

## SPECIAL CONSIDERATIONS

Premature infants should be vaccinated according to the schedule recommended for other infants, beginning at age 2 months.

### *Lapsed Schedule*

According to ACIP guidelines on general recommendations for immunization, an interruption in a vaccination schedule does not require restarting the entire series of a vaccine or toxoid nor does it require the addition of extra doses. The series should be resumed with the next dose in the series, and any subsequent doses should be administered at the same interval as if the series had not been interrupted.

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## HEPATITIS A AND HEPATITIS A/B VACCINES

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### SHORELAND VACCINE RECOMMENDATIONS FOR TRAVELERS

#### *Indications for Travelers*

- Hepatitis A virus (HAV) infection is moderately to highly endemic in all developing countries, and all travelers to those destinations should receive hepatitis A vaccine.
- Travelers who do not perceive that their own itineraries warrant hepatitis A vaccine should be reminded that many cases of travel-related hepatitis A occur in travelers staying in deluxe accommodations in major cities and on “standard” tourist or resort itineraries, even if they exhibit caution in food- and beverage-consumption behaviors.
- Risk is highest for long-stay travelers; those with adventurous eating habits; those who travel outside pre-arranged, fixed itineraries (including common tourist packages), especially in rural areas; and those who eat or drink frequently in settings of poor sanitation.
- Some non-developing countries may have increased risk of hepatitis A associated with risk behaviors (including those listed above) that may warrant vaccination of such travelers or at least of those risk-averse travelers who desire maximum pre-travel protection.
- Shoreland recommends the use of hepatitis A vaccine for traveling children  $\geq 1$  year of age.
  - ♦ Hepatitis A vaccines are licensed in the U.S. and Canada for children as young as 1 year of age.
  - ♦ In the U.S., hepatitis A vaccine is a routine immunization for children at age 1 year.
- A single dose of single-antigen hepatitis A vaccine given any time before travel will provide adequate protection for most healthy persons.
- Travelers who are immunocompromised or who have chronic liver disease or other chronic medical conditions and are planning to depart in less than 2 weeks should receive both the initial dose of hepatitis A vaccine and IG.
- Travelers who choose not to receive vaccine or cannot receive vaccine due to allergy should receive 1 dose of IG.

- Risk of clinical illness is practically nonexistent for infants < 12 months of age who are staying or residing in settings with good hygiene (i.e., babies who are breastfed or bottle fed using safe water for formula reconstitution; babies eating commercial baby food with no exposure to locally prepared foods that adults would eat). IG is not routinely advised and is rarely given in this situation.
- Risk of mild clinical illness is low for infants < 12 months of age who are staying or residing in situations where there is significant exposure to local foods that adults would eat. IG may be given to these infants but only if there is concern about transmission of hepatitis A to unvaccinated household contacts.
- The combination hepatitis A/B vaccine is recommended in the U.S. for persons 18 years of age or older who are at risk for both forms of hepatitis.

**Note:** *Shoreland's vaccine recommendations, which focus primarily on the risk to the individual traveler, reflect a synthesis and reconciliation of available advice from CDC, ACIP, AAP, and WHO, as well as ongoing global surveillance and the published literature. These recommendations may differ from those of individual countries' public health authorities.*

## WHAT'S NEW

On January 14, 2010, ACIP published the 2010 adult immunization schedule for the U.S. (CDC: *MMWR* 59, No. 01: 1-4). Hepatitis A vaccine is now indicated for persons with close contact with children adopted from countries where hepatitis A is common. Close contacts include family members, baby sitters, and others expected to be in ongoing close contact with an international adoptee within 60 days of arrival. (See *Table ADT-1*.)

On January 8, 2010, ACIP published the recommended immunization schedules for 2010 for children aged 0-6 years (see *Table CH-1*) and for children and adolescents aged 7-18 years (see *Table CH-2*), as well as catch-up schedules (see *Tables CAT-1 and CAT-2*) for both age groups (*MMWR* 58, No. 51-52: 1-4). This schedule is also approved by AAP and AAFP.

**Author's Note:** ACIP, AAP, AAFP, and AMA strongly recommend a routine preventive care and immunization visit at age 11-12 years. This visit is an opportunity for the health care provider to administer routine and other vaccines (e.g., hepatitis A) that may be recommended for certain adolescents.

## GENERAL INFORMATION

### *Disease*

Hepatitis A is a viral infection of the liver characterized by malaise, fever, nausea, vomiting, and jaundice. HAV infection results in lifelong immunity to hepatitis A.

Transmission is primarily via person-to-person contact, generally through fecal contamination and oral ingestion. The virus can be spread through contaminated food (such as uncooked fruits and vegetables), shellfish, ice, and water. Transmission is facilitated by poor personal hygiene, poor sanitation, and intimate (intra-household or sexual) contact. Blood-borne transmission is uncommon but is possible via blood transfusion or contaminated blood products.

- Hepatitis A virus (HAV) is inactivated by boiling or cooking to > 185°F (85°C) for 1 minute, but it is possible for foods to become contaminated after cooking. Sufficient chlorination of water, as recommended in the U.S., will inactivate the virus.

The incubation period is usually 15-50 days (average 28). The disease usually does not last longer than 2 months, although 10-15% of symptomatic patients have signs and

symptoms for as long as 6 months. With HAV infections, relapsing hepatitis occurs; fulminant hepatitis is rare, and chronic hepatitis does not occur.

CDC estimates that before vaccine licensure in the U.S., approximately 22,000 to 36,000 hepatitis A cases were reported annually, but the actual number of infections was substantially higher. The highest incidence was in children 5-14 years. Since the late 1990s, coincident with implementation of vaccine recommendations, hepatitis A rates have declined to the lowest level ever recorded.

HAV infection is highly endemic throughout developing countries. For travelers to countries with intermediate or high levels of transmission, risk of HAV infection increases with duration of travel. Risk is highest for persons who live in or visit rural areas, trek in back country, eat or drink frequently in settings of poor sanitation, or have close physical contact with local persons (especially young children) in settings with poor sanitary conditions. Nevertheless, many cases of travel-related hepatitis A occur in travelers with “standard” tourist itineraries, accommodations, and food- and beverage-consumption behaviors.

### ***Vaccines - U.S.***

#### ***Hepatitis A vaccines***

- Havrix®, which has 2 formulations:
  - ♦ pediatric: Each 0.5 mL dose contains 720 ELISA Units.
  - ♦ adult: Each 1.0 mL dose contains 1,440 ELISA Units.
  - ♦ Havrix is thimerosal free and preservative free.
  - ♦ The tip cap and plunger of the syringe contain dry natural latex rubber.
- Vaqta®, which has 2 formulations:
  - ♦ pediatric/adolescent: each 0.5 mL dose contains approximately 25 units of hepatitis A virus antigen
  - ♦ adult: each 1.0 mL dose contains approximately 50 units of hepatitis A virus antigen
  - ♦ Vaqta is thimerosal free.
  - ♦ The vial stopper and syringe plunger contain dry natural latex rubber.

#### ***Combination hepatitis A/B vaccine***

- Twinrix® is composed of Havrix and Engerix-B.
  - ♦ Twinrix is not approved for persons < 18 years of age in the U.S.
  - ♦ Each 1.0 mL dose contains 720 ELISA units of hepatitis A virus antigen and 20 µg of hepatitis B virus antigen.
  - ♦ Twinrix is thimerosal free and preservative free.
  - ♦ The tip cap and plunger of the syringe contain dry natural latex rubber.

In contrast to immune globulin, hepatitis A vaccine is not derived from blood products. It is an inactivated, viral antigen vaccine.

Currently licensed hepatitis A vaccines can be used interchangeably.

Clinical studies for all currently licensed hepatitis A vaccines have demonstrated excellent protective efficacy, immunogenicity, and safety.

See “Immune Globulin” for information on IG used for prevention of hepatitis A.

***Vaccines - available outside the U.S.******Hepatitis A vaccine:***

- Avaxim® (sanofi pasteur) is available in Canada and elsewhere. In Canada, Avaxim is available in adult and pediatric formulations for ages  $\geq 12$  years and 1-15 years, respectively. A booster is given after 6-12 months.
  - ♦ This vaccine may have different approved age ranges and booster schedules in other countries. Check the package insert for the country of use.
  - ♦ This vaccine is thimerosal free.
- Havrix® (GSK) is available in Canada.
  - ♦ This vaccine is thimerosal free.
- Epaxal® (Berna) is licensed but not currently available in Canada.
  - ♦ This vaccine contains thimerosal.

***Combination hepatitis A/B vaccine:*** Twinrix (GSK) is available in adult and pediatric (Twinrix Junior) formulations in Canada and Europe.

- This vaccine contains a trace amount of thimerosal and should be considered equivalent to thimerosal-free products.

***Combination hepatitis A/typhoid vaccines:*** Several combined inactivated hepatitis A and Vi polysaccharide typhoid vaccines are available outside the U.S. Check package inserts carefully for full prescribing information.

- Vivaxim® (sanofi pasteur), for use in persons  $\geq 16$  years of age, is available in Canada, Europe, and many other countries. One dose of the combination vaccine administered IM is followed by a booster dose of hepatitis A vaccine 6-12 months later. Protection against typhoid lasts about 3 years. This vaccine is thimerosal free.
  - ♦ This vaccine is also known as Viatim in some countries.
- Viatim® (sanofi pasteur), for use in persons  $\geq 16$  years of age, is available in Europe. One dose of the combination vaccine administered IM is followed by a booster dose of hepatitis A vaccine 6-36 months later. Protection against typhoid lasts about 3 years. This vaccine is thimerosal free.
- Hepatyrix® (GSK), for use in persons  $\geq 15$  years of age, is available in the U.K. One dose of the combination vaccine administered IM is followed by a booster dose of hepatitis A vaccine 6-12 months later. Protection against typhoid lasts about 3 years. This vaccine is thimerosal free.

***Indications for Vaccination (ACIP, AAP)***

Routine childhood immunization with hepatitis A vaccine:

- All children should receive a dose of hepatitis A vaccine at age 1 year (i.e., 12-23 months), with a second dose given at least 6 months later.
  - ♦ Children not fully vaccinated by age 2 years can be vaccinated at subsequent visits.
- Vaccination is recommended for unvaccinated older children who live in areas where vaccination programs target older children; who are at increased risk of infection; or for whom immunity is desired.

- ◆ Catch-up vaccination of unvaccinated children ages 2-18 years can also be considered in areas without an existing program for vaccination of this age group, especially in the context of increasing incidence or ongoing outbreaks among children or adolescents.

Vaccinate any person seeking protection from hepatitis A virus (HAV) infection.

Vaccinate persons with the following indications:

- **Travel:** all susceptible persons traveling to or working in areas of intermediate or high risk for hepatitis A transmission, and especially persons who plan frequent trips or who have prolonged stays
  - ◆ Risk is highest for persons who live in or visit rural areas, trek in back country, eat or drink frequently in settings of poor sanitation, or have close physical contact with local persons (especially young children) in settings with poor sanitary conditions.
  - ◆ This recommendation does not include travelers to North America (except Mexico), Japan, Australia, New Zealand, or Western Europe.
  - ◆ A single dose of single-antigen hepatitis A vaccine given at any time before departure can provide adequate protection for most healthy persons.
  - ◆ Older adults, immunocompromised persons, and those who have chronic liver disease or other chronic medical conditions who are planning to depart in  $\leq 2$  weeks should receive the initial dose of hepatitis A vaccine and IG.
  - ◆ Children  $< 1$  year of age should receive IG.
- **Behavioral:** men who have sex with men; persons who use injection drugs
- **Occupational:** persons working with HAV-infected primates or with HAV in a research laboratory setting
- **Medical:** persons with chronic liver disease (including persons waiting for or who have received liver transplants); persons who receive clotting factor concentrates
- **Other:** Unvaccinated persons who anticipate close personal contact (household or regular babysitting) with an international adoptee from a country with high or intermediate endemicity during the first 60 days after arrival of adoptee in the U.S. should consider vaccination. The first dose should be administered as soon as adoption is planned, ideally  $> 2$  weeks before arrival of adoptee.

The combination hepatitis A/B vaccine is recommended for persons 18 years of age or older who are at risk for both forms of hepatitis.

### ADMINISTRATION: HAVRIX, TWINRIX

Federal law mandates that all U.S. health care providers who administer hepatitis A vaccine must provide the patient with the most current copy of CDC's *Vaccine Information Statement (VIS)* for hepatitis A prior to administering each dose of this vaccine. If the vaccinee is a child, the information should be given to the child's legal representative. If a combination hepatitis A/B vaccine is administered, a *VIS* for hepatitis B and a *VIS* for hepatitis A must be provided. Both the date the *VIS* was given to the patient and the publication date of the *VIS* should be recorded in the patient's chart. (See "Recordkeeping.")

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Vaccine doses administered  $\leq 4$  days before the minimum interval or age can be counted as valid, but this 4-day "grace-period" should not be used when scheduling future vaccination visits. Doses administered  $\geq 5$  days before the minimum age or interval should not be counted as valid doses and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval.

Also see "Accelerated Immunization Schedules."

**Pediatric (1-18 years)**

Hepatitis A vaccines are licensed in the U.S. for use in persons ages 1 year and older. Twinrix is licensed only for persons  $\geq 18$  years of age in the U.S. Adult and pediatric formulations are available in Canada and Europe.

***Dose/Route***

0.5 mL (720 ELISA Units), intramuscular, deltoid area; avoid buttock

***Schedule*** (see Tables CH-1 and CH-2)**Primary:**

Havrix - 2 doses (0, 6-12 months)

- Routine schedule for children age 1 year:
  - ♦ Give the first dose at age 1 year (12-23 months).
  - ♦ Give the second dose at least 6 months later.
- Schedule for unimmunized travelers age 1-18 years:
  - ♦ The first dose may be given at any time before departure, per ACIP (2-4 weeks per AAP; 2 weeks per manufacturer).
    - Persons with certain medical conditions and older adults should receive both hepatitis A vaccine and IG if departing in  $\leq 2$  weeks.
  - ♦ The second dose should be given 6-12 months after first dose (or at any time after 6 months have elapsed since the first dose). For persons with lapsed hepatitis A immunization (i.e.,  $> 12$  months), the second dose can be given regardless of the amount of time elapsed since the initial dose of vaccine. (See "Special Considerations.")
- Schedule for other persons at high risk: two doses given at least 6 months apart
  - ♦ WHO recommends the second dose be given anytime from 6 to 24 months after the first dose.
  - ♦ The literature suggests a good booster effect even when the second dose is administered up to 5 years later.

Twinrix - not licensed for persons  $< 18$  years of age

**Booster:** not yet determined

**Adult ( $> 19$  years)**

Note: Twinrix is licensed for persons  $\geq 18$  years of age in the U.S.

***Dose/Route***

Havrix: 1.0 mL (1,440 ELISA Units), intramuscular, deltoid area; avoid buttock

Twinrix: 1.0 mL (20  $\mu$ g of hepatitis B [Engerix-B] and 720 ELISA units of hepatitis A [Havrix]), intramuscular, in deltoid muscle for persons  $\geq 18$  years of age

**Schedule** (see Table ADT-1)**Primary:**

Havrix - 2 doses (0, 6-12 months)

- For travelers, give the first dose at any time before departure, per ACIP and AAP (2 weeks per manufacturer).
  - ♦ Older adults and persons with certain medical conditions should receive both hepatitis A vaccine and IG if departing in  $\leq 2$  weeks.
- Give the second dose 6-12 months after first dose (or at any time after 6 months have elapsed since the first dose). For persons with lapsed hepatitis A immunization (i.e.,  $> 12$  months), the second dose can be given regardless of the amount of time elapsed since the initial dose of vaccine. (See "Special Considerations.")
  - ♦ WHO recommends the second dose be given anytime from 6 to 24 months after the first dose.
  - ♦ The literature suggests a good booster effect even when the second dose is administered up to 5 years later.

Twinrix - 3 doses (0, 1, 6 months)

- Routine schedule: 1 dose each at 0, 1, and 6 months. First dose given at elected time; second dose given 1 month after first dose; third dose given 6 months after first dose.
- Accelerated schedule: 4 doses total—1 dose each on days 0, 7, and 21-30 and a fourth dose at 12 months. (The 4-day "grace period" does not apply to this accelerated schedule.) This accelerated regimen should be considered for departures occurring in less than 6 months where hepatitis B protection is needed.

Note: A complete hepatitis A series consists of any of the following combinations:

- 2 doses of hepatitis A vaccine
- 3 doses of Twinrix
- 2 doses of Twinrix + 1 dose hepatitis A vaccine\*
- 1 dose of Twinrix + 2 doses of hepatitis A vaccine\*

\* If a hepatitis A series was begun with but not completed using Twinrix, additional hepatitis A-containing vaccine is required, because the hepatitis A antigen content in a dose of Twinrix is half that of the hepatitis A antigen content in a dose of adult hepatitis A vaccine.

**Booster:** not yet determined

- Per WHO, a booster dose is not recommended.

## ADMINISTRATION: VAQTA

Federal law mandates that all U.S. health care providers who administer hepatitis A vaccine must provide the patient with the most current copy of CDC's *Vaccine Information Statement (VIS)* for hepatitis A prior to administering each dose of this vaccine. If the vaccinee is a child, the information should be given to the child's legal representative. Both the date the *VIS* was given to the patient and the publication date of the *VIS* should be recorded in the patient's chart. (See "Recordkeeping.")

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Vaccine doses administered  $\leq 4$  days before the minimum interval or age can be counted as valid, but this 4-day “grace-period” should not be used when scheduling future vaccination visits. Doses administered  $\geq 5$  days before the minimum age or interval should not be counted as valid doses and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval.

Also see “Accelerated Immunization Schedules.”

**Pediatric (1-18 years)**

Hepatitis A vaccines are licensed in the U.S. for use in persons ages 1 year and older.

***Dose/Route***

0.5 mL (approximately 25 units of hepatitis A virus antigen), intramuscular, deltoid muscle preferred; avoid buttock

***Schedule (see Tables CH-1 and CH-2)***

Primary: 2 doses (0, 6-18 months)

- Routine schedule for children age 1 year:
  - ♦ Give the first dose at age 1 year (12-23 months).
  - ♦ Give the second dose at least 6 months later (6-18 months).
- Schedule for unimmunized travelers age 1-18 years:
  - ♦ The first dose may be given at any time before departure, per ACIP and AAP (2 weeks per manufacturer).
    - Persons with certain medical conditions should receive both hepatitis A vaccine and IG if departing in  $\leq 2$  weeks.
  - ♦ Give the second dose 6-18 months after first dose (or at any time after 6 months have elapsed since the first dose). For persons with lapsed hepatitis A immunization (i.e.,  $> 18$  months), the second dose can be given regardless of the amount of time elapsed since the initial dose of vaccine. (“See *Special Considerations*.”)
- Schedule for other persons at high risk: 2 doses given at least 6 months apart (6-18 months)
- WHO recommends the second dose be given anytime from 6 to 24 months after the first dose.
- The literature suggests a good booster effect even when the second dose is administered up to 5 years after the first dose.

Booster: not yet determined

- Per WHO, a booster dose is not recommended.

**Adult ( $\geq 19$  years)*****Dose/Route***

1.0 mL (approximately 50 units of hepatitis A virus antigen), intramuscular, deltoid muscle preferred

***Schedule (see Table ADT-1)***

Primary: 2 doses (0, 6-18 months)

- For travelers, give the first dose at any time before departure, per ACIP and AAP (2 weeks per manufacturer).
  - ♦ Older adults and persons with certain medical conditions should receive both hepatitis A vaccine and IG if departing in  $\leq 2$  weeks.
- Give the second dose 6-18 months after first dose (or at any time after 6 months have elapsed since the first dose). For persons with lapsed hepatitis A immunization (i.e.,  $> 18$  months), the second dose can be given regardless of the amount of time elapsed since the initial dose of vaccine. (See "Special Considerations.")

Booster: not yet determined

## SIDE EFFECTS

Side effects tend to be mild and transient.

No serious adverse events have been observed.

Side effects of the combination hepatitis A/B vaccine (Twinrix) are reportedly similar in type and frequency to those of the individual vaccines (Havrix and Engerix-B) when given concurrently.

Suspected allergic or adverse effects or medical care required after any immunization should be reported through the Vaccine Adverse Event Reporting System (VAERS). See VAERS form and information.

### *Havrix*

In adults, the most frequent side effects are soreness at the injection site, headache, and malaise.

In children, the most frequent side effects are soreness and/or induration at the injection site, feeding problems, and headache.

### *Vaqta*

In clinical trials with both children and adults, the most frequent complaints were injection site reactions (pain, tenderness, warmth, and swelling).

Some adults also complained of headache, but this was less likely to occur in children and adolescents.

### *Twinrix*

Per package insert, the most common reactions are pain, redness, and swelling at the injection site. Secondary respiratory tract infections have been reported.

## PRECAUTIONS AND CONTRAINDICATIONS

### *General*

Consider postponing vaccination in persons with moderate or severe illness (with or without a fever) until recovery to minimize potential adverse effects.

Anaphylactic or other hypersensitive reaction to a previous dose contraindicates further immunization with that particular vaccine.

- Anaphylactic or other hypersensitive reaction to a vaccine constituent contraindicates the use of vaccines containing that substance.
- Havrix should not be administered to persons with a history of hypersensitive reaction to aluminum, aluminum hydroxide, or the preservative 2-phenoxyethanol.
- Vaqta should not be administered to persons with a history of hypersensitive reaction to aluminum or aluminum hydroxide.
- Twinrix should not be administered to persons with a history of hypersensitive reaction to neomycin, yeast, aluminum, 2-phenoxyethanol, or formalin.
- The tip cap and plunger of the syringes for Havrix and Twinrix contain dry natural latex rubber.
- The vial stopper and syringe plunger for Vaqta contain dry natural latex rubber.

Persons who are allergic to a vaccine component or choose not to receive the vaccine should receive a single dose of IG (0.02 mL/kg), which provides effective protection for up to 3 months. (See *"Immune Globulin"* for more information.)

### ***Bleeding Disorders***

This is an IM injection and may pose a risk for persons with bleeding disorders. See *"Guidelines on Vaccinating Persons with Bleeding Disorders."*

### ***Compromised Immunity***

No special precautions need to be taken in vaccination of immunocompromised persons.

If administered to persons with malignancies, immune disorders, or those on immunosuppressive therapy, the expected immune response may not be obtained.

### ***Pregnancy***

The safety of hepatitis A vaccine during pregnancy has not been determined; however, because hepatitis A vaccine is produced from inactivated hepatitis A virus, the theoretical risk to the developing fetus is expected to be low.

- The risk associated with vaccination should be weighed against the risk for hepatitis A in pregnant women who may be at high risk for exposure to hepatitis A virus.
- Immune globulin (IG) is a safe and effective means of preventing HAV, but immunization with 1 of the HAV vaccines gives a more complete and prolonged protection.

Per package insert, Twinrix should be given to pregnant women only if clearly indicated.

## **COMPATIBILITY**

There is no known incompatibility with other immunizations.

- For IG, see *"Special Considerations."*

Immunizations administered concurrently should be given at different sites.

## **SPECIAL CONSIDERATIONS**

### ***Postexposure prophylaxis***

ACIP and AAP recommendations:

- Hepatitis A vaccine (a single dose of single-antigen vaccine) is preferred over IG for healthy persons aged 12 months to 40 years.

- IG is preferred for persons > 40 years of age, but hepatitis A vaccine can be used if IG is unavailable.
- Children < 12 months of age, immunocompromised persons, persons with chronic liver disease, and those for whom vaccine is contraindicated should receive IG.

Per Canadian National Advisory Committee on Immunization, hepatitis A vaccine is recommended in preference to IG for postexposure prophylaxis of persons > 1 year of age.

Because hepatitis A has a relatively long incubation period, the vaccine may not prevent the disease in individuals who have an unrecognized hepatitis A infection at the time of vaccination.

**Duration of long-term protection:** Hepatitis A vaccines are highly immunogenic, with demonstration of antibodies to HAV persisting for at least 15 years. Based on this and other current scientific evidence, protection is considered to be lifelong after a complete hepatitis A vaccination schedule (2 doses).

**Prevaccination serologic testing** may be indicated for adult travelers who are likely to have had HAV infection, if testing costs less than vaccination and if testing will not interfere with completion of the vaccine series.

- This may include persons > 40 years of age, those with a history of hepatitis, older adolescents and adults in certain population groups (i.e., American Indians, Alaskan natives and Hispanics), adults in certain groups that have a high prevalence of infection (e.g., men who have sex with men), and adults who were either born in or lived for extensive periods in geographic areas that have a high endemism of hepatitis A infection.
- Anti-HAV IgM represents acute hepatitis A infection and antibodies decline over several months.
- Anti-HAV IgG represents previous hepatitis A infection and antibodies may persist for life.

**Postvaccination serologic testing** is not indicated because of the high rate of vaccine response among adults and children. In addition, not all testing methods used for routine diagnostic use in the U.S. have the sensitivity to detect low but protective anti-HAV concentrations after vaccination.

- It is not yet known what level of anti-HAV antibody is needed to give protection against infection.
- Persons tested for anti-HAV after immunization may not have detectable antibody but still may be protected.

Vaccination of an immune person is not contraindicated and does not increase the risk for adverse effects.

Different strengths and/or concentrations of Havrix may be available or may be used for different patient populations in some countries. If questions arise concerning these other formulations, contact the manufacturer directly.

### **Lapsed Schedule**

According to ACIP guidelines on general recommendations for immunization, an interruption in a vaccination schedule does not require restarting the entire series of a vaccine or toxoid nor does it require the addition of extra doses. The series should be resumed with the next dose in the series, and any subsequent doses should be administered at the same interval as if the series had not been interrupted.

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## HEPATITIS B AND HEPATITIS B COMBINATION VACCINES

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### SHORELAND VACCINE RECOMMENDATIONS FOR TRAVELERS

#### *Indications for Travelers*

Shoreland recommendations take into account destination, level of risk of hepatitis B in the country, duration of stay, and likelihood of high-risk activities. In the U.S. and many countries, hepatitis B is a routine childhood vaccine so that all children and adolescents should be vaccinated regardless of travel plans.

Indications for travelers to areas with high risk of hepatitis B include:

- prolonged stays
- frequent shorter stays in the same or other high-risk areas
- travelers with any possibility of a new sexual partner during the stay
- travelers with high potential to require medical or dental care in local facilities
  - ◆ those with underlying medical illness
  - ◆ those traveling for the purpose of seeking medical or dental care or consultation
  - ◆ adventure travelers
  - ◆ those who anticipate extensive use of local or public transportation
- travelers who might engage in tattooing, body piercing, or acupuncture
- health care workers
- any short-stay traveler who wishes to be protected against hepatitis B in the event of requiring medical care from local facilities

Indications for travelers to areas of lower risk of hepatitis B include:

- travelers with any possibility of a new sexual partner during the stay
- health care workers
- risk-averse travelers who desire maximum pre-travel protection

The combination hepatitis A/B vaccine is recommended for persons 18 years of age and older who are at risk for both forms of hepatitis.

**Note:** *Shoreland's vaccine recommendations, which focus primarily on the risk to the individual traveler, reflect a synthesis and reconciliation of available advice from CDC, ACIP, AAP, and WHO, as well as ongoing global surveillance and the published literature. These recommendations may differ from those of individual countries' public health authorities.*

### WHAT'S NEW

On January 14, 2010, ACIP published the 2010 adult immunization schedule for the United States (CDC: *MMWR* 59, No. 01: 1-4). See *Table ADT-1*.

On January 8, 2010, ACIP published the recommended immunization schedules for 2010 for children aged 0-6 years (see *Table CH-1*) and for children and adolescents aged 7-18

years (see Table CH-2), as well as catch-up schedules (see Tables CAT-1 and CAT-2) for both age groups (MMWR 58, No. 51-52: 1-4). This schedule is also approved by AAP and AAFP.

**Author's Note:** ACIP, AAP, AAFP, and AMA strongly recommend a routine preventive care and immunization visit at age 11-12 years, which should include initiation or completion of the 3-dose hepatitis B series, if indicated.

A *Vaccine Information Statement (VIS)* for multiple pediatric vaccines is available and can be used in place of individual VISs whenever more than 1 of the routine birth through 6-month vaccines (i.e., DTaP, IPV, Hib, Hepatitis B, PCV, or Rotavirus) are administered at the same visit; this also includes combination vaccines (e.g., Pediarix® or Comvax®) that contain these vaccine components. Providers may use either the multiple vaccine VIS, when appropriate, or the individual VISs for each of these pediatric vaccines.

## GENERAL INFORMATION

### Disease

Hepatitis B (formerly known as serum hepatitis) is a serious infection of the liver caused by the hepatitis B virus (HBV). More than 2 billion people worldwide have been infected with HBV, and more than 350 million have chronic, lifelong infections. HBV infection is a major cause of acute and chronic hepatitis and cirrhosis, and is the cause of up to 80% of hepatocellular carcinomas. The average incubation period of hepatitis B is 90 days (range: 60-150 days).

HBV infection may occur in 2 phases: acute or chronic.

- The acute phase occurs just after the person is infected and lasts from several weeks to a few months, although about 50% of infected adults are asymptomatic.
- The chronic phase follows the acute phase in some instances, and the person becomes a “chronic carrier” with HBV remaining in the liver and blood.

Modes of transmission include:

- exposure to contaminated blood and blood products
- use of contaminated needles, razors, dental and medical equipment, and tattooing and body-piercing devices
- sexual contact with infected individuals
- perinatal transmission from mother to infant, primarily at the time of birth
  - ♦ Ninety percent of infants infected by perinatal transmission become chronic carriers and 25% eventually die of hepatic carcinoma or other liver disease.
  - ♦ Breastfeeding by an HBsAg-positive mother does not add to the risk of the infant acquiring HBV.

The frequency of HBV infection and patterns of transmission vary markedly in different parts of the world. Per CDC, the prevalence of chronic HBV infection is low (< 2%) in the general population in northern and western Europe, North America, Australia, New Zealand, Mexico, and southern South America. Prevalence is intermediate (2-7%) in south-central and southwest Asia, Israel, Japan, eastern and southern Europe, Russia, most areas surrounding the Amazon River basin, Honduras, and Guatemala. Prevalence is high (> 8%) in all socioeconomic groups in Africa; Southeast Asia (including China, Korea, Indonesia, and the Philippines); the Middle East (except Israel); South and Western Pacific islands; the interior Amazon River basin; and parts of the Caribbean (Haiti and the Dominican Republic).

### **Vaccines - U.S.**

Five hepatitis B immunization products are licensed in the U.S.: 2 single-antigen hepatitis B vaccines (various formulations; *see below*) and 3 combination vaccines. This is a recombinant, inactivated viral antigen vaccine.

#### ***Hepatitis B vaccines***

- Recombivax HB<sup>®</sup>, which has 3 formulations:
  - ♦ pediatric/adolescent: 10 µg/mL; each 0.5 mL dose contains 5 µg of HBsAg.
    - thimerosal free
  - ♦ adult: 10 µg/mL; each 1 mL dose contains 10 µg of HBsAg.
    - thimerosal free
  - ♦ dialysis: 40 µg/mL; each 1 mL dose contains 40 µg of HBsAg.
    - Per manufacturer, if the suggested formulation is not available, the appropriate dose can be achieved by using another formulation, provided the total volume of vaccine does not exceed 1 mL. However, the dialysis formulation should be used only for adult predialysis/dialysis patients.
    - thimerosal free
  - ♦ The vials and the tip cap and plunger of the syringes contain latex.
- Engerix-B<sup>®</sup>, which has 2 formulations:
  - ♦ pediatric/adolescent: 10 µg/0.5 mL; each 0.5 mL dose contains 10 µg of HBsAg.
  - ♦ adult: 20 µg / 1 mL; each 1 mL dose contains 20 µg of HBsAg.
  - ♦ These formulations are preservative free and thimerosal free.
  - ♦ The tip cap and plunger of the syringe contain dry natural latex rubber.
  - ♦ Providers should visually inspect vials and syringes for cracks prior to use.

#### ***Hepatitis B-containing combination vaccines***

- Comvax<sup>®</sup> (Hib/HepB) combination vaccine is composed of PedvaxHIB<sup>®</sup> (*Haemophilus b* conjugate [meningococcal protein conjugate]) and Recombivax HB [hepatitis B recombinant vaccine].
  - ♦ Comvax is approved for use in children aged 6 weeks to 15 months; 1 dose is 0.5 mL.
  - ♦ This vaccine should be administered at approximately 2, 4, and 12-15 months of age to infants of HBsAg-negative mothers. (*See the administration section for further details.*)
  - ♦ Comvax<sup>®</sup> is thimerosal free.
  - ♦ The vial stopper contains natural rubber latex.
- Twinrix<sup>®</sup> (HepA/B) is a combination of Engerix-B and Havrix (hepatitis B and hepatitis A vaccines).
  - ♦ Adult: each 1.0 mL dose contains 720 ELISA units of hepatitis A virus antigen and 20 µg of hepatitis B virus antigen.
  - ♦ Twinrix is not approved for use in persons < 18 years of age in the U.S.

- ◆ Twinrix is thimerosal free and preservative free.
- ◆ The tip cap and plunger of the syringe contain dry natural rubber latex.
- Pediarix® (DTaP/HepB/IPV) is a combination of Inactivated Poliovirus Vaccine, Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, and Hepatitis B (Recombinant) vaccines.
  - ◆ Approved for use in children aged 6 weeks to 7 years; 1 dose is 0.5 mL.
  - ◆ Pediarix is licensed only for the first 3 doses of the series and is usually given at 2, 4, and 6 months of age.
    - Per manufacturer, Pediarix may be administered as early as 6 weeks of age.
  - ◆ Pediarix is preservative free and thimerosal free.
  - ◆ The tip cap and plunger of the syringe contain dry natural rubber latex.

Recombivax HB, Engerix-B, and Twinrix are genetically engineered, so there is no risk of contracting the HIV virus through them. However, plasma-derived vaccine is used in many other countries.

Recombivax HB and Engerix-B contain different concentrations of HBsAg protein but have the same efficacy and can be used interchangeably.

Thirty to fifty-five percent (30-55%) of healthy adults  $\leq$  40 years of age develop protective anti-HBs (antibodies) after the first dose of hepatitis B vaccine; about 75% do so after the second dose, and 90% after the third.

- Per WHO, because of the long incubation period of hepatitis B, some protection will be afforded to most travelers following the second dose given before travel. The final dose should always be given upon return.

In worldwide clinical trials of Twinrix, 1 month after completing the 3-dose schedule, seroconversion for antibodies against HAV was elicited in 99.9% of vaccinees and protective antibodies against HBV were detected in 98.5%.

### *Vaccines - available outside the U.S.*

**Combination hepatitis A/B vaccine:** Twinrix (GSK) is available in adult and pediatric (Twinrix Junior) formulations in Canada and Europe.

- This vaccine contains a trace amount of thimerosal and should be considered equivalent to thimerosal-free products.

### *Indications for Vaccination (CDC, WHO)*

CDC recommends hepatitis B immunization for all unvaccinated adults at risk for HBV infection and all adults requesting protection from HBV infection.

CDC recommends hepatitis B immunization for all infants, children, and adolescents < 19 years of age.

**Birth dose:** The first dose (of monovalent hepatitis B vaccine) should be given to all newborns at birth (or before hospital discharge).

Infants born to mothers who are HBsAg-positive should receive both hepatitis B vaccine and HBIG within 12 hours of birth.

- Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg at age 9-18 months, after completion of the vaccine series.

- Preterm infants weighing < 2,000 g born to HBsAg-positive mothers should receive both hepatitis B vaccine and HBIG within 12 hours of birth.
  - ♦ Administer 3 additional hepatitis B vaccine doses: either single-antigen vaccine at ages 1, 2-3, and 6 months, or combination vaccine: Pediarix at 2, 4, and 6 months, or Comvax at 2, 4, and 12-15 months.
- These infants should be tested for HBsAg and anti-HBs after completion of at least 3 doses of the series, at age 9-18 months.

Infants born to mothers whose HBsAg status is unknown should receive hepatitis B vaccine within 12 hours of birth. The mother should have blood drawn as soon as possible to determine her HBsAg status; if her results are positive, the infant should receive HBIG as soon as possible but no later than age 7 days.

- If the mother is HBsAg-positive, the infant should be tested for HBsAg and antibody to HBsAg at age 9-18 months, after completion of the vaccine series.
- Because of the potentially decreased immunogenicity of vaccine in preterm infants weighing < 2,000 g born to mothers of unknown HBsAg status, these infants should receive both hepatitis B vaccine and HBIG if the mother's HBsAg status cannot be determined *within 12 hours of birth*.
  - ♦ Administer 3 additional hepatitis B vaccine doses: either single-antigen vaccine at 1, 2-3, and 6 months, or combination vaccine: Pediarix at 2, 4, and 6 months, or Comvax at 2, 4, and 12-15 months.

Infants born to mothers who are HBsAg-negative should receive hepatitis B vaccine at birth or before hospital discharge.

- The birth dose of hepatitis B vaccine should be delayed until age 1 month or given at hospital discharge for preterm infants weighing < 2,000 g born to HBsAg-negative mothers.
  - ♦ Complete the vaccine series with single-antigen vaccine at 2 and 6-18 months, or combination vaccine: Pediarix at 2, 4, and 6 months or Comvax at 2, 4, and 12-15 months.

#### *Completion of the childhood series*

- The hepatitis B series should be completed with either single-antigen hepatitis B vaccine or a combination vaccine containing hepatitis B vaccine. (Combination vaccines cannot be used for the birth dose or for children < 6 weeks of age.)
  - ♦ The second dose should be given at age 1-2 months.
  - ♦ The final dose should be given at age  $\geq$  24 weeks.
- Administering 4 doses of hepatitis B vaccine is permitted (e.g., when combination vaccines are administered after the birth dose). If single-antigen vaccine is used, a dose at age 4 months is not needed.
- Preterm infants weighing < 2,000 g whose mothers are HBsAg-positive or of unknown status who receive hepatitis B vaccine at birth require an additional 3 doses (4 total doses) to complete the series, as the birth dose is not countable in these infants. (*See the administration section for details.*)
- Preterm infants weighing < 2,000 g whose mothers are HBsAg-negative should complete the series with single-antigen vaccine at ages 2 months and 6-18 months, or Pediarix at ages 2, 4, and 6 months, or Comvax at ages 2, 4, and 12-15 months.
- The final dose in the vaccine series should not be given before age 24 weeks.

### *Catch-up schedule*

Children and adolescents not previously vaccinated should receive 3 doses. (See the administration section.)

- A 2-dose series of adult formulation Recombivax HB is licensed for children aged 11-15 years.

### *Pregnant women*

CDC recommends routine screening for HBsAg during an early prenatal visit (i.e., during the first trimester) in each pregnancy, even if previously vaccinated or tested, because HBV infection during pregnancy can cause serious disease in the mother and chronic infection in the newborn.

Pregnant women who are identified as being at risk for hepatitis B virus infection during pregnancy (e.g., those who have had more than 1 sex partner in last 6 months, have been evaluated or treated for an STD, recent or current injection drug use, or have had an HBsAg-positive sex partner) should be vaccinated.

### *Other high-risk groups*

Hepatitis B immunization is also recommended for the following high-risk groups:

- international travelers, when indicated (see “Travelers,” below)
- unvaccinated children < 19 years of age who are Alaskan natives or Pacific Islanders and children who reside in households of first-generation immigrants from countries or regions where HBV infection is of high or intermediate endemicism (e.g., Africa, Asia)
- adoptees from countries where HBV infection is endemic and the household contacts of HBV-positive adoptees (When possible, parents should learn the HBV status of the child and vaccinate household contacts, as needed, prior to adoption.)
- workers and students in health care or public safety whose tasks may entail exposure to human blood, especially via needle sticks, or other potentially infectious body fluids (See “Health Care Workers.”)
- persons with chronic liver disease
- persons with end-stage renal disease
- hemodialysis patients
- persons receiving a solid organ transplant prior to transplantation, if seronegative
- persons with HIV infection
- household contacts and sex partners of persons with chronic HBV infection
- staff and residents of institutions for the developmentally disabled
- injection drug users (current or recent)
- men who have sex with men
- sexually active persons who have a history of sexual activity with more than 1 partner in the past 6 months
- persons seeking evaluation or treatment for a sexually transmitted disease (STD); all clients of STD clinics

- inmates of juvenile detention centers and long-term correctional facilities who have histories of high-risk behavior
- subpopulations with a known high incidence of hepatitis
- Per 1997 consensus conference of National Institutes of Health (NIH), persons who test positive for hepatitis C virus should receive HepB (*JAMA* 277, No. 16: 1268-69, April 23/30, 1997).
  - ♦ In August 1998, FDA approved hepatitis B vaccine (Engerix-B) for use in individuals suffering from chronic hepatitis C infection.

### *Adults*

- Hepatitis B vaccine is recommended for all unvaccinated adults at risk for HBV infection.
- Hepatitis B vaccine can be given to any adult seeking protection against HBV infection.

### *Settings where hepatitis B vaccination is recommended for all adults:*

- STD treatment facilities
- HIV testing and treatment facilities
- facilities providing drug-abuse treatment and prevention services
- health care settings providing services for injection drug users or men who have sex with men
- correctional facilities
- end-stage renal disease facilities
- facilities for chronic hemodialysis patients
- institutions and non-residential facilities for persons with developmental disabilities

*Special formulation indications:* for adult patients receiving hemodialysis and other immunocompromised adults, 1 dose of 40  $\mu\text{g}/\text{mL}$  (Recombivax HB) administered on a 3-dose schedule or 2 doses of 20  $\mu\text{g}/\text{mL}$  (Engerix-B), administered simultaneously, on a 4-dose schedule at 0, 1, 2, and 6 months.

### *Travelers*

Per CDC, hepatitis B immunization is recommended for the following groups of travelers:

- all unvaccinated travelers to areas with intermediate to high levels of endemic HBV transmission (i.e., HBsAg prevalence > 2%)
  - ♦ Modes of HBV transmission in areas of high risk or intermediate levels of chronic HBV that are important for travelers to consider are contaminated injection or other equipment used for health care procedures and blood transfusions from unscreened donors.
- persons working in health care fields in high or moderate HBV-endemic areas
- regardless of destination, all unvaccinated travelers who might engage in practices that might put them at risk for HBV infection (e.g., unprotected sex and sharing illegal drug injection equipment)

Per WHO, consider vaccination for virtually all non-immune travelers to areas with moderate to high levels of endemic HBV infection.

**Following HBV exposure**

Infants born to mothers who are HBsAg-positive or of unknown HBsAg status: See "Birth dose," above. (Also see MMWR 54, No. RR-16, 2005.)

Occupational settings (see MMWR 50, No. RR-11, 06/29/01):

- Hepatitis B vaccine should be initiated (or the vaccine series completed) within 7 days (preferably 24 hours) of any percutaneous or permucosal exposure unless the exposed person has been vaccinated and has an adequate anti-HBs level.
- When indicated, passive prophylaxis with HBIG should be administered as soon as possible after exposure (preferably within 24 hours).
- Any blood or body fluid exposure should lead to initiation of the hepatitis B vaccine series if unvaccinated.

Non-occupational settings (see MMWR 55, No. RR-16, 12/08/06):

- HBsAg-positive exposure source
  - ♦ Persons with written documentation of a complete vaccine series but who did not receive post-vaccination testing should receive a single booster dose of hepatitis B vaccine.
  - ♦ Persons who are in the process of being vaccinated but who have not completed the series should receive HBIG and complete the vaccine series.
  - ♦ Unvaccinated persons should receive both HBIG and hepatitis B vaccine as soon as possible after exposure (preferably within 24 hours) and complete the vaccine series.
- unknown HBsAg status exposure source
  - ♦ Persons with written documentation of a complete hepatitis B vaccine series require no further treatment.
  - ♦ Persons who are not fully vaccinated should complete the series.
  - ♦ Unvaccinated persons should receive the hepatitis B vaccine series with the first dose administered as soon as possible after exposure (preferably within 24 hours).

**Combination hepatitis A/B vaccine**

Combination hepatitis A/B vaccine is recommended for persons  $\geq 18$  years of age who are at risk for both forms of hepatitis.

## ADMINISTRATION: HEPATITIS B VACCINES AND HEPATITIS B COMBINATION VACCINES

Federal law mandates that all U.S. health care providers must provide the most current *Vaccine Information Statement (VIS)* for hepatitis B before this vaccine is given. If the vaccinee is a child, the information should be given to the child's legal representative. If a combination hepatitis A/B vaccine is administered, a *VIS* for hepatitis B must be provided and a *VIS* for hepatitis A, while not required by federal law, may be provided. Both the date the *VIS* was given to the patient and the publication date of the *VIS* must be recorded in the patient's chart. (See "Recordkeeping.")

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Vaccine doses administered  $\leq 4$  or fewer days before the minimum interval or age can be counted as valid, but this 4-day “grace-period” should not be used when scheduling future vaccination visits. Doses administered  $\geq 5$  days before the minimum age or interval should not be counted as valid doses and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval.

For schedule modifications for persons who will be traveling internationally and for children and adolescents completing the primary series, see “Accelerated Immunization Schedules.”

See “Vaccines” for explanation of mL/ $\mu$ g variations.

**Pediatric (< 19 years)**

Note: In the U.S., Twinrix is approved only for use in persons  $\geq 18$  years of age. A pediatric formulation, Twinrix Junior, is available in Canada and Europe.

**Dose:** dependent on vaccine, age, and hepatitis B surface antigen (HBsAg) status of mother

- Recombivax HB: 5  $\mu$ g (0.5 mL)
  - ♦ Recombivax HB has also been approved as a 2-dose schedule for adolescents 11-15 years of age using the 10  $\mu$ g/mL *adult formulation*, with the 2 doses given 4-6 months apart.
- Engerix-B: 10  $\mu$ g (0.5 mL)
  - ♦ Per manufacturer, 20  $\mu$ g should be administered when Engerix-B is used with an alternate schedule (0, 1, 2, 12 months) for 11-19 year olds.
  - ♦ ACIP does not currently address this dosage issue with the alternate schedule. See “Accelerated Immunization Schedules.”
- Comvax: 5  $\mu$ g HBsAg and 7.5  $\mu$ g *Haemophilus b* PRP (0.5 mL)
- Pediarix: DTaP/HepB/IPV combination vaccine (0.5 mL)
- Twinrix: See “Administration - Adult,” for persons  $\geq 18$  years of age. (In the U.S., Twinrix is approved only for use in persons  $\geq 18$  years of age.)

**Route:** Intramuscular; deltoid muscle is preferred, but in neonates and infants the anterolateral thigh may be more suitable (avoid buttock).

- Per manufacturer, Comvax should be given IM; anterolateral thigh is preferred.
- Per manufacturer, Pediarix should be given IM; the anterolateral thigh or deltoid muscle are the preferred sites.

**Schedule** (see Tables CH-1, CH-2, CAT-1, and CAT-2)

- Only single-antigen hepatitis B vaccine can be used for the birth dose.
- Give 3 doses if using single-antigen hepatitis B vaccine for the series, unless otherwise indicated:
  - ♦ Preterm infants weighing  $< 2,000$  grams at birth: When a birth dose is given in these infants, it is not a countable dose, and these infants should receive an additional 3 doses (for a total of 4 doses).
  - ♦ The birth dose of hepatitis B vaccine may be delayed until age 1 month in preterm infants weighing  $< 2,000$  g born to HBsAg-negative mothers.
- If the series is completed with combination vaccine (hepatitis B/Hib or DTaP/Hep B/IPV), 4 doses will be given (1 single-antigen dose at birth, followed by 3 doses of combination vaccine).

- When Pediarix is used following a birth dose of vaccine, the third dose of Pediarix should be given at least 16 weeks after the first Pediarix dose and at least 8 weeks after the second Pediarix dose but not before age 24 weeks.
- The last dose in the vaccine series (whether third or fourth dose) should not be given before age 24 weeks.

See "Accelerated Immunization Schedules" for accelerated schedule options for children and adolescents completing the primary series.

**Primary:** dependent upon age of child and/or HBsAg status of mother:

***Infants born to mothers who are HBsAg-positive:***

- Give first dose of hepatitis B vaccine and 0.5 mL HBIG (IM) at separate sites within 12 hours of birth.
  - ♦ Preterm infants < 2,000 g: the birth dose of hepatitis B vaccine is not countable and the infant will need 3 additional doses (total of 4 doses). The 3 additional doses are given at ages 1, 2-3, and 6 months if using single-antigen vaccine, or ages 2, 4, and 12-15 months if using Comvax, or at ages 2, 4, and 6 months if using Pediarix.
- Give second dose of vaccine at age 1-2 months, and the third dose at age 6 months. The last dose in the series (whether third or fourth dose) should not be given before age 24 weeks.
- These infants should be tested for HBsAg and anti-HBs at 9-18 months of age after completion of the vaccine series.
- Engerix-B package insert lists 2 schedule options for newborns of HBsAg-positive mothers: the standard schedule (0, 1, and 6 months) and an alternate schedule (0, 1, 2, and 12 months). Per ACIP, there is no clear evidence that the 4-dose schedule provides greater protection than the standard 3-dose schedule.
- See "Post-Vaccination Testing" under "Special Considerations."

***Infants born to mothers whose HBsAg status is unknown:***

- Infants born to mothers whose HBsAg status is unknown should receive hepatitis B vaccine within 12 hours of birth. The mother should have blood drawn as soon as possible to determine her HBsAg status. If her results are positive, the infant should also receive 0.5 mL HBIG (IM) as soon as possible (no later than 7 days after birth), given at a separate site; however, per ACIP, if HBIG is given > 48 hours after birth, efficacy is not known.
  - ♦ Because of the potentially decreased immunogenicity of vaccine in preterm infants weighing < 2,000 g born to mothers of unknown HBsAg status, these infants should receive both hepatitis B vaccine and HBIG if the mother's HBsAg status cannot be determined *within 12 hours of birth*.
    - If the mother's status is found to be HBsAg-positive, these infants should be tested for HBsAg and anti-HBs at 9-18 months of age after completion of the vaccine series. See "Post-Vaccination Testing" under "Special Considerations."
  - ♦ Preterm infants < 2,000 g: the birth dose of hepatitis B vaccine is not countable and the infant will need 3 additional doses (total of 4 doses). The 3 additional doses are given at ages 1, 2-3, and 6 months if using single-antigen vaccine, or ages 2, 4, and 12-15 months if using Comvax, or at ages 2, 4, and 6 months if using Pediarix.

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- Give the second dose of vaccine at age 1-2 months, and third dose at age 6 months. The last dose in the series (whether third or fourth dose) should not be given before age 24 weeks.

*Infants born to HBsAg-negative mothers:*

- Give 3 doses—first dose at birth (or before hospital discharge).
  - ♦ Preterm infants weighing < 2,000 g born to HBsAg-negative mothers: the first dose of hepatitis B vaccine should be postponed until chronological age 1 month or given at hospital discharge. Complete the series with single-antigen vaccine at ages 2 months and 6-18 months, or Pediarix at 2, 4, and 6 months, or Comvax at 2, 4, and 12-15 months.
- Give the second dose at least 1 month after the first (range, 1-2 months of age).
  - ♦ If combination vaccine is used to complete the series, do not give before 6 weeks of age.
- Give the third dose at least 16 weeks after the first dose and at least 8 weeks after the second dose (range, 6-18 months of age for single-antigen vaccine).
- The last dose in the series (third or fourth dose) should not be given before age 24 weeks.
  - ♦ Per CDC, limited data from Merck Research Laboratories suggest there is an augmented response when the third dose is given after 12 months of age.
- In populations with currently or previously high rates of childhood HBV infection (Alaskan Natives; Pacific Islanders; and immigrant families from Asia, Africa, and other regions with intermediate or high endemic rates of infection), the first dose should be given at birth and the final dose at age 6-12 months.
- The manufacturer of Engerix-B recommends a 0, 1, 6-month schedule for infants of HBsAg-negative mothers, although the 0, 1, 2, 12-month schedule is acceptable under certain circumstances, such as travel to high-risk areas. Per ACIP, there is no clear evidence that the 4-dose schedule provides greater protection than the standard 3-dose schedule.
- Per manufacturer, when immunization is initiated at age 2 months, Comvax (a combination of PedvaxHIB and Recombivax HB) may be used and continued at 4 months and 12-15 months of age.
  - ♦ Comvax requires an interval between the first 2 doses of at least 2 months and an interval between the second and third dose as close as possible to 8-11 months.
- Per manufacturer, when immunization is initiated at age 2 months, Pediarix (DTaP/HepB/IPV) may be used and continued at 4 and 6 months of age. The third dose should be given at least 16 weeks after the first dose and at least 8 weeks after the second dose, but not before age 24 weeks.

*Previously unimmunized infants (age 4 months or older) and children:*

- Give 3 doses, using a 0, 1, 6-month schedule; the second and third doses should be administered 1 and 6 months, respectively, after the first dose.
  - ♦ An acceptable alternative schedule is 0, 1-2, 4 months. The second dose should be administered at least 1 month after the first dose, and the third dose should be given at least 4 months after the first dose and at least 2 months after the second dose. The third dose must be given *at or after age 6 months* to be countable.

- The manufacturer of Engerix-B recommends the 0, 1, 6-month schedule for infants of HBsAg-negative mothers, although the 0, 1, 2, 12-month schedule is acceptable under certain circumstances, such as travel to high-risk areas. Per ACIP, there is no clear evidence that the 4-dose schedule provides greater protection than the standard 3-dose schedule.
- For infants and children < 7 years of age who start the series late or are more than a month behind in the immunization schedule, *see Table CAT-1* for administering hepatitis B vaccine in conjunction with other routine immunizations.
- For persons age  $\geq 7$  years, *see Table CAT-2* for administering hepatitis B vaccine in conjunction with other routine immunizations.

*Previously unimmunized adolescents:*

- For adolescents who are not fully immunized, the 3-dose series should be initiated, continued, or completed at any visit. The second dose should be given at least 1 month after the first dose, and the third dose should be given at least 4 months after the first dose and at least 2 months after the second dose.
- Recombivax HB can be given using an alternate, 2-dose schedule for children age 11-15 years, using the 10  $\mu\text{g}/\text{mL}$  adult formulation, with the 2 doses given 4-6 months apart. When scheduled to receive the second dose and if the adolescent is > 15 years of age, switch to a 3-dose series, with doses 2 and 3 consisting of the pediatric formulation administered on an appropriate schedule.
- For children and adolescents 11-19 years of age, the manufacturer of Engerix-B lists an alternate schedule (20  $\mu\text{g}$ ) at 0, 1, 2, 12 months, although per ACIP there is no clear evidence that this schedule provides greater protection than the standard 3-dose schedule.
  - ♦ An alternate schedule approved for Engerix-B for adolescents is 0, 12, and 24 months.
- *See "Accelerated Immunization Schedules" for accelerated schedule options for children and adolescents completing the primary series.*

**Booster:** The need for routine booster doses has not yet been determined. (*See also "Compromised Immunity" and "Post-Vaccination Testing" under "Special Considerations."*)

### **Adult ( $\geq 19$ years)**

Note: Twinrix is approved in the U.S. for use in persons  $\geq 18$  years of age. A pediatric formulation is available in Canada and Europe.

#### ***Dose/Route***

Recombivax HB: 10  $\mu\text{g}$  (1.0 mL), intramuscular, in deltoid muscle (not in buttock)

Engerix-B: 20  $\mu\text{g}$  (1.0 mL), intramuscular, in deltoid muscle (not in buttock)

Twinrix: 1.0 mL (20  $\mu\text{g}$  of hepatitis B [Engerix-B] and 720 ELISA units of hepatitis A [Havrix]), intramuscular, in deltoid muscle. (Licensed for use in persons  $\geq 18$  years of age in the U.S.)

#### ***Schedule*** (*see Table ADT-1*)

##### **Primary:**

- Recombivax HB or Engerix-B: Give 3 doses—1 dose each at 0, 1, and 6 months.

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- ◆ The first dose is given at the elected time; the second dose is given 1 month after the first dose; the third dose is given 6 months after the first dose.
- ◆ The routine schedule (0, 1, 6 months) can also be given using the following ranges: 0, 1-2, and 4-6 months, as long as the third dose is given at least 2 months after the second, and at least 4 months after the first.
- ◆ Engerix-B lists an alternate schedule of 0, 1, 2, and 12 months for certain travelers to high-risk destinations.
- ◆ See “Accelerated Immunization Schedules” for accelerated hepatitis B vaccine schedules for adult travelers.
- Twinrix
  - ◆ Routine schedule (3 doses): 1 dose each at 0, 1, and 6 months. The first dose is given at the elected time; the second dose is given 1 month after the first dose; the third dose is given 6 months after the first dose.
  - ◆ Accelerated schedule (4 doses): 4 doses total—1 dose each on days 0, 7, and 21-30, and a fourth dose at 12 months.
    - Consider this accelerated regimen for departures scheduled in less than 6 months’ time from areas where hepatitis B protection is needed.

For international travel, vaccination should—ideally—be initiated at least 6 months before travel in order to complete the hepatitis B vaccine series prior to departure. When time does not allow completion according to the routine schedule, an accelerated schedule can be considered.

Note: Any combination of 3 doses of adult hepatitis B vaccine and Twinrix is considered a complete hepatitis B adult primary series.

Booster: The need for booster doses has not yet been determined.

- Per AAP, hemodialysis and other immunocompromised patients at continued risk of infection should have anti-HBs testing annually and should be boosted if the anti-HBs concentration is < 10 mIU/mL. (See “Compromised Immunity” and “Post-Vaccination Testing” under “Special Considerations.”)

## SIDE EFFECTS

Pain at the site of injection and fever > 37.7°C are the most commonly reported side effects; others reported include tenderness, redness and/or itching at the injection site, headache, and nausea. These effects are usually mild and do not require special treatment.

Side effects of Comvax (PedvaxHIB + Recombivax HB) are reportedly similar to those of the individual vaccines given concurrently.

Side effects of Twinrix (Havrix + Engerix-B) are reportedly similar to those of the individual vaccines given concurrently.

Side effects of Pediarix (DTaP/HepB/IPV vaccine) are similar to those of the individual vaccines given concurrently.

- Per manufacturer, Pediarix is associated with higher rates of fever relative to separately administered component vaccines.

Suspected allergic or adverse effects, or medical care required after any immunization, should be reported through the Vaccine Adverse Event Reporting System (VAERS). See VAERS form and information.

## PRECAUTIONS AND CONTRAINDICATIONS

### *General*

Moderate or severe illness, with or without a fever, is considered a contraindication; delay vaccination until recovery.

Anaphylactic reaction to a previous dose contraindicates further immunization *with that particular vaccine*.

Anaphylactic reaction to a vaccine constituent contraindicates the use of vaccines containing that substance.

- Engerix-B contains trace amounts of thimerosal and should be considered equivalent to thimerosal-free products.
  - ♦ Most patients do not develop reactions to the thimerosal component of vaccines, even when patch or intradermal tests indicate thimerosal hypersensitivity.
  - ♦ ACIP notes that when post-vaccination thimerosal reactions are reported, they are typically the delayed, localized type.
- Twinrix should not be administered to persons with a history of hypersensitive reaction to neomycin, yeast, aluminum, 2-phenoxyethanol, or formalin.
- The tip cap and plunger of Engerix-B syringes contain dry natural rubber latex.
- The vials and the tip cap and plunger of the syringes of Recombivax HB contain latex.
- The vial stopper for Comvax contains natural rubber latex.
- The tip cap and plunger of Pediarix syringes contain dry natural rubber latex.

Hypersensitivity to yeast is a contraindication, since hepatitis B vaccines are developed in baker's yeast.

Do not use Comvax or Pediarix in infants younger than 6 weeks of age.

### *Bleeding Disorders*

All hepatitis B and hepatitis B-containing vaccines are IM injections and may pose a risk for persons with bleeding disorders. See "*Guidelines on Vaccinating Persons with Bleeding Disorders*."

### *Compromised Immunity*

Hepatitis B vaccine is recommended for immunocompromised persons, including those with HIV, persons with end-stage renal disease (including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients), and persons with pre-end-stage renal disease before they become dialysis-dependent.

- Per ACIP, higher hepatitis B doses are recommended for adult dialysis patients and other immunocompromised persons. Serologic testing of these persons is recommended 1-2 months after administration of the final dose of the primary vaccine series to determine the need for revaccination. In addition, booster doses may be needed. (See MMWR 55, No. RR-16 for additional information on pre- and post-vaccination serologic testing.)
- Per AAP, specific dosage requirements have not been made for children undergoing dialysis. Some experts recommend increased doses of hepatitis B vaccine for these children.

Although data concerning the response of pediatric hemodialysis patients to vaccination with standard pediatric doses are lacking, protective levels of antibody occur in 75-97% of children who receive higher doses (20ug) on either the 3- or 4-dose schedule, per ACIP.

- Humoral response to hepatitis B vaccination is also reduced in other children and adolescents who are immunocompromised. Modified dosing regimens, including a doubling of the standard antigen dose or administration of additional doses, might increase response rates; however, data on response to these alternative vaccination schedules are limited.
- Research indicates that HIV-infected children may need as much as twice the recommended dose of HBV vaccine for the primary series (Choudhury SA, et al.).

See “HIV- or AIDS-Infected Travelers” and “Immunocompromised Travelers.”

### ***Pregnancy and Lactation***

Hepatitis B vaccine may be administered during pregnancy and lactation and is recommended for pregnant women at risk for HBV infection.

- Limited data indicate no apparent risk for adverse events to developing fetuses when hepatitis B vaccine is administered to a pregnant woman. Current vaccines contain noninfectious HBsAg and should cause no harm to the fetus.
- All pregnant women should be screened for HBsAg during an early prenatal visit (i.e., during the first trimester) in each pregnancy, even if previously vaccinated or tested, because HBV infection during pregnancy can cause serious disease in the mother and chronic infection in the newborn.
- Pregnant women who are identified as being at risk for hepatitis B virus infection during pregnancy should be vaccinated (e.g., those who have had more than 1 sex partner in the last 6 months, have been evaluated or treated for an STD, have had recent or current injection drug use, or have had an HBsAg-positive sex partner).

Per package insert, Twinrix should be given to pregnant women only if clearly indicated.

## **COMPATIBILITY**

There is no known incompatibility with other immunizations, immune globulin, or medications, but injections should be given in different sites.

Per manufacturer, Comvax has no known incompatibility with DTaP booster at 15 months or MMR vaccine. There are no data available regarding compatibility with IPV, Varivax, or the primary series of DTaP.

## **SPECIAL CONSIDERATIONS**

### ***Interchangeability of Vaccines***

Recombivax HB and Engerix-B are equally immunogenic and may be used interchangeably, according to their recommended doses.

### ***Lapsed Schedule***

According to ACIP guidelines on general recommendations for immunization, an interruption in a vaccination schedule does not require restarting the entire series of a vaccine or toxoid nor does it require the addition of extra doses. The series should be resumed with the next dose in the series, and any subsequent doses should be administered at the same interval as if the series had not been interrupted.

## Post-Vaccination Testing and Management of Nonresponders

### Post-vaccination testing and revaccination

Post-vaccination serological testing for immunity is not recommended on a routine basis. However, testing is recommended for persons whose subsequent management depends on knowing their immune status, or for whom a suboptimal response may be anticipated, including:

- health care workers (and students) and public safety workers at high risk for continued exposure to blood or bodily fluids, to determine the need for revaccination and to guide PEP
- chronic dialysis patients, HIV-infected persons, and others with immune compromise, to determine the need for revaccination and the type of follow-up testing
- sex partners of HBsAg-positive persons, to determine the need for revaccination and for other methods of protection against HBV infection
- infants born to mothers who are HBsAg-positive or mothers with unknown HBsAg status (*see below*)
- persons vaccinated by intradermal or subcutaneous injection, or in the buttocks

For those persons indicated above, the following recommendations apply. (Note: When post-vaccination testing is indicated, it is recommended 1 month [or later] after administration of the last dose of the vaccine series.)

For persons who have had:

- 3-shot series (documented) and titer > 10 IU/ml (tested 1 month or later after the final dose): no boosters and no further serology
  - ♦ Immunocompromised persons might need annual testing to assess anti-HBs concentrations. (*See "Booster doses," below.*)
- 3-shot series (documented) and titer > 10 IU/ml at *any* time: no boosters and no further serology
  - ♦ Immunocompromised persons might need annual testing to assess anti-HBs concentrations. (*See "Booster doses," below.*)
- 3-shot series and documented titer < 10 IU/ml (tested at 1 month or later after final dose):
  - ♦ Repeat 3-dose series and test 1 month after last dose.
    - When nonresponders to the primary vaccination series are revaccinated, 25-50% produce an adequate antibody response after 1 additional dose, and 44-100% produce an adequate response after 3 additional doses.
    - Data suggest that when nonresponders to a primary series that was given in the buttock are revaccinated in the arm, > 75% achieve adequate antibody response.
    - If titer > 10 IU/ml: No further serology and no further boosters are required.
    - If titer < 10 IU/ml \*: The person is a true non-responder and will need HBIG with every exposure.
- 3-shot series (documented) and *current* titers < 10 IU/ml (i.e., titers drawn at some time *significantly* later than the usual 1-month testing time):
  - ♦ Give 1 booster dose and draw titers 1 month later.

- If titer > 10 IU/ml: No further serology and no further boosters (proves a memory response due to adequate prior immunization) are required.
- If titer < 10 IU/ml: Complete the 3-dose series (i.e., give 2 more doses) and check titers 1 month after the third dose.
  - If titer > 10 IU/ml, no further serology and no further boosters are required.
  - If titer < 10 IU/ml, the person is a true non-responder and will need HBIG with every exposure.\*

\* Persons who do not have a protective concentration of anti-HBs after receiving a total of 6 doses should be tested for HBsAg.

- If the HBsAg result is positive, the person should receive appropriate management, and any household, sex, or needle-sharing contacts should be identified and vaccinated.
- If the HBsAg result is negative, the person should be considered susceptible to HBV infection and should be counseled about precautions to prevent HBV infection and the need to obtain HBIG postexposure prophylaxis for any known or likely parenteral exposure to HBsAg-positive blood.

Infants of HBsAg-positive mothers and of mothers of unknown HBsAg status should have follow-up testing for HBsAg and anti-HBs at 9-18 months of age, after completion of the vaccine series.

- Per ACIP, a study of infants born to HBsAg-positive mothers who did not respond to the primary series indicated that infants not infected with hepatitis B responded satisfactorily to a repeat 3-dose series. No data suggest that children who have no detectable antibodies after 6 doses would benefit from additional doses.

### ***Booster doses***

Booster doses are not routinely recommended for immunized persons with normal immune status. Serologic testing is not routinely recommended to assess antibody concentrations in any age group, except in certain circumstances. (See *"Post-vaccination testing and revaccination,"* above.)

For hemodialysis patients, 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. 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. When anti-HBs levels decline to < 10 mIU/mL, annual anti-HBs testing and booster doses should be considered for persons with an ongoing risk for exposure.