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Summary of Seroprotection after Recombinant Hepatitis B Vaccine Administered to Newborn Infants (defined as the first 30 days of Life)

Background: The primary outcome assessed in the review of 54 identified studies (43 reported by Schillie [2013] and 11 reviewed by WHO [2016]) was seroprotection, defined as concentration of antibody to hepatitis B surface antigen (anti-HBs) ≥ 10 mIU/mL after a primary hepatitis B vaccination series.(1,2) The secondary outcome was the geometric mean titer (GMT) or geometric mean concentration (GMC) of anti-HBs after the final dose of the vaccination series.

Influential variables included the pregnant mother's hepatitis B surface antigen (HBsAg) and her "e" antigen [HBeAg]) status (positive, negative), the infant's birth weight (<2000 or ≥2000 grams), timing of the first dose of hepatitis B vaccine (within ≤24 hours of birth, or later), whether the infant received hepatitis B immune globulin (HBIG), the vaccine dosage, the number and timing of hepatitis B vaccine doses (schedule), and the timing of post-vaccination GMT/GMC testing. Schillie (2013) included studies reporting seroprotection and GMT/GMCs assessed within 3 months of the final vaccine dose (see Tables 2 and 3).(1) The WHO (2016) review reported seroprotection and GMT/GMCs measured up to 24 months of age, as indicated in the footnotes (see Supplementary Tables 2 and 3). (2) Interpretation of results should take into account the time after the final vaccine dose that anti-HBs levels were assessed; anti-HBs levels undergo an initial rapid decline from a peak at 4-12 weeks, and then decline more slowly in the second year. (3) As with any review, information on a substantial number of key variables was not reported, and the number of available trials evaluating each influential variable was small.

Results and Discussion: The median seroprotection proportions after ≥3-doses of hepatitis B vaccine were 98% (range 52%-100%) and 85% (range 39%-100%) in Schillie (2013) and WHO (2015), respectively. The final median seroprotection proportions did not vary appreciably by maternal HBsAg status or HBIG administration. The median seroprotection proportions were lower among infants born to HBeAg-positive women than infants born to HBeAg-negative women (84%, range 67%-99% and 94%, range 63%-96%, respectively.) One study in the WHO review found similar results by maternal HBeAg status (Kang, ref 5). Higher compared to lower vaccine dosage resulted in earlier increases in anti-HBs GMTs but not in final seroprotection proportions.

Infants with birth weight <2000 grams compared to infants with birth weights ≥2000 grams had lower median seroprotection proportions (93%, range 77%-100%, and 98%, range 93%-100%, respectively), and lower GMTs (469 mIU/mL, range 89-2431 mIU/mL, and 1000mIU/mL, range 538-4804mIU/mL, respectively). Infants with birth weight <2000 grams who started vaccination at 0-3 days of life compared to 1-3 months of life also had lower seroprotection proportions (67% and 69%, and 90% and 100%, respectively), and lower GMTs in two arms of one study. Infants with birth weights ≥2000 grams starting vaccination at 0-3 days of life compared to 1-3 months of life had similar seroprotection proportions (96%, range 91%-100%, and 99%, range 97%-100%); GMTs were high overall, but lower with vaccination starting at 0-3 days compared to 1-3 months of life.

Three-dose schedules completed in the first 3 months of life ("compressed schedules", with or without a 4th dose of vaccine) had slightly lower median seroprotection proportions than non-compressed schedules in Schillie (2013) (97%, range 74%-100%, and 100%, range 89%-100%, respectively), and in a small number of evaluable trials the WHO review. Schillie (2013) found lower GMTs after the third, and after the final dose of the hepatitis B vaccine series with compressed schedules compared to non-compressed schedules. The significance of these differences is unknown.

In summary, these data suggest that recombinant hepatitis B vaccination starting at birth achieves high levels of seroprotection among (term) infants with birth weight ≥2000 grams. Infants with birth weights <2000 grams have lower levels of seroprotection with vaccination starting at birth, and might require an additional dose(s) of hepatitis B vaccine to achieve similar levels of seroprotection as infants with higher birth weights.

References

1. Schillie SF, Murphy TV. Seroprotection after recombinant hepatitis B vaccination among newborn infants: a review. Vaccine 2013;31:2506-16.
2. Soares-Weiser K et al. Enhanced Reviews Ltd, Consultant to WHO, 2016
3. Ko SC, Schillie SF, Walker T, et al. Hepatitis B vaccine response among infants born to hepatitis B surface antigen-positive women. Vaccine 2014;32:2127-33.

Supplementary Table 2. Publication year, hepatitis B vaccine, vaccine manufacturer, and country for 11 additional studies[1]					
Author	Ref no.	Year	Recombinant Vaccine	Vaccine Manufacturer	Country
Alexander	1	2013	Gene Vac-B Shanvac-B	Serum Institute of India Ltd, Pune Shantha Biotechnics Private Ltd, Hyderabad	India
Cheang	2	2013	Hepavax-Gene (prior to 2002) Engerix-B (after 2002)	Crucell, Leiden, The Netherlands GlaxoSmithKline Biologicals, Rixensart, Belgium	Malaysia
Foaud	3	2015	Euvax B	LG (Life Sciences Ltd), Korea	Egypt
Zhang	4	2014	NR	Beijing Tiantan Biological Products Corp., Ltd., Beijing, China	China
Kang	5	2015	NR	Beijing Tiantan Biological Products Corp., Ltd., Beijing, China	China
Ko	6	2014	NR	NR	USA
Li	7	2015	NR	NR	China
Miralha	8	2013	Butang	Instituo Butanta, San Paulo, Brazil	Brazil
Pande	9	2013	NR	NR	India
Sellier	10	2015	NR	NR	France
Tong	11	2013	NR	NR	UK

NR, not reported.

1. WHO sponsored review covering studies published from 2013-2015. Study periods span 2002-2014.

References

1. Alexander AM, Prasad JH, Abraham P, Fletcher J, Muliyil J, and Balraj V. (2013). Evaluation of a programme for prevention of vertical transmission of hepatitis B in a rural block in southern India. *Indian Journal of Medical Research 2013;*137:356-362.
2. Cheang HK, Wong HT, Ho SC, et al. Immune response in infants after universal hepatitis B vaccination: a community-based study in Malaysia. Singapore medical journal 2013;54:224-6.
3. Foaud H, Maklad S, Mahmoud F, and El-Karaksy H. (2015). Occult hepatitis B virus infection in children born to HBsAg-positive mothers after neonatal passive-active immunoprophylaxis. *Infection* 2015;43:307-314.

4. Zhang L, Gui X-en, Teter C, et al. (2014). Effects of hepatitis B immunization on prevention of mother-to-infant transmission of hepatitis B virus and on the immune response of infants towards hepatitis B vaccine. *Vaccine* 32:6091-6097.
5. Kang G, Ma F, Chen H, et al. (2015). Efficacy of antigen dosage on the hepatitis B vaccine response in infants born to hepatitis B-uninfected and hepatitis B-infected mothers. *Vaccine* 2015;33:4093-4099.
6. Ko SC, Schillie S F, Walker T, et al. (2014). Hepatitis B vaccine response among infants born to hepatitis B surface antigen-positive women. *Vaccine 2014;* 32:2127-2133.
7. Li J, Hu J, Liang X, Wang F, Li Y, and Yuan Z-an. (2015). Predictors of poor response after primary immunization of hepatitis B vaccines for infants and antibody seroprotection of booster in a metropolis of China. *Asia-Pacific Journal of Public Health 2015;*27: 1457-66.
8. Miralha A , Malheiro A, Miranda AE, Rutherford GW, and Alecrim G.C. (2013). Response to the complete hepatitis B vaccine regimen in infants under 12 months of age: A case series. *Brazilian Journal of Infectious Diseases* 2013;17:82-85.
9. Pande C, Sarin SK, Patra S, et al. (2013). Hepatitis B vaccination with or without hepatitis B immunoglobulin at birth to babies born of HBsAg-positive mothers prevents overt HBV transmission but may not prevent occult HBV infection in babies: A randomized controlled trial. *Journal of Viral Hepatitis* 2013;20:801-810.
10. Sellier P, Maylin S, Amarsy R, et al. (2015). Untreated highly viraemic pregnant women from Asia or sub-Saharan Africa often transmit hepatitis B virus despite serovaccination to newborns. *Liver International* 2015;35:409-16.
11. Tong CY.W, Robson C, Wu Y, et al. (2013). Post-vaccination serological test results of infants at risk of perinatal transmission of hepatitis B using an intensified follow-up programme in a London centre. *Vaccine* 2013;31:3174-3178.

Supplementary Table 3. Seroprotection proportions (anti-HBs threshold of 10 mIU/mL) and Geometric Mean Titers (GMT) from 11 additional studies.[1]

Author (Ref)	HBsAg/HBeAg	HBIG	Gestation (weeks)	BW (g)	Dosage (µg)	Schedule (ages)[2]	Age at first dose	Response[3]							
								After first dose		After second dose		After third dose		After fourth dose	
								SP% (n)	GMT (n)	SP% (n)	GMT (n)	SP% (n)	GMT(n)	SP% (n)	GMT (n)
Alexander (1)	Pos/Both	Yes 3/131			10	0,1,2	<24 hours[4]					92 (53)[5]	138		
						0,1,3	<24 hours								
						0,1,4-6	<24 hours								
Cheang (2)	Pos/	Yes				0,1,6						93 (14)[6]			
	Neg/	No				0,1,6						~97 (426)[6]			
	Unkn					0,1,6						~97 (132)[6]			
Foaud (3)	Pos/	Yes 46/64			10	0,1 2,4,6	Median <2 hours; range 1-36 hours					NR (64)[7]	Median 259		
Zhang (4)	Pos/Both	Yes			10	0,1,6	<24 hours					85 (985)[8]			
	Pos/Both	No 188[9]			10	0,1,6	<24 hours					84 (177)[8]			
	Neg/				5	0,1,6	<24 hours					93 (271)[10]	Median 374		
	Neg/				5	0,1,6	<24 hours					84 (268)[11]	Median 149		
Kang (5)	Pos/Pos				5	0,1,6	<24 hours			75 (44)	35	89 (44)	234		
	Pos/Pos				10	0,1,6	<24 hours			81 (43)	34	91 (43)	207		
	Pos/Neg				5	0,1,6	<24 hours			100 (46)	86	100 (46)	341		
	Pos/Neg				10	0,1,6	<24 hours			94 (47)	70	96 (47)	334		
	Neg/				5	0,1,6	<24 hours					98 (83)	275		
	Neg/				10	0,1,6	<24 hours					98 (87)	392		
Ko (6)	Pos/Pos	Yes										96 (357)[12]			
	Pos/Neg	Yes										95 (759)[12]			
	Pos/	Yes		<2000		≥ 3 doses[13]						95 (986)[12]			
	Pos/	Yes		≥2000		≥ 3 doses						95 (5557)[12]			
Li (7)	Both/Both			<2500	5 or 10	0,1,6						100 (48)[14]			
	Both/Both			2500-4000	5 or 10	0,1,6						98 (1870)[14]			
	Both/Both			>4000	5 or 10	0,1,6						99 (129)[14]			
	Both/Both				5	0,1,6						98(1531)[14]			
	Both/Both				10	0,1,6						>99 (516)[14]			
Miralha (8)	Neg or Unkn		Mean	Mean		3 doses[15]	58% ≤48					90 (36)[16]			

			38	2787			hours								
	Neg or Unkn			<2000		3 doses[15]						97 (29)[16]			
	Neg or Unkn			≥2000		3 doses[15]						80 (8)[16]			
Pander (9)	Pos/Both	Yes			10	0,6,10,14 weeks								25 (106)[17]	
	Pos/Both	No			10	0,6,10,14 weeks								30 (116)[17]	
Sellier (10)	Pos/Both	Yes 38/41				0,1,2-6	<12 hours					39 (41)[18]			
Tong (11)	Pos/	Yes 24/219										100 (15)	Median 59	93 (14)	Median 534
	Pos/	No										97 (119)	Median 376	100 (76)	Median >1000

BW, birth weight; AGA, appropriate for gestational age; n= number of subjects examined; GMT= Geometric mean titer in mIU/mL or IU/L; Unkn= unknown.

1. The twelve studies summarized in this table were published from 2013-2015.
2. Age is in months unless reported otherwise.
3. Infants were assessed for seroprotection at the times indicated in footnotes. Infants screened ≥ 3 months after the final dose were excluded from Schillie and Murphy [2013].
4. 16 infants received the first dose of vaccine at >48 hours of life.
5. Infants were assessed for seroprotection at age 6-24 months after receiving 3 doses of hepatitis B vaccine. 91% (112/113) of infants seroconverted (% with detectable anti-HBs.)
6. Infants were assessed for seroprotection at age 6-48 months. Data on seroprotection were available for 553 of 572 enrolled children (97%); seroprotection (SP) data are not provided by maternal serostatus. Therefore, SP rates by maternal status are estimates.
7. Median (range) age of assessment, 8 months (6-132 months). Minimum and maximum GMT were 3.4 and 1303, respectively.
8. Seroprotection was assessed at age 8-12 months.
9. From 2008-2010, study hospitals experienced a shortage of HBIG; 188 infants received 3 doses of hepatitis B vaccine without HBIG.
10. Seroprotection was assessed at age 7-15 months.
11. Seroprotection was assessed at age 16-24 months.
12. Seroprotection was assessed at age 9-18 months. Comparisons by maternal HBeAg status and birth weight < or ≥2000 grams were among subsets in the database.
13. Among infants weighing <2000 grams at birth, 810 (92%) received 3 doses of hepatitis B vaccine rather than the US-CDC-ACIP recommended 4 doses.
14. Seroprotection was assessed at age 7-18 months; 47% of infants were age 7-12 months; 53% of infants were age 13-18 months. Results are for both "low" and "adequate response", defined as anti-HBs ≥10mIU/mL.
15. Vacination series completed by age 6 months.
16. Seroprotection was assessed at age 7-12 months.
17. Seroprotection was assessed at age 18 weeks.
18. Seroprotection defined by anti-HBs ≥10 mIU/mL *and without* HBsAg or HBcAb.