Seroprotection after Hepatitis B Vaccination among Newborn Infants: a Review

Rania Tohme, MD, MPH

Team Lead— Global Immunization Division, US CDC

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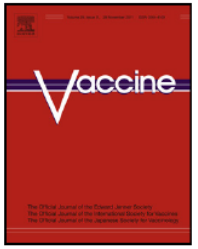

Review

Seroprotection after recombinant hepatitis B vaccination among newborn infants: A review☆

Sarah F. Schillie*, Trudy V. Murphy

Division of Viral Hepatitis, Vaccine Research and Policy Team, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, United States

Slides adapted from Sarah Schillie's presentation to the WHO IVR Meeting on optimizing schedules for hepatitis B vaccine in 2015

Objectives

- Summarize seroprotection and immunogenicity of recombinant hepatitis B vaccine (HepB) when administered starting within 30 days of birth

- Highlight gaps of knowledge related to the widespread use of HepB for prevention of perinatal and early horizontal transmission of HBV

Methods

- Electronic search using MEDLINE (via PubMed) and EMBASE (via OVID)
- Search terms
  - hepatitis b vaccin*,hbv vaccin*, hepatitis b immuni*, hbv immuni*, immunogeni*,immune response, antibody, neona*, infan*, birth
- Publication dates: 1987– 2011
- Manual review of files and reference lists from published studies
- Inclusion criteria
  - Published studies with a primary focus of reporting seroprotective response to monovalent recombinant hepatitis B vaccine administered to infants in the first 30 days of life
    - antibody to hepatitis B surface antigen [anti-HBs] ≥ 10 mIU/mL

Data Extraction

- Review parameters for each study arm:
  - Maternal HBsAg status
  - Maternal HBeAg status
  - HBIG administration
  - Birth weight (<2000g vs. ≥2000g)
  - Vaccine dosage (low: 2.5–10 mcg vs. high: 5–20 mcg)
  - Vaccine schedule (compressed within 3 months of age vs. not compressed)
  - Age at first dose (HepB-BD)
- Median and range proportions with anti-HBs ≥10 mIU/mL and median GMTs reported overall and by review parameter

Results

- 43 studies (20 randomized trials) included
  - 9368 infants subjects
  - 100 study arms
- Infants generally healthy
  - Males slightly outnumbered females when reported
- Median final seroprotection proportion across all study arms: 98% (range: 52–100%)
  - Median VE among infants of HBsAg+ mothers: 79–98%
- No major adverse events following immunization

Results by Maternal HBsAg Positivity (11 studies)

- HepB birth dose (HepB-BD) administered within 24 hours of birth in 10 studies and up to 5 days in 1 study
- Birth weight generally ≥ 2000 g
- Some infants received HBIG

		1st dose	2nd dose	Final dose
HBsAg+ mothers	Median seroprotection (range)	23% (11–100) 3 studies	67% (30–100) 6 studies	94% (63–100) 11 studies
	Median GMT mIU/mL (range)	60 (3–161) 5 studies	24 (8–228) 8 studies	355 (73–7985) 9 studies

Results by Maternal HBeAg Status (3 studies)

- Birth weight generally ≥ 2000 g
- HBIG administered in 2 studies to infants of HBeAg +ve and HBeAg-ve mothers

	Final dose	
	Median seroprotection (range)	**Median GMT mIU/mL (range)**
HBeAg +ve mothers	84% (67–99)	511 (347–675)
HBeAg –ve mothers	94% (63–96)	494 (300–688)

Results by HBIG Administration (5 studies)

- HBIG dosage: 100 IU–260 IU
- Birth weight generally ≥ 2000 g

	1st dose (2 studies)		Final dose	
	Seroprotection (range)	**GMT mIU/mL (range)**	**Seroprotection (range)**	**GMT mIU/mL (range)**
HepB-BD with HBIG	88% (76–100)	61 (60–61)	94% (86–100)	4119 (168–7985) 4 studies
HepB-BD without HBIG	31% (11–50)	8 (6–10)	96% (69–100)	3148 (306–17,630) 4 studies

Results by Birth Weight (7 studies)

- Mothers HBsAg negative
- HBIG not administered

	Final dose	
	Median seroprotection (range)	**Median GMT mIU/mL (range)**
<2000 g	93% (77–100)	469 (89–2431) 5 studies
≥ 2000 g	98% (93–100)	1000 (538–4804) 5 studies

Results by Vaccine Dosage (6 studies)

- Mothers HBsAg +ve and HBsAg –ve
- HBIG administered in one study

		1st dose	2nd dose (2 studies)	Final dose (6 studies)
Low dosage 2.5–10mcg	Seroprotection (range)	25% (25–76) 2 studies	56% (39–61)	98% (88–100)
	GMT mIU/mL (range)	31 (2–161) 3 studies	11 (8–14)	244 (78–6703)
High dosage 5–20 mcg	Seroprotection (range)	41% (23–76) 2 studies	80% (36–86)	96% (88–100)
	GMT mIU/mL (range)	33 (3–127) 3 studies	23 (11–35)	274 (168–7104)

Results by Vaccine Schedule (6 studies)

- Mothers HBsAg positive in 2 studies
- Birth weight generally ≥ 2000 g

		3rd dose	Final dose
Compressed schedule (3 doses by age 3 months ± 4th dose at age 11–12 months	Seroprotection (range)	97% (74–100) 4 studies	97% (91–100)
	GMT mIU/mL (range)	119 (68–298) 5 studies	315 (123–10,495)
Non-compressed schedule (0,1,6 months)	Seroprotection (range)	100% (92–100) 5 studies	
	GMT mIU/mL (range)	530 (147–3,142) 4 studies	

Results by Age at First Dose—Birth weight ≥2000 g (2 studies)

- Mothers HBsAg negative

	Final dose	
	Median seroprotection (range)	**Median GMT mIU/mL**
First dose at 0-3 days of age	96% (91–100)	5401
First dose at ≥1 months of age	99% (97–100)	11,130

Results by Age at First Dose—Birth weight <2000 g (1 study)

- Mothers HBsAg negative

	Final dose Seroprotection
First dose at 0-3 days of age	67%–69%
First dose at ≥1 months of age	90%–100%

Limitations

- Search strategy limited to English language
- Outcomes were serologic correlates of protection rather than efficacy
- Unable to perform meta-analysis and test for statistically significant associations
- Majority of the studies that fulfilled the inclusion criteria did not use combination vaccines

Conclusions

- High levels of seroprotection (98%) achieved from recombinant Hepatitis B vaccine starting with the birth dose
- Final median seroprotections did not vary appreciably by:
  - Maternal HBsAg status
  - HBIG administration
  - Vaccine schedule and dosage
- No conclusion could be drawn regarding any difference in the seroprotection and immunity of infants based on mother's HBeAg status
  - Limited number of studies
- Earlier increases in seroprotection seen with HBIG and higher vaccine dosage however final seroprotection did not vary

Conclusions

- Compared to non-compressed schedules, compressed schedules can induce anti-HBs at an earlier age
  - Shorter interval between dose 2&3 associated with lower seroprotection and GMT after the third dose
  - Addition of 4th dose might boost seroprotection
  - Potential implications on HepB combination vaccine schedules in some countries (e.g 0, 6, 10, 14 weeks; 0,2,3,4 months)
- Seroprotection was lower among infants with birth weight <2000g vaccinated soon after birth
  - Addition of 4th dose might help increase seroprotection
- More studies are needed to further define immunology of hepatitis B vaccination starting in infancy and its effect on long-term protection

Thank You

For more information, contact CDC
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TTY: 1-888-232-6348 www.cdc.gov

Extra slides

Table 1
Hepatitis B vaccine schedules for term newborn infants (birth weight ≥2000 g), by maternal hepatitis B surface antigen (HBsAg) status.

Maternal HBsAg status	Single-antigen vaccine		Single antigen + combination vaccine	
	Dose	Age	Dose	Age
Positive	1[a]	Birth (≤12 h)	1[a]	Birth (≤12 h)
	HBIG[b]	Birth (≤12 h)	HBIG[b]	Birth (≤12 h)
	2	1–2 mos	2	2 mos
	3[c]	6 mos	3	4 mos
			4[c]	6 mos (Pediarix) or 12–15 mos (Comvax)
Unknown[d]	1[a]	Birth (≤12 h)	1[a]	Birth (≤12 h)
	2	1–2 mos	2	2 mos
	3[c]	6 mos	3	4 mos
			4[c]	6 mos (Pediarix) or 12–15 mos (Comvax)
Negative	1[a,e]	Birth (before discharge)	1[a,e]	Birth (before discharge)
	2	1–2 mos	2	2 mos
	3[c]	6–18 mos	3	4 mos
			4[c]	6 mos (Pediarix) or 12–15 mos (Comvax)

[a] Recombivax HB or Engerix-B should be used for the birth dose. Comvax and Pediarix cannot be administered at birth or before age 6 weeks.
[b] Hepatitis B immune globulin (0.5 mL) administered intramuscularly in a separate site from vaccine.
[c] The final dose in the vaccine series should not be administered before age 24 weeks (164 days).
[d] Mothers should have blood drawn and tested for HBsAg as soon as possible after admission for delivery; if the mother is found to be HBsAg positive, the infant should receive HBIG as soon as possible but no later than age 7 days.
[e] 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 ≥2000 g and whose mother is HBsAg negative, but only if a physician's order to withhold the birth dose and a copy of the mother's original HBsAg-negative laboratory report are documented in the infant's medical record.

Table 2
Publication year, vaccine, manufacturer, and country for 43 included studies.

Author	Ref. no.	Year	Vaccine	Vaccine manufacturer	Country
Alikasifoglu	[41]	2001	Engerix-B, GenHevac B, HepavaxGen	SmithKline Beecham, Pasteur, Korea Green	Turkey
Arora	[38]	2002	EnivacHB	Panacea Biotec	India
Assateerawatt	[26]	1993	GenHevac B	Pasteur	Thailand
Ballesteros-Trujillo	[63]	2001	Engerix-B	SmithKline Beecham	Mexico
Bassily	[47]	1995	Recombivax HB	Merck, Sharp and Dohme	Egypt
Belloni	[45]	1993	Engerix-B	SmithKline Beecham	Italy
Belloni	[37]	1998	NR	NR	Italy
Bhave	[64]	2002	Shanvac B	Shantha Biotechnics	India
Blondheim	[36]	1998	Engerix-B	SmithKline Beecham	Israel
del Canho	[44]	1993	Engerix-B	SmithKline Beecham	Netherlands
Goldfarb	[43]	1994	Engerix-B	SmithKline Beecham	US
Golebiowska	[34]	1999	Engerix-B	SmithKline Beecham	Poland
Gunn	[65]	1989	Engerix-B	SmithKline Beecham	New Zealand
Halliday	[25]	1992	Betagen	Connaught Laboratories	China
Huang	[54]	1997	H-B-Vax II	Merck, Sharp and Dohme	Taiwan
Junqueira	[66]	2010	Butang	Institute Butantan	Brazil
Kabir	[24]	2006	Heberbiovac-HB	Heber Biotec	Iran
Kim	[53]	1997	Recombivax HB	Merck, Sharp and Dohme	US
Kojouharova	[67]	2001	Euvax B	Lucky Goldstar Chemicals	Bulgaria
Lau	[68]	1992	Engerix-B	SmithKline Beecham	Hong Kong
Lee	[23]	1991	Engerix-B	SmithKline Beecham	Taiwan
Lee	[40]	1995	B-Hepavac II	Merck, Sharp and Dohme	Hong Kong
Lolekha	[22]	2002	H-B-Vax II	Merck, Sharp and Dohme	Thailand
Losonsky	[69]	1999	Recombivax HB	Merck, Sharp and Dohme	US
Madalinski	[42]	2004	Bio-Hep-B	Biotechnology General	Poland
Martins	[70]	2004	Butang, Engerix-B	Institute Butantan, SmithKline Beecham	Brazil
Milne	[27]	2002	H-B-Vax II	Merck, Sharp and Dohme	Vietnam
Da Motta	[35]	2002	Engerix-B	SmithKline Beecham	Brazil
Patel	[46]	1997	Recombivax HB	Merck, Sharp and Dohme	US
Poovorawan	[21]	1989	Engerix-B	SmithKline Beecham	Thailand
Ribeiro	[71]	2006	Engerix-B, Euvax B, HepavaxGen	SmithKline Beecham, Lucky Goldstar Chemicals, Korea Green	Brazil
Hassanjani-Roshan	[31]	2002	Heberbiovac-HB	Heber Biotec	Iran
Sadeck	[33]	2004	Recombivax HB	Merck, Sharp and Dohme	Brazil
Sapru	[72]	2007	Engerix-B, GeneVacB	SmithKline Beecham, Serum Institute of India	India
Seto	[73]	1999	Engerix-B, Recombivax HB	SmithKline Beecham, Merck, Sharp and Dohme	US
Shokri	[39]	2001	Heberbiovac-HB	Heber Biotec	Iran
Sood	[32]	2002	Engerix-B	SmithKline Beecham	India
Soulie	[29]	1991	GenHevac B	Pasteur	France
Tregnaghi	[74]	2004	Engerix-B, Euvax-B	SmithKline Beecham, Lucky Goldstar Chemicals	Argentina
Velu	[30]	2007	Engerix-B, GeneVacB, Shanvac B,	SmithKline Beecham, Serum Institute of India, Shantha Biotechnics	India
Watanaveeradej	[75]	2002	NR	NR	Thailand
Yang	[28]	2003	Engerix-B, Recombivax HB	SmithKline Beecham, Merck, Sharp and Dohme	Taiwan
Yerushalmi	[76]	1997	Bio-Hep-B, Engerix-B	Biotechnology General, SmithKline Beecham	Israel

NR, not reported.

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