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

 Prepared by

Eric E. Mast, MD1, Harold S. Margolis, MD,1 Anthony E. Fiore, MD,1 Edward W. Brink, MD,2 Susan T. Goldstein, MD,1 Susan A. Wang, MD,1 Linda A. Moyer,1 Beth P. Bell, MD,1 Miriam J. Alter, PhD1

1Division of Viral Hepatitis, National Center for Infectious Diseases,
2Immunization Services Division, National Immunization Program

The material in this report originated in the National Center for Infectious Diseases, Rima F. Khabbaz, MD, Director, Division of Viral Hepatitis, John W. Ward, MD, Director; and the National Immunization Program, Anne Schuchat, MD, Director, Immunization Services Division, Lance E. Rodewald, MD, Director.

Corresponding preparer: Eric E. Mast, MD, Division of Viral Hepatitis, National Center for Infectious Diseases, 1600 Clifton Road, NE, MS G-37, Atlanta, GA 30333. Telephone: 404-371-5460; Fax: 404-371-5221; E-mail: emast@cdc.gov.

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.

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 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:

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 frequently 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-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 107--109 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 102--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 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).

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 immuno-prophylaxis 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).

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 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 postvaccination

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 neuritis, 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 acute phase of 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

vaccination 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

Management of Infants Born to Women Who Are HBsAg Positive

Management of Infants Born to Women with Unknown HBsAg Status

Vaccination of Pregnant Women

Implementation

Delivery Hospital Policies and Procedures

Case-Management Programs to Prevent Perinatal HBV Infection

Recommendations

Implementation

Recommendations

Implementation

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A. Halsey, MD, Johns Hopkins Bloomberg School of Public Health and Johns Hopkins School of Medicine, Baltimore, Maryland;

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References

Terms and Abbreviations Used in This Report

Advisory Committee on Immunization Practices

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ACIP Hepatitis Vaccines Working Group

Chair: Tracy Lieu, MD, Boston, Massachusetts.

Members: Jon Abramson, MD, Winston-Salem, North Carolina; Beth Bell, MD, Atlanta, Georgia; James E. Cheek, MD, Albuquerque, New

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Centers for Disease Control and Prevention
1600 Clifton Rd, MailStop E-90, Atlanta, GA
30333, U.S.A
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