity between Asian/Pacific Islander and other children is consistent with recent observations noting a decline in seroprevalence of HBV infection after successful implementation of routine hepatitis B vaccination among Asians who have recently immigrated to the United States (*74,75*). However, as hepatitis B incidence has declined among U.S.-born children, unvaccinated foreign-born children account for a high proportion of infections. During 2001–2002, of 19 children born after 1991 in whom acute hepatitis B had been verified, eight (42%) were foreign born (*76*).

Prevalence

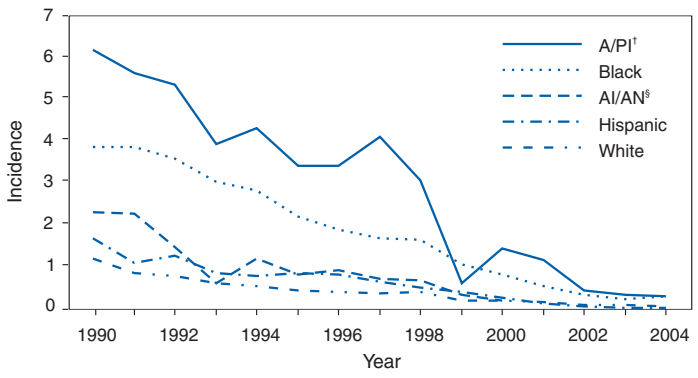
In the U.S. population, the overall age-adjusted prevalence of HBV infection (including persons with chronic infection and those with previous infection) was 4.9% in the third

FIGURE 2. Reported acute hepatitis B incidence,* by age group and year — United States, 1990–2004



* Per 100,000 population.

FIGURE 3. Reported acute hepatitis B incidence* among persons aged <19 years, by race/ethnicity and year — United States, 1990–2004



* Per 100,000 population.
† Asian/Pacific Islander.
§ American Indian/Alaska Native.

National Health and Nutrition Examination Survey (NHANES III, 1988–1994) (*77*). Foreign-born persons (particularly Asian/Pacific Islanders) who have emigrated from countries in which HBV is endemic (Figure 1 and Box 2) contribute disproportionately to the burden of chronic HBV infection in the United States. The prevalence of chronic HBV infection among foreign-born persons immigrating to the United States from Central and Southeast Asia, the Middle East, and Africa varies (range: 5%–15%) and reflects the patterns of HBV infection in the countries and regions of origin for these persons. During 1994–2003, approximately 40,000 immigrants with chronic HBV infection were admitted annually to the United States for permanent residence (*78*; CDC, unpublished data, 2005).

Prophylaxis Against HBV Infection

Hepatitis B Vaccine

HBsAg is the antigen used for hepatitis B vaccination (*79,80*). Vaccine antigen can be purified from the plasma of persons with chronic HBV infection or produced by recombinant DNA technology. Vaccines available in the United States use recombinant DNA technology to express HBsAg in yeast, which is then purified from the cells by biochemical and biophysical separation techniques (*81,82*). Hepatitis B vaccines licensed in the United States are formulated to contain 10–40 μg of HBsAg protein/mL. Since March 2000, hepatitis B vaccines produced for distribution in the United States do not contain thimerosal as a preservative or contain only a trace amount (<1.0 mcg mercury/mL) from the manufacturing process (*83,84*).

Hepatitis B vaccine is available as a single-antigen formulation and also in fixed combination with other vaccines. Two single-antigen vaccines are available in the United States: Recombivax HB® (Merck & Co., Inc., Whitehouse Station, New Jersey) and Engerix-B® (GlaxoSmithKline Biologicals, Rixensart, Belgium). Of the three licensed combination vaccines, one (Twinrix® [GlaxoSmithKline Biologicals, Rixensart, Belgium]) is used for vaccination of adults, and two (Comvax® [Merck & Co., Inc., Whitehouse Station, New Jersey] and Pediarix® [GlaxoSmithKline Biologicals, Rixensart, Belgium]) are used for vaccination of infants and young children. Twinrix contains recombinant HBsAg and inactivated hepatitis A virus. Comvax contains recombinant HBsAg and *Haemophilus influenzae* type b (Hib) polyribosylribitol phosphate conjugated to *Neisseria meningitidis* outer membrane protein complex. Pediarix contains recombinant HBsAg, diphtheria and tetanus toxoids and acellular pertussis adsorbed (DTaP), and inactivated poliovirus (IPV).

HBIG

HBIG provides passively acquired anti-HBs and temporary protection (i.e., 3–6 months) when administered in standard doses. HBIG is typically used as an adjunct to hepatitis B vaccine for postexposure immunoprophylaxis to prevent HBV infection. HBIG administered alone is the primary means of protection after an HBV exposure for nonresponders to hepatitis B vaccination.

HBIG is prepared from the plasma of donors with high concentrations of anti-HBs. The plasma is screened to eliminate donors who are positive for HBsAg, antibodies to HIV and hepatitis C virus (HCV), and HCV RNA. In addition, proper manufacturing techniques for HBIG inactivate viruses (e.g., HBV, HCV, and HIV) from the final product (*85,86*). No evidence exists that HBV, HCV, or HIV ever has been transmitted by HBIG commercially available in the United States. HBIG that is commercially available in the United States does not contain thimerosal.

Vaccination Schedules and Results of Vaccination

Preexposure Vaccination

Infants and Children

Primary vaccination consists of ≥3 intramuscular doses of hepatitis B vaccine (Table 2). Vaccine schedules for infants and children (Tables 3–5) are determined on the basis of immunogenicity data and the need to integrate hepatitis B vaccine into a harmonized childhood vaccination schedule. Although not all possible schedules for each product have been evaluated in clinical trials, available licensed formulations for both single-antigen vaccines produce high (>95%) levels of seroprotection among infants and children when administered in multiple schedules (*87–91*).

The immunogenicity of the combined hepatitis B-Hib conjugate vaccine (Comvax) and the combined hepatitis B-DTaP-IPV vaccine (Pediarix) is equivalent to that of their individual antigens administered separately. However, these vaccines cannot be administered to infants aged <6 weeks; only single-antigen hepatitis B vaccine may be used for the birth dose. Use of 4-dose hepatitis B vaccine schedules, including schedules with a birth dose, has not increased vaccine reactogenicity (*92,93*). Anti-HBs responses after a 3-dose series of hepatitis B-containing combination vaccines among infants who were previously vaccinated at birth with single-antigen hepatitis B vaccine are comparable to those observed after a 3-dose series of combination vaccine without a birth dose (*93*).

TABLE 2. Recommended doses of currently licensed formulations of hepatitis B vaccine, by age group and vaccine type

	Single-antigen vaccine				Combination vaccine					
	Recombivax HB		Engerix-B		Comvax*		Pediarix†		Twinrix§	
Age group	Dose (μg)¶	Volume (mL)	Dose (μg)¶	Volume (mL)	Dose (μg)¶	Volume (mL)	Dose (μg)¶	Volume (mL)	Dose (μg)¶	Volume (mL)
Infants (<1 yr)	5	0.5	10	0.5	5	0.5	0	0.5	NA**	NA
Children (1–10 yrs)	5	0.5	10	0.5	5*	0.5	10†	0.5	NA	NA
Adolescents										
11–15 yrs	10††	1.0	NA	NA	NA	NA	NA	NA	NA	NA
11–19 yrs	5	0.5	10	0.5	NA	NA	NA	NA	NA	NA
Adults (≥20 yrs)	10	1.0	20	1.0	NA	NA	NA	NA	20§	1.0
Hemodialysis patients and other immunocompromised persons										
<20 yrs§§	5	0.5	10	0.5	NA	NA	NA	NA	NA	NA
≥20 yrs	40¶¶	1.0	40***	2.0	NA	NA	NA	NA	NA	NA

* Combined hepatitis B–*Haemophilus influenzae* type b conjugate vaccine. This vaccine cannot be administered at birth, before age 6 weeks, or after age 71 months.
† Combined hepatitis B–diphtheria, tetanus, and acellular pertussis-inactivated poliovirus vaccine. This vaccine cannot be administered at birth, before age 6 weeks, or at age ≥7 years.
§ Combined hepatitis A and hepatitis B vaccine. This vaccine is recommended for persons aged ≥18 years who are at increased risk for both hepatitis B virus and hepatitis A virus infections.
¶ Recombinant hepatitis B surface antigen protein dose.
** Not applicable.
†† Adult formulation administered on a 2-dose schedule.
§§ Higher doses might be more immunogenic, but no specific recommendations have been made.
¶¶ Dialysis formulation administered on a 3-dose schedule at age 0, 1, and 6 months.
*** Two 1.0-mL doses administered at one site, on a 4-dose schedule at age 0, 1, 2, and 6 months.

Birth Dose

Hepatitis B vaccine can be administered soon after birth with only minimal decrease in immunogenicity, compared with administration at older ages, and no decrease in protective efficacy (*87*). Administration of a birth dose of hepatitis B vaccine is required for effective postexposure immunoprophylaxis to prevent perinatal HBV infection. Although infants who require postexposure immunoprophylaxis should be identified by maternal HBsAg testing, administering a birth dose to infants even without HBIG serves as a "safety net" to prevent perinatal infection among infants born to HBsAg-positive mothers who are not identified because of errors in maternal HBsAg testing or failures in reporting of test results (*13*). The birth dose also provides early protection to infants at risk for infection after the perinatal period. Administration of a birth dose has been associated with higher rates of on-time completion of the hepatitis B vaccine series (*15,94*). In certain populations, the birth dose has been associated with improved completion rates for all other infant vaccines (*95*), although findings have not been consistent (*15,94*).

Adolescents

Recommended vaccination schedules for adolescents balance available immunogenicity data with the need to achieve compliance with vaccination in this age group (Tables 2 and 5). Both licensed single-antigen hepatitis B vaccines administered intramuscularly at 0, 1, and 6 months produce a >95% sero-protection rate in adolescents. Equivalent seroprotection rates are achieved among adolescents vaccinated at 0, 1–2, and 4 months and 0, 12, and 24 months. The adult (10 μg) dose of Recombivax-HB administered in a 2-dose schedule to children and adolescents aged 11–15 years at 0 and 4–6 months produces antibody levels equivalent to those obtained with the 5-μg dose administered on a 3-dose schedule (*96,97*). However, no data on long-term antibody persistence or protection are available for 2-dose schedules. No combination vaccines containing hepatitis B vaccine antigen are approved for use in adolescents aged 11–17 years.

Nonstandard Vaccine Schedules

No apparent effect on immunogenicity has been documented when minimum spacing of doses is not achieved precisely. Increasing the interval between the first 2 doses has little effect on immunogenicity or final antibody concentration (*98–100*). The third dose confers the maximum level of seroprotection but acts primarily as a booster and appears to provide optimal long-term protection (*101*). Longer intervals between the last 2 doses result in higher final antibody levels but might increase the risk for acquisition of HBV infection among persons who have a delayed response to vaccination. No differences in immunogenicity have been observed when 1 or 2 doses of hepatitis B vaccine produced by one manufacturer are followed by doses from a different manufacturer (*102*).

TABLE 3. Hepatitis B vaccine schedules for newborn infants, by maternal hepatitis B surface antigen (HBsAg) status*

Maternal HBsAg status	Single-antigen vaccine		Single antigen + combination vaccine	
	Dose	Age	Dose	Age
Positive	1†	Birth (≤12 hrs)	1†	Birth (≤12 hrs)
	HBIG§	Birth (≤12 hrs)	HBIG	Birth (≤12 hrs)
	2	1–2 mos	2	2 mos
	3¶	6 mos	3	4 mos
			4¶	6 mos (Pediarix) or 12–15 mos (Comvax)
Unknown**	1†	Birth (≤12 hrs)	1†	Birth (≤12 hrs)
	2	1–2 mos	2	2 mos
	3¶	6 mos	3	4 mos
			4¶	6 mos (Pediarix) or 12–15 mos (Comvax)
Negative	1†,††	Birth (before discharge)	1†,††	Birth (before discharge)
	2	1–2 mos	2	2 mos
	3¶	6–18 mos	3	4 mos
			4¶	6 mos (Pediarix) or 12–15 mos (Comvax)

* See Table 4 for vaccine schedules for preterm infants weighing <2,000 g.
† Recombivax HB or Engerix-B should be used for the birth dose. Comvax and Pediarix cannot be administered at birth or before age 6 weeks.
§ Hepatitis B immune globulin (0.5 mL) administered intramuscularly in a separate site from vaccine.
¶ The final dose in the vaccine series should not be administered before age 24 weeks (164 days).
** Mothers should have blood drawn and tested for HBsAg as soon as possible after admission for delivery; if the mother is found to be HBsAg positive, the infant should receive HBIG as soon as possible but no later than age 7 days.
†† On a case-by-case basis and only in rare circumstances, the first dose may be delayed until after hospital discharge for an infant who weighs ≥2,000 g and whose mother is HBsAg negative, but only if a physician's order to withhold the birth dose and a copy of the mother's original HBsAg-negative laboratory report are documented in the infant's medical record.

TABLE 4. Hepatitis B immunization management of preterm infants weighing <2,000 g, by maternal hepatitis B surface antigen (HBsAg) status

Maternal HBsAg status	Recommendation
Positive	• HBIG* + hepatitis B vaccine (≤12 hrs of birth) • Continue vaccine series beginning at age 1–2 mos according to recommended schedule for infants born to HBsAg-positive mothers (see Table 3). • Do not count birth dose as part of the vaccine series. • Test for HBsAg and antibody to HBsAg after completion of the vaccine series at age 9–18 mos (i.e., next well-child visit).
Unknown	• HBIG + hepatitis B vaccine (≤12 hrs of birth) • Test mother for HBsAg. • Continue vaccine series beginning at age 1–2 mos according to recommended schedule based on the mother's HBsAg result (see Table 3). • Do not count birth dose as part of the vaccine series.
Negative	• Delay first dose of hepatitis B vaccine until age 1 mo or hospital discharge. • Complete the vaccine series (see Table 3).

* Hepatitis B immune globulin.

Response to Revaccination

A study of infants born to HBsAg-positive mothers who did not respond to a primary vaccine series indicated that all those not infected with HBV responded satisfactorily to a repeat 3-dose revaccination series (*103*). No data suggest that children who have no detectable antibody after 6 doses of vaccine would benefit from additional doses.

Groups Requiring Different Vaccination Doses or Schedules

Preterm infants. Preterm infants weighing <2,000 g at birth have a decreased response to hepatitis B vaccine administered before age 1 month (*104–106*). By age 1 month, medically stable preterm infants, regardless of initial birth weight or gestational age, have a response to vaccination that is comparable to that of full-term infants (*107–110*).

Hemodialysis patients and other immunocompromised persons. Although data concerning the response of pediatric hemodialysis patients to vaccination with standard pediatric doses are lacking, protective levels of antibody occur in 75%–97% of those who receive higher dosages (20-μg) on either the 3- or the 4-dose schedule (*111–114*). Humoral response to hepatitis B vaccination is also reduced in other children and adolescents who are immunocompromised (e.g., hematopoietic stem cell transplant recipients, patients undergoing chemotherapy, and HIV-infected persons) (*115–119*). Modified dosing regimens, including a doubling of the standard antigen dose or administration of additional doses, might increase response rates (*120*). However, data on response to these alternative vaccination schedules are limited (*121*).

Immune Memory

Anti-HBs is the only easily measurable correlate of vaccine-induced protection. Immunocompetent persons who achieve anti-HBs concentrations ≥10 mIU/mL after preexposure vaccination have virtually complete protection against both acute disease and chronic infection even if anti HBs concentrations subsequently decline to <10 mIU/mL (*122–125*). Although immunogenicity is lower among immunocompromised persons, those who achieve and maintain a protective antibody response before exposure to HBV have a high level of protection from infection.

After primary immunization with hepatitis B vaccine, anti-HBs concentrations decline rapidly within the first

TABLE 5. Hepatitis B vaccine schedules for children, adolescents, and adults*

Age	Schedule
Children (1–10 yrs)	0, 1, and 6 mos†
	0, 2, and 4 mos†
	0, 1, 2, and 12 mos†§
Adolescents (11–19 yrs)	0, 1, and 6 mos†
	0, 1, and 4 mos†
	0, 2, and 4 mos†
	0, 12, and 24 mos†
	0 and 4–6 mos¶**
	0, 1, 2, and 12 mos†¶
Adults (≥20 yrs)	0, 1, and 6 mos**††
	0, 1, and 4 mos**
	0, 2, and 4 mos**
	0, 1, 2, and 12 mos¶**

* Children, adolescents, and adults may be vaccinated according to any of the schedules indicated, except as noted. Selection of a schedule should consider the need to optimize compliance with vaccination

† Pediatric/adolescent formulation.

¶ A 2-dose schedule of Recombivax-HB adult formulation (10 μg) is licensed for adolescents aged 11–15 years. When scheduled to receive the second dose, adolescents aged >15 years should be switched to a 3-dose series, with doses 2 and 3 consisting of the pediatric formulation administered on an appropriate schedule.

§ A 4-dose schedule of Engerix B is licensed for all age groups.

** Adult formulation.

†† Twinrix may be administered to persons aged ≥18 years at 0, 1, and 6 months.

year and more slowly thereafter. Among children who respond to a primary vaccine series with antibody levels ≥10 mIU/mL, 15%–50% have low or undetectable concentrations of anti-HBs (anti-HBs loss) 5–15 years after vaccination (*126–130*). The persistence of detectable anti-HBs after vaccination, in the absence of exposure to HBV, depends on the level of post-vaccination antibody concentration.

Despite declines in anti-HBs to <10 mIU/mL, nearly all vaccinated persons are still protected against HBV infection. The mechanism for continued vaccine-induced protection is thought to be the preservation of immune memory through selective expansion and differentiation of clones of antigen-specific B and T lymphocytes (*131*). Persistence of vaccine-induced immune memory among persons who responded to a primary childhood vaccine series 13–23 years earlier but then had levels of anti-HBs below 10 mIU/mL has been demonstrated by an anamnestic increase in anti-HBs levels in 67%–76% of these persons 2–4 weeks after administration of an additional vaccine dose (*132,133*). Although direct measurement of immune memory is not yet possible, these data indicate that a high proportion of vaccine recipients retain immune memory and would develop an anti-HBs response upon exposure to HBV.

Studies of cohorts of immunocompetent persons vaccinated as children or infants also indicate that, despite anti-HBs loss years after immunization, nearly all vaccinated persons who respond to a primary series remain protected from HBV infection. No clinical cases of hepatitis B have been observed in follow-up studies conducted 15–20 years after vaccination among immunocompetent vaccinated persons with antibody levels ≥10 mIU/mL. Certain studies have documented breakthrough infections (detected by the presence of anti-HBc or HBV DNA) in a limited percentage of vaccinated persons (*130,131*), but these infections are usually transient and asymptomatic; chronic infections have been documented only rarely (*134*). Breakthrough infections resulting in chronic infection have been observed only among vaccinated infants born to HBsAg-positive women.

Limited data are available on the duration of immune memory after hepatitis B vaccination in immunocompromised persons (e.g., HIV-infected patients, dialysis patients, patients undergoing chemotherapy, or hematopoietic stem cell transplant patients). No clinically important HBV infections have been documented among immunocompromised persons who maintain protective levels of anti-HBs. In studies of long-term protection among HIV-infected persons, breakthrough infections occurring after a decline in anti-HBs concentrations to <10 mIU/mL have been transient and asymptomatic (*135*). However, among hemodialysis patients who respond to the vaccine, clinically significant HBV infection has been documented in persons who have not maintained anti-HBs concentrations of ≥10 mIU/mL (*136*).

Postexposure Prophylaxis

Both passive-active postexposure prophylaxis (PEP) with HBIG and hepatitis B vaccine and active PEP with hepatitis B vaccine alone have been demonstrated to be highly effective in preventing transmission after exposure to HBV (*137–140*). HBIG alone has also been demonstrated to be effective in preventing HBV transmission (*141–144*), but with the availability of hepatitis B vaccine, HBIG typically is used as an adjunct to vaccination.

The major determinant of the effectiveness of PEP is early administration of the initial dose of vaccine. The effectiveness of PEP diminishes the longer it is initiated after exposure (*17,145,146*). Studies are limited on the maximum interval after exposure during which PEP is effective, but the interval is unlikely to exceed 7 days for perinatal (*147*) and needlestick (*140–142*) exposures and 14 days for sexual exposures (*122, 138,139,143,144*).

No data are available on the efficacy of HBsAg-containing combination vaccines when used to complete the vaccine series for PEP, but the efficacy of combination vaccines is expected to be similar to that of single-antigen vaccines because the HBsAg component induces a comparable anti-HBs response.

Perinatal HBV Exposure

Passive-active PEP. PEP with hepatitis B vaccine and HBIG administered 12–24 hours after birth, followed by completion of a 3-dose vaccine series, has been demonstrated to be 85%–95% effective in preventing acute and chronic HBV infection in infants born to women who are positive for both HBsAg and HBeAg (*137*). Although clinical trials have evaluated the efficacy of passive-active PEP with hepatitis B vaccine and HBIG administered only within 24 hours of birth, studies of passive immunoprophylaxis have demonstrated that HBIG provided protection when administered as late as 72 hours after exposure. The majority of clinical trials have evaluated the efficacy of passive-active PEP when the second vaccine dose was administered at age 1 month (*137*). Administration of HBIG plus vaccine at birth, 1 month, and 6 months and at birth, 2 months, and 6 months has demonstrated comparable efficacy in prevention of acute and chronic infection among infants born to women who were both HBsAg and HBeAg positive (Cladd E. Stevens, MD, New York Blood Center, personal communication, 1994).

Infants born to HBsAg-positive/HBeAg-negative mothers who receive passive-active PEP with HBIG and hepatitis B vaccine should have the same high degree of protection as infants born to women who are HBsAg positive/HBeAg positive. However, the efficacy of this regimen has not been examined in controlled clinical trials because the low infection rate would require an unattainable sample size.

Active PEP. Active PEP with hepatitis B vaccine alone (i.e., without HBIG) is frequently used in certain remote areas (e.g., Alaska and the Pacific Islands) where implementation of maternal HBsAg testing is difficult because no access exists to a laboratory. In randomized, placebo-controlled clinical trials, administration of hepatitis B vaccine in a 3- or 4-dose schedule without HBIG beginning ≤12 hours after birth has been demonstrated to prevent 70%–95% of perinatal HBV infections among infants born to women who are positive for both HBsAg and HBeAg (*58,148–152*). Population-based studies in areas with a high endemicity of HBV infection have demonstrated that active postexposure vaccination is highly effective in preventing infection when the first dose is administered soon after birth, the second at age 1–2 months, and the third at age 6–8 months (*153–155*).

Vaccine Safety

Hepatitis B vaccines have been demonstrated to be safe when administered to infants, children, adolescents, and adults. Since 1982, an estimated >60 million adolescents and adults and >40 million infants and children have been vaccinated in the United States.

Vaccine Reactogenicity

The most frequently reported side effects among persons receiving hepatitis B vaccine are pain at the injection site (3%–29%) and fever >99.9° F (>37.7° C) (1%–6%) (*156,157*). However, in placebo-controlled studies, these side effects were reported no more frequently among persons receiving hepatitis B vaccine than among persons receiving placebo (*87*). Administration of hepatitis B vaccine soon after birth has not been associated with an increased rate of elevated temperatures or microbiologic evaluations for possible sepsis in the first 21 days of life (*158*).

Adverse Events

A causal association has been established between receipt of hepatitis B vaccine and anaphylaxis (*159*). On the basis of data from the Vaccine Safety Datalink (VSD) project, the estimated incidence of anaphylaxis among children and adolescents who received hepatitis B vaccine is one case per 1.1 million vaccine doses distributed (95% confidence interval = 0.1–3.9) (*160*).

Early postlicensure surveillance of adverse events suggested a possible association between Guillain-Barré syndrome and receipt of the first dose of plasma-derived hepatitis B vaccine among U.S. adults (*161*). However, in a subsequent analysis of Guillain-Barré syndrome cases reported to CDC, FDA, and vaccine manufacturers, among an estimated 2.5 million adults who received ≥1 dose of recombinant hepatitis B vaccine during 1986–1990, the rate of Guillain-Barré syndrome occurring after hepatitis B vaccination did not exceed the background rate among unvaccinated persons (CDC, unpublished data, 1992). A review by persons with clinical expertise concluded that evidence was insufficient to reject or accept a causal association between Guillain-Barré syndrome and hepatitis B vaccination (*159,162*).

Multiple sclerosis (MS) has not been reported after hepatitis B vaccination among children. However, one retrospective case-control study (*163,164*) reported an association between hepatitis B vaccine and MS among adults. Multiple other studies (*165–168*) have demonstrated no association between hepatitis B vaccine and MS. Reviews of these data by panels of persons with clinical expertise have favored rejection of a causal association between hepatitis B vaccination and MS (*169,170*).

Chronic illnesses that have been reported in rare instances after hepatitis B vaccination include chronic fatigue syndrome (*171*), neurologic disorders (e.g., leukoencephalitis, optic neu-

ritis, and transverse myelitis) (*172–174*), rheumatoid arthritis (*175,176*), type 1 diabetes (*177*), and autoimmune disease (*178*). No evidence of a causal association between these conditions or other chronic illnesses and hepatitis B vaccine has been demonstrated (*159,169,170,179–182*).

Reported episodes of alopecia (hair loss) after rechallenge with hepatitis B vaccine suggest that vaccination might, in rare cases, trigger episodes of alopecia (*183*). However, a population-based study determined no statistically significant association between alopecia and hepatitis B vaccine (*184*).

No evidence exists of a causal association between hepatitis B vaccination, including administration of the birth dose, and sudden infant death syndrome (SIDS) or other causes of death during the first year of life (*185–187*). Infant death rates, including rates of SIDS, declined substantially in the United States during the 1990s, coincident with an increase in infant hepatitis B vaccination coverage from <1% to >90% and implementation of efforts to reduce SIDS through infant sleep positioning and separation from other persons in bed (*188*).

The safety of hepatitis B vaccine and other vaccines is assessed continuously through ongoing monitoring of data from VSD, the Vaccine Adverse Events Reporting System (VAERS), and other surveillance systems. Any adverse events after vaccination should be reported to VAERS; report forms and assistance are available from CDC at telephone 1-800-822-7967 or at http://www.vaers.hhs.gov.

Contraindications and Precautions

Hepatitis B vaccination is contraindicated for persons with a history of hypersensitivity to yeast or to any vaccine component (*92,189–191*). Despite a theoretic risk for allergic reaction to vaccination in persons with allergy to *Saccharomyces cerevisiae* (baker's yeast), no evidence exists that documents adverse reactions after vaccination of persons with a history of yeast allergy.

Persons with a history of serious adverse events (e.g., anaphylaxis) after receipt of hepatitis B vaccine should not receive additional doses. As with other vaccines, vaccination of persons with moderate or severe acute illness, with or without fever, should be deferred until the illness resolves (*192*). Vaccination is not contraindicated in persons with a history of MS, Guillain-Barré syndrome, autoimmune disease (e.g., systemic lupus erythematosis or rheumatoid arthritis), or other chronic diseases.

Pregnancy is not a contraindication to vaccination. Limited data indicate no apparent risk for adverse events to developing fetuses when hepatitis B vaccine is administered to pregnant women (*193*). Current vaccines contain noninfectious HBsAg and should cause no risk to the fetus.

Future Considerations

Implementation of the recommendations and strategies in this document should ultimately lead to the elimination of HBV transmission in the United States. New information will have implications for this effort, and adjustments and changes are expected to occur.

Long-Term Protection and Booster Doses

Studies are needed to assess long-term protection after vaccination and the possible need for booster doses of vaccine. The longest follow-up studies of vaccine protection have been conducted in populations with an initially high endemicity of HBV infection (i.e., ≥8% prevalence of chronic infection) (*130*). Implementation of hepatitis B vaccination programs in populations with a high endemicity of HBV infection has resulted in virtual elimination of new HBV infections by providing vaccine-induced immunity to susceptible persons. In these populations, ongoing exposure of vaccinated persons to persons with chronic HBV infection might complicate future efforts to assess long-term hepatitis B vaccine efficacy. Assessment of efficacy provided by hepatitis B immunization after 15–20 years will require studies among populations that continue to have exposures to HBsAg-positive persons (e.g., communities of immigrants from highly endemic countries, populations of injection-drug users, or health-care workers) and studies among populations with a low prevalence of infection.

Immunization Escape Mutants

Mutations in the S gene of HBV can lead to conformational changes in the *a* determinant of the HBsAg protein, which is the major target for neutralizing anti-HBs. These variants have been detected in humans infected with HBV, and concern has been expressed that these variants might replicate in the presence of vaccine-induced anti-HBs or anti-HBs contained in HBIG (*194,195*). Although no evidence suggests that S gene immunization escape mutants pose a threat to existing programs using hepatitis B vaccines (*196*), further studies and enhanced surveillance to detect the emergence of these variants are high priorities for monitoring the effectiveness of current vaccination strategies.

Recommendations for Hepatitis B Vaccination of Infants, Children, and Adolescents

This section outlines updated ACIP recommendations and associated implementation strategies for hepatitis B vaccina-

tion of infants, children, and adolescents. These recommendations have been summarized (Box 3).

Prevention of Perinatal HBV Infection and Management of Pregnant Women

Recommendations

Prenatal HBsAg Testing

- All pregnant women should be tested routinely for HBsAg during an early prenatal visit (e.g., first trimester) in each pregnancy, even if they have been previously vaccinated or tested.
- Women who were not screened prenatally, those who engage in behaviors that put them at high risk for infection (e.g., injection-drug use, having had more than one sex partner in the previous 6 months or an HBsAg-positive sex partner, evaluation or treatment for a sexually transmitted disease [STD], or recent or current injection-drug use) and those with clinical hepatitis should be tested at the time of admission to the hospital for delivery.
- All laboratories that provide HBsAg testing of pregnant women should use an FDA-licensed or -approved HBsAg test and should perform testing according to the manufacturer's labeling, including testing of initially reactive specimens with a licensed neutralizing confirmatory test. When pregnant women are tested for HBsAg at the time of admission for delivery, shortened testing protocols may be used and initially reactive results reported to expedite administration of immunoprophylaxis to infants.
- Women who are HBsAg positive should be referred to an appropriate case-management program to ensure that their infants receive timely postexposure prophylaxis and follow-up (see Case-Management Programs to Prevent Perinatal HBV Infection). In addition, a copy of the original laboratory report indicating the pregnant woman's HBsAg status should be provided to the hospital where delivery is planned and to the health-care provider who will care for the newborn.
- Women who are HBsAg positive should be provided with or referred for appropriate counseling and medical management (Appendix A). HBsAg-positive pregnant women should receive information concerning hepatitis B that discusses
  - — modes of transmission;
  - — perinatal concerns (e.g., infants born to HBsAg-positive mothers may be breast fed);
  - — prevention of HBV transmission to contacts, including the importance of postexposure prophylaxis for the newborn infant and hepatitis B vaccination for household, sexual, and needle-sharing contacts;
  - — substance abuse treatment, if appropriate; and
  - — medical evaluation and possible treatment of chronic hepatitis B.
- When HBsAg testing of pregnant women is not feasible (i.e., in remote areas without access to a laboratory), all infants should receive hepatitis B vaccine ≤12 hours of birth and should complete the hepatitis B vaccine series according to a recommended schedule for infants born to HBsAg-positive mothers (Tables 2 and 3).

Management of Infants Born to Women Who Are HBsAg Positive

- All infants born to HBsAg-positive women should receive single-antigen hepatitis B vaccine (Table 2) and HBIG

BOX 3. Summary of hepatitis B vaccination recommendations for infants, children, and adolescents

Maternal hepatitis B surface antigen (HBsAg) testing
- All pregnant women should be tested routinely for HBsAg.

Vaccination of infants

At birth
- Infants born to mothers who are HBsAg positive should receive hepatitis B vaccine and hepatitis B immune globulin (HBIG) ≤12 hours of birth.
- Infants born to mothers whose HBsAg status is unknown should receive hepatitis B vaccine ≤12 hours of birth. The mother should have blood drawn as soon as possible to determine her HBsAg status; if she is HBsAg positive, the infant should receive HBIG as soon as possible (no later than age 1 week).
- Full-term infants who are medically stable and weigh ≥2,000 g born to HBsAg-negative mothers should receive single-antigen hepatitis B vaccine before hospital discharge.
- Preterm infants weighing <2,000 g born to HBsAg-negative mothers should receive the first dose of vaccine 1 month after birth or at hospital discharge.

After the birth dose
- All infants should complete the hepatitis B vaccine series with either single-antigen vaccine or combination vaccine, according to a recommended vaccination schedule (see Tables 3 and 4).
- Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg after completion of the hepatitis B vaccine series at age 9–18 months.

Vaccination of children and adolescents
- All unvaccinated children and adolescents aged <19 years should receive the hepatitis B vaccine series.

(0.5 mL) ≤12 hours of birth, administered at different injection sites. The vaccine series should be completed according to a recommended schedule for infants born to HBsAg-positive mothers (Table 3). The final dose in the vaccine series should not be administered before age 24 weeks (164 days).

- For preterm infants weighing <2,000 g, the initial vaccine dose (birth dose) should not be counted as part of the vaccine series because of the potentially reduced immunogenicity of hepatitis B vaccine in these infants; 3 additional doses of vaccine (for a total of 4 doses) should be administered beginning when the infant reaches age 1 month (Tables 3 and 4).
- Postvaccination testing for anti-HBs and HBsAg should be performed after completion of the vaccine series, at age 9–18 months (generally at the next well-child visit). Testing should not be performed before age 9 months to avoid detection of anti-HBs from HBIG administered during infancy and to maximize the likelihood of detecting late HBV infection. Anti-HBc testing of infants is not recommended because passively acquired maternal anti-HBc might be detected in infants born to HBV-infected mothers to age 24 months.
  - — HBsAg-negative infants with anti-HBs levels ≥10 mIU/mL are protected and need no further medical management.
  - — HBsAg-negative infants with anti-HBs levels <10 mIU/mL should be revaccinated with a second 3-dose series and retested 1–2 months after the final dose of vaccine.
  - — Infants who are HBsAg positive should receive appropriate follow-up (Appendix A).
- Infants of HBsAg-positive mothers may be breast fed beginning immediately after birth.
- Although not indicated in the manufacturer's package labeling, HBsAg-containing combination vaccines may be used for infants aged ≥6 weeks born to HBsAg-positive mothers to complete the vaccine series after receipt of a birth dose of single-antigen hepatitis B vaccine and HBIG.

Management of Infants Born to Women with Unknown HBsAg Status

- Women admitted for delivery without documentation of HBsAg test results should have blood drawn and tested as soon as possible after admission.
- While test results are pending, all infants born to women without documentation of HBsAg test results should receive the first dose of single-antigen hepatitis B vaccine (without HBIG) ≤12 hours of birth (Tables 2 and 3).
  - — If the mother is determined to be HBsAg positive, her infant should receive HBIG as soon as possible but no later than age 7 days, and the vaccine series should be completed according to a recommended schedule for infants born to HBsAg-positive mothers (Table 3).
  - — If the mother is determined to be HBsAg negative, the vaccine series should be completed according to a recommended schedule for infants born to HBsAg-negative mothers (Table 3).
  - — If the mother has never been tested to determine her HBsAg status, the vaccine series should be completed according to a recommended schedule for infants born to HBsAg-positive mothers (Table 3). Administration of HBIG is not necessary for these infants.
- Because of the potentially decreased immunogenicity of vaccine in preterm infants weighing <2,000 g, these infants should receive both single-antigen hepatitis B vaccine and HBIG (0.5 mL) if the mother's HBsAg status cannot be determined ≤12 hours of birth. The birth dose of vaccine should not be counted as part of the 3 doses required to complete the vaccine series; 3 additional doses of vaccine (for a total of 4 doses) should be administered according to a recommended schedule on the basis of the mother's HBsAg test result (Table 3).

Vaccination of Pregnant Women

- Pregnant women who are identified as being at risk for HBV infection during pregnancy (e.g., having more than one sex partner during the previous 6 months, been evaluated or treated for an STD, recent or current injection-drug use, or having had an HBsAg-positive sex partner) should be vaccinated.
- Pregnant women at risk for HBV infection during pregnancy should be counseled concerning other methods to prevent HBV infection.

Implementation

Delivery Hospital Policies and Procedures

- All delivery hospitals should implement policies and procedures (Box 4) to ensure 1) identification of infants born to HBsAg-positive mothers and infants born to mothers with unknown HBsAg status (see Prenatal HBsAg Testing), and 2) initiation of immunization for these infants). Such policies and procedures should include the following standing orders:
  - — for all pregnant women, review of HBsAg test results at the time of admission for delivery;
  - — for women who do not have a documented HBsAg test result, HBsAg testing as soon as possible after admission for delivery;

BOX 4. Delivery hospital policies and procedures to prevent perinatal HBV transmission

At time of admission for delivery

- Review hepatitis B surface antigen (HBsAg) status of all pregnant women.
- Record maternal HBsAg test results on both labor and delivery record and on infant's delivery summary sheet.
- Perform HBsAg testing as soon as possible on women who
  - — do not have a documented HBsAg test result,
  - — were at risk for HBV infection during pregnancy (e.g., more than one sex partner in the previous 6 months, evaluation or treatment for a sexually transmitted disease, recent or current injection-drug use, or HBsAg-positive sex partner), or
  - — had clinical hepatitis since previous testing.

After delivery

HBsAg-positive mothers and their infants

- Administer single-antigen hepatitis B vaccine and hepatitis B immune globulin (HBIG) to all infants born to HBsAg-positive mothers ≤12 hours after birth and record date and time of administration of HBIG and hepatitis B vaccine in infant's medical record.
- Provide information regarding hepatitis B to HBsAg-positive mothers, including
  - — advice that they may breast feed their infants upon delivery;
  - — modes of HBV transmission;
  - — need for vaccination of their susceptible household, sexual, and needle-sharing contacts;
  - — need for substance abuse treatment, if appropriate; and
  - — need for medical management and possible treatment for chronic hepatitis B.

Mothers with unknown HBsAg status and their infants

- Administer single-antigen hepatitis B vaccine (without HBIG) to all infants born to mothers with unknown HBsAg status ≤12 hours after birth and record date and time of administration of hepatitis B vaccine on infant's medical record.
- Alert infant's pediatric health-care provider if an infant is discharged before the mother's HBsAg test result is available; if the mother is determined to be HBsAg positive, HBIG should be administered to the infant as soon as possible, but no later than age 7 days.

All mothers and their infants

- Administer a dose of single-antigen hepatitis B vaccine to all infants weighing ≥2,000 g.
- Ensure that all mothers have been tested for HBsAg prenatally or at the time of admission for delivery and document test results.

At time infant is discharged

- Provide infant's immunization record to mother and remind her to take it to the infant's first visit to pediatric health-care provider.
  - — identification and management of all infants born to HBsAg-positive mothers;
  - — identification and management of all infants born to mothers with unknown HBsAg status; and
  - — for all infants, documentation on the infant's medical record of maternal HBsAg test results, infant hepatitis B vaccine administration, and administration of HBIG (if appropriate).
- Delivery hospitals should enroll in the federally funded Vaccines for Children (VFC) program to obtain free hepatitis B vaccine for administration of the birth dose to newborns who are eligible (i.e., Medicaid eligible, American Indian or Alaska Native, underinsured, or uninsured).

Case-Management Programs to Prevent Perinatal HBV Infection

- States and localities should establish case-management programs (Box 5), including appropriate policies, procedures, laws, and regulations, to ensure that
  - — all pregnant women are tested for HBsAg during each pregnancy, and
  - — infants born to HBsAg-positive women and infants born to women with unknown HBsAg status receive recommended case management.
- The location of these programs and the methods by which they operate will depend on multiple factors (e.g., population density and annual caseload of HBsAg-positive women). Programs may be located in state or local health departments, private health-care systems (e.g., health maintenance organizations), or institutions (e.g., correctional facility systems). Program administrators will need to work with prenatal care providers, delivery hospital staff, pediatric care providers, private health-care systems, and health departments.

Universal Vaccination of Infants

Recommendations

- All infants should receive the hepatitis B vaccine series as part of the recommended childhood immunization schedule (Table 5 and Appendix B). (For recommendations on management of infants born to HBsAg-positive mothers and infants born to mothers with unknown HBsAg status, see Prevention of Perinatal HBV Infection and Management of Pregnant Women.)
- For all medically stable infants weighing ≥2,000 g at birth and born to HBsAg-negative mothers, the first dose of vaccine should be administered before hospital discharge. Only single-antigen hepatitis B vaccine should be used for the birth dose.

BOX 5. Components of case-management programs to prevent perinatal hepatitis B virus infection

Test all pregnant women for hepatitis B surface antigen (HBsAg)

- Health-care providers should test all pregnant women for HBsAg during each pregnancy.
- HBsAg testing should be incorporated into standard prenatal testing panels (e.g., blood type, human immunodeficiency virus) infection, Rh factor, rubella antibody titer, and syphilis infection) used by all health-care providers caring for pregnant women.
- Delivery hospitals should ensure that all pregnant or delivering women have been tested for HBsAg before hospital discharge.
- Reporting of HBsAg test status should be included on hospital-based electronic birth certificates or neonatal metabolic screening requests.

Report and track HBsAg-positive women

- All HBsAg-positive pregnant women and all women of childbearing age with HBsAg-positive laboratory results should be reported to state or local perinatal hepatitis B prevention programs.
- All HBsAg-positive pregnant women should be entered into case-management tracking systems.

Provide prenatal HBsAg testing records to delivery hospitals

- HBsAg test results should be included on all forms (hard copy, electronic) used by practitioners to record and transmit information regarding care during pregnancy.
- For all pregnant women, a copy of the original laboratory report of HBsAg test results should be transferred from the prenatal care provider to the delivery hospital.
- Practitioners should document that HBsAg-positive pregnant women have a copy of the original laboratory report, that a copy of the original laboartory report is transferred from the prenatal care provider to the delivery hospital, and that patients are informed of their HBsAg test status and advised to notify delivery staff.

Identify and manage infants born to HBsAg-positive mothers

- Delivery hospitals should implement policies and procedures to ensure identification and initiation of postexposure immunization of infants born to HBsAg-positive mothers (see Delivery Hospital Policies and Procedures).
- Delivery hospitals should document the date and time of birth and the date and time of administration of hepatitis B immune globulin (HBIG) and hepatitis B vaccine for all infants born to HBsAg-positive mothers.

Identify and manage infants born to mothers without HBsAg test results

- Delivery hospitals should implement policies and procedures to ensure identification and initiation of postexposure immunization of infants born to mothers with unknown HBsAg status at delivery (see Delivery Hospital Policies and Procedures).
- Delivery hospitals should document the date and time of birth, date and time of administration of hepatitis B vaccine, and maternal HBsAg test results for all infants born to mothers with unknown HBsAg status at the time of delivery.

Complete the hepatitis B vaccine series

- Practitioners should document the dates of administration of all doses of the hepatitis B vaccine series for all infants born to HBsAg-positive mothers.

Complete postvaccination testing

- Health-care providers should document the results of testing for HBsAg and antibody to hepatitis B surface antigen (anti-HBs) after completion of the hepatitis B vaccine series for all infants born to HBsAg-positive mothers.

Monitor and evaluate the case management program

- Annually, each program should track
  - — the number of HBsAg-positive pregnant women;
  - — the proportion of infants born to HBsAg-positive women receiving postexposure prophylaxis ≤12 hours of birth, third vaccine dose by age 6 months, and postvaccination serologic testing for HBsAg and anti-HBs;
  - — the number of delivering women with unknown HBsAg status; and
  - — the proportion of infants born to mothers with unknown HBsAg status receiving hepatitis B vaccine within 12 hours of birth.
- Programs should determine reasons for
  - — >10% difference between expected and identified number of HBsAg-positive pregnant women;
  - — <90% completion rates for HBIG and hepatitis B vaccine ≤12 hours of birth, third dose by age 6 months, and postvaccination testing for infants born to HBsAg-positive mothers; and
  - — <90% completion rates for hepatitis B vaccine ≤12 hours of birth for infants born to mothers with unknown HBsAg status.

- On a case-by-case basis and only in rare circumstances, the first dose may be delayed until after hospital discharge for an infant who weighs ≥2,000 g and whose mother is HBsAg negative.
  - — When such a decision is made, a physician's order to withhold the birth dose and a copy of the original laboratory report indicating that the mother was HBsAg negative during this pregnancy should be placed in the infant's medical record.
  - — For infants who do not receive a first dose before hospital discharge, the first dose should be administered no later than age 2 months.
  - — Situations in which the birth dose should not be delayed include any high-risk sexual or drug-using practices of the infant's mother during pregnancy (e.g., having had more than one sex partner during the previous 6 months or an HBsAg-positive sex partner, evaluation or treatment for an STD, or recent or current injection-drug use) and expected poor compliance with follow-up to initiate the vaccine series.
- Preterm infants weighing <2,000 g and born to HBsAg-negative mothers should have their first vaccine dose delayed until 1 month after birth or hospital discharge (Table 4). For these infants, a copy of the original laboratory report indicating that the mother was HBsAg negative during this pregnancy should be placed in the infant's medical record.
- The vaccine series should be completed according to a recommended schedule with either single-antigen vaccine or a combination vaccine that contains the hepatitis B vaccine antigen (e.g., Hib-hepatitis B or DTaP-IPV-hepatitis B) (Table 2). The final dose in the vaccine series should not be administered before age 24 weeks (164 days).
- Administration of 4 doses of hepatitis B vaccine to infants is permissible in certain situations (e.g., when combination vaccines are administered after the birth dose).
- In populations with currently or previously high rates of childhood HBV infection (i.e., Alaska Natives; Pacific Islanders; and immigrant families from Asia, Africa, and other regions with intermediate or high endemic rates of infection [Figure 1 and Box 2]), the first dose of hepatitis B vaccine should be administered at birth and the final dose at age 6–12 months.

Implementation

- All delivery hospitals should implement standing orders for administration of hepatitis B vaccination as part of routine medical care of all medically stable infants weighing ≥2,000 g at birth (Box 4).
- All delivery hospitals should implement policies and procedures for management of infants weighing <2,000 g at birth, including the following:
  - — ensuring initiation of postexposure immunization of infants born to HBsAg-positive mothers and infants born to mothers not screened for HBsAg prenatally (see Prevention of Perinatal HBV Infection and Management of Pregnant Women), and
  - — documentation of maternal HBsAg test results on the infant's medical record.
- Prenatal care education should include information regarding the rationale for and importance of newborn hepatitis B vaccination.
- States are encouraged to adopt regulations or laws that require hepatitis B vaccination for entry into child care and also for entry into kindergarten and/or elementary school to ensure high vaccine coverage among infants and children.

Vaccination of Children and Adolescents Who Were Not Previously Vaccinated

Recommendations

- Hepatitis B vaccination is recommended for all children and adolescents aged <19 years.
- Children and adolescents who have not previously received hepatitis B vaccine should be vaccinated routinely at any age with an appropriate dose and schedule (Tables 2 and 5). Selection of a vaccine schedule should consider the need to achieve completion of the vaccine series. In all settings, vaccination should be initiated even though completion of the vaccine series might not be ensured.

Implementation

- To ensure high vaccination coverage among children and adolescents, the following measures are recommended:
  - — All children aged 11–12 years should have a review of their immunization records and should complete the vaccine series if they were not previously vaccinated or were incompletely vaccinated.
  - — All children and adolescents aged <19 years (including internationally adopted children) who were born in Asia, the Pacific Islands, Africa, or other intermediate- or high-endemic countries (Figure 1 and Box 2) or who have at least one parent who was born in one of these areas should have a review of their immunization records and should complete the vaccine series if they were not previously vaccinated or were incompletely vaccinated.

— States are encouraged to adopt regulations or laws that require hepatitis B vaccination before entry into middle school or its equivalent.
— Vaccination requirements should be considered for older high school students and for students before college entry, when feasible.
— States are encouraged to expand or implement immunization registries to include adolescents.
— Hepatitis B vaccine should be offered to all unvaccinated adolescents in settings that provide health-care services to this age group (Box 6), particularly those who engage in behaviors that place them at high risk for HBV infection.

BOX 6. Health-care settings in which hepatitis B vaccine should be offered to all unvaccinated children and adolescents

Primary care clinics
Substance abuse treatment facilities
Family planning clinics
Institutions for the developmentally disabled
Juvenile correctional facilities
Nonresidential daycare facilities for the developmentally disabled
Sexually transmitted disease clinics
School-based clinics

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Appendix A

Case Finding and Management of Hepatitis B Surface Antigen (HBsAg)–Positive Persons During Delivery of Vaccination Services

Chronically infected persons are at high risk for chronic liver disease and are a major reservoir of hepatitis B virus (HBV) infection. Foreign-born persons, especially persons from Africa, Asia, and the Pacific Islands, have high* rates of chronic HBV infection. During delivery of recommended hepatitis B vaccination services (e.g., HBsAg screening of pregnant women and serologic testing to assess susceptibility), vaccination providers will identify persons who are HBsAg positive. These persons require counseling and medical management for chronic HBV infection to reduce their risk for chronic liver disease. Their susceptible household, sexual, and needle-sharing contacts also need to be vaccinated against hepatitis B.

Few programs have been implemented to identify HBsAg-positive persons, provide or refer these persons for appropriate medical management, and provide vaccination to their contacts (*1*). Extending these services to persons identified as HBsAg positive will help prevent serious sequelae in chronically infected persons and enhance vaccination strategies for elimination of HBV transmission. This Appendix addresses case finding and management of persons with chronic HBV infection in the context of vaccine delivery. The recommendations are not intended to represent a comprehensive prevention program for chronically infected persons.

Case Finding in the Context of Vaccination Service Delivery

- All foreign-born persons (including immigrants, refugees, asylum seekers, and internationally adopted children) born in Asia, the Pacific Islands, Africa, and other regions with high endemicity of HBV infection (Box A-1) should be tested for HBsAg, regardless of vaccination status.
  - — For all persons born in high-endemic countries who are applying for permanent U.S. residence, HBsAg screening and appropriate follow-up on the basis of HBsAg test results should be included as part of the required overseas premigration and domestic adjustment-of-visa status medical examination process (*2*). HBsAg-positive persons should be considered eligible for migration and adjustment-of-visa status and counseled and recommended for follow-up medical evaluation and management in U.S. resettlement communities.
  - — Providers should identify children born in high-endemic countries and provide HBsAg testing and follow-up in all settings that provide health care. Retesting of persons who were tested for HBsAg in other countries should be considered.
- Other persons who should be tested for HBsAg as part of vaccination services include
  - — all pregnant women (See Prevention of Perinatal HBV Infection and Management of Pregnant Women),
  - — persons who receive prevaccination testing for susceptibility and who test positive for anti-HBc (See Prevaccination Testing for Susceptibility),
  - — hemodialysis patients, and
  - — nonresponders to vaccination (See Appendix B, Postvaccination Testing for Serologic Response).

BOX A-1. Geographic areas with high* hepatitis B virus endemicity

Africa: all countries except Algeria, Egypt, Lybia, and Tunisia
South Asia: all countries except Afghanistan, Bangladesh, Bhutan, India, Malaysia, Maldives, Nepal, Pakistan, and Sri Lanka
Western Pacific: all countries except Australia, Guam, Japan, and New Zealand
Middle East: Jordan and Saudi Arabia
Eastern Europe and Newly Independent States of the former Soviet Union: Albania, Armenia, Azerbaijan, Bulgaria, Croatia, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Tajikistan, Turkmenistan, and Uzbekistan
Western Europe: Malta
North America: Alaska Natives and indigenous populations in Northern Canada and Greenland
South America: Amazonian areas of Bolivia, Brazil, Columbia, Peru, and Venezuela

* Hepatitis B surface antigen prevalence of ≥8%.

Management of Persons Identified as HBsAg Positive

- All persons with HBsAg-positive laboratory results should be reported to the state or local health department.
- To verify the presence of chronic HBV infection, HBsAg-positive persons should be retested. The absence of immu-

* Hepatitis B surface antigen prevalence of ≥8%.

noglobulin M antibody to HBcAg or the persistence of HBsAg for 6 months indicates chronic HBV infection.

- Persons with chronic HBV infection should be referred for evaluation by a physician experienced in the management of chronic liver disease (*3*). Certain patients with chronic hepatitis B will benefit from early intervention with antiviral treatment or screening to detect hepatocellular carcinoma at an early stage.
- Household, sexual, and needle-sharing contacts of chronically infected persons should be identified. Unvaccinated sex partners and household and needle-sharing contacts should be tested for susceptibility to HBV infection (see Prevaccination Serologic Testing for Susceptibility) and should receive the first dose of hepatitis B vaccine immediately after collection of the blood sample for serologic testing. Susceptible persons should complete the vaccine series using an age-appropriate vaccine dose and schedule (see Tables 2 and 6) Persons who are not fully vaccinated should complete the vaccine series.
- Sex partners of HBsAg-positive persons should be counseled to use methods (e.g., condoms) to protect themselves from sexual exposure to infectious body fluids (e.g., semen or vaginal secretions) unless they have been demonstrated to be immune after vaccination (i.e., anti-HBs ≥10 mIU/mL) or previously infected (anti-HBc positive).
- To prevent or reduce the risk for transmission to others, HBsAg-positive persons should be advised concerning the risks for
  - — perinatal transmission to infants born to HBsAg-positive women and the need for such infants to receive hepatitis B vaccine beginning at birth (see Prevention of Perinatal HBV Infection and Management of Pregnant Women) and
  - — transmission to household, sexual, and needle-sharing contacts and the need for such contacts to receive hepatitis B vaccine.
- HBsAg-positive persons should also be advised to
  - — use methods (e.g., condoms) to protect nonimmune sex partners from acquiring HBV infection from sexual activity until the sex partners can be vaccinated and immunity documented;
  - — cover cuts and skin lesions to prevent the spread of infectious secretions or blood;
  - — refrain from donating blood, plasma, tissue, or semen (organs may be donated to HBV-immune or chronically infected persons needing a transplant); and
  - — refrain from sharing household articles (e.g., toothbrushes, razors, or personal injection equipment) that could become contaminated with blood.
- To protect the liver from further harm, HBsAg-positive persons should be advised to
  - — avoid or limit alcohol consumption because of the effects of alcohol on the liver;
  - — refrain from beginning to take any new medicines, including over-the-counter and herbal medicines, without consulting their health-care provider; and
  - — obtain vaccination against hepatitis A if chronic liver disease is found to be present.
- When seeking medical or dental care, HBsAg-positive persons should be advised to inform those responsible for their care of their HBsAg status so they can be evaluated and their care managed appropriately.
- Other counseling messages:
  - — HBV is not spread by breastfeeding, kissing, hugging, coughing, ingesting food or water, sharing eating utensils or drinking glasses, or casual contact.
  - — Persons should not be excluded from school, play, child care, work, or other settings on the basis of their HBsAg status unless they are prone to biting (*4*).
  - — Involvement with a support group might help patients cope with chronic HBV infection.

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Appendix B

Immunization Management Issues

Hepatitis B Vaccine Dose and Administration

- Recommended vaccine doses vary by product, age of recipient, and needs of special populations (see Table 2). Administration of single-antigen or combination vaccine simultaneously with other childhood vaccines produces no clinically significant interference in antibody responses (*1–13*). Although the antigen contents of vaccines differ, vaccines made by different manufacturers are interchangeable, except for the 2-dose schedule used for adolescents aged 11–15 years, for which only Recombivax HB is approved. Combination vaccines are not approved for use as a birth dose because of potential suppression of the immune response to subsequent doses of the *Haemophilus influenzae* type b (Hib) component in Comvax (*14*) and possible decreased immunogenicity of the diphtheria component of Pediarix when administered at birth.
- Hepatitis B vaccine should be administered by intramuscular injection. Injection into the buttock is associated with decreased immunogenicity (*15–18*). Intradermal administration can result in a lower seroconversion rate and final concentration of antibody to hepatitis B surface antigen compared with intramuscular administration; limited data are available to assess long-term protection from this route of administration (*19,20*).
- The anterolateral thigh muscle is the recommended site of administration for neonates (aged <1 month) and infants (aged 1–12 months). For toddlers (aged 1–2 years) and older children, either the anterolateral thigh or the deltoid muscle may be used if the muscle mass is adequate. The deltoid muscle is the preferred site of administration for adolescents.
- For intramuscular injection, the needle should be long enough to reach the muscle mass and prevent vaccine from seeping into subcutaneous tissue, but not so long as to involve underlying nerves and blood vessels or bone (*21*). The appropriate needle length is usually $^5/_8$" for neonates, $^7/_8$"–1" for infants, and $^7/_8$"–1$^1/_4$" for toddlers, older children, and adolescents. A 22- to 25-gauge needle should be used.
- Hepatitis B vaccine administered by any route or site other than intramuscularly in the anterolateral thigh or deltoid muscle should not be counted as valid and should be repeated unless serologic testing indicates that an adequate response has been achieved (see Postvaccination Testing for Serologic Response).
- Hepatitis B vaccine and other vaccines administered during the same visit should be administered in different injection sites. When more than one injection must be administered in the same limb, the anterolateral thigh is usually the preferred site, with injections separated by 1"–2" to avoid overlap in local reactions.
- For persons at risk for hemorrhage (e.g., persons with hemophilia), the risk of bleeding after intramuscular injection can be minimized by use of a 23-gauge (or smaller) needle, application of direct pressure to the injection site for ≥2 minutes, and administration of vaccine immediately after infusion of coagulation factor. Subcutaneous administration of vaccine can be considered for these persons but might result in lower response and an increased local reaction.
- Hepatitis B vaccine should be stored at 35°–46° F (2°–8° C) and should not be frozen.
- A vaccine information statement (VIS) must be provided to recipients of hepatitis B vaccine. The National Childhood Vaccine Injury Act of 1986 (42 U.S.C. § 300aa-26) requires vaccine providers to give a copy of the most current vaccine-specific VIS to all recipients (children or their guardians) of vaccines that are included on the National Vaccine Injury Compensation Program table maintained by the Health Resources and Services Administration (available at http://www. hrsa.gov). Hepatitis B vaccine is included on this table. The most current VIS for hepatitis B vaccine is available at http://www.cdc.gov/nip/publications/vis. Statements in languages other than English are available from the Immunization Action Coalition at http://www.immunize.org.

Hepatitis B Immune Globulin (HBIG) Dose and Administration

- The standard dose of HBIG is 0.5 mL for postexposure prophylaxis of infants born to hepatitis B surface antigen (HBsAg)–positive women and 0.06 mL/kg for all other applications.
- HBIG may be administered simultaneously with hepatitis B vaccine but in a different injection site.
- HBIG is administered by intramuscular injection. For infants, HBIG should be administered intramuscularly

in the anterolateral thigh using a 22–25-gauge needle that is 7/8"–1" in length. For older children and adolescents, an appropriate muscle mass (i.e., deltoid or gluteal) should be chosen in which to deliver the larger volumes of HBIG required for these age groups by using a needle length appropriate for the person's age and size (*21*).
- Vaccination with certain live-virus vaccines (measles, mumps, rubella, and varicella) should be deferred for at least 3 months after administration of HBIG because HBIG can inhibit the response to these vaccines (*21*).
- HBIG should be stored at 35°–46° F (2°–8° C) and should not be frozen.

Unknown or Uncertain Vaccination Status

- A reliable vaccination history is defined as a written, dated record (personal, school, physician, or immunization registry) of each dose of a complete series.
- In the majority of clinical practice settings and in situations when postexposure prophylaxis is indicated (see Appendix C), providers should accept only written and dated records (e.g., personal, school, physician, or immunization registry) as evidence of vaccination. Although vaccinations should not be postponed if records cannot be located, providers should try to locate missing records by contacting previous health-care providers and searching for personally held records.
- Persons whose records cannot be located should be considered susceptible and started or continued on the age-appropriate vaccine schedule.
- Persons who reside in the United States but were vaccinated in other countries should be considered fully vaccinated if they have written documentation of ≥3 doses of vaccine administered at recommended minimum intervals, including the third dose at age ≥24 weeks. If they were not vaccinated according to recommended minimum intervals, they should be revaccinated (see Minimum Dosing Intervals and Management of Persons Who Were Incorrectly Vaccinated). Persons without written documentation of full vaccination should complete the age-appropriate vaccine series.

Interrupted Vaccine Schedules

- When the hepatitis B vaccine schedule is interrupted, the vaccine series does not need to be restarted.
- If the series is interrupted after the first dose, the second dose should be given as soon as possible, and the second and third doses should be separated by an interval of at least 8 weeks.
- If only the third dose is delayed, it should be administered as soon as possible, after age 24 weeks (164 days).
- It is not necessary to restart the vaccine series for infants switched from one vaccine brand to another, including combination vaccines.

Minimum Dosing Intervals and Management of Persons Who Were Incorrectly Vaccinated

- The third dose of vaccine must be administered at least 8 weeks after the second dose and should follow the first dose by at least 16 weeks; the minimum interval between the first and second doses is 4 weeks. In infants, administration of the final dose is not recommended before age 24 weeks (164 days).
- Inadequate doses of hepatitis B vaccine (see Table 2) or doses received after a shorter-than-recommended dosing interval should be readministered.

Accelerated Vaccine Schedules

- The Food and Drug Administration (FDA) has not approved accelerated schedules in which hepatitis B vaccine is administered more than once in a month. If clinicians choose to use an accelerated schedule (i.e., doses at days 0, 7, and 14 days), the patient should also receive a booster dose at least 6 months after the start of the series to promote long-term immunity.

Hemodialysis Patients and Other Immunocompromised Persons

- Standard hepatitis B vaccine doses (see Table 2) are approved by FDA for vaccination of all persons aged <20 years. For hemodialysis patients and other immunocompromised persons, higher doses might be more immunogenic, but no specific recommendations have been made.
- Serologic testing of hemodialysis patients and other immunocompromised persons is recommended 1–2 months after administration of the final dose of the primary vaccine series to determine the need for revaccination (see Postvaccination Testing for Serologic Response). In addition, booster doses of vaccine might be needed (see Booster Doses).

Prevaccination Serologic Testing for Susceptibility

- Because of the low prevalence of HBV infection among infants, children, and adolescents born in the United States, prevaccination testing for susceptibility usually is not indicated for these age groups.
- Prevaccination testing for susceptibility is recommended for unvaccinated household, sexual, and needle-sharing contacts of HBsAg-positive persons.
- Anti-HBc is the test of choice for prevaccination testing.
- Persons tested for anti-HBc and found to be anti-HBc negative are susceptible and should complete the vaccine series.
- Persons found to be anti-HBc positive should be tested for HBsAg. HBsAg testing may be performed on the same specimen collected for anti-HBc testing. If the HBsAg test result is positive, the person should receive appropriate management (see Appendix A).
- In most situations, the first vaccine dose should be administered immediately after collection of the blood sample for serologic testing.

Postvaccination Testing for Serologic Response

Recommendations for postvaccination testing of infants born to HBsAg-positive women are provided in this report (see Management of Infants Born to Women Who Are HBsAg Positive). This section provides recommendations for postvaccination testing of other persons.

- Serologic testing for immunity is not necessary after routine vaccination of infants, children, or adolescents.
- Testing after vaccination is recommended only for the following persons whose subsequent clinical management depends on knowledge of their immune status:
  - — health-care workers;
  - — chronic hemodialysis patients, HIV-infected persons, and other immunocompromised persons (e.g., hematopoietic stem-cell transplant recipients or persons receiving chemotherapy), to determine the need for revaccination and the type of follow-up testing; and
  - — sex partners of HBsAg-positive persons, to determine the need for revaccination and the need for other methods of protection against HBV infection.
- Testing should be performed 1–2 months after administration of the last dose of the vaccine series by using a method that allows determination of a protective level of anti-HBs (≥10 mIU/mL).
- Persons found to have anti-HBs levels of ≥10 mIU/mL after the primary vaccine series are considered to be immune.
  - — Immunocompetent persons have long-term protection and do not need further periodic testing to assess anti-HBs levels.
  - — Immunosuppressed persons might need annual testing to assess anti-HBs levels (see Booster Doses).
- Persons found to have anti-HBs levels of <10 mIU/mL after the primary vaccine series should be revaccinated. Administration of three doses on an appropriate schedule (Table 7), followed by anti-HBs testing 1–2 months after the third dose, is usually more practical than serologic testing after one or more doses of vaccine.
- Persons who do not respond to revaccination should be tested for HBsAg.
  - — If the HBsAg test result is positive, the persons should receive appropriate management (see Appendix B), and any household, sexual, or needle-sharing contacts should be identified and vaccinated (see Appendix A).
  - — Persons who test negative for HBsAg should be considered susceptible to HBV infection and should be counseled about precautions to prevent HBV infection and the need to obtain HBIG postexposure prophylaxis for any known or likely parenteral exposure to HBsAg-positive blood (see Appendix C).

Booster Doses

- Booster doses are not recommended for persons with normal immune status who were vaccinated as infants, children, or adolescents. Serologic testing is not recommended to assess antibody levels in any age group, except in specific circumstances (see Postvaccination Testing for Serologic Response).
- For hemodialysis patients, the need for booster doses should be assessed by annual antibody to hepatitis B survace antigen (anti-HBs) testing. A booster dose should be administered when anti-HBs levels decline to <10 mIU/mL.
- For other immunocompromised persons (e.g., HIV-infected persons, hematopoietic stem cell transplant recipients, and persons receiving chemotherapy), the need for booster doses has not been determined. Annual anti-HBs testing and booster doses when anti-HBs levels decline to <10 mIU/mL should be considered in persons with an ongoing high risk for exposure.

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Appendix C

Postexposure Prophylaxis of Persons with Discrete Identifiable Exposures to Hepatitis B Virus (HBV)

This appendix provides recommendations for management of persons who are exposed to HBV through a discrete, identifiable exposure to blood or body fluids that contain blood. Recommendations for management of infants born to mothers who test positive for hepatitis B surface antigen (HBsAg)-positive mothers are provided in this report (see Prevention of Perinatal HBV Transmission and Management of Pregnant Women).

HBsAg-Positive Source

- Unvaccinated persons (Table C-1) or persons known not to have responded to a complete hepatitis B vaccine series should receive both hepatitis B immune globulin (HBIG) and hepatitis B vaccine as soon as possible after exposure (preferably ≤24 hours). For sexual exposures, HBIG should not be administered more than 14 days after exposure. Hepatitis B vaccine may be administered simultaneously with HBIG in a separate injection site. The hepatitis B vaccine series should be completed using the age-appropriate vaccine dose and schedule (see Tables 2 and 3).
- Persons who are in the process of being vaccinated but who have not completed the vaccine series should receive the appropriate dose of HBIG and should complete the vaccine series.
- Children and adolescents who have written documentation of a complete hepatitis B vaccine series and who were did not receive postvaccination testing should receive a single vaccine booster dose.

Source with Unknown HBsAg Status

- Unvaccinated persons (Table C-1) should receive the hepatitis B vaccine series with the first dose initiated as soon as possible after exposure, preferably ≤24 hours. The vaccine series should be completed using the age-appropriate dose and schedule (see Tables 2, 3, and 5).
- Persons who are not fully vaccinated should complete the vaccine series.
- Children and adolescents with written documentation of a complete hepatitis B vaccine series require no further treatment.

TABLE C-1. Guidelines for postexposure immunoprophylaxis of unvaccinated persons who are exposed to blodo or body fluids that contain blood

Cause	Action
Discrete exposure to an HBsAg*-positive source	
Percutaneous (e.g., bite, needlestick) or mucosal exposure to HBsAg-positive blood or body fluids that contain blood	Administer hepatitis B vaccine and hepatitis B immune globulin (HBIG)†
Sexual or needle-sharing contact of an HBsAg-positive person	Administer hepatitis B vaccine and HBIG†
Victim of sexual assault/abuse by a perpetrator who is HBsAg-positive	Administer hepatitis B vaccine and HBIG†
Discrete exposure to a source with unknown HBsAg status	
Victim of sexual assault/abuse by a perpetrator with unknown HBsAg status	Administer hepatitis B vaccine†
Percutaneous (e.g., bite or needclestick) or mucosal exposure to blood or body fluids that contain blood from a source with unknown HBsAg status	Administer hepatitis B vaccine†

* Hepatitis B surface antigen.
† Immunoprophylaxis should be administered as soon as possible, preferably ≤24 hours. Studies are limited on the maximum interval after exposure during which postexposure prophylaxis is effective, but the interval is unlikely to exceed 7 days for percutaneous exposures and 14 days for sexual exposures. The hepatitis B vaccine series should be completed.

Glossary

Terms and Abbreviations Used in This Report

ACIP	Advisory Committee on Immunization Practices
ALT	alanine aminotransferase
Anti-HBc	antibody to hepatitis B core antigen
Anti-HBe	antibody to hepatitis B e antigen
Anti-HBs	antibody to hepatitis B surface antigen
DTaP	diphtheria and tetanus toxoids and acellular pertussis adsorbed
FDA	Food and Drug Administration
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e antigen
HBIG	hepatitis B immune globulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
IgM	immunoglobulin M
IPV	inactivated poliovirus
MS	multiple sclerosis
NHANES	National Health and Nutrition Examination Survey
VAERS	Vaccine Adverse Events Reporting System
VSD	Vaccine Safety Datalink

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Continuing Education Activity Sponsored by CDC

A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States

Recommendations of the Advisory Committee on Immunization Practices (ACIP) Part 1: Immunization of Infants, Children, and Adolescents

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Goal and Objectives

This report updates the immunization strategy to eliminate hepatitis B virus (HBV) transmission in the United States. The report includes new recommendations and implementation strategies for immunization of infants, children, and adolescents. The goal of the report is to provide guidance for health-care professionals to implement these recommendations and strategies to prevent perinatal HBV transmission, to promote universal vaccination of infants as part of the routine childhood vaccination schedule, and to promote vaccination of children and adolescents who were not previously vaccinated. Upon completion of this educational activity, the reader should be able to a) identify ways to maintain high hepatitis B surface antigen (HBsAg) screening rates among pregnant women, b) describe the components of a case management program for HBsAg-positive women, c) describe methods to ensure that newborn infants of HBsAg-positive mothers and mothers with unknown HBsAg status receive appropriate immunoprophylaxis, d) describe how to structure programs to increase the number of infants who receive a birth dose of hepatitis B vaccine, e) list ways to increase vaccine coverage among adolescents, and f) identify ways to increase rates of HBsAg screening and hepatitis B vaccination of foreign-born persons.

To receive continuing education credit, please answer all of the following questions.

1. **Components of a health department case-management program to enhance prevention of perinatal hepatitis B virus (HBV) infection should ensure that…(*Indicate all that apply.*)**
   - A. all pregnant women are tested for HBsAg.
   - B. HBsAg-positive women are reported and tracked.
   - C. prenatal HBsAg testing records are received by maternity hospitals before delivery.
   - D. infants born to HBsAg-positive mothers and infants born to mothers with unknown HBsAg status are identified and managed.
   - E. all of the above.

2. **All delivery hospitals should implement standing orders for administration of hepatitis B vaccination before hospital discharge as part of routine medical care to all medically stable infants weighing >2,000 g at birth. (*Choose the one correct answer.*)**
   - A. True.
   - B. False

3. **Which of the following statement(s) regarding HBsAg screening and vaccination of immigrants and international adoptees is true? (*Indicate all that apply.*)**
   - A. All foreign-born persons (including immigrants, refugees, asylum seekers, and internationally adopted children) from Asia, the Pacific Islands, and Africa and other countries with HBsAg prevalence ≥2% should be tested for HBsAg.
   - B. Persons who test positive for HBsAg should receive appropriate follow-up, including counseling, evaluation for chronic liver disease and antiviral treatment, and vaccination of susceptible household and sexual contacts.
   - C. Persons who reside in the United States but who were vaccinated in other countries should be considered fully vaccinated if they have written documentation of at least three doses of vaccine administered at recommended minimum intervals.
   - D. All of the above.

4. **Identify health-care settings in which hepatitis B vaccine should be offered to all unvaccinated adolescents. (*Indicate all that apply.*)**
   - A. Drug treatment facilities.
   - B. Institutions for the developmentally disabled.
   - C. College health clinics.
   - D. Family planning clinics.
   - E. All of the above.

5. **Which of the following statements regarding the hepatitis B vaccination schedule in infants and children are true? (*Indicate all that apply.*)**
   - A. Administration of the final dose to infants is not recommended before age 24 weeks.
   - B. A vaccine series started with a birth dose of single-antigen vaccine cannot be completed with 3 doses of combination vaccine.
   - C. No differences in immunogenicity have been observed when one or two doses of hepatitis B vaccine produced by one manufacturer are followed by dose(s) from a different manufacturer.
   - D. Currently licensed formulations for both single-antigen vaccines have been demonstrated to produce high (>95%) levels of seroprotection among infants, children, and adolescents when administered in different schedules.
   - E. All of the above.

6. **Which of the following statements regarding the management of perinatal HBV exposure are true? (*Indicate all that apply.*)**
   - A. Passive-active prophylaxis with hepatitis B vaccine and HBIG should be administered within 12 hours after birth.
   - B. A vaccine series started with a birth dose of single-antigen vaccine can be completed with three doses of combination vaccine.
   - C. Active postexposure prophylaxis with hepatitis B vaccine alone (i.e., without HBIG) beginning at birth is frequently used in areas where implementation of maternal HBsAg testing is difficult (e.g., in Alaska, Pacific Islands, and developing countries).
   - D. Although rates of perinatal HBV transmission are higher from HBeAg-positive mothers compared with HBeAg-negative mothers, testing of HBsAg-positive pregnant women for HBeAg is not warranted for the management of the infant because postexposure prophylaxis is recommended for all infants born to HBsAg-positive women.
   - E. All of the above.

7. **Which best describes your professional activities:**
   - A. Physician.
   - B. Nurse.
   - C. Health educator.
   - D. Office staff.
   - E. Other.

8. **I plan to use these recommendations as the basis for…(*Indicate all that apply.*)**
   - A. health education materials.
   - B. insurance reimbursement policies.
   - C. local practice guidelines.
   - D. public policy.
   - E. other.

9. **Overall, the length of the journal report was…**
   - A. much too long.
   - B. a little too long.
   - C. just right.
   - D. a little too short.
   - E. much too short.

10. **After reading this report, I am confident I can identify ways to maintain high hepatitis B surface antigen (HBsAg) screening rates among pregnant women.**
    - A. Strongly agree.
    - B. Agree.
    - C. Undecided.
    - D. Disagree.
    - E. Strongly disagree.

11. **After reading this report, I am confident I can describe the components of a case management program for HBsAg-positive women.**
    - A. Strongly agree.
    - B. Agree.
    - C. Undecided.
    - D. Disagree.
    - E. Strongly disagree.

12. After reading this report, I am confident I can describe methods to ensure that newborn infants of HBsAg-positive mothers and mothers with unknown HBsAg status receive appropriate immunoprophylaxis.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

13. After reading this report, I am confident I can describe how to structure programs to increase the number of infants who receive a birth dose of hepatitis B vaccine.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

14. After reading this report, I am confident I can increase vaccine coverage among adolescents.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

15. After reading this report, I am confident I can identify ways to increase rates of HBsAg screening and hepatitis B vaccination of foreign-born persons.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

16. The learning outcomes (objectives) were relevant to the goal of this report.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

17. The instructional strategies used in this report (text, tables, figures, boxes, and appendices) helped me learn the material.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

18. The content was appropriate given the stated objectives of the report.

A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

(Continued on pg CE-4)

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A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Part 1: Immunization of Infants, Children, and Adolescents

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4.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	17.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E			
5.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	18.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E			
6.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	19.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E			
7.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	20.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E			
8.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	21.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E			
9.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	22.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E			
10.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	23.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E			
11.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	24.	[ ]A	[ ]B						
12.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	25.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	[ ]F		
13.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E									

Signature ***Date I Completed Exam***

19. The content expert(s) demonstrated expertise in the subject matter.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

20. Overall, the quality of the journal report was excellent.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

21. These recommendations will improve the quality of my practice.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

22. The availability of continuing education credit influenced my decision to read this report.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

23. The *MMWR* format was conducive to learning this content.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

24. Do you feel this course was commercially biased? *(Indicate yes or no; if yes, please explain in the space provided.)*
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F. Other.

Correct answers for questions 1–6.
1. E; 2. A; 3. D; 4. E; 5. A, C, and D; 6. E.

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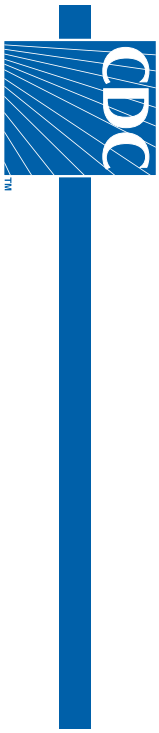

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