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Hepatitis B Vaccine Issues
June 16, 2016
The recommendations to be discussed are primarily those of the ACIP:

- composed of 15 experts in clinical medicine and public health who are not government employees
- provides guidance on the use of vaccines and other biologic products to the Department of Health and Human Resources, CDC, and the U.S. Public Health Service

www.cdc.gov/vaccines/acip/
Background on Hepatitis B

• Hepatitis B is a liver infection caused by the hepatitis B virus (HBV)
• HBV is found in the blood and other body fluids of infected people (e.g., serum, semen, saliva, and vaginal secretions)
• Transmission occurs by contact with infected blood or other body fluid of an acutely or chronically infected person
  – in the U.S. the most commonly identified risk factors are sexual contact and injection drug use
Natural History of Hepatitis B Virus (HBV) Infection

HBV can cause acute or chronic infection

Chronic HBV infection can lead to liver failure and liver cancer

Acute HBV infection (may be symptomatic or asymptomatic)

Chronic HBV infection

Resolved and immune (over years)

Resolved and immune

Liver cirrhosis and cancer
Hepatitis B Virus Infection

- Established cause of chronic hepatitis and cirrhosis
- Human carcinogen - cause of up to 80% of hepatocellular carcinomas
- More than 240 million chronically infected worldwide (1-2 million in the U.S.)
- More than 780,000 deaths per year worldwide due to complications of hepatitis B infection (estimated 1,800 per year in the U.S.)

World Health Organization data, 2015
Perinatal Hepatitis B Transmission

- An infant can acquire HBV from:
  - an infected mother (transmitted at birth)
  - a chronically infected member of the household
- In the absence of post-exposure treatment up to 90% of infants born to an HBsAg positive woman will be infected
Risk of Developing Chronic Hepatitis B by Age at Infection

- Infant: 90%
- 1-5 Years: 30%
- > 5 years: <5%
Incidence of acute hepatitis B, by year
United States, 1980-2014

Reported Number of Cases

Year

0 5,000 10,000 15,000 20,000 25,000 30,000

www.cdc.gov/hepatitis/statistics/index.htm
HBV Disease Burden in the United States

- **Prevaccine era**
  - estimated 300,000 persons infected annually, including 24,000 infants and children

- **2014**
  - 2,953 reported acute cases
  - estimated 19,200 cases (range, 11,000-47,100) based on under-reporting
  - estimated 800 perinatal infections

Figure 3.2. Incidence of acute hepatitis B, by age group — United States, 2000–2014

Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)
Hepatitis B Vaccine

- Contains recombinant HBsAg
- Intramuscular administration only
- Usual schedule: 0, 1, 6 months
- Variant schedules are acceptable (0, 1, 4 months, 0, 2, 4 months, 0, 1, 2, 12 months)
- No less than 16 weeks between doses 1 and 3
- Duration of immunity more than 20 years

*MMWR 2013;62(RR-10):1-19*
Hepatitis B Vaccine Formulations

- **Recombivax HB (Merck)**
  - 5 mcg/0.5 mL (pediatric)
  - 10 mcg/1 mL (adult)
  - 40 mcg/1 mL (dialysis)

- **Engerix-B (GSK)**
  - 10 mcg/0.5 mL (pediatric)
  - 20 mcg/1 mL (adult)
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Recombivax HB Dose (mcg)</th>
<th>Engerix-B Dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants and children</td>
<td>0.5 mL (5)</td>
<td>0.5 mL (10)</td>
</tr>
<tr>
<td>&lt;11 years of age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolescents 11-19</td>
<td>0.5 mL (5)</td>
<td>0.5 mL (10)</td>
</tr>
<tr>
<td>years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults ≥20 years</td>
<td>1.0 mL (10)</td>
<td>1.0 mL (20)</td>
</tr>
</tbody>
</table>
Hepatitis B Vaccine Administration Errors

• If less than an age-appropriate dose is given (0.5 mL to a person $\geq 20$ years)
  – if the error is discovered while the person is still in the office give another 0.5 mL dose immediately
  – if the error is discovered later give a full age-appropriate dose

• If more than an age-appropriate dose is given (1.0 mL to a person $<20$ years)
  – count the dose
  – continue the schedule as usual

CDC personal communication
Hepatitis B Vaccine
Long-term Efficacy

• Immunologic memory established following vaccination
• Exposure to HBV results in anamnestic anti-HBs response
• Chronic infection rarely documented among vaccine responders
• Upper limit of duration of protection is not known – at least 20 years
Hepatitis B Vaccine

Routine booster doses are NOT routinely recommended for any group, including healthcare providers.
# Hepatitis B Vaccine

## Routine Infant Schedule

<table>
<thead>
<tr>
<th>Dose+</th>
<th>Usual Age</th>
<th>Minimum Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary 1</td>
<td>Birth</td>
<td>-</td>
</tr>
<tr>
<td>Primary 2</td>
<td>1-2 months</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Primary 3</td>
<td>6-18 months*</td>
<td>8 weeks**</td>
</tr>
</tbody>
</table>

* infants who mothers are HBsAg+ or whose HBsAg status is unknown should receive the third dose at 6 months of age
** at least 16 weeks after the first dose and 24 weeks of age
+ an additional dose at 4 months is acceptable if the clinician prefers to use a combination vaccine that contains hepatitis B vaccine
Why a Birth Dose?

• The primary goal of administering hepatitis B vaccine at birth is to protect babies from chronic HBV infection

• Approximately 25% of infants with perinatal HBV infection will die prematurely as a result of complications of cirrhosis or liver cancer
Effectiveness of Hepatitis B Vaccine Starting at Birth

• Post-exposure prophylaxis of infants born to infected women is 85–95% effective when started within 12 hours of birth
  – post-exposure prophylaxis: hepatitis B vaccine + hepatitis B immune globulin (HBIG) at birth, completion of hepatitis B vaccine series, post-vaccination testing for response at 9-12 months of age*
• Hepatitis B vaccination starting at birth even without HBIG will prevent transmission of the infection in 70–95% of infants born to chronically infected women

*Or 1–2 months after the final dose of the HepB vaccine series if completion of the series is delayed. MMWR 2015:64:1118-20
The Opportunity To Prevent Perinatal Hepatitis B Virus Infection

• Hospitals have an opportunity to protect the future health of infants born in their facilities
  – each year in the U.S., an estimated 25,000 infants are born to mothers who are infected with HBV, and not all of their infants receive post-exposure prophylaxis
  – some infants are first exposed shortly after birth to HBV by household members or caretakers who have chronic HBV infection

• Most infants can be protected if hospitals routinely provide a birth dose of hepatitis B vaccine to all newborn infants
The Problem

• Many infants in the United States are not receiving the birth dose of hepatitis B vaccine
  – In 2014 only 72% of U.S. infants received hepatitis B vaccine within 3 days of birth
  – States’ coverage rates varied between 48% and 88% (81% in MO)
• There is room for improvement in protecting newborn infants in every state

Why Should All Newborns Receive a Birth Dose of Hepatitis B Vaccine

- **Prevents mother-to-infant transmission:** Prevents 70–95% of infection among infants born to HBsAg-positive women
- **Prevents household transmission:** Protects infants from infected family members and other caregivers
- **Protects when medical errors occur:** Provides a safety net to prevent perinatal HBV infection when medical errors occur
Perinatal Hepatitis B Management Errors

• Ordering the wrong hepatitis B screening test
• Misinterpreting or mistranscribing the hepatitis B test results
• Failing to communicate the HBsAg test results to or within the hospital
• Not giving hepatitis B vaccine to infants born to mothers of unknown HBsAg status within 12 hours of birth
• Not giving prophylaxis to an infant even when the mother’s HBsAg-positive status is documented
All birthing hospitals should implement policies and procedures to administer the recommended universal hepatitis B vaccine birth dose, ensuring that every newborn infant receives hepatitis B vaccine at birth, or no later than hospital discharge.

MMWR 2005;54(RR-16) www.cdc.gov/mmwr/PDF/rr/rr5416.pdf
Give birth to the end of Hep B

Protect newborns - Administer hepatitis B vaccine at birth

The Immunization Action Coalition (IAC) is urging hospitals and birthing centers to meet the national standard of care by providing a universal birth dose of hepatitis B vaccine.

- It prevents mother-to-infant transmission
- It prevents household transmission
- It provides protection if medical errors occur

Prevents 70%-95% of transmission to infants born to HBsAg-positive women
Protects infants from infected family members and other caregivers
Provides a safety net to prevent perinatal transmission when medical errors occur

www.immunize.org/protect-newborns/
## Hepatitis B Vaccine
### Adolescent and Adult Schedule

<table>
<thead>
<tr>
<th>Dose</th>
<th>Usual Interval</th>
<th>Minimum Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary 1</td>
<td>---</td>
<td>- - -</td>
</tr>
<tr>
<td>Primary 2</td>
<td>1 month</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Primary 3</td>
<td>5 months</td>
<td>8 weeks*</td>
</tr>
</tbody>
</table>

*third dose must be separated from first dose by at least 16 weeks*
Interruption of the Hepatitis B Vaccine Series

• It is not necessary to restart the series or add doses if the hepatitis B vaccine series is interrupted, regardless of the interval since the last dose.

MMWR 2013;62(RR-10):1-19
Adults at Risk for HBV Infection

• Sexual exposure
  – sex partners of HBsAg-positive persons
  – sexually active persons not in a long-term, mutually monogamous relationship*
  – persons seeking evaluation or treatment for a sexually transmitted disease
  – men who have sex with men

*persons with more than one sex partner during the previous 6 months
Adults at Risk for HBV Infection

- Percutaneous or mucosal exposure to blood
  - current or recent IDU
  - household contacts of HBsAg-positive persons
  - residents and staff of facilities for developmentally disabled persons
  - healthcare and public safety workers with risk for exposure to blood or blood-contaminated body fluids
  - persons with end-stage renal disease
  - persons with diabetes mellitus

MMWR 2006;55(RR-16):6-8
Adults at Risk for HBV Infection

• Others groups
  – international travelers to regions with high or intermediate levels (HBsAg prevalence of 2% or higher) of endemic HBV infection
  – persons with HIV infection

*MMWR* 2006;55(RR-16):6-8
Prevaccination Serologic Testing

- Not indicated before routine vaccination of infants, children, and most adolescents and adults

- Recommended for
  - all persons born in Africa, Asia, the Pacific Islands, and other regions with HBsAg prevalence of 2% or higher
  - household, sex, and needle-sharing contacts of HBsAg-positive persons
  - men who have sex with men
  - injection drug users
Postvaccination Serologic Testing

• Not routinely recommended following vaccination of infants, children, adolescents, or most adults

• Recommended for:
  – chronic hemodialysis patients
  – other immunocompromised persons
  – persons with HIV infection
  – sex partners of HBsAg+ persons
  – infants born to HBsAg+ women
  – healthcare personnel
Hepatitis B Evidence of Immunity for Healthcare Personnel (HCP)

- Written documentation of a properly spaced 3-dose series of hepatitis B vaccine, and
- Confirmation of immunity (antibody to hepatitis B surface antigen [anti-HBs] ≥ 10 mIU/mL) 1 to 2 months after the third dose
- CDC recommends that HCP have both documentation of vaccination and a positive anti-HBs
- HCP lacking documentation of vaccination should be considered unvaccinated

*MMWR 2013;62(RR-10):1-19*
The “New” Hepatitis B Serology Issue: HCP Vaccinated as Infants or Adolescents

• Routine hepatitis B vaccination of infants was first recommended in 1991
• Catch-up vaccination of adolescents recommended in 1995
• Vaccination coverage among 19-35 month-old children first exceeded 90% in 2000
• The oldest cohorts vaccinated as infants are now in their early 20s
• Routine serologic testing of infants is not recommended (except if mother is HBsAg positive)

*MMWR 2013;62(RR-10):1-19*
Hepatitis B Vaccination

- 95% of healthy infants will achieve seroprotection against hepatitis B 1 to 2 months after a complete 3-dose series.
- By 18 years after vaccination approximately 84% of persons vaccinated at younger than 1 year of age will not have detectable anti-HBs.

*MMWR* 2013;62(RR-10):1-19
CDC Guidance for Evaluating Health-Care Personnel for Hepatitis B Virus Protection and for Administering Postexposure Management
FIGURE 6. Pre-exposure evaluation for health-care personnel previously vaccinated with complete, ≥3-dose HepB vaccine series who have not had postvaccination serologic testing*

Measure antibody to hepatitis B surface antigen (anti-HBs)

anti-HBs < 10 mIU/mL

Administer 1 dose of HepB vaccine, postvaccination serologic testing*

anti-HBs < 10 mIU/mL

Administer 2 more doses of HepB vaccine, postvaccination serologic testing*

anti-HBs < 10 mIU/mL

Health-care personnel need to receive hepatitis B evaluation for all exposures*

anti-HBs ≥ 10 mIU/mL

No action for hepatitis B prophylaxis (regardless of source patient hepatitis B surface antigen status)

anti-HBs ≥ 10 mIU/mL

MMWR 2013;62(RR-10):1-19
Hepatitis B Vaccine and HCP

- Management of HCP who have written documentation of a complete series of hepatitis B vaccine doses in the past who were not tested for antibody response following the vaccination series and who now test negative for anti-HBs
  - administer 1 dose of hepatitis B vaccine then test for anti-HBs 1 to 2 months later
  - if positive (anti-HBs $\geq 10$ mIU/mL) the person is immune and nothing else needs to be done

*MMWR 2013;62(RR-10):1-19*
Management of Nonresponse to Hepatitis B Vaccine

- For persons who remain seronegative after the “booster” dose
  - complete a second series of three doses (i.e., 2 more doses)
  - use the usual schedule of 0, 1 and 6 months
  - may use a compressed schedule (0, 1, 4 months)
  - retest for anti-HBs 1 to 2 months after completing the second series

*MMWR* 2013;62(RR-10):1-19
Hepatitis B Revaccination

- 47% of 3-dose series recipients without protective antibody levels after a primary vaccination series develop vaccine-induced seroprotection after one additional dose of hepatitis B vaccine.

- 69% of initial nonresponders will develop seroprotection after 3 revaccination doses.

Persistent Nonresponse to Hepatitis B Vaccine

• Less than 5% of vaccinees do not develop anti-HBs after 6 valid doses
• May be nonresponder or "hyporesponder"
• ACIP does not recommend revaccination with more than 3 doses (i.e., more than 6 total doses)
• Check HBsAg and anti-HBc status if not already done
• If exposed, treat as nonresponder with HBIG postexposure prophylaxis

MMWR 2013;62(RR-10):1-19
TABLE 2. Postexposure management of health-care personnel after occupational percutaneous and mucosal exposure to blood and body fluids, by health-care personnel HepB vaccination and response status

<table>
<thead>
<tr>
<th>Health-care personnel status</th>
<th>Postexposure testing</th>
<th>Postexposure prophylaxis</th>
<th>Postvaccination serologic testing†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Source patient (HBsAg)</td>
<td>HCP testing (anti-HBs)</td>
<td>HBIG*</td>
</tr>
<tr>
<td>Documented responder after complete series (≥3 doses)</td>
<td>Positive/unknown</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>No action needed</td>
<td></td>
</tr>
<tr>
<td>Documented nonresponder after 6 doses</td>
<td>Positive/unknown</td>
<td>&lt;10mIU/mL**</td>
<td>HBIG x1</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>No action needed</td>
<td>Initiate revaccination</td>
</tr>
<tr>
<td>Response unknown after 3 doses</td>
<td>Positive/unknown</td>
<td>&lt;10mIU/mL</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>No action needed</td>
<td>Complete vaccination</td>
</tr>
<tr>
<td></td>
<td>Any result</td>
<td>≥10mIU/mL</td>
<td>No action needed</td>
</tr>
<tr>
<td>Unvaccinated/incompletely vaccinated or vaccine refusers</td>
<td>Positive/unknown</td>
<td>—</td>
<td>HBIG x1</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>—</td>
<td>Complete vaccination</td>
</tr>
</tbody>
</table>

Abbreviations: HCP = health-care personnel; HBsAg = hepatitis B surface antigen; anti-HBs = antibody to hepatitis B surface antigen; HBIG = hepatitis B immune globulin.
* HBIG should be administered intramuscularly as soon as possible after exposure when indicated. The effectiveness of HBIG when administered >7 days after percutaneous, mucosal, or nonintact skin exposures is unknown. HBIG dosage is 0.06 mL/kg.
† Should be performed 1–2 months after the last dose of the HepB vaccine series (and 4–6 months after administration of HBIG to avoid detection of passively administered anti-HBs) using a quantitative method that allows detection of the protective concentration of anti-HBs (≥10 mIU/mL).
8 A responder is defined as a person with anti-HBs ≥10 mIU/mL after ≥3 doses of HepB vaccine.
9 A nonresponder is defined as a person with anti-HBs <10 mIU/mL after ≥6 doses of HepB vaccine.
** HCP who have anti-HBs <10mIU/mL, or who are unvaccinated or incompletely vaccinated, and sustain an exposure to a source patient who is HBsAg-positive or has unknown HBsAg status, should undergo baseline testing for HBV infection as soon as possible after exposure, and follow-up testing approximately 6 months later. Initial baseline tests consist of total anti-HBc; testing at approximately 6 months consists of HBsAg and total anti-HBc.
Hepatitis B Serologic Testing

• HCP who have written documentation of a complete 3 (or more) hepatitis B vaccine series AND subsequent postvaccination anti-HBs level of 10 mIU/mL or higher are considered to be immune.

• Immunocompetent persons have long-term protection against HBV infection and do not need further periodic testing to assess anti-HBs levels.

*MMWR* 2013;62(RR-10):1-19
Resources

• General Recommendations on Immunization. *MMWR* 2011;60(RR-2):1-61

• Immunization of Healthcare Workers. *MMWR* 2011;69(RR-7):1-45


• Immunization Action Coalition
  www.immunize.org