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Review

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

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ABSTRACT

Introduction: Hepatitis B vaccination starting at birth provides a safety net for infants exposed to hepatitis B virus (HBV) during delivery or in early life. Hepatitis B vaccine is recommended in the United States for infants prior to birthing facility discharge, and within the first 12 h of life for infants born to hepatitis B surface antigen (HBsAg)-positive mothers. We performed a literature review and summarized the response to recombinant hepatitis B vaccine among infants.

Methods: Studies published between 1987 and 2011 assessing seroprotection from recombinant hepatitis B vaccine starting within the first 30 days of life were eligible. Seroprotection was defined using an antibody to hepatitis B surface antigen (anti-HBs) threshold of 10 mIU/mL at series completion. Infant seroprotection was compared in trial arms varying by maternal hepatitis B antigen status (e antigen [HBeAg], HBsAg), hepatitis B immune globulin (HBIG) administration, birth weight, vaccine dosage, schedule, and age at first dose.

Results: Forty-three studies were included. The median seroprotection proportion overall was 98% (range 52%, 100%). The final median seroprotection proportions did not vary appreciably by maternal HBsAg status, HBIG administration, or schedule. Higher compared to lower dosage resulted in earlier increases in anti-HBs but not in final seroprotection proportions. Infants with birth weights <2000 g compared to ≥2000 g had lower median seroprotection proportions (93% and 98%, respectively). Median seroprotection proportions were also lower when infants with birth weights <2000 g were vaccinated at 0–3 days of age compared to 1 month of age or older (68% versus 95%, respectively).

Conclusion: High levels of protection from recombinant hepatitis B vaccine are achieved in term infants vaccinated at birth, effectively preventing transmission of HBV and resultant morbidity and mortality. Implications, if any, for long-term protection are unknown for differences in responses among infants vaccinated at birth compared to ages older than 1 month.

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1. Introduction

Chronic hepatitis B virus (HBV) infection is one of the leading causes of liver failure and cancer worldwide [1]. Chronic HBV infection occurs in approximately 90% of infected infants, in contrast to fewer than 5% of persons infected at 5 years of life or older [2]. Historically, perinatal or childhood transmission accounted for 30–40% of chronic HBV infections in the United States [2]. Pregnant women with acute or chronic HBV infection are an important source of hepatitis B for their infants. Although a small proportion of infants are infected in utero, exposure to

Abbreviations: ACIP, Advisory Committee on Immunization Practices; AGA, appropriate for gestational age; anti-HBs, antibody to HBsAg; BW, birth weight; CDC, Centers for Disease Control and Prevention; EIA, enzyme immunoassay; GMT, geometric mean titer; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; mIU/mL, milli-international units per milliliter; RIA, radioimmunoassay; SRU, sample ratio units; WHO, World Health Organization.

☆ The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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blood or body fluids during birth is a major route of transmission for HBV infection among infants [3]. Early life transmission also occurs through contact with infected siblings or care providers who may be unaware of their infection [4–8]. Although chronic HBV infections acquired in early life are largely asymptomatic, up to a quarter of these infections result in premature death from complications including cirrhosis, liver failure, or liver cancer [9]. Persons with chronic HBV infection are the main reservoir for transmission [2,10].

The first hepatitis B vaccine consisted of plasma-derived hepatitis B surface antigen (HBsAg). In 1982, the Advisory Committee on Immunization Practices (ACIP) recommended administration of hepatitis B immune globulin (HBIG) for infants born to HBsAg-positive mothers, followed by hepatitis B vaccination beginning at three months of age [11]. Clinical trials were structured so that infants received the initial dose of vaccine at birth, followed by completion of a 3 or 4 dose vaccine series [12–14]. Among high-risk infants, the efficacy of plasma-derived vaccine plus HBIG ranged from 66% to 100% [15].

Recombinant hepatitis B vaccines containing yeast-derived HBsAg replaced the plasma-derived vaccines in the United States by the late 1980s. Hepatitis B vaccination has been universally recommended for infants in the United States since 1991. The recommendation specified administration of the first dose by 2 months of age, with a preference for administration before birthing facility discharge [16]. In 2005, an update to the recommendation specified the first dose should be a "birth dose," i.e., administered to infants with birth weights ≥2000 g before birthing facility discharge as a safety net for early life prevention of HBV infection, or to all infants born to HBsAg-positive mothers within 12 h of birth [2]. As such, hepatitis B vaccination starting at birth is unique from other routine infant immunizations recommended in most countries that commence at 6 weeks to 2 months of life or later [17]. Prevention of perinatal or early life HBV infection underlies the recommendation for hepatitis B vaccination starting at birth.

Primary infant hepatitis B vaccination in the United States consists of three doses of 5 or 10 μg of monovalent recombinant vaccine administered intramuscularly on a 0, 1–2, and 6–18 months schedule. Other schedules are available in the United States (Table 1). Either of two monovalent vaccines (Recombivax HB® [Merck & Co, Inc., Whitehouse Station, NJ, US] and Engerix-B® [GlaxoSmithKline Biologicals, Rixensart, Belgium]) may be used. Combination vaccines may be used for doses administered at ages 6 weeks or older provided other indications are heeded [2].

In this review, we summarize the seroprotection proportions and immunogenicity of recombinant hepatitis B vaccine found in trials that administered recombinant hepatitis B vaccine starting within the first 30 days of life. We highlight some of the issues and gaps in knowledge related to the widespread use of hepatitis B vaccine for prevention of perinatal and early life acquisition of HBV infection.

2. Materials and methods

2.1. Search strategy

An electronic search of MEDLINE (via PubMed) and EMBASE (via Ovid) using combinations of search terms (hepatitis b vaccin*, hbv vaccin*, hepatitis b immuni*, hbv immuni*, immunogeni*, immune response, antibody, neona*, infan*, birth) was performed, including errata. Limits included publication date from January 1, 1987 (1988 for EMBASE) through December 16, 2011, English language, humans, and age birth through one month (through one year for EMBASE), without restriction for country where the trial was carried out. A manual review of personal files and reference lists from published studies was conducted concurrently.

2.2. Inclusion criteria

Published studies with a primary focus of reporting seroprotective (defined using an antibody to hepatitis B surface antigen [anti-HBs] threshold of 10 mIU/mL) response to monovalent recombinant hepatitis B vaccine administered to infants in the first 30 days of life were included.

2.3. Exclusion criteria

Studies were excluded when seroprotection was assessed in conjunction with administration of other vaccines, when a combination vaccine containing HBsAg was administered, or when vaccine was not administered intramuscularly. When two studies reported results for duplicate subjects, one study was excluded. Studies also were excluded when seroprotection was not reported within three months after the final dose in the series or when seroprotection using an anti-HBs threshold of 10 mIU/mL was not reported. Because of varying definitions, studies were excluded if antibody levels defining "seroconversion" or "seroprotection" were not reported. Studies were not excluded when a fraction of subjects meeting an exclusion criterion was deemed unlikely to affect the findings.

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.

2.4. Seroprotection and vaccine efficacy

A serologic correlate of protection against chronic HBV infection after completion of a primary vaccination series was used for this review [18,19]. Threshold values included induction of 10 sample ratio units (SRU) of anti-HBs by radioimmunoassay (RIA), which was approximately equal to 10 mIU/mL using the WHO Anti-HBs Reference Preparation, or positive by enzyme immunoassay (EIA) [20]. We considered these values the lower limit of the immune response to vaccination that provides protection against acute disease symptoms and development of chronic infection. Although some infants achieve an anti-HBs response of ≥10 mIU/mL after one or two doses of vaccine (summarized here), the relevance of these levels for protection when the series has not been completed is not established [2].

2.5. Data extraction and categorization

Data elements were recorded and analyzed for each trial arm when possible. Maternal HBsAg/HBeAg status, HBIG administration, birth weight, vaccine dosage, schedule, and age at first dose (termed "review parameters") were recorded. Median and range proportions with anti-HBs ≥10 mIU/mL (defined as seroprotection proportions when following the final dose) and GMTs were reported overall and by review parameter. Results from different laboratories were likely to vary by the assay used and with testing across time; eligibility criteria, characteristics of the infants, and settings also would have varied across studies. To minimize these effects, comparisons were made between results from different arms of the same study. For parameters with results reported for three or more strata (i.e., birth weight and dosage), values from the lowest and highest strata were used to calculate medians and ranges specific for a parameter.

When possible, information was extracted or converted to be consistent across studies. Age at first dose was recorded as 0 when reported as immediately after delivery or within the first 24 h of life. Birth weight was divided by 0.0022 and recorded in grams when reported in pounds. Unless stated otherwise, term infants were assumed to weigh ≥2000 g and preterm infants were assumed to weigh <2000 g. A schedule was defined as being compressed when the first three doses of vaccine were given within the first three months of life, regardless of administration or timing of a 4th dose. Results were recorded after each dose when possible, including a 4th dose. When multiple immune response measurements were reported reflecting anti-HBs levels at different intervals after a specified dose, the result from the interval nearest to one month after that dose was recorded. Included studies generally reported seroprotection proportions for uninfected infants only and GMT values for infants who seroconverted after vaccination. When studies reported obtaining blood for serologic measurements at the same time as vaccination, the blood draw was assumed to occur prior to vaccination. Although general conclusions were drawn from a synthesis of the results, no attempt was made to perform a formal meta-analysis, to critically assess the strength of the evidence in each study, nor to test for statistically significant differences.

3. Results

The electronic search yielded 833 studies (available upon request). Based on review of titles and/or abstracts, full texts were retrieved and reviewed for 93 studies (11.2%). Of these, 34 (36.6%) met study criteria. An additional 13 studies were identified from manual review of personal files and reference lists. Four studies were excluded for reporting on duplicate subjects. A total of 43 studies reporting on 9368 infant subjects in 100 arms were included in this review (Table 2). Twenty were randomized trials. Vaccine containing both preS1 and preS2 antigens (Bio-Hep-B®) was administered to infants in two studies and vaccine containing preS2 antigen (GenHevac B®) was administered to infants in three studies. Infants were generally healthy; males slightly outnumbered females in most studies when reported (Table 3).

For infants of HBsAg-positive mothers (including those who did and did not receive HBIG), vaccine efficacy ranged from 79 to 98% in seven studies [21–27]. The median seroprotection proportion across all studies including HBsAg-positive and HBsAg-negative mothers was 98% (range 52%, 100%). The vaccine was well tolerated overall; one infant experienced collapse and dyspnea possibly related to vaccination [27].

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.

3.1. Maternal HBsAg positivity

Eleven trials examined the immune responses of infants born to HBsAg-positive mothers. Ten trials included infants born to HBeAg-positive mothers. Some infants received HBIG. Birth weight was generally ≥2000 g. Vaccine was administered within the first 24 h of life in most trials, but up to 5 days of life in one trial [28]. After the first dose, the median proportion with anti-HBs ≥10 mIU/mL and GMT (three and five trials, respectively) were 23% (range 11%, 100%) and 60 mIU/mL (range 3 mIU/mL, 161 mIU/mL) [21,23,25,29,30]. After the second dose, the median proportion with anti-HBs ≥10 mIU/mL and median GMT (six and eight trials, respectively) were 67% (range 30%, 100%) and 24 mIU/mL (range 8 mIU/mL, 228 mIU/mL). The higher GMTs after the first dose (versus after the second dose) likely resulted from passively acquired antibody from HBIG. After the final dose of the series, the median seroprotection proportion (11 trials) was 94% (range 63%, 100%) and the median GMT (nine trials) was 355 mIU/mL (range 73 mIU/mL, 7985 mIU/mL).

3.2. Maternal HBeAg positivity

Three trials compared infant immune response by maternal HBeAg status [27,28,31]. All mothers were HBsAg-positive. HBIG was administered in two trials [28,31] to infants of both HBeAg-positive and HBeAg-negative mothers. Birth weight was generally ≥2000 g. Data were available after the final dose of vaccine. The median seroprotection proportion among infants born to HBeAg-positive mothers was 84% (range 67%, 99%), which was lower than the median proportion among infants born to HBeAg-negative mothers, 94% (range 63%, 96%). However, the median GMTs (two trials) [27,28] were similar for infants born to HBeAg-positive and negative women, 511 mIU/mL (range 347 mIU/mL, 675 mIU/mL) and 494 mIU/mL (range 300 mIU/mL, 688 mIU/mL), respectively.

3.3. HBIG

Five trials compared immune response with and without HBIG administration [24–26,28,29]. HBIG dosages varied from 100 IU to 260 IU in four studies. Mothers were generally HBsAg-positive and most infants had birth weights ≥2000 g. After the first dose of vaccine and HBIG, the median proportion with anti-HBs ≥10 mIU/mL (two trials) [25,29] was greater for infants who received HBIG plus vaccine compared to infants who received vaccine alone (probably reflecting passively acquired antibody from HBIG), 88% (range 76%, 100%) and 31% (range 11%, 50%). Median GMTs were 61 mIU/mL (range 60 mIU/mL, 61 mIU/mL) and 8 mIU/mL (range 6 mIU/mL, 10 mIU/mL), respectively. The final median seroprotection

Table 3
Seroprotection proportions (anti-HBs threshold of 10 mIU/mL) and Geometric Mean Titers (GMT) of included studies.

Author (Ref.)	HBsAg/HBeAg	HBIG	Gestation (weeks)	BW (g)	Dosage (μg)	Schedule	Age at dose 1[a]	Response							
								After first dose		After second dose		After third dose		After fourth dose	
								SP% (*n*)	GMT	SP% (*n*)	GMT	SP% (*n*)	GMT	SP% (*n*)	GMT
Alikasifoglu [41]	Neg[b]/		40	3450	10	0, 1, 2, 12	11	25 (36)	2	61 (36)	14	97 (35)	68	100 (24)	268
	Neg[b]/		39	3512	20	0, 1, 6	9	41 (29)	6	86 (29)	35	100 (26)	169		
	Neg[b]/		40	3397	20	0, 1, 2, 12	9	23 (31)	3	80 (30)	23	100 (28)	114	100 (24)	274
	Neg[b]/		40	3395	10	0, 1, 6	11	25 (32)	2	56 (32)	11	100 (28)	147		
	Neg[c]/		40	3379	20	0, 1, 2, 12	11	23 (31)	2	52 (31)	10	87 (31)	46	100 (26)	236
	Neg[d]/		39	3307	10	0, 1, 6	10	23 (44)	5	72 (43)	29	98 (40)	171		
Arora [38]	Neg/		34	1770	10	0, 1.5, 2.5, 3.5	3					87 (82)	204	99 (82)	799
	Neg/		38	2120	10	0, 1.5, 2.5, 3.5	1					97 (60)	615	98 (60)	1023
Assateerawatt [26]	Pos/Pos	Yes	Term	>2500	20	0, 1, 2, 12				100 (26)	67	96 (26)	277	100 (26)	7985
	Pos/Pos	No	Term	>2500	20	0, 1, 2, 12				62 (23)	18	95 (23)	279	96 (23)	4542
Ballesteros-Trujillo [63]			33	1398	10	0, 1, 5, 9	9			100 (29)	52	100 (29)	133	100 (29)	133
Bassily [47]	Neg/			≥2000	2.5	0, 2, 6	0					91 (178)	306		
	Neg/			≥2000	2.5	2, 4, 9						97 (167)	1492		
Belloni [45]	Neg/		≥32	>1500	10	0, 1, 3	4					97 (231)			
	Neg/		≥32	>1500	10	0, 1, 6	4					99 (273)			
Belloni [37]	Neg/		26–29		10	0, 1, 6	4					100 (8)			
	Neg/		30–32		10	0, 1, 6	4					100 (13)			
	Neg/		33–37		10	0, 1, 6	4					97 (220)			
	Neg/		≥38		10	0, 1, 6	4					97 (1727)			
Bhave [64]			<34	1489	10	0, 1, 2, 12	20	67		100		100 (21)			
			34–36	1842	10	0, 1, 2, 12	10	57		100		100 (18)			
			Term	2051	10	0, 1, 2, 12	8	70		100		100 (25)			
			Term	2741	10	0, 1, 2, 12	1	50		100		100 (24)			
Blondheim[e] [36]	Neg/		32	1557	10	0, 1, 5	2					89 (176)	469		
			39	3400	10	0, 1, 5	0					93 (46)	701		
del Canho [44]	Neg/		40	3330	20	3, 4, 5, 11						100 (45)	264	100 (42)	20,768
	Neg/		40	3340	20	0, 1, 6					56	100 (51)	3090		
	Neg/		40	3240	20	0, 1, 2, 11							135	100 (48)	10,495
Goldfarb [43]	Neg/			3318	10	0, 1, 6	Within 72 h			49 (77)	12	96 (52)	3142		
	Neg/			3273	10	0, 1, 2	Within 72 h			51 (79)	15	91 (69)	123		
Golebiowska [34]	Neg/		25–36	≤2000	10	0, 1, 2, 12	1[f]							98 (40)	2431
	Neg/		25–36	>2000	10	0, 1, 2, 12	1[g]							100 (23)	4804
Gunn [65]	Neg/		Term	AGA	20	0, 1, 6	Within 72 h	5 (93)	20			99 (91)	1259		
Halliday [25]	Pos/Both	No		>1600	20	0, 1, 6	0	11 (46)	6	30 (46)	9	89 (46)	306		
	Pos/Both	Yes		>1600	20	0, 1, 6	0	76 (50)	60	36 (50)	11	88 (50)	168		
	Pos/Both	Yes		>1600	10	0, 1, 6	0	76 (49)	60	39 (49)	8	90 (49)	189		
Huang[54]	Neg/		33	1731	5	1, 2, 7						95 (44)	257		
	Neg/		35	2214	5	0, 1, 6						90 (41)	194		
Junqueira [66]	Neg/			3270		0, 1, 6	0					98 (224)	428		
	Neg/			3340		0, 1, 6	0					98 (250)	572		
Kabir[e] [24]	Pos/Both	Yes			10	0, 1.5, 9	0					86 (42)			
	Pos/Both	No			10	0, 1.5, 9	0					69 (64)			

Kim [53]	Neg/	No	31	1615	2.5	0, 1, 6	–[h]	19 (87)				90 (87)	200			
Kojouharova [67]	NR/	No			10	0, 1, 6	0					99 (140)	1012			
Lau [68]	Both/	Yes[i]	31	1336	10	0, 1, 5	≥1000 g			58 (57)	5	79 (57)	61			
	Both/	Yes[i]	31	1313	10	0, 1, 5	≥2000 g			70 (42)	13	91 (42)	262			
	Both/	Yes[i]	Term	3114	10	0, 1, 4	0			96 (24)	83	100 (43)	679			
Lee [23]	Pos/Pos	Yes		3247	20	0, 1, 2, 12	3		127				107	93 (54)	355	
	Pos/Pos	Yes		3311	10	0, 1, 2, 12	3		161				95	98 (56)	244	
	Pos/Pos	Yes		3219	20	0, 1, 6	3		115		58					
Lee [40]	Neg/		Term		5	0, 1, 3	0					94 (279)	168			
	Neg/		Term		2.5	0, 1, 3	0					88 (308)	78			
Lolekha [22]	Pos/Pos	No		3100	5	0, 1, 6	0–3			63 (46)	228	92 (37)	530			
	Pos/Pos	No		3040	5	0, 1, 2, 12	0–3					74 (38)	298	94 (36)	710	
Losonsky [69]	Neg/		25	761	2.5	0, 1–3, 6–8	Within 7 days			12 (34)	52	52 (31)	222			
	Neg/		29	1230	2.5	0, 1–3, 6–8	Within 7 days			28 (29)	112	68 (28)	373			
	Neg/		32	1846	2.5	0, 1–3, 6–8	Within 7 days			23 (48)	91	84 (43)	562			
Madalinski [42]	Neg/			>2500	2.5	0, 1, 6						100 (15)	6703			
	Neg/			>2500	5	0, 1, 6						100 (13)	7104			
Martins [70]	Neg[j]/			≥2000	10	0, 1, 6						94 (284)	351			
	Neg[d]/			≥2000	10	0, 1, 6						98 (282)	1531			
Milne [27]	Neg/	No		>2000	5[k]	0, 1, 2						98 (151)	218			
	Pos/Neg	No		>2000	5	0, 1, 2						96 (102)	300			
	Pos/Pos	No		>2000	5	0, 1, 2						99 (70)	347			
da Motta [35]	Neg/		33	1380	10	0, 1–2, 5–7	5					77 (53)	187			
	Neg/		39	3260	10	0, 1–2, 5–7	4					98 (57)	538			
Patel [46]	Neg/			≤1000	2.5	0, 1, 6	Within 72 h			17 (12)		67 (12)				
	Neg/			1001–1500	2.5	0, 1, 6	Within 72 h			15 (13)		69 (13)				
	Neg/			≤1000	2.5	1, 2, 7	1 month			30 (10)		90 (10)				
	Neg/			1001–1500	2.5	1, 2, 7	1 month			33 (15)		100 (15)				
Poovorawan [21]	Pos/Pos	No		≥2000	10	0, 1, 2, 12	0		3		12		244	100 (46)	3531	
Ribeiro [71]	Both/					0, 1, 6	Within 48 h[l]					90 (174)	741			
Hassanjani-Roshan[e] [31]	Pos/Neg	Yes				0, 1.5, 9						63 (84)				
	Pos/Pos	Yes				0, 1.5, 9						67 (9)				
Sadeck[33]	Neg/		33	1905	5	0, 1, 6	0					93 (27)				
	Neg/		≥37		5	0, 1, 6	0					100 (14)				
Sapru [72]	Both[m]/				10	0, 1.5, 3.5	4	11 (132)	13	54 (132)	25	97 (132)	383			
	Both[d]/				10	0, 1.5, 3.5	4	10 (130)	24	58 (130)	32	95 (130)	285			
Seto [73]	Neg[n]/			3227	10; 2.5[o]	0, 1, 6	Within 7 days					98 (53)	587			
	Neg[p]/			3318	10; 2.5[o]	0, 1, 6	Within 7 days					96 (52)	666			

Table 3 (*Continued*)

Author (Ref.)	HBsAg/HBeAg	HBIG	Gestation (weeks)	BW (g)	Dosage (μg)	Schedule	Age at dose 1[a]	Response							
								After first dose		After second dose		After third dose		After fourth dose	
								SP% (*n*)	GMT	SP% (*n*)	GMT	SP% (*n*)	GMT	SP% (*n*)	GMT
Shokri [39]	Both/			≥2500	2.5	0, 1.5, 9						92 (238)	4502		
	Both/			≥2500	5	0, 1.5, 9						97 (266)	5824		
	Both/			≥2500	10	0, 1.5, 9						96 (231)	6104		
Sood [32]	Neg/		39	3100	10	0, 1.5, 6	Within 3 days			100 (20)	1000	100 (20)	1000		
	Neg/		34	2140	10	0, 1.5, 6	Within 3 days			85 (20)	152	95 (20)	235		
	Neg/		33	1600	10	0, 1.5, 6	Within 3 days			50 (20)	9	80 (20)	89		
Soulie [29]	Neg/	No		≥2500	20	0, 1, 2, 12	0	50 (19)	10	88 (19)	85	100 (19)	467	100 (18)	17,630
	Pos/	Yes		≥2500	20	0, 1, 2, 12	0	100 (18)	61	94 (18)	102	100 (18)	407	100 (17)	7550
Tregnaghi [74]	NR[q]/		Term		10	0, 1, 6	15					100 (97)	2468		
	NR[d]/		Term		10	0, 1, 6	17					100 (96)	1715		
	NR[r]/		Term		10	0, 1, 6	17					100 (95)	2075		
Velu [30]	Pos/Both[m]	No			10	0, 1, 6	0	23 (58)	12	83 (48)	35	100 (48)	94		
	Pos/Both[d]	No			10	0, 1, 6	0	19 (50)	8	71 (43)	24	100 (38)	81		
	Pos/Both[s]	No			10	0, 1, 6	0	17 (50)	8	67 (45)	19	100 (32)	73		
Watanaveeradej[t] [75]	Neg/		Term		10	0, 1, 6						95 (21)	342		
Yang [28]	Pos/Neg	Yes	Term		20; 5[u]	0, 1, 6	3–5			98 (94)	90	94 (66)	688		
	Pos/Neg	No	Term		20; 5[u]	0, 1, 6	3–5			55 (122)	13	98 (89)	1754		
	Pos/Pos	Yes	Term		20; 5[u]	0, 1, 6	3–5			100 (19)	62	84 (19)	675		
Yerushalmi [76]	Neg[v,w]/	No		≥2500	2.5	0, 1, 6	0	54 (129)	11			100 (119)			
	Neg[d,w]/	No		≥2500	10	0, 1, 6	0	7 (44)	2			100 (38)			

BW, birth weight; AGA, appropriate for gestational age.

[a] In days unless reported otherwise.
[b] HepavaxGen administered to infants in this arm.
[c] GenHevac B administered to infants in this arm.
[d] Engerix-B administered to infants in this arm.
[e] Units for anti-HBs assumed to be mIU/mL.
[f] Vaccine administered in the first day of life in 37.5% of infants.
[g] Vaccine administered in the first day of life in 69.6% of infants.
[h] Mean of 5 weeks.
[i] HBIG given if mother HBsAg-positive.
[j] Butang administered to infants in this arm.
[k] 2nd and 3rd dose were 2.5 μg.
[l] 1st dose administered within 48 h for 43% of subjects.
[m] GeneVacB administered to infants in this arm.
[n] Engerix-B for dose 1, Recombivax HB for dose 2 and 3.
[o] Engerix-B dosage was 10 μg, Recombivax HB dosage was 2.5 μg.
[p] Engerix-B for dose 1 and 2, Recombivax HB for dose 3.
[q] Euvax-B administered to infants in this arm.
[r] Engerix-B for dose 1, Euvax-B for dose 2 and 3.
[s] Shanvac B administered to infants in this arm.
[t] Results from 6 HIV-positive infants not reported.
[u] Engerix-B dosage was 20 μg, Recombivax HB dosage was 5 μg.
[v] Bio-Hep-B administered to infants in this arm.
[w] Four infants total in study born to HBsAg-positive women.

proportion was 94% (range 86%, 100%) among infants who received HBIG with vaccine, which was similar to the median proportion among infants who received vaccine alone, 96% (range 69%, 100%). Final median GMTs (four trials) [25,26,28,29] were 4119 mIU/mL (range 168 mIU/mL, 7985 mIU/mL) among infants who received HBIG with vaccine, and 3148 mIU/mL (range 306 mIU/mL, 17,630 mIU/mL) among infants who received vaccine alone.

3.4. Birth weight <2000 g

Seven trials compared immune responses by infant birth weight <2000 g versus ≥2000 g [32–38]. Mothers were HBsAg-negative and HBIG was not administered. No study reported results after the first dose of hepatitis B vaccine; one study reported results after the second dose. The final median seroprotection proportion was 93% (range 77%, 100%) among infants with birth weights <2000 g, which was lower than the proportion among infants with birth weights ≥2000 g, 98% (range 93%, 100%). The final median GMT (five trials) [32,34–36,38] was also lower, 469 mIU/mL (range 89 mIU/mL, 2431 mIU/mL) among infants with birth weights <2000 g, and 1000 mIU/mL (range 538 mIU/mL, 4804 mIU/mL) among infants with birth weights ≥2000 g.

3.5. Vaccine dosage

Six trials compared immune response by vaccine dosage [23,25,39–42]. Dosages varied from 2.5 to 10 μg in the low dosage arms, and from 5 to 20 μg in the high dosage arms. Trials included mothers who were HBsAg-negative and positive. Birth weight was generally ≥2000 g. The first dose median proportions with anti-HBs ≥10 mIU/mL (two trials, three arms) [25,41] were consistently lower among infants receiving lower dosages (25% [range 25%, 76%]) compared to infants receiving higher dosages (41% [range 23%, 76%]). However, the median GMTs (three trials) [23,25,41] were similar among infants receiving lower dosages, 31 mIU/mL [range 2 mIU/mL, 161 mIU/mL] compared with infants receiving higher dosages, 33 mIU/mL [range 3 mIU/mL, 127 mIU/mL]. The second dose proportions and GMTs (two trials, three arms) [25,41] were also lower with lower dosage compared to higher dosage vaccine (56% [range 39%, 61%] and 80% [range 36%, 86%]), respectively, and 11 mIU/mL [range 8 mIU/mL, 14 mIU/mL] and 23 mIU/mL [range 11 mIU/mL, 35 mIU/mL], respectively). The overall decline in median GMT from the first to second dose may have been due to HBIG administration with the first dose in one trial. Final median seroprotection proportions were similar for lower and higher dosage groups, 98% (range 88%, 100%) and 96% (range 88%, 100%), respectively. Final median GMTs were also similar among lower and higher dosage groups, 244 mIU/mL (range 78 mIU/mL, 6703 mIU/mL) and 274 mIU/mL (range 168 mIU/mL, 7104 mIU/mL), respectively.

3.6. Compressed schedules

Six trials compared immune response by compressed (i.e., administration of three doses by three months of life, with or without administration of a fourth dose [at 11 or 12 months of life in four trials]) and non-compressed (0,- 1-, 6-month) vaccine schedules. Mothers were HBsAg-negative in four trials [41,43–45] and HBsAg-positive in two trials [22,23]. Birth weight was generally ≥2000 g. The third dose median proportion with anti-HBs ≥10 mIU/mL (four trials) [22,41,43,45] among infants who had received vaccine on a compressed schedule was 97% (range 74%, 100%), which was slightly lower than the final (third) dose proportion for infants vaccinated on a non-compressed schedule, 100% (range 92%, 100%). Third dose GMTs (five trials)[22,23,41,43,44] among infants vaccinated on a compressed schedule were 119 mIU/mL [range 68 mIU/mL, 298 mIU/mL), which was also lower than the final (third) dose GMTs attained among infants vaccinated on a non-compressed schedule, 530 mIU/mL (range 147 mIU/mL, 3142 mIU/mL). The final median seroprotection proportion measured after completion of the full series at 11–12 months of age was 97% (range 91%, 100%) among infants vaccinated on a compressed schedule, which was slightly lower than the final median proportion for infants vaccinated on a non-compressed schedule measured at approximately 7 months of age, 100% (range 92%, 100%). Final median GMTs (five trials) [22,23,41,43,44] were 315 mIU/mL (range 123 mIU/mL, 10,495 mIU/mL) among infants vaccinated on a compressed schedule, compared with 530 mIU/mL (range 147 mIU/mL, 3142 mIU/mL) among infants vaccinated on a non-compressed schedule.

3.7. Age at first dose: 0–3 days of life and ≥1 month of life

Three trials compared immune response by age at first dose administration; two were among infants with birth weights ≥2000 g and one was among infants with birth weights <2000 g [44,46,47]. Response was assessed when the first dose was administered within the first three days of life (251 infants), and was compared to the response when the first dose was administered between one and three months of life (234 infants). Mothers were HBsAg-negative. Among infants with birth weights ≥2000 g, the final median seroprotection proportion was 96% (range 91%, 100%) among infants vaccinated within the first three days of life, and 99% (range 97%, 100%) among infants vaccinated between one and three months of life. The final median GMT was 5401 mIU/mL among infants vaccinated in the first three days of life, compared to 11,130 mIU/mL among infants vaccinated between one and three months of life. Among infants with birth weight <2000 g, final seroprotection proportions from two arms of one study were lower among those vaccinated within the first three days of life (67% and 69%) when compared to those vaccinated at one month of age (90% and 100%).

4. Discussion

This review provides a summary of 43 studies of recombinant hepatitis B vaccine conducted among infants since 1987. The studies included more than 9000 infants in 20 countries, with 15 vaccines from 13 manufacturers. Most trials were designed to examine the response to vaccination starting at birth, under a variety of conditions. Overall, a median 98% (range 52%, 100%) of infants achieved seroprotective concentrations of anti-HBs after 3 or 4 doses of hepatitis B vaccine, including infants born to HBsAg-positive and HBsAg-negative mothers, and infants who received HBIG with the initial dose of vaccine. Vaccine efficacy of recombinant vaccine reported in seven studies (79–98%) [21–27] was consistent with previously reported efficacy results for recombinant vaccine [15,48]. The combined results demonstrate high effectiveness of hepatitis B vaccination initiated at birth to elicit titers of anti-HBs which correlate with protection against perinatal and early life acquisition of HBV infection [18,49–51].

Infants at highest risk of perinatal HBV infection are those born to HBeAg-positive women. The median (but not the minimum and maximum) seroprotection proportion among infants born to HBeAg-positive mothers in the three trials included in this review was lower than proportions among infants born to HBeAg-negative mothers, but the GMTs were similar [27,28,31]. Based on the small number of trials, no conclusion could be made regarding a difference, if any, in the responsiveness of infants born to HBeAg-positive compared to HBeAg-negative (HBsAg-positive) women.

Compressed schedules (e.g., 0, 1, 2 months) can induce anti-HBs at an earlier age than schedules with longer intervals between doses. However, with compressed schedules, the shorter interval between dose two and three is associated with decreased seroprotection proportions and lower GMTs after the third dose [19,41,52]. It is not known how small differences in seroprotection proportions or GMTs in the first 6 months of life might affect efficacy against hepatitis B virus exposures during this period. Some compressed schedules include an additional (4th) dose of hepatitis B vaccine at 12 months of age; the additional dose increases seroprotection proportions and GMTs to levels as high as or higher than those achieved after three-dose standard schedules. Four-dose schedules rely on compliance with extended follow-up to complete the series.

Response proportions and GMTs among infants with birth weights <2000 g are notably lower than among infants ≥2000 g. The median seroprotection proportion for infants with lower birth weights was 93% (range 77%, 100%) when vaccine was first administered within 5 days of birth. Delaying the first dose of vaccine until one month of life (preferred for preterm infants born to women with laboratory-confirmed HBsAg-negative status) increased the proportion of preterm infants achieving seroprotection. Patel et al. reported seroprotection in 68% of infants weighing ≤1500 g at birth when vaccine was administered before the third day of life, compared to 96% of infants with similar birth weights vaccinated at one month of age ($p < 0.02$) [46]. Other studies among preterm infants found significantly higher responses when vaccination started later (e.g., at 1 month of life) compared to starting at birth [53,54]. These findings underlie the ACIP recommendation to vaccinate infants weighing <2000 g (when the documented maternal HBsAg result is negative) at one month of age and to add a dose of hepatitis B vaccine when the infant weighing <2000 g is vaccinated at birth for maternal HBsAg-positive or unknown result [2].

Response proportions and GMTs among infants weighing ≥2000 g were also higher when vaccination was initiated at 1 month of age or later compared to within 3 days of life. The capacity for more a robust immunological response increases during the first few months of life. Higher GMTs are associated with longer persistence of measurable anti-HBs [55]. The duration of measurable anti-HBs also depends on a variety of other factors that include the size of the early life pool of available plasma cells [56]. Protection against illness with acute HBV infection and development of chronic HBV infection among healthy persons vaccinated at birth has been shown to persist for at least 15 years [57], and is likely to be present even after anti-HBs is no longer measurable, based on response to a booster dose of hepatitis B vaccine, rare breakthrough cases, and animal studies [57,58]. The capacity to prime memory cells for accelerated increases in anti-HBs (booster) response after re-exposure to HBsAg is thought to be present even before birth [56]. However, it is uncertain whether the same proportion of persons vaccinated starting at birth will respond to booster doses of hepatitis B vaccine after 20–25 years as persons vaccinated later in life. The developmental steps for these responses have not been fully elucidated [59–61].

Co-administration of HBIG with the first dose of vaccine and vaccine dosage also influence concentrations of anti-HBs after early doses. Receipt of HBIG simultaneously with the first dose of hepatitis B vaccine produces passive increases in anti-HBs GMTs, but has little or no effect on seroprotection proportions or GMTs at completion of the vaccination series. Others have suggested that the benefits of HBIG at birth should be weighed against the possibility that HBIG might modify (lessen) early induction of immunological memory required for long-term protection, but this finding has not been confirmed [62].

Higher compared to lower vaccine dosages (without HBIG) also achieve higher early anti-HBs GMTs after the first (and second) doses of hepatitis B vaccine. With plasma-derived vaccine, higher dosage was associated with greater protective efficacy when administered without HBIG [15]. It is not known whether there is an advantage to the higher early vaccine-induced anti-HBs GMTs. A theoretical advantage for higher dosage with recombinant vaccine might be prevention of infection after unrecognized perinatal or early life exposure to HBV when HBIG is not administered. After completion of the series, differences in GMTs were no longer apparent overall.

This review has several limitations. The search strategies may not have resulted in identification of all applicable studies. We attempted to exclude studies which reported results on duplicate subjects, although in some cases it might not have been possible to identify such studies. We included trials from many vaccines and different countries, and only studies reported in English and evaluating monovalent hepatitis B vaccines were retained. We did not do a detailed examination of the quality of the study methods and design, or tests for statistically significant differences; some results come from only a few studies. Information could not be summarized across studies because trials employed different laboratory assays and study populations. Outcomes consisted of serological correlates of protection (anti-HBs levels) rather than efficacy trials, which are no longer possible for ethical reasons. We did not assess long-term protection induced by vaccination at birth, which would not have been possible from these studies.

5. Conclusions

High levels of seroprotection are achieved after recombinant hepatitis B vaccination starting at birth, regardless of maternal HBsAg status. As such, hepatitis B vaccination at birth prevents perinatal transmission of HBV and HBV-related morbidity and mortality. Administration of HBIG with the first dose of hepatitis B vaccine did not affect the response to vaccination. Seroprotection was lower among infants with birth weights <2000 g but improved when vaccination was initiated at ≥30 days of age for those infants whose mothers were HBsAg-negative. Studies are needed to further define the immunology of hepatitis B vaccination starting in infancy and its effect on long-term protection.

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References

[1] IOM (Institute of Medicine). Hepatitis and liver cancer: a national strategy for prevention and control of hepatitis B and C. Washington, DC: The National Academies Press; 2010.
[2] Mast EE, Margolis HS, Fiore AE, Brink EW, Goldstein ST, Wang SA, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. MMWR Recomm Rep 2005 Dec 23;54(RR-16):1–31.
[3] Ghendon Y. Perinatal transmission of hepatitis B virus in high-incidence countries. J Virol Methods 1987;17(August (1–2)):69–79.
[4] Ni YH. Natural history of hepatitis B virus infection: pediatric perspective. J Gastroenterol 2011;46(January (1)):1–8.
[5] Szmuness W, Prince AM, Hirsch RL, Brotman B. Familial clustering of hepatitis B infection. N Engl J Med 1973;289(November (22)):1162–6.
[6] Lok AS, Lai CL, Wu PC, Wong VC, Yeoh EK, Lin HJ. Hepatitis B virus infection in Chinese families in Hong Kong. Am J Epidemiol 1987;126(September (3)):492–9.
[7] Dumpis U, Holmes EC, Mendy M, Hill A, Thursz M, Hall A, et al. Transmission of hepatitis B virus infection in Gambian families revealed by phylogenetic analysis. J Hepatol 2001;35(July (1)):99–104.
[8] Prince AM, White T, Pollock N, Riddle J, Brotman B, Richardson L. Epidemiology of hepatitis B infection in Liberian infants. Infect Immun 1981;32(May (2)):675–80.

[9] Hepatitis B FAQs for Health Professionals. Available from: http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm [cited 21.03.11].
[10] Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR Recomm Rep 2006;55(December (RR-16)):1–33 [quiz CE1–4].
[11] Centers for Disease Control and Prevention. Recommendation of the Immunization Practices Advisory Committee (ACIP) inactivated hepatitis B virus vaccine; 1982.
[12] Wong VC, Ip HM, Reesink HW, Lelie PN, Reerink-Brongers EE, Yeung CY, et al. Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis-B vaccine and hepatitis-B immunoglobulin. Double-blind randomised placebo-controlled study. Lancet 1984;1(April (8383)):921–6.
[13] Xu ZY, Liu CB, Francis DP, Purcell RH, Gun ZL, Duan SC, et al. Prevention of perinatal acquisition of hepatitis B virus carriage using vaccine: preliminary report of a randomized, double-blind placebo-controlled and comparative trial. Pediatrics 1985;76(November (5)):713–8.
[14] Esteban JI, Genesca J, Esteban R, Hernandez JM, Seijo G, Buti M, et al. Immunoprophylaxis of perinatal transmission of the hepatitis B virus: efficacy of hepatitis B immune globulin and hepatitis B vaccine in a low-prevalence area. J Med Virol 1986;18(April (4)):381–91.
[15] Andre FE, Zuckerman AJ. Review: protective efficacy of hepatitis B vaccines in neonates. J Med Virol 1994;44(October (2)):144–51.
[16] Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR Recomm Rep 1991;40(November (RR-13)):1–25.
[17] Recommended Immunization Schedule for Persons Aged 0 through 6 Years. Available from: http://www.cdc.gov/vaccines/recs/schedules/downloads/child/0-6yrs-schedule-pr.pdf [accessed 09.01.11].
[18] Jack AD, Hall AJ, Maine N, Mendy M, Whittle HC. What level of hepatitis B antibody is protective? J Infect Dis 1999;179(February (2)):489–92.
[19] Hadler SC, Margolis HS, Hepatitis. B immunization: vaccine types, efficacy, and indications for immunization. Curr Clin Top Infect Dis 1992;12:282–308.
[20] Centers for Disease Control and Prevention. Sensitivity of the test for antibody to hepatitis B surface antigen – United States. MMWR Morb Mortal Wkly Rep 1993;42(September (36)):707–10.
[21] Poovorawan Y, Sanpavat S, Pongpunlert W, Chumdermpadetsuk S, Sentrakul P, Safary A. Protective efficacy of a recombinant DNA hepatitis B vaccine in neonates of HBe antigen-positive mothers. JAMA 1989;261(June (22)):3278–81.
[22] Lolekha S, Warachit B, Hirunyachote A, Bowonkiratikachorn P, West DJ, Poerschke G. Protective efficacy of hepatitis B vaccine without HBIG in infants of HBeAg-positive carrier mothers in Thailand. Vaccine 2002;20(November (31–32)):3739–43.
[23] Lee CY, Huang LM, Chang MH, Hsu CY, Wu SJ, Sung JL, et al. The protective efficacy of recombinant hepatitis B vaccine in newborn infants of hepatitis B e antigen–positive-hepatitis B surface antigen carrier mothers. Pediatr Infect Dis J 1991;10(April (4)):299–303.
[24] Kabir A, Alavian SM, Ahanchi N, Malekzadeh R. Combined passive and active immunoprophylaxis for preventing perinatal transmission of the hepatitis B virus in infants born to HBsAg positive mothers in comparison with vaccine alone. Hepatol Res 2006;36(December (4)):265–71.
[25] Halliday ML, Kang LY, Rankin JG, Coates RA, Corey PN, Hu ZH, et al. An efficacy trial of a mammalian cell-derived recombinant DNA hepatitis B vaccine in infants born to mothers positive for HBsAg, in Shanghai, China. Int J Epidemiol 1992;21(June (3)):564–73.
[26] Assateerawatt A, Tanphaichitr VS, Suvatte V, Yodthong S. Immunogenicity and efficacy of a recombinant DNA hepatitis B vaccine, GenHevac B Pasteur in high risk neonates, school children and healthy adults. Asian Pac J Allergy Immunol 1993;11(June (1)):85–91.
[27] Milne A, West DJ, Chinh DV, Moyes CD, Poerschke G. Field evaluation of the efficacy and immunogenicity of recombinant hepatitis B vaccine without HBIG in newborn Vietnamese infants. J Med Virol 2002;67(July (3)):327–33.
[28] Yang YJ, Liu CC, Chen TJ, Lee MF, Chen SH, Shih HH, et al. Role of hepatitis B immunoglobulin in infants born to hepatitis B e antigen-negative carrier mothers in Taiwan. Pediatr Infect Dis J 2003;22(July (7)):584–8.
[29] Soulie JC, Devillier P, Santarelli J, Goudeau A, Vermeulen P, Guellier M, et al. Immunogenicity and safety in newborns of a new recombinant hepatitis B vaccine containing the S and pre-S2 antigens. Vaccine 1991;9(August (8)):545–8.
[30] Velu V, Nandakumar S, Shanmugam S, Jadhav SS, Kulkarni PS, Thyagarajan SP. Comparison of three different recombinant hepatitis B vaccines: GeneVac-B, Engerix B and Shanvac B in high risk infants born to HBsAg positive mothers in India. World J Gastroenterol 2007;13(June (22)):3084–9.
[31] Mohammad-Reza, Hassanjani-Roshan YZ-P. Efficacy of HBIG and vaccine in infants of HBsAg positive carrier mothers. Arch Intern Med 2002;5(1):21–3.
[32] Sood A, Singh D, Mehta S, Midha V, Kumar R. Response to hepatitis B vaccine in preterm babies. Indian J Gastroenterol 2002;21(March–April (2)):52–4.
[33] Sadeck LS, Ramos JL. Immune response of preterm infants to hepatitis B vaccine administered within 24 hours after birth. J Pediatr (Rio J) 2004;80(March–April (2)):113–8.
[34] Golebiowska M, Kardas-Sobantka D, Chlebna-Sokol D, Sabanty W. Hepatitis B vaccination in preterm infants. Eur J Pediatr 1999;158(April (4)):293–7.
[35] Freitas da Motta MS, Mussi-Pinhata MM, Jorge SM, Tachibana Yoshida CF, Sandoval de Souza CB. Immunogenicity of hepatitis B vaccine in preterm and full term infants vaccinated within the first week of life. Vaccine 2002;20(February (11–12)):1557–62.
[36] Blondheim O, Bader D, Abend M, Peniakov M, Reich D, Potesman I, et al. Immunogenicity of hepatitis B vaccine in preterm infants. Arch Dis Child Fetal Neonatal Ed 1998;79(November (3)):F206–8.
[37] Belloni C, Chirico G, Pistorio A, Orsolini P, Tinelli C, Rondini G. Immunogenicity of hepatitis B vaccine in term and preterm infants. Acta Paediatr 1998;87(March (3)):336–8.
[38] Arora NK, Ganguly S, Agadi SN, Irshad M, Kohli R, Deo M, et al. Hepatitis B immunization in low birthweight infants: do they need an additional dose? Acta Paediatr 2002;91(9):995–1001.
[39] Shokri F, Jafarzadeh A. High seroprotection rate induced by low doses of a recombinant hepatitis B vaccine in healthy Iranian neonates. Vaccine 2001;19(August (31)):4544–8.
[40] Lee SS, Lo YC, Young BW, Wong KH, Lim WL. A reduced dose approach to hepatitis B vaccination for low-risk newborns and preschool children. Vaccine 1995;13(March (4)):373–6.
[41] Alikasifoglu M, Cullu F, Kutlu T, Arvas A, Tastan Y, Erginoz E, et al. Comparison study of the immunogenicity of different types and dosages of recombinant hepatitis B vaccine in healthy neonates. J Trop Pediatr 2001;47(February (1)):60–2.
[42] Madalinski K, Sylvan SP, Hellstrom U, Mikolajewicz J, Dzierzanowska-Fangrat K. Presence of anti-preS1, anti-preS2, and anti-HBs antibodies in newborns immunized with Bio-Hep-B vaccine. Med Sci Monit 2004;10(January (1)):PI10–7.
[43] Goldfarb J, Baley J, Medendorp SV, Seto D, Garcia H, Toy P, et al. Comparative study of the immunogenicity and safety of two dosing schedules of Engerix-B hepatitis B vaccine in neonates. Pediatr Infect Dis J 1994;13(January (1)):18–22.
[44] del Canho R, Grosheide PM, Voogd M, Huisman WM, Heijtink RA, Schalm SW. Immunogenicity of 20 micrograms of recombinant DNA hepatitis B vaccine in healthy neonates: a comparison of three different vaccination schemes. J Med Virol 1993;41(September (1)):30–4.
[45] Belloni C, Orsolini P, Martinetti M, Chirico G, Cerbo RM, Comolli G, et al. Control of hepatitis B: evaluation of two different vaccinal schedules in newborns from HBsAg negative mothers. New Microbiol 1993;16(July (3)):237–44.
[46] Patel DM, Butler J, Feldman S, Graves GR, Rhodes PG. Immunogenicity of hepatitis B vaccine in healthy very low birth weight infants. J Pediatr 1997;131(October (4)):641–3.
[47] Bassily S, Kotkat A, Gray G, Hyams KC, Brown FM, Imam IZ, et al. Comparative study of the immunogenicity and safety of two dosing schedules of hepatitis B vaccine in neonates. Am J Trop Med Hyg 1995;53(October (4)):419–22.
[48] Plotkin S, Orenstein W. Vaccines. 4th ed. Philadelphia: Elsevier; 2004.
[49] Craxi A, Vinci M, Almasio P, Pagliaro L. Hepatitis B vaccination of relatives of hepatitis B virus DNA positive carriers: an experience with plasma-derived vaccine. Eur J Epidemiol 1989;5(March (1)):65–9.
[50] Beasley RP, Hwang LY, Lee GC, Lan CC, Roan CH, Huang FY, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. Lancet 1983;2(November (8359)):1099–102.
[51] Lee C, Gong Y, Brok J, Boxall EH, Gluud C. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis. BMJ 2006;332(February (7537)):328–36.
[52] Jilg W, Schmidt M, Deinhardt F. Vaccination against hepatitis B: comparison of three different vaccination schedules. J Infect Dis 1989;160(November (5)):766–9.
[53] Kim SC, Chung EK, Hodinka RL, DeMaio J, West DJ, Jawad AF, et al. Immunogenicity of hepatitis B vaccine in preterm infants. Pediatrics 1997;99(April (4)):534–6.
[54] Huang FY, Lee PI, Lee CY, Huang LM, Chang LY, Hepatitis Liu SC. B vaccination in preterm infants. Arch Dis Child Fetal Neonatal Ed 1997;77(September (2)):F135–8.
[55] Are booster immunisations needed for lifelong hepatitis B immunity? European Consensus Group on Hepatitis B Immunity. Lancet 2000;355(February (9203)):561–5.
[56] Siegrist CA, Aspinall R. B-cell responses to vaccination at the extremes of age. Nat Rev Immunol 2009;9(March (3)):185–94.
[57] Leuridan E, Van Damme P. Hepatitis B and the need for a booster dose. Clin Infect Dis 2011;53(July (1)):68–75.
[58] Banatvala J, Van Damme P, Oehen S. Lifelong protection against hepatitis B: the role of vaccine immunogenicity in immune memory. Vaccine 2000;19(November (7–8)):877–85.
[59] Ota MO, Vekemans J, Schlegel-Haueter SE, Fielding K, Whittle H, Lambert PH, et al. Hepatitis B immunisation induces higher antibody and memory Th2 responses in new-borns than in adults. Vaccine 2004;22(January (3–4)):511–9.
[60] Samandari T, Fiore AE, Negus S, Williams JL, Kuhnert W, McMahon BJ, et al. Differences in response to a hepatitis B vaccine booster dose among Alaskan children and adolescents vaccinated during infancy. Pediatrics 2007;120(August (2)):e373–81.
[61] McMahon BJ, Dentinger CM, Bruden D, Zanis C, Peters H, Hurlburt D, et al. Antibody levels and protection after hepatitis B vaccine: results of a 22-year follow-up study and response to a booster dose. J Infect Dis 2009;200(November (9)):1390–6.

[62] Boxall EH, AS J, El-Shuhkri N, Kelly DA. Long-term persistence of immunity to hepatitis B after vaccination during infancy in a country where endemicity is low. J Infect Dis 2004;190(October (7)):1264–9.
[63] Ballesteros-Trujillo A, Vargas-Origel A, Alvarez-Munoz T, Aldana-Valenzuela C. Response to hepatitis B vaccine in preterm infants: four-dose schedule. Am J Perinatol 2001;18(November (7)):379–85.
[64] Bhave S, Bhise S, Chavan SC, Naik SS, Pusapati RV, Bavdekar A, et al. Hepatitis B vaccination in premature and low birth weight (LBW) babies. Indian Pediatr 2002;39(July (7)):625–31.
[65] Gunn TR, Bosley A, Woodfield DG. The safety and immunogenicity of a recombinant hepatitis B vaccine in neonates. N Z Med J 1989;102(January (860)):1–3.
[66] Junqueira AL, Tavares VR, Martins RM, Frauzino KV, da Costa e Silva AM, Minamisava R, et al. Safety and immunogenicity of hepatitis B vaccine administered into ventrogluteal vs. anterolateral thigh sites in infants: a randomised controlled trial. Int J Nurs Stud 2010;47(September (9)):1074–9.
[67] Kojouharova M, Teoharov P, Bahtchevanova T, Maeva I, Eginlian A, Deneva M. Safety and immunogenicity of a yeast-derived recombinant hepatitis B vaccine in Bulgarian newborns. Infection 2001;29(December (6)):342–4.
[68] Lau YL, Tam AY, Ng KW, Tsoi NS, Lam B, Lam P, et al. Response of preterm infants to hepatitis B vaccine. J Pediatr 1992;121(December (6)):962–5.
[69] Losonsky GA, Wasserman SS, Stephens I, Mahoney F, Armstrong P, Gumpper K, et al. Hepatitis B vaccination of premature infants: a reassessment of current recommendations for delayed immunization. Pediatrics 1999;103(February (2)):E14.
[70] Martins RM, Bensabath G, Arraes LC, Oliveira Mde L, Miguel JC, Barbosa GG, et al. Multicenter study on the immunogenicity and safety of two recombinant vaccines against hepatitis B. Mem Inst Oswaldo Cruz 2004;99(December (8)):865–71.
[71] Ribeiro TM, Azevedo RS. Seroconversion of hepatitis B vaccine in infants related to the mother's serostatus in a community of Sao Jose dos Campos, state of Sao Paulo, Brazil. Clinics (Sao Paulo, Brazil) 2006;61(October (5)):387–94.
[72] Sapru A, Kulkarni PS, Bhave S, Bavdekar A, Naik SS, Pandit AN. Immunogenicity and reactogenicity of two recombinant hepatitis B vaccines in small infants: a randomized, double-blind comparative study. J Trop Pediatr 2007;53(October (5)):303–7.
[73] Seto D, West DJ, Gilliam RR, Ioli VA, Ferrara DK, Rich B. Antibody responses of healthy neonates of two mixed regimens of hepatitis B vaccine. Pediatr Infect Dis J 1999;18(September (9)):840–2.
[74] Tregnaghi M, Ussher J, Baudagna AM, Calvari M, Grana G. Comparison of two recombinant hepatitis B vaccines and their interchangeability in Argentine infants. Pan Am J Public Health 2004;15(January (1)):35–40.
[75] Watanaveeradej V, Samakoses R, Kerdpanich A, Aree C, Nitayabhan S, Viputtikul K, et al. Antibody response to hepatitis B vaccine in infants of HIV-positive mothers. Int J Infect Dis 2002;6(September (3)):240–1.
[76] Yerushalmi B, Raz R, Blondheim O, Shumov E, Koren R, Dagan R. Safety and immunogenicity of a novel mammalian cell-derived recombinant hepatitis B vaccine containing Pre-S1 and Pre-S2 antigens in neonates. Pediatr Infect Dis J 1997;16(June (6)):587–92.