

An Evidence-based Practical Guide to Vaccination for Hepatitis B Virus

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Abstract: The hepatitis B virus (HBV) is highly infectious, with over 292 million chronically infected people worldwide and up to 2.4 million in the United States. Following infection, clinically silent liver damage can ensue, but symptoms or signs of advanced disease, including cirrhosis and hepatocellular carcinoma, can take decades to emerge. HBV has the heaviest public health burden of all hepatitis viruses and has now surpassed other major communicable diseases (eg, HIV, diarrheal disease, malaria, tuberculosis) as a leading cause of death globally. Preventing transmission is essential,

and efforts are in place to reinforce screening, vaccination, and routine follow-up. Three safe and effective vaccines are available in the United States and other countries for HBV prevention, and the benefits of vaccination in preventing infection and its sequelae have been substantiated. For the first time in over 25 years, a new Food and Drug Administration-approved vaccine is available that offers a high degree of immunogenicity after 2, rather than 3, injections. Persistent challenges include the underutilization of vaccination, choice of vaccine, incomplete vaccinations, varying needs in different populations, management of nonresponders or those with undocumented or incompletely documented vaccination courses, and questions about whether and when booster injections may be needed. A panel of US academic hepatologists with expertise and experience in preventing and managing HBV infection have collaborated to write this practical clinical paper intended to guide clinicians in vaccinating for HBV and address questions that regularly arise in the clinic.

Key Words: hepatitis B, vaccine, seroprotection, boosters, non-responders, immunosuppression, diabetes, renal failure, HIV

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Chronic infection with hepatitis B virus (HBV) is characterized by persistent expression of hepatitis B surface antigen (HBsAg) and affects ~292 million people worldwide.¹ The global burden of HBV is greatest in the African, Western Pacific, and Southeast Asian regions.^{1,2} US estimations, based on National Health and Nutrition Examination Survey (NHANES) data, approximate that 850,000 persons live with HBV,³ but immigration and census data indicate that the total may be as high as 2.4 million.^{2,4-7} Although it is difficult to get accurate US estimates of HBV prevalence in foreign-born persons, data from 1974 to 2008 indicate that these individuals account for almost all (~95%) newly reported HBV infections and 4.6% of chronic HBV infections.⁸ The majority of foreign-born individuals in the United States with HBV are Asians/Pacific Islanders and persons born in sub-Saharan Africa.⁴ The incidence of acute HBV, with its attendant risk of morbidity and even mortality, has decreased in recent years, but the 2018 Centers for Disease Control and Prevention (CDC) still estimated 21,600 cases.⁹ Rising new cases are, in part, a consequence of the growing injection-drug use epidemic.¹⁰

HBV is highly infectious and is usually transmitted by perinatal, percutaneous, sexual exposure, or close person-to-person contact (eg, open cuts and sores). Persons with chronic infection (ie, those with persistent HBsAg in the serum for at least 6 mo following acute infection) serve as the main reservoir for HBV transmission.¹¹ In endemic countries in Asia and the Pacific Islands, perinatal transmission remains the predominant cause of HBV, whereas

horizontal transmission is dominant in sub-Saharan Africa.¹² Following perinatal infection, an immune-tolerant phase frequently develops with high viral levels but minimal to no liver inflammation. The transition to the immune-active phase in late childhood or adulthood results in chronic hepatitis and hepatic fibrosis,¹³ which can progress to cirrhosis. Hepatocellular carcinoma (HCC) may develop in 10% to 25% of people with chronic hepatitis B infection,¹⁴ with a higher risk in those with cirrhosis, but may occur in the absence of any fibrosis. The most recent estimates from the World Health Organization (WHO) attributed almost 1 million global deaths to HBV in 2015, largely from cirrhosis and HCC.¹⁵

Despite nearly 40 years of safe and effective vaccines, HBV transmission continues to occur on a widespread scale, with marked disparities in the rates of universal HBV infant vaccination birth dose among countries.¹⁵ Even in highly developed countries, the need to screen for and administer vaccinations against HBV infection in patients at increased risk for harboring infection or becoming infected is under-recognized. Vaccination guidelines and recommendations have long been published, but clinicians often have questions about how and when to vaccinate patients in many clinical situations. The purpose of this work is to update readers on the appropriate use of available HBV vaccines, including a recently licensed vaccine with a simplified dosing

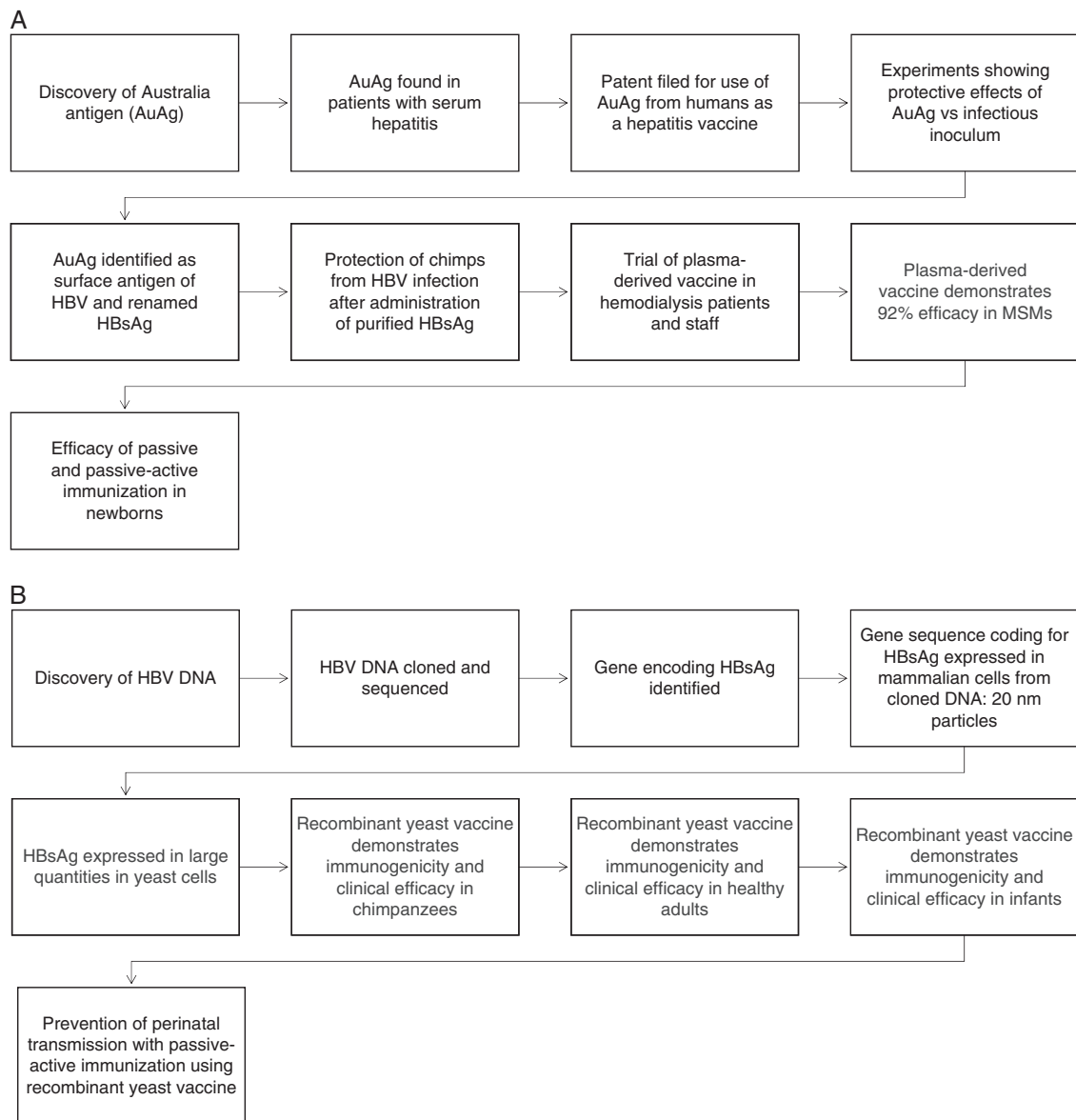


FIGURE 1. A¹⁶⁻⁴³ and B, The history of hepatitis B vaccines. A, Key events in the development of plasma-derived hepatitis B vaccine. B, Key events in the development of recombinant hepatitis B vaccine. AuAg indicates Australia antigen; HBV, hepatitis B virus; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; MSMs, men who have sex with men.

regimen and robust immunogenicity. We focus on individualized management in different populations, including people whose detectable hepatitis B surface antibodies (anti-HBs) have become undetectable years after vaccination. In addition, we discuss the related topic of “booster” injections and individuals with uncertain vaccination histories. We discuss the vaccination of nonresponders and the approach to groups of persons with differential rates of response to vaccination or enhanced vulnerability to HBV-induced liver disease, including those with other nonhepatitis B liver diseases.

THE HISTORY, EFFICACY, AND SAFETY OF FDA-APPROVED HBV VACCINES

The development of HBV vaccines was one of the great triumphs of global public health in the second half of the 20th century. Figure 1A^{16–27} outlines key events, from the historic discovery of the “Australia antigen” by Blumberg and colleagues in 1964 to the development of a plasma-derived vaccine and its approval in the early 1980s. The advent of plasma-derived vaccines coincided with the HIV epidemic and, despite their ultimately demonstrated safety, impacted acceptance. Figure 1B^{28–42} depicts the events starting with the establishment of a foundation for a recombinant vaccine with the cloning and sequencing of HBV DNA.^{29–31} Subsequent laboratory and clinical investigations led to the development and approval of the first 2 recombinant hepatitis B vaccines in 1986 and 1989, respectively. Routine immunization of infants was implemented in the United States in 1991. Two recombinant vaccines, Recombivax (Merck) and Engerix-B (GSK), both produced from yeast cells and given in identical schedules at 0, 1, and 6 months at doses of 10 or 20 µg per dose in adults, respectively, have been the mainstay of HBV immunization in the United States for over 30 years. Accelerated regimens entailing administration at 0, 1, 2, and 12 months may also be given. Both vaccines are approved for use in patients from birth through adulthood and in people on dialysis.^{41,42}

A consistent finding with both recombinant 3-dose vaccines has been lower overall response rates and peak antibody levels in older age groups. Seroprotection rates (SPRs), defined by anti-HBs levels higher than 10 mIU/mL 1 month after the third dose, are reported in the package inserts as 99% in infants, 98% to 99% in young adults 20 to 29 years of age, and 88% to 89% in persons older than 40 years (Table 1).^{41,42,44} A meta-analysis showed that males have lower response rates than females, as do persons who suffer from obesity, cirrhosis, inflammatory bowel disease, and immunosuppression, and those who smoke cigarettes.⁴⁵

Two-dose Vaccine

In 2018, a 2-dose vaccine designated as Heplisav-B [formerly HBsAg-108 (Dynavax)], was introduced. Distinctive to this vaccine is the combination of 20 µg recombinant HBsAg with a toll-like receptor 9 agonist adjuvant, consisting of 3000 µg of a synthetic phosphothioate oligodeoxynucleotide termed 1018 (the adjuvant in Engerix-B is 500 µg of aluminum). The rationale for the toll-like receptor 9 agonist is to stimulate plasmacytoid dendritic cells and B cells to augment both humoral and cellular immune responses to the vaccine. The vaccine is administered intramuscularly at 0 and 1 month of age. Heplisav-B is approved for use in adults 18 years of age or older.⁴⁴

Two randomized trials of a 2-dose regimen of Heplisav-B versus Engerix-B in 3 doses at 0, 1, and 6 months were conducted, 1 in persons 18 to 55 years of age and the other in persons 40 to 70 years of age. The primary endpoint was SPR ≥ 10 mIU/mL 8 weeks after dose 2 for Heplisav-B and 4 weeks after dose 3 for Engerix-B. Table 2^{46–50} summarizes the data from these trials, indicating that in both trials, SPRs were higher with Heplisav-B, and the geometric mean titers (GMT) of anti-HBs postvaccination were comparable or higher.^{46,47}

Other studies of Heplisav summarized in Table 2 include a comparison of Heplisav-B with Engerix-B in over 8000 subjects 18 to 70 years of age. SPRs in 961 patients with diabetes, the primary endpoint, were higher in both that group and the overall patient population. A trial of Heplisav-B versus Engerix-B evaluated 3 doses of Heplisav-B (0, 4, and 24 wk) versus 4 double-doses of Engerix-B (0, 4, 8, and 24 wk) in patients with chronic kidney disease (CKD), showing higher SPRs at 52 weeks with Heplisav.⁴⁹ Finally, in a study of over 10,000 adults designed to evaluate adherence, 45% of adults who initiated the 2-dose vaccine (Heplisav-B), compared with 26% of those who initiated the 3-dose vaccine (Engerix-B), completed the series.⁵⁰ While these rates are likely substantially lower than in many other settings, Heplisav may improve compliance over a 3-dose regimen in patients in whom compliance is a potential concern. However, the suboptimal adherence rates with even the 2-dose vaccine in this study underscore the “real-world” challenge facing clinicians of adherence to HBV vaccine completion.

A Triple Antigen Vaccine

The most recently introduced hepatitis B vaccine is derived from mammalian cells and contains pre-S1, pre-S2, and S-surface antigens (Sci-B-Vac, VBI Vaccines, Rehovot, Israel). A recently published phase 3 trial comparing this vaccine dosed at 10 µg on days 0, 28, and 168 with 3 doses of 20 µg of Engerix-B in 1607 subjects yielded SPR at a 28-day follow-up in 91.4% and 76.5%, respectively, in the overall study population of ages 18 and up, and 89.4% versus 73.1% in those 45 years and older.⁵¹ The study showed noninferiority of the 3-dose regimen, but it did not meet the secondary noninferiority efficacy endpoint for 2 doses of Sci-B-Vac (at day 168) compared with 3 doses of Engerix-B (at day 196) in all subjects aged 18 years and older.⁵² Higher rates of mild or moderate injection site pain, tenderness, and myalgia were observed in the trivalent vaccine recipients no other safety profile differences were noted.⁵¹ On the basis of this and a second phase 3 pivotal trial,⁵³ this vaccine was initially approved in Israel in 2020 and subsequently in the United States as PreHevbrio on December 1, 2021.⁵⁴

Vaccine Safety

The Advisory Committee for Immunization Practice (ACIP) compared pooled data from almost 9871 patients who had received 2 or 3 doses of Heplisav-B to 4385 patients who had received 3 or 4 doses of Engerix-B. Mild adverse events, serious adverse events, and cardiovascular events were experienced in 45.6%, 5.4%, and 0.27%, respectively, of patients who had received Heplisav-B, and in 45.7%, 6.3%, and 0.14%, respectively, of patients who had received Engerix-B. All events were deemed grade 1.⁴

The Heplisav-B package insert reported common adverse events, such as injection-site pain, fatigue, and headache.⁴⁴ The Engerix-B package insert reported similar mild events of injection-site soreness and fatigue.⁴² A systematic review examining 30 years of safety data on

TABLE 1. Recombinant Hepatitis B Vaccines

| | Recombivax HB⁴¹ | Engerix-B⁴² | Heplisav-B⁴⁴ |
|--|--|--|--|
| Dosing | 3-dose regimen Persons from birth through 19 y: 3 doses (0.5 mL each) given on a 0-, 1-, 6-mo schedule Adolescents 11-15 y: either 3 doses (0.5 mL each) given on a 0-, 1-, 6-mo schedule or 2 doses (1.0 mL) on a 0- and 4-6-mo schedule) Persons 20 y and older: 3 doses (1.0 mL each) given on a 0-, 1-, 6-month schedule Recombivax HB dialysis formulation: adults undergoing pre-dialysis or dialysis: 3 doses (1.0 mL each) given on a 0-, 1-, 6-month schedule | 3-dose regimen Persons from birth through 19 y: 3 doses (0.5 mL each) on a 0-, 1-, 6-mo schedule Persons 20 y and older: 3 doses (1 mL each) on a 0-, 1-, 6-mo schedule Adults undergoing hemodialysis: 4 doses (2 mL each) as a single 2-mL dose or as two 1-mL doses on a 0-, 1-, 2-, 6-mo schedule | 2-dose regimen Adults 18 y of age and older: 0.5 mL IM at 0 and 1 mo |
| Dosage forms and strengths | 0.5 mL (5 mcg) pediatric/adolescent formulation: single-dose vials and prefilled syringes 1 mL (10 mcg) adult formulation: single-dose vials and prefilled syringes Dialysis formulation: 1 mL (40 mcg) single-dose vials | 0.5-mL (10 mcg) prefilled syringes 1-mL (20 mcg) single-dose vials and prefilled syringes | A single dose is 0.5 mL |
| Immunogenicity in children and adults* | Following a 3-dose regimen, SPR was achieved in: Infants: 100% Children: 99% Adolescents: 99% Adults 20-29 y: 98% Adults 30-39 y: 94% Adults ≥ 40 y: 89% | Among infants administered the 3-mo schedule, 100% of evaluable patients (n = 52) seroconverted by month 7, and 97% had seroprotective levels (≥ 10 mIU/mL). 6 mo through 10 y: 1-2 mo after third dose, 98% 11-19 y: 97%-99% 16-65 y: 96% at month 7 (1 mo after third dose) > 40 y: 88% at month 7 | Following a 2-dose regimen, SPR was achieved in: 18-64 y: 96% 65-70 y: 90% |

*Results not stratified by predialysis or hemodialysis status.
IM indicates intramuscular; SPR, seroprotection rate.

Engerix-B found that the most common adverse events were injection site reactions (local) and fatigue, headache, fever, and gastrointestinal events (systemic). Of the 58 serious adverse events reported, only 1 (reactive airway disease) was deemed to be related to vaccine use.⁵⁵ Evidence indicates a causal relationship between HBV vaccines and anaphylaxis in yeast-sensitive persons; thus, all 3 vaccines were contraindicated in these patients.⁴

The cardiovascular safety of HBV vaccinations has come into question. A registration study of over 8000 patients comparing Heplisav-B to Engerix-B monitored serious adverse events for 13 months after the first dose of vaccine.⁴⁸ Acute myocardial infarction was reported in 0.25% (n = 14) of Heplisav-B recipients and in 0.04% (n = 1) of Engerix-B recipients, a difference not noted in the other 2 registration studies^{46,47,56} or in the 961 diabetic patients who were the primary focus in the 1 study that did show an arithmetic increase in myocardial infarction in the overall study population.⁵⁶ All of these subjects had 1 or more baseline risk factors for cardiovascular disease. The rate of myocardial infarction was no higher than expected in this study and was lower than expected in the Engerix-B group.⁵⁶ Overall, the evidence does not support a causal relationship between Heplisav-B administration and acute myocardial infarction.⁴⁴ The lack of a boxed warning in the label suggests that the Food and Drug Administration does not perceive increased cardiac risk with any HBV vaccine.⁴⁴ Concerns in the lay press about potential increased risk of autism or Guillain-Barré

syndrome with regard to vaccines have never been substantiated.⁵⁷ In a large study conducted in Alaska, no evidence that HBV vaccines result in an increased incidence of Guillain-Barré syndrome was found.⁵⁸ In accordance with available data and recommendations, this panel feels that safety should not be an issue when administering any of the 3 approved HBV vaccines.

GLOBAL STATUS OF HBV VACCINATION: POLICIES, IMPLEMENTATION, AND DEMONSTRATED IMPACT ON OUTCOMES

Deaths from viral hepatitis increased from 0.89 million in 1990 to 1.45 million in 2013. During this same period, viral hepatitis moved from the tenth to the seventh leading cause of global deaths, while other major communicable diseases (eg, diarrheal disease, malaria, tuberculosis) improved in ranking.⁵⁹ Across the globe, action is required to eliminate HBV. There are 10 genotypes in the world (A through J), and evidence shows that the vaccine protects against all 10 genotypes. Despite the fact that mutants have appeared and there have been a few cases of infection that have resulted in disease, the public health impact of HBsAg escape mutants is negligible.

The benefits of HBV vaccination have been demonstrated most profoundly in studies in Asia and Alaska. The results of population-wide immunization programs, especially in infants and children, have documented decreases in

TABLE 2. Summary of Data Comparing Heplisav-B to Engerix-B

| References | Design | Results |
|-------------------------------|---|--|
| Halperin et al ⁴⁶ | 2-dose regimen of Heplisav-B vs. 3-dose regimen of Engerix-B in persons 18-55 y The primary endpoint was SPR \geq 10 mIU/mL 8 wk after dose 2 for Heplisav-B and 4 wk after dose 3 for Engerix-B | In the 2415 participants, the primary endpoint was met in 95% of patients administered Heplisav-B and 81% of patients administered Engerix-B GMT of anti-HBs were not significantly different at week 28 |
| Heyward et al ⁴⁷ | 2-dose regimen of Heplisav-B-B vs. 3-dose regimen of Engerix-B in persons 40-70 y The primary endpoint was SPR \geq 10 mIU/mL 8 wk after the last dose of either vaccine | Primary endpoint (through week 52) was met in 90% of patients administered Heplisav-B-B and 70.5% of patients administered Engerix-B |
| Jackson et al ⁴⁸ | 2-dose regimen of Heplisav-B vs. 3-dose regimen of Engerix-B in persons 18-70 y | Among the 8374 randomized participants, 961 participants in the per-protocol population had type 2 diabetes mellitus. In the diabetes participants, the SPR in the Heplisav-B group at week 28 was 90.0%, compared with 65.1% in the Engerix-B group—a difference of 24.9% (95% CI: 19.3%-30.7%) |
| Janssen et al ⁴⁹ | 3 single doses of Heplisav-B at 0, 4, and 24 wk vs. 4 double-doses of Engerix-B given at 0, 4, 8, and 24 wk (for a total of 8 injections) were administered in patients with CKD | Among the 467 participants in the modified ITT population, at the primary endpoint at week 28, the SPR (anti-HBs \geq 10 mIU/mL) in the Heplisav-B group (89.9%) met the criteria for noninferiority and superiority to the SPR in the Engerix-B group (81.8%) |
| Bruxvoort et al ⁵⁰ | To assess whether recipients of a 2-dose Heplisav-B are more likely to complete their series compared with recipients of a 3-dose vaccine with Engerix-B | 4727 individuals initiated the Heplisav-B vaccine series, and 6161 individuals initiated the Engerix-B vaccine series 45% of adults who initiated the 2-dose vaccine (Heplisav-B) vs. 26% of those who initiated the 3-dose vaccine (Engerix-B) completed the series, indicating potentially better adherence with a shorter series |

CI indicates confidence interval; CKD, chronic kidney disease; GMT, geometric mean titers; ITT, intent-to-treat; SPR, seroprotection rates.

HBsAg prevalence, cases of acute hepatitis B, cases of chronic hepatitis B, and, importantly, HCC, including in children. Key studies demonstrating the impact of vaccination on these outcomes are outlined in Table 3.⁶⁰⁻⁶⁷

Global efforts to control the public health threat of HBV have been in place for 30 years, with the most recent goal enunciated by the WHO being “elimination” by 2030 (defined as a 90% reduction in incidence and a 65% reduction in mortality compared with the 2015 baseline).⁶⁸ All 194 member states of the WHO have committed to this endeavor, which can be achieved through what is described as “5 synergistic prevention and treatment interventions”: (1) immunization, (2) prevention of mother-to-child transmission of HBV, (3) blood and injection safety by including adoption of universal birth dose, (4) prevention of transmission among persons who inject drugs through harm reduction services and HBV vaccination, and (5) testing and treatment.⁶⁸ These important efforts are not without challenges. The CDC recommends screening for persons born in geographic regions with an HBsAg prevalence $>$ 2% (Table 4),⁴ but in reality, this applies to many developing nations.⁶⁹ Worldwide, access to affordable HBV testing is limited; as such, the WHO estimates that only 9% of HBV-infected persons (22 million) are diagnosed, and of those, only 8% (1.7 million) receive treatment.⁶⁰ To prevent vertical transmission, all pregnant women should also be tested for HBV (Table 4),⁴ but this is not routine in most countries, including some that are considered high income.¹⁵

The benefits of widespread HBV immunization have led to efforts to scale up global HBV vaccinations in all populations. These efforts have been successful, with 85% of children across the globe completing 3 doses of vaccination in 2019 compared with only 30% in 2000. HBV vaccination at birth is also advised. Although this occurs

in 43% of infants worldwide, the distribution is uneven (eg, 34% in the WHO Eastern Mediterranean Region, 6% in the WHO African Region).⁷⁰ Unfortunately, the birth dose of HBV vaccines is not included in the Global Alliance for Vaccine Initiative (GAVI) program, which supplies childhood vaccines at no cost to many countries with limited resources. An HBV vaccine is included in a pentavalent formulation, with the first dose given at 2 to 4 months of age. This means that perinatal transmission from an infected mother to her newborn is not prevented by the current schedule. Unless funders offer the HBV birth dose to all countries, the 2030 WHO HBV elimination goals for HBV vaccination are unlikely to be reached.

CURRENT RECOMMENDATIONS FOR HBV SCREENING AND VACCINATING IN THE UNITED STATES

In 2018, the ACIP and the CDC published updated recommendations regarding the prevention of HBV infection. Table 4 provides details on all these recommendations and highlights those that are new. Prevacination serological testing which consists of testing for HBsAg, anti-HBs, and antibodies to anti-HBc—is recommended to avoid the cost of vaccinating persons who are already immune,⁴ though no harm is done by vaccinating persons with any HBV serologic marker.

The 2018 update expanded the list of individuals recommended for HBV vaccinations to include those with chronic liver disease (CLD), as the development of chronic HBV infection might increase the risk of progressive liver disease. This list continued to expand (Table 4), and one or more of the criteria likely applied to the majority of the population. However, the need to simplify vaccination

TABLE 3. Global Benefits of HBV Vaccinations

| | |
|--------------------------------|---|
| Decrease in HBsAg prevalence | By the end of 2018, 189 countries had adopted the universal HBV vaccination program, which reduced the global prevalence of HbsAg in children younger than 5 y from 4.7% in the prevaccine era to 1.3% in 2015. ⁴³ China's HBV prevention policy has been evaluated through nationally representative serologic surveys. Compared with the 1992 prerecombinant vaccine survey, HbsAg prevalence declined 46% by 2006 and 52% by 2014. Among children younger than 5 y, the decline was 97%. ⁶¹ |
| Decline in acute HBV incidence | In Alaskan natives, mass universal newborn immunization with the HBV vaccine and mass population screening eliminated acute symptomatic HBV over 25 y. The incidence in persons younger than 20 y went from 19 cases per 100,000 persons in 1981-1982 to 0 cases in 100,000 persons in 1993-1994. No cases of acute HBV have occurred in children since 1992. ⁶² In individuals in Hong Kong, the reported number of acute HBV infections decreased steadily, from 250 cases in 1988 to 41 cases in 2014. This is likely due to concerted preventative efforts applied since the late 1980s (eg, community-based vaccination; public awareness programs and measures such as antiviral subsidies and specialist referrals for treatment; institution-based infection control to prevent occupational exposure; and methadone treatment programs for drug users to prevent infections of blood-borne pathogens). ⁶³ |
| Decline in chronic HBV | In individuals in Hong Kong, chronic HBV infections in new blood donors dropped from 8.0% in 1990 to 0.8% in 2014 (1.0% for males and 0.7% for females). This is attributed to the reasons listed above. ⁶³ |
| Decrease in HCC incidence | In the Alaskan study described above, the incidence of HCC in persons younger than 20 y decreased from 3 cases per 100,000 persons in 1984-1988 to 0 cases per 100,000 persons in 1995-1999. No cases of HCC have occurred in children since 1999. ⁶² In Taiwan, the HBV vaccination was launched in 1984. The incidence of HCC in boys born after 1984 significantly decreased compared with those born before 1978 (RR = 0.72; <i>P</i> = 0.002). No significant decrease was observed in girls, reaffirming HCC-associated male predominance. ⁶⁴ In 1509 Taiwanese patients, the HCC incidence per 10 ⁵ person-years was 0.92 in the unvaccinated cohort and 0.23 in the vaccinated birth cohorts. The RRs for HCC in patients 6-9 y, 10-14 y, 15-19 y, and 20-26 y who were vaccinated vs. unvaccinated were 0.26 (95% CI, 0.17-0.40), 0.34 (95% CI, 0.25-0.48), 0.37 (95% CI, 0.25-0.51), and 0.42 (95% CI, 0.32-0.56), respectively. ⁶⁵ |
| Longstanding immunity | Immunization of infants against HBV reduces their risk of developing HCC as children and young adults. ⁶⁵ Forty-four patients vaccinated with plasma-derived HBV vaccine in 1981 were longitudinally followed. Cellular immunity lasted 32 y, as 100% of the participants, regardless of their anti-HBs level, tested positive for TNF- α , IL-10, or IL-6 production by HBV surface antigen-specific T cells. The frequency of natural killer T cells correlated with the level of anti-HBs (<i>P</i> = 0.008). ⁶⁶ In 1981, 1578 Alaskan natives were immunized with the plasma-derived HBV vaccine. Thirty years later, $\geq 90\%$ of the participants had evidence of protection (anti-HBs levels ≥ 10 mIU/mL), 23 anti-HBc breakthrough infections occurred, none had clinically recognized acute hepatitis, and none had developed chronic HBV infection. ⁶⁷ |

CI indicates confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; RR, relative risk.

policy remained; universal vaccination would simplify vaccination practices and likely increase vaccination penetrance and improve public health. In an important recent development during the editorial review of this paper, on November 3, 2021 the ACIP voted unanimously to recommend universal vaccination against HBV in all persons aged 19 to 59, and of persons 60 and older if there are risk factors or if requested by the individual.⁷¹

CONSIDERATIONS IN PREGNANCY, THE NEONATAL PERIOD, AND PEDIATRIC POPULATIONS

Mother-to-child transmission remains an important mechanism of HBV infection, as patients who are infected at birth have up to a 90% risk of becoming chronic carriers.⁷² Children exposed to HBV after birth, as well as 30% to 50% of children infected before 6 years of age, develop chronic HBV. After the first 5 years of life, the rate of chronicity progressively drops to ~5% for those infected as adults.¹⁵ Table 4 highlights the latest CDC recommendations intended to optimize protection against HBV infection in infants.⁴ To prevent perinatal transmission, the CDC recommends that all pregnant women be tested for HBsAg (Table 4).⁴ Since HBV infections transmitted during the birth process have the greatest risk of resulting in

chronicity,⁷³ infants born to HBsAg-positive women require immunoprophylaxis, consisting of a first-dose HBV vaccine and hepatitis B immune globulin (HBIG) within 12 hours of birth, followed by completion of an HBV vaccine series. This approach has demonstrated 90% to 95% efficacy in preventing chronic HBV in infants.⁷⁴

The authors of this manuscript recommend triple-panel testing for HBsAg, anti-HBc, and anti-HBs for all pregnant women in whom there is no documentation that they previously received a full course of HBV vaccine. If the triple panel is negative, pregnant women should receive the Recombivax or Engerix-B HBV vaccine (Table 3). Heplisav-B administration in pregnant women cannot be recommended at this time due to limited safety data.⁴ For fully vaccinated pregnant women, HBsAg screening alone would be sufficient.

The CDC further recommends that HBsAg-positive pregnant women undergo quantitative testing for HBV DNA to guide the use of targeted third-trimester maternal antiviral therapy in addition to universal immunoprophylaxis for exposed newborns.⁴ We advise HBV testing at the earliest prenatal appointment for each pregnancy to allow for timely and necessary prophylaxis. The best results are correlated with the earliest time after birth that the vaccine is administered. If HBIG is unavailable, prompt vaccination still prevents a very high proportion of neonatal

TABLE 4. Updated CDC Recommendations for HBV Screening and Vaccination in the United States⁴

| | |
|-----------------------------------|---|
| Prevaccination serologic testing | <p>Persons recommended to receive serologic testing before vaccination*:</p> <ul style="list-style-type: none"> Household, sexual, or needle contacts of HbsAg+persons† HIV-positive persons† Persons with elevated ALT/AST of unknown etiology† Hemodialysis patients† MSMs† Past or current IDUs† Persons born in countries with high and intermediate HBV endemicity (HbsAg prevalence ≥ 2%) US-born persons not vaccinated as infants whose parents were born in countries with high HBV endemicity (≥ 8%) Persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or GI disorders Donors of blood, plasma, organs, tissues, or semen Household, sexual, or needle-sharing contacts of HbsAg-positive persons HIV-positive persons Persons with elevated ALT/AST of unknown etiology |
| HBV vaccination | <p>Persons recommended to receive HBV vaccination:</p> <ul style="list-style-type: none"> All infants within 24 h of birth for medically stable infants weighing ≥ 2000 g (NEW) Unvaccinated children younger than 19 y Persons at risk for infection by sexual exposure: <ul style="list-style-type: none"> Sex partners of HBsAg-positive persons Sexually active persons who are not in a long-term, mutually monogamous relationship (eg, persons with > 1 sex partner during the previous 6 mo) Persons seeking evaluation or treatment for a sexually transmitted infection MSMs Persons at risk for infection by percutaneous or mucosal exposure to blood: <ul style="list-style-type: none"> Current or recent IDUs Household contacts of HBsAg-positive persons Residents and staff of facilities for developmentally disabled persons Health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids Patients undergoing hemodialysis or predialysis, peritoneal dialysis, or home dialysis Persons with diabetes aged 19-59 y; persons with diabetes aged 60 y at the discretion of the treating clinician Others <ul style="list-style-type: none"> International travelers to countries with high or intermediate levels of endemic HBV infection (HBsAg prevalence of 0.2%) Persons with HCV infection Persons with CLD (including, but not limited to, persons with cirrhosis, NAFLD, ALD, hepatitis, and an ALT or AST level > 2X ULN) (NEW) Persons with HIV infection Incarcerated persons All other persons seeking protection from HBV infection |
| Postvaccination serologic testing | <p>Testing for anti-HBs after vaccination is recommended for the following persons:</p> <ul style="list-style-type: none"> Infants born to HBsAg-positive women and infants born to women whose HBsAg status remains unknown (eg, infants safely surrendered shortly after birth) (NEW) HCPs and public safety workers at risk of blood or body fluid exposure Hemodialysis patients (and other persons who might require outpatient hemodialysis), HIV-infected persons, and other immunocompromised persons (eg, hematopoietic stem-cell transplant recipients or persons receiving chemotherapy) Sex partners of HBsAg-positive persons |
| Pregnant women | <p>Testing</p> <ul style="list-style-type: none"> All HBsAg-positive pregnant women should be tested for HBV DNA to guide the use of maternal antiviral therapy during pregnancy for the prevention of perinatal HBV transmission (NEW) If not tested prenatally, those with clinical hepatitis and those whose behaviors place them at high risk for HBV infection‡ should be tested at the time of admission to the hospital or birthing facility for delivery <p>Vaccination</p> <ul style="list-style-type: none"> Vaccinate those identified as being at risk for HBV infection during pregnancy‡ |

*Serologic testing comprises testing for HBsAg, antibody to HBsAg, and antibody to HBcAg.

†Denotes persons also recommended for HBV vaccination. Serologic testing should occur prior to vaccination. Serologic testing should not be a barrier to vaccination for susceptible persons. The first dose of vaccine should typically be administered immediately after collection of blood for serologic testing.

‡For example, recent or current injection drug use, having had > 1 sex partner in the previous 6 months or an HBsAg-positive sex partner, having been evaluated or treated for a sexually transmitted infection.

ALD indicates alcoholic liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLD, chronic liver disease; GI, gastrointestinal; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCPs, healthcare professionals; HCV, hepatitis C virus; IDUs, injection drug users; MSMs, men who have sex with men; NAFLD, nonalcoholic fatty liver disease; ULN, upper limit of normal.

TABLE 5. HBV Vaccine (Recombivax HB or Engerix HB*) and HBIG Schedule for Newborns⁴

| Maternal HBsAg | Infant Birth Weight: ≥ 2000 g | Infant Birth Weight: < 2000 g |
|----------------|--|---|
| Positive | Ideally in the delivery room but at least within 12 h of birth: HBV vaccine and HBIG | Ideally in the delivery room but at least within 12 h of birth: HBV vaccine and HBIG Do not count birth dose as part of vaccine series |
| Unknown | Ideally in the delivery room but at least within 12 hours of birth: HBV vaccine† | Ideally in the delivery room but at least within 12 hours of birth: HBV vaccine and HBIG Do not count birth dose as part of vaccine series |
| Negative | Within 24 h of birth (NEW): HBV vaccine | At age 1 mo or hospital discharge: HBV vaccine |

*Maternal status should be determined as soon as possible, and if HBsAg-positive, the infant should receive HBIG as soon as possible but no later than 7 days of age.

†Heplisav-B is not approved for use in infants.

HBIG indicates hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

infections.^{75,76} A retrospective analysis examined the level of maternal HBV DNA below which transmission is rare in infants receiving HBV and HBIG vaccination at birth; a cutoff of 200,000 IU/m should be used, above which tenofovir-based antiviral therapy should be given at the beginning of the third trimester and for 4 to 6 weeks postpartum to infected mothers unless the mother meets the criteria for earlier chronic therapy.^{12,77}

For infants born to HBsAg-negative mothers, the CDC guidance has removed the permissive language for delaying the birth dose of vaccine until after hospital discharge and now recommends universal vaccination as soon as possible—but within 24 hours of birth for medically stable infants weighing 2000 g or more (Table 5).⁴ We recommend that vaccine prophylaxis be given in the delivery room to prevent delays in vaccination and to serve as a safety net to prevent HBV transmission for infants not identified due to errors in maternal HBsAg testing, transcription of results, or reporting. Vaccine response is lower among infants who weigh < 2000 g when administered within the first few days of life; in these cases, the first dose should be administered upon hospital discharge or at 1 month of age.⁴

For infants born to HBsAg-positive mothers, the response to the vaccine series requires evaluation via post-vaccination serologic testing (PVST), which consists of testing for HBsAg and anti-HBs. PVST should be conducted at 9 to 12 months of age or, if the initial series is delayed, 1 to 2 months after the final dose.⁴ Prompt PVST avoids unnecessary revaccinations, reduces the time that nonresponder infants are at risk for transmission from household contacts with HBV, enables prompt revaccination for those infants needing revaccination, and conserves public health resources involved in providing case management services. It is important to test within the 9- to 12-month window. Early PVST increases the chance of detecting anti-HBs from HBIG administered at birth and decreases the likelihood of detecting late HBV infection. Late PVST, on the other hand, often results in false negatives (< 10 mIU/mL), leading to unnecessary revaccinations.⁷⁸ Overall, anti-HBc testing of infants is not recommended because passively acquired maternal anti-HBc might be detected in infants born to HBsAg-positive mothers up to age 24 months. If PVST demonstrates non-response, single-dose revaccination is now recommended in this population. A new CDC recommendation is that, following a series of vaccinations and PVST in infants born to

HBsAg-positive mothers, HBsAg-negative infants with anti-HBs < 10 mIU/mL should be revaccinated with a single dose of vaccine. If PVST (1 to 2 mo later) still demonstrates anti-HBs < 10 mIU/mL, then 2 additional vaccinations are recommended with PVST 1 to 2 months after the final dose.⁴

PROTECTING AGAINST HBV IN SPECIAL POPULATIONS

Chronic HBV develops more frequently in immunosuppressed persons, including those with HIV infection, chronic renal failure, cirrhosis, diabetes, solid organ transplantation, and those on immunosuppressive medications. Unfortunately, immunocompromised patients are frequently nonresponders to traditional regimens with recombinant vaccines, and special considerations involving increased dosage and number of inoculations have been implemented (below and Table 6).

HIV

Viral hepatitis remains the most common cause of liver-related deaths in those infected with HIV.⁸¹ While this underscores the importance of HBV vaccinations in these patients, vaccine coverage is suboptimal ($< 60\%$ in the United States). The immune response to the traditional 20 μ g, 3-dose schedule has resulted in a lower frequency of SPR (34% to 88.6%) in HIV-infected individuals.^{4,82} Therefore, the CDC endorses the utilization of a 40 μ g, 3-dose regimen (at 0, 1, and 6 mo) of either recombinant vaccine (Table 6). It is clear that patients with undetectable or minimal HIV RNA and a preserved CD4⁺ cell count pre-vaccine are likelier to have a successful response to the higher dose (40 μ g) of vaccine. For example, in a randomized, double-blind study of 210 HIV-infected individuals, 60% of whom had CD4 counts ≥ 350 mm³, a 3-dose regimen of 20 or 40 μ g doses of recombinant vaccine was administered. A statistically significant higher seroconversion rate was associated with 40 μ g dosing when CD4 cell counts were ≥ 350 , or HIV RNA level was $< 10,000$ copies, but the higher dose made no difference in seroconversion rates in persons with CD4 counts below 350 or those with $> 10,000$ copies of HCV RNA.⁸³

For HIV-infected nonresponders to traditional recombinant vaccines, some experts advocate a second series of recombinant HBV vaccines, but current data suggest that responses are highly variable (40% to 70%).⁸⁴ Therefore, revaccination in nonresponders cannot be universally

recommended, but instead should be considered in individuals who have obtained good HIV infection control.

A measure that could potentially maximize the number of initial responders would be the use of a more immunogenic vaccine in the primary series (Table 6). In a small (n=64), single-centered study of a 2-dose regimen of Heplisav-B in HIV-infected patients, 81% seroconverted, with the nonresponders demonstrating lower average CD4 counts (273, nadir count 121) compared with the responders (680, nadir count 363).⁸⁵ Although preliminary, these data suggest that Heplisav-B may play a preferred role in HIV-infected patients. Studies are needed to address whether and in whom a third dose of this vaccine should be given, and whether initial failure to respond to recombinant vaccines is more optimally managed with a course of Heplisav-B.

CKD

CKD is associated with a reduced response to the HBV vaccine, potentially due to defects in the adaptive immune response and/or malnutrition.⁸⁶ Hemodialysis patients have demonstrated 50% to 70% response rates to HBV vaccinations, but only 40% maintain protective antibody levels 3 years postvaccination.^{86,87} Fortunately, over the last 20 years, infection control precautions and HBV vaccinations have resulted in 95% declines in new HBV cases in dialysis units.⁴

Table 6 details vaccination recommendations for CKD patients.^{80,88} Enderix-B is approved as a 40 µg, 4-dose regimen in hemodialysis patients, and Recombivax is approved as a 40 µg, 3-dose regimen in patients on predialysis or dialysis.^{41,42} Several clinical studies have demonstrated that patients with moderate CKD (serum creatinine <4 mg/dL) respond better to the HBV vaccine when compared with individuals who require dialysis⁸⁹; thus, vaccination should be given early in the course of progressive renal disease to maximize the likelihood of vaccine-induced immunity. This approach is particularly important if future renal transplantation is being considered.⁹⁰ For patients who are nonresponders to the initial vaccine series, a second series with either recombinant vaccine given as three doses of 40

µg/mL has a demonstrated response in 50% to 70% of hemodialysis patients and has been endorsed by the CDC.⁸⁰

Heplisav-B may deserve consideration as an alternative for hemodialysis patients in both the initial vaccination and the repeat vaccination whenever there is a failed response to an initial series (Table 6). In a study of 467 CKD patients that included hemodialysis-dependent individuals, a 3-dose 20 µg regimen of Heplisav-B was compared with a 4-dose 40 µg regimen of Enderix-B. The percentage of participants with anti-HBs ≥ 100 mIU/mL at week 28 was significantly higher with Heplisav-B (73.6% vs. 63.2%), and this trend continued through week 52, with higher geometric mean concentrations of anti-HBs in the Heplisav-B group.⁴⁹ In a recent open-label, single-arm study of Heplisav-B in 119 hemodialysis patients, the vaccine was delivered as a 4-dose 20-µg regimen (0, 4, 8, and 16 wk). This resulted in seroprotection in 89.3% of individuals, and the percentage of participants with anti-HBs ≥ 100 mIU/mL was 81.3%.⁷⁹

CLD

CLD patients, particularly those with cirrhosis, are at an increased risk of HBV complications; thus, HBV vaccinations are particularly important, as recently recommended by the CDC for all CLD patients.⁴ Recent data indicate that hepatitis B vaccination has been delivered to only 30% of patients with CLD in the United States. Response rates in patients with cirrhosis are suboptimal (38% to 53%), with variations depending on the vaccine regimen.^{91,92} According to 2014 and 2015 National Health Interview Survey data, compliance is also an issue (<30% completion of vaccine series in CLD patients).⁹³ In 1 retrospective study, 278 patients undergoing evaluation for liver transplantation received 4 doses of a recombinant vaccine (40 µg at 0, 1, 2, and 6 mo). Multivariate analysis demonstrated that a lower Model for End-Stage Liver Disease (MELD) score, absence of diabetes, and isolated anti-HBc status were associated with higher response rates. In the same study, 57 nonresponders were given a second identical series. Overall response occurred in 40% of patients, and the median anti-HBs level was 100 mIU/mL (range 11 to > 1000 mIU/mL).⁹⁴

TABLE 6. Vaccinating for HBV in Special Populations*

| Special Population | Consider the Following: |
|--------------------|---|
| HIV-infected | A 3-dose, 40 µg vaccination regimen ⁴ PVST 1–2 mo after completion of vaccine series Nonresponders are recommended to have a repeat series of traditional vaccines or Heplisav-B Failure to respond to a second series of injections warrants testing for HBsAg, but not additional vaccinations Consider vaccination with Heplisav-B for the primary series |
| CKD | Early vaccination is encouraged to optimize response 4-dose, 40 µg regimen of Enderix-B is approved for patients undergoing hemodialysis ⁴² 3-dose, 40 µg regimen of Recombivax is approved for patients undergoing predialysis or dialysis ⁴¹ Heplisav-B may be preferable in patients undergoing hemodialysis ^{49,79} PVST 1-2 mo after completion of vaccine series The CDC recommends annual testing and revaccination if anti-HBs <10 mIU/mL ⁸⁰ |
| CLD | PVST 12 mo after completion of vaccine series in persons with cirrhosis Consider vaccination with Heplisav-B |
| Diabetics | Vaccination is recommended for patients with diabetes aged 19-59 Patients with diabetes aged 60 y or older should be vaccinated at the discretion of the treating clinician based on potentially serious comorbid medical disorders PVST 1-2 mo after completion of vaccine series |

*All immunosuppressed populations should have routine anti-HBs quantification testing 1 to 2 months after completion of series. CDC indicates Centers for Disease Control and Prevention; CKD, chronic kidney disease; CLD, chronic liver disease; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; PVST, postvaccination serological testing.

Addressing the potential for increased immunogenicity of a hepatitis B vaccine in CLD patients, a retrospective study of 166 CLD patients, including 56 with cirrhosis (mean MELD score 10), demonstrated that a 2-dose regimen of Heplisav-B was almost 3 times likelier to achieve immunity (adjusted odds ratio: 2.74, 95% confidence interval: 1.31-5.71, $P=0.01$) than a 3-dose regimen of Engerix-B. A seroprotective level of anti-HBs occurred more frequently in the cirrhotic patients given Heplisav-B than in those given Engerix-B (45% vs. 26%), but the differences were not statistically significant.⁹⁵ In patients with cirrhosis, Heplisav-B may be an attractive alternative to either the initial or the second course of vaccination for patients with cirrhosis.

Liver Transplantation

The standard of care is to vaccinate all individuals who are awaiting liver transplantation to prevent de novo infection, which has been reported to occur in 1% to 3% of transplant recipients.⁹⁶ Unfortunately, attempts to successfully vaccinate all individuals before or after solid organ transplantation remain problematic due to low response rates and failure to complete vaccination in some instances.⁹²⁻⁹⁷ Studies of HBV vaccination after liver transplantation, on the other hand, have met with variable success despite the routine use of repeat vaccination employing 40 µg/mL.⁹⁸ This area warrants further study using a more immunogenic vaccine, such as Heplisav-B.

Another important issue related to HBV vaccination pertains to the use of allografts removed from donors who are anti-HBc positive. Recipients of these organs are currently given long-term antiviral therapy for HBV prophylaxis against de novo infection. A systematic analysis of anti-HBc-positive liver donation has shown that the frequency of de novo hepatitis B is strongly correlated with the recipient's HBV serologic status. In one systematic review, the frequency of de novo infection in 300 HBsAg-negative individuals, none of whom had been given antiviral prophylaxis, correlated with the serologic status of the recipients (1.4% when anti-HBs and anti-HBc were positive, 9.7% for anti-HBs alone, 13% for anti-HBc alone, and 48% for HBV naive).⁹⁹ These observations underscore the need for HBV screening and conscientious attention to vaccination of all HBV naive patients who grant permission to accept livers from anti-HBc-positive donors, with the only exception being persons who are reactive for both convalescent antibodies.

Diabetes

Patients with diabetes have impaired immunity due to the suppression of cytokine production, defects in phagocytosis, and dysfunction of immune cells.¹⁰⁰ Diabetic patients do not respond as well to vaccines as do nondiabetic immune-competent individuals. Moreover, HBV infection rates are 60% higher in patients with diabetes compared to those without diabetes, likely due to percutaneous exposure through the misuse of needlestick devices and insulin administration.¹⁰¹

The CDC recommends that diabetics between the ages of 19 and 59 receive HBV vaccinations (Table 6), whereas those over the age of 60 should be vaccinated at the discretion of the treating clinician.⁴ However, diabetics do not vigorously respond to traditional recombinant vaccines. In one study, the 2-dose regimen of Heplisav-B was compared with the 3-dose regimen of Engerix-B in 60- to 70-year-old diabetics. SPRs at week 28 were significantly higher (85.8% vs. 58.5%), and the GMT of the anti-HBs were higher with Heplisav-B.¹⁰²

Immunosuppression Due to Biologic Agent Therapy

The current version of the American Association for the Study of Liver Disease (AASLD) practice guidelines states that all patients on immunosuppressive medications should be screened for HBV.¹² Persons taking immunosuppressive drugs for chronic inflammatory disorders have suboptimal responses to the HBV vaccine, and may have impaired protection after exposure to HBV.¹⁰³ Studies are awaited as to whether higher doses of recombinant vaccines would prove more effective than standard dosing or whether Heplisav-B is safe and possibly more immunogenic in persons undergoing biologic agent therapy for underlying autoimmune-like illnesses.

ADDITIONAL CONSIDERATIONS IN HBV VACCINE USE

In 2016, the reported HBV vaccination coverage (≥ 3 doses) was 24.8% for adults 19 years or older, 32.9% for adults 19 to 49 years, and 15.9% for adults 50 years or older. Among adults 19 to 49 years, HBV vaccination coverage for Blacks (27.0%) and Hispanics (25.8%) was lower than that for Whites (36.2%).⁹ These figures may be an underestimate since typical vaccination coverage calculations do not consider whether vaccines were administered within the recommended schedules. There is a clear need for initiatives to implement full vaccinations for all adults.

“Catch-up Vaccinations”

In clinical practice, it is common to encounter patients who have initiated HBV vaccination but cannot recall how many doses they received, and others who are uncertain of whether they have ever received any doses of HBV vaccination. A retrospective database analysis found that only 31% of adults who initiated the HBV series completed all 3 doses within 2 years of the minimum dose spacing, with adherence highest in persons aged 60 to 64 years at the time of vaccine initiation. Therefore, many HBV-vaccinated adults may not receive the full protective benefits defined by the presence of anti-HBs.¹⁰⁴ Finally, analysis of NHANES data from 2013 to 2014 found that among adults at high risk for HBV infection, the prevalence of undetectable immunity (as defined by the presence of anti-HBs) was 69.4%, or 64 million Americans. Although this prevalence decreased overall from the 2003 to 2004 estimate of 83%, it remained unchanged in men who have sex with men, intravenous drug users, those with diabetes, patients with hepatitis C, and populations with elevated liver enzymes,¹⁰⁵ all of which are high-risk groups that have been highlighted throughout this review. Catch-up vaccinations can use either the 2-dose Heplisav-B vaccine regimen or the 3-dose Recombivax or Engerix-B regimen. There is no need to check anti-HBs levels or titers after catch-up vaccination is completed, except in very special populations (see the Protecting Against HBV in Special Populations Section).

This panel recommends triple panel prescreening and, if tests indicate all 3 HBV tests are negative, catch-up vaccinations in adolescents and adults with HBV vaccine to complete a full dose schedule (3 doses of one of the 3-dose vaccines, or 2 doses of the 2-dose vaccine) and no follow-up antibody testing is advised.

Testing and Management of Nonresponders

Nonresponders comprise a population in whom a repeat course of vaccination might be considered. Testing for immunity soon after a previous course of HBV

vaccination is advised only for people in whom knowledge of their immune status would potentially lead to the recommendation that a repeat course of vaccination should be administered. These groups include infants born to HBsAg-positive mothers and infants born to women whose HBsAg status remains unknown health care and public safety workers at high risk for continued percutaneous or mucosal exposure to blood or body fluids; hemodialysis patients; people with HIV; other immunocompromised people (eg, hematopoietic stem cell transplant recipients or people receiving chemotherapy); and sex partners of people with chronic HBV infection.¹⁰⁵

In a systematic review and meta-analysis of 13 publications encompassing 16 studies focusing on healthy adult nonresponders, David et al¹⁰⁶ found that seroconversion rates after 3 doses of 20 µg HBsAg given IM, 40 µg IM, or 5 mg intradermally were 81%, 53%, and 85%, while in 1 study of 20 µg given intradermally seroconversion occurred in 90% after 2 doses. The differences among groups were not statistically significant. In a series of 48 nonresponders who received a double dose of HBV vaccine incorporated into combined hepatitis A and B vaccine (Twinrix) at 0, 1, and 6 months, seroconversion was noted in 59% of the subjects. In the responders, lower titers of anti-HBs were noted compared with 20 previously unvaccinated controls.¹⁰⁷

Further affirmation of relatively high response rates in primary vaccine nonresponders was provided by a recent randomized open-label trial in the Netherlands, which compared the immunogenicity of 3 registered hepatitis vaccines in 468 healthy vaccine nonresponders in the Netherlands. These included 2 vaccines not approved in the United States: Fendrix, which has an AS04 adjuvant containing 3'-deacylated monophosphoryl lipid A and aluminum salt, and HBVaxPro, adsorbed on amorphous aluminium hydroxyphosphate sulfate at a standard dose of 10 µg. Patients in the control group received either Engerix-B 20 µg or HBVaxPro 10 mg again, while the other 3 groups received Twinrix 20 µg (combined hepatitis A and B vaccine containing 20 µg HBsAg), Fendrix 20 µg, or HBVaxPro 40 µg. Response rates 1 month after the third dose of revaccination were 67%, 80%, 87%, and 83%, respectively. Although the differences among the active treatment groups were small, only the latter 2 groups had response rates significantly higher than the control group.¹⁰⁸ An editorial accompanying the Netherlands study highlighted the need for more information on the potential efficacy of Heplisav-B in the nonresponder population.¹⁰⁹ In a recent small case series of military patients without response to 6 or more previous doses of standard vaccination, a 2-dose course of Heplisav-B conferred seroprotection in 12 of 13 healthy adults. GMT were not provided.¹¹⁰ In the context of data in adult nonresponders on several revaccination strategies, including revaccination with the same dose, double-dose revaccination, intradermal revaccination, and the introduction of Heplisav, newer, comparative data are needed to identify a clear preference for this population. At the present time, a full course of revaccination with a 3-dose series or Heplisav-B can be considered. The identity of the initial 3-dose hepatitis B vaccine (Engerix-B or Recombinax) to which nonresponse occurred does not influence the subsequent approach, nor are there current recommendations for Heplisav-B nonresponders.

What Is Considered Protection From HBV Infection?

Protection from HBV infection following HBV vaccination has been associated with an anti-HBs level of ≥ 10 mIU/mL, while response is defined as a level of

> 2 mIU/mL. Those who achieve between 2 and 10 mIU/mL have been called hyporesponders, as they usually will achieve an anti-HBs level > 10 mIU/mL after a fourth dose. Those who have an anti-HBs level of < 2 mIU/mL are considered vaccine failures. In these cases, a fourth dose, a new double-dose series, or the Heplisav-B 2-dose series would be the next logical choice. It is important to note that achieving > 10 mIU/mL does not provide lifetime protection against infection in all patients, as vaccinated persons have later been found to have acquired anti-HBc (although detection of HBsAg after a full course of vaccination is extremely rare). Thus, vaccination appears to provide lifetime protection against a symptomatic acute HBV chronic carrier state after exposure to HBV.⁶⁷

Can Anti-HBs Levels Following Vaccination Decline Over Time?

Following vaccination, anti-HBs levels decline over time. Anti-HBs ≥ 10 mIU/mL is considered a correlate of vaccine-induced protection for people who have completed an approved vaccination series. Immunocompetent people who achieve an anti-HBs level ≥ 10 mIU/mL 1 to 2 months after completing the HBV series remain protected, even if their anti-HBs levels decline to < 10 mIU/mL beyond that time (presumably due to persistent cellular immunity).^{67,111–113} In a study of 420 16- to 19-year old Americans vaccinated neonatally or in infancy, 24% had anti-HBs ≥ 10 IU/mL.¹¹⁴ The kinetics of anti-HBs loss have more recently been better defined in adults and can, if needed, be back-calculated from the rate of complete anti-HBs loss as a time function.⁶⁶ In a study of 159 healthcare workers (HCWs) vaccinated initially between ages 18 to 60, anti-HBs levels were < 12 mIU/mL in 9 of 50 (18%), 13 of 50 (26%), and 14 of 59 (24%) HCWs 10 to 15, 16 to 20, and > 20 years postvaccination, respectively. Anti-HBs status after initial vaccination was not available. Among adults, older age at vaccination was the only predictor of inadequate anti-HBs level.¹¹¹ Four subjects had anti-HBc, but none had HBsAg supporting the concept of long-term protection after vaccination even with senescence of B-cell immunity. Thirty-four of 36 (94%) of such subjects who received a booster injection developed seroprotective anti-HBs levels within 3 weeks, suggesting that most had been initial responders.¹¹¹ In one of the few prospective studies on long-term persistence of anti-HBs, 91% of a cohort of mostly young adult HCWs immunized in the 1980s had anti-HBs > 1000 IU/mL after primary immunization (good responders), and 84% of these had persistent anti-HBs after 30 years.¹¹⁵

How Long Does Clinical Protection From the HBV Vaccine Last, and Are Booster Doses Recommended?

Clinical and immunological responses are evident following HBV vaccination, and as described above and in Table 2, data has demonstrated decades of long-term protection following vaccinations. One study observed 176 young adults who were vaccinated for HBV as neonates 20 years earlier. They were evaluated before and after single-dose HBV vaccine boosts. Before boosting, 101 volunteers were considered "serosusceptible" (anti-HBs < 10 IU/mL), and 75 volunteers were considered seroprotected. However, preservation of cell-mediated immunity (determined via concentration levels of interleukin-2 and interferon) was found in 84 of the 101 serosusceptible volunteers, indicating that 159 (90%) volunteers maintained their vaccine-induced immunity.¹¹² In the largest and longest study to date of

TABLE 7. Recommendations for Vaccinating for Hepatitis B

| | |
|---|--|
| Current, standard recommendations | |
| Universal vaccinations | There is still a need to simplify vaccination policy, and universal vaccination would not only achieve this but also serve the greater good |
| Safety | Safety should not be an issue when administering any of the three approved HBV vaccines |
| Pregnancy | In pregnant women, prenatal testing for HBsAg (and HBV DNA, if HBsAg-positive) is required and should be performed at an initial prenatal appointment for each pregnancy. Pregnant women at risk for HBV vaccination who are seronegative for HBV markers should be offered HBV vaccination, as its safety during pregnancy is well established |
| Newborns | Vaccinating newborns for HBV is the most effective preventative approach, and vaccination recommendations, dependent on birth weight and maternal HBsAg status, should be followed. Infants born to HBsAg-positive mothers require PVST at 9-12 mo of age or 1-2 mo after the final dose if the initial series is delayed |
| Catch-up vaccinations | Catch-up vaccinations are recommended in unvaccinated adolescents and adults |
| Revaccination | Revaccination (ie, boosters) is generally not recommended, with the exception of infants born to HBsAg-positive mothers, guided by PSVT results showing anti-HBs <10 mIU/mL at 9-12 mo of age (or 1-2 mo after the final vaccine dose, if vaccination was delayed). Revaccination is also recommended for health care workers who do not respond to the initial series. Special populations may also be candidates for revaccination, as noted in the text |
| Additional expert panel recommendations | |
| Serological testing | The inability to perform prevaccination serological testing should not impede vaccinating, particularly in susceptible populations. However, we recommend universal testing with the HBV triple panel, if feasible, as this will help identify the “missing millions” who have chronic HBV infection and link them to care without the stigma attached to chronic HBV infection that hinders testing those at risk. For patients with anti-HBc without HBsAg, providers and patients can avoid costly vaccination and revaccination, and the patient can be linked to education about reactivation risk and possible testing for occult HBV infection |
| 2-dose vaccination | Vaccinating with Heplisav-B may offer better adherence and advantages due to a shorter series of injections, and higher immunogenicity in older persons; persons who are at risk for completion of the 3-dose series, such as persons who inject drugs and homeless persons; persons with chronic illnesses or who are immunocompromised; and health care workers who fail to respond to the initial series |
| Unanswered questions | Poor compliance with third dose Poor advocacy by health professionals Failure to test and take action in at-risk populations (eg, cirrhotics) |

HBsAg indicates hepatitis B surface antigen; HBV, hepatitis B virus; PVST, postvaccination serological testing.

persons who responded to a full series of plasma-derived vaccines in 1981 and were followed-up with at regular intervals, 35 years later, no participants had developed acute symptomatic HBV infection or reached the chronic carrier stage.⁶⁷ Almost 90% still had evidence of immunologic memory, having either retained levels of anti-HBs > 10 mIU/mL or achieved a level above that when given a booster dose. Furthermore, when examining cellular memory in a subset of these individuals, the Alaska group found that all had T cell and cytokine recognition of HBsAg.¹¹² These findings indicate that both humoral and cellular immunity to HBV was intact 35 years after the initial vaccination series. In accordance with other data,⁶⁷ this study determined that booster doses are not generally needed.¹¹³ However, among vaccinated cohorts who initiated hepatitis B vaccination at birth, long-term follow-up studies are ongoing to determine the duration of vaccine-induced immunity.¹¹⁶ In the large study of the 16- to 19-year old Americans cited above, 92% responded to a challenge dose with seroprotective levels of anti-HBs, prompting the authors to conclude that a booster dose is not necessary in adolescents vaccinated after birth.¹¹⁴

The CDC does not recommend routine serologic testing for health care providers after routine infant or adolescent hepatitis B vaccination. However, it allows for preexposure assessment upon initial hire or matriculation (with the ability of the potential employee to decline vaccination), followed in those with initial anti-HBs <10 mIU/mL by one or more doses of vaccine and retesting for anti-HBs to ensure future protection against HBV-containing blood or body fluids. If anti-HBs is not

assessed after the first dose or an anamnestic response is not seen, a full course should be completed.⁴ If there is lack of documentation or uncertainty about whether 3 courses were received at an earlier age, a full vaccine series should be given.¹⁰⁴ It is useful to keep in mind that routine hepatitis immunization of infants was introduced in the United States in late 1991.

The CDC does not recommend routine revaccinations for immunocompetent persons. However, an exception to this is hemodialysis patients. When annual testing for antibodies to the anti-HBs shows a decrease to <10 mIU/mL in these patients, a booster dose should be administered. For other immunocompromised people (including those with HIV, hematopoietic stem cell transplant recipients, and people receiving chemotherapy), the need for booster doses has not been determined. When anti-HBs levels decrease to <10 mIU/mL, annual anti-HBs testing and booster doses should be considered for those with an ongoing risk of exposure. There are no data that vaccinated dentists, surgeons, and other HCWs need screening or boosting, but in its recommendations, the CDC states that completely vaccinated health care providers with anti-HBs <10 mIU/mL are among the groups that should receive an additional dose of vaccine and be retested 1 to 2 months later to determine if additional doses are needed.⁴ HBV revaccination should be individualized based on the risk setting, and only test and vaccinate if the individual works in a particularly high-risk blood exposure setting, such as vascular or trauma surgery. There are no data showing that retesting and boosting persons who inject drugs play a clinical role after the full series of HBV vaccinations is completed.

How Do We Manage Anti-HBc-positive Patients?

Anti-HBc-positive testing improved markedly in 2002 with the development of second-generation core antibody tests. After 2002, this test had a false-positive rate of 2/1000.¹¹⁷ Even after HBsAg clearance following acute infection, nearly all anti-HBc-positive persons are thought to harbor persistent intranuclear covalently closed circular DNA (cccDNA), which can result in the reactivation of viral replication under certain conditions that usually involve immunosuppression with particular agents.¹¹⁸ Anti-HBc-positive patients do not need vaccine boosting, and they need to be educated about their HBV reactivation risk with certain types of immunosuppressive agents (especially if anti-HBs-negative). However, some patients with isolated anti-HBc may have detectable plasma HBV DNA, referred to as “occult HBV infection”, and consultation with a liver specialist is recommended if the alanine transaminases are elevated or if there are signs of CLD on imaging or laboratory testing.

CONCLUSION

Given the current recommendations for screening, vaccinations, and routine follow-up in place, the widespread availability of three safe and effective vaccines, and the decades of data on the benefits of vaccinating for HBV, the significant public health burden caused by this virus can and should be eliminated. This can be done by aggressively administering these vaccines to unvaccinated persons and ensuring that all newborns worldwide receive the birth dose of HBV vaccination, followed by the current GAVI 3-dose pentavalent series that contains the HBV vaccine. Additional unmet needs include identifying the large percentage of patients who either do not have adequate protection from HBV or are infected with chronic HBV. A summary of the panel recommendations for HBV vaccination can be found in Table 7.

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