Preventing Perinatal Hepatitis B Virus (HBV) Transmission

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MCAAP Immunization Initiative Webinar Series
September 20, 2018
Disclaimer

- 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.

- Antiviral therapy during pregnancy for the prevention of perinatal HBV infection represents an unlabeled use of a product.
Learning Objectives

As a result of this activity, learners should be able to:

- Describe how Hepatitis B Virus (HBV) infection in a pregnant woman poses a serious risk to her infant at birth
- Review recommendations for prevention of HBV infection
- Discuss strategies and tools for increasing the Hepatitis B (HepB) birth dose coverage
Abbreviations

- HBV = hepatitis B virus
- HepB vaccine = hepatitis B vaccine
- HBIG = hepatitis B immune globulin
- HBsAg = hepatitis B surface antigen
- Anti-HBs = antibody to hepatitis B surface antigen
- Anti-HBc = antibody to hepatitis B core antigen
- HBeAg = hepatitis B e antigen
- Anti-HBe = antibody to hepatitis B e antigen
Hepatitis B Infection among Infants

- Primary source of infection: Mother-to-child transmission (perinatal), from mucosal exposure to infected blood and other body fluids
  - An infant can also acquire HBV from an infected household member
Chronic Hepatitis B

- Chronic infection develops in
  - 90% of infected infants
  - 30% of infected children aged <5 years
  - <5% of infected persons aged ≥5 years

- Persons with chronic HBV have a 15-25% risk of premature death from cirrhosis or liver cancer
Risk for Perinatal Infection

- **Without prophylaxis (HepB vaccine and hepatitis B immune globulin [HBIG]), perinatal HBV occurs in:**
  - ~90% infants born to HBsAg-positive/HBeAg-positive mothers
  - 5-20% of infants born to HBsAg-positive/HBeAg-negative mothers

- **Prophylaxis is 95% effective in preventing perinatal HBV transmission**

Nelson et al., JPIDS 2014
CDC/ACIP Guidance Documents for HepB Vaccination
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
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 (injection drug users, men who have sex with men, occupational, travel, multiple sex partners, family with HBV, others)
  - Any adult requesting protection from HBV without acknowledgment of a specific risk factor
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\(^1\)
  - Booster doses not routinely recommended
- Since 1986, recombinant (e.g., yeast-derived) vaccine used in U.S.
- U.S.-licensed formulations thimerosal-free

\(^1\)Bruce 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

- 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.
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)
  - American Association for the Study of Liver Diseases (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
## HepB Vaccine and HBIG Schedule for Newborns

<table>
<thead>
<tr>
<th>Maternal HBsAg status</th>
<th>Infant birth weight: ≥2,000 grams</th>
<th>Infant birth weight: &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>
</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>
</tr>
<tr>
<td>Negative</td>
<td>HepB vaccine within 24 hours of birth <em>(new recommendation)</em></td>
<td>Delay first dose of HepB vaccine until age 1 month or hospital discharge</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 1<sup>st</sup> dose: 4.3 (95% CI, 2.2-8.4)


Healthy People 2020 Target: 85%

*One dose by 3 days
101-bed hospital in Texas
- ~600 births/yr
- Level 1 nursery, single OB/GYN group, 2 full-time pediatric hospitalists

2016-2017: Staff and parent education regarding HepB birth dose
- Introduced at monthly staff meetings
- Practice situations with open discussion
- Encourage case-by-case discussion with attending hospital physician

Face-to-face discussion with parents who declined HepB vaccine at birth increased birth dose from 88.7%-94.5% over 1 year

Thakrar, TX, Oct 2017 Presentation to PHBPP
Improving Birth Dose Coverage, cont.

- Children’s Hospital at Montefiore (Bronx, NY)
  - ~2,200 births/yr
  - Diverse urban population

- Starting Dec 2014: Plan-Do-Study-Act cycles, fishbone diagram
  - Educational sessions with postpartum nurses and physicians, nurses and families in labor room, family medicine and OB physicians
  - Amended post-delivery order set to include HepB vaccine for all newborns

- Administration of HepB birth dose within 12 hours increased from 13% to ≥65%; administration of HepB birth dose prior to hospital discharge increased from 94% to 98%

Nemerofsky et al. AJMQ 2017.
Immunization Action Coalition (IAC)
HepB Birth Dose Honor Roll

- Launched 2013
- Recognizes hospitals and birthing centers that have attained high HepB birth dose coverage
- Criteria for inclusion:
  - ≥90% coverage over 12 months
    - Includes parent refusals
    - Excludes infants transferred out
  - Implemented policies to protect newborns from HBV
HepB Birth Dose Honor Roll

- Currently 419 institutions on Honor Roll
- Benefits
  - Announcement in *IAC Express*, sent to ~50,000 subscribers
  - Peer recognition
  - Certificate
- To enroll: [www.immunize.org/honor-roll/birthdose](http://www.immunize.org/honor-roll/birthdose)
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

- **Previous 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 HepB 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 HepB 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 HepB 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)

- 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
## Anti-HBs Decline over Time among Infants born to HBsAg-positive Mothers, cont.

<table>
<thead>
<tr>
<th>Interval from final vaccine dose to postvaccination serologic testing</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

| Prenatal | Newborn | 3-5 day | By 1 mo | 2 mo | 4 mo | 6 mo | 9 mo | 12 mo | 15 mo | 18 mo | 24 mo | ...
|----------|---------|---------|---------|------|------|------|------|-------|-------|-------|-------|------|

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

45 of 62
Revaccination

- **Single-dose revaccination (new recommendation)**
  - For infants born to HBsAg-positive mothers who have anti-HBs <10 mIU/mL after 3-dose series
  - 1 HepB dose followed by PVST one month later
    - 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
    - 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
Maternal Antiviral Therapy during Pregnancy to Prevent HBV Perinatal Transmission

- AASLD suggests antiviral therapy to reduce perinatal HBV transmission when maternal HBV DNA > 200,000 IU/mL
  - In addition to HepB vaccine and HBIG for infant, starting at birth
- Tenofovir preferred agent
- Started at 28-32 weeks
  - Generally discontinued at birth-3 months postpartum
Antiviral Therapy during Pregnancy

- Most studies show reduction in maternal HBV DNA and perinatal transmission with tenofovir, lamivudine, telbivudine
- Telbivudine and lamivudine associated with resistance (even during short periods during pregnancy); tenofovir not associated with resistance
- Maternal and fetal safety reassuring
  - More data needed regarding tenofovir and bone safety
  - GI side effects with tenofovir
  - ALT flare with telbivudine

Antiviral Therapy to Prevent Perinatal Transmission

- Pan et al (2016):
  - 200 infants with maternal HBV DNA >200,000 IU/mL
  - Randomly assigned to usual care without antiviral therapy or tenofovir (all infants received prophylaxis)
  - Perinatal transmission lower in tenofovir arm
    - Intention-to-treat analysis (transmission 5% of infants [5 of 97] vs. 18% [18 of 100], p=0.007)
    - Per-protocol analysis (transmission 0 vs. 7% [6 of 88], p=0.01)

Pan et al. NEJM 2016
Antiviral Therapy to Prevent Perinatal Transmission, cont.

- **Jourdain et al (2018):**
  - 331 HBeAg-positive pregnant women
  - Randomly assigned to tenofovir or placebo (infants received HBIG at birth and HepB vaccine at birth, 1, 2, 4, 6 months)
  - 0/147 infants in tenofovir arm infected vs. 3/147 in placebo arm (p=0.12)
  - Infant growth at 6 months did not vary significantly between groups

Jourdain et al. NEJM 2018
Efficacy and Safety of Tenofovir in Preventing Perinatal Transmission

- **Li et al (2018): Meta-analysis of 9 studies**
  - 6-China; 1-Austria; 1-Turkey; 1-Canada

- **Infant HBsAg-positivity (5 studies)**
  - Tenofovir group had significantly lower rate of HBsAg-positivity (RR=0.25, 95% CI: 0.16,0.38; p<0.001)
    - At birth, 6 months, and 12 months

- **Maternal and infant adverse events not significantly different between tenofovir and comparison group**

Li et al. BMC Gastroenterology 2018.
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
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

- 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 ≥10 mIU/mL is a correlate of protection only when following a complete, documented HepB series
Acknowledgements

- Nancy Fenlon, RN, MS
- Aaron Harris, MD, MPH
- Noele Nelson, MD, PhD, MPH
- Alaya Koneru, MPH
Thank You

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.