New Hepatitis A and Hepatitis B Vaccine Recommendations

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Current issues in Immunization Webinar

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Hepatitis A Vaccines

Update: Recommendations of the Advisory Committee on Immunization Practices for Use of Hepatitis A Vaccine For Post-exposure Prophylaxis and for International Travel

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- Approved February 2018 ACIP meeting
- Publication anticipated: November 2018

Hepatitis A Vaccine for Post-Exposure Prophylaxis

- **Recommendations for post-exposure prophylaxis (PEP) for hepatitis A**
  - Hepatitis A (HepA) vaccines should be administered for post-exposure prophylaxis for all persons age ≥12 months
  - In addition to hepatitis A vaccine, IG may be administered to persons age >40 years depending on the providers' risk assessment
    - Factors to consider in the decision to use IG in addition to vaccine
      - Age
      - Immune status and underlying conditions
      - Exposure type (risk of transmission)
      - Availability of IG

Hepatitis A Vaccine for Post-Exposure Prophylaxis, cont.

Infants aged <12 months and persons for whom vaccine is contraindicated

- Infants aged <12 months and persons for whom vaccine is contraindicated (persons who have had a life-threatening allergic reaction after a dose of hepatitis A vaccine, or have a severe allergy to any part of this vaccine) should receive IG (0.1 mL/kg) instead of vaccine as soon as possible and within 2 weeks after exposure

- Note: The recommended interval for administration of MMR vaccine is no earlier than 3 months after IG administration for hepatitis A prophylaxis

Approved; unpublished

Hepatitis A Vaccine for Post-Exposure Prophylaxis, cont.

Persons aged ≥12 months

- Persons aged ≥12 months who have been exposed to hepatitis A virus (HAV) within the prior 14 days and have not previously completed the 2-dose HepA vaccine series should receive a single dose of HepA vaccine as soon as possible
- In addition to HepA vaccine, IG (0.1 mL/kg) may be administered to persons aged >40 years depending on the providers' risk assessment
- For long-term immunity, the HepA vaccine series should be completed with a second dose at least 6 months after the first dose; the second dose is not necessary for PEP

Approved; unpublished

Hepatitis A Vaccine for Post-Exposure Prophylaxis, cont.

Persons aged ≥12 months who are immunocompromised or have chronic liver disease

- Immunocompromised persons and persons with chronic liver disease who have been exposed to HAV within the prior 14 days and have not previously completed the 2-dose HepA vaccine series should receive both IG (0.1 mL/kg) and HepA vaccine simultaneously in a different anatomical site as soon as possible after exposure

- For long-term immunity, the HepA vaccine series should be completed with a second dose at least 6 months after the first dose; the second dose is not necessary for PEP

Approved; unpublished

Hepatitis A Vaccines for International Travelers

- **Recommendations for pre-exposure protection against hepatitis A for travelers**
  - Hepatitis A vaccine should be administered to infants age 6-11 months traveling outside the United States when protection against hepatitis A is recommended
    - The travel-related dose for infants age 6-11 months does not count towards the routine 2-dose series
      - Therefore, the 2-dose hepatitis A vaccine series should be initiated at age 12 months according to the routine, age-appropriate vaccine schedule

Hepatitis A Vaccines for International Travelers, cont.

Rationale

- IG cannot be administered simultaneously with MMR vaccine, which is recommended for all infants aged ≥6–11 months traveling internationally from the U.S., because antibody-containing products such as IG can inhibit the immune response to measles and rubella vaccines for ≥3 months
- Due to the greater severity of measles in infancy compared to HAV infection in infancy, MMR vaccine should be administered preferentially to IG for HAV infection pre-exposure prophylaxis
- Administration of HepA vaccine (indication for off-label use) and MMR vaccine to infants aged 6–11 months provides protection against both HAV and measles and allows for simultaneous prophylactic administration

Hepatitis A Vaccines for International Travelers, Cont.

Infants aged <6 months, and travelers who elect not to receive vaccine or for whom vaccine is contraindicated

- Infants aged <6 months, and travelers who elect not to receive vaccine or for whom vaccine is contraindicated should receive a single dose of IG (0.1 mL/kg for travel up to 1 month; 0.2 mL/kg for travel up to 2 months) prior to travel when protection against hepatitis A is recommended

- If travel is 2 months or longer, a repeat dose of 0.2 mL/kg every 2 months should be administered

Approved; unpublished

Hepatitis A Vaccines for International Travelers, Cont.

Infants aged 6-11 months

- Hepatitis A vaccine should be administered to infants aged 6–11 months traveling outside the United States when protection against hepatitis A is recommended

- This vaccine dose does not count towards the 2-dose series.
  - The 2-dose HepA vaccine series should then be initiated at age 12 months (at any interval after the dose administered for international travel pre-exposure prophylaxis) according to the routine, age-appropriate vaccine schedule

Approved; unpublished

Hepatitis A Vaccines for International Travelers, Cont.

Healthy persons aged ≥12 months–40 years

- Healthy persons aged ≥12 months–40 years who are planning travel to an area with high or intermediate hepatitis A endemicity and have not received HepA vaccine should receive a single dose of HepA vaccine as soon as travel is considered and complete the 2-does series according to the routine schedule

Approved; unpublished

Hepatitis A Vaccines for International Travelers, Cont.

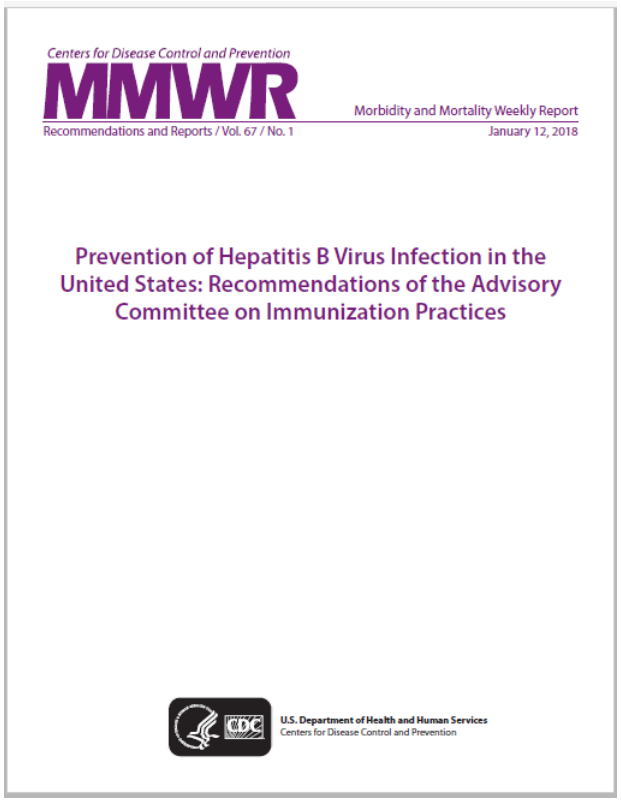
Older adults, immunocompromised persons, persons with chronic liver disease

- Persons with chronic liver disease as well as older adults (aged >40 years), immunocompromised persons, and persons with other chronic medical conditions planning to depart to a risk area in <2 weeks should receive the initial dose of vaccine, and also simultaneously can be administered IG at a separate anatomic injection site (0.1 mL/kg for travel up to 1 month at a separate anatomic injection site; 0.2 mL/kg for travel up to 2 months; repeat dose of 0.2 mL/kg every two months)

Approved; unpublished

Hepatitis B Vaccines

New ACIP Hepatitis B Recommendations, January 2018



Schillie S, Vellozzi C, Reingold A, Harris A, Haber P, Ward JW, Nelson NP. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018;67(No. RR-1):1–31. DOI: http://dx.doi.org/10.15585/mmwr.rr6701a1

New ACIP Recommendations

- Single document with guidance for:
  - Hepatitis B (HepB) vaccination of infants, children, adolescents, and adults
  - Testing pregnant women for Hepatitis B surface antigen(HBsAg), and, if positive, hepatitis B virus (HBV) DNA
  - HepB pre-vaccination and postvaccination serologic testing
  - HBV post-exposure prophylaxis (occupational and non-occupational exposures)

New ACIP Recommendations, cont.

- Incorporates previously-published recommendations from:
  - ACIP
  - CDC
- Augmented with American Association for the Study of Liver Diseases (AASLD) recommendation 8A: *The AASLD suggests antiviral therapy to reduce the risk of perinatal transmission of hepatitis B in HBsAg-positive pregnant women with an HBV DNA level >200,000 IU/mL*

Birth Dose

- All infants born to HBsAg-positive women should receive HepB vaccine and (hepatitis B immune globulin) HBIG within 12 hours of birth, administered at different injection sites
  - Only single-antigen HepB vaccine should be used for the birth dose
- Recommend hepatitis B vaccine birth dose within **24 hours of birth** for medically stable infants weighing ≥2,000 grams and born to HBsAg-negative mothers
  - Aligns with the World Health Organization (WHO) recommendations

Testing Pregnant Women for HBV DNA

- HBsAg-positive pregnant women should be tested for HBV DNA to guide the use of maternal antiviral therapy for preventing perinatal transmission (new recommendation)
  - AASLD suggests maternal antiviral therapy when maternal HBV DNA is >200,000 IU/mL (new recommendation)

Testing Pregnant Women, cont.

- Commercial laboratories should be encouraged to capture pregnancy status for women tested for HBsAg to aid in identification of HBV-infected pregnant women (new recommendation)

Transferred Infants

- For infants transferred to a different facility after birth (e.g., hospital with higher level of neonatal care), staff at the transferring and receiving facilities should communicate regarding the infant's HepB vaccination and HBIG receipt status to ensure prophylaxis is administered in a timely manner (new recommendation)

Mothers with Unknown Status

- Infants born to women for whom HBsAg testing results during pregnancy are not available but other evidence suggestive of maternal HBV infection exists (e.g., presence of HBV DNA, HBeAg-positive, or mother known to be chronically infected with HBV) should be managed as if born to an HBsAg-positive mother (new recommendation)

Postvaccination Serologic Testing (PVST)

- Recommended for infants born to:
  - HBsAg-positive mothers
  - Mothers whose HBsAg status remains unknown indefinitely (e.g., infants safely surrendered shortly after birth) (new recommendation)
- Performed after completion of HepB vaccine series (age 9-12 months) (new recommendation) and at least 1 month after last HepB vaccine dose (to avoid detecting HBsAg from vaccine)

Revaccination

- Single-dose revaccination (new recommendation)
  - For infants born to HBsAg-positive mothers who have anti-HBs <10 mIU/mL after 3-dose series
  - Follow with PVST one month following vaccination
    - If still anti-HBs <10 mIU/mL then 2 more doses + PVST
  - Alternate strategy: 3-dose revaccination then PVST

Summary of Revised ACIP Guidance for Perinatal HBV Transmission

- Universal HepB vaccination within 24 hours of birth for infants ≥2,000 grams
- Removal of permissive language for delaying birth dose
- Testing HBsAg-positive pregnant women for HBV DNA to guide maternal antiviral therapy
- Postvaccination serologic testing for infants whose maternal HBsAg status remains unknown indefinitely
- Single-dose revaccination for infants born to HBsAg-positive mothers not responding to the initial vaccine series

HepB Vaccine and HBIG Schedule for Newborns

Maternal HBsAg status	Infant birth weight: ≥2,000 grams	Infant birth weight: <2,000 grams
Positive	HepB vaccine and HBIG within 12 hours of birth	HepB vaccine and HBIG within 12 hours of birth; do not count birth dose as part of vaccine series
Unknown	HepB vaccine within 12 hours of birth*	HepB vaccine and HBIG within 12 hours of birth; do not count birth dose as part of vaccine series
Negative	HepB vaccine within 24 hours of birth (new recommendation)	Delay first dose of HepB vaccine until age 1 month or hospital discharge

*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 age 7 days

Adults Recommended for HepB Vaccination

- **Persons at risk for infection through sexual exposure**
  - Sex partners of hepatitis B surface antigen (HBsAg)–positive persons
  - Sexually active persons not in a long-term, mutually monogamous relationship
  - Persons seeking evaluation or treatment for a sexually transmitted infection
  - Men who have sex with men
- **Persons with a history of current or recent injection drug use**
- **Persons at risk for infection by percutaneous or mucosal exposure to blood**
  - 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
  - Hemodialysis patients and predialysis, peritoneal dialysis, and home dialysis patients
  - Persons with diabetes mellitus aged <60 years and persons with diabetes mellitus aged ≥60 years at the discretion of the treating clinician
- **International travelers to countries with high or intermediate levels of endemic HBV infection (HBsAg prevalence ≥2%)**
- **Persons with hepatitis C virus infection (new recommendation), persons with chronic liver disease (including, but not limited to, those with cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal)**
- **Persons with HIV**
- **Incarcerated persons**
- **Other persons seeking protection from hepatitis B virus infection (even without acknowledgment of a specific risk factor)**

Chronic Liver Disease

- Vaccination for persons with chronic liver disease (including, but not limited to, those with hepatitis C virus (HCV) infection, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and liver function tests >2 times the upper limit of normal)
  - ≥3-dose HepB vaccine coverage among adults aged ≥19 years with chronic liver conditions (2014): 29.8% (95% CI, 23.9-36.5)

New Advisory Committee on Immunization Practices (ACIP) Hepatitis B Recommendations, 2018

Morbidity and Mortality Weekly Report

Recommendations of the Advisory Committee on Immunization Practices for Use of a Hepatitis B Vaccine with a Novel Adjuvant

Sarah Schillie, MD[1]; Aaron Harris, MD[1]; Ruth Link-Gelles, PhD[1]; José Romero, MD[2]; John Ward, MD[1]; Noele Nelson, MD[1]

Hepatitis B (HepB) vaccination is the primary means of preventing infections and complications caused by hepatitis B virus (HBV). On February 21, 2018, the Advisory Committee on Immunization Practices (ACIP) recommended Heplisav-B (HepB-CpG), a yeast-derived vaccine prepared with a novel adjuvant, administered as a 2-dose series (0, 1 month) for use in persons aged ≥18 years. The ACIP Hepatitis Vaccines Work Group conducted a systematic review of the evidence, including data from four randomized controlled trials assessing prevention of HBV infection and six randomized controlled trials assessing adverse events in adults. Seroprotective antibody to hepatitis B surface antigen (anti-HBs) levels were achieved in 90.0%–100.0% of subjects receiving HepB-CpG (Dynavax Technologies Corporation), compared with 70.5%–90.2% of subjects receiving Engerix-B (GlaxoSmithKline Biologicals). The benefits of protection with 2 doses administered over 1 month make HepB-CpG an important option for prevention of HBV.

Introduction

Vaccination is the primary means for preventing hepatitis B virus (HBV) infection and its complications. Existing hepatitis B (HepB) vaccines use an aluminum adjuvant. On November 9, 2017, Heplisav-B (HepB-CpG), a single-antigen HepB vaccine with a novel immunostimulatory sequence adjuvant, was approved by the Food and Drug Administration for the prevention of HBV in persons aged ≥18 years. The vaccine is administered as 2 doses, 1 month apart (*1*). On February 21, 2018, the Advisory Committee on Immunization Practices (ACIP)* recommended HepB-CpG for use in persons aged ≥18 years.

HepB-CpG contains yeast-derived recombinant HepB surface antigen (HBsAg) and is prepared by combining purified HBsAg with small synthetic immunostimulatory cytidine-phosphate-guanosine oligodeoxynucleotide (CpG-ODN) motifs (1018 adjuvant). The 1018 adjuvant binds to Toll-like receptor 9 to stimulate a directed immune response to HBsAg (*1*).

HepB-CpG is available in single-dose 0.5 mL vials. Each dose contains 20 μg of HBsAg and 3,000 μg of 1018 adjuvant. HepB-CpG is formulated without preservatives and is administered as an intramuscular injection in the deltoid region of the upper arm (*1*).

HepB-CpG is the fifth inactivated HepB vaccine currently recommended for use in the United States. This report contains ACIP guidance specific to HepB-CpG and augments the 2018 ACIP recommendations for the prevention of HBV infection (*2*). This report does not include new guidance for populations recommended to receive HepB vaccination or immunization management issues other than those that pertain specifically to HepB-CpG. The intended audience for this report includes clinical and public health personnel who provide HepB vaccination services to adults. These recommendations are meant to serve as a source of guidance for health care providers; health care providers should always consider the individual clinical circumstances of each patient.

Methods

From February 2016 to January 2018, the ACIP Hepatitis Vaccines Work Group† participated in three teleconference meetings to review the quality of evidence for immunogenicity and safety of HepB-CpG and implementation issues. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for evaluating evidence was adopted by ACIP in 2010 (https://www.cdc.gov/vaccines/acip/recs/grade/). The Work Group identified critical and important outcomes for inclusion in the GRADE tables, conducted a systematic review of the evidence, and subsequently reviewed and discussed findings and evidence quality (*3*). Key outcomes were designated as critical (hepatitis B infection, severe adverse events, and cardiovascular safety) or important (mild adverse events). Factors considered in determining the recommendation included benefits and harms and evidence type. Values and preferences and economic factors were not systematically considered.

* ACIP is chartered as a federal advisory committee that provides expert external advice and guidance to the Director of CDC on use of vaccines and related agents for the control of vaccine-preventable diseases in the U.S. civilian population. ACIP recommendations adopted by the CDC Director become agency guidelines on the date published in *MMWR*.

† The ACIP Hepatitis Vaccines Work Group comprises professionals from academic medicine (family medicine, internal medicine, pediatrics, obstetrics, infectious disease, occupational health, and preventive medicine specialists), federal and state public health entities, and medical societies.

Schillie S, Harris A, Link-Gelles R, Romero J, Ward J, Nelson N. 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 Apr 20;67(15):455-458

New Vaccine: HEPLISAV-B®

- FDA licensed 11/9/17
- 5th inactivated HBV vaccine licensed for use in US (others: Engerix-B®, Recombivax HB®, Pediarix®, & Twinrix ®)
- Indicated for active immunization against infection caused by all known subtypes of HBV in persons aged ≥18 years
- Series of 2 doses, separated by 1 month
  - Likely improved adherence compared to 3 dose/6 month schedule
- Uses 1018 adjuvant, which binds Toll-like receptor 9 to stimulate directed immune response to hepatitis B surface antigen (HBsAg)

www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm584752.htm

Schillie S, Harris A, Link-Gelles R, Romero J, Ward J, Nelson N. 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 Apr 20;67(15):455-458.

Immunogenicity of HEPLISAV-B®

- Studies demonstrate high rates of seroprotection
- 90-100% of subjects receiving HEPLISAV-B® vs. 70.5-90.2% of subjects in comparison group
- Type 2 diabetes mellitus: 90% (HEPLISAV-B®) vs. 65.1% (comparator)
- Chronic kidney disease: 89.9% (HEPLISAV-B®,3 doses) vs. 81.1% (comparator, 4 double doses)

Halperin et al. *Vaccine*. 2006;24:20-26; Halperin et al. *Vaccine*. 2012;30:2556-2563; Heyward et al. *Vaccine*. 2013;31:5300-5305; Jackson et al. *Vaccine*. 2018;36:668-674;
Janssen et al. *Vaccine*. 2013;31:5306-5313; HEPLISAV-B package insert 11/2017.

Safety & Reactogenicity for HEPLISAV-B®

- Mild and serious adverse events similar*
  - Mild: 45.6% (HEPLISAV-B) vs. 45.7% (comparator)
  - Serious: 5.4% (HEPLISAV-B) vs. 6.3% (comparator)
- Cardiovascular events: 0.27% (HEPLISAV-B) vs. 0.14% (comparator)
- Potentially immune-mediated adverse events**
  - 0.1%-0.2% (HEPLISAV-B) vs. 0.0%-0.7% (comparator)
- Safety to be further assessed through post-marketing studies

*Herpes zoster: 0.68% (HEPLISAV-B) vs. 0.32% (comparator) (RR=2.1, 95% CI=1.0-4.0)
**e.g., granulomatosis with polyangiitis, Tolosa-Hunt Syndrome, autoimmune thyroiditis, vitiligo

Halperin et al., Vaccine 2006;24:20-26.
Halperin et al., Vaccine 2012;30:2556-2563.
Heyward et al., Vaccine 2013; 31:53005305.
Jackson et al., Vaccine 2018;36:668-674.
Janssen et al. Vaccine 2013;31:5306-5313.
HEPLISAV-B package insert 11/2017
U.S. FDA, HEPLISAV-B (https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm584752.htm)

Interchangeability and Dosing Schedule

- Data are limited on the safety and immunogenicity effects when HEPLISAV-B is interchanged with HepB vaccines from other manufacturers
- When feasible, the same manufacturer's vaccines should be used to complete the series
- Vaccination should not be deferred when the manufacturer of the previously administered vaccine is unknown or when the vaccine from the same manufacturer is unavailable

Dosing Considerations

- The 2-dose series only applies when all doses in the series consist of HEPLISAV-B

- When a vaccine series initiated with one dose of a vaccine from a different manufacturer must be completed with HEPLISAV-B, 3 total HepB vaccine doses should be administered

- Minimum intervals should be heeded (Exception: A series containing two doses of HEPLISAV-B administered at least 4 weeks apart is valid, even if the patient received a single earlier dose from another manufacturer)

HEPLISAV-B Summary

- HEPLISAV-B likely to improve Hepatitis B vaccine series completion and result in earlier protection (2 doses over 1 month)
  - Especially beneficial in persons with anticipated low adherence (e.g., injection drug users)
- Improved immunogenicity in populations with typically poor vaccine response
  - e.g., elderly, diabetes, dialysis
- Post-marketing surveillance studies and additional data, including safety, pertaining to the use of HEPLISAV-B will be reviewed by ACIP as they become available, and recommendations will be updated as needed
  - Prior to preferential consideration
- Future economic analyses may inform cost-effectiveness considerations of HEPLISAV-B, including its use among persons at an increased risk for vaccine non-response

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.