Advisory Committee on Immunization Practices (ACIP)
Hepatitis B Updates

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2018 Texas Perinatal Hepatitis B Summit
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The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Strategies to Eliminate Hepatitis B, United States

- **Perinatal and childhood**
  - Screen all pregnant women for HBsAg
  - Prophylaxis (HepB vaccine and HBIG) within 12 hours of birth for all infants born to HBsAg-positive women
  - Universal vaccination of all infants weighing ≥2,000 grams beginning at birth (within 24 hours) *(new recommendation)* as a safety net
  - Routine vaccination of previously unvaccinated children and adolescents aged <19 years

- **Adults**
  - Vaccination of adults at risk for HBV (IDU, MSM, occupational, travel, multiple sex partners, family with HBV, others)
  - Any adult requesting protection from HBV without acknowledgment of a specific risk factor
CDC/ACIP Guidance Documents for HepB Vaccination
New ACIP Recommendations

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

- Published (MMWR) January 12, 2018
New ACIP Recommendations, cont.

- Incorporates previously-published recommendations from:
  - ACIP
  - CDC

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

- Safe, immunogenic, effective
- Administered starting at birth
- 2-, 3-, or 4-dose series
  - 2-dose series for adolescents/adults
- Protection lasts ≥30 years
  - Booster doses not routinely recommended
- Since 1986, recombinant (e.g., yeast-derived) vaccine used in U.S.
- U.S.-licensed formulations thimerosal-free

1Bruce et al., JID 2016; Middleman et al, Pediatrics 2014.
HepB Vaccines, cont.

- **Monovalent formulations**
  - Engerix-B®
  - Recombivax-HB®
  - Heplisav-B®: ≥18 yrs

- **Combination formulations (not used for birth dose)**
  - Pediarix® (DTaP, IPV, HepB): 6 wks through 6 yrs
  - Twinrix® (HepA, HepB): ≥18 yrs
Testing Pregnant Women
Testing Pregnant Women

- Identify HBV-infected mothers through routine HBsAg testing of all pregnant women during an early prenatal visit
  - Testing should occur during each pregnancy, even if woman has been previously vaccinated or tested
- Testing women known to be chronically infected provides documentation of the positive HBsAg test result during pregnancy
  - Helps to ensure infant identified for timely prophylaxis
Analysis of Claims Data (Marketscan, 2011-2014)

- 82-88% of pregnant women tested for HBsAg
- Testing occurred more often among:
  - Commercially-insured women (87.7%) vs. Medicaid-insured women (83.6%)
  - High-risk pregnancies (87.3%-87.8% vs. 82.9%-84.8%)
  - First pregnancy vs. subsequent pregnancies (82.3% vs. 60.7-79.7%)
  - Aged 20-39 (82.9%-84.4%) vs. younger (73.2%) or older (59.7%)

Harris et al., IDOB 2018; Kolasa et al., PID 2017.
Timing of HBsAg Screening Among Pregnant Women Relative to Infant Birth – United States, 2008-2012 (N=14,981)

- 13,316 (88.9%) screened during current pregnancy
- 1,160 (7.7%) screened during week of or at delivery
  - 304 (26.2%) not previously screened
  - 856 (73.8%) screened during previous pregnancy
Testing Pregnant Women for HBV DNA

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

- All HBsAg-positive pregnant women should be referred to their jurisdiction’s Perinatal Hepatitis B Prevention Program for case management.
- A copy of the original laboratory report indicating the pregnant women’s HBsAg status should be provided to the hospital or birthing facility where the delivery is planned and to the health provider who will care for the infant.
- HBsAg-positive pregnant women should receive information concerning HBV.
Testing Pregnant Women, cont.

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

- At time of admission to hospital for delivery if high risk, e.g.:
  - Injection drug use
  - More than 1 sex partner in previous 6 months
  - HBsAg-positive sex partner
  - Evaluation or treatment for a sexually transmitted
  - With clinical hepatitis
Infant HepB Vaccination
## HepB Vaccine and HBIG Schedule for Newborns

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

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

- Infants born to HBsAg-positive mothers in British Columbia, 1984-1989 (n=770)

<table>
<thead>
<tr>
<th>Age at first dose (days)</th>
<th>Proportion of participants (%)</th>
<th>Infection rate per 1,000</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>96</td>
<td>47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4-7</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8-61</td>
<td>1</td>
<td>222</td>
<td></td>
</tr>
<tr>
<td>≥62</td>
<td>1</td>
<td>333</td>
<td></td>
</tr>
</tbody>
</table>

- aOR for increase in infection with increasing age at 1st dose: 4.3 (95% CI, 2.2-8.4)


Healthy People 2020 Target: 85%

*One dose by 3 days
Receipt of HepB Vaccine and HBIG within 12 Hours of Birth for Infants Born to HBsAg-Positive Mothers – Enhanced PHBPP*, 2007-2013

*Florida, Michigan, Minnesota, New York City, and Texas (excluding cities of Houston and San Antonio)

Schillie et al. Pediatrics 2015
Administration of HepB Vaccine and HBIG

- Should be administered at different anatomic injection sites
  - E.g., different limbs
Transferred Infants

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

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

- **Existing Language**
  - On a case-by-case basis and only in rare circumstances, the first dose may be delayed until after hospital discharge for an infant who weighs ≥2,000 grams and whose mother is HBsAg-negative.

- **Revised Language (new recommendation)**
  - Permissive language removed
Removal of Permissive Language

- Universal birth dose prior to hospital discharge serves as a safety net to prevent HBV transmission for infants not identified due to errors in:
  - Maternal HBsAg testing
  - Transcription of maternal HBsAg test results
  - Reporting maternal HBsAg test results
Completion of Vaccine Series
Completion of Vaccine Series

- Recommended for all infants
- Completed at:
  - 6 months of age for infants born to HBsAg-positive mothers
  - 6-18 months of age for infants born to HBsAg-negative mothers
Completion of Vaccine Series, cont.

- Final dose should not be administered before age 24 weeks (164 days)
- In populations with currently or previously high rates of childhood HBV infection (e.g., Alaska Natives; Pacific Islanders; and immigrant families from Asia, Africa, and countries with intermediate or high endemic rates of infection), the first dose of HepB vaccine should be administered at birth and the final dose at age 6-12 months
Completion of Vaccine Series, cont.

- For infants <2,000 grams born to HBsAg-positive mothers, the birth dose should not be counted as part of the vaccine series
  - Because of potentially reduced immunogenicity
- 3 additional doses (4 total) should be administered beginning when the infant is aged 1 month
Catch-up

- HepB vaccination is recommended for all unvaccinated children and adolescents aged <19 years
- Children and adolescents who have not previously received HepB vaccine should be vaccinated routinely at any age (i.e., catch-up)
Postvaccination Serologic Testing (PVST)
Postvaccination Serologic Testing (PVST)

- To determine infant infection status and need for revaccination
- Consists of testing for:
  - HBsAg
  - Anti-HBs
Postvaccination Serologic Testing (PVST)

- Recommended for infants born to:
  - HBsAg-positive mothers
  - Mothers whose HBsAg status remains unknown indefinitely (e.g., infants safely surrendered shortly after birth) (new recommendation)

- Performed after completion of HepB vaccine series (age 9-12 months) (new recommendation) and at least 1 month after last HepB vaccine dose (to avoid detecting HBsAg from vaccine)
When Mother’s Status Remains Unknown

- Postvaccination serologic testing for infants whose mother’s HBsAg status remains unknown indefinitely
  - For example, when a parent or person with lawful custody surrenders an infant confidentially shortly after birth

- All 50 states have some form of safe-haven law to reduce risk of infant abandonment
PVST Interpretation

- HBsAg-negative infants
  - anti-HBs $\geq 10$ mIU/mL: Protected; no further medical management for HBV
    - Immunocompetent persons remain protected, even if anti-HBs later declines to $<10$ mIU/mL
  - anti-HBs $<10$ mIU/mL: Revaccinate and re-test 1-2 months after the final dose

- HBsAg-positive infants:
  - Should receive appropriate clinical care follow-up
PVST Considerations

- **PVST should not be performed before age 9 months**
  - To avoid detection of anti-HBs from HBIG administered at birth
  - To maximize the likelihood of detecting late HBV infection

- **Anti-HBc testing of infants is not recommended**
  - Passively acquired maternal anti-HBc might be detected in infants born to HBV-infected mothers to age 24 months

- **Delayed PVST may result in false negative anti-HBs and unnecessary revaccination**
Anti-HBs Decline over Time among Infants Born to HBsAg-positive Mothers

Ko et al. Vaccine 2014
### Interval from final vaccine dose to postvaccination serologic testing vs. Odds of lower anti-HBs

<table>
<thead>
<tr>
<th>Interval</th>
<th>Odds of Lower anti-HBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to &lt;4 months</td>
<td>ref</td>
</tr>
<tr>
<td>4 to &lt;8 months</td>
<td>1.8 (1.2-2.8)</td>
</tr>
<tr>
<td>8 to &lt;12 months</td>
<td>4.4 (1.3-14.5)</td>
</tr>
</tbody>
</table>

Euler et al. PIDJ 2003
Advantages of a Shortened Interval (from final dose to PVST)

- Avoids unnecessary revaccination
- Reduction in the time that non-responder infants are at risk for transmission from household contacts with Hepatitis B
- Earlier PVST enables prompt revaccination for those infants needing a second series
- Conserves public health resources involved in providing case management services
American Academy of Pediatrics: Ages for Recommended Preventive Health Care

Recommended interval for PVST

<table>
<thead>
<tr>
<th>Pre-natal</th>
<th>New-born</th>
<th>3-5 day</th>
<th>By 1 mo</th>
<th>2 mo</th>
<th>4 mo</th>
<th>6 mo</th>
<th>9 mo</th>
<th>12 mo</th>
<th>15 mo</th>
<th>18 mo</th>
<th>24 mo</th>
<th>...</th>
</tr>
</thead>
</table>

Hepatitis B series completed for infants born to HBsAg-positive mothers
Revaccination
Revaccination

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

1 dose HepB vaccine, PVST

- Anti-HBs ≥10 mIU/mL → Protected
- Anti-HBs <10 mIU/mL → 2 doses HepB vaccine, PVST

2 doses HepB vaccine, PVST

- Anti-HBs ≥10 mIU/mL → Protected
- Anti-HBs <10 mIU/mL → No additional doses; seek prophylaxis for discrete exposures

3 doses HepB vaccine, PVST

- Anti-HBs ≥10 mIU/mL → Protected
- Anti-HBs <10 mIU/mL → No additional doses; seek prophylaxis for discrete exposures

Alternate strategy
## Cost of Single-Dose vs. Three-Dose Revaccination

<table>
<thead>
<tr>
<th>Strategy</th>
<th>N</th>
<th>Cost per individual (all visits unscheduled)</th>
<th>Cost per individual (all visits scheduled)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 dose revaccination</td>
<td>1,190</td>
<td>$314.02</td>
<td>$240.49</td>
</tr>
<tr>
<td>3 dose revaccination</td>
<td>1,190</td>
<td>$469.74</td>
<td>$293.22</td>
</tr>
</tbody>
</table>

Hall et al. PHR 2018
Single Dose Revaccination (vs. Three Dose Revaccination)

- **Advantages**
  - Fewer vaccine doses for most infants
  - Shorter duration of case management
  - Less costly overall (even when revaccination doses given during previously-scheduled well-child visits)

- **Disadvantages**
  - Additional blood draw for some infant
  - Having two options (single-dose revaccination and three-dose revaccination) requires provider/parent decision making
Summary of Revised ACIP Guidance for Perinatal HBV Transmission

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

- There are no maximum intervals
- **Minimum intervals:**
  - Dose 1-2: 4 weeks
  - Dose 2-3: 8 weeks
  - Dose 1-3: 16 weeks (final dose not before age 24 weeks in infants)
- 4-day grace period (except for accelerated schedule of Twinrix)
- Doses administered at shorter-than-recommended intervals should be repeated
Other Immunization Management Issues

- When feasible, vaccine from the same manufacturer should be used for all doses in the series
  - However, if a different brand is administered, the dose should be considered valid and does not need to be repeated
- Providers should only accept dated records as evidence of HepB vaccination
- Vaccination should be initiated even though completion of the series may not be ensured
Antibodies to HBs (Anti-HBs) as Correlate of Protection

- Anti-HBs after HepB vaccine series wanes over time
  - Even when anti-HBs decreases to <10 mIU/mL, breakthrough HBV infection uncommon in immunocompetent vaccine responders\(^1\)

- Anti-HBs <10 mIU/mL at a time distant from vaccine completion does not distinguish:
  - Initial responders
  - Non-responders (susceptible to infection after 6 doses of vaccine)

- Anti-HBs \(\geq 10\) mIU/mL is a correlate of protection only when following a complete, documented HepB series
Adults
Adults Recommended for HepB Vaccination

- Persons at risk for infection through sexual exposure
  - Sex partners of hepatitis B surface antigen (HBsAg)–positive persons
  - Sexually active persons not in a long-term, mutually monogamous relationship
  - Persons seeking evaluation or treatment for a sexually transmitted infection
  - Men who have sex with men

- Persons with a history of current or recent injection drug use
Adults Recommended for HepB Vaccination, cont.

- Persons at risk for infection by percutaneous or mucosal exposure to blood
  - Household contacts of HBsAg-positive persons
  - Residents and staff of facilities for developmentally disabled persons
  - Health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids
  - Hemodialysis patients and predialysis, peritoneal dialysis, and home dialysis patients
  - Persons with diabetes mellitus aged <60 years and persons with diabetes mellitus aged ≥60 years at the discretion of the treating clinician
Adults Recommended for HepB Vaccination, cont.

- International travelers to countries with high or intermediate levels of endemic HBV infection (HBsAg prevalence ≥2%)
- Persons with hepatitis C virus infection *(new recommendation)*, persons with chronic liver disease (including, but not limited to, those with cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal)
- Persons with HIV
- Incarcerated persons
- Other persons seeking protection from hepatitis B virus infection (even without acknowledgment of a specific risk factor)
Postvaccination Serologic Testing

Recommended for the following adults:

- Healthcare personnel and public safety workers
- Hemodialysis patients and others who may require outpatient hemodialysis (e.g., predialysis, peritoneal dialysis, and home dialysis patients)
- HIV-infected persons
- Other immunocompromised persons (e.g., hematopoietic stem cell transplant recipients or persons receiving chemotherapy)
- Sex partners of HBsAg-positive persons
Postvaccination Serologic Testing for Adults

- **Anti-HBs 1-2 months after last dose in series**
- **Persons with anti-HBs <10 mIU/mL should be revaccinated**
  - 1 more dose → anti-HBs → if anti-HBs <10 mIU/mL: 2 more doses → anti-HBs
  - 3 more doses → anti-HBs
- **Administration of more than 2 complete Hepatitis B vaccine series (i.e., 6 doses) is generally not recommended, except for hemodialysis patients and other immunocompromised persons**
Heplisav-B
Heplisav-B

- FDA licensed November 9, 2017
- Indicated for active immunization against infection caused by all known subtypes of HBV in persons aged ≥18 years
- Series of 2 doses, separated by 1 month
- Uses 1018 adjuvant (immunostimulatory cytidine-phosphate-guanosine [CpG] motifs), which binds Toll-like receptor 9 to stimulate directed immune response to hepatitis B surface antigen (HBsAg)
Heplisav-B, cont.

- Administered by intramuscular injection
- Available in single-dose 0.5 mL vials. Each dose contains:
  - 20 micrograms HBsAg
  - 3000 micrograms 1018 adjuvant
- Formulated without preservative
- Contraindication
  - History of severe allergic reaction (e.g. anaphylaxis) after a previous dose of any Hepatitis B vaccine or to any component of HEPLISAV-B, including yeast
Immunogenicity

- **Studies demonstrate high rates of seroprotection:**
  - 90.0%-100.0% of subjects receiving HEPLISAV-B vs. 70.5%-90.2% of subjects in the comparison group
    - Type 2 diabetes mellitus: 90.0% (HEPLISAV-B) vs. 65.1% (comparator)
    - Chronic kidney disease: 89.9% (HEPLISAV-B, 3 doses) vs. 81.1% (comparator, 4 double doses)

Halperin et al., Vaccine 2012;30:2556-2563.
Heyward et al., Vaccine 2013; 31:53005305.
Jackson et al., Vaccine 2018;36:668-674.
HEPLISAV-B package insert 11/2017
Proportion of subjects with anti-HBs ≥10 mIU/mL following Heplisav-B or comparison vaccine

Healthy adults aged 18-55 years; n=1548-1557 (Heplisav-B);

Healthy adults aged 40-70 years; n=1101-1123 (Heplisav-B);

Halperin et al., Vaccine 2012;30:2556-2563.
Heyward et al., Vaccine 2013; 31:53005305.
Safety and Reactogenicity

- **Mild and serious adverse events similar***
  - Mild: 45.6% (HEPLISAV-B) vs. 45.7% (comparator)
  - Serious: 5.4% (HEPLISAV-B) vs. 6.3% (comparator)

- **Cardiovascular events:** 0.27% (HEPLISAV-B) vs. 0.14% (comparator)

- **Potentially immune-mediated adverse events**
  - 0.1%-0.2% (HEPLISAV-B) vs. 0.0%-0.7% (comparator)

- **Safety to be further assessed through post-marketing studies**

*Herpes zoster: 0.68% (HEPLISAV-B) vs. 0.32% (comparator) (RR=2.1, 95% CI=1.0-4.0)

**e.g., granulomatosis with polyangiitis, Tolosa-Hunt Syndrome, autoimmune thyroiditis, vitiligo

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

- The 2-dose series only applies when all doses in the series consist of Heplisav-B.
- When a vaccine series initiated with one dose of a vaccine from a different manufacturer must be completed with Heplisav-B, 3 total HepB vaccine doses should be administered.
- Minimum intervals should be heeded (Exception: A series containing two doses of Heplisav-B administered at least 4 weeks apart is valid, even if the patient received a single earlier dose from another manufacturer.)
Heplisav-B Summary

- **HEPLISAV-B likely to improve Hepatitis B vaccine series completion and result in earlier protection (2 doses over 1 month)**
  - Especially beneficial in persons with anticipated low adherence (e.g., injection drug users)

- **Improved immunogenicity in populations with typically poor vaccine response**
  - e.g., elderly, diabetes, dialysis

- **Post-marketing surveillance studies and additional data, including safety, pertaining to the use of HEPLISAV-B will be reviewed by ACIP as they become available, and recommendations will be updated as needed**
  - Prior to preferential consideration

- **Future economic analyses may inform cost-effectiveness considerations of HEPLISAV-B, including its use among persons at an increased risk for vaccine non-response**
Contact: sschillie@cdc.gov

For more information, contact CDC
1-800-CDC-INFO (232-4636)

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

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