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Hepatitis B Vaccine

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Number: 0410

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Policy

Scope of Policy

This Clinical Policy Bulletin addresses hepatitis B vaccine.

1. **Medical Necessity**

   Aetna considers hepatitis B (HepB) vaccine a medically necessary preventive service according to the recommendations of the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP).

   1. **Vaccination Indications**

      Aetna considers CDC ACIP's recommendations for the hepatitis B vaccine medically necessary for members with *any* of the following indications:

      1. Infants, regardless of hepatitis B surface antigen (HBsAg) status of the mother; *or*
      2. Children and adolescents less than 19 years of age who have not previously completed vaccination; *or*
      3. Adults aged 19 to 59 years who have not previously completed vaccination; *or*
      4. Adults 60 years of age and older with or without known risk factors for hepatitis B infection, including:

         1. Persons at risk for infection by sexual exposure:

            1. Men who have sex with men
            2. Persons seeking evaluation or treatment for a sexually transmitted infection (STI)
            3. Persons with a history of multiple sex partners
            4. Sex partners of persons testing positive for HBsAg
         2. Persons at risk for infection by percutaneous or mucosal exposure to blood:

            1. Health care professionals (HCP)Footnote*
            2. Household contacts of persons testing positive for HBsAg
            3. Injection drug users
            4. Persons on maintenance dialysis, including in-center or home hemodialysis and peritoneal dialysis, and persons who are predialysis
            5. Persons with diabetes at the discretion of the treating clinician
            6. Residents and staff members of facilities for persons with developmental disabilitiesFootnote*
         3. Others

            1. International travelers to geographic areas of high endemicityFootnote*

2. Persons with chronic liver disease (including, but not limited to, persons with cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase or aspartate aminotransferase level greater than twice the upper limit of normal)
3. Persons who are incarceratedFootnote*
4. Persons with hepatitis C virus infection
5. Persons with HIV infection; *or*

5. Pregnant women who are identified as being at risk for HBV infection during pregnancy (e.g., having more than one sex partner during the previous 6 months, been evaluated or treated for an STI, recent or current injection-drug use, or having had an HBsAg-positive sex partner); *or*
6. Transplant candidates of any age.

2. **Booster / Revaccination**

Aetna considers CDC ACIP's recommendations for revaccination / booster medically necessary in certain circumstances when antibody to hepatitis B surface antigen (anti-HBs) is less than 10 mIU/mL:

1. Infants born to HBsAg-positive mothers. Per the CDC, HBsAg-negative infants with anti-HBs less than 10 mIU/mL should be revaccinated with a single dose of HepB vaccine, and retested 1 - 2 months later. Infants whose anti-HBs remains less than 10 mIU/mL following single dose revaccination should receive two additional doses of HepB vaccine on a vaccine schedule to complete the second series, followed by anti-HBs testing 1 - 2 months later. Alternatively, these infants may be revaccinated with a second 3-dose series and retested (HBsAg and anti-HBs) 1 - 2 months after the final dose of vaccine.
2. Persons on hemodialysis. Per the CDC, for persons on hemodialysis treated in outpatient centers, the need for booster doses should be assessed by annual anti-HBs testing. A booster dose is considered medically necessary when anti-HBs levels decline to less than 10 mIU/mL. Anti-HBs testing 1 - 2 months following the booster dose to assess response is not recommended.
3. When anti-HBs levels decline to less than 10 mIU/ml, annual anti-HBs testing and booster doses are considered medically necessary for other immunocompromised persons (e.g., HIV-infected persons, hematopoietic stem-cell transplant recipients, and persons receiving chemotherapy) with an ongoing risk for exposure. According to the CDC, for these other immunocompromised persons, the need for booster doses has not been determined.
4. Health care professionals (HCP)Footnote*. Per the CDC, completely vaccinated HCP with anti-HBs less than 10 mIU/mL should receive an additional dose of HepB vaccine, followed by anti-HBs testing 1–2 months later.

3. For persons with normal immune status who have been vaccinated, booster doses are considered not medically necessary.

2. **Experimental, Investigational, or Unproven**

Aetna considers hepatitis B vaccine experimental, investigational, or unproven for all other indications (including prevention of lymphoma) because its effectiveness for indications other than the ones listed above has not been established.

3. **Policy Limitations and Exclusions**

Footnote1* **Note:** Aetna generally does not cover immunizations required for travel or because of work-related risk. Check contract language, limitations and exclusions for coverage details.

Table:

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

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Code	Code Description
CPT codes covered if selection criteria are met:	

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Code	Code Description
90636, 90739 - hyphen 90748	Hepatitis B vaccine

HCPCS codes covered if selection criteria are met:

G0010	Administration of hepatitis B vaccine

ICD-hyphen10 codes covered if selection criteria are met:

A50.01 -hyphen A64	Infections with a predominantly sexual mode of transmission
B17.10 -hyphen B17.11 B18.2 B19.20 -hyphen B19.21	Hepatitis C
B20	Human immunodeficiency virus [HIV] disease
B97.35	Human immunodeficiency virus, type 2 [HIV 2] as the cause of diseases classified elsewhere
D65 -hyphen D68.9	Coagulation defects [hemophiliacs]
D69.1	Qualitative platelets defects
E08.00 -hyphen E13.9	Diabetes mellitus
F11.10 -hyphen F19.99	Drug dependence and nondependent abuse of drugs [injecting-hyphendrug users]
F70	Mild intellectual disabilities
F71	Moderate intellectual disabilities
F72	Severe intellectual disabilities
F78.A1 -hyphen F78.A9	Other intellectual disabilities
F79	Unspecified intellectual disabilities
F80.0 -hyphen F8.9	Specific developmental disorders of speech and language
K70.0 -hyphen K70.9, K73.0 - hyphen K73.9, K74.0 -hyphen K74.69, K75.4, K76.0 -hyphen K76.1, K76.81 - hyphen K76.9	Chronic liver diseases and cirrhosis
O35.3xx0 -hyphen O35.3xx9	Maternal care for (suspected) damage to fetus from viral disease in mother [pregnant women at risk for infection]
O98.111 -hyphen O98.119	Syphilis complicating pregnancy
O98.211 -hyphen O98.219	Gonorrhea complicating pregnancy
O98.311 -hyphen O98.319	Other infections with a predominantly sexual mode of transmission complicating pregnancy
O98.32	Other infections with a predominantly sexual mode of transmission complicating childbirth
O98.33	Other infections with a predominantly sexual mode of transmission complicating the puerperium
O98.411 -hyphen O98.43	Viral hepatitis complicating pregnancy [pregnant women at risk for infection]
O98.811 -hyphen O98.819	Viral hepatitis complicating the puerperium
O98.82	Other maternal infectious and parasitic diseases complicating childbirth
O98.83	Other maternal infectious and parasitic diseases complicating the puerperium
P00.89	Newborn affected by other maternal conditions

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description
P00.2	Newborn affected by maternal infectious and parasitic diseases
Z00.110	Health examination for newborn under 8 days old
Z00.111	Health examination for newborn 8 to 28 days old
Z00.121	Encounter for routine child health examination with abnormal findings
Z00.129	Encounter for routine child health examination without abnormal findings
Z00.3	Encounter for examination for adolescent development state
Z02.0	Encounter for examination for admission to educational institution [school children age 0-hyphen18]
Z02.1	Encounter for pre-hyphenemployment examination [healthcare workers]
Z02.2	Encounter for examination for admission to residential institution [students]
Z02.89	Encounter for other administrative examination [admission to prison] [pregnant women at risk for infection]
Z11.3	Encounter for screening for infections with a predominantly sexual mode of transmission
Z20.2	Contact with and (suspected) exposure to infections with a predominantly sexual mode of transmission
Z20.5	Contact with and (suspected) exposure to viral hepatitis
Z20.818	Contact with and (suspected) exposure to other bacterial communicable diseases
Z20.828	Contact with and (suspected) exposure to other viral communicable diseases
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status
Z22.4	Carrier of infections with a predominantly sexual mode of transmission
Z22.50 -hyphen Z22.59	Carrier of viral hepatitis
Z23	Encounter for immunization
Z51.11	Encounter for antineoplastic chemotherapy
Z57.0 -hyphen Z57.9	Occupational exposure to risk factors
Z59.3	Problems related to living in residential institution
Z65.1	Imprisonment and other incarceration
Z71.84	Encounter for health counseling related to travel
Z72.51 -hyphen Z72.53	High risk sexual behavior [history of multiple sex partners]
Z76.82	Awaiting organ transplant status
Z94.0	Kidney transplant status
Z94.1	Heart transplant status
Z94.2	Lung transplant status
Z94.3	Heart and lung transplant status
Z94.4	Liver transplant status
Z94.6	Bone transplant status
Z94.81	Bone marrow transplant status
Z94.82	Intestine transplant status
Z94.83	Pancreas transplant status
Z94.84	Stem cells transplant status
Z94.89 -hyphen Z94.9	Other and unspecified transplanted organ and tissue status
Z99.2	Dependence on renal dialysis

Background

Pre-exposure immunization of susceptible persons with hepatitis B vaccine is the most effective means to prevent hepatitis B virus (HBV) transmission. To reduce transmission of HBV and eventually to eliminate it, universal immunization is necessary. Vaccination against HBV has been recommended as part of routine early childhood immunizations since 1991. Accordingly, immunization of all children before or during adolescence is necessary and recommended. Along with universal immunization efforts, immunization of adults belonging to identified high-risk groups is appropriate. Post-exposure evaluation and treatment,

including diagnostic testing and immunization in selected cases, is also appropriate to prevent HBV infection among individuals of all ages regardless of the presence or absence of risk factors.

These indications blend the recommendations of the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP). These 3 groups, working with federal agencies, have approved a unified childhood immunization schedule. The recommendations for hepatitis B vaccine in the unified schedule are generally similar to those recommended by the U.S. Preventive Services Task Force (USPSTF). However, routine hepatitis B vaccine was recommended only in infancy in the unified schedule, whereas the USPSTF also recommends its routine use in all children and adolescents not previously immunized. The ACIP and AAP have subsequently revised their recommendations for hepatitis B vaccine to include all children who have not previously been vaccinated.

In 2018, the Centers for Disease Control and Prevention (CDC) published ACIP recommendations that newborns should receive the hepatitis B vaccine within 24 hours of birth. The American Academy of Family Physicians (AAFP), American Academy of Pediatrics (AAP), and American College of Obstetricians and Gynecologists (ACOG) were all in agreement with the recommendation to vaccinate newborns within 24 hours of birth. AAP included this in its published Red Book 2018–2021: Report of the Committee on Infectious Diseases (Wexler, 2018).

Three doses of hepatitis B vaccine are required for complete immunization. For infants, the Centers for Disease Control and Prevention (CDC) and the ACIP recommend hepatitis B vaccine be incorporated into the routine vaccination schedules for children.

Hepatitis B vaccine has been administered using an accelerated immunization protocol for persons who are candidates for solid organ, bone marrow or stem cell transplantation to reduce the risk of hepatitis infection from administration of blood products and transplanted organs.

Advisory Committee on Immunization Practices (ACIP)

The Centers for Disease Control (CDC) and Prevention's Advisory Committee on Immunization Practices (ACIP) provide recommendations for the hepatitis B vaccine. The following include persons recommended to receive the hepatitis B vaccination (CDC, 2022):

- All infants
- Unvaccinated persons aged less than 19 years
- Adults aged 19-59 years
- Adults aged 60 years and older with risk factors for hepatitis B:
    - Persons at risk for infection by sexual exposure
        - Sex partners of persons testing positive for HBsAg
        - Sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than one sex partner during the previous 6 months)
        - Persons seeking evaluation or treatment for a sexually transmitted infection
        - Men who have sex with men
    - Persons at risk for infection by percutaneous or mucosal exposure to blood
        - Persons with current or recent injection drug use
        - Household contacts of persons testing positive for HBsAg
        - Residents and staff members of facilities for persons with developmental disabilities
        - Health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids
        - Persons on maintenance dialysis, including in-center or home hemodialysis and peritoneal dialysis, and persons who are predialysis
        - Persons with diabetes at the discretion of the treating clinician
    - Others
        - International travelers to countries with high or intermediate levels of endemic hepatitis B virus infection (HBsAg prevalence of ≥2%)
        - Persons with hepatitis C virus infection
        - Persons with chronic liver disease (including, but not limited to, persons with cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase or aspartate aminotransferase level greater than twice the upper limit of normal)
        - Persons with HIV infection

    - Persons who are incarcerated

- Adults aged 60 years and older without known risk factors for hepatitis B but seeking protection may receive hepatitis B vaccines.

For booster/revaccination recommendations, see Booster Dose Vaccination below.

Associations Between Interleukin-4 Genetic Polymorphisms and HBV Infection Risk

Cui and colleagues (2013) evaluated the associations between functional polymorphisms in the interleukin-4 (IL4) gene and individuals' responses to hepatitis B vaccine and their susceptibility to HBV infection. A literature search on articles published before December 1st, 2012 was conducted in PubMed, Embase, Web of Science and China BioMedicine (CBM) databases. Crude ORs with 95 % CIs were calculated. Statistical analyses were performed using the STATA 12.0 software. A total of 8 studies were eligible for inclusion in this meta-analysis, including 5 cross-sectional studies on individual's response to hepatitis B vaccine and 3 case-control studies on HBV infection risk. The meta-analysis results showed that the T allele of rs2243250, the T allele of rs2070874, and the C allele of rs2227284 in IL4 gene were associated with high responses to hepatitis B vaccine. Further subgroup analysis by ethnicity showed that there was a significant association between IL4 genetic polymorphisms and an individual's responses to hepatitis B vaccine among Asian populations, but similar association was not found among Caucasian populations. However, there was no evidence indicating a correlation between IL4 genetic polymorphism and susceptibility to HBV infection. The authors concluded that the findings of this meta-analysis suggested that rs2243250, rs2070874 and rs2227284 polymorphisms in IL4 gene may play an important role in determining the response to hepatitis B vaccine, especially among Asian populations. However, they stated that further studies are still needed to evaluate the associations between IL4 genetic polymorphisms and HBV infection risk.

Booster Dose Vaccination

In a Cochrane review, Poorolajal et al (2010) evaluated the benefits and harms of booster dose hepatitis B vaccination for preventing hepatitis B infection. Randomized clinical trials addressing anamnestic immune response to booster of hepatitis B vaccine 5 years or more after primary vaccination in apparently healthy participants, vaccinated in a 3-dose or 4-dose schedules of hepatitis B vaccine without receiving additional dose or immunoglobulin were included in this analysis. Two authors made the decisions if the identified publications on studies met the inclusion criteria or not. Primary outcome measures included the proportion with anamnestic immune response in non-protected participants and signs of HBV infection. Secondary outcomes were the proportion with local and systemic adverse event events developed following booster dose injection. Weighted proportion were planned to be reported with 95 % confidence interval. There were no eligible RCTs fulfilling the inclusion criteria of this review. The authors were unable to identify RCTs on the topic. They stated that there is a need for RCTs to formulate future booster policies for preventing HBV infection.

In a Cochrane review, Poorolajal and Hooshmand (2016) evaluated the benefits and harms of booster dose hepatitis B vaccination, more than 5 years after the primary vaccination, for preventing HBV infection in healthy individuals previously vaccinated with the hepatitis B vaccine, and with hepatitis B surface antibody (anti-HBs) levels below 10 mIU/ml. These investigators searched the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, Science Citation Index Expanded, conference databases, and reference lists of articles to January 2016. They also contacted authors of articles. In addition, they searched ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform for ongoing trials (May 2016). Randomized clinical trials addressing anamnestic immune response to a booster dose of hepatitis B vaccine, more than 5 years after the primary vaccination, in apparently healthy participants, vaccinated in a 3-dose or 4-dose schedule of the hepatitis B vaccine during the primary vaccination, without receiving an additional dose or immunoglobulin. Both review authors decided if the identified studies met the inclusion criteria or not. Primary outcomes included the proportion of participants with anamnestic immune response in non-protected participants and signs of HBV infection. Secondary outcomes were the proportion of participants that developed local and systemic adverse events following a booster dose injection. These researchers planned to report the weighted proportion with 95 % CIs. There were no eligible randomized clinical trials fulfilling the inclusion criteria of this review. The authors were unable to include any randomized clinical trials on the topic; only randomized clinical trials will be able to provide an answer as to whether a booster dose vaccination is able to protect against hepatitis B infection.

The CDC's AdvisoryCommittee on Immunization Practices (ACIP) state that "persons who have completed a HepB vaccination series at any point or who have a history of HBV infection should not receive additional HepB vaccination, although there is no evidence that receiving additional vaccine doses is harmful. However, there are cases where revaccination might be indicated as specified in the 2018 ACIP recommendation (e.g., nonresponder infants born to persons testing positive for hepatitis B surface antigen [HBsAg], health care providers, and persons on hemodialysis). Providers should only accept dated records as evidence of HepB vaccination" (Weng et al, 2022).

The 2018 ACIP recommendations are as follows for HepB revaccination (Schillie et al, 2018):

- Revaccination (i.e., booster dose, challenge dose, or revaccination with a complete series) is not generally recommended for persons with a normal immune status who were vaccinated as infants, children, adolescents, or adults. Available data

do not suggest a maximum number of booster doses. Revaccination when anti-HBs is <10 mIU/mL is recommended for the following persons:

- Infants born to HBsAg-positive mothers. HBsAg-negative infants with anti-HBs <10 mIU/mL should be revaccinated with a single dose of HepB vaccine, and retested 1–2 months later. Infants whose anti-HBs remains <10 mIU/mL following single dose revaccination should receive two additional doses of HepB vaccine on a vaccine schedule to complete the second series, followed by anti-HBs testing 1–2 months later. Alternatively, these infants may be revaccinated with a second 3-dose series and retested (HBsAg and anti-HBs) 1–2 months after the final dose of vaccine.
- Health care professionals (HCP). Completely vaccinated HCP with anti-HBs <10 mIU/mL should receive an additional dose of HepB vaccine, followed by anti-HBs testing 1–2 months later. HCP whose anti-HBs remains <10 mIU/mL should complete the second series (usually 6 doses total), followed by repeat anti-HBs testing 1–2 months after the final dose. Alternatively, it might be more practical for very recently vaccinated HCP with anti-HBs <10 mIU/mL to receive the second complete series (usually 6 doses total), followed by anti-HBs testing 1–2 months after the final dose.
- Hemodialysis patients. For hemodialysis patients treated in outpatient centers, the need for booster doses should be assessed by annual anti-HBs testing. A booster dose should be administered when anti-HBs levels decline to <10 mIU/mL. Anti-HBs testing 1–2 months following the booster dose to assess response is not recommended.
- Other immunocompromised persons. For other immunocompromised persons (e.g., HIV-infected persons, hematopoietic stem-cell transplant recipients, and persons receiving chemotherapy), the need for booster doses has not been determined. Annual anti-HBs testing and booster doses should be considered for persons with an ongoing risk for exposure.

FDA-Approved Hepatitis B Vaccines

The following hepatitis B vaccine formulations have been approved by the U.S. Food and Drug Administration (FDA):

- Single-antigen hepatitis B vaccines
  - Engerix-B
  - Recombivax HB
  - Heplisav-B (adults 18 years and older)
- Three-antigen hepatitis B vaccine
  - PreHevbrio (adults 18 years and older)
- Combination vaccines
  - Pediarix (combination hepatitis B, diphtheria, tetanus, acellular pertussis, and inactived poliovirus)
  - Twinrix (combination hepatitis A-hepatitis B) (adults 18 years and older)
  - Vaxelis (combination diphtheria, tetanus, acellular pertussis, inactivated poliovirus, Haemophilus influenza type b, and hepatitis B)

On February 21, 2018, the ACIP voted unanimously in favor of including Heplisav-B (HepB-CpG) on its list of ACIP recommended products for use to vaccinate adults against hepatitis B. Heplisav-B was approved by the Food and Drug Administration (FDA) in November 2017; it is indicated for prevention of infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older. The CDC's ACIP (2018) has published its guidance on use of Heplisav-B. The vaccine is recommended for adults at risk for acquiring HBV. These include people at risk from sexual transmission, incarcerated people, people with HIV, injection drug users, and household contacts of infected people, among others. The new vaccine is one of 5 approved inactivated HBV vaccines. Heplisav-B contains a novel immuno-stimulatory sequence adjuvant; 2 doses are administered just 1 month apart, making it "an important option for prevention of HBV", the authors wrote in MMWR. In randomized trials, sero-protective antibody to hepatitis B surface antigen levels were obtained in 90 to 100 % of subjects receiving Heplisav-B, versus 71 % to 90 % of those receiving another HBV vaccine, Engerix-B. The vaccine's safety has not been tested in pregnancy, so the committee recommends that pregnant women receive an alternative HBV vaccine.

In 2019, the U.S. FDA approved Pediarix [diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant) and inactivated poliovirus vaccine] (GlaxoSmithKline Biologicals) for use as a 3-dose series in infants born of hepatitis B surface antigen (HBsAg)-negative mothers. Pediarix is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis, infection caused by all known subtypes of hepatitis B virus, and poliomyelitis. It may be given as early as 6 weeks of age through 6 years of age (prior to the 7th birthday).

Immune Response to Hepatitis B Vaccine in Patients with Chronic Hepatitis C Infection

Liu and colleagues (2018) stated that hepatitis B virus and hepatitis C virus (HCV) co-infection can add to the severity of hepatitis and the risks of liver cirrhosis and hepato-cellular carcinoma (HCC). Whether chronic HCV infection decreases antibody response to hepatitis B vaccination is still controversial. These researchers evaluated the influence of HCV infection on antibody response to hepatitis B vaccination by a systematic review of published works with a meta-analysis of clinical trials. The random-effects model of DerSimonian and Laird with heterogeneity and sensitivity analyses were used in this study. The end-point of interest was the rate of patients showing sero-conversion of antibody responses at completion of hepatitis B vaccination schedule among patients with chronic HCV infection versus healthy controls. These investigators identified 11 studies involving 704 patients with HCV and 812 controls. The results showed a significant decrease in antibody sero-conversion rates among patients with HCV versus healthy controls (pooled OR = 0.17 [95 % CI: 0.11 to 0.28]). The p-value was 0.21 for the test of study heterogeneity. Stratified analysis in subgroups of interest and sensitivity analysis did not meaningfully change these results. The meta-analysis showed patients with hepatitis C infection had a statistically significant lower rate of sero-conversion in comparison to healthy controls, both in cirrhotic and non-cirrhotic patients. The authors concluded that chronic HCV infection can decrease the immune response to a standard schedule of hepatitis B vaccination; further studies are needed to examine the optimum vaccination schedule for patients with chronic HCV infection.

Immune Response to Hepatitis B Vaccine in Patients with Chronic Kidney Disease

Fabrizi et al (2012) stated that patients with chronic kidney disease typically show an impaired immune response to HBV vaccine compared with healthy individuals. A variety of inherited or acquired factors have been implicated in this diminished response. Some authors suggested a benefit with adjuvantation to improve the immunogenicity of existing HBV vaccines. In a meta-analysis, these investigators evaluated the safety and effectiveness of adjuvantation for HBV vaccine in patients with chronic kidney disease. Only prospective, RCTs were included. These researchers used the random effects model of DerSimonian and Laird with heterogeneity and subgroups analyses. The primary end-point of interest was the sero-protection rate after HBV vaccination with recombinant vaccine plus adjuvants (study group) versus recombinant vaccine alone (control group). These investigators identified 10 studies involving 1,228 unique patients with chronic kidney disease. Pooling of study results did not show a significant increase in sero-protection rate among study (HBV recombinant vaccine plus adjuvants) versus control (HBV recombinant alone) patients; the pooled odds ratio (OR) of sero-protection rate was 1.47 (95 % CI: 0.88 to 2.46, NS). The pooled OR for sero-response rate after HBV vaccine (adjuvanted recombinant vaccine versus recombinant vaccine alone) did not change in the subgroup of studies based on novel adjuvant systems (i.e., HBV-AS04 or HBV-AS02), the pooled OR was 2.22 (95 % CI: 0.72 to 6.78), NS. Q-test for heterogeneity being 10.819 (p = 0.004). The authors concluded that this meta-analysis showed that adjuvanted hepatitis B vaccine did not significantly improve the sero-protection rate in patients with renal insufficiency. These results do not support adjuvantation as an approach to increase the immunogenicity of existing recombinant vaccines towards HBV in this high-risk population.

Immune Response to Hepatitis B Vaccine in Patients with HIV

In a randomized controlled trial (RCT), Cornejo-Juarez et al (2006) found that an increase dose of HBV vaccine did not increase the rate of response in HIV infected subjects. These researchers assessed 2 doses of recombinant HBV vaccine (10 or 40 microg), intra-muscular (IM) at 0, 1 and 6 months. Vaccination response was measured 30 to 50 days after last dose; titers of greater than 9.9 IU/L were considered positive. A total of 79 patients were included, 48 patients (60.7 %) sero-converted. Thirty-nine patients (49.3 %) received 10 microg vaccine dose, 24 patients (61.5 %) sero-converted. Forty patients (50.7 %) received 40 microg vaccine dose, 24 (60 %) sero-converted. There were no differences between the 2 doses. A statistically significant higher sero-conversion rate was found for patients with CD4 cell counts at vaccination greater than or equal to 200 cell/mm3 (33 of 38 patients, 86.8 %), compared with those with CD4 less than 200 cell/mm3 (15 of 41, 36.6 %), (odds ratio of 11.44, 95 % confidence interval [CI]: 3.67 to 35.59, p = 0.003), there were no differences between 2 vaccine doses. Using the logistic regression model, CD4 count less than 200 cell/mm3 were significantly associated with non-serological response (p = 0.003). None other variables such as gender, age, risk exposure for HIV, viral load, type or duration of highly active anti-retroviral therapy or AIDS-defining illness, were associated with sero-conversion. The authors concluded that an increase dose of HBV vaccine did not show to increase the rate of response in HIV infected subjects. The only significant findings associated to the response rate was that a CD4 count greater than or equal to 200 cell/mm3, these investigators suggested this threshold at which HIV patients should be vaccinated.

Pasricha and colleagues (2006) evaluated the effectiveness of recombinant vaccine in treatment-naive HIV-positive patients and healthy controls, and ascertained differences if any, in different limbs of immune response. A total of 40 HIV-positive patients and 20 HIV-negative controls, negative for HBsAg, HBsAbs and HBcAbs were vaccinated with 3 doses of 40 microg and 20 microg of vaccine, respectively. Patients were divided into high-CD4 and low-CD4 group based on CD4+ lymphocytes of 200 and less than 200/mm3, respectively. Group II consisted of healthy controls. Detection of phenotypic markers was done by flow cytometry. Cytokine estimation was done by sandwich ELISA. HBsAbs were estimated in serum by ELISA. After vaccination, CD4+, CD8+ and CD3+ cells increased significantly in all the groups. There was no increase in natural killer cell activity in patients with high CD4+ lymphocytes and only a marginal increase in patients with low CD4+ lymphocytes (170 to 293/mm3) whereas a marked increase was observed in controls (252 to 490/mm3). After vaccination, although an increase in memory cells was observed in HIV-positive patients, yet HBsAb levels were significantly lower than controls ($p < 0.05$) indicating a functional defect of memory cells in HIV/AIDS patients. Basal interferon-gamma levels were also significantly lower in HIV/AIDS patients ($p < 0.01$). Although the levels increased after vaccination, the peak level remained lower than in controls. HBsAb titers were much lower in HIV-positive patients compared to controls. (high-CD4+ group: 8834 mIU/ml, low-CD4+ group: 462 mIU/ml

versus controls: 16,906 mIU/ml). IL-4 and IL-10 were low in patients. The authors concluded that despite a double dose in patients, IL-4 and IL-10, which regulate antibody response, were also lower in patients, and this together with low CD4+ counts and lack of T help, accounted for low HBsAb levels. Vaccination in patients with CD4+ lymphocytes less than 50/mm3 was ineffective.

Immunization with Hepatitis B Immunoglobulin (HBIG)

Zhang et al (2014) noted that combined immunization with hepatitis B immunoglobulin (HBIG) plus hepatitis B vaccine (HB vaccine) can effectively prevent peri-natal transmission of hepatitis B virus (HBV). With the universal administration of HB vaccine, anti-HBs conferred by HB vaccine can be found increasingly in pregnant women, and maternal anti-HBs can be passed through the placenta. These researchers evaluated the effect of hepatitis B immunization on preventing mother-to-infant transmission of HBV and on the immune response of infants towards HB vaccine. From 2008 to 2013, a prospective study was conducted in 15 centers in China. HBsAg-positive pregnant women and their infants aged 8 to 12 months who completed immunoprophylaxis were enrolled in the study and tested for HBV markers (HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBc). Ante-partum administration of HBIG to HBsAg-positive women was based on individual preference. HBsAg-negative pregnant women and their infants of 7 to 24 months old who received HB vaccines series were enrolled and tests of their HBV markers were performed. A total of 1,202 HBsAg-positive mothers and their infants aged 8 to 12 months were studied and 40 infants were found to be HBsAg positive with the immunoprophylaxis failure rate of 3.3 %. Infants with immunoprophylaxis failure were all born to HBeAg-positive mothers of HBV-DNA greater than or equal to 6 $\log_{10}$copies/ml. Among infants of HBeAg-positive mothers, immunoprophylaxis failure rate in vaccine plus HBIG group, 7.9 % (29/367), was significantly lower than the vaccine-only group, 16.9 % (11/65), p = 0.021; there was no significant difference in the immunoprophylaxis failure rate whether or not antepartum HBIG was given to the pregnant woman, 10.3 % (10/97) versus 9.0 % (30/335), p = 0.685. Anti-HBs positive rate was 56.3 % (3,883/6,899) among HBsAg-negative pregnant women and anti-HBs positive rate was 94.2 % in cord blood of anti-HBs-positive mothers. After completing the HB vaccine series, anti-HBs positive rate among infants with maternal anti-HBs titers of less than 10 IU/L, 10 to 500 IU/L and greater than or equal to 500 IU/L was 90.3 % (168/186), 90.5 % (219/242) and 80.2 % (89/111), respectively, p = 0.011. Median titers of anti-HBs (IU/L) among infants in the 3 groups was 344.2, 231.9 and 161.1, respectively, p = 0.020. The authors concluded that HBIG plus HB vaccine can effectively prevent mother-to-infant transmission of HBV, but no HBV breakthrough infection was observed in infants born to HBeAg-negative mothers who received HB vaccine with or without HBIG after birth. They stated that ante-partum injection of HBIG has no effect on preventing HBV mother-to-infant transmission; high maternal titer of anti-HBs can transplacentally impair immune response of infants towards HB vaccine.

Machaira et al (2015) stated that the cost-effectiveness of augmenting immunization against hepatitis B infection with hepatitis B immune globulin (HBIG) remains controversial, particularly for the subpopulation of babies of HBsAg+/HBeAg- mothers that are considered as low-infective. These researchers evaluated the effectiveness of vaccine alone compared with vaccine plus HBIG for the immunization of babies of HBsAg+/HBeAg- mothers. They searched PubMed, Scopus and Cochrane Central Register of Controlled Trials databases to identify studies comparing the effectiveness of combined immunization (vaccine plus HBIG) with vaccine alone in neonates of HBsAg+/HBeAg- mothers. A systematic review and meta-analysis of eligible studies was performed. A total of 9 eligible studies were identified (4 RCTs). No difference was found regarding the primary outcome of this meta-analysis, namely occurrence of hepatitis B infection, between neonates who received vaccine only, compared with those who received both vaccine and HBIG (4 studies, 3,426 patients, OR = 0.82, 95 % CI: 0.41 to 1.64). This finding was consistent with regards to sero-protection rate (4 studies, 1,323 patients, OR = 1.24, 95 % CI: 0.97 to 1.58). Safety data were not reported in the included studies. The authors concluded that available limited published evidence suggested that vaccine alone seems to be equally effective to the combination of HBIG and hepatitis B vaccine for neonates of HBsAg+/HBeAg- mothers in preventing infection. They stated that further studies are needed in order to clarify the potential benefit of combined immunization to this specific subgroup of patients.

Possible Protective Effect of Hepatitis B Vaccine Against Lymphomas

Lia and colleagues (2022) noted that in the last few years the possible etiological role of the HBV in the outbreak of extra-hepatic pathologies has being studied, including lymphomas. The WHO estimates that around 257 million people live with chronic HBV infection, to-date the vaccine is the most effective means of prevention. In a systematic review, these researchers examined if the vaccination against hepatitis B could result in reduction in lymphoma cases and have a protective role. They carried out a literature search in April 2020 using the databases Scopus, PubMed and ISI Web of Science. Search terms included: "Hepatitis B vaccination AND lymphoma". All articles were selected evaluating the association between hepatitis B vaccination and the prevention of lymphoma. No limits were applied. A total of 8 studies were eligible to be included in the review. Data showed that association between lymphoma and HBV infection is not the same for all types of lymphoma, but it appeared to be more significant for non-Hodgkin lymphoma (NHL). The results from all the considered studies were not unitary. This is because studies came from many different countries with different endemicity of hepatitis B, different vaccination coverage, treatment of chronic hepatitis and prevention of its complications, as well as the availability of data for researchers. No statistically significant association was found between HBV vaccination and development of lymphomas. The authors concluded that although the literature is still largely lacking regarding the protective effect of anti-HBV vaccination on lymphoma subtypes, the association between HBV infection and lymphoma has been confirmed in several studies.

Furthermore, National Comprehensive Cancer Network's clinical practice guideline on ''B-cell lymphomas " (Version 1.2022) and "T-cell lymphomas" (Version 2.2022) do not mention hepatitis B vaccination as a method for prevention of lymphomas.

Pregnant Women at Risk for Infection or an Adverse Infection-Related Pregnancy Outcome

Lin and Vickery (2009) searched for large, high-quality studies related to hepatitis B screening in pregnancy that have been published since the 2004 USPSTF recommendation. English-language studies indexed in PubMed and the Cochrane Database of Systematic Reviews and published between January 1, 2001 and March 5, 2008 were included in this study. For benefits of screening and newborn prophylaxis, these investigators included systematic reviews; meta-analyses; and RCTs. For harms of screening, they included systematic reviews; meta-analyses; RCTs; cohort studies; case-control studies; and case series of large, multi-site databases. Abstracts and full articles were independently reviewed for inclusion by both reviewers. Data on the benefits of screening, including benefits of hepatitis B immune globulin and hepatitis B vaccine prophylaxis of newborns of HBsAg-positive mothers, were extracted by 1 reviewer. No new studies met inclusion criteria. A 2006 systematic review of RCTs found that newborn prophylaxis reduced peri-natal transmission of HBV infection; all relevant trials were published in 1996 or earlier. The authors concluded that no new evidence was found on the benefits or harms of screening for HBV infection in pregnant women. Previously published RCTs support the 2004 USPSTF recommendation for screening.

In a Cochrane review, Sangkomkamhang and colleagues (2011) evaluated the effectiveness and adverse effects of hepatitis B vaccine administered to pregnant women for preventing HBV infection in infants. Randomized controlled trials assessing hepatitis B vaccination compared with placebo or no treatment during pregnancy for preventing infant infection were included in this analysis. These investigators excluded quasi-RCTs and cross-over studies. Two review authors independently assessed trial eligibility. They were not able to include any studies. The authors found no RCTs that assessed the effects of hepatitis B vaccine during pregnancy for preventing infant infection. Consequently, this review can not provide guidance for clinical practice in this area. However, it does identify the need for well-designed RCTs for the effect of hepatitis B vaccine during pregnancy on the incidence of infant infection and adverse effects.

According to the CDC, pregnancy is not a contraindication to hepatitis B vaccination. The CDC states that limited data indicate no apparent risk for adverse events to developing fetuses when hepatitis B vaccine is administered to pregnant women. Current vaccines contain noninfectious HBsAg and should cause no risk to the fetus. The CDC states that pregnant women who are identified as being at risk for HBV infection during pregnancy (e.g., having more than 1 sex partner during the previous 6 months, been evaluated or treated for an sexually transmitted disease, recent or current injection drug use, or having had an HBsAg-positive sex partner) should be vaccinated.

The CDC (2020) released an updated schedule for adult vaccines including those for hepatitis B. It states that “For hepatitis B, a new addition to the list of vulnerable patients who may possibly benefit from vaccination is pregnant women at risk for infection or an adverse infection-related pregnancy outcome”.

Prevention of Mother-to-Child Transmission in HBV Surface Antigen (HBsAg)-Positive Pregnant Women

Guidelines from the Centers for Disease Control and Prevention (Schillie, et al., 2018) state that perinatal HBV transmission can be prevented by identifying HBV-infected (i.e., hepatitis B surface antigen [HBsAg]-positive) pregnant women and providing hepatitis B immune globulin and hepatitis B vaccine to their infants within 12 hours of birth.

In a systematic review and meta-analysis, Chen and colleagues (2020) examined the benefits and harms of hepatitis B immune globulin (HBIG) and hepatitis B vaccine (HBVac) in preventing mother-to-child transmission (MTCT) in HBV surface antigen (HBsAg)-positive pregnant women during ante-natal period. A total of 7 electronic databases including PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), WanFang Database, Chinese Biomedical Literature Database (CBM), VIP Database for Chinese Technical Periodicals (VIP), and 3 clinical trial registry platforms were searched from inception date to December 2017; only RCTs were included in this study. The Cochrane risk of bias tool was used to evaluate the risk of bias. The outcomes were analyzed by Review Manager 5.3 software. A total of 16 RCTs involving 2,440 HBsAg-positive pregnant women were included in the meta-analysis. Compared with placebo group, HBIG and HBVac group had a significant decrease in the number of newborns who were HBsA- positive (relative risks [RR]: 0.2, 95 % CI: 0.18 to 0.40, $p < 0.00001$) and HBV-DNA-positive (RR: 0.25, 95 % CI: 0.09 to 0.71], $p = 0.010$), and had a significant increase in the number of anti-HBs-positive newborns (RR: 3.95, 95 % CI: 3.11 to 5.00, $p < 0.00001$). After 1-year follow-up, the number of HBsAg-positive newborns continued to decline (RR: 0.09, 95 % CI: 0.04 to 0.20, $p < 0.00001$) and the number of anti-HBs-positive newborns continued to increase in HBIG and HBVac group (RR: 1.30, 95 % CI: 1.22 to 1.38], $p < 0.00001$). Compared with HBIG group, HBIG and HBVac group had no significant difference in the number of HBsAg-positive newborns (RR: 1.68, 95 % CI: 0.66 to 4.30, $p = 0.28$), and had a significant decrease in the number of HBsAg-positive newborns (RR: 0.31, 95 % CI: 0.12 to 0.84, $p = 0.02$). Furthermore, only 1 study reported 2 swelling cases, 4 studies reported no adverse events (AEs), and 11 studies did not report AEs. The authors concluded that HBIG and HBVac could be an effective alternative for HBsA- positive pregnant women to prevent MTCT; however, due to the limitations of the study, the long-term safety and efficacy of HBIG and HBVac still need long-term and high-quality research to confirm.

The authors stated that this study had several drawbacks. First, only 1 study conducted personnel evaluation, blinding of outcome assessment, and subjects; thus, these researchers could not examine the risks of bias of the results. Second, this study was not registered in a database; however, before these researchers initiated the study, they had made a pre-defined protocol. Third, these investigators searched all the electronic databases from inception date to December 2017. After

screening the studies, they included 16 RCTs from 2000 to 2017; approximately 17 years from the 1st publication and last publication may have affected the results due to the time factor. Fourth, because most of the trials did not report the AEs, these researchers could not confirm the safety for pregnant women and newborns. Fifth, these investigators reviewed the 16 included RCTs, but they could not be sure that HBIG and HBVac were the same contents. Furthermore, HBV infection was the major cause of end-stage liver diseases in China, among which 30 % to 50 % were due to MTCT and were associated with increased risk of morbidity and mortality later in life. Anti-viral therapies could also provide benefits in HBsAg-positive pregnant women, but this review was not designed to examine the efficacy of these agents. And the authors found no comparative benefits and harms between HBIG+HBVac and anti-virals; therefore, they could not draw comparative conclusions.

SBP (HBsAg-Binding Protein) Adjuvant for Hepatitis B Vaccine

Wang and colleagues (2017) stated that although adjuvants are a common component of many vaccines, there are few adjuvants licensed for use in humans due to concerns about their toxic effects. There is a need to develop new and safe adjuvants, because some existing vaccines have low immunogenicity among certain patient groups. In this study, SBP, a hepatitis B surface antigen binding protein that was discovered through screening a human liver cDNA expression library, was introduced into hepatitis B vaccine. A good laboratory practice, non-clinical safety evaluation was performed to identify the side effects of both SBP and SBP-adjuvanted hepatitis B vaccine. The results indicated that SBP could enhance the HBsAg-specific immune response, thus increasing the protection provided by the hepatitis B vaccine. The authors concluded that given the encouraging safety data obtained in this study, further evaluation of SBP as a vaccine adjuvant for human use is warranted. They stated that this research has the potential to accelerate adjuvant development for HBV vaccine and for other vaccine types in the future.

Association Between 2-Dose Versus 3-Dose Hepatitis B Vaccine and Acute Myocardial Infarction

Bruxvoort et al (2022) stated that the 2-dose hepatitis B vaccine with a cytosine phosphoguanine adjuvant (HepB-CpG vaccine; Heplisav-B) generated higher sero-protection in pre-licensure trials than did a 3-dose hepatitis B vaccine with an aluminum hydroxide adjuvant (HepB-alum vaccine; Engerix-B). However, in 1 trial, a higher number of acute myocardial infarction (MI) events were observed among those who received the HepB-CpG vaccine than among those who received the HepB-alum vaccine, an outcome requiring further study. In a prospective, non-inferiority study, these researchers compared the rate of acute MI between recipients of HepB-CpG vaccine and HepB-alum vaccine. This trial was carried out at Kaiser Permanente Southern California (KPSC), an integrated health care system with 15 medical centers and approximately 4.7 million members. It included 69,625 adults not undergoing dialysis who received at least 1 dose of a hepatitis B vaccine in either family medicine or internal medicine departments at KPSC from August 7, 2018, to October 31, 2019 (November 30, 2020, final follow-up). Participants received either HepB-CpG vaccine or the HepB-alum vaccine; the 1st dose during the study period was the index dose. Individuals were followed-up for 13 months after the index dose for occurrence of type 1 acute MI. Potential events were identified using diagnosis codes and adjudicated by cardiologists. The adjusted hazard ratio (HR) of acute MI was estimated comparing recipients of HepB-CpG vaccine with recipients of HepB-alum vaccine, with inverse probability of treatment weighting (IPTW) to adjust for demographic and clinical characteristics. The upper limit of the 1-sided 97.5 % CI was compared with a non-inferiority margin of 2. Of the 31,183 recipients of HepB-CpG vaccine (median age of 49 years; inter-quartile range [IQR], 38 to 56 years), 51.2 % (n = 15,965) were men, and 52.7 % (n = 16,423) were Hispanic. Of the 38,442 recipients of HepB-alum (median age of 49 years; IQR, 39 to 56 years), 50.8 % (19,533) were men, and 47.1 % (n = 18 125) were Hispanic. Characteristics were well-balanced between vaccine groups after IPTW. A total of 52 type 1 acute MI events were confirmed among recipients of HepB-CpG vaccine for a rate of 1.67 per 1,000-person-years, and 71 type 1 acute MI events were confirmed among recipients of HepB-alum vaccine for a rate of 1.86 per 1,000 person-years (absolute rate difference, -0.19 [95 % CI: -0.82 to 0.44]; adjusted HR, 0.92 [1-sided 97.5 % CI, ∞ to 1.32], which was below the non-inferiority margin; $p < 0.001$ for non-inferiority). The authors concluded that in this cohort study, receipt of HepB-CpG vaccine compared with HepB-alum vaccine did not meet the statistical criterion for increased risk of acute MI.

Protective Role for Anti-Hepatitis B Virus Antibodies Against COVID-19

Gdoura et al (2022) noted that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for COVID-19 disease that is known to have a broad clinical spectrum, from asymptomatic to critical presentation leading to death. Many investigators have examined the factors impacting the course of the disease. These researchers' previous in silico study suggested a possible protective effect of hepatitis B, tetanus and measles vaccines against COVID-19. In continuity, they carried out a cross-sectional clinical study to confirm their in-silico assumptions regarding the HBs-Ag antibodies. These investigators selected a representative sex- and age-matched sample of patients with confirmed COVID-19 (n = 340). All clinical presentations were equally represented. Using an ELISA test, each patient benefited of a serology for the detection and measurement of the anti-HBs specific IgG antibodies. The obtained results allowed determining the different correlations between these antibody titers and the disease severity. The R software and the MedCalc software served to calculate the Spearman's coefficient of rank correlation (rho) for the obtained titers per severity group as well as the different other calculations and figure representations. They found a significant positive correlation with the anti-HBs titers (rho = 0.107; $p = 0.04$). High anti-HBs titers were significantly associated with the mild presentation of COVID-19. A significant difference was found between the obtained titers per severity class (Chi-2 test, $p = 0.03$). The authors concluded that these findings showed that anti-HBs titers were significantly higher for patients having mild COVID-19 presentations. These researchers presumed that

being immunized against HB may play a protective role in the course of the disease. This study provided more key elements in understanding the disparity of the clinical spectrum among regions.

References

The above policy is based on the following references:

1. Abara WE, Qaseem A, Schillie S, et al; High Value Care Task Force of the American College of Physicians and the Centers for Disease Control and Prevention. Hepatitis B vaccination, screening, and linkage to care: Best practice advice from the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med. 2017;167(11):794-804.
2. American Academy of Pediatrics (AAP). 2000 Red Book: Report of the Committee on Infectious Diseases. 25th ed. Elk Grove Village, IL: AAP; 2000.
3. Atkinson WL, Pickering LK, Schwartz B, et al. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). MMWR Recomm Rep. 2002;51(RR-2):1-35.
4. Bar-On ES, Goldberg E, Fraser A, et al. Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB). Cochrane Database Syst Rev. 2009;(3):CD005530.
5. Beran J. Ten year's experience with combined hepatitis A and B vaccine. Klin Mikrobiol Infekc Lek. 2008;14(1):13-14, 16-23.
6. Bruxvoort K, Slezak J, Qian L, et al. Association between 2-dose vs 3-dose hepatitis B vaccine and acute myocardial infarction. JAMA. 2022;327(13):1260-1268.
7. Castells L, Esteban R. Hepatitis B vaccination in liver transplant candidates. Eur J Gastroenterol Hepatol. 2001;13(4):359-361.
8. Centers for Disease Control (CDC). Hepatitis B virus: A comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination: Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR Recomm Rep. 1991;40(RR-13):1-25.
9. Centers for Disease Control and Prevention (CDC). Recommendations of the Advisory Committee on Immunization Practices for use of a hepatitis B vaccine with a novel adjuvant. MMWR Morb Mortal Wkly Rep. 2018;67(15):455-458.
10. Centers for Disease Control and Prevention (CDC). Recommended childhood and adolescent immunization schedule - United States, 2006. MMWR. 2006;54(52):Q1-Q4.
11. Centers for Disease Control and Prevention (CDC). Update: Recommendations to prevent hepatitis B virus transmission -- United States. MMWR Morb Mortal Wkly Rep. 1995;44(30):574-575.
12. Centers for Disease Control and Prevention (CDC). Update: Recommendations to prevent hepatitis B virus transmission -- United States -- update. MMWR Morb Mortal Wkly Rep. 1999;48(2):33-34.
13. Centers for Disease Control and Prevention (CDC). Updated CDC recommendations for the management of hepatitis B virus-infected health-care providers and students. MMWR Recomm Rep 2012;61(RR-3):1-12.
14. Centers for Disease Control and Prevention. Use of hepatitis B vaccination for adults with diabetes mellitus: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2011;60(50);1709-1711.
15. Chau KF, Cheng YL, Tsang DN, et al. Efficacy and side effects of intradermal hepatitis B vaccination in CAPD patients: A comparison with the intramuscular vaccination. Am J Kidney Dis. 2004;43(5):910-917.
16. Chen W, Gluud C. Vaccines for preventing hepatitis B in health-care workers. Cochrane Database Syst Rev. 2005;(4):CD000100.
17. Chen Z, Zeng M, Liu D, et al. Antenatal administration of hepatitis B immunoglobulin and hepatitis B vaccine to prevent mother to child transmission in hepatitis B virus surface antigen positive pregnant women: A systematic review and meta-analysis. Medicine (Baltimore). 2020;99(16):e19886.
18. Cornejo-Juárez P, Volkow-Fernández P, Escobedo-López K, et al. Randomized controlled trial of Hepatitis B virus vaccine in HIV-1-infected patients comparing two different doses. AIDS Res Ther. 2006;3:9.
19. Cui W, Sun CM, Deng BC, Liu P. Association of polymorphisms in the interleukin-4 gene with response to hepatitis B vaccine and susceptibility to hepatitis B virus infection: A meta-analysis. Gene. 2013;525(1):35-40.
20. Di Paolo D, Lenci I, Trinito MO, et al. Extended double-dosage HBV vaccination after liver transplantation is ineffective, in the absence of lamivudine and prior wash-out of human Hepatitis B immunoglobulins. Dig Liver Dis. 2006;38(10):749-754.
21. Dynavax Technologies Corporation. Dynavax's Heplisav-B™ [Hepatitis B vaccine (recombinant), adjuvanted] recommended by CDC Advisory Committee on Immunization Practices for the prevention of hepatitis B in adults. Press Release. Berkeley, CA: Dynavax; February 21, 2018.
22. Eleftheriadis T, Pissas G, Antoniadi G, et al. Factors affecting effectiveness of vaccination against hepatitis B virus in hemodialysis patients. World J Gastroenterol. 2014;20(34):12018-12025.
23. Fabrizi F, Dixit V, Bunnapradist S, Martin P. Meta-analysis: The dialysis mode and immunological response to hepatitis B virus vaccine in dialysis population. Aliment Pharmacol Ther. 2006;23(8):1105-1112.
24. Fabrizi F, Dixit V, Martin P. Meta-analysis: The adjuvant role of thymopentin on immunological response to hepatitis B virus vaccine in end-stage renal disease. Aliment Pharmacol Ther. 2006;23(11):1559-1566.

25. Fabrizi F, Dixit V, Messa P, Martin P. Hepatitis B virus vaccine in chronic kidney disease: Improved immunogenicity by adjuvants? A meta-analysis of randomized trials. Vaccine. 2012;30(13):2295-2300.
26. Fonseca MO, Pang LW, de Paula Cavalheiro N, et al. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. Vaccine. 2005;23(22):2902-2908.
27. Gasim GI, Bella A, Adam I. Immune response to hepatitis B vaccine among patients on hemodialysis. World J Hepatol. 2015;7(2):270-275.
28. Gdoura M, Touati R, Kalthoum S, et al. Presumed protective role for anti-hepatitis B virus antibodies against COVID-19 severe cases: A clinical study confirming in silico hypothesis. Front Med (Lausanne). 2022;9:909660.
29. Girndt M, Kohler H. Hepatitis B virus infection in hemodialysis patients. Semin Nephrol. 2002;22(4):340-350.
30. GlaxoSmithKline Biologicals (GSK). Pediarix [diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant) and inactivated polioviurs vaccine], suspension for intramuscular injection. Prescribing Information. Research Triangle Park, NC: GSK; revised November 2019.
31. Hayney MS, Welter DL, Reynolds AM, et al. High-dose hepatitis B vaccine in patients waiting for lung transplantation. Pharmacotherapy. 2003;23(5):555-560.
32. Helvaci M, Kizilgunesler A, Kasirga E, et al. Efficacy of hepatitis B vaccination and interferon-alpha-2b combination therapy versus interferon-alpha-2b monotherapy in children with chronic hepatitis B. J Gastroenterol Hepatol. 2004;19(7):785-791.
33. Kim DK, Riley LE, Harriman KH, et al. Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older - United States, 2017. MMWR Morb Mortal Wkly Rep. 2017;66(5):136-138.
34. Kochhar GS, Mohan BP, Khan SR, et al. Hepatitis-B vaccine response in inflammatory bowel disease patients: A systematic review and meta-analysis. Inflamm Bowel Dis. 2021;27(10):1610-1619.
35. Krogsgaard K. Introduction of hepatitis B vaccine in the childrens immunization programme in Denmark: A health technology assessment. Danish Health Technology Assessment. Copenhagen, Denmark: Danish Centre for Evaluation and Health Technology Assessment (DACEHTA); 2003;3(1).
36. Lee C, Gong Y, Brok J, et al. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: Systematic review and meta-analysis. BMJ. 2006;332(7537):328-336.
37. Lee C, Gong Y, Brok J, et al. Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers. Cochrane Database Syst Rev. 2006;(2):CD004790.
38. Lee H, Lok ASF. Hepatitis B and pregnancy. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2021.
39. Lia L, Grima D, Amici F, et al. The possible protective effect of hepatitis B vaccine against lymphomas: A systematic review. Curr Pharm Biotechnol. 2022;23(15):1864-1872.
40. Lin K, Vickery J. Screening for hepatitis B virus infection in pregnant women: Evidence for the U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med. 2009;150(12):874-876.
41. Liu J, Wu H, Chen H. Immune response to hepatitis B vaccine in patients with chronic hepatitis C infection: A systematic review and meta-analysis. Hepatol Res. 2018;48(2):119-126.
42. Machaira M, Papaevangelou V, Vouloumanou EK, et al. Hepatitis B vaccine alone or with hepatitis B immunoglobulin in neonates of HBsAg+/HBeAg- mothers: A systematic review and meta-analysis. J Antimicrob Chemother. 2015;70(2):396-404.
43. Martinez-Sernandez V, Figueiras A. Central nervous system demyelinating diseases and recombinant hepatitis B vaccination: A critical systematic review of scientific production. J Neurol. 2013;260(8):1951-1959.
44. Mast EE, Margolis HS, Fiore AE; Advisory Committee on Immunization Practices (ACIP). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. MMWR Recomm Rep. 2005;54(RR-16):1-31.
45. Mast EE, Weinbaum CM, Fiore AE, et al; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: Immunization of adults. MMWR Recomm Rep. 2006;55(RR-16):1-33.
46. Mathew JL, El Dib R, Mathew PJ, et al. Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status. Cochrane Database Syst Rev. 2008;(3):CD006481.
47. Molrine DC, Hibberd PL. Vaccines for transplant recipients. Infect Dis Clin North Am. 2001;15(1):273-305, xii.
48. Mosby-Year Book, Inc. Mosby's GenRx: The Complete Reference for Generic and Brand Drugs. 9th ed. St. Louis, MO: Mosby; 1999.
49. Mouchet J, Salvo F, Raschi E, et al. Hepatitis B vaccination and the putative risk of central demyelinating diseases - A systematic review and meta-analysis. Vaccine. 2018;36(12):1548-1555.
50. National Comprehensive Cancer Network (NCCN). B-cell lymphomas. NCCN Clinical Practice Guidelines in Oncology, Version 1.2022. Plymouth Meeting, PA: NCCN; 2022.
51. National Comprehensive Cancer Network (NCCN). T-cell lymphomas. NCCN Clinical Practice Guidelines in Oncology, Version 2.2022. Plymouth Meeting, PA: NCCN: 2022.
52. Opri R, Veneri D, Mengoli C, Zanoni G. Immune response to Hepatitis B vaccine in patients with celiac disease: A systematic review and meta-analysis. Hum Vaccin Immunother. 2015;11(12):2800-2805.
53. Pasricha N, Datta U, Chawla Y, et al. Immune responses in patients with HIV infection after vaccination with recombinant Hepatitis B virus vaccine. BMC Infect Dis. 2006;6:65.
54. Poorolajal J, Hooshmand E. Booster dose vaccination for preventing hepatitis B. Cochrane Database Syst Rev. 2016;(6):CD008256.

55. Poorolajal J, Mahmoodi M, Haghdoost A, et al. Booster dose vaccination for preventing hepatitis B. Cochrane Database Syst Rev. 2010;(11):CD008256.
56. Rieger MA, Hofmann F, Michaelis M. Simultaneous vaccination against hepatitis A and B: Results of an open, randomized study from the occupational health point of view. Int J Occup Med Environ Health. 2004;17(3):379-391.
57. Saari TN, American Academy of Pediatrics Committee on Infectious Diseases. Immunization of preterm and low birth weight infants. American Academy of Pediatrics Committee on Infectious Diseases. Pediatrics. 2003;112(1 Pt 1):193-198.
58. Sangare L, Manhart L, Zehrung D, Wang CC. Intradermal hepatitis B vaccination: A systematic review and meta-analysis. Vaccine. 2009;27(12):1777-1786.
59. Sangkomkamhang US, Lumbiganon P, Laopaiboon M. Hepatitis B vaccination during pregnancy for preventing infant infection. Cochrane Database Syst Rev. 2011;3:CD007879.
60. Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep. 2018;67(1):1-31.
61. Schroth RJ, Hitchon CA, Uhanova J, et al. Hepatitis B vaccination for patients with chronic renal failure. Cochrane Database Syst Rev. 2004;(3):CD003775.
62. So S, Terrault N, Conners EE. Universal adult hepatitis B screening and vaccination as the path to elimination. JAMA. 2023;329(19):1639-1640.
63. Swift D. ACIP updates recommendations for adult vaccines. Medscape Medical News. February 03, 2020. Available at: https://www.medscape.com/viewarticle/924692. Accessed April 19, 2022.
64. U.S. Department of Health and Human Services, National Institutes of Health (NIH). Management of Hepatitis C. NIH Consensus Statement. Bethesda, MD: NIH; March 24, 1997.
65. U.S. Preventive Services Task Force. Guide to Clinical Preventive Services. 2nd ed. Baltimore, MD; Williams and Wilkins; 1996.
66. U.S. Public Health Service. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. MMWR Recomm Rep. 2001;50(RR-11):1-52.
67. UK National Health Service (NHS), National Library for Health (NLH). Which groups of patients should GPs be offering free hepatitis B immunisation for? Primary Care Question Answering Service. London, UK: NHS; May 20, 2005. Available at: http://www.clinicalanswers.nhs.uk/index.cfm?question=565/index.cfm. Accessed July 1, 2005.
68. Wang J, Su C, Liu R, et al. A pre-clinical safety evaluation of SBP (HBsAg-Binding Protein) adjuvant for hepatitis B vaccine. PLoS One. 2017;12(1):e0170313.
69. Weng MK, Doshani M, Khan MA, et al. Universal hepatitis B vaccination in adults aged 19-59 years: Updated recommendations of the Advisory Committee on Immunication Practices - United States, 2022. MMWR Recomm Rep. 2022;71(13):477-483.
70. Weiser J, Perez A, Bradley H, et al. Low prevalence of hepatitis B vaccination among patients receiving medical care for HIV infection in the United States, 2009 to 2012. Ann Intern Med. 2018;168(4):245-254.
71. Wexler, D. Technically speaking: CDC publishes recommendations that newborns receive hepatitis B vaccine within 24 hours of birth - AAFP, AAP and ACOG concur. Immunize.org [online]. July/August 2018. Available at: https://www.immunize.org/technically-speaking/20180724.asp. Accessed April 12, 2022.
72. Yu AS, Cheung RC, Keeffe EB. Hepatitis B vaccines. Clin Liver Dis. 2004;8(2):283-300.
73. Zhang L, Gui XE, Teter C, et al. Effects of hepatitis B immunization on prevention of mother-to-infant transmission of hepatitis B virus and on the immune response of infants towards hepatitis B vaccine. Vaccine. 2014;32(46):6091-6097.

Policy History

- Last Review 06/13/2024

  Effective: 04/27/2000

  Next Review: 04/24/2025

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