Cost-Effectiveness of Active-Passive Prophylaxis and Antiviral Prophylaxis during Pregnancy to Prevent Perinatal Hepatitis B Virus Infection
Shortened Interval for Post-Vaccination Serologic Testing of Infants Born to Hepatitis B-Infected Mothers

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Cost-Effectiveness of Active-Passive Prophylaxis and Antiviral Prophylaxis during Pregnancy to Prevent Perinatal Hepatitis B Virus Infection

Fan L, Owusu-Edusei K Jr, Schillie SF, Murphy TV. Cost-effectiveness of active-passive prophylaxis and antiviral prophylaxis during pregnancy to prevent perinatal hepatitis B virus infection. Hepatology. 2016 May;63(5):1471-80.

Number of Infants with Complications from Perinatal Hepatitis B

Strategy	Chronic HBV infection	HCC	DCC	Liver transplant
Universal HepB vaccination	1,985	338	316	66
Universal HepB vaccination + HBIG for infants born to HBsAg-positive mothers "current strategy"	979	90	4	32
Universal HepB vaccination + HBIG for infants born to HBsAg-positive mothers; anti-viral prophylaxis for women with HBV DNA $\geq 10^6$ copies/mL	490	45	2	16

Fan et al. Hepatology 2016

Cost-Effectiveness Results

Strategy	Total cost (million)	Incremental cost (million)	Total QALY (life-years)	Incremental QALY	ICER
Universal HepB vaccination	499.6	-4.6	190,017,200	-13,600	6,957
Universal HepB vaccination + HBIG for infants born to HBsAg-positive mothers "current strategy"	594.2	--	190,030,800	--	--
Universal HepB vaccination + HBIG for infants born to HBsAg-positive mothers; anti-viral prophylaxis for women with HBV DNA $\geq 10^6$ copies/mL	591.4	-2.8	190,031,600	800	Domin.

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Cost-effectiveness of Current Strategy and Anti-viral Prophylaxis

- Compared to universal HepB vaccination, the current strategy:
  - Prevented 1,006 chronic HBV infections
  - Saved 13,600 QALYs (ICER: $6,957/QALY saved)
- Antiviral prophylaxis dominated the current strategy
  - Prevents additional 489 chronic infections
  - Saves 800 QALYs and $2.8 million
- Results robust over wide range of assumptions

Fan et al. Hepatology 2016

Shortened Interval for Post-Vaccination Serologic Testing of Infants Born to Hepatitis B-Infected Mothers

Schillie S, et. al. Update: Shortened Interval for Postvaccination Serologic Testing of Infants Born to Hepatitis B-Infected Mothers. MMWR. 2015 Oct 9;64(39):1118-20.

Advisory Committee on Immunization Practices (ACIP) Recommendations for Post-Vaccination Serologic Testing (PVST)

- Persons recommended for PVST
  - Infants born to HBsAg-positive mothers
  - Healthcare personnel
  - Chronic hemodialysis patients, HIV-infected persons, and other immunocompromised persons
  - Sex partners of HBV-infected persons

Mast et al. MMWR 2005, 2006

PVST for Infants Born to HBsAg-positive Mothers

- Testing for both anti-HBs and HBsAg is necessary to confirm whether the infant is immune or infected
  - Alone, an anti-HBs result ≥10 mIU/mL does not confirm that the infant is uninfected and protected; anti-HBs can become positive with recovery from infection
  - A negative HBsAg test result by itself does not indicate whether the infant is protected or susceptible

Schillie et al. MMWR 2015

Timing of Infant PVST

- Recommended at age 9-12 months
- PVST occurring at an increasing interval after the final dose of vaccine misclassifies some infants as non-responders
  - Results in unnecessary revaccination
- PVST should not occur before 9 months of age in order to:
  - Detect HBV infections following a longer incubation period, which might occur after receipt of HBIG
  - Avoid detection of passive anti-HBs from HBIG administered at birth

Schillie et al. MMWR 2015

Update: Shortened Interval for Post-Vaccination Serologic Testing of Infants Born to HBsAg-Positive Mothers

Morbidity and Mortality Weekly Report

Update: Shortened Interval for Postvaccination Serologic Testing of Infants Born to Hepatitis B-Infected Mothers

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Infants born to hepatitis B-infected mothers receive postexposure prophylaxis to reduce their risk for perinatal hepatitis B virus (HBV) infection (*1*). Postexposure prophylaxis consists of hepatitis B (HepB) vaccine and hepatitis B immune globulin administered within 12 hours of birth, followed by completion of the 3-dose or 4-dose HepB vaccine series (*1*). Postvaccination serologic testing (PVST) assesses an infant's response to HepB vaccination and has typically occurred at age 9–18 months (*1*). This report provides a CDC update recommending shortening the interval for PVST from age 9–18 months to age 9–12 months. Providers should order PVST (consisting of hepatitis B surface antigen [HBsAg] and antibody to HBsAg [anti-HBs]) for infants born to HBsAg-positive mothers at age 9–12 months (or 1–2 months after the final dose of the vaccine series, if the series is delayed). This recommendation was prompted by the discontinuation of production of Hib/HepB vaccine (Comvax) and new data from the Enhanced Perinatal Hepatitis B Prevention Program supporting PVST 1–2 months after receipt of the last HepB vaccine dose, and at age ≥9 months.

An estimated 25,000 infants are born to HBsAg-positive mothers each year in the United States (*2*). Perinatal HBV infection, acquired in utero or during delivery, results in chronic HBV infection in 90% of infected infants (*1*). Approximately 25% of infants with HBV infection acquired perinatally will die prematurely as a result of complications of cirrhosis or liver cancer (*1*). Before the widespread availability of postexposure prophylaxis, up to 90% of infants born to HBsAg-positive mothers developed HBV infection (*1*). Postexposure prophylaxis is highly effective in preventing perinatal HBV transmission. In recent years in the United States, approximately 1% of infants receiving postexposure prophylaxis develop infection (*3*).

PVST consists of two tests: measurement of HBsAg and anti-HBs (*1*). Infants born to HBsAg-positive mothers who are HBsAg negative with anti-HBs levels ≥10 mIU/mL after having received a complete, 3-dose or 4-dose HepB vaccine series are identified as vaccine responders and considered seroprotected (*4,5*). Infants who are HBsAg negative with anti-HBs levels <10 mIU/mL require revaccination with a second 3-dose HepB vaccine series, followed by retesting for anti-HBs 1–2 months after the final vaccine dose (*4*).

Postvaccination seroprotection is achieved in 98% of healthy full-term infants who received a 3-dose or 4-dose HepB vaccine series, although it is lower among infants with birthweights <4.4 lbs (<2,000 g) (*5*). Vaccine efficacy studies have demonstrated protection against acute and chronic hepatitis B disease in immunocompetent vaccine responders (*6*). Anti-HBs levels following vaccination decline over time (*6*). Immunocompetent persons who achieve an anti-HBs level ≥10 mIU/mL 1–2 months after a complete HepB series remain protected, even if anti-HBs levels decline to <10 mIU/mL beyond that time, presumably because of persistent cellular immunity (*7*).

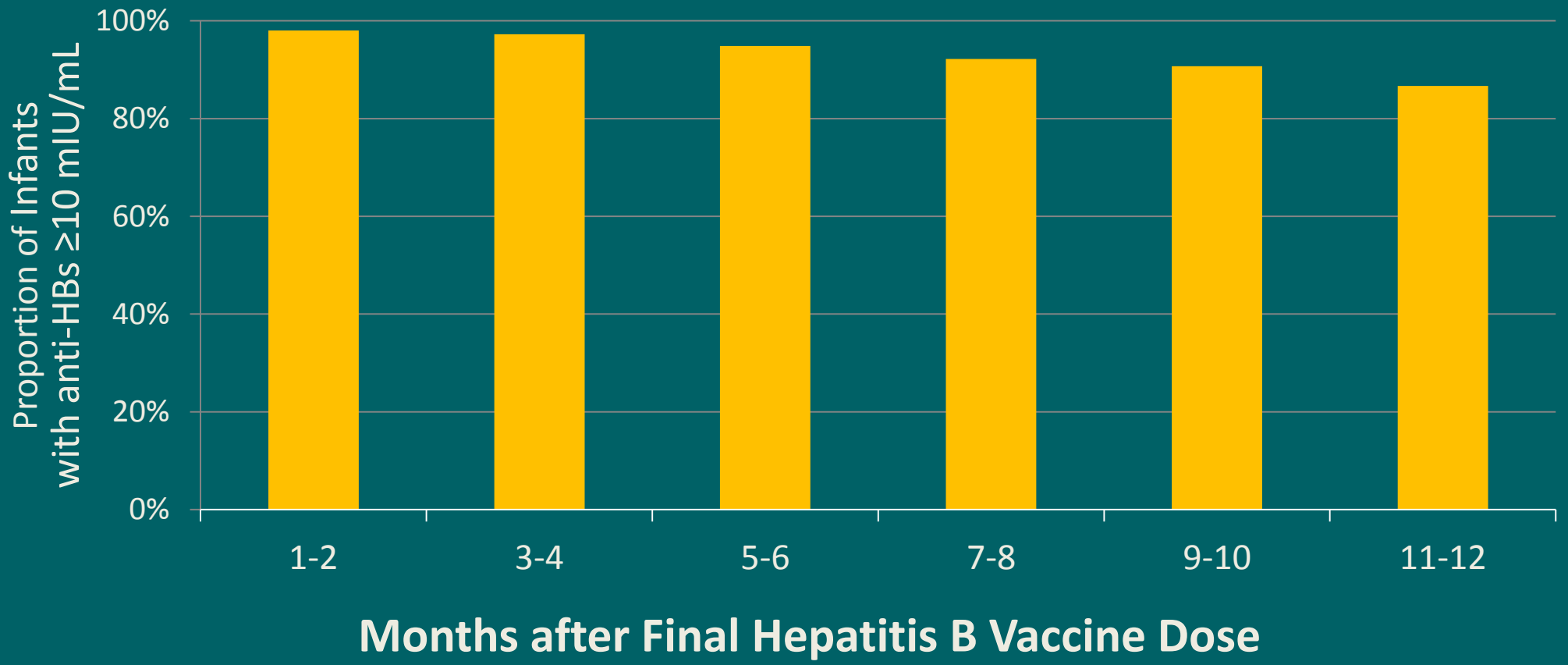
HepB vaccine doses subsequent to the monovalent HepB vaccine birth dose are administered as either monovalent or combination vaccine (*1*). Before December 31, 2014, two combination vaccines containing recombinant HBsAg were available in the United States for infants aged ≥6 weeks: 1) Hib/HepB vaccine (Comvax, Merck and Co, Inc.) and 2) DTaP-HepB-IPV vaccine (Pediarix, GlaxoSmithKline Biologicals) (*1*). Hib/HepB vaccine (Comvax) production has been discontinued. For infants born to HBsAg-positive mothers, the final dose of the HepB vaccine series is administered at age 6 months when monovalent or DTaP-HepB-IPV vaccine (Pediarix) is used to complete the series (*1*). When Hib/HepB vaccine (Comvax) was used to complete the series, the final dose was administered at age 12–15 months (*1*).

The optimal timing for PVST to detect a vaccine response generally is 1–2 months after the final dose of the HepB vaccine series (*1*). Results of tests for HBsAg can be transiently positive for 1–18 days after vaccination. PVST should be performed no earlier than age 9 months to avoid detection of passive anti-HBs from hepatitis B immune globulin administered at birth and to maximize the likelihood of detecting late HBV infection (*1*).

In developing this update to shorten the interval for PVST to age 9–12 months, CDC subject matter experts reviewed the shortened interval with professionals from academia and public health and considered existing (*8*) and new data (*9*) on anti-HBs levels among infants born to HBsAg-positive mothers. Among 348 infants born to HBsAg-positive mothers enrolled in the Enhanced Surveillance: Perinatal Hepatitis B Program in Dallas County, Texas, PVST performed at 4–7 months and 8–11 months after the final vaccine dose was associated with lower anti-HBs levels (odds ratios = 1.8 and 4.4, respectively; 95% confidence intervals = 1.2–2.8 and 1.3–14.5, respectively), when compared with PVST 1–3 months after vaccination (*8*). In a study analyzing data collected from 8,105 HBsAg-negative infants born to HBsAg-positive mothers enrolled in

Schillie et al. MMWR 2015

Anti-HBs Decline over Time



Schillie et al. MMWR 2015

Anti-HBs Decline over Time, cont.

Interval from final vaccine dose to postvaccination serologic testing	Odds of lower anti-HBs
1 to <4 months	ref
4 to <8 months	1.8 (1.2-2.8)
8 to <12 months	4.4 (1.3-14.5)

Euler et al. PIDJ 2003

American Academy of Pediatrics: Ages for Recommended Preventive Health Care

Recommended interval for PVST

Pre-natal	New-born	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 (single antigen and Pediarix)

Advantages of a Shortened Interval

- 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

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

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.