HBV: Who to screen and vaccinate and vaccine safety

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Relevant Disclosures

Consultant for

- VBI
- Dynavax

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Prevaccination Testing

- In populations with high rates of previous/current HBV infection, prevaccination testing might reduce costs.
- Testing for HBsAg, anti-HBs, and anti-HBc.
- Testing not requirement for vaccination, and in settings where testing is not feasible, vaccination of recommended persons should continue.
- The first dose of HepB vaccine should typically be administered immediately after collection of the blood for serologic testing.
- **Prevaccination testing is recommended** for the following persons:
  - household, sexual, or needle-sharing contacts of HBsAg-positive persons;
  - HIV-positive persons;
  - persons with elevated alanine aminotransferase (ALT)/aspartate aminotransferase (AST) of unknown etiology;
  - hemodialysis patients;
  - MSM; past or current injection-drug users.

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Testing for HBV Infection

- Testing for HBV infection (HBsAg, anti-HBs, and anti-HBc) is also recommended for the following persons:
  - persons born in countries of high and intermediate HBV endemicity (HBsAg prevalence ≥2%);
  - U.S.-born persons not vaccinated as infants whose parents were born in countries with high HBV endemicity (≥8%);
  - persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastroenterologic disorders; and
  - donors of blood, plasma, organs, tissues, or semen.
- All pregnant women should be tested for HBsAg during each pregnancy.
- Pregnant women with positive HBsAg tests should be tested for HBV DNA.

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Re-Testing HBsAg-Negative Pregnant Women

At time of admission to hospital for delivery if:

- Injection drug use
- More than 1 sex partner in previous 6 months
- HBsAg-positive sex partner
- Evaluation or treatment for a sexually transmitted disease
- With clinical hepatitis

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

- 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

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)
  - HBsAg
  - Anti-HBs
- 76%* (8,558/11,310) of infants born in 2014 in PHBPP received PVST

*Excludes Philadelphia, preliminary and subject to change

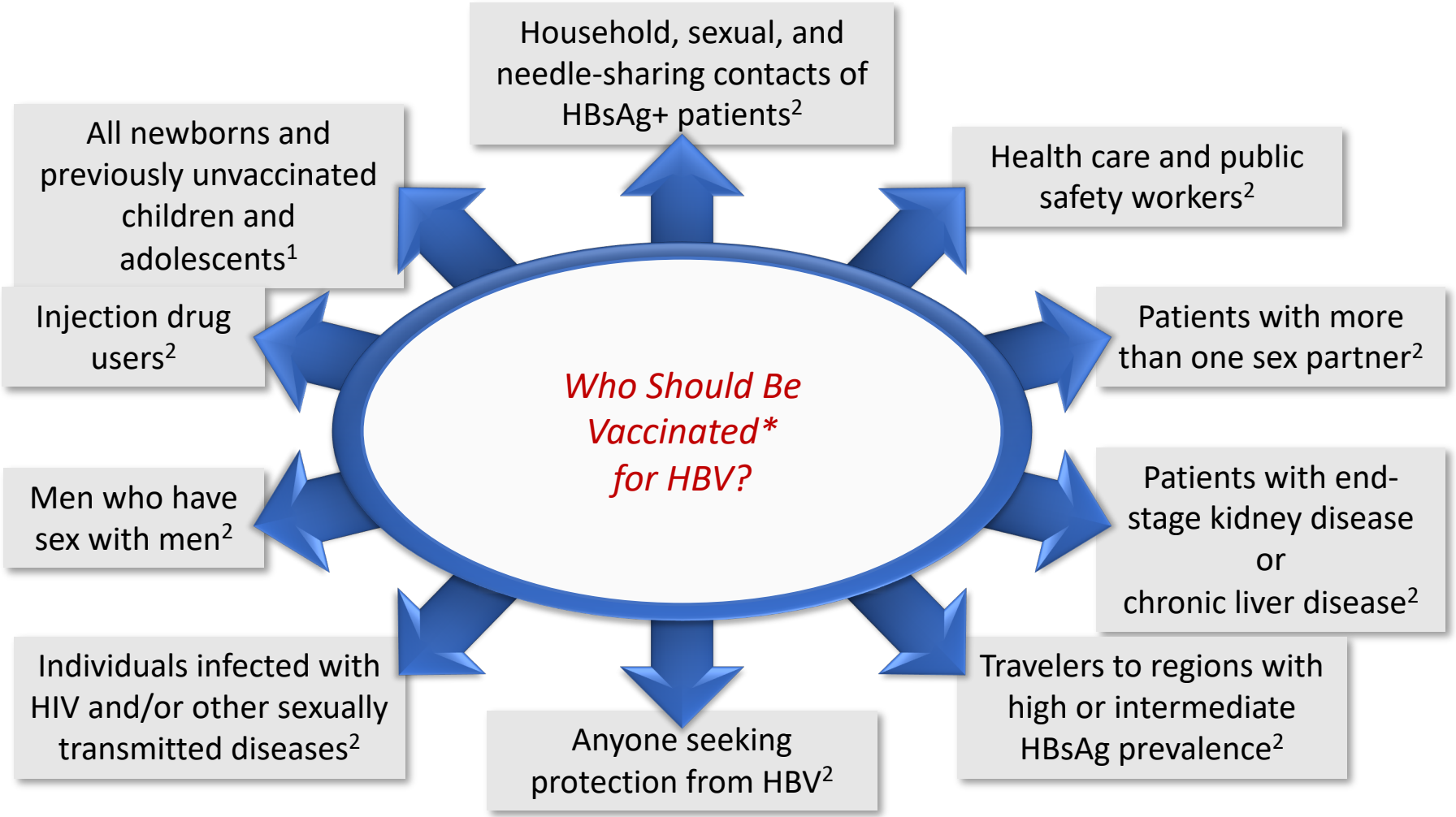
Summary of Revised ACIP Guidance for Perinatal HBV Transmission

- 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

HBV Vaccines

- Available since 1980s
- Initially plasma derived, then yeast derived
- Gradual implementation of recommendations to vaccinate decreased reported acute HBV in USA
  - high risk groups
  - Children of HBsAg positive mothers
  - All children
  - Adolescents
  - Immune compromised
- We have not yet gotten to saying “universal vaccination” but its close

Vaccination Candidates



*Active immunization consists of a series of three shots of recombinant HBsAg

1. Centers for Disease Control and Prevention. *Morb Mortal Wkly Rep.* 2005;54:1-39.
2. Centers for Disease Control and Prevention. *Morb Mortal Wkly Rep.* 2006;55:1-340.

Adults Recommended to Receive HepB Vaccination

Persons at risk for infection by sexual exposure

- Sex partners of HBV-infected persons: **multiple partners**, MSM ; **STD treatment**

Persons at risk for infection by percutaneous/mucosal exposure

- Current/ recent PWID; incarcerated persons
- Household contacts of HBV pts; Residents/staff in developmentally disabled facilities
- Healthcare and public safety workers
- Persons with end-stage renal disease and HD, PD; **diabetes**

Others

- International travelers to regions with high/intermediate HBV infection
- Persons with **chronic liver disease**
- All persons with HIV infection; immune compromised
- All other persons seeking protection from HBV infection

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Available Hepatitis B Vaccines

Consists of recombinant HBsAg grown in yeast cells; thimerosal-free

1. Recombivax-HB (monovalent, aluminum adjuvant) any age
   - 10 mcg antigen dose
   - 40 mcg antigen dose (Dialysis Formulation- 3 dose: HD, immune compromised)
2. Engerix-B (monovalent, aluminum adjuvant) any age
   - 20 mcg antigen dose
   - No 40 mcg dose, but double dose approved in dialysis with 4 dose schedule- 0,1,2,6 months)
3. HEPLISAV-B (monovalent, CpG 1018 adjuvant) adults $\geq$ 18 years, 2-dose over 1 mo
   - 20 mcg HBsAg antigen + TLR9 Agonist
4. Pediarix (diphtheria, tetanus, pertussis, HBV, poliomyelitis combination)
   - 6 weeks to 6 years of age - 10 mcg HBsAg
5. Twinrix (combination HepA-HepB) adults $\geq$ 18 years
   - 20 mcg HBsAg antigen dose (+720 ELISA Units of inactivated hepatitis A virus)

Vaccine Safety

- HepB vaccines are safe with rare side effects/adverse reactions
- Most frequent side effects are pain at injection site and fever
- Evidence supports association between HepB vaccine and anaphylaxis in yeast-sensitive persons
  - Estimate incidence 1.1 per million doses administered (95% CI 0.1-3.9)
  - Vaccination is **contraindicated** for these persons

[1]Lewis et al, Pediatr Infect Dis J 2001; [2]IOM 2011; [3]Bohlke et al. Pediatr 2003; [4]Schillie et al MMWR 2018

New or Updated Adult HepB Vaccine Recommendations*

- Universal hepatitis B (HepB) vaccination within 24 hours of birth for medically stable infants weighing ≥2,000g
- Removal of permissive language for delaying the birth dose until after hospital discharge
- Postvaccination serologic testing for infants whose mother's HBsAg status remains unknown indefinitely
- Single-dose revaccination for infants born to HBsAg-positive women not responding to the initial vaccine series
- Testing HBsAg-positive pregnant women for HBV DNA*
- Vaccination for persons with chronic liver disease or elevated ALT AST
- HEPLISAV-B may be used to vaccinate persons aged 18 years and older against infection caused by all known subtypes of HBV (non-preferential)

*This report also briefly summarizes American Association for the Study of Liver Diseases (AASLD) guidelines for maternal antiviral therapy to reduce perinatal HBV transmission, published previously and Recommendations from the Infectious Diseases Society of America (IDSA) regarding vaccination of the immunocompromised host are published separately.

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HEPLISAV-B

- Series of 2 doses, separated by 1 month
  - Likely improved adherence compared to 3 dose/6 month schedule
- Contains CpG 1018 + recombinant HBsAg (20 mcg)
- CpG 1018
  - **CpG**: 5'—C—phosphate—G—3' , that is, cytosine and guanine separated by only one phosphate group
  - 22 base synthetic oligonucleotide
  - Binds to TLR9 (sensing receptor for innate immune responses) expressed on dendritic cells and memory B cells
  - Leads to enhanced T and B memory for HBsAg

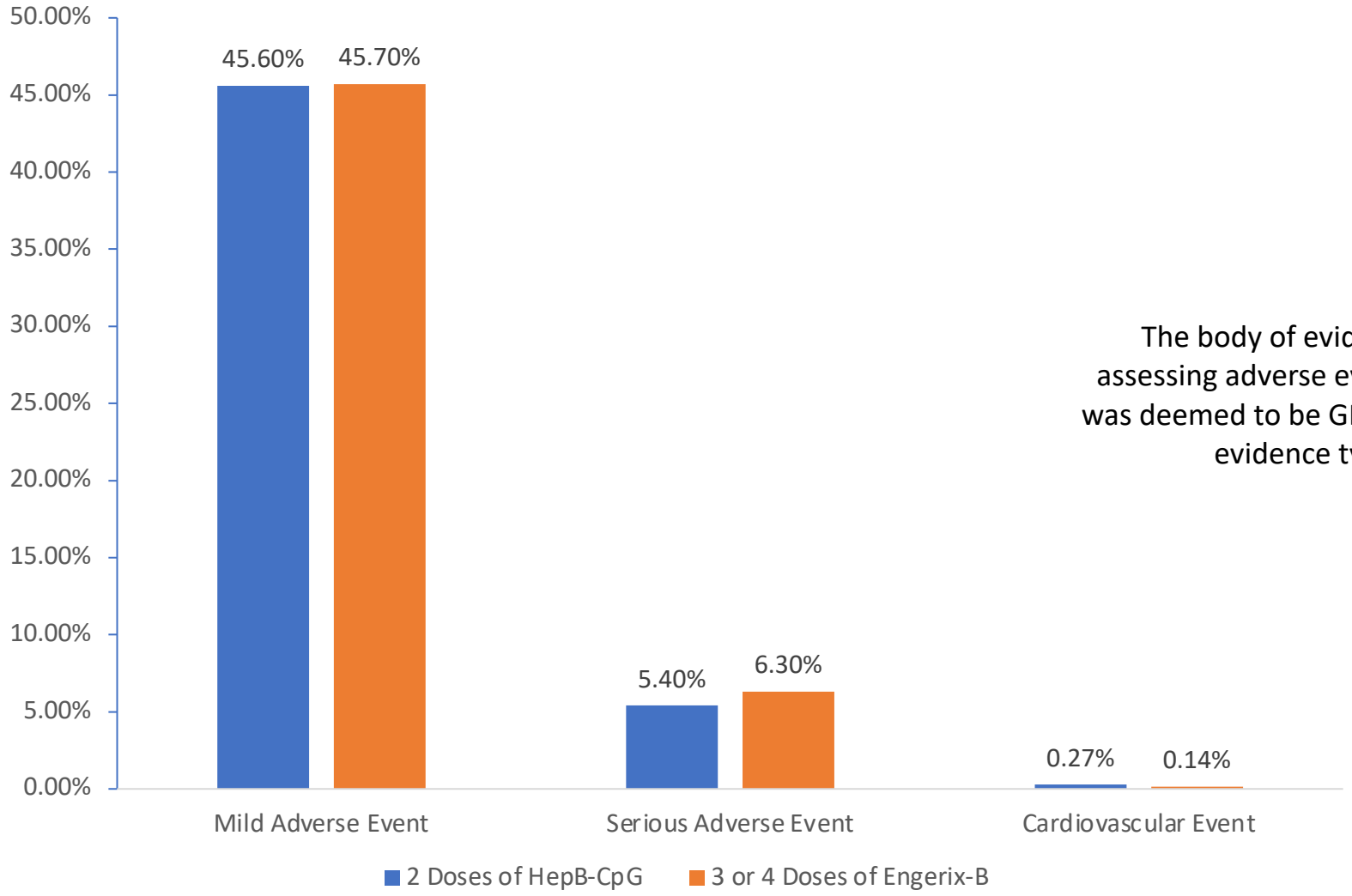
Halperin et al., Vaccine 2006;24:20-26; Halperin et al., Vaccine 2012;30:2556-2563; Heyward et al., Vaccine 2013; 31:53005305. Jackson et al., Vaccine 2018;36:668-674.Janssen et al. Vaccine 2013;31:5306- 5313.HEPLISAV-B package insert 11/2017

Safety of HEPLISAV-B

- Mild and serious adverse events similar*
  - Mild: 45.6% (HEPLISAV-B) vs. 45.7% (comparator)
  - Serious: 5.4% (HEPLISAV-B) vs. 6.3% (comparator)
- Cardiovascular events: 0.27% (HEPLISAV-B) vs. 0.14% (comparator)
- Safety further assessed through post-marketing studies in 9365 Heplisav-B and 3867 Engerix: no difference in AEs including cardiovascular events

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

HBV vaccine safety



The body of evidence assessing adverse events was deemed to be GRADE evidence type 1

The 2-dose Vaccine Showed a Safety Profile Comparable to the 3-dose Vaccine in 3 Pivotal Clinical Trials of Over 10,000 Subjects With Up to 12 Months of Follow-up[17]

Percentage of subjects with an unsolicited adverse event

			Unsolicited Adverse Events*		Serious Adverse Events	Immune-mediated Adverse Events*
Trial 1	**2-dose vaccine** N=1810	Within 28 days of any injection	42.0%	Within 7 months of the first vaccine dose	1.5%	0.2%
	3-dose vaccine N=605		41.3%		2.1%	0.7%
Trial 2	**2-dose vaccine** N=1968	Within 28 days of any injection	35.4%	Within 12 months of the first vaccine dose	3.9%	0.3%
	3-dose vaccine N=481		36.2%		4.8%	0.0%
Trial 3	**2-dose vaccine** N=5587	Within 28 days of any injection	20.1%	Within 13 months of the first vaccine dose	6.2%	0.1%
	3-dose vaccine N=2781		20.1%		5.3%	0%

*For Trial 3, only unsolicited, medically attended adverse events (i.e., those for which a subject sought medical care) were captured.
Indication: HEPLISAV-B [Hepatitis B Vaccine (Recombinant), Adjuvanted] is indicated for the prevention of infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older

Please see additional Important Safety Information throughout this presentation and accompanying full Prescribing Information.

Thank you!

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