Pathways to Controlling Hepatitis A and B:
Vaccination, Prevention, and Treatment

A peer-reviewed monograph component of the AAFP Video CME program

American Academy of Family Physicians

EB CME
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Introduction

Hepatitis A and B are among the most common vaccine-preventable illnesses in the United States. During the last several decades, the incidence of viral hepatitis has decreased in the United States as the result of improved sanitation and living conditions, widespread changes in some high-risk behaviors, and the adoption of childhood vaccination. However, the incidence of viral hepatitis remains higher than it should, and preventable infections still account for thousands of deaths and tens of thousands of acute episodes of viral hepatitis each year in the United States. Although infection with either virus can produce significant hepatic injury, hepatitis B in particular is a serious public health concern because of the high risk of maternal-to-infant transmission, chronic infection that may lead to progressive liver disease, and eventual liver cancer or liver failure.

Vaccines have been available for the hepatitis A virus (HAV) for nearly a decade, and for the hepatitis B virus (HBV) for more than two decades. Numerous clinical and epidemiological studies have documented that vaccination produces a strong immunologic response in nearly all children and the large majority of adults. In controlled clinical trials and large community studies performed around the world, vaccination has been shown to reduce susceptibility to HAV and HBV infection and to decrease the likelihood of serious liver disease in neonates, infants, children, adolescents, and adults. Data from millions of patients who have received HAV or HBV vaccination have clearly demonstrated that these vaccines are safe and well tolerated by nearly all patients. At the same time, large epidemiologic studies have helped define high-risk groups for HAV and HBV infection.

Despite advances in the understanding of patient risk factors and the development of safe and effective vaccines, many people remain at high risk of contracting viral hepatitis. Children and adults at risk for infection are often not recognized, and many individuals never receive effective counseling about reducing their risk of infection. Efforts to vaccinate at-risk adults and even children and adolescents have produced limited success. Family physicians are uniquely positioned to help reduce the spread of hepatitis A and B. HAV and HBV infections occur in all racial, ethnic, geographic, and socioeconomic groups: patients who are at risk are seen routinely in family practice. Whether by ensuring that children receive their vaccinations at the appropriate time, identifying children who require catch-up immunizations, or recognizing, counseling, and immunizing high-risk adults, family physicians can significantly reduce rates of viral hepatitis.

This monograph provides an update on the prevention of HAV and HBV infection in family practice. It briefly reviews recent trends in the impact of these disorders, risk factors for infection, and specific recommendations for vaccinating children and adults using currently approved HAV and HBV vaccines. Specific algorithms are provided for a number of special topics in vaccination, such as the assessment of vaccine nonresponse, managing missed vaccines and poor vaccine response, and the use of immune globulin in combination with vaccination for postexposure prophylaxis. The chronic treatment of hepatitis B using agents such as interferon-alfa or lamivudine, which is usually conducted by or in consultation with a specialist, is not addressed in this monograph.

Impact of HAV and HBV Infection

HAV is the most common cause of viral hepatitis in the United States, accounting for nearly half of all reported cases. The most common route of infection is oral-fecal. The most commonly identified sources of infection include household or sexual contact with an infected individual, enrollment or employment at a children’s daycare center, or infection during international travel. Smaller but significant numbers of cases in the United States are attributable to contaminated food or water, the use of illicit drugs (injected or noninjected), and male homosexual activity. No definitive source of infection is identifiable in about one half of cases of hepatitis A.
It is difficult to precisely estimate the number of new HAV infections annually because the disease is often clinically silent or produces nonspecific symptoms. It has been estimated that in the year 2001 (the most recent year for which information is available), approximately 10,600 acute cases of hepatitis A were reported—45,000 total acute cases and 93,000 new HAV infections. In the United States, the prevalence of HAV infection is highest among Alaskan Indians (121 cases per 100,000 population) and American Indians (21 cases per 100,000), and lowest in non-Hispanic whites, blacks, and Asians (4.6 to 6 per 100,000; Figure 1). Widespread outbreaks of HAV in the United States occur approximately one time each decade, with relatively stable lower infection rates between outbreaks (Figure 2). The prevalence of hepatitis A is highest in the western half of the United States. Eleven states (Arizona, Alaska, Oregon, New Mexico, Utah, Washington, Oklahoma, South Dakota, Idaho, Nevada, and California) account for only about 22% of the US population but 50% of all cases of hepatitis A.

Several other groups of people are at significantly increased risk of HAV infection:

- Travelers: Travelers from developed countries traveling to regions with high HAV prevalence rates who do not receive prophylaxis before travel have a markedly increased risk of infection (about 3/1,000 to 5/1,000 or greater for each month of travel), even when measures are taken to reduce the risk of exposure (eg, treating water before drinking, residing only in tourist hotels).
- Men who have sex with men: Recurring HAV outbreaks have been reported among homosexual men in the United States, Canada, Europe, and Australia.
- Users of illegal injection and noninjection drugs: HAV outbreaks have been associated with the use of illegal injectable drugs. However, users of illegal noninjectable drugs (eg, methamphetamine) are also at increased risk (likely because of other associated high-risk behaviors).
- Patients with clotting-factor disorders: Some US and European individuals with clotting-factor disorders developed HAV infection in the 1990s following exposure to contaminated Factor VII and Factor IX concentrates. Newer techniques have lessened the likelihood of this possibility.

Although the risk of HAV infection is not generally greater among employees at food service establishments, schools, or healthcare centers than it is among the general population, if employees of these types of businesses become infected, they have the potential to infect a substantial number of others.

The impact of HAV on health resource use and expenditures can be significant. Data from the Centers for Disease Control and Prevention (CDC) suggest that 10% to 11% of all patients with hepatitis A require hospitalization (3% to 7% of children and 13% to 14% of adults). The average

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**Figure 1.** Rates of Reported Hepatitis A, by Race/Ethnicity—United States, 1994. (From Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1999;48(RR12):6.)
cost per hospitalization case is $433 to $1,492 for children and $1,817 to $2,459 for adults. Indirect costs include lost work days and costs associated with immune globulin (IG) prophylaxis for other exposed individuals. A 1989 HAV epidemic was associated with total annual costs that exceeded $200 million.

**Hepatitis B**

Hepatitis B is a significant public health problem in the United States and around the world. It is estimated that 2 billion people worldwide have been infected with HBV and 350 million are chronically infected. Because HBV substantially increases the risk of hepatocellular carcinoma (HCC), it is the second leading cause of cancer worldwide. In the United States, reports estimate that 1.25 million people are chronically infected with HBV, and about 100,000 new infections and 5,000 HBV-related deaths occur each year. HBV is the second most common cause of viral hepatitis in the United States, accounting for about one third of all cases.

HBV is transmitted by percutaneous or mucous membrane exposure to infected blood or serum-derived body fluids. In the United States, most cases of HBV are the result of sexual transmission among older adolescents or young adults. There are many other potential routes of transmission for HBV that are present in relatively small numbers of infections. These include infection from blood transfusions or improperly sterilized medical instruments, during surgical or dental procedures performed by an infected healthcare worker; occupational exposure among healthcare or medical laboratory workers; or nonsexual person to person transmission occurring after prolonged exposure, such as among household contacts of a chronically infected person.

In regions where HBV infection is endemic, perinatal infection of infants from infected mothers, or infection among children as a result of exposure to other HBV-infected children or family members, is common. Infections from an infected mother can occur if the mother is a carrier of HBV or has active hepatitis B disease during her third trimester of pregnancy. In the United States, maternal-infant transmission is of particular importance in communities that have large populations of immigrants from regions where HBV is endemic. It is estimated that the number of children in the United States at risk for perinatal or early-childhood HBV infection has grown substantially in past decades as the number of immigrants from highly endemic areas (Asia in particular) has increased. A review of studies performed in 1991 that examined HBV serological markers estimated that a total of 16,000 children younger than 10 years were infected. By 1998, this number increased to an estimated 6,800 perinatal infections and an additional 18,700 infections in children younger than 10 years. Horizontal transmission among children is not restricted to children living in the same household. While nonsexual transmission to children living in households where no other HBV-positive individuals reside is uncommon, it has been documented.

![Figure 2. Rates of Reported Hepatitis A, by Age—United States, 1983-1997. (From Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1999;48(RR12):6.)](image-url)

Level of Evidence: Grade I: Evidence from multiple well-designed randomized controlled trials each involving a number of participants to be of sufficient statistical power.

In cases for which a risk factor can be identified, heterosexual exposure to an infected partner or partners is the most common cause of HBV infection. A large community study conducted by the CDC over a 17-year period found that heterosexual exposure accounted for 27.4% of all observed cases. Other common risk factors included intravenous drug use (18.2% of cases) and male homosexual activity (13.5% of cases). Exposure to an infected household member accounted for 3.6% of cases, and occupational exposure to blood accounted for another 1.6%. For about one third of patients, no particular high-risk behavior could be identified. In many cases in which a risk factor is not identified, it is important to note that the patient may be unable to recall or unwilling to report their high-risk behaviors. For chronic HBV infection, high-risk groups include recent immigrants from regions where HBV is endemic; patients with blood clotting disorders or who are undergoing cancer chemotherapy or dialysis; male homosexuals and heterosexuals with multiple sexual partners; and medical professionals.

As with HAV infection, HBV infection is to blame for a large financial burden on the healthcare system. HBV infection is associated with a hospitalization rate of about 20% and a mortality rate of about 1%. Estimates place the lifetime costs associated with the treatment of a single patient with HBV infection at approximately $87,000. This estimate excludes the cost of liver transplantation.

Impact of Vaccination Programs

Vaccines for hepatitis A have been available since the 1990s, and two HAV vaccines are currently approved for use in the United States. Randomized, double-blind clinical trials have shown that both vaccines significantly reduce the transmission of HAV and the likelihood of disease. The efficacy of Havrix was examined in a placebo-controlled, double-blind study conducted in more than 40,000 children between the ages of 1 and 16 years living in a region of high HAV prevalence in Thailand. Forty cases of hepatitis A were identified during a follow-up period of more than one year after randomization. Thirty-eight of the 40 cases were among the children who received placebo. At the end of the study, all children who had initially been assigned to placebo were vaccinated. At 10-month follow-up, only a single case of hepatitis A was reported among the entire study population. In a study conducted in the US, no HAV infections occurred during 6 years of follow-up among approximately 1,000 vaccinated children living in a high-risk community in New York, although infections continued to occur in children who were not vaccinated.

At the community level, several studies have demonstrated that HAV vaccination reduces the incidence of HAV infection and interrupts the emergence of new hepatitis A outbreaks. In the United States, the number of reported cases of HAV infection has fallen from more than 30,000 in 1997 to fewer than 11,000 in 2001. The dropping number of cases corresponds with an increase in the use of vaccination.

A vaccine for hepatitis B first became available in the United States in 1982. Before the introduction of HBV vaccine, estimates were that 200,000 to 300,000 new HBV infections occurred each year. The Advisory Committee on Immunization Practices (ACIP) of the CDC initially recommended a strategy of vaccination that focused on adults at high risk of contracting HBV. When it became apparent in 1991 that this strategy was not resulting in a marked reduction in HBV infections, the ACIP revised their recommendations to encourage universal childhood vaccination. In 1995, the recommendations were amended to include adolescent vaccination. During this time a growing number of states began to require hepatitis B vaccination as a prerequisite for school enrollment. By 2001, the nationwide incidence of new infections had decreased to about 79,000 per year (Figure 3). Data from the CDC has shown that the decrease in the incidence of hepatitis was most pronounced among children between the ages of 10 and 19 years (72.5% decrease), and the 20- to 29-year age group (70.6% decrease). It has been estimated that HBV immunization in the United States prevents 16,000 infections annually and that immunization of a single one-year birth cohort may prevent the eventual deaths of 2,700 vaccinees from chronic liver disease.

Studies also have shown that childhood vaccination significantly reduces chronic HBV infection in communities in which HBV prevalence is high. In a community-wide study of routine infant immunization conducted among Alaskan Indians, the prevalence of chronic HBV infection declined from about 16% among persons born before the introduction of immunization, to 0% among those immunized. Other studies have shown that HBV vaccination significantly reduces the incidence of HCC. In Taiwan, a large-scale immunization program began in 1984 for newborns born to HBV-infected mothers. Immunization was expanded to all preschool children by 1987. This study documented a significant decrease in the incidence of HCC beginning in 1993. Among children aged between 6 and 14 years, the average incidence of HCC decreased from 0.7 per 100,000 children (1981 to 1986) to 0.36 per 100,000 (1990 to 1994).
Despite the effectiveness of vaccination for reducing the incidence of disease, many persons at high risk remain unvaccinated. A study of 3,432 male homosexuals between the ages of 15 and 22 years in seven metropolitan areas in the United States found that 11% of participants had serologic evidence of HBV infection but only 9% had serologic evidence of HBV vaccination.20 A study of intravenous drug users attending sexually transmitted disease (STD) clinics found that only 6% of attendees were vaccinated against HBV.16 Liver damage is not the only risk that makes HBV particularly important in these persons. Infection may also exacerbate hepatitis C (HCV) or human immunodeficiency virus (HIV) infection, diseases which are also relatively common in these populations.

**Hepatitis A and B in Family Practice**

**Hepatitis A**

The symptoms of hepatitis A infection begin to appear after an average incubation period of 25 days.10 In adults, hepatitis A symptoms may include acute-onset malaise, anorexia, and abdominal discomfort, followed by jaundice.15 Many adults remain asymptomatic or develop only mild flu-like symptoms without jaundice. Infection is usually self-limited, resolving completely within 2 weeks to several months, and severe illness is unusual. Four patterns of symptomatic HAV infection have been identified:

- **Classical hepatitis A** occurs in about 80% of cases. This pattern is characterized by abrupt onset of mild prodromal illness (fever, headache, malaise, vomiting, nonspecific gastrointestinal symptoms), followed approximately 1 week later by the appearance of dark-colored urine. A another week later, symptoms of jaundice and pale or clay-colored stool become present. Classical HAV is self-limiting and lasts about 8 weeks. Extrahepatic manifestations (eg, vasculitis, arthritis, cryoglobulinemia) occur rarely.

- **Relapsing hepatitis A**, characterized by a second rise in ALT associated with recurrent symptoms 2 to 3 months after initial presentation, occurs in about 4% to 20% of cases.

- **Cholestatic Hepatitis A** occurs in about 10% of symptomatic patients. It persists for several months, and is characterized by fever, marked pruritus, and jaundice.

- **Fulminant hepatitis A** occurs in only about 0.35% of cases, but it can cause severe liver damage and liver failure. The mortality rate associated with fulminant hepatitis A is greater among older persons and those with other chronic liver disease, including patients with HBV, HCV infection, or chronic alcoholism.

In children, HAV infection is usually clinically silent or produces nonspecific symptoms suggesting viral infection. Adults are at their greatest infectivity during the 2-week period before the appearance of jaundice, whereas children may shed HAV for up to several months after the onset of illness.3 Because they shed virus for a long time and usually do not exhibit symptoms of infection, children are often an important source of HAV infection for adults.

Anti-HAV antibodies appear in all patients shortly before the onset of symptoms and persist for life.10 For this reason, determination of total anti-HAV may help identify...
patients previously exposed to HAV. Determination of total anti-HAV is not useful in the diagnosis of acute hepatitis. An ongoing HAV infection is diagnosed by the detection of immunoglobulin M (IgM) anti-HAV, which is detectable within 1 to 2 weeks after HAV exposure and persists for 3 to 6 months. HAV infections cannot be distinguished from other forms of viral hepatitis on the basis of clinical signs or symptoms or laboratory tests of liver function. Serologic testing to detect specific viral markers is required to confirm a diagnosis of acute HAV infection.

In the current National Health and Nutrition Examination Survey (NHANES) conducted by the CDC, serologic markers of infection demonstrate that the prevalence of HAV infection increases with age. Serologic evidence of a previous HAV infection was identified in 23% of persons younger than 20 years and increased to 78% among those older than 40 years (www.cdc.gov.nchs/data/nhanes/databriefs/viralhep.pdf).

**Hepatitis B**

HBV has an average incubation period of 75 days. A cute HBV infection can produce symptoms resembling those of other forms of viral hepatitis (eg, fatigue, jaundice, abdominal pain). About one third of infected persons report no symptoms.21 A approximately 1% of infected persons develop fulminant hepatitis, characterized by coagulopathy, encephalopathy, and cerebral edema.22

Several serologic markers are used to test for the presence of HBV infection or to monitor the course of the infection. Some of the most important are described in the callout box at the bottom of this page.22

The clinical course of acute HBV infection corresponds with characteristic changes in these serologic markers.10

Serum concentrations of HBV DNA and viral antigens increase during the incubation period. At about the same time symptoms appear, anti-HBcAg appears in serum, together with aminotransferase elevation. If present, HBeAg elevation occurs at this stage. The resolution of acute symptoms is accompanied by the appearance of anti-HBsAg, which confers long-lasting immunity.10 The diagnosis of acute HBV infection is best made by testing for the presence of IgM anti-HB core antigen, which appears soon after infection and declines after 4 to 5 months. HBsAg elevation may indicate chronic hepatitis B or the hepatitis B carrier state rather than an acute infection. Once acute infection subsides, HBeAg, HBV DNA, and HBsAg levels usually decline. The persistence of HBV DNA or HBeAg for longer than 6 weeks suggests a high likelihood of chronic hepatitis B development.10

In contrast to HAV infection, many people infected with HBV develop chronic infection lasting years or decades. Patients who have jaundice during the acute stage are less likely to progress to the chronic carrier state; therefore, many individuals who have chronic HBV infection have never manifested clinically notable symptoms and are unaware of their infection. The disorder is often found when the virus is identified during blood tests for another purpose, such as blood donation. The likelihood of chronic HBV infection is strongly related to the age at which infection occurs. Children infected with HBV are much more likely than those who are first infected in adulthood to become chronic carriers of the disease. About 90% of infants who are infected with HBV develop chronic HBV infection, compared with about 30% to 60% of those infected in adolescence and 5% to 10% of those infected in adulthood.6

The most common symptom of chronic hepatitis B infection is fatigue. Other common symptoms include sleep disturbances, difficulty concentrating, and right upper quadrant pain. The diagnosis of chronic HBV infection is confirmed by the presence of HBV DNA in serum or HBsAg in the liver. HBeAg is found in the serum of most, but not all, patients with chronic HBV.25

In the absence of treatment, 8% to 20% of patients with chronic HBV infection progress to cirrhosis within 5 years.9 The rate of progression is greater in patients with the HBeAg-negative form of HBV infection or in patients who use any hepatotoxic chemicals such as alcohol. Once the disease has progressed to the stage where histological cirrhosis is identified, some patients develop decompensated cirrhosis or HCC. In a study of untreated patients with histological evidence of cirrhosis resulting from HBV infection, the 5-year incidence of HCC was 9% and the 5-year incidence of decompensation unrelated to HCC was 16%.26 The long-term prognosis for patients with decompensated cirrhosis is poor, with 5-year survival estimates of 14% to 28%.9

**HBV Serologic Markers**

- **Hepatitis B surface antigen (HBsAg):** The HBV viral envelope. A antibody to HBsAg (anti-HBsAg): Confers immunity to HBV infection. May become undetectable over time following infection.
- **Hepatitis B core antigen (HBcAg):** The HBV core antigen is the structure that encloses the viral DNA. A antibody to HBcAg (anti-HBcAg): Not protective, but detected in nearly all persons after exposure.
- **Hepatitis B e antigen (HBeAg):** A protein exported from infected liver cells and a marker of active infection. Some patients who are infected with mutant HBV strains do not produce detectable levels of HBeAg. The presence of the HBeAg-positive form of HBV infection is associated with at least a 10-fold greater risk of transmission and also a significantly elevated risk of HCC.23,24
- **HBV deoxyribonucleic acid (DNA):** Best indicator of active viral replication.
- **IGM anti-HBcAg:** Elevated soon after infection but decreases gradually over a period of months.
Immunization Guidelines for HAV

Immunity to HAV may be conferred by passive immunization with IG or by active immunization with one of two licensed inactivated vaccines. Routine prevaccination screening is usually not necessary in children because of the relatively low incidence of HAV, the low cost of vaccination, and the low risk of vaccine-related adverse events. Prevaccination screening may be considered in older patients or in those who come from regions where the prevalence of HAV is very high.

HAV Vaccination

The goals of HAV vaccination are to protect individuals from infection, to reduce the incidence of new infections, and ultimately to eliminate HAV disease. Current CDC recommendations place high priority on the vaccination of children because of their relatively high rate of HAV infection and their importance in transmitting the virus. Two HAV vaccines are currently available, Havrix and VAQTA. Both are inactivated-virus vaccines. Recommended HAV vaccination schedules are printed in Table 1.

Havrix contains purified, inactivated HAV derived from live HAV grown in cell culture. The activity of Havrix is expressed in Enzyme-Linked Immunosorbent Assay Units (EL.U.). Havrix is provided in a 1-mL formulation (1440 EL.U.) for adults, and two children’s formulations (360 EL.U. or 720 EL.U. per 0.5-mL vial). In a series of clinical trials that enrolled more than 400 adults, a single Havrix dose of 1440 EL.U. produced seroconversion within 1 month of vaccination in 96% of subjects. In two additional studies in which subjects received a second dose after 6 months, seroconversion was noted in 100% of subjects. In patients with chronic liver disease, the rate of seroconversion and the average antibody titers were lower after the first dose than in healthy subjects, but the rate of seroconversion was similar between the two groups after a second vaccination. In a series of clinical trials that enrolled a total of 762 child patients, seroconversion occurred in 99% of subjects who received two vaccine doses, and all patients seroconverted within 1 month of a third dose.

VAQTA is also an inactivated HAV vaccine that is manufactured using a cell-culture system. VAQTA is provided in an adult formulation (50 U HAV antigen in 1 mL) and a children’s formulation (25 U HAV antigen in 0.5 mL). In clinical studies of 1,230 children and adolescents who were vaccinated, seroconversion occurred in 97% within 4 weeks of a single dose and 94% 2 weeks post-vaccination. In studies of 1,411 adults, the seroconversion rate was 95% within 4 weeks after a single dose.

HAV Vaccination in Neonates and Infants

The immunogenicity of HAV vaccine is diminished in the presence of preexisting anti-HAV antibody. HAV vaccines are not approved for children younger than 2 years. HAV Vaccination in Children and Adolescents

In 1996, the ACIP recommended HAV vaccination for children living in communities where the risk of HAV infection was greater than twice the national average and for adults at high risk of contracting HAV. However, a subsequent evaluation of the effectiveness of this vaccination strategy suggested that too few children were being vaccinated to substantially affect the overall prevalence of HAV infection. Therefore, revised guidelines issued in 1999 recommend the routine vaccination of children in states, counties, or communities where the incidence of HAV is twice the national average (≥ 20 cases per 100,000 population)

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<tr>
<th>Table 1. Recommended Dosages of VAQTA and HAVRIX</th>
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<td><strong>Vaccine Recipient Age (years)</strong></td>
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*— Units.
†— Enzyme-linked immunosorbent assay (ELISA) units.
‡— 0 months represents timing of the initial dose; subsequent numbers represent months after the initial dose.

and consideration of routine vaccination of children in states, counties, or communities where the rates of HAV infection exceed the national average (>10 cases but <20 cases per 100,000 population).

For children and adolescents between the ages of 2 and 18 years, Havrix is administered in two injections 6 to 12 months apart at a dose of 720 EL.U. (0.5 mL). With VAQTA, patients between the ages of 2 and 17 years should receive two doses, at 6-month to 18-month intervals, at a dose of 25 U (0.5 mL).

HAV Vaccination in Adults

Routine vaccination is recommended for adolescents and adults who are at increased risk of hepatitis A, including:

- Persons traveling to or working in countries with high or intermediate infection risk: Vaccination should be administered at least 4 weeks prior to departure. If travel is anticipated before 4 weeks have elapsed, supplemental administration of IG should be considered. Vaccination is preferred for older children, adolescents and adults, whereas IG is preferred for younger children.
- Men who have sex with men: Adolescents and adults who engage in male homosexual activity.
- Illegal drug users: Vaccination is recommended for users of illegal injected and illegal noninjected illicit drugs.
- Persons at increased occupational risk of exposure: Persons who work with HAV in a research laboratory setting or who work with nonhuman primates should be vaccinated. Other groups have not been shown to be at increased risk of HAV infection as a result of occupational exposure.

For adults, Havrix is administered as two injections, 6 to 12 months apart, of 1440 EL.U. (1.0 mL). When administering VAQTA, patients older than 17 years should receive two doses at 6-month intervals, at a dose of 50 U (0.5 mL).

Passive Immunization Using HAV Immune Globulin

The passive transfer of anti-HAV antibody using IG may be used to provide short-term pre-exposure or postexposure prophylaxis. IG administered by intramuscular injection at a dose of 0.2 mL/kg provides pre-exposure anti-HAV protection for up to 3 months; administration of 0.06 mL/kg provides protection for up to 6 months. For postexposure use, CDC guidelines recommend that persons who are exposed to HAV and who have not been vaccinated should receive prophylactic IG if treatment can be administered within 2 weeks of HAV exposure. If administered shortly after HAV exposure, IG at a dose of 0.02 mL/kg prevents the appearance of active hepatitis in most cases, and administration later in the incubation period may still reduce the severity of symptoms. CDC guidelines further recommend:

- IG should be administered into the deltoid or gluteal muscle
- Children younger than 24 months be administered IG in the anterolateral thigh muscle
- Treatment be repeated every 5 months if exposure to HAV continues
- Persons with immunoglobulin A (IgA) deficiency not receive IG because of an increased risk of anaphylaxis
- Mumps-rubella (MMR) vaccination be delayed for at least 3 months, and varicella vaccination for at least 5 months, following IG administration
- IG not be administered within the 2 weeks following MMR immunization or 3 weeks following varicella immunization unless the benefit of IG is expected to outweigh that of the MMR or varicella vaccination

Immunization Guidelines for HBV

As with HAV, immunity against HBV may be conferred using active immunity or passive immunity (hepatitis B immune globulin [HBIG]). Standard vaccination practices should be followed with any vaccine, but are especially important with HBV vaccination. HBV vaccines should be administered only by intramuscular (IM) injection into the anterolateral thigh or the deltoid muscle. CDC guidelines recommend that injections to any other site should not be counted toward completion of the vaccination series. The use of other injection sites or unapproved administration procedures (eg, splitting the vaccine dose into smaller doses of equal volume) may reduce the immunogenicity of the vaccine and should be avoided. Routine HBV susceptibility screening is not recommended for children and adolescents. In adults, it may be considered in groups in which the rate of exposure is high (for example, among users of illegal injection drugs, HIV-infected persons, homosexual men, or household contacts of HBV carriers), taking into consideration the relative costs of screening and vaccination.

Practice Recommendation: Sexual and household contacts of carriers should be tested for HBV (HBsAg and anti-HBs) and if negative receive hepatitis B vaccination (http://www.guideline.gov/summary/summary.aspx?doc_id=3446&nbr=2672&string=hepatitis).

Level of Evidence: Grade II: Evidence from at least one large well-designed clinical trial with or without randomization, from cohort or case-control analytic studies, or well-designed meta-analysis.

HBV Vaccination

The primary objective of HBV immunization is the prevention of chronic HBV infection and associated liver disease.
Two HBV vaccines are currently licensed for use in the United States. Both Recombivax HB and Engerix-B are produced without human plasma using recombinant technology. Both vaccines are administered in a 3-dose series, with the second and third doses administered at 1-month and 6-month intervals following the first dose. Recommended HBV vaccination dose schedules are summarized in Table 2.

Engerix-B is a purified suspension of HBsAg. It is available in an adult formulation (1 mL dose containing 20 mg of HBsAg) and in a children's formulation (0.5 mL dose containing 10 mg HBsAg). Both formulations are preservative free. In clinical studies of neonatal transmission of HBV from infected (HBsAg and HBeAg-positive) mothers, a three-dose course of Engerix-B resulted in an approximately 95% reduction in the number of children who became HBV carriers. In several clinical trials of neonates, young children, adolescents, and adults, seroconversion rates of 96% to 100% were observed following the three-dose regimen. A ducts older than 40 years exhibit a lower rate of seroconversion (88%) and lower average antibody titers.

Like Engerix-B, Recombivax HB is a purified preparation derived from the HBsAg antigen. Recombivax HB is available, either with or without preservative, in an adult formulation (1.0 mL dose containing 10 mg HBsAg) and a children's formulation (0.5 mL dose containing 5 mg HBsAg). A formulation is also available for patients on dialysis (1 mL dose containing 40 mg HBsAg). The three-dose vaccination series with Recombivax produced protective antibody levels in 94% to 98% of young adults and adolescents and 89% of adults older than 40 years. In childhood patients, protective antibody levels are produced in 99% to 100% of those vaccinated. Recombivax has been shown to reduce the likelihood of maternal-infant HBV transmission by an estimated 95%.

**HBV Vaccination in Neonates and Infants**

Before the ACIP guidelines began to focus on childhood vaccination in 1991, about one third of all chronic HBV infections in the United States occurred in infants born to infected mothers or infected by other children. One obstacle to a vaccination strategy focusing on high-risk mothers is that many mothers who are positive for HBsAg are not identified, or their infection status is not conveyed from the maternity care provider to the infant's physician. Family physicians providing both maternity and well infant care can assure this continuity. In 1991, the ACIP recommended routine vaccination of all infants, and in January of 2002, revised this to recommend that the first administration of HBV vaccine be performed at the time of birth. Infants born to HBsAg-positive mothers should also receive HBIG (addressed in the following section), and should be tested for anti-HBs between the ages of 9 to 15 months to identify the need for repeat vaccination.

**HBV Vaccination in Older Children**

For children who are not vaccinated during infancy, ACIP guidelines recommend catch-up HBV vaccination at any visit during childhood. In family practice, there are several natural opportunities to perform catch-up vaccination. Family physicians often see young children who require

### Table 2. Recommended Doses of Currently Licensed Hepatitis B Vaccines

<table>
<thead>
<tr>
<th>Group</th>
<th>Recombivax HB* Dose: (µg)</th>
<th>(mL)</th>
<th>Engerix-B* Dose: (µg)</th>
<th>(mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants of HBsAg-negative mothers and children age &lt;11 years</td>
<td>2.5</td>
<td>(0.25)</td>
<td>10.0</td>
<td>(0.5)</td>
</tr>
<tr>
<td>Infants of HBsAg-positive mothers; prevention of parinatal infection</td>
<td>5.0</td>
<td>(0.5)</td>
<td>10.0</td>
<td>(0.5)</td>
</tr>
<tr>
<td>Children and adolescents aged 11 to 19 years</td>
<td>5.0</td>
<td>(0.5)</td>
<td>20</td>
<td>(1.0)</td>
</tr>
<tr>
<td>Adults aged &gt;20 years</td>
<td>10.0</td>
<td>(1.0)</td>
<td>20.0</td>
<td>(1.0)</td>
</tr>
<tr>
<td>Dialysis patients and other immunocompromised persons</td>
<td>40.0</td>
<td>(1.0)‡</td>
<td>40.0</td>
<td>(2.0)§</td>
</tr>
</tbody>
</table>

*— Both vaccines are routinely administered in a three-dose series. Engerix-B has also been licensed for a four-dose series administered at age 0, 1, 2 and 13 months.
†— HBsAg = Hepatitis B surface antigen.
‡— Special formulation.
§— Two 1.0-mL doses administered at one site, in a four-dose schedule at age 0, 1, 2 and 6 months.

other vaccinations or for vaccinations before beginning school. Changes to the childhood immunization schedule in 2002 emphasized the importance of a preadolescent visit. The CDC recommends catch-up vaccination at this time for children aged 11 to 12 years who have not been previously vaccinated against HBV.

HBV Vaccination in Adolescents and Adults

CDC guidelines recommend vaccination of adolescents in high-risk groups, such as those who use illegal drugs or who have multiple sexual partners (defined as more than 1 partner in a 6-month period). For adults, the CDC recommends HBV vaccination for the following high-risk groups:\n- Occupational risk (eg, healthcare or public safety workers at risk of exposure to blood)
- Clients or staff of residential institutions for the developmentally disabled, or staff of nonresidential institutions that are occupied by known HBV carriers
- Hemodialysis patients (vaccination should occur as early in the course of disease as possible)
- Recipients of blood clotting factor concentrates
- Household contacts or sexual partners of those known to be HBsAg positive.
- Adoptees from regions where HBV is endemic
- Illegal injection drug users
- Sexually active homosexual or bisexual men
- Sexually active heterosexual men or women who are currently being treated for a sexually transmitted disease, prostitutes, or those with multiple sexual partners

The CDC does not recommend a specific schedule for routine HBV vaccination for travelers. People traveling to regions of high HBV endemicity should be vaccinated if they plan to stay longer than 6 months or can expect a high risk of exposure through blood, sexual contact with someone in the local population, or local medical treatment.

Combined Hepatitis A and B Vaccine

The FDA approved a combined HAV and HBV vaccine for the prevention of hepatitis A and hepatitis B in adults. Twinrix, approved in 2001, contains the inactivated HAV strain used in Havrix and the HBsAg used in Engerix-B. Each 1.0 mL dose contains at least 720 EL.U. of inactivated HAV and 20 mg of HBsAg. The immunogenicity of Twinrix was evaluated in a series of clinical studies that enrolled 1,551 healthy subjects between the ages of 17 and 70 years. Following 3 doses, seroconversion for HAV (anti-HAV greater than either 20 mIU/mL or 33 mIU/mL, depending on which of two commercially available assays was used for a particular sample) was noted for 99.9% of participants, and seroprotection for HBV (anti-HBsAg titer ≥ 10 mIU/mL) was noted for 98.5% of participants. In a randomized clinical trial in which subjects were assigned to either Twinrix or separate injections of Havrix and Engerix-B, Twinrix produced rates of HAV seroconversion and HBV seroprotection that were very similar to (and not statistically different from) the rates produced by the two individual vaccine regimens. Patients in the Twinrix arm of the study exhibited higher average antibody titers, although the clinical significance of this difference is not known (Table 3). Twinrix is indicated for the prevention of HAV and HBV infection in persons aged 18 years or older. Twinrix should be administered using the same schedule as HBV vaccination (ie, 3 doses at months 0, 1, and 6).

Immunization guidelines produced by the AAFP and the ACIP recommend combination vaccines where possible. Individual vaccines must never be mixed in the same syringe unless specifically approved for this use. Guidelines suggest that the use of approved combination vaccines is preferable to the use of multiple individual vaccines, and that combination vaccines are appropriate whenever one or more vaccines are indicated and none of the component vaccines are contraindicated. For infants, a combination HBV vaccine with the Haemophilus influenzae vaccine is administered.

Postexposure HBV Prophylaxis

Individuals who require postexposure HBV prophylaxis are commonly encountered in family practice, especially in the context of occupational exposure among healthcare workers. HBV vaccines are used for postexposure HBV prophylaxis.

Table 3. Geometric Mean Titers

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>N</th>
<th>Time-point</th>
<th>GMT to Hepatitis A (95%CI)</th>
<th>GMT to Hepatitis B (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twinrix</td>
<td>263</td>
<td>Month 1</td>
<td>335</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>259</td>
<td>Month 2</td>
<td>636</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>264</td>
<td>Month 7</td>
<td>4,756 (4,152 to 5,448)</td>
<td>2,099 (1,663 to 2,649)</td>
</tr>
<tr>
<td>Havrix and Engerix-B</td>
<td>268</td>
<td>Month 1</td>
<td>444</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>269</td>
<td>Month 2</td>
<td>257</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>269</td>
<td>Month 7</td>
<td>2,948 (2,638 to 3,294)</td>
<td>1,871 (1,428 to 2,450)</td>
</tr>
</tbody>
</table>

GMT = geometric mean titers; N = number
either alone or combination with HBIG. The public health service periodically reviews and updates its recommendations regarding occupational exposure to infectious agents. These recommendations were recently reviewed for the family practice setting, and postexposure prophylaxis recommendations for HBV infection are shown in Table 4. Postexposure prophylaxis is recommended whenever risk of infection is possible.

Interrupted or Incomplete Vaccinations

Patients who receive the first dose of a vaccine series should receive the appropriate follow-up doses even if the subsequent doses are delayed or are administered using a different vaccine. There is no need for the addition of vaccine doses beyond the standard regimen, and no need to restart the vaccination sequence if it interrupted. Several studies suggest that administration of a second dose of Havrix and VAQTA, produces an increase in anti-HAV levels even when delayed for several years after the first dose. Data from childhood vaccination studies suggest that children who receive doses of different licensed vaccines during their vaccination series have acceptable immunologic responses for both HAV and HBV. Results of a study of adult healthcare workers demonstrated that antibody titers after HBV vaccination were similar for patients who received either three doses of Recombivax Hb or two doses of Recombivax HB followed by a final dose of Engerix-B. Although the average antibody titers were somewhat higher among patients who completed the three-dose series with Engerix-B, the difference in antibody production between the two vaccination strategies was not statistically significant.

A catch-up schedule, developed by the AAFP, CDC, and the American Academy of Pediatrics, is available to help determine the appropriate timing of missed or interrupted vaccinations, including HBV. The full catch-up schedule for HBV immunizations available from the AAFP and may be obtained via the Internet at http://www.aap.org/policy/2003Catchup.pdf.

### Table 4. Recommended Postexposure Prophylaxis for Exposure to Hepatitis B Virus

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Source HbsAg† positive</th>
<th>Source HbsAg† negative</th>
<th>Source unknown or not available for testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unvaccinated</td>
<td>HBIG‡ x 1 and initiate HB vaccine series§</td>
<td>Initiate HB vaccine series</td>
<td>Initiate HB vaccine series</td>
</tr>
<tr>
<td>Previously vaccinated</td>
<td>No treatment</td>
<td>No treatment</td>
<td>No treatment</td>
</tr>
<tr>
<td>Known responder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known nonresponder</td>
<td>HBIG x 1 and initiate vaccination or HBIG x2**</td>
<td>Test exposed person for anti-HBs***</td>
<td>If known high-risk source, treat as if source were HbsAg positive</td>
</tr>
<tr>
<td>Antibody response unknown</td>
<td>Test exposed person for anti-HBs***</td>
<td>If adequate,§ no treatment is necessary</td>
<td>Test exposed person for anti-HBs</td>
</tr>
<tr>
<td></td>
<td>If inadequate,¶ administer HBIG x 1 and vaccine booster</td>
<td>If inadequate,§ administer vaccine and booster and recheck titer in 1 to 2 months</td>
<td></td>
</tr>
</tbody>
</table>

HbsAg = hepatitis B surface antigen; HB - hepatitis B; HBIG = hepatitis B immune globulin.

*— Persons who have previously been infected with hepatitis B virus are immune to reinfection and do not require postexposure prophylaxis.
†— Hepatitis B surface antigen.
‡— Hepatitis B immune globulin; dose is 0.06 mL per kg intramuscularly.
§— Hepatitis B vaccine.
||— A responder is a person with adequate levels of serum antibody to HbsAg (ie, anti-HBs >10 mIU per mL.)
¶— A nonresponder is a person with inadequate response to vaccination (ie, serum anti-HBs <10 mIU per mL.)
**— The option of giving one dose of HBIG and reinitiating the vaccine series is preferred for nonresponders who have not completed a second three-dose vaccine series. For persons who previously completed a second vaccine series but failed to respond, two doses of HBIG are preferred.
***— Antibody to HbsAg.

(Adapted from Centers for Disease Control and Prevention. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. MMWR. 2001;50(RR-11):22.)
Assessing Vaccine Response and Managing Nonresponse

**HEPATITIS A**

It is not necessary to test for seroconversion after HAV vaccination because the rate of vaccination response to even a single dose is very high. Both Havrix and VAQTA produce protective antibody levels in more than 90% of adults and children older than 2 years after even a single dose, and in nearly all patients who receive both doses. Protection against HAV lasts several years following completion of the vaccination series. Some studies suggest the presence of protective antibody levels for as many as 20 years. Some individuals may produce quantities of anti-HAV antibody that are lower than the typical response but sufficient to provide protection against infection. For example, the administration of HAV vaccine in combination with IG typically reduces the amount of protective antibody that is produced, although antibody production remains well above protective levels. Older individuals and those with chronic liver disease may also produce lower, but therapeutic, levels of anti-HAV.

**HEPATITIS B**

The complete three-dose series is required for optimal HBV prevention. Routine testing of immune response following vaccination is not necessary because more than 95% of children and 90% of healthy adults younger than 40 years exhibit seroconversion (the appearance of anti-HBs ≥ 10 mIU/mL) following the completion of vaccination. The immunogenicity of the vaccine is somewhat less in older individuals, declining to about 75% in those older than 60 years. Other factors also may reduce the likelihood of seroconversion, including:

- Prematurity with low birth weight
- Immunosuppression
- Renal failure
- Obesity
- Tobacco use

Because preterm, low-birthweight newborns are at increased risk of failure to seroconvert, delaying vaccination in infants that weigh less than 2 kg is recommended unless the mother is HBsAg positive.

Zimmerman and colleagues recently reviewed the role of post-vaccination HBV antibody monitoring in family practice. Post-vaccination testing of anti-HBs may be desirable for certain high-risk groups, such as infants born to HBsAg-positive mothers or sexual contacts of an HBV-infected individual. Antibody testing should be performed annually for individuals with compromised immune function or for dialysis patients. Booster vaccinations should be administered when antibody levels fall below 10 mIU/mL. If antibody testing is required, it should be performed 1 to 2 months after completion of the vaccine series in older children and adults, and at age 9 to 15 months in infants. A systematic approach to the management of vaccine nonresponse is shown in Figure 4.

The duration of the effectiveness of HBV vaccination is unknown. Several studies have found serologic evidence of HBV protection for more than 10 years in 70% to 80% of those who are vaccinated. Even if antibodies are no longer detectable, immunologic memory provides protection against HBV infection for many years after vaccination. Booster doses are not recommended for immunologically normal adolescents or adults who were vaccinated in childhood. However, considering that several years may elapse between childhood vaccination and the risk of sexual transmission of HBV, testing for the persistence of anti-HBs may be considered for those with other high-risk behaviors or exposure and who are vaccinated as infants. Patients who are undergoing dialysis have a shorter duration of protection and lower average antibody titers.

**Vaccine Adverse Reactions, Contraindications, and Precautions**

As with any medication, adverse reactions are possible following immunization. Adverse events thought to be associated with hepatitis vaccination should be reported to the National Vaccine Adverse Events Reporting System (VAERS). VAERS may be contacted by telephone at 800-822-7967 or via the Internet at www.fda.gov/cber/vaers/vaers.htm.

HAV and HBV vaccines have only one true contraindication: severe allergic reaction to a previous dose or to a vaccine component. Moderate or severe illness, with or without fever, should be considered a precaution for both vaccines (that is, vaccination should be delayed unless the risk of delaying the vaccination is thought to exceed the risk of additional vaccine-related adverse events). Minor illnesses, with or without fever, local injection-site reactions to a previous dose, or current antimicrobial therapy should not prevent or delay vaccination. Some clinicians feel that HBV vaccine should not be administered to patients who are pregnant or who have autoimmune disease—but note the CDC recommends vaccinating these patients.

**HEPATITIS A: ADVERSE EFFECTS**

Serious adverse effects are rare with either of the marketed hepatitis A vaccines. The most common adverse events noted in clinical trials of more than 30,000 individuals vaccinated with Havrix were injection-site soreness (56% of adults, 21% of children) and headache (14% of adults, 9% of children). General adverse events, such as fatigue or fever (≥37.5°C) were reported by less than 10% of patients. Clinical experience with nearly 9,200 patients suggests VAQTA has a similar safety profile.
was reported by 18.7% of patients and tenderness by 16.9%;
fever was noted by 3.1% of vaccinees and abdominal pain
by 1.6%. According to the CDC guidelines for HAV
vaccination, no serious adverse events have been clearly
attributable to HAV vaccination in more than 65 million
vaccinated individuals.

**Hepatitis B: Adverse Effects**

The most common adverse event reported with HBV vacci-
nation is injection-site soreness, which occurs in about
20% of vaccinees. Other side effects such as fatigue,
headache, and fever occur in fewer than 10% of those

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**Figure 4.** Algorithm for Hepatitis B Revaccination in Known or Suspected Nonresponders. (Adapted from Poland GA. Hepatitis B immunization

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*— Recombivax = 10 µg/dose; Engerix-B = 20 µg/dose*
A naphylaxis has been reported to occur at a rate of approximately 1 per 600,000. A study of more than 5600 children performed in a health maintenance organization in San Francisco compared the rates of febrile episodes, allergic reactions, seizures, or neurological disorders between children vaccinated for HBV in the first 21 days of life, versus children who were not vaccinated. These investigators found no evidence for increased serious adverse outcomes associated with vaccination. For example, fever was noted for 26 children in the vaccinated group (0.8%) and 25 children in the non-vaccinated group (1.1%). One child in each group exhibited an allergic reaction during the first 21 days.

**Combination HAV and HBV Vaccine: Adverse Effects**

A dverse events were studied in 2,299 persons who received a total of 6,594 Twinrix doses in 14 clinical trials before licensing. The incidence of adverse events was similar to the incidence among vaccinees that received vaccination with both single-agent vaccines. The most common adverse events were local injection-site reactions (induration) and upper respiratory tract infections, both reported in less than 10% of injections. No serious adverse events were observed with Twinrix administration.

A comparative study examined the incidence of adverse events among 773 adults aged 18 to 70 years who were vaccinated with either Twinrix or with the individual HAV and HBV vaccines (administered concurrently in opposite arms). A dverse events reported following each administration are reported in Table 5. The incidence of adverse events with the combination vaccine was similar to the event rates for the monovalent vaccines for all adverse events, and did not increase with successive vaccinations.

**Vaccination Safety Concerns**

**HIV/AIDS**

Because the original HBV vaccine was manufactured using human plasma, some clinicians raised concerns that vaccination could potentially lead to HIV infection. No cases of HIV infection from HBV vaccination have ever been confirmed. Vaccines currently in use are manufactured using cell culture techniques that do not rely on human blood products, and there is no risk of HIV infection with these vaccines.

**Thimerosal and Mercury**

The preservative thimerosal has long been used to prevent bacterial and fungal contamination of vaccines, including HBV vaccines. In recent years, there has been growing public concern about the possibility of mercury exposure as a result of vaccines containing thimerosal (which is composed largely of mercury). Reports in the popular press and

| Table 5. Rate of Adverse Events Reported After Administration of Twinrix or Engerix-B and Havrix |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Adverse Event | Twinrix Dose 1 | Dose 2 | Dose 3 | Engerix-B Dose 1 | Dose 2 | Dose 3 | Havrix Dose 1 | Dose 2 |
| Soreness | (N =385) | % | % | (N =382) | % | % | (N =376) | % | % |
| Local | 37 | 35 | 41 | 41 | 25 | 30 | 47 | 53 | 47 |
| Redness | 8 | 9 | 11 | 6 | 7 | 9 | 7 | 9 |
| Swelling | 4 | 4 | 6 | 3 | 5 | 5 | 5 | 5 |
| General | (N =385) | % | % | (N =382) | % | % | (N =376) | % | % |
| Headache | 22 | 15 | 13 | 19 | 12 | 14 | 14 | 9 | 10 |
| Fatigue | 14 | 13 | 11 | 14 | 9 | 10 | 5 | 3 | 3 |
| Diarrhea | 5 | 4 | 6 | 5 | 3 | 3 | 7 | 3 | 5 |
| Nausea | 4 | 3 | 2 | 4 | 2 | 4 | 1 | 1 | 1 |
| Fever | 4 | 3 | 2 | 4 | 2 | 4 | 1 | 1 | 1 |
| Vomiting | 1 | 1 | 0 | 1 | 1 | 1 |

from anti-vaccine advocacy groups have highlighted concerns about the risk of neurodevelopmental disorders, including autism or attention deficit/hyperactivity disorder (A D H D), among children who were vaccinated with thimerosal-containing vaccines. At the request of the CDC, the Institute of Medicine (IOM) of the National Academy of Sciences conducted a detailed assessment of the association between thimerosal use and mercury exposure. The IOM report found that, although the association between thimerosal exposure and neurodevelopmental disorders was biologically plausible, the available evidence did not support the hypothesis that children who receive thimerosal-containing vaccines are at increased risk. The report noted the following:

- Low-dose thimerosal has not been shown to affect functioning of the nervous system
- Although it is true that prenatal exposure to methylmercury (the form of mercury released by thimerosal) has been shown to increase the risk of developmental disorders, no such association has been observed with postnatal exposure
- Thimerosal exposure via vaccines has not been shown to produce toxic levels of mercury
- Autism is thought to be the result of a prenatal, not postnatal, developmental disorder

No published epidemiologic studies have assessed the relationship between thimerosal and neurodevelopmental disorders. Unpublished data reviewed by the IOM were inconclusive.

A temporary response to the concerns about thimerosal, several professional societies, including the AAFP, recommended that the first vaccine dose be administered at age 2 to 6 months for infants born to HBsAg-negative mothers. Both hepatitis B vaccines marketed in the United States are now available without thimerosal, and the AAFP and the Public Health Service again recommend that HBV vaccination be performed at birth.

Multiple Sclerosis or Other Demyelinating Disorders

Isolated reports have described cases of demyelinating syndromes (eg, multiple sclerosis, Guillian-Barré syndrome) among individuals who have received HAV vaccination. However, analyses of data from millions of patients in the United States, Europe, and Asia have found that the likelihood of these syndromes among vaccinees is no higher than the incidence among the general population. For example, the incidence of Guillian-Barré disease among adults treated with HAV vaccines was 0.2 cases per 100,000 person-years, and estimates of the natural rate of Guillian-Barré suggest an incidence of 0.5 to 2.4 cases per 100,000 person-years.

Other early isolated case reports suggested that the HBV vaccine might have been associated with an increased risk of demyelinating disorders. However, as with HAV vaccine, there is no evidence that the rate of these disorders is any greater among patients who are vaccinated than among the population in general. A second large case-control study compared the likelihood of previous HBV vaccination between 190 nurses with multiple sclerosis and 534 healthy control nurses. The investigators found that the proportion of subjects who had been vaccinated for HBV was similar for healthy nurses and nurses with multiple sclerosis (84% of patients with multiple sclerosis and 87% of controls had received the three-dose series). A large study examined the relationship between vaccination and demyelinating disorders in more than 130,000 members of a Health Maintenance Organization in the United States (27,000 vaccinated subjects and 107,000 nonvaccinated subjects matched on the basis of age and sex). No significant differences were found between vaccinated and unvaccinated individuals in the incidence of demyelinating disorders over a three-year period following vaccination. For patients in the youngest age group (0 to 14 years), the trend was toward a lower incidence of demyelinating disorders with vaccination, with rates of 3.8 per 100,000 in the vaccinated group and 9.5 per 100,000 in the unvaccinated group, although this difference was not statistically significant. Several health organizations, including the World Health Organization, have concluded that HBV vaccination does not increase the risk of central nervous system demyelinating disorders.

Patient Education

With the growth of the Internet and the increasing activity of anti-vaccine groups, it is more important than ever that family physicians are prepared to discuss the risks and benefits of vaccination with their patients. Patients often have questions or concerns about vaccination safety. Whether from reports in the news media, from Internet sites, or from anti-vaccination advocacy groups, many patients may be unsure of vaccine safety and may require reassurance about the need for vaccination, especially of small children. Patients often have erroneous beliefs about vaccines, such as the belief that vaccination weakens a child’s immune system. Some parents may not wish to accept any risk of vaccine-related side effects. The fact that vaccination programs have generally been so successful at reducing the rates of many diseases has led many to believe that universal vaccination is not necessary. For these reasons, parents may require additional education to understand that failing to vaccinate significantly increases their child’s risk of a serious illness and also contributes to a public health risk for everyone. The CDC provides an information resource for healthcare professionals that describes several common misconceptions patients have about vaccination, with accurate and effective materials to help educate patients about the benefits of vaccination. This booklet may be obtained via the Internet at www.cdc.gov/nip/publications/6mishome.htm.
A number of office-based strategies can be implemented that also may increase the rate of vaccination:

• Assign administration of vaccines and obtaining vaccination history to nursing staff when taking vital signs
• Obtain a vaccination history when taking vital signs
• Develop standing orders for vaccination, rather than writing orders for each patient individually
• Provide pamphlets and displaying posters on vaccination in patient waiting areas
• Identify patients who need vaccination, using computer billing records—identify characteristics such as patient age, high-risk medical conditions, and vaccination history, and place vaccination reminders in patient charts
• Advise patients to obtain vaccination
• Formulate a specific vaccination goal for the medical office or clinic
• Provide feedback to individual physicians about vaccination rates among their patients

The CDC has also produced several resources for patients, many of which may be obtained via the Internet. These include patient fact sheets about hepatitis A and B, as well as “Frequently Asked Questions” sheets that provide more detail on viral hepatitis, risk groups, vaccination, and treatment. The CDC also requires that Vaccine Information Sheets be provided to all patients (or the patient’s parent or legal guardian, in the case of childhood vaccinations) before each vaccine dose. Vaccine Information Sheets are available directly from the CDC, or they may be obtained in several different languages from the Immunization Action Coalition at www.immunize.org.

Considering that sexual transmission remains a common source of transmission for both HAV and HBV in the United States, adopting risk-counseling approaches that are commonly used in sexually transmitted disease education may be helpful. Several strategies have been suggested for risk-factor reduction for STDs, including HBV infection, in family practice:

• Individualize information about hepatitis to the patient’s stage of development and their understanding of sexual issues
• Communicate with respect and compassion in a non-judgmental way
• Address misconceptions about the patient’s degree of risk, especially in adolescents and young adults
• Adopt systematic but non-intensive counseling, taking advantage of opportunities such as physical examinations or contraceptive refills
• Educate and counsel about condom information, especially if the patient or a sexual partner is infected with HBV or their infection status is unknown
• Suggest abstinence as the only method to completely reduce the risk of viral infection; emphasize the importance of abstinence if the patient or a partner is receiving treatment for a STD

Another important tool in risk factor counseling is the use of patient intake forms. Patients are often asked to fill out detailed history questionnaires in the physician’s office, but their responses to the questionnaires are frequently never reviewed or used to develop a risk assessment. Patient history questionnaires should include questions about potential risk factors for HAV and HBV infection. These questionnaires should be updated periodically (yearly, for example), and the patient’s responses to questions about risk factors should be reviewed during office visits.

Conclusion

CDC guidelines for the prevention of HAV and HBV emphasize the need for childhood vaccination. In the case of HAV, children rarely exhibit significant symptoms but shed the virus for long periods of time, thereby increasing the likelihood of transmitting infection to other children or to susceptible adults. With HBV, nearly all cases of chronic infection follow HBV exposure at the time of birth or shortly thereafter. For this reason, the CDC, the AAFP, and the AAP recommend routine HBV vaccination for all children, with the first dose administered soon after birth and before hospital discharge. Certain adult populations are at particularly high risk of HAV or HBV infection. Identifying these persons, along with vaccination or risk factor modification can significantly reduce the likelihood of infection and severe liver disease.
Hepatitis A

Hepatitis A is a disease in your liver that is caused by a virus. There are many kinds of hepatitis caused by different kinds of viruses. The virus lives in your liver cells and uses the cells to make more of the virus. Different kinds of hepatitis are spread from one person to another in different ways.

Hepatitis A virus is a serious liver infection and is found in the stool of people with hepatitis A. The illness usually lasts a few weeks with your liver returning to normal in about 2 months. Hepatitis A is usually spread from person to person by close personal contact or by putting something in your mouth that is contaminated with the stool of a person with hepatitis A. Some ways hepatitis A can be spread are:

- Living with an infected person
- Having sex with an infected person
- Eating food or drinking water that has the virus in it
- Touching surfaces with the virus on them and placing your hands near or in your mouth

The disease is contagious before you see any symptoms. Some people with hepatitis A do not have any symptoms. If you do have symptoms, they might be:

- Low-grade fever
- Nausea
- Diarrhea
- Abdominal (stomach) pain
- Decreased appetite
- Fatigue (feeling very tired)
- Dark urine or light stools
- Yellow eyes or skin (jaundice)

The best way to not get the hepatitis A virus is to get a shot (vaccination). The shot is very effective. Also, because hepatitis A is spread by close contact with an infected person, you should always practice good personal cleanliness, especially by washing your hands often.

Hepatitis B

There is no cure for hepatitis B, but there are ways your doctor can treat it. Hepatitis B is found in many body fluids of infected people and is spread most commonly by infected blood, blood products and semen. You can get the virus through contact with blood of a person who has the disease or through contact with other body fluids like semen and vaginal fluids. Many people are infected with hepatitis B but never have any symptoms. If you do have symptoms they might be:

- Fatigue (feeling very tired)
- Mild fever
- Muscle and joint pain
- Nausea
- Vomiting
- Loss of appetite
- Mild stomach pain
- Yellow skin or eyes (jaundice)

Many people are at risk for getting the hepatitis B virus. You should talk to your doctor about it if you are having sex with multiple partners, if your job involves contact with human blood or body fluids, if you inject drugs, or if you plan to travel to another country.

There is a shot (vaccine) that protects you from getting hepatitis B. The shot is given to you in the muscle of your arm in 3 separate shots. You will get your first shot when you and your doctor think it is best, your second shot will be 1 month later and the third shot will be 6 months after the first one.

Another way to avoid getting hepatitis B is to avoid doing things that put you at risk. For example:

- Practice safe sex—use condoms every time
- Don’t shoot illegal drugs
- Don’t share personal care items (razors, toothbrushes, nail clippers)