Optimizing the Hepatitis B vaccination schedules

Systematic review of safety and efficacy of childhood schedules using of hepatitis B containing vaccines.

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Cochrane

Targeted Update

Immunogenicity of recombinant DNA HBV vaccines: difference in the number of doses in infants

Included studies

Argentina 2011 (quasi-RCT)[1]
Australia 2001-A (RCT)[2]
China 1986-A (RCT)[3]
India 2013 (Retrospective cohort)[4]
Italy 1997-A (Cohort)[5]
Lao People's Democratic Republic (Retrospective cohort)[6]
Malaysia 2008 (RCT)[7]
Netherlands 1993-A (RCT)[8]
Philippines 2005 (RCT)[9]
Philippines 2007 (RCT)[10]
Singapore 2004 (RCT)[11]
South Africa 2013 (RCT)[12]
Thailand 1992 A (quasi-RCT)[13]
Thailand 2002-B (RCT)[14]
Turkey 2001-A (RCT)[15]
USA 2002-B (RCT)[16]
Taiwan 1991 (Quasi-RCT)[17,18]
Thailand 1992-B (Cohort)[19-23]
Thailand 2002-A (Cohort)[23]

What's new

Latest search was performed: **June 2016**

Schedules with a higher number of doses seems to increase the rate of seroprotection for bo+3 v 3p and bo+1p v bo+2p in high endemicity areas. There seemed to be no difference in the proportion of infants becoming seroprotected 1-3 months post-vaccination for all other comparisons. These results are based on a few studies of limited quality.

There is some evidence indicating that vaccination schedules with a higher number of doses and possibly a birth dose were associated with higher antibody concentrations (GMCs) at 1-3 months post-vaccination.

There were very few data on serious adverse events and other clinical outcomes, and no data on all-cause deaths. The quality of evidence for these comparisons is very limited.

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Background

In 1992, the WHO set a goal for all countries to integrate HBV vaccination into the Expanded Program on Immunization (EPI). The WHO recommends that all infants receive their first dose of HBV vaccine as soon as possible after birth. The birth dose should then be followed by two or three additional doses with a minimum interval of four weeks.

Objectives

To evaluate whether the administration of different number of doses of recombinant DNA hepatitis B vaccines for infants affects seroconversion (from antibody negative to antibody positive) to hepatitis B surface antigen (anti-HBs), presented as the absolute levels of antibodies (GMCs) and the percentage levels of antibody to hepatitis B surface antigen (anti-HBs) with a threshold of ≥ 10 IU/ml, and clinical outcomes.

Search methods

Search strategies were developed specifically for each database. We searched The Cochrane Library, latest issue; MEDLINE (January 1946 to June 2016); EMBASE (January 1980 to June 2016); and CINAHL (January 1981 to June 2016). We also searched the metaRegister of Controlled Trials (mRCT) (http://www.controlled-trials.com/mrct/) in June 2016.

Selection criteria

Two reviewers independently screened and selected studies, discrepancies were resolved in consultation with a senior reviewer. Randomised controlled trials and observational studies of children vaccinated with any licensed recombinant DNA hepatitis B vaccine, measuring immunological and clinical outcomes, were included. We also included retrospective studies from 2012.

Data collection and analysis

Two reviewers extracted data independently, discrepancies were resolved in consultation with a senior reviewer. Risk ratios were calculated for binary outcome data. For continuous data, values were log-transformed and presented as GMCs. Meta-analysis for most comparisons could not be performed because of lack of data.

Main Results

We included 19 studies (11 RCTs, 3 quasi-RCTs, 3 cohort studies, and 2 retrospective cohort studies), published between 1986 and 2016. The risk of bias was high for 6 included RCTs/quasi-RCTS and moderate or high for included cohort studies. Comparison of bo+3p vs. bo+2p was reported in 8 studies, bo+1p vs. bo+2p was reported in one study, bo+3p vs. 3p was reported in 7 studies; 4p vs. bo+2p was reported in one study, and 2 studies reported comparisons of 3 doses versus 2 doses without a birth dose.

Schedules with a higher number of doses seems to increase the rate of seroprotection for bo+3 v 3p and bo+1p v bo+2p in high endemicity areas. There seemed to be no difference in the proportion of infants becoming seroprotected 1-3 months post-vaccination for all other comparisons. These results are based on a few studies of limited quality.

There is some evidence indicating that vaccination schedules with a higher number of doses and possibly a birth dose were associated with higher antibody concentrations (GMCs) at 1-3 months post-vaccination.

There were very few data on serious adverse events and other clinical outcomes, and no data on all cause deaths. The quality of evidence for these comparisons is very limited.

Implications and conclusions

There is limited confidence in the evidence about the effects of the number of doses of recombinant DNA HBV vaccine on the outcomes of HBsAg seroprevalence or GMCs of anti-HBs, and clinical outcomes.

Summary of Findings: Recombinant DNA HBV vaccines birth dose plus 3 primary doses vs. birth dose plus 2 primary doses

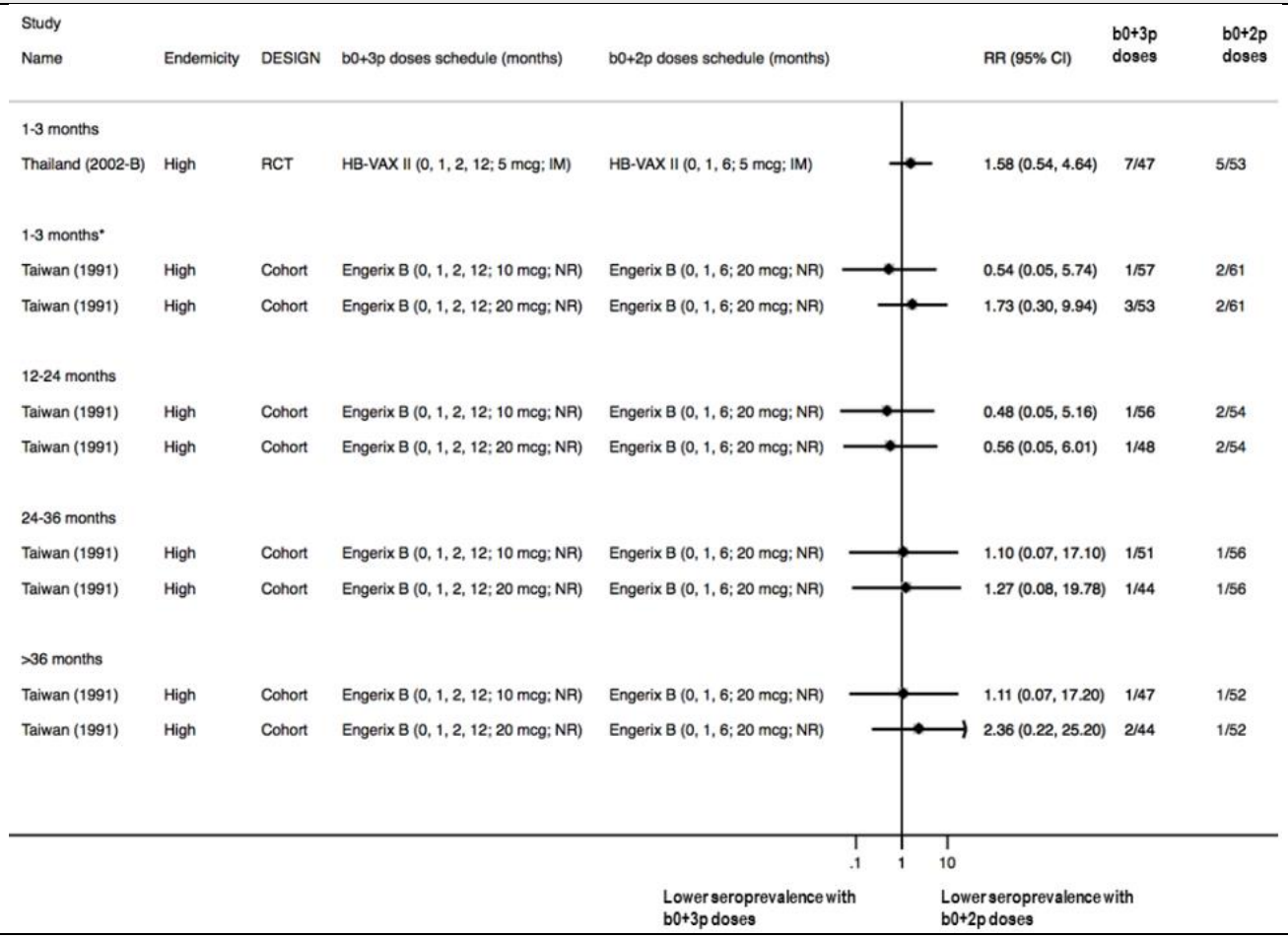
***Patients and setting*: Infants in Malaysia, the Netherlands, Taiwan, and Thailand.**
***Comparison:* Recombinant DNA HBV vaccines given bo+3p vs. bo+2p.**

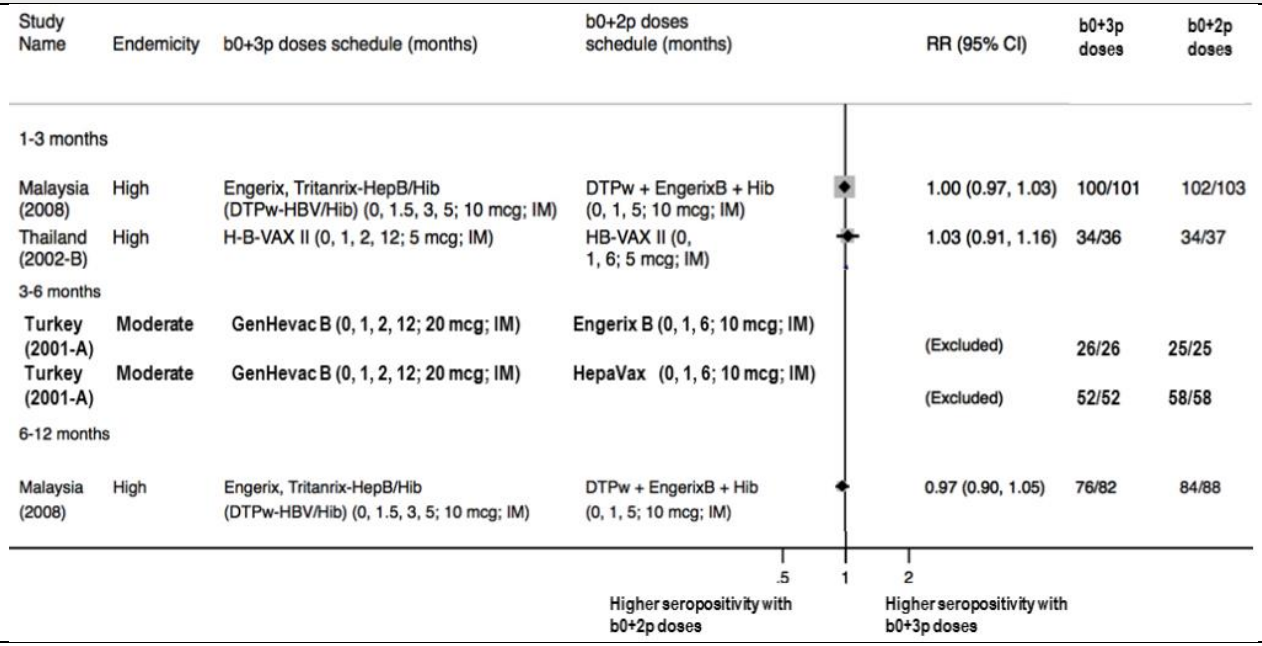
Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Control (bo+3p)	Intervention (bo+2p)		
HBsAg seroprevalence	We are uncertain about the effect of bo + 3p vs. bo + 2p recombinant DNA HBV vaccines on HBsAg seroprevalence, because the evidence is of very low quality.	7/47 (15.0%) (data at 1-3 months from 1 RCT)	Not estimable (no summary relative effect)	No summary relative effect (no meta-analysis) 332 participants, 2 studies (1 RCT; 1 cohort study)	⊕OOO VERY LOW [1,2,3]
Anti-HBs seroprotection - RCTs	There is probably little or no difference between bo + 3p vs. bo + 2p recombinant DNA HBV vaccines on Anti-HBs seroprotection	134/137 (97.8%) (data at 1-3 months from 2 RCTs)	Not estimable (no summary relative effect)	No summary relative effect (no meta-analysis) 412 participants, 3 RCTs, data from 1 RCT excluded	⊕⊕⊕O MODERATE [2]
Anti-HBs seroprotection – cohort studies	We are uncertain about the effect of bo + 3p vs. bo + 2p recombinant DNA HBV vaccines on Anti-HBs seroprotection from cohort studies, because the evidence is of very low quality. However, results are consistent with RCTs.	353/371 (95%) (data at 1-3 months from 3 cohort studies)	Not estimable (no summary relative effect)	No summary relative effect (no meta-analysis) 803 participants, 3 cohort studies	⊕OOO VERY LOW [1,2,3]
GMCs of anti-HBs	We are uncertain about the effect of bo + 3p vs. bo + 2p recombinant DNA HBV vaccines on GMCs of anti-HBs, because the evidence is of very low quality.	Not estimable	Not estimable (no summary relative effect)	No summary relative effect (no meta-analysis) 991 participants, 4 studies (2 RCTs; 2 cohort studies)	⊕OOO VERY LOW [1,2,5]

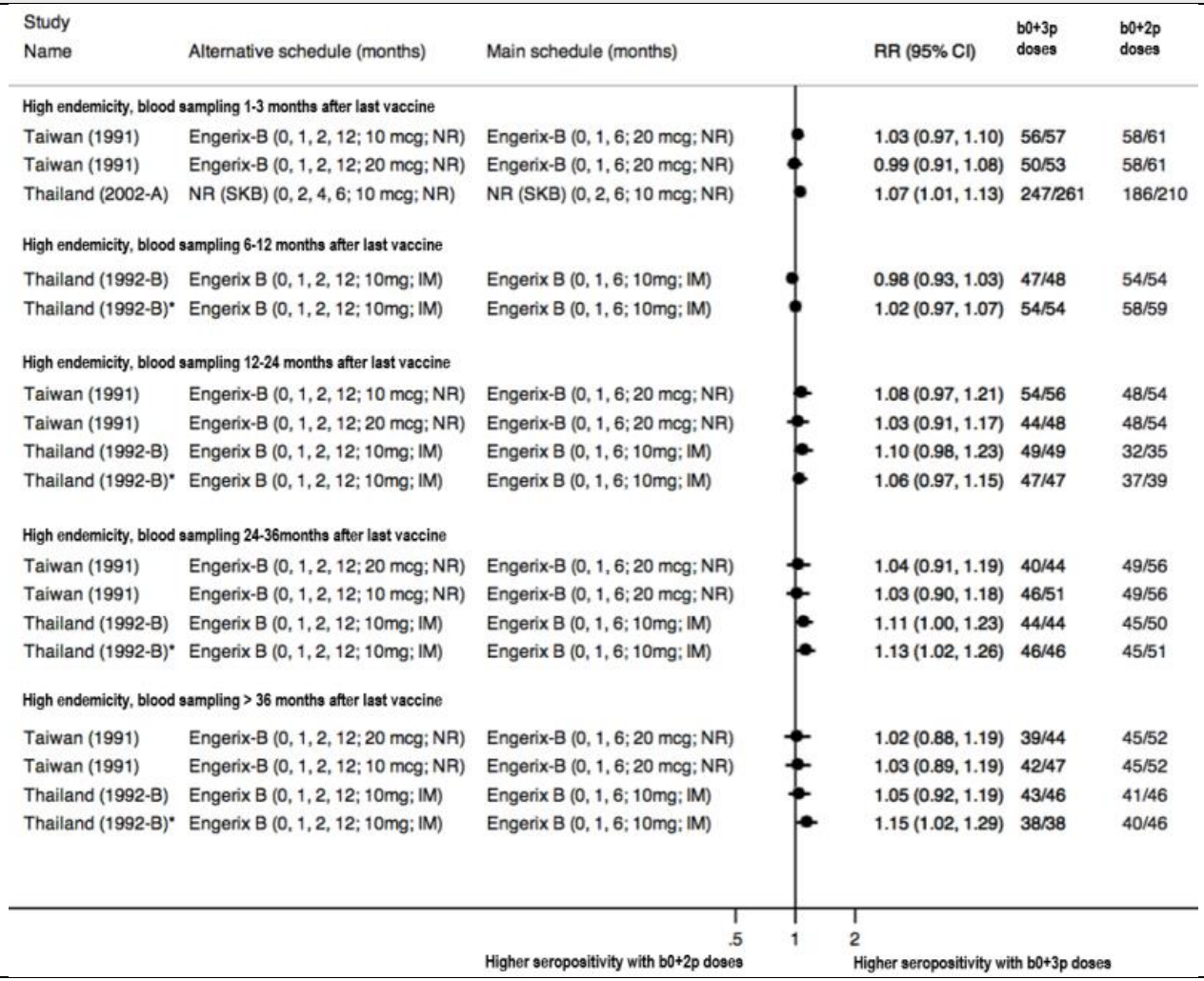
[1]Downgraded one level for study design: studies of different design, including one or more cohort study.
[2]Downgraded one level for risk of bias: included studies were of high risk of bias.
[3]Downgraded one level for imprecision: wide confidence intervals.
[4]Downgraded two levels for study design: cohort studies were included.
[5]Downgraded one level for inconsistency: some studies favoured bo+2p schedule whereas other studies favoured bo+3p schedule.

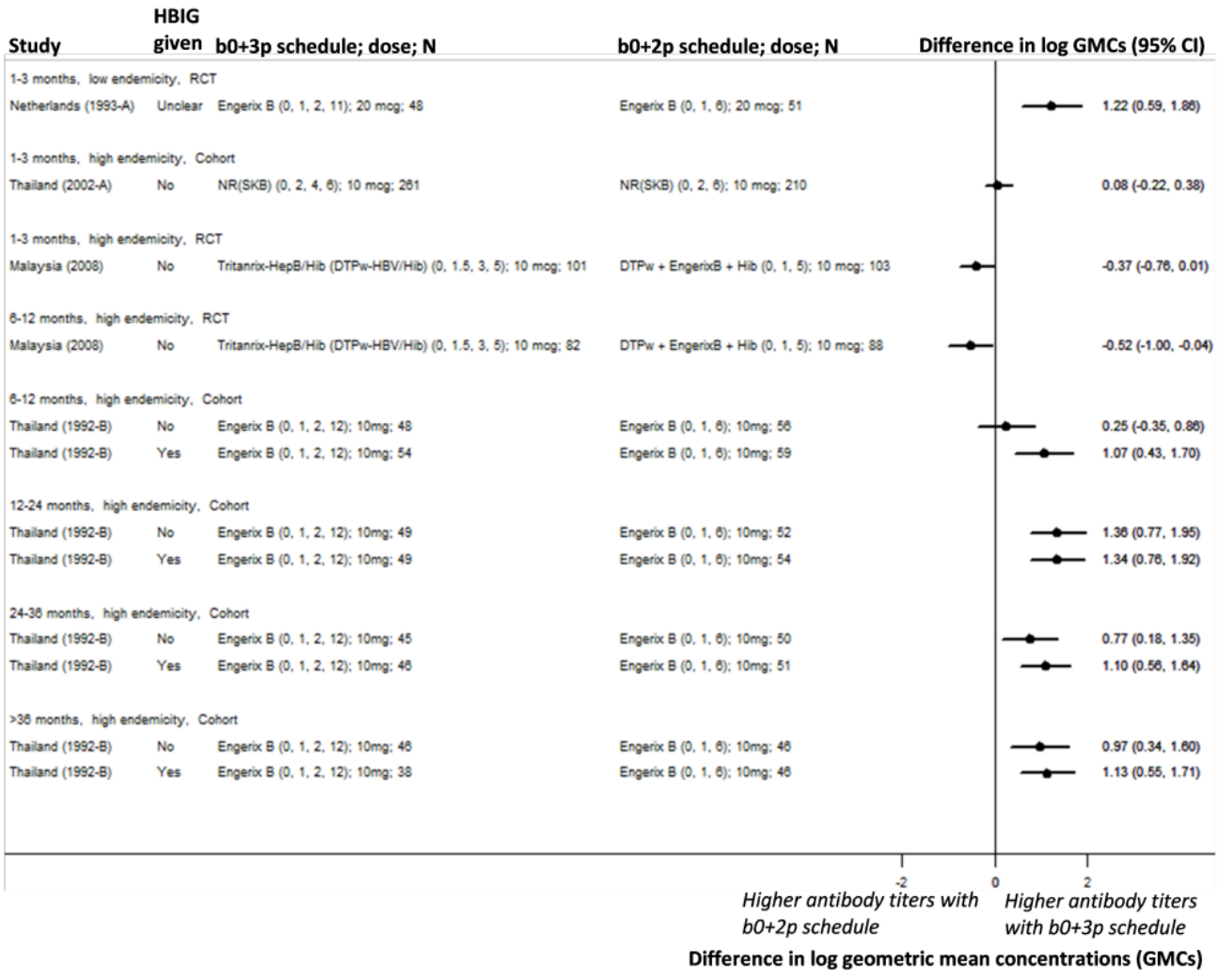
Forest plots and summaries per outcome: Recombinant DNA HBV vaccines birth dose plus 3 primary doses vs. birth dose plus 2 primary doses

***Patients and setting*: Infants in Malaysia, the Netherlands, Taiwan, and Thailand.**
***Comparison:* Recombinant DNA HBV vaccines given bo+3p vs. bo+2p.**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
HBsAg seroprevalence There was no evidence of a difference in seropositivity rates between schedules at any of the time points for the two studies with different methodological design.		⊕OOO VERY LOW [1,2,3]

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection - RCTs There was no evidence of a difference in seroprotection rates between schedules at 1-3 months, 3-6 months or 6-12 months post vaccination.		⊕⊕⊕O MODERATE

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection – cohort studies The data do not show any evidence of a difference in seroprotection rates between schedules at 1-3 months after immunization, 6-12 months and 24-36 months. One study (Thailand 19992-B) showed higher seroprotection with b0+3p than b0+2p at 12-24 months (RR 1.13, 95% CI 1.02, 1.26) and >36 months follow-up (RR 1.15, 95% CI 1.02, 1.29), for schedules in which HBIG was given at birth.		⊕OOO VERY LOW

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
GMCs of anti-HBs Results at 1-3 months after vaccination were very heterogeneous with one RCT in low endemicity region (Netherlands 1993-A) favouring the b0+3p schedule, WMD in log GMCs of 1.22 (95% CI 0.59, 1.85); this corresponds to a GMC ratio of 3.39 (95% CI 1.80-6.34) which indicates that the b0+3p schedule gave higher antibody concentrations 1-3 months post vaccination compared to the b0+2p schedule. Whereas, one RCT in a high endemicity region (Malaysia 2008) showed no difference between the two schedules at 1-3 and 6-12 months. A cohort study from a high endemicity region (Thailand 2002-A) showed no difference at 1-3 months after vaccinations, but showed results favouring the b0+3p schedule in the low endemicity region at 12-24, 24- 36 and above 36 months.		⊕OOO VERY LOW

Summary of Findings: Recombinant DNA HBV vaccines birth dose + 2 primary doses versus 3 primary doses – retrospective cohort studies published since 2012

***Patients and setting*: Infants in India**
***Comparison:* Recombinant HBV vaccines birth dose + 2 primary doses versus 3 primary doses**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		3 primary doses	Birth dose with 2 primary doses		
HBsAg seroprevalence – measured 2-5 years after last dose	We are uncertain about the effect of birth dose + 2 primary doses versus 3 primary doses, because the evidence is of very low quality.	1/15 (6.67%)	6/108 (5.56%)	No summary relative effect (no meta-analysis) 1 retrospective cohort study, 131 participants	⊕OOO VERY LOW [1,2]

[1]Downgraded 2 points for study design: non-random comparison
[2]Downgraded 2 points for serious imprecision: very low number of events

Summary of Findings: Recombinant DNA HBV vaccines birth dose + 1 primary dose vs. birth dose + 2 primary doses

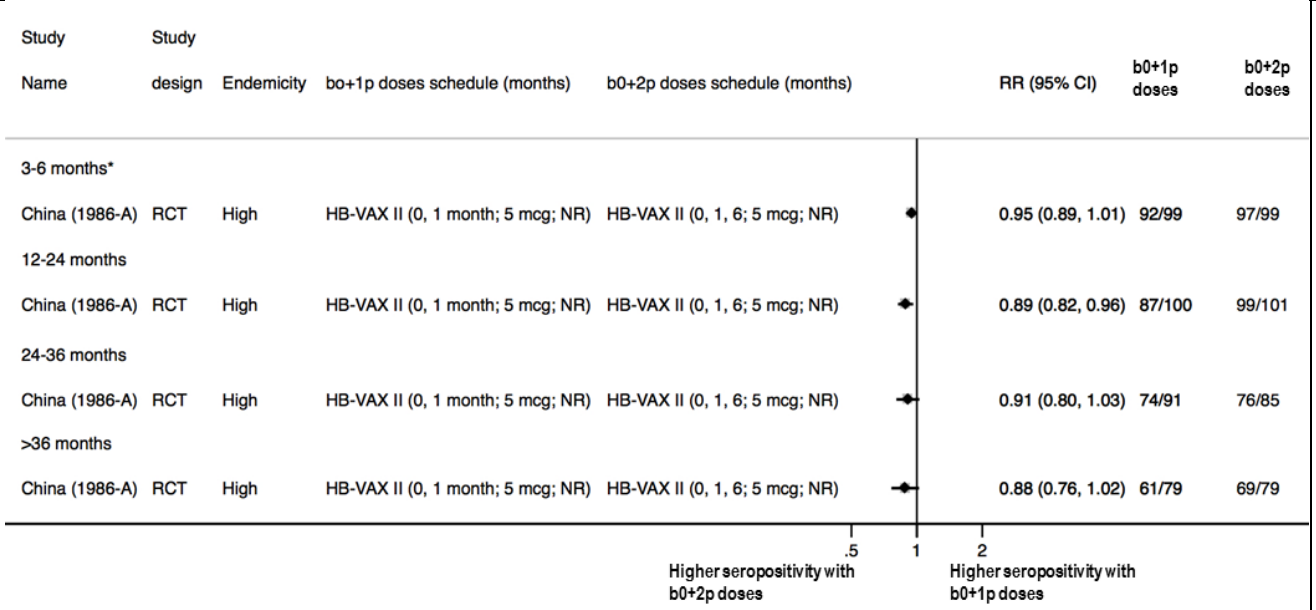
***Patients and setting*: Infants in China.**
***Comparison:* Recombinant DNA HBV vaccines birth dose + 1 primary dose vs. birth dose + 2 primary doses.**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Bo+1p	Bo+2p		
HBsAg seroprevalence	There is no evidence about the effects of birth dose + 1 primary dose vs. birth dose + 2 primary doses of recombinant DNA HBV vaccines on HBsAg seroprevalence; no study reported on this outcome.				
Anti-HBs seroprotection Follow-up: 3-6 months Endemicity: High	There may be little or no difference between birth dose + 1 primary dose compared with birth dose + 2 primary doses of recombinant DNA HBV vaccines on Anti-HBs seroprotection.	92/99 (92.9%) (data at 3-6 months from 1 RCT)	97/99 (92.9%) (data at 3-6 months from 1 RCT)	RR 0.95 (0.89 to 1.01) 198 participants, 1 RCT	⊕⊕OO LOW [1,2]
GMCs of anti-HBs	There is no evidence about the effects of birth dose + 1 primary dose vs. birth dose + 2 primary doses of recombinant DNA HBV vaccines on GMCs of anti-HBs; no study reported on this outcome.				

[1]Downgraded one level for risk of bias: included study at high risk of bias.
[2]Downgraded one level for imprecision: small sample size (198 participants).

Forest plots and summaries per outcome: Recombinant DNA HBV vaccines birth dose + 1 primary dose vs. birth dose + 2 primary doses

***Patients and setting*: Infants in China.**
***Comparison:* Recombinant DNA HBV vaccines birth dose + 1 primary dose vs. birth dose + 2 primary doses.**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
HBsAg seroprevalence	There is no evidence about the effects of bo given ≤2 weeks of life vs. no bo of recombinant DNA HBV vaccines on HBsAg seroprevalence; none of the included studies reported on this outcome.	N/A
Anti-HBs seroprotection There was no evidence of a difference in seroprotection rates between the schedules at 3-6 months after immunization, 24-36 months and >36 months. At 12-24 months, higher seroprotection for bo+2p was found (RR 0.89, 95% CI 0.82, 0.96).		⊕⊕OO LOW
GMCs of anti-HBs	There is no evidence about the effects of birth dose + 1 primary dose vs. birth dose + 2 primary doses of recombinant DNA HBV vaccines on GMCs of anti-HBs; no study reported on this outcome.	⊕OOO VERY LOW

Summary of Findings: Recombinant DNA HBV vaccines birth dose + 3 primary doses versus 3 primary doses

***Patients and setting*: Infants in Argentina, Australia, Philippines, USA and South Africa**
***Comparison:* Recombinant DNA HBV vaccines, birth dose + 3 primary doses versus 3 primary doses**

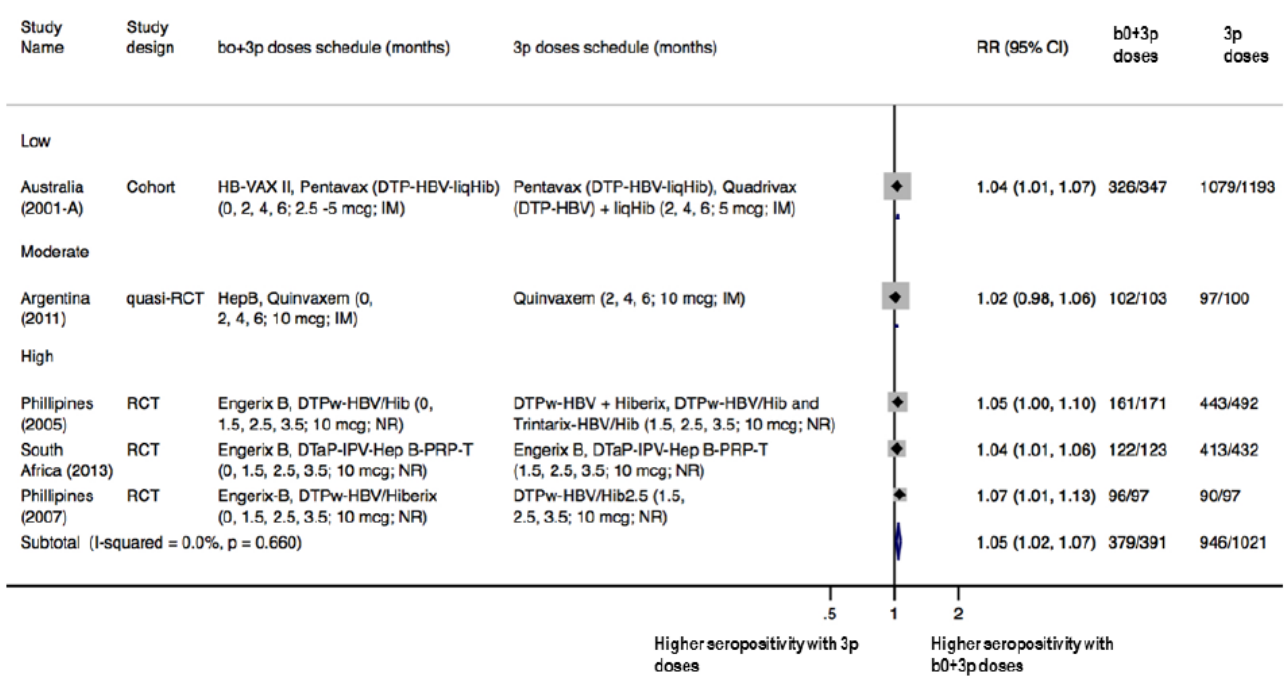
Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Birth dose + 3 primary doses (bo+3p)	3 primary doses (3p)		
HBsAg seroprevalence	None of the included studies assessed this outcome.	Not measured	Not measured	6 studies, 3325 participants	Not estimable
Anti-HBs seroprotection	It is uncertain whether birth dose + 3 primary doses compared to 3 primary doses alone improves seroprotection, because the evidence is of very low quality	Low endemicity			⊕OOO VERY LOW [1]
		326/347 (93.95%)	1079/1193 (90.44%)	RR 1.04 (95% CI 1.01 to 1.07) 1 Cohort study, 1540 participants	
	Birth dose + 3 primary doses schedules may lead to little or no difference in seroprotection, compared to 3 primary doses only.	Moderate endemicity			⊕⊕OO LOW [1,2]
		102/103 (99.03%)	97/100 (97.0%)	RR 1.02 (95% CI 0.98 to 1.06) 1 Quasi-RCT, 203 participants	
	Birth dose + 3 primary doses schedules probably improves slightly seroprotection compared to 3 primary doses only.	High endemicity			⊕⊕⊕O MODERATE [1]
		371/391 (94.89%)	946/1021 (92.65%)	RR 1.05 (95% CI 1.02 to 1.07) 3 RCTs, 1412 participants	
GMCs of anti-HBs	Birth dose + 3 primary doses schedules probably improves GMCs compared to 3 primary doses only.	Low endemicity			⊕⊕⊕O MODERATE [1]
		Not reported	Not reported	Mean difference in log GMCs of -0.88 (95% CI -1.23 to -0.53) (Corresponds to GMC ratios of 0.41, 95% CI 0.29 to 0.59) 1 RCT, 170 participants	

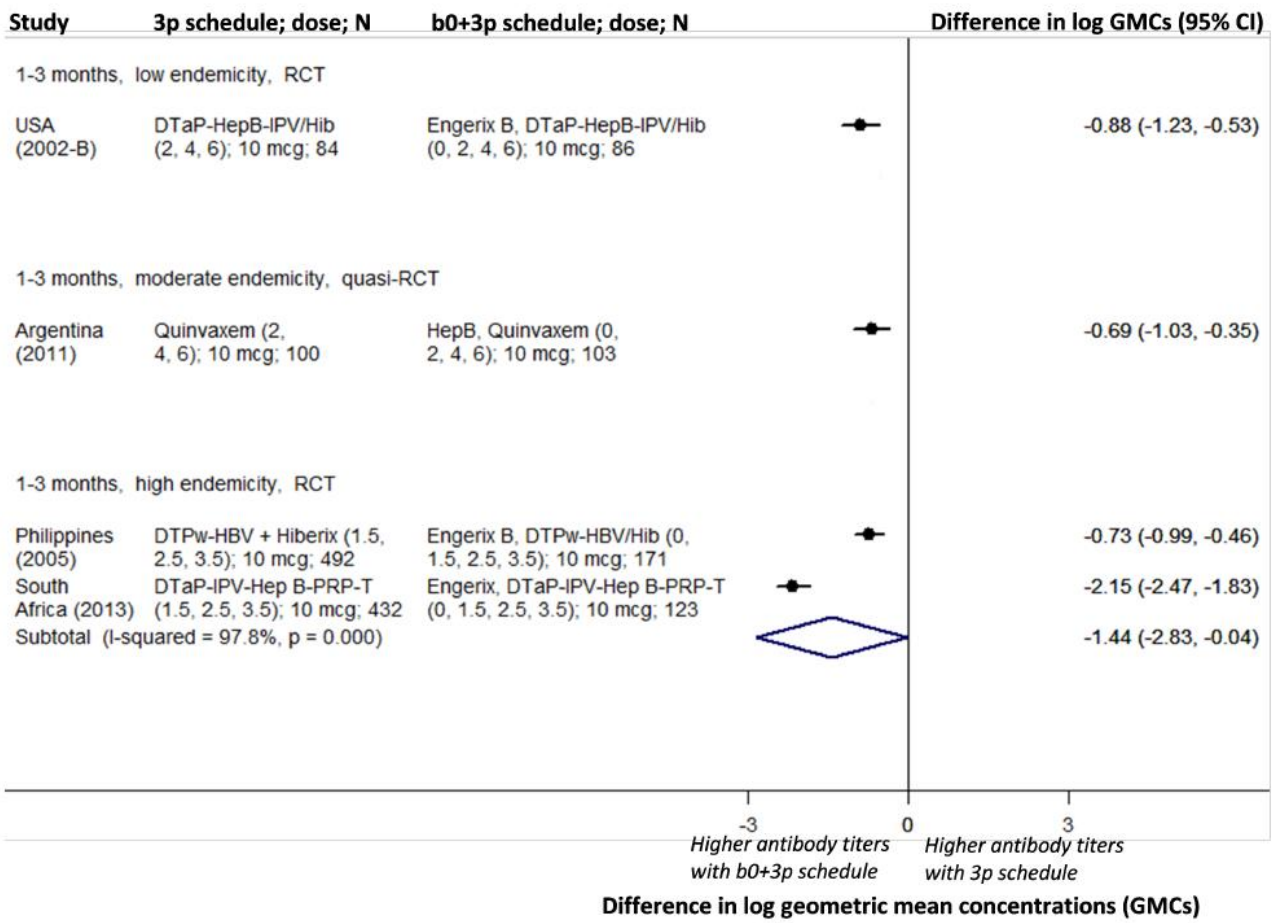
Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Birth dose + 3 primary doses (bo+3p)	3 primary doses (3p)		
		Moderate endemicity			
		Not reported	Not reported	Mean difference in log GMCs of -0.69 (95% CI -1.03 to -0.35) (Corresponds to GMC ratios of 0.50, 95% CI 0.36 to 0.70) 1 Quasi-RCT, 203 participants	
		High endemicity			
		Not reported	Not reported	Mean difference in log GMCs of -1.44 (95% CI -2.83 to -0.04) (Corresponds to a GMC ratio of 0.24, 95% CI 0.06 to 0.96) 2 RCTs, 1218 participants	

[1]Downgraded 1 point for serious risk of bias, [2]Downgraded 1 point for imprecision (95% CI includes null effect)

Forest plots and summaries per outcome: Recombinant DNA HBV vaccines birth dose + 3 primary doses vs. 3 primary doses

***Patients and setting*: Infants in Argentina, Australia, Philippines, USA and South Africa**
***Comparison:* Recombinant DNA HBV vaccines, birth dose + 3 primary doses versus 3 primary doses**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection *Low endemicity* It is uncertain whether birth dose + 3 primary doses compared to 3 primary doses alone improves seroprotection, because the evidence is of very low quality *Moderate endemicity* Birth dose + 3 primary doses schedules may lead to little or no difference in seroprotection, compared to 3 primary doses only. *High endemicity* Birth dose + 3 primary doses schedules probably improves slightly seroprotection compared to 3 primary doses only.		Low endemicity ⊕OOO VERY LOW Moderate endemicity ⊕⊕OO LOW High endemicity ⊕⊕⊕O MODERATE

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
GMCs of anti-HBs Birth dose + 3 primary doses schedules probably improves GMCs compared to 3 primary doses only.		⊕⊕⊕O MODERATE

Summary of Findings: Recombinant DNA HBV vaccines birth dose + 3 primary doses versus 3 primary doses, retrospective cohort studies published since 2012

***Patients and setting*: Infants in Lao People's Democratic Republic**
***Comparison:* Recombinant HBV vaccines birth dose + 3 primary doses versus 3 primary doses**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		3 primary doses	Birth dose with 3 primary doses		
HBsAg seroprevalence – measured 1-2 years after last dose of vaccine	We are uncertain about the effect of birth dose + 3 primary doses versus 3 primary doses, because the evidence is of very low quality.	14/41 (34.15%)	1/14 (7.14%)	No summary relative effect (no meta-analysis) 1 retrospective cohort study, 197 participants	⊕OOO VERY LOW [1,2]

[1]Downgraded 2 points for study design: non-random comparison
[2]Downgraded 2 points for serious imprecision: very low number of events

Summary of Findings: Recombinant DNA HBV vaccines 4 primary doses vs. birth dose + 2 primary doses

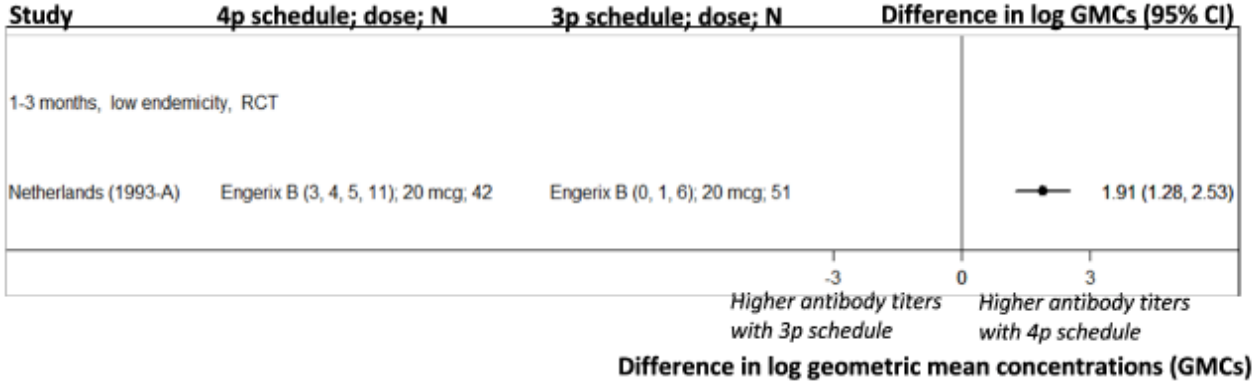
***Patients and setting*: Infants in the Netherlands.**
***Comparison:* Recombinant DNA HBV vaccines 4 primary doses vs. birth dose + 2 primary doses.**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Bo+2p	4p		
HBsAg seroprevalence	There is no evidence about the effects of bo given ≤2 weeks of life vs. no bo of recombinant DNA HBV vaccines on HBsAg seroprevalence; no study reported on this outcome.				
Anti-HBs seroprotection	There is no evidence about the effects of four primary doses vs. birth dose + 2 primary doses of recombinant DNA HBV vaccines on Anti-HBs seroprotection; no study reported on this outcome.				
GMCs of anti-HBs Follow-up: 1-3 months Endemicity: Low	4p. schedule may give higher antibody concentrations than bo+2p. schedules of recombinant DNA HBV vaccines.	N/A	N/A	MD 1.91 (1.28 to 2.53) 93 participants, 1 RCT	⊕⊕OO LOW [1,2]

[2]Downgraded one level for risk of bias: most included studies were of high risk of bias.
[6]Downgraded one level for imprecision: very small sample size (93 participants).

Forest plots and summaries per outcome: Recombinant DNA HBV vaccines 4 primary doses vs. birth dose + 2 primary doses

***Patients and setting*: Infants in the Netherlands.**
***Comparison:* Recombinant DNA HBV vaccines 4 primary doses vs. birth dose + 2 primary doses.**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
HBsAg seroprevalence	There is no evidence about the effects of bo given ≤2 weeks of life vs. no bo of recombinant DNA HBV vaccines on HBsAg seroprevalence; no study reported on this outcome.	N/A
Anti-HBs seroprotection	There is no evidence about the effects of four primary doses vs. birth dose + 2 primary doses of recombinant DNA HBV vaccines on Anti-HBs seroprotection; no study reported on this outcome.	N/A
GMCs of anti-HBs Results at 1-3 months after vaccination favoured the 4p schedule, with a WMD in log GMCs of 1.91 (95% CI 1.28, 2.53); this corresponds to a GMC ratio of 6.75 (95% CI 3.60-12.55) which indicates that the 4p schedule gave higher antibody concentrations 1-3 months post vaccination compared to the bo+2p schedule.		⊕⊕OO LOW

Summary of Findings: Recombinant DNA HBV vaccines 3 primary doses versus 2 primary doses

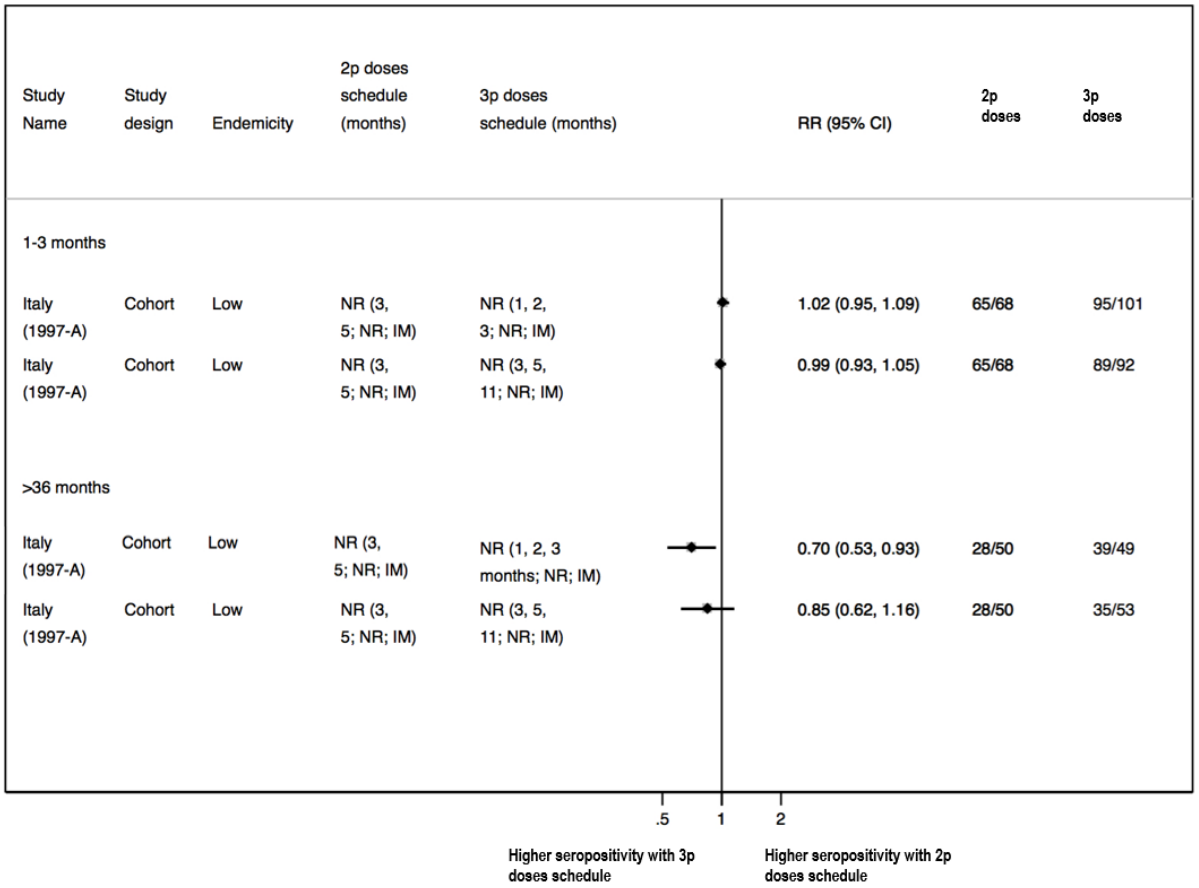
***Patients and setting*: Infants in Singapore, Malaysia and Italy**
***Comparison:* Recombinant DNA HBV vaccines given as 3 primary doses versus 2 primary doses**

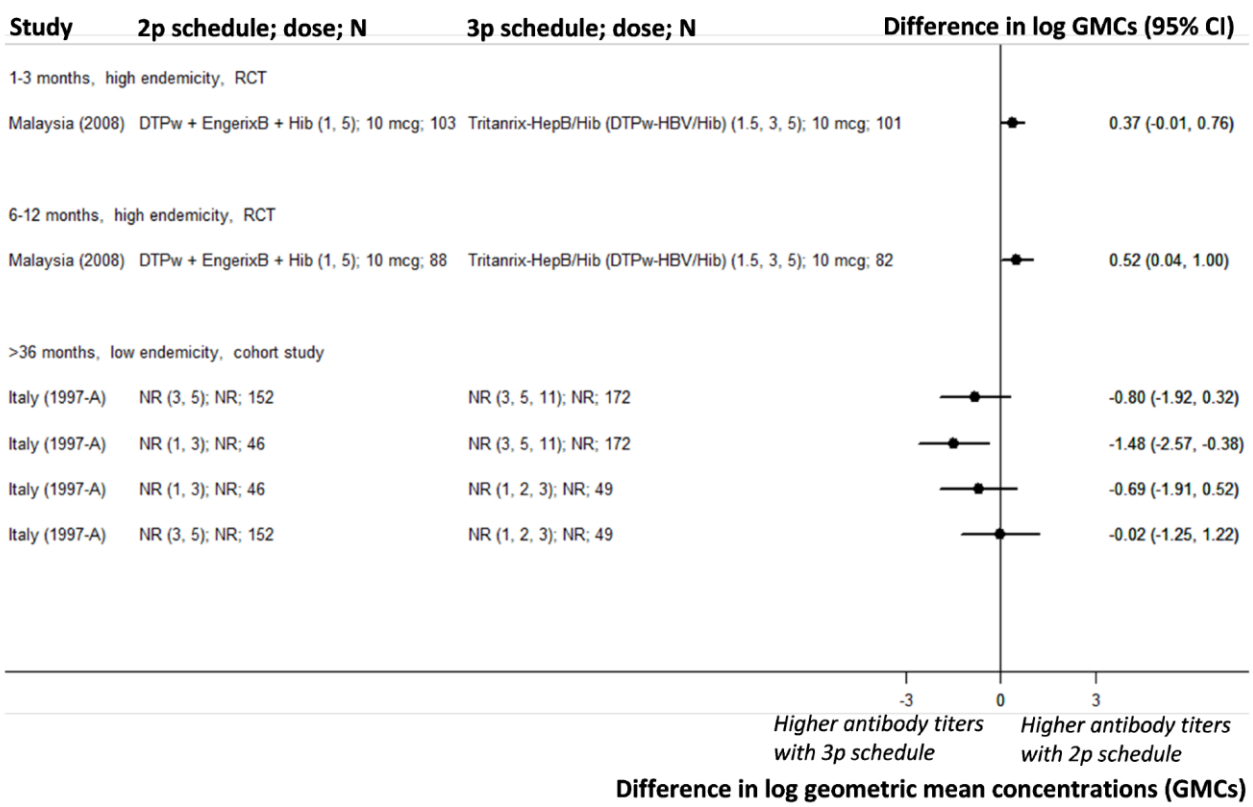
Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Control (no bo)	Intervention (bo)		
HBsAg seroprevalence	No data reported	NA	NA	NA	NA
Anti-HBs seroprotection – Cohort (1-3 months)	We are very uncertain in the effect of different dosing schedules on seroprotection at 1 to 3 months.	Triple primary dosing at 1,2 & 5 months		RR 1.02 (0.95 to 1.09) 1 cohort study (169 participants)	⊕OOO VERY LOW [1,2,]
		65/68 (95.6%)	95/101 (94%)		
		Triple primary dosing at 3, 5 and 11 months		0.99 (0.93 to 1.05) 1 cohort study (160 participants)	
		65/68 (95.6%)	89/92 (96.7%)		
Anti-HBs seroprotection (>36 months)	We are very uncertain in the effect of different dosing schedules on seroprotection at 36 months or later.	Triple primary dosing at 1,2 & 5 months		RR 0.70 (95% CI 0.53-0.93) 1 cohort study (99 participants)	⊕OOO VERY LOW [1,2,]
		28/50 (56%)	39/49 (79.6%)		
		Triple primary dosing at 3, 5 and 11 months		RR 0.85 (0.62 to 1.16) 1 cohort study (103 participants)	
		28/50 (56%)	35/53 (66%)		
GMCs of anti-HBs	We are very uncertain in the effect of different dosing schedules in areas of low endemicity.	Low endemicity: -0.8 (-1.92 to 0.32) | 1 cohort study comparing double dosing at 3& 5 months with triple dosing at 3, 5 & 11 months (324 participants)			⊕OOO VERY LOW [1,2,5]
		Low endemicity: -1.48 (-2.57 to -0.38) | 1 cohort study comparing double dosing at 1 & 3 months with triple dosing at 3, 5 & 11 months (218 participants)			
		Low endemicity: -0.69 (-1.91 to 0.52) | 1 cohort study comparing double dosing at 1 & 3 months with triple dosing at 1,2 & 3 months (95 participants)			
		Low endemicity: -0.02 (-1.25 to 1.22) | 1 cohort study comparing double dosing at 3 & 5 months with triple dosing at 1,2 & 3 months (201 participants)			
		High endemicity: 0.37 (-0.01 to 0.76), 1 RCT (204 participants)			
		High endemicity: 0.52 (95% CI 0.04 to 1), 1 RCT (190 participants)			

[1]Downgraded 2 points for study design: high risk of bias
[2]Downgraded 1 point for imprecision: single study with small sample size

Forest plots and summaries per outcome: Recombinant DNA HBV vaccines, 3 primary doses versus 2 primary doses

***Patients and setting*: Infants in Singapore, Malaysia and Italy.**
***Comparison:* Recombinant DNA HBV vaccines given as 3 primary doses versus 2 primary doses**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection – cohort studies There was no difference in seroprotection rates at 1-3 months after immunization; at >36 months higher seroprotection was found for the 3p schedule when a 3, 5 month schedule was compared with a 1, 2, 3 schedule, but not when compared with 3, 5, 11 months.		⊕OOO VERY LOW

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
GMCs of anti-HBs There was no difference in the antibody concentrations (GMCs) was shown at 1-3 months in the high endemicity study; higher antibody titres were shown in the 2p group at 6-12 months post-vaccination. In the cohort study, higher antibody titres were seen with the 3p schedule when a 1, 3 month schedule was compared with a 1, 2, month schedule. There was no difference for the other comparisons.		⊕⊕OO LOW

Summary of Findings: Recombinant DNA HBV vaccines, clinical and subclinical outcomes for studies comparing different numbers of doses

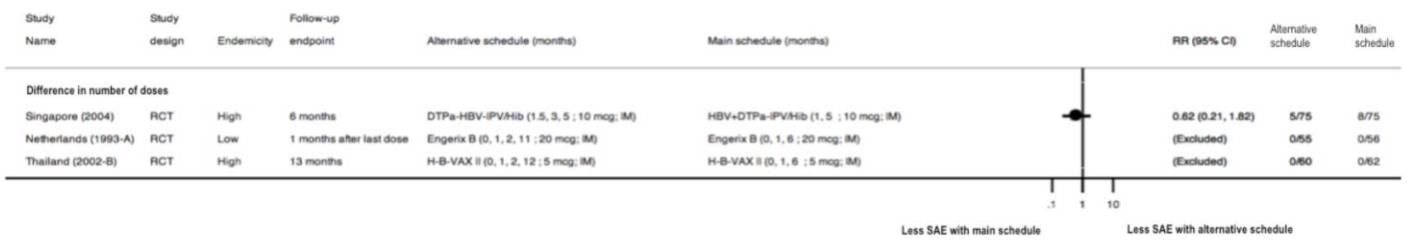
***Patients and setting*: Netherlands, Singapore, Thailand, Italy**
***Comparison:* Recombinant HBV vaccines studies comparing different numbers of doses**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Dose schedule	Alternative dose schedule		
Anti-HBc	We are uncertain of the effect on anti-HBc as the evidence is very low quality. A single RCT reported no events of seropositivity to anti-HBc when a 0, 1, 2, 11 months schedule was compared to a 0, 1, 6 months schedule.	No analysis			⊕OOO VERY LOW[1,2]
Serious adverse events	Three RCTs provided data on serious adverse events 1-13 months after schedules with different number of doses were administered. There was no evidence of a difference in the serious adverse events between vaccine schedules of two vs. three primary doses. The two other studies reported no events.	No analysis of the other two studies		3 RCTs, 383 participants	⊕OOO VERY LOW[1,2]
		3 primary doses 5/75 (6.67%)	2 primary doses 8/75 (10.67%)	0.62 (95% CI 0.21 to 1.82) 1 RCT, 150 participants	
HBV infection	A single RCT reported no HBV infection when a 0, 1, 2, 11 months schedule was compared to a 0, 1, 6 months schedule.	No analysis			⊕OOO VERY LOW[1,2]
Chronic HBV infection	A single RCT reported no chronic HBV infection when a 0, 1, 3 months schedule was compared to a 0, 1, 6 months schedule.	No analysis			⊕OOO VERY LOW[1,3]

[1]Downgraded 1 point for study design: high risk of bias
[2]Downgraded 2 points for serious imprecision: very low number of events and participants
[3]Downgraded by 1 point for study design: unclear risk of bias

Forest plots: Recombinant DNA HBV vaccines, clinical and subclinical outcomes for studies comparing different numbers of doses

***Patients and setting*: Netherlands, Singapore, Thailand, Italy**
***Comparison:* Recombinant HBV vaccines studies comparing different numbers of doses**

Outcome	Forest plots	Certainty of the evidence (GRADE)
Anti-HBc	No analysis	⊕OOO VERY LOW
Serious adverse events Three RCTs provided data on serious adverse events 1-13 months after schedules with different number of doses were administered. There was no evidence of a difference in the serious adverse events between vaccine schedules of two vs. three primary doses. The two other studies reported no events.		⊕OOO VERY LOW
HBV infection	No analysis	⊕OOO VERY LOW[2]
Chronic HBV infection	No analysis	⊕OOO VERY LOW

Bibliographic references

1. Gentile A, Umido V, Czerniuk P, et al. Immunogenicity and reactogenicity of a combined fully liquid DTPw-HepB-Hib pentavalent vaccine in healthy infants: no clinically relevant impact of a birth dose of hepatitis B vaccine. *Int J Infect Dis* 2011; **15**(1): e24-9.
2. Nolan T, Hogg G, Darcy MA, Skeljo M, Carlin J, Boslego J. A combined liquid Hib (PRP-OMPC), hepatitis B, diphtheria, tetanus and whole-cell pertussis vaccine: controlled studies of immunogenicity and reactogenicity. *Vaccine* 2001; **19**(15-16): 2127-37.
3. But DY-K, Lai C-L, Lim W-L, Fung J, Wong DK-H, Yuen M-F. Twenty-two years follow-up of a prospective randomized trial of hepatitis B vaccines without booster dose in children: final report. *Vaccine* 2008; **26**(51): 6587-91.
4. Alexander AM, Prasad JH, Abraham P, Fletcher J, Muliyil J, Balraj V. Evaluation of a programme for prevention of vertical transmission of hepatitis B in a rural block in southern India. *The Indian journal of medical research* 2013; **137**(2): 356-62.
5. Da Villa G, Pelliccia MG, Peluso F, Ricciardi E, Sepe A. Anti-HBs responses in children vaccinated with different schedules of either plasma-derived or HBV DNA recombinant vaccine. *Res Virol* 1997; **148**(2): 109-14.
6. Black AP, Nouanthong P, Nanthavong N, et al. Hepatitis B virus in the Lao People's Democratic Republic: a cross sectional serosurvey in different cohorts. *BMC Infect Dis* 2014.
7. Wong S-L, Soosai P, Teoh Y-L, Han H-H, Lefevre I, Bock HL. Four is better than nine. a combined diphtheria-tetanus-pertussis-hepatitis B-Haemophilus influenzae type b vaccine for routine immunization in Malaysia. *Southeast Asian J Trop Med Public Health* 2008; **39**(3): 474-83.
8. 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**(1): 30-4.
9. Gatchalian S, Reyes M, Bernal N, et al. A new DTPw-HBV/Hib vaccine is immunogenic and safe when administered according to the EPI (Expanded Programme for Immunization) schedule and following hepatitis B vaccination at birth. *Hum* 2005; **1**(5): 198-203.
10. Ortega-Barria E, Kanra G, Leroux G, et al. The immunogenicity and reactogenicity of DTPw-HBV/Hib 2.5 combination vaccine: results from four phase III multicenter trials across three continents. *Vaccine* 2007; **25**(50): 8432-40.
11. Cheng HK, Rajadurai VS, Amin Z, et al. Immunogenicity and reactogenicity of two regimens of diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio and Haemophilus influenzae type b vaccines administered to infants primed at birth with hepatitis B vaccine. *Southeast Asian J Trop Med Public Health* 2004; **35**(3): 685-92.
12. Madhi SA, Koen A, Cutland C, Groome M, Santos-Lima E. Antibody persistence and booster vaccination of a fully liquid hexavalent vaccine coadministered with measles/mumps/rubella and varicella vaccines at 15-18 months of age in healthy South African infants. *Pediatr Infect Dis J* 2013; **32**(8): 889-97.
13. Assateerawatt A, Suvatte V, Tanphaichitr VS. Long term efficacy of hepatitis B immunoprophylaxis in neonates at risk: using different vaccine and schedule. *J Med Assoc Thai* 1992; **75**(6): 328-36.
14. 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**(31-32): 3739-43.
15. Alikasifoglu M, Cullu F, Kutlu T, 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**(1): 60-2.
16. Pichichero ME, Blatter MM, Reisinger KS, et al. Impact of a birth dose of hepatitis B vaccine on the reactogenicity and immunogenicity of diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type b combination vaccination. *Pediatr Infect Dis J* 2002; **21**(9): 854-9.

17. Lee PI, Lee CY, Huang LM, Chang MH. Long-term efficacy of recombinant hepatitis B vaccine and risk of natural infection in infants born to mothers with hepatitis B e antigen. *J Pediatr* 1995; **126**(5 Pt 1): 716-21.
18. Lee CY, Huang LM, Chang MH, 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**(4): 299-303.
19. Poovorawan Y, Hutagalung Y, Chongsrisawat V, Thaemboonlers A, Lefevre I. Long-term antibody persistence in children primed and boosted with a DTPw-HBV vaccine at 2, 4, 6, 18, months of age. *Vaccine* 2008; **26**(12): 1535-40.
20. Poovorawan Y, Chongsrisawat V, Theamboonlers A, et al. Long-term benefit of hepatitis B vaccination among children in Thailand with transient hepatitis B virus infection who were born to hepatitis B surface antigen-positive mothers. *J Infect Dis* 2009; **200**(1): 33-8.
21. Poovorawan Y, Chongsrisawat V, Theamboonlers A, Leroux-Roels G, Crasta PD, Hardt K. Persistence and immune memory to hepatitis B vaccine 20 y after primary vaccination of Thai infants, born to HBsAg and HBeAg positive mothers. *Human Vaccines and Immunotherapeutics* 2012; **8**(7): 896-904.
22. Poovorawan Y, Chongsrisawat V, Theamboonlers A, Bock HL, Leyssen M, Jacquet J-M. Persistence of antibodies and immune memory to hepatitis B vaccine 20 years after infant vaccination in Thailand. *Vaccine* 2010; **28**(3): 730-6.
23. Chunsuttiwat S, Biggs BA, Maynard JE, Thammapormpilas P, M OP. Comparative evaluation of a combined DTP-HB vaccine in the EPI in Chiangrai Province, Thailand. *Vaccine* 2002; **21**(3-4): 188-93.

Cochrane

Targeted Update

Immunogenicity of recombinant DNA HBV vaccines: timing of first dose

Included studies

Argentina 2011 (quasi-RCT)[1]
Cambodia 2013 (retrospective cohort)[2]
China 1992-B (Cohort)[3]
China 1992-C (quasi-RCT)[4]
China 1998-B (Cohort)[5]
China 2013 (retrospective cohort)[6]
Egypt 1995 (RCT)[7]
India 2009 (RCT)[8]
Israel 2002 (Cohort)[9]
Ivory Coast 2008 (quasi-RCT)[10]
Japan 1989 (Cohort)[11]
Netherlands 1993-A (RCT)[12]
Netherlands 1994-B (RCT)[13,14]
Philippines 2005 (RCT)[15]
Philippines 2007 (RCT)[16]
Philippines 2008 (RCT)[17]
South Africa 2013 (RCT)[18]
Spain 2006 (RCT)[19,20]
Taiwan 1997 (Cohort)[21]
Turkey 2004-A (quasi-RCT)[22]
Turkey 2010 (Cohort)[23]
USA 1997-A (RCT)[24]
USA 2002-A (RCT)[25]
USA 2002-B (RCT)[26]

What's new

Latest search was performed: **June 2016**

No studies compared recombinant DNA HBV vaccinations with a birth dose administered at ≤ 24 hours vs. those with a birth dose administered at ≥ 24 hours.

We are uncertain about the effect of timing of birth dose compared with no birth dose doses of recombinant DNA HBV vaccines on HBsAg seroprevalence or anti-HBs seroconversion.

There is low quality evidence of higher antibody titres with a birth dose (≤ 24 hours of life) schedule compared to schedules without birth dose.

There was also no evidence of a difference in the number of deaths or serious adverse events between vaccine schedules for all comparisons.

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Background

In 1992, the WHO set a goal for all countries to integrate HBV vaccination into the Expanded Program on Immunization (EPI). The WHO recommends that all infants receive their first dose of HBV vaccine as soon as possible after birth. The birth dose should then be followed by two or three additional doses with a minimum interval of four weeks.

Objectives

To evaluate whether the timing of administration of birth dose of recombinant DNA hepatitis B vaccines for infants induces higher levels of seroconversion (from antibody negative to antibody positive) to hepatitis B surface antigen (anti-HBs), presented as the absolute levels of antibodies (GMCs) and the percentage levels of antibody to hepatitis B surface antigen (anti-HBs) with a threshold of ≥ 10 IU/ml, and clinical outcomes.

Search methods

Search strategies were developed specifically for each database. We searched The Cochrane Library, latest issue; MEDLINE (January 1946 to June 2016); EMBASE (January 1980 to June 2016); and CINAHL (January 1981 to June 2016). We also searched the metaRegister of Controlled Trials (mRCT) (http://www.controlled-trials.com/mrct/) in June 2016.

Selection criteria

Two reviewers independently screened and selected studies, discrepancies were resolved in consultation with a senior reviewer. Randomised controlled trials and prospective observational studies of children vaccinated with any licensed recombinant DNA hepatitis B vaccine, measuring immunological or clinical outcomes, were included. We also included retrospective studies from 2012.

Data collection and analysis

Two reviewers extracted data independently, discrepancies were resolved in consultation with a senior reviewer. Risk ratios were calculated for binary outcome data. For continuous data, values were log-transformed and presented as GMCs. Meta-analysis for most comparisons could not be performed because of lack of data.

Main Results

We included 24 studies (12 RCTs, 4 quasi-RCTs, 6 cohort studies and 2 retrospective cohort studies), published between 1991 and 2016.

The risk of bias was high for 5 included RCTs/quasi-RCTS and moderate to serious for included cohort studies.

No studies comparing recombinant DNA HBV vaccinations with a birth dose administered at ≤ 24 hours vs. those with a birth dose administered at ≥ 24 hours were identified. Timing of birth dose was reported as ≤ 24 hours of life in 10 studies, 0-3 days of life in 2 studies, ≤ 2 weeks of life in 3 studies, and not specified in the remaining studies.

There seems to be no difference in the proportion of infants becoming seroprotected 1-3 months post-vaccination when infants with schedules that contained a birth dose are compared with infants starting vaccination after the first month of life, regardless of when the birth dose was given; these results remained consistent after a longer follow up period.

There is some evidence indicating that vaccination schedules containing a birth dose were associated with higher antibody concentrations (GMCs) at 1-3 months post-vaccination when compared with schedules in which vaccination began after the first month of life. Weak evidence also showed no difference with regard to serious adverse events, all-cause deaths and clinical outcomes among infants who received a birth dose compared with those who began vaccination after one month of life. However, the quality of evidence for these comparisons is limited.

Four studies reported on the effect of recombinant DNA vaccines in low-birth-weight (pre-term) infants. It is uncertain whether delaying vaccination in low-birth weight infants improves seroprotection rates and GMCs as the quality of this evidence is very low.

Implications and conclusions

There is very limited confidence in the evidence about the effects of the timing of birth dose administration of recombinant DNA HBV vaccine on the outcomes of HBsAg seroprevalence or anti-HBs seroprotection. However, vaccination schedules containing a birth dose appear to be associated with higher antibody concentrations (GMCs) at 1-3 months post-vaccination when compared with schedules in which vaccination began after the first month of life.

Summary of Findings: HBV vaccines birth dose given at ≤24 hours vs. birth dose given at ≥24 hours

***Patients and setting*: Infants**

***Comparison:* HBV vaccines given at ≤24 hours vs. birth dose given at ≥24 hours.**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		birth dose ≥24 h	Birth dose ≤24 h		
HBsAg seroprevalence	There is no evidence about the effects of the administration of the first dose of recombinant DNA or plasma HBV vaccines at ≤ 24 hours or later during the first month of life; none of the included studies evaluated this comparison.				
Anti-HBs seroprotection					
GMCs of anti-HBs					

Summary of Findings: Recombinant DNA HBV vaccines birth dose within 24 hours vs no birth dose

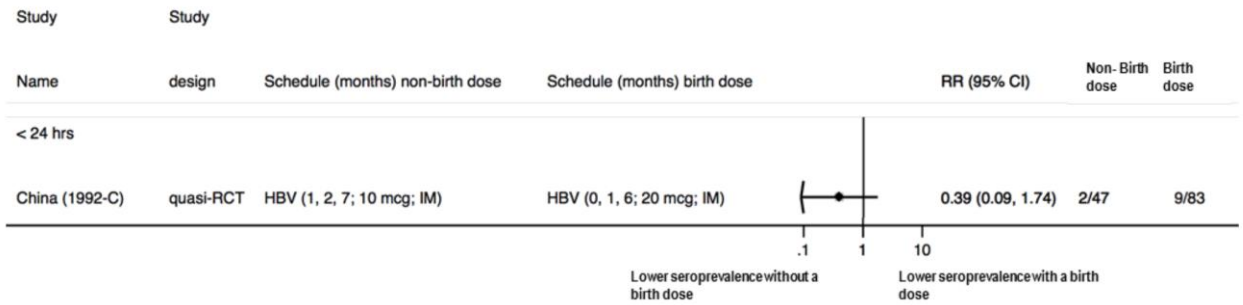
***Patients and setting*: Infants in China, Spain, USA, Argentina, South Africa, Philippines, India, Egypt**
***Comparison:* Recombinant DNA HBV vaccines birth dose within 24 hours vs no birth dose**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Control (no bo)	Intervention (bo)		
HBsAg seroprevalence	We are uncertain about the effect of birth dose versus no birth dose, because the evidence is of very low quality.	2/47 (4.26%)	9/83 (10.84%)	RR 0.39 (95% CI 0.09 to 1.74) 1 quasi RCT, 130 participants	⨁OOO VERY LOW [1,2]
Anti-HBs seroprotection	We are uncertain about the effect of birth dose versus no birth dose, because the evidence is of very low quality. Meta-analysis was only possible for three RCTs from high endemicity regions in which no difference in seroprotection rates was observed. There was also no evidence of a difference in seroprotection rates between vaccine schedules for most comparisons, except for one study (Egypt 1995), which showed higher seroprotection without a birth dose (RR 1.12, 95% CI 1.01, 1.25) at 12-24 months post-immunization	Meta-analysis not performed for all studies		9 studies (7 RCTs and 2 quasi-RCTs)	⨁OOO VERY LOW [1,2,3]
		686/716 (95.81%)	98.77% (95% CI 97.77% to 100%)	RR 0.97 (95% CI 0.95 to 0.98) 3 RCTs, 1136 participants	
GMCs of anti-HBs	There is low quality evidence of higher antibody titres with a birth dose (≤ 24 hours of life) schedule compared to schedules without birth dose.	Low endemicity			⨁⨁OO LOW [4]
		N/A	N/A	-0.71 (95% CI -1.00 to -0.42) 2 RCTs, 606 participants	
		Moderate endemicity			
		N/A	N/A	-0.69 (95% CI -1.03 to -0.35) 1 quasi RCT, 203 participants	
		High endemicity			
		N/A	N/A	-1.61 (95% CI -2.67 to -0.54) 2 RCTs, 942 participants	

[1]Downgraded 2 points for study design: lack of randomisation, [2]Downgraded 1 point for imprecision: low number of events, [3]Downgraded 1 point for inconsistency: effect favours both birth dose and no birth dose, [4]Downgraded 2 points for study design: lack of randomisation and unclear risk of bias in some studies

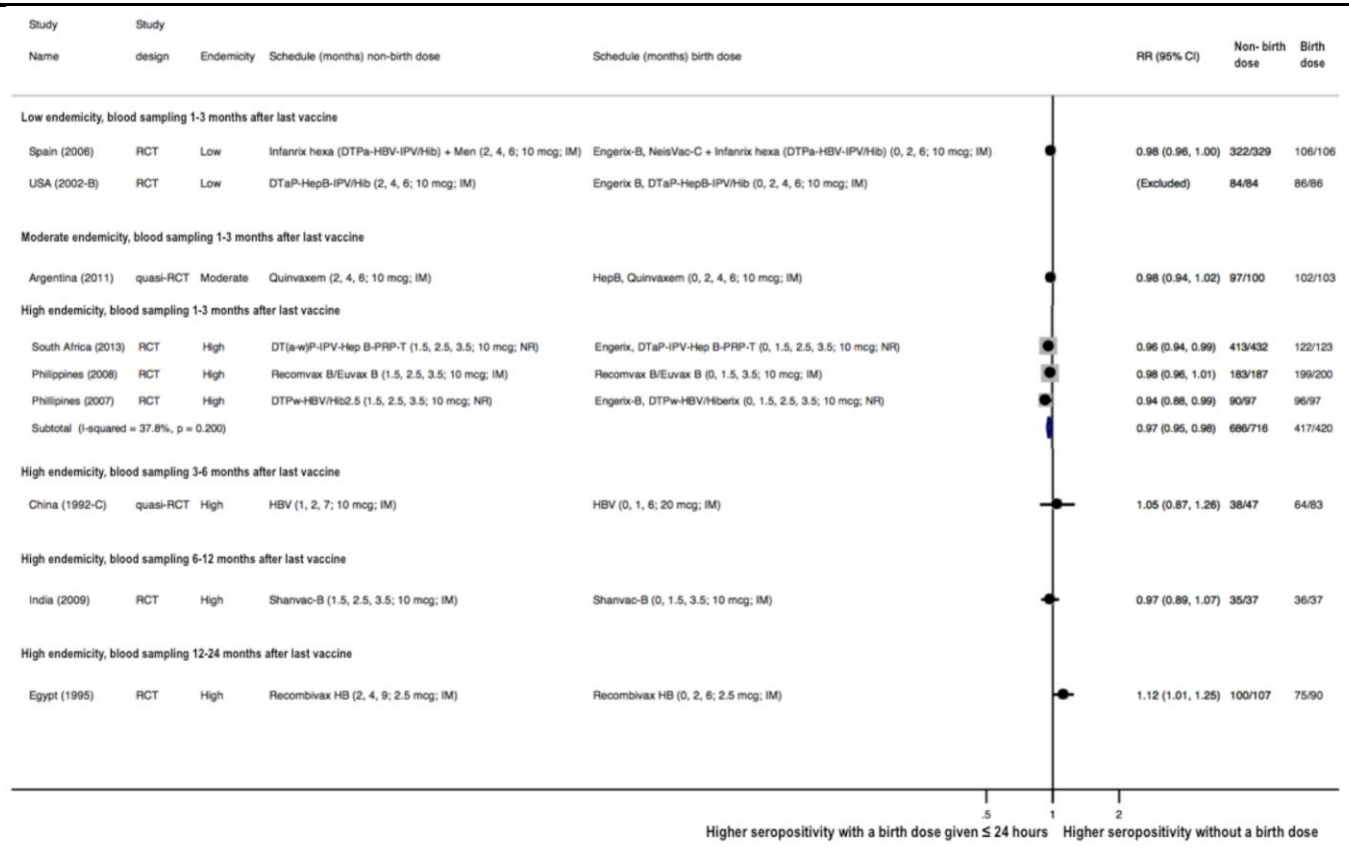
Forest plots and summaries per outcome: Recombinant DNA HBV vaccines birth dose within 24 hours vs no birth dose

Patients and setting: Infants in China, Spain, USA, Argentina, South Africa, Philippines, India, Egypt
Comparison: Recombinant DNA HBV vaccines birth dose within 24 hours vs no birth dose

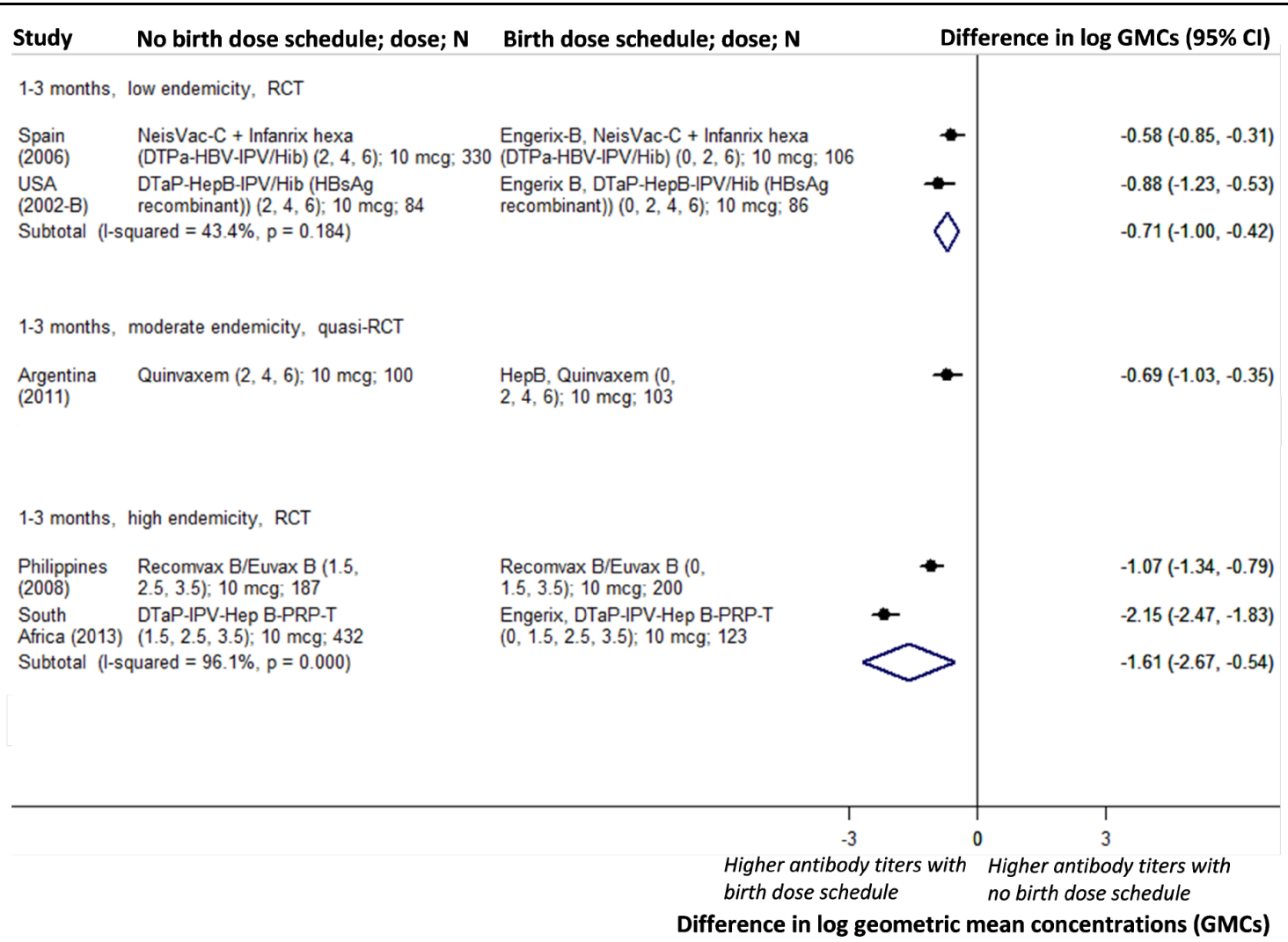
Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
HBsAg seroprevalence We are uncertain about the effect of birth dose versus no birth dose, because the evidence is of very low quality.		⊕OOO VERY LOW

Anti-HBs seroprotection

Meta-analysis was only possible for three RCTs from high endemicity regions in which no difference in seroprotection rates was observed. There was also no evidence of a difference in seroprotection rates between vaccine schedules for most comparisons, except for one study (Egypt 1995), which showed higher seroprotection without a birth dose



⊕OOO
VERY LOW

GMCs of anti-HBs There is low quality evidence of higher antibody titres with a birth dose (≤ 24 hours of life) schedule compared to schedules without birth dose.		⊕⊕OO LOW

Summary of Findings: Recombinant DNA HBV vaccines birth dose given at 0 to 3 days of life versus no birth dose

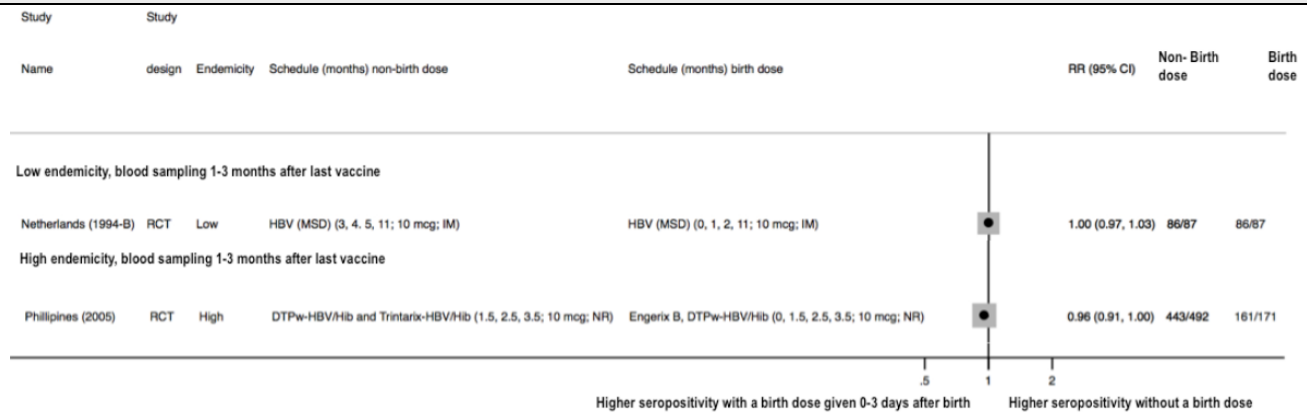
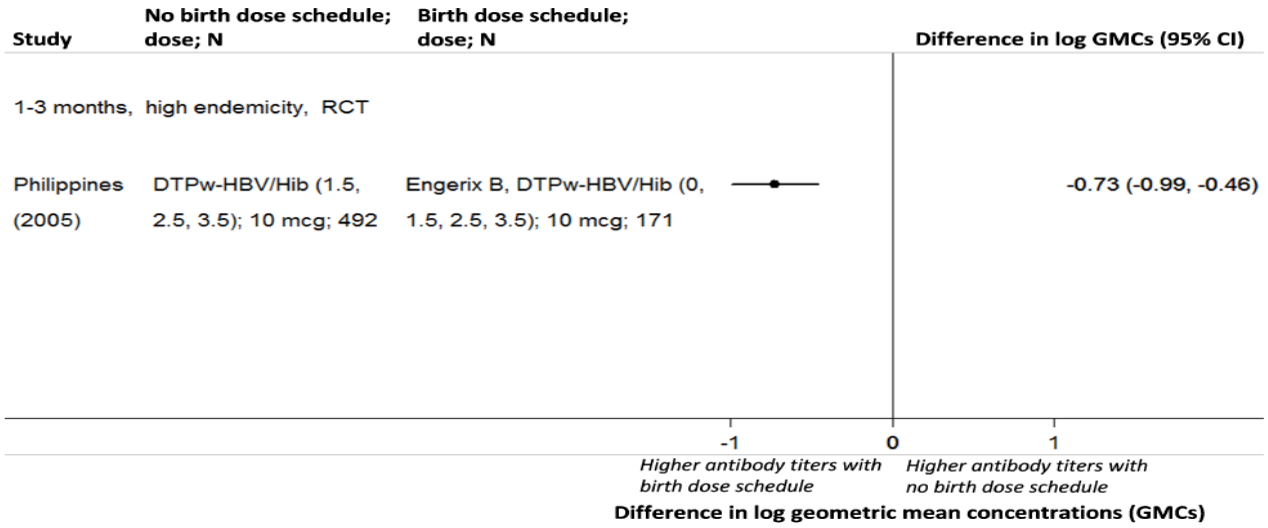
***Patients and setting*: Infants in Netherlands and Philippines**
***Comparison:* Recombinant DNA HBV vaccines birth dose given at 0 to 3 days versus no birth dose**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Control (No birth dose)	Intervention (Birth dose at 0 to 3 days of life)		
HBsAg seroprevalence	None of the included studies assessed this outcome.	Not measured	Not measured	2 RCTs, 837 participants	Not estimable
Anti-HBs seroprotection	Birth dose given at 0 to 3 days may lead to little or no difference in seroprotection.	Low endemicity			⊕⊕OO LOW [1,2]
		86/87 (98.85%)	86/87 (98.85%)	RR 1.0 (95% CI 0.97 to 1.03) 1 RCT, 174 participants	
		High endemicity			
		443/492 (90.04%)	161/171 (94.15%)	0.96 (0.91 to 1.00) 1 RCT, 663 participants	
GMCs of anti-HBs	Birth dose given at 0 to 3 days of life probably leads to higher antibody concentrations.	Not reported	Not reported	Mean difference in log GMCs: -0.73 (95% CI -0.99 to -0.46) (Corresponds to a GMC ratio: 0.48, 95% CI 0.37 to 0.63) 1 RCT, 663 participants	⊕⊕⊕O MODERATE[1]

[1]Downgraded one level for risk of bias: included studies were of high risk of bias
[2]Downgraded one level for imprecision: 95% CI includes null effect

Forest plots and summaries per outcome: Recombinant DNA HBV vaccines birth dose given at 0 to 3 days of life versus no birth dose

***Patients and setting*: Infants in Netherlands and Philippines**
***Comparison:* Recombinant DNA HBV vaccines birth dose given at 0 to 3 days versus no birth dose**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection Birth dose given at 0 to 3 days may lead to little or no difference in seroprotection.		⊕⊕OO LOW
GMCs of anti-HBs Birth dose given at 0 to 3 days of life probably leads to higher antibody concentrations.		⊕⊕⊕O MODERATE

Summary of Findings: Recombinant DNA HBV vaccines birth dose given ≤2 weeks of life vs. no birth dose

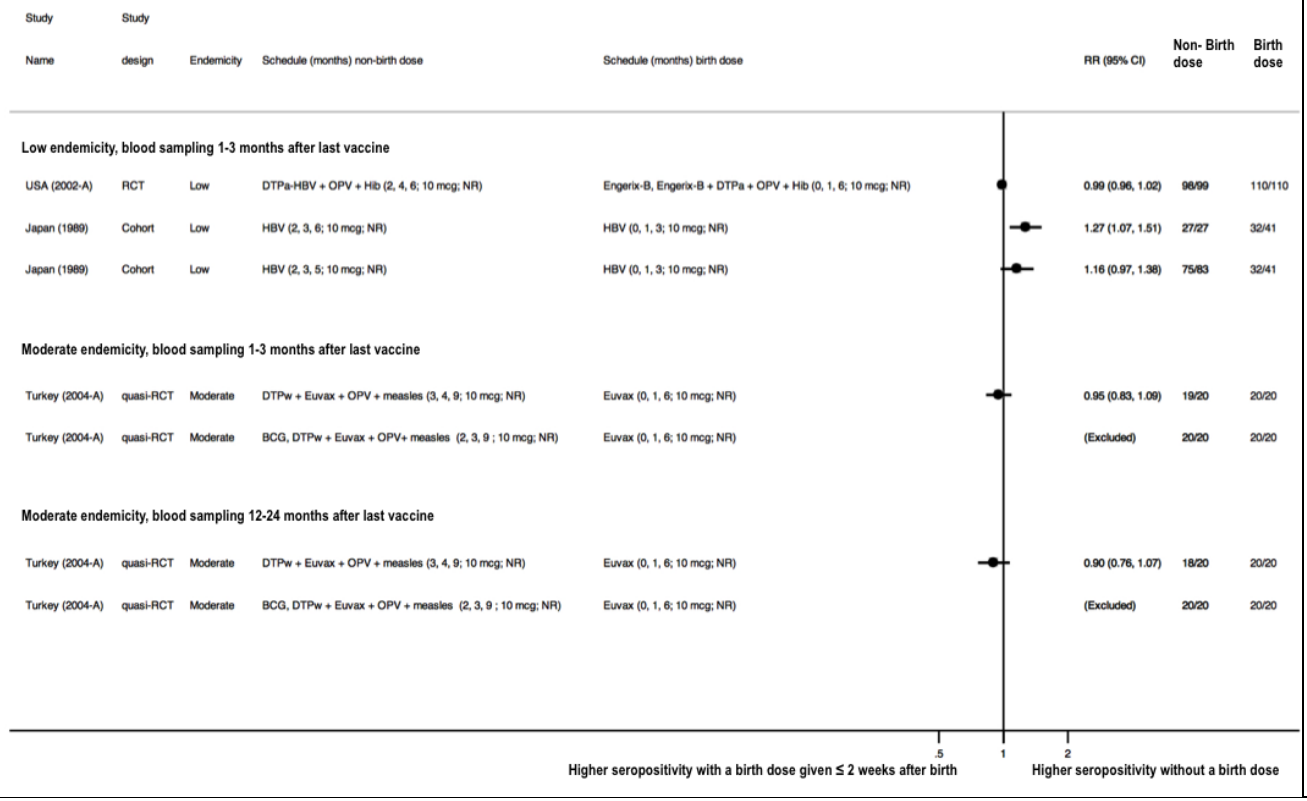
***Patients and setting*: Infants in Japan, Turkey and the USA.**
***Comparison:* Recombinant DNA HBV vaccines given bo≤2 weeks of life vs. no birth dose.**

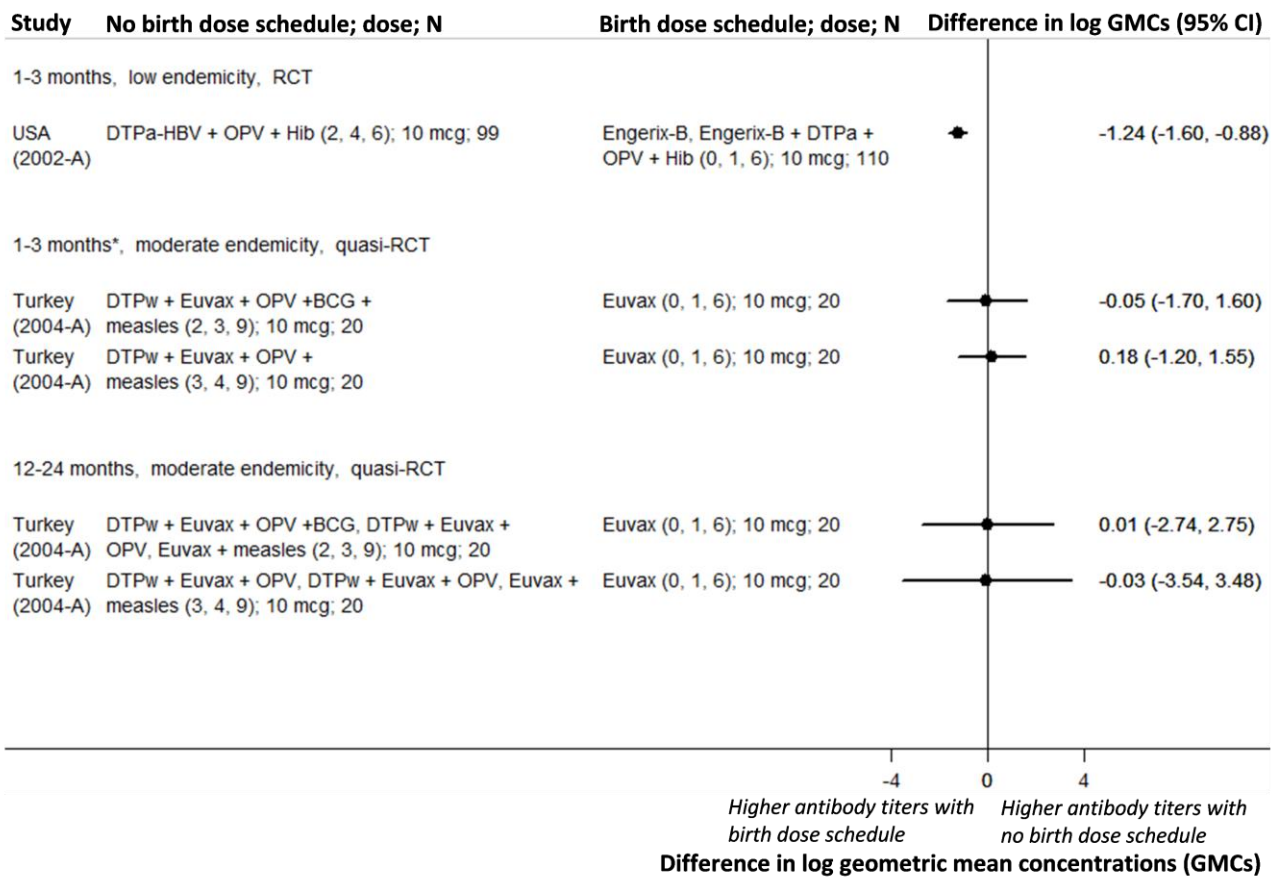
Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		No birth dose	Birth dose ≤2 weeks		
HBsAg seroprevalence	There is no evidence about the effects of bo given ≤2 weeks of life vs. no bo of recombinant DNA HBV vaccines on HBsAg seroprevalence; none of the included studies reported on this outcome.				
Anti-HBs seroprotection Follow-up: 1-3 months Endemicity: Low-Mod	We are uncertain about the effect of bo given ≤2 weeks of life vs. no bo of recombinant DNA HBV vaccines on Anti-HBs seroprotection because the evidence is of very low quality.	217/229 (94.8%) (data at 1-3 months from 2 RCTs and 1 cohort study)	Not estimable (no summary relative effect)	No summary relative effect (no meta-analysis) 373 participants, 3 studies (2 RCTs; 1 cohort study)	⊕OOO VERY LOW [1,2,3]
GMCs of anti-HBs Follow-up: 1-3 months Endemicity: Low-Mod	We are uncertain about the effect of bo given ≤2 weeks of life vs. no bo of recombinant DNA HBV vaccines on GMCs of anti-HBs because the evidence is of very low quality.	Not estimable	Not estimable (no summary relative effect)	No summary relative effect (no meta-analysis) 269 participants, 2 RCTs	⊕OOO VERY LOW [4,5,6]

[1]Downgraded one level for study design: studies of different design, including one or more non randomised study.
[2]Downgraded one level for risk of bias: most included studies were of high risk of bias.
[3]Downgraded one level for inconsistency: most studies found no difference between the two groups, one cohort study found results favouring no birth dose schedule.
[4]Downgraded one level for risk of bias: one study was at high, the other at unclear risk of bias.
[5]Downgraded one level for inconsistency: one RCT found no difference between the two groups, another RCT found results favouring birth dose schedule.
[6]Downgraded one level for imprecision: small sample size (269 participants).

Forest plots and summaries per outcome: Recombinant DNA HBV vaccines birth dose given ≤2 weeks of life vs. no birth dose

***Patients and setting*: Infants in Japan, Turkey and the USA.**
***Comparison:* Recombinant DNA HBV vaccines given bo≤2 weeks of life vs. no birth dose.**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
HBsAg seroprevalence	There is no evidence about the effects of bo given ≤2 weeks of life vs. no bo of recombinant DNA HBV vaccines on HBsAg seroprevalence; none of the included studies reported on this outcome.	N/A
Anti-HBs seroprotection There was no evidence of a difference in seroprotection rates between vaccine schedules for the RCT and quasi-RCT. A cohort study performed in Japan with HBsAg and HBeAg positive mothers showed higher seroprotection rates without a birth dose.		⊕OOO VERY LOW

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
GMCs of anti-HBs One RCT in a low endemicity region showed a WMD in log GMCs of -1.24 (95% CI -1.60 to -0.88). This corresponds to a GMC ratio of 0.30 (95% CI 0.20 to 0.41), which indicates that the birth dose schedule gave higher antibody concentrations 1-3 months post vaccination compared to the schedule without a birth dose. A quasi-RCT reported data at 1-3 and 12-24 months after immunization, and results showed no difference in log GMCs for the compared schedules.		⊕OOO VERY LOW

Summary of Findings: Recombinant DNA HBV vaccines birth dose give at "o months", exact timing not reported

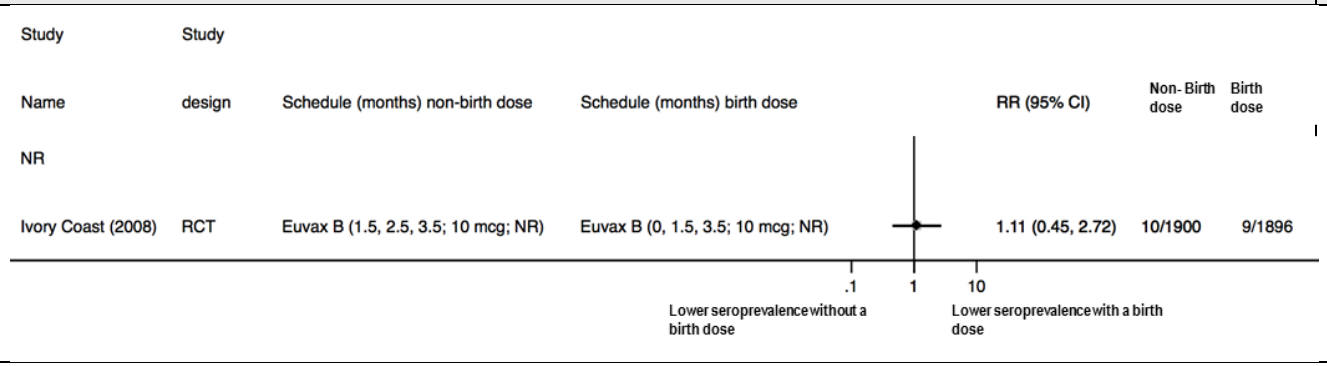
***Patients and setting*: Infants in China, Ivory Coast, the Netherlands, Turkey.**
***Comparison:* Recombinant DNA HBV vaccines given at "o months", exact timing not reported, vs. no birth dose.**

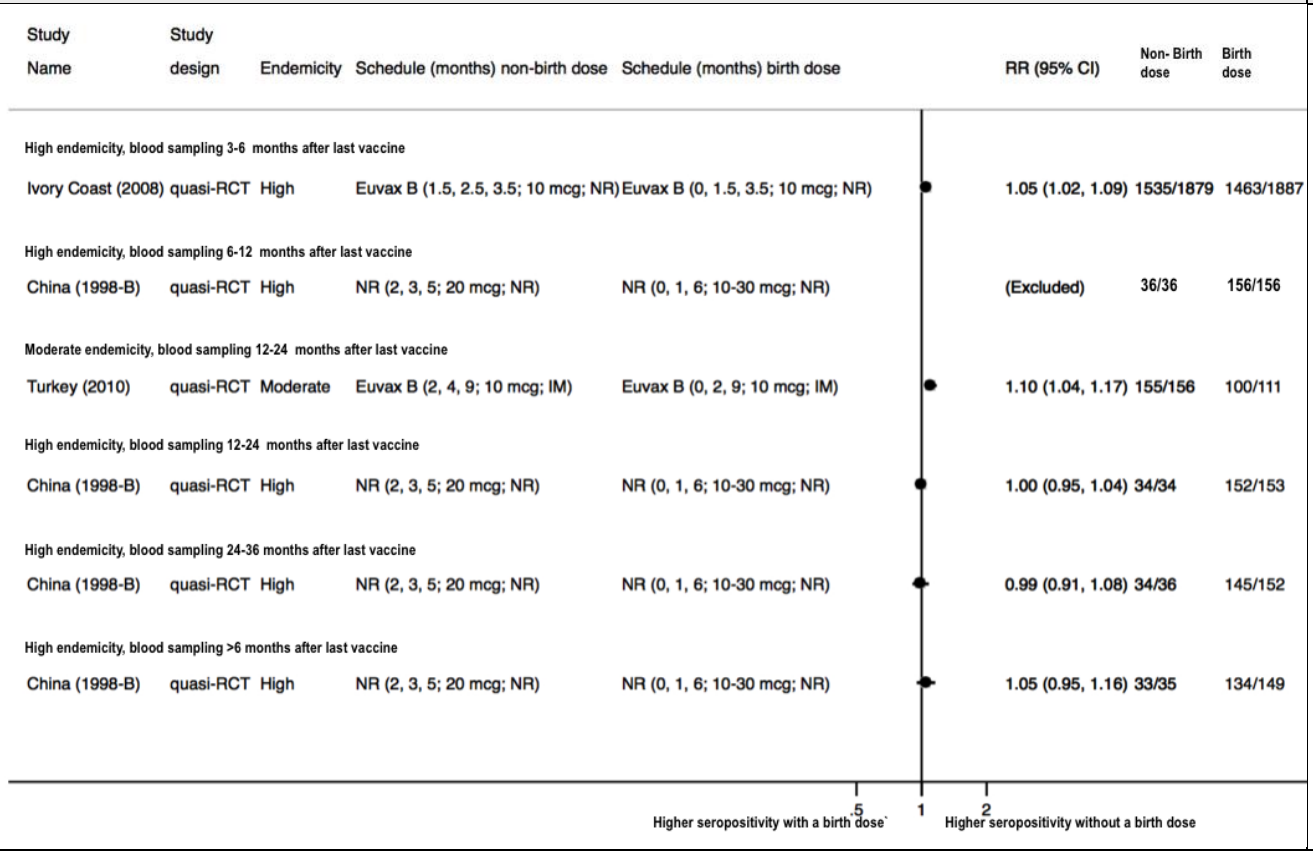
Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		No birth dose	Birth dose "o months"		
HBsAg seroprevalence Follow-up: not reported Endemicity: High	There may be little or no difference between birth dose given at "o months", exact timing not reported, and no birth dose of recombinant DNA HBV vaccines on HBsAg seroprevalence.	10/1900 (0.5%) (data from 1 RCTs, time point not reported)	9/1896 (0.5%) (data from 1 RCT, time point not reported)	RR 1.11 (0.45 to 2.72) 3796 participants, 1 RCT	⊕⊕OO LOW [1,2]
Anti-HBs seroprotection Follow-up: 3-24 months Endemicity: Mod-High	We are uncertain about the effect of birth dose given at "o months", exact timing not reported, and no birth dose of recombinant DNA HBV vaccines on Anti-HBs seroprotection because the evidence is of very low quality.	1724/2069 (83.3%) (data at 3-24 months from 3 quasi-RCTs)	Not estimable (no summary relative effect)	No summary relative effect (no meta-analysis) 4220 participants, 3 quasi-RCTs	⊕OOO VERY LOW [3,4,5]
GMCs of anti-HBs Follow-up: 1-3 months Endemicity: Low	Schedule with birth dose given at "o months", exact timing not reported, may give lower antibody concentrations than no birth dose schedules of recombinant DNA HBV vaccines.	Not estimable	Not estimable (no summary relative effect)	No summary relative effect (no meta-analysis) 1 RCT	⊕⊕OO LOW [1,6]

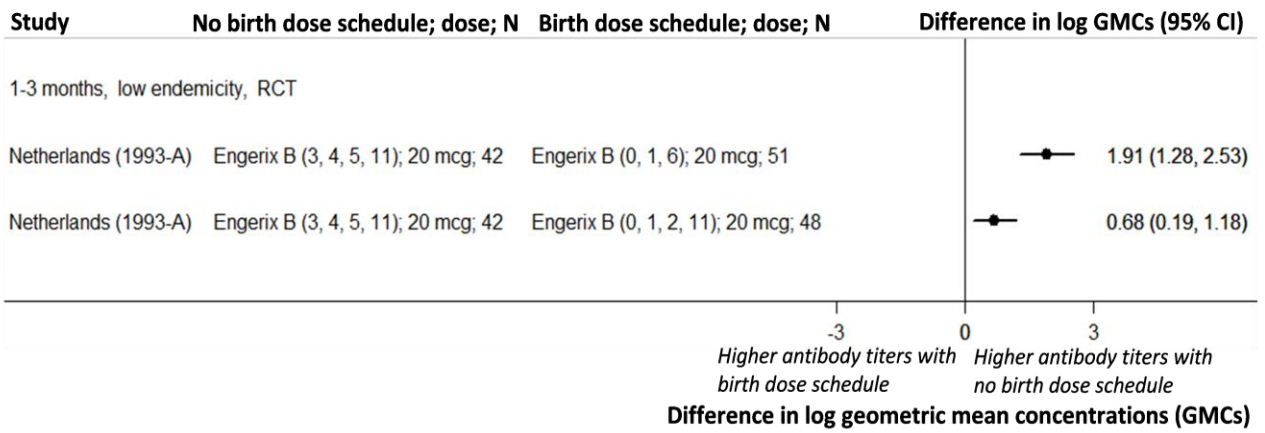
[1]Downgraded one level for risk of bias: the included study was at high risk of bias.
[2] Downgraded one level for imprecision: the 95% CI includes benefit for both interventions in the comparison.
[3]Downgraded one level for study design: most studies were observational studies.
[4]Downgraded one level for risk of bias: two studies were at high, one at moderate risk of bias.
[5]Downgraded one level for inconsistency: one RCT and one observational study found results favouring birth dose schedule, one observational study found no difference between intervention arms.
[6]Downgraded one level for imprecision: small sample size (141 participants).

Forest plots and summaries per outcome: Recombinant DNA HBV vaccines birth dose given at "0 months", exact timing not reported, vs. no birth dose

***Patients and setting*: Infants in China, Ivory Coast, the Netherlands, Turkey.**
***Comparison:* Recombinant DNA HBV vaccines given at "0 months", exact timing not reported, vs. no birth dose.**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
HBsAg seroprevalence There was no evidence of a difference in seroprevalence rates between vaccine schedules, in the blood sampling collected 3-6 months after immunization.		⊕⊕OO LOW

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection For the study performed in a region of moderate endemicity, results 12-24 months after vaccination showed a marginally significant effect, with higher seroprotection when a birth dose was not given (N= 267, RR 1.10, 95% CI 1.04, 1.17). There was no evidence of a difference in seroprotection rates between vaccine schedules for studies conducted in high endemicity regions, for all time points.		⊕OOO VERY LOW

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
GMCs of anti-HBs One RCT favored the schedule without a birth dose 1-3 months after vaccination. The figure shows a WMD in log GMCs of 1.91 (95% CI 1.28, 2.53) for the schedule 0, 1, 6 vs. 3, 4, 5, 11 months, and of 0.68 (95% CI 0.19, 1.18) for the schedule 0, 1, 2, 11 vs. 3, 4, 5, 11 months. This corresponds to GMC ratios of 6.75 (95% CI 3.60, 12.55) 1.97 (95% CI 1.21, 3.25), respectively, which indicates that the birth dose schedule gave lower antibody concentrations 1-3 months post vaccination compared to the schedule without a birth dose.		⊕⊕OO LOW

Summary of Findings: Recombinant DNA HBV vaccines birth dose vs no birth dose – retrospective cohort studies published since 2012

***Patients and setting*: Infants in China and Cambodia.**
***Comparison:* Recombinant HBV vaccines birth dose versus no birth dose**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		No birth dose[1,2]	Birth dose[3]		
HBsAg seroprevalence	We are uncertain about the effect of birth dose versus no birth dose, because the evidence is of very low quality.	17/236 (7.2%) (Cambodia study, measured 4-5 years after last dose)	13/1827 (0.71%) (Cambodia study, measured 4-5 years after last dose)	No summary relative effect (no meta-analysis) 31184 participants, 2 retrospective cohort studies	⨁◯◯◯ VERY LOW [1,3,4]
		106/5247 (2.02%) (China study, measured 1-13 years after last dose)	193/21529 (0.90%) (China study, measured 1-13 years after last dose)		

[1]Downgraded 1 point for indirectness: Unclear from one study (Cambodia) that describes "no vaccine given" in a table column headed "Interval from birth to first dose", whether no birth dose given, or no vaccine at all
[2]Primary dose (no birth dose group) given 28 days or later in one study (China)
[3]Downgraded 1 point for indirectness: Timing of birth dose recommended within 24 hours in one study (Cambodia), but exact timing unknown
[4]Downgraded 2 points for non-random comparison

Summary of Findings: Recombinant DNA HBV vaccine schedules with a birth dose versus without a birth dose, clinical and subclinical outcomes

***Patients and setting*: Infants in Netherlands, Turkey, USA, Philippines, Spain and Australia**
***Comparison:* Recombinant DNA HBV vaccine schedules with a birth dose versus without a birth dose, clinical and subclinical outcomes**

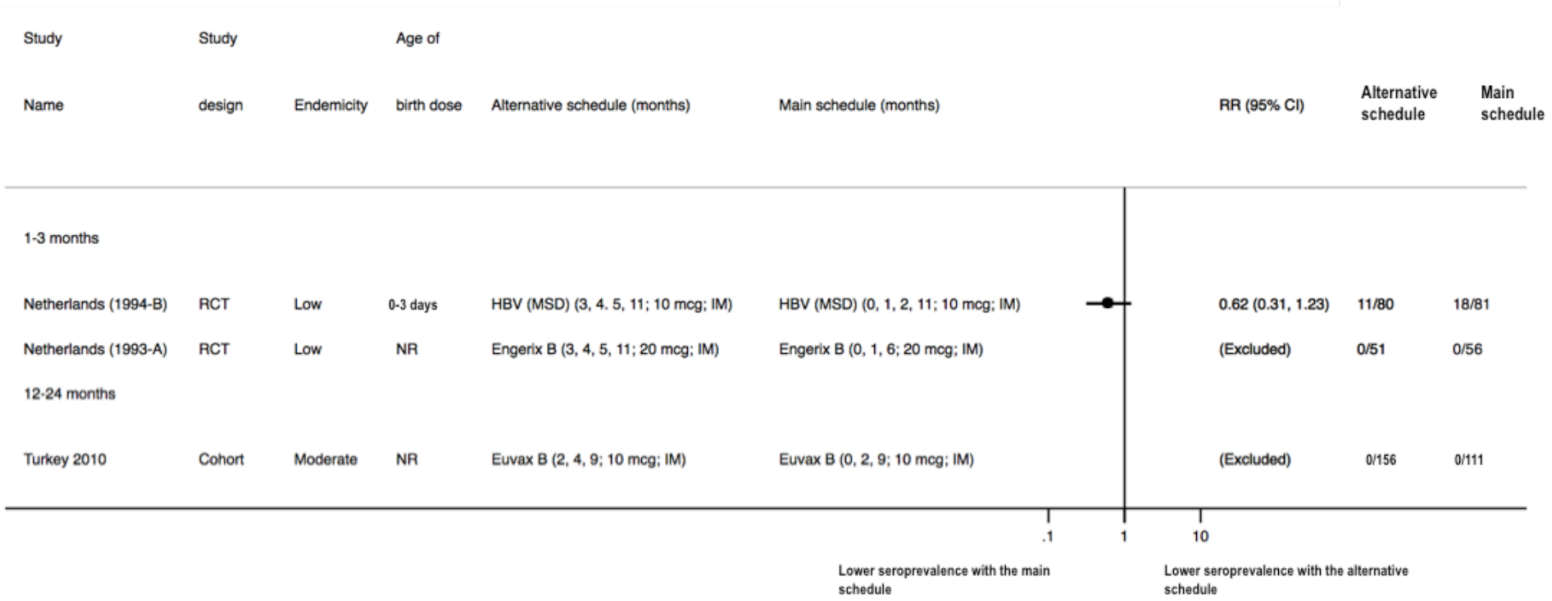
Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Control (no bo)	Intervention (bo)		
Anti-HBc	We are uncertain of the effects of three-dose schedules with or without a birth dose, as the quality of evidence is very low. Two studies reported seroprotection in all infants, and a single RCT showed no evidence of a difference in seroprevalence rate.	Meta-analysis not performed for all studies (two studies contributed no data)		3 studies (2 RCTs, one cohort), 535 participants	⊕OOO VERY LOW [1,2]
		11/80 (13.75%)	18/81 (22.22%)	RR 0.62, 95% CI 0.31 to 1.23 1 RCT, 161 participants	
All-cause **deaths**	We are uncertain of the effects of three-dose schedules with or without a birth dose, as the quality of evidence is very low. Few events were reported with the birth dose schedule and none with the non-birth dose schedule; however, there was no evidence of a difference in the number of deaths between vaccine schedules for all comparisons.	Meta-analysis not performed		3 RCTs, 1,205 participants	⊕OOO VERY LOW [3,4]
Serious Adverse Events	We are uncertain of the effect on serious adverse events comparing schedules with a birth dose given in the first months with schedules that did not include a birth dose, as the quality of evidence is very low. Meta-analysis was not possible as two studies randomized more than two groups; however, there was no evidence of a difference in the number of serious adverse events between vaccine schedules for all comparisons.	Meta-analysis not performed		6 RCTs, 3,380 participants	⊕OOO VERY LOW [2,3,5]

[1]Downgraded 2 points for study design: lack of randomisation, and studies at high or unclear risk of bias
[2]Downgraded 1 point for imprecision: low number of events
[3]Downgraded 1 point for study design: studies at high or unclear risk of bias
[4]Downgraded 2 points for imprecision: very low number of events
[5]Downgraded 1 point for inconsistency: different direction of effect in different studies

Forest plots and summaries per outcome: Recombinant DNA HBV vaccines birth dose vs. no birth dose, clinical and subclinical

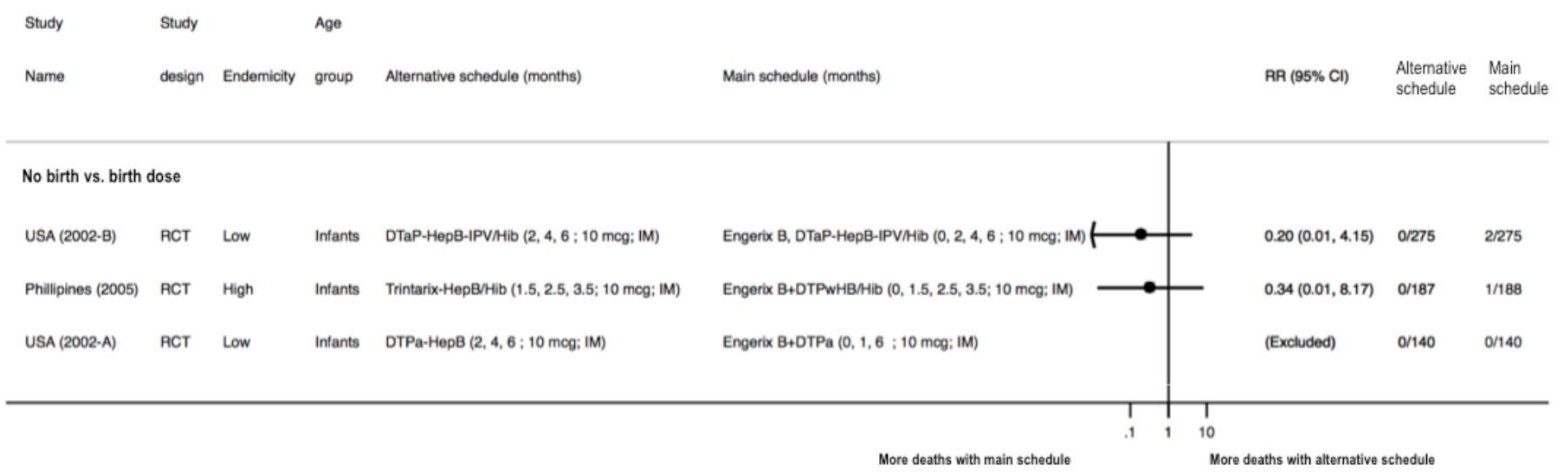
outcomes

***Patients and setting*: Infants in Netherlands, Turkey, USA, Philippines, Spain and Australia**
***Comparison:* Recombinant DNA HBV vaccine schedules with a birth dose versus without a birth dose, clinical and subclinical outcomes**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBc Two studies reported seroprotection in all infants, and a single RCT showed no evidence of a difference in seroprevalence rate.		⊕OOO VERY LOW

All-cause deaths

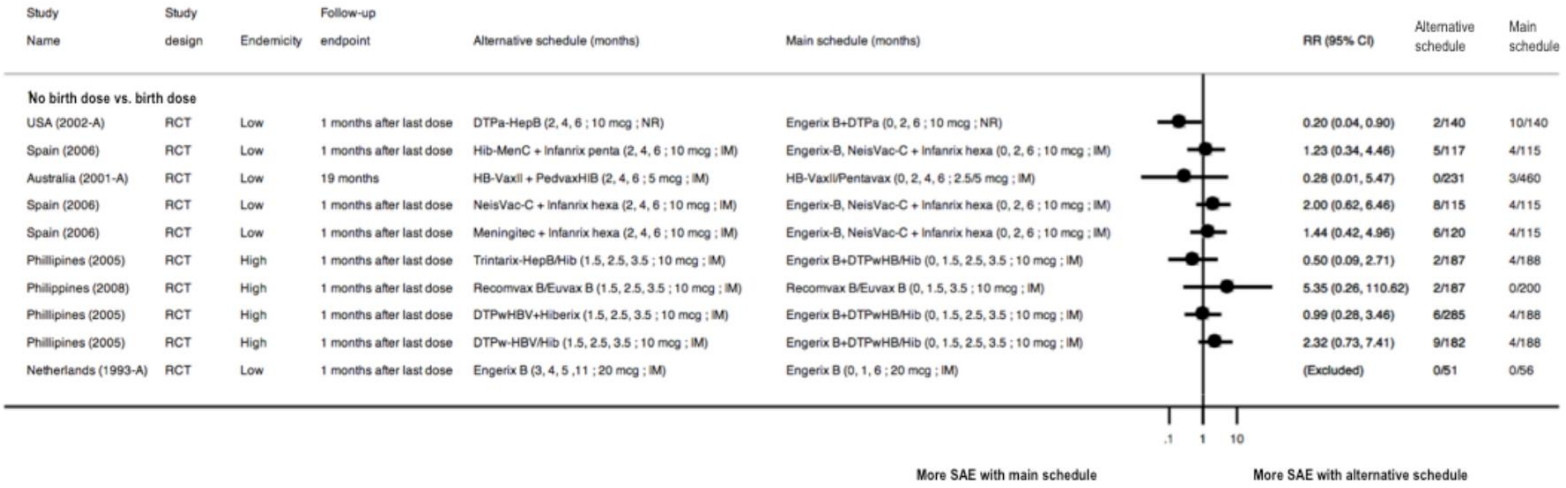
Few events were reported with the birth dose schedule and none with the non-birth dose schedule; however, there was no evidence of a difference in the number of deaths between vaccine schedules for all comparisons.



⊕OOO VERY LOW

Serious Adverse Events

Meta-analysis was not possible as two studies randomized more than two groups; however, there was no evidence of a difference in the number of serious adverse events between vaccine schedules for all comparisons.



⊕OOO VERY LOW

Summary of Findings: Recombinant DNA HBV vaccines birth dose started at different birth weights

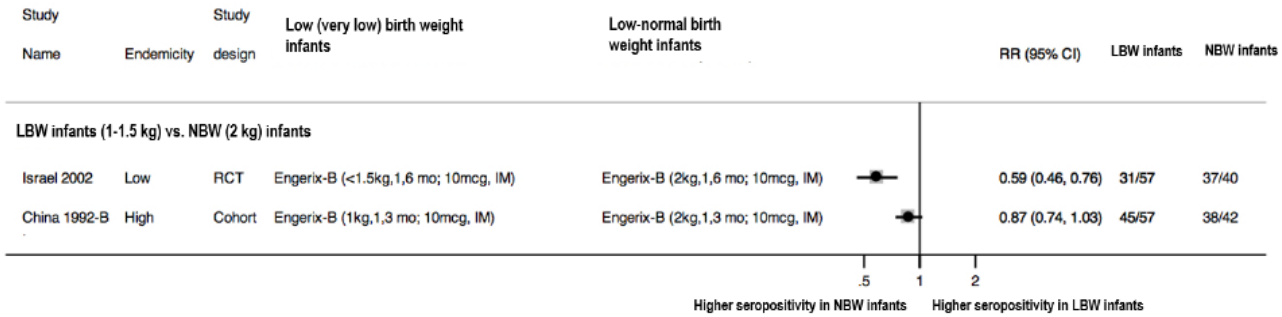
***Patients and setting*: Low birth weight infants (1.0 to 2.0 kg) in Israel and China**
***Comparison:* Recombinant DNA HBV vaccines started at 1.0 to 1.5 kg versus 2.0 kg**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Birth weight 1.0 to 1.5 kg	Birth weight 2.0 kg		
HBsAg seroprevalence	None of the included studies assessed this outcome.	Not measured	Not measured	2 Cohort studies, 196 participants	Not estimable
Anti-HBs seroprotection	It is uncertain whether delaying vaccination until a weight of 2.0 kg compared to early vaccination at 1.0 to 1.5 kg improves seroprotection, because the evidence is of very low quality.	Low endemicity			⊕OOO VERY LOW [1,2]
		31/57 (54.39%)	37/40 (92.50%)	RR 0.59 (95% CI 0.46 to 0.76) 1 Cohort study, 97 participants	
		High endemicity			
		45/57 (78.95%)	38/42 (90.48%)	RR 0.87 (95% 0.74 to 1.03) 1 Cohort study, 99 participants	
GMCs of anti-HBs	It is uncertain whether delaying vaccination until a weight of 2.0 kg compared to early vaccination at 1.0 to 1.5 kg improves GMCs, because the evidence is of very low quality.	Low endemicity			⊕OOO VERY LOW [1,2]
		Not reported	Not reported	GMCs measured by radioimmunoassay, GMC (IU/L) Mean (SD): *Birth weight 1.0 to 1.5 kg*: 14.2 (SD not reported); N=57 participants *Birth weight 2.0 kg*: 119 (4.8); N=40 participants 1 cohort study	
		High endemicity			
		Not reported	Not reported	GMTs measured by enzyme immunoassay, HBsAb: *Birth weight 1.0 to 1.5 kg*: 61, 95% CI 27 to 138; N=57 participants *Birth weight 2.0 kg*: 262, 95% CI 101 to 680; N=40 participants 1 Cohort study	

[1]Downgraded one level for risk of bias: included studies were of high risk of bias
[2]Downgraded one level for imprecision: 95% CI includes null effect

Forest plots and summaries per outcome: Recombinant DNA HBV vaccines birth dose started at different birth weights

***Patients and setting*: Low birth weight infants (1.0 to 2.0 kg) in Israel and China**
***Comparison:* Recombinant DNA HBV vaccines started at 1.0 to 1.5 kg versus 2.0 kg**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection It is uncertain whether delaying vaccination until a weight of 2.0 kg compared to early vaccination at 1.0 to 1.5 kg improves seroprotection, because the evidence is of very low quality.		⊕OOO VERY LOW

Summary of Findings: Recombinant DNA HBV vaccines birth dose started at different birth weights

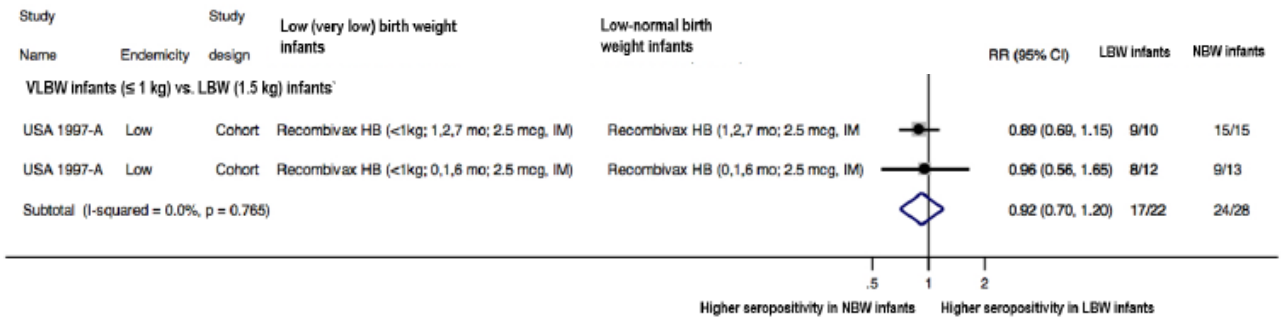
***Patients and setting*: Very low birth weight infants (≤ 1.5 kg) in the USA**
***Comparison:* Recombinant DNA HBV vaccines started at ≤ 1.0 kg vs. 1.5 kg**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Birth weight ≤ 1.0 kg	Birth weight 1.5 kg		
Anti-HBs seroprotection	It is uncertain whether starting vaccination at 1.5 kg compared to starting at ≤ 1.0 kg improves seroprotection, because the evidence is of very low quality.	17/22 (77.27%)	24/28 (85.71%)	RR 0.92 (0.70 to 1.20) Non-randomised data from 1 RCT, 50 participants	⊕OOO VERY LOW [1,2]

[1]Downgraded one level for risk of bias: included studies were of high risk of bias
[2]Downgraded one level for imprecision: 95% CI includes null effect

Forest plots and summaries per outcome: Recombinant DNA HBV vaccines birth dose started at different birth weights

***Patients and setting*: Very low birth weight infants (≤ 1.5 kg) in the USA**
***Comparison:* Recombinant DNA HBV vaccines started at ≤ 1.0 kg vs. 1.5 kg**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection No difference was found between 1 kg and 1-1.5 kg for either a 0, 1, 6 month schedule or a 1, 2, 7 month schedule.		⊕OOO VERY LOW

Bibliographic references

1. Gentile A, Umido V, Czerniuk P, et al. Immunogenicity and reactogenicity of a combined fully liquid DTPw-HepB-Hib pentavalent vaccine in healthy infants: no clinically relevant impact of a birth dose of hepatitis B vaccine. *Int J Infect Dis* 2011; **15**(1): e24-9.
2. Mao B, Patel MK, Hennessey K, Duncan RJ, Wannemuehler K, Soeung SC. Prevalence of chronic hepatitis B virus infection after implementation of a hepatitis B vaccination program among children in three provinces in Cambodia. *Vaccine* 2013; **31**(40): 4459-64.
3. Lau YL, Tam AY, Ng KW, et al. Response of preterm infants to hepatitis B vaccine. *J Pediatr* 1992; **121**(6): 962-5.
4. Qing L, Shuchen D, Qirong Z, et al. The comparison in efficacy between single use of HBV vaccine of different dosages and combined use of HBV vaccine and HBIG of different dosages. [Chinese]. *Acta Academiae Medicinae Shanghai* 1992; **19**(6): 448-52.
5. Zhang X, Xing Y, Shen L. [Follow-up on hepatitis B immunized neonates born to HBsAg positive mothers]. *Chung Hua Yu Fang I Hsueh Tsa Chih* 1998; **32**(2): 97-9.
6. Cui F, Li L, Hadler SC, et al. Reprint of: Factors associated with effectiveness of the first dose of hepatitis B vaccine in China: 1992-2005. *Vaccine* 2013; **31 Suppl 9**: J56-61.
7. Bassily S, Kotkat A, Gray G, 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**(4): 419-22.
8. Das RR, Mathew JL, Ratho RK, Dutta S. Randomized clinical trial comparing hepatitis B vaccine administered by 0, 6 and 14 week versus 6, 10 and 14 week schedule in healthy infants. *J Trop Pediatr* 2009; **55**(5): 328-31.
9. Linder N, Vishne TH, Levin E, et al. Hepatitis B vaccination: long-term follow-up of the immune response of preterm infants and comparison of two vaccination protocols. *Infection* 2002; **30**(3): 136-9.
10. Ekra D, Herbinger K-H, Konate S, et al. A non-randomized vaccine effectiveness trial of accelerated infant hepatitis B immunization schedules with a first dose at birth or age 6 weeks in Cote d'Ivoire. *Vaccine* 2008; **26**(22): 2753-61.
11. Kobayashi M, Koike M, Sumiyama K, Okuda S, Kusumoto S. The efficacy of additional revaccination with hepatitis B when anti-HBs became negative on long follow-up. *Acta Paediatr Jpn* 1989; **31**(6): 674-80.
12. 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**(1): 30-4.
13. Grosheide PM, del Canho R, Voogd M, Heijtink RA, Schalm SW. Anti-HBs levels in infants of hepatitis B carrier mothers after delayed active immunization with recombinant vaccine concomitant with DTP-polio vaccine: is there need for a second dose of HBIg? Dutch Study Group on Prevention of Neonatal Hepatitis B. *Vaccine* 1994; **12**(12): 1059-63.
14. Schalm SW, Mazel JA, de Gast GC, et al. Prevention of hepatitis B infection in newborns through mass screening and delayed vaccination of all infants of mothers with hepatitis B surface antigen. *Pediatrics* 1989; **83**(6): 1041-8.
15. Gatchalian S, Reyes M, Bernal N, et al. A new DTPw-HBV/Hib vaccine is immunogenic and safe when administered according to the EPI (Expanded Programme for Immunization) schedule and following hepatitis B vaccination at birth. *Hum* 2005; **1**(5): 198-203.
16. Ortega-Barria E, Kanra G, Leroux G, et al. The immunogenicity and reactogenicity of DTPw-HBV/Hib 2.5 combination vaccine: results from four phase III multicenter trials across three continents. *Vaccine* 2007; **25**(50): 8432-40.
17. Capeding MR, Cadorna-Carlos J, Book-Montellano M, Ortiz E. Immunogenicity and safety of a DTaP-IPV//PRP~T combination vaccine given with hepatitis B vaccine: A randomized open-label trial. *Bull World Health Organ* 2008; **86**(6): 443-51.

18. Madhi SA, Koen A, Cutland C, Groome M, Santos-Lima E. Antibody persistence and booster vaccination of a fully liquid hexavalent vaccine coadministered with measles/mumps/rubella and varicella vaccines at 15-18 months of age in healthy South African infants. *Pediatr Infect Dis J* 2013; **32**(8): 889-97.
19. Tejedor JC, Moro M, Ruiz-Contreras J, et al. Immunogenicity and reactogenicity of primary immunization with a novel combined Haemophilus influenzae type b and Neisseria meningitidis serogroup C-tetanus toxoid conjugate vaccine coadministered with a diphtheria-tetanus- acellular pertussis-hepatitis B-inactivated poliovirus vaccine at 2, 4 and 6 months. *Pediatr Infect Dis J* 2007; **26**(1): 1-7.
20. Tejedor JC, Moro M, Ruiz-Contreras J, et al. Immunogenicity and reactogenicity of primary immunization with a hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio-Haemophilus influenzae type B vaccine coadministered with two doses of a meningococcal C-tetanus toxoid conjugate vaccine. *Pediatr Infect Dis J* 2006; **25**(8): 713-20.
21. Huang FY, Lee PI, Lee CY, Huang LM, Chang LY, Liu SC. Hepatitis B vaccination in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1997; **77**(2): F135-8.
22. Artan R, Erol M, Velipasaoglu S, Yegin O. The effect of concurrent use of hepatitis B and Bacille Calmette-Guerin vaccination on anti-hepatitis B response. *Saudi Med J* 2004; **25**(12): 1939-42.
23. Agladioglu S, Beyazova U, Camurdan AD, Sahin F, Atak A. Immunogenicity of recombinant hepatitis B vaccine: comparison of two different vaccination schedules. *Infection* 2010; **38**(4): 269-73.
24. 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**(4): 641-3.
25. Greenberg DP, Wong VK, Partridge S, Howe BJ, Ward JI. Safety and immunogenicity of a combination diphtheria-tetanus toxoids-acellular pertussis-hepatitis B vaccine administered at two, four and six months of age compared with monovalent hepatitis B vaccine administered at birth, one month and six months of age. *Pediatr Infect Dis J* 2002; **21**(8): 769-77.
26. Pichichero ME, Blatter MM, Reisinger KS, et al. Impact of a birth dose of hepatitis B vaccine on the reactogenicity and immunogenicity of diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type b combination vaccination. *Pediatr Infect Dis J* 2002; **21**(9): 854-9.

Cochrane

Targeted Update

Immunogenicity of recombinant DNA HBV vaccines: same schedule, different intervals

Included studies

China 1992-C (Quasi-RCT)[1]
India 1994 (Quasi-RCT)[2]
India 2005 (RCT)[3]
India 2006 (RCT)[4]
Italy 1993-A (RCT)[5]
Italy 1997-A (Cohort)[6]
Italy 1998-A (Quasi-RCT)[7]
Tahiti 1994 (Quasi-RCT)[8]
Turkey 2004-A (Quasi-RCT)[9]
USA 1994-B (RCT)[10]

What's new

Latest search was performed: **June 2016**

There seemed to be no difference in rates of seroprotection with different intervals between doses in bo+2p and 3p dose schedules. For 2p schedules it is uncertain whether there is a difference as the available evidence is of very low quality.

There seemed to be no difference in antibody concentrations (GMCs) at 1-3 months post-vaccination and at longer follow up periods for bo+2p schedules. For 3p schedules, a 3,5,11 months vaccine schedule may result in higher antibody concentrations compared with a 2,4,6 months schedule, but the evidence is of low quality.

There is no evidence of the effects of different intervals between doses in clinical and safety outcomes.

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Background

In 1992, the WHO set a goal for all countries to integrate hepatitis B virus (HBV) vaccination into the Expanded Program on Immunization (EPI). The WHO recommends that all infants receive their first dose of HBV vaccine as soon as possible after birth. The birth dose should then be followed by two or three additional doses with a minimum interval of four weeks.

Objectives

To evaluate whether the administration of the same schedule with different intervals between doses of recombinant DNA hepatitis B vaccines for infants induces higher levels of seroconversion (from antibody negative to antibody positive) to hepatitis B surface antigen (anti-HBs), presented as the absolute levels of antibodies (GMCs) and the percentage levels of antibody to hepatitis B surface antigen (anti-HBs) with a threshold of ≥ 10 IU/ml, and clinical outcomes.

Search methods

Search strategies were developed specifically for each database. We searched The Cochrane Library, latest issue; MEDLINE (January 1946 to June 2016); EMBASE (January 1980 to June 2016); and CINAHL (January 1981 to June 2016). We also searched the metaRegister of Controlled Trials (mRCT) (http://www.controlled-trials.com/mrct/) in June 2016.

Selection criteria

Two reviewers independently screened and selected studies, discrepancies were resolved in consultation with a senior reviewer. Randomised controlled trials and prospective observational studies of children vaccinated with any licensed recombinant DNA hepatitis B vaccine, measuring immunological or clinical outcomes, were included. We also included retrospective studies from 2012.

Data collection and analysis

Two reviewers extracted data independently, discrepancies were resolved in consultation with a senior reviewer. Risk ratios were calculated for binary outcome data. For continuous data, values were log-transformed and presented as GMCs. Meta-analysis for most comparisons could not be performed because of lack of data.

Main Results

We included 10 studies (4 RCTs, 5 quasi-RCTs and 1 cohort study), published between 1992 and 2016.

The risk of bias was high for 5 included RCTs and quasi-RCTs, and serious for the cohort study.

One study compared different intervals in schedules with 2 primary doses (2p), 4 studies in schedules with 3 primary doses (3p) and the remaining studies in schedules with a birth dose followed by 2 primary doses (b0+2p).

There seemed to be no difference in rates of seroprotection with different intervals between doses in b0+2p and 3p dose schedules. For 2p schedules it is uncertain whether there is a difference as the available evidence is of very low quality.

There seemed to be no difference in antibody concentrations (GMCs) at 1-3 months post-vaccination and at longer follow up periods for b0+2p schedules. For 3p schedules, a 3,5,11 months vaccine schedule may result in higher antibody concentrations compared to a 2,4,6 months schedule, but the evidence is of low quality.

There is no evidence of the effects of different intervals between doses in clinical and safety outcomes.

Implications and conclusions

There is limited confidence in the evidence about the effects the administration of the same schedule with different intervals between doses on the outcomes of HBsAg and anti-HBs seroprotection. There appears to be no difference in seroprotection rates and antibody concentrations (GMCs) when vaccination schedules with containing b0+2p with different intervals compared. For 3p, there appears to be no difference in seroprotection rated, but there may be higher antibody concentrations with a 3,5,11 months schedule compared with a 2,4,6 months schedule; however, the evidence is of low quality. We are uncertain about the effects with 2p.

10.1.1 Summary of Findings: Recombinant DNA HBV vaccines, same schedules, different intervals (all ≥1 month)

***Patients and setting*: Infants in China, India, Italy, USA and Tahiti**
***Comparison:* Different intervals, birth dose + 2 primary doses (bo+2p)**

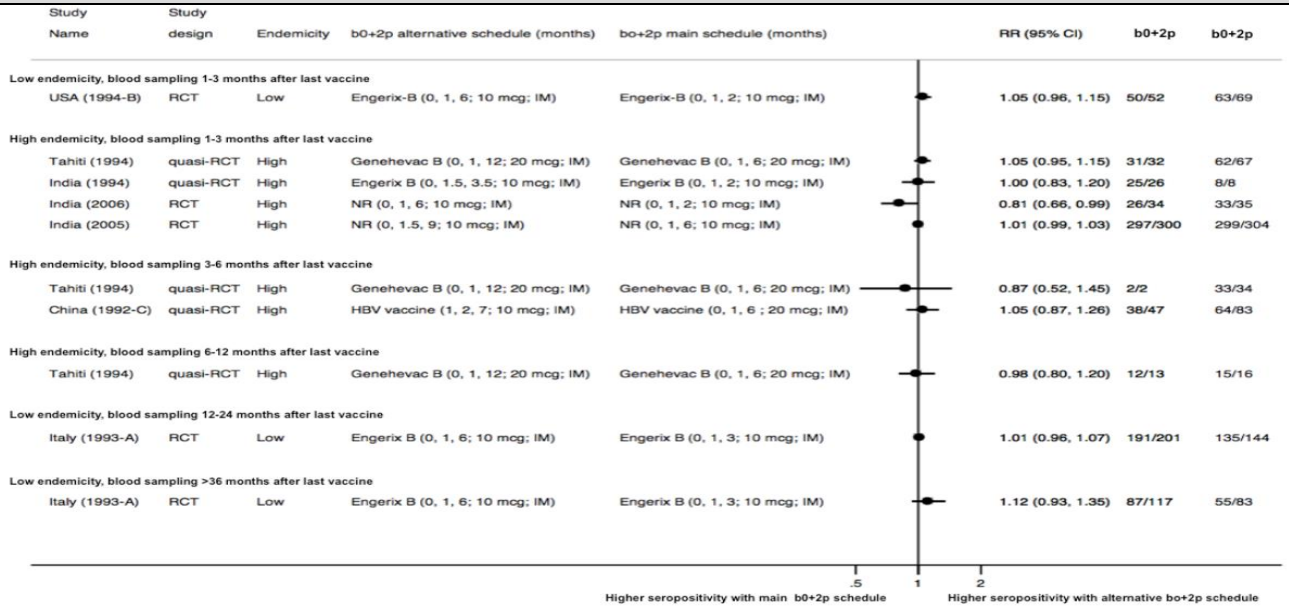
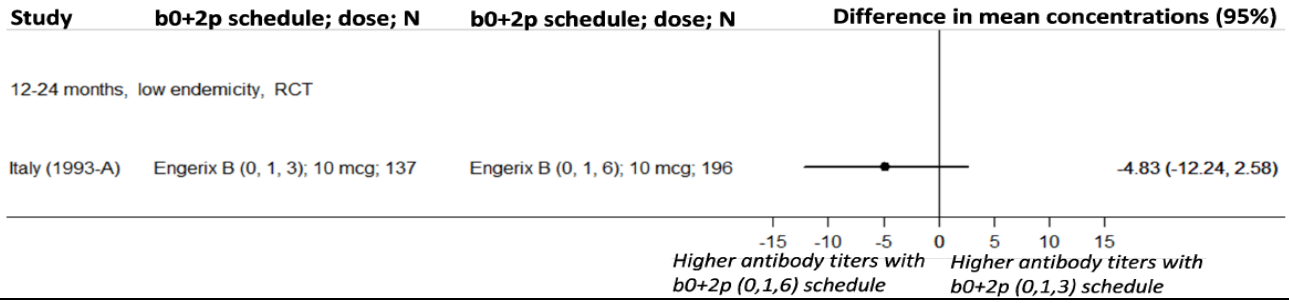
Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		bo+2p (Alternative interval, months)	bo+2p (Main interval, months) – in general the schedule for main was 0,1,2 or 0,1,6 months		
HBsAg seroprevalence	None of the included infants were HBsAg positive in serology performed 1-3 months after vaccination in both studies.	Low endemicity			⊕⊕OO LOW [1,2]
		0/117	0/83	Relative effect not estimable 1 RCT, 200 participants	
		High endemicity			
		0/26	0/8	Relative effect not estimable 1 Quasi-RCT, 34 participants	⊕OOO VERY LOW [2,3]
Anti-HBs seroprotection	All the studies reported vaccine intervals above the recommended 4 weeks. There was no evidence of a difference among comparisons, although our confidence in the findings is limited because of small samples and flaws in the conduct of included studies.	Low endemicity, blood sampling 1-3 months after last vaccine			⊕⊕OO LOW [1,2]
		50/52 (96.15%)	63/69 (91.30%)	RR 1.05 (0.96 to 1.15) 1 RCT, 121 participants	
		Low endemicity, blood sampling 12-24 months after last vaccine			
		191/201 (95.03%)	135/144 (93.75%)	1.01 (0.96 to 1.07) 1 RCT, 345 participants	
		Low endemicity, blood sampling > 36 months after last vaccine			
		87/117 (74.36%)	55/83 (66.27%)	1.12 (0.93 to 1.35) 1 RCT, 200 participants	
		High endemicity, blood sampling 1-3 months after last vaccine			⊕OOO VERY LOW [2,3]
		31/32 (96.88%)	62/67 (92.54%)	1.05 (0.95 to 1.15) 1 Quasi-RCT, 99 participants	
		25/26 (96.15%)	8/8 (100%)	1.0 (0.83 to 1.20) 1 Quasi-RCT, 34 participants	⊕OOO VERY LOW [2,3]
		26/34 (76.47%)	33/35 (94.29%)	0.81 (0.66 to 0.99) 1 RCT, 69 participants	⊕⊕OO LOW [1,2]
		297/300 (99.0%)	299/304 (98.36%)	1.01 (0.99 to 1.03) 1 RCT, 604 participants	

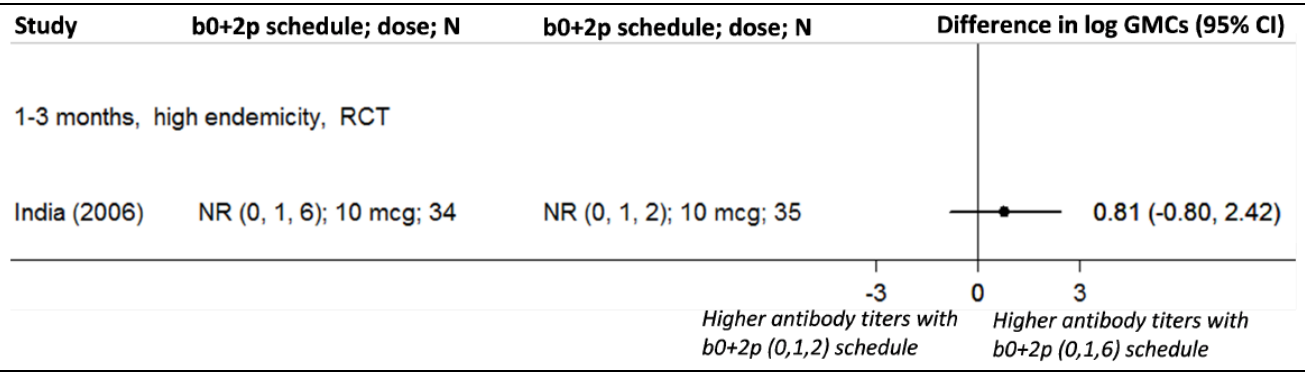
Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		bo+2p (Alternative interval, months)	**bo+2p (Main interval, months) – in general the schedule for main was 0,1,2 or 0,1,6 months**		
		High endemicity, blood sampling 3-6 months after last vaccine			⊕OOO VERY LOW [2,3]
		2/2	33/34	0.87 (0.52 to 1.45) 1 Quasi-RCT, 36 participants	
		38/47 (80.85%)	64/83 (77.11%)	1.05 (0.87 to 1.26) 1 Quasi-RCT, 130 participants	
		High endemicity, blood sampling 6-12 months after last vaccine			
		12/13	15/16	0.98 (0.80 to 1.20) 1 Quasi-RCT, 29 participants	
GMCs of anti-HBs	0,1,6 months vaccination schedule may result in little or no difference in anti-body concentrations compared to 0,1,3 months schedule.	Low endemicity			⊕⊕OO LOW [1,2]
		Not reported	Not reported	Difference in mean concentrations (95% CI) -4.83 (-12.24 to 2.58) 1 RCT, 333 participants	
	0,1,6 months vaccination schedule may result in little or no difference in anti-body concentrations compared to 0,1,2 months schedule.	High endemicity			
		Not reported	Not reported	Difference in log GMCs (95% CI) 0.81 (-0.80 to 2.42) 1 RCT, 69 participants	

[1]Downgraded 1 point for serious risk of bias[2]Downgraded 1 point for serious imprecision
[3]Downgraded 2 points for very serious risk of bias

10.1.1 Forest plots and summaries per outcome: Recombinant DNA HBV vaccines, same schedules, different intervals (all ≥1 month)

***Patients and setting*: Infants in China, India, Italy, USA and Tahiti**
***Comparison:* Different intervals, birth dose + 2 primary doses (bo+2p)**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection All the studies reported vaccine intervals above the recommended 4 weeks. There was no evidence of a difference among comparisons, although our confidence in the findings is limited because of small samples and flaws in the conduct of included studies.		⊕⊕OO LOW ⊕OOO VERY LOW
GMCs of anti-HBs *Low endemicity* 0,1,6 months vaccination schedule may result in little or no difference in anti-body concentrations compared to 0,1,3 months schedule. *High endemicity*		⊕⊕OO LOW


Study
b0+2p schedule; dose; N
b0+2p schedule; dose; N
Difference in log GMCs (95% CI)
1-3 months, high endemicity, RCT
India (2006)
NR (0, 1, 6); 10 mcg; 34
NR (0, 1, 2); 10 mcg; 35
0.81 (-0.80, 2.42)
-3
0
3
Higher antibody titers with b0+2p (0,1,2) schedule
Higher antibody titers with b0+2p (0,1,6) schedule

10.1.2 Summary of Findings: Recombinant DNA HBV vaccines, same schedules, different intervals (all ≥1 month)

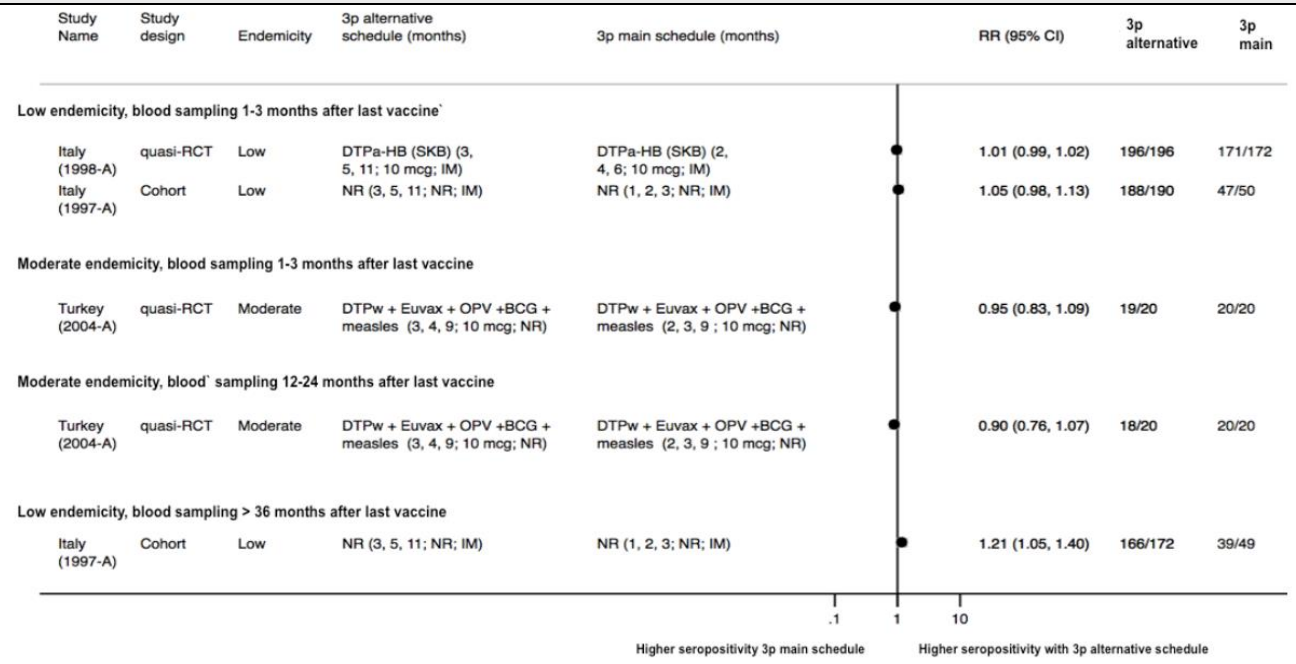
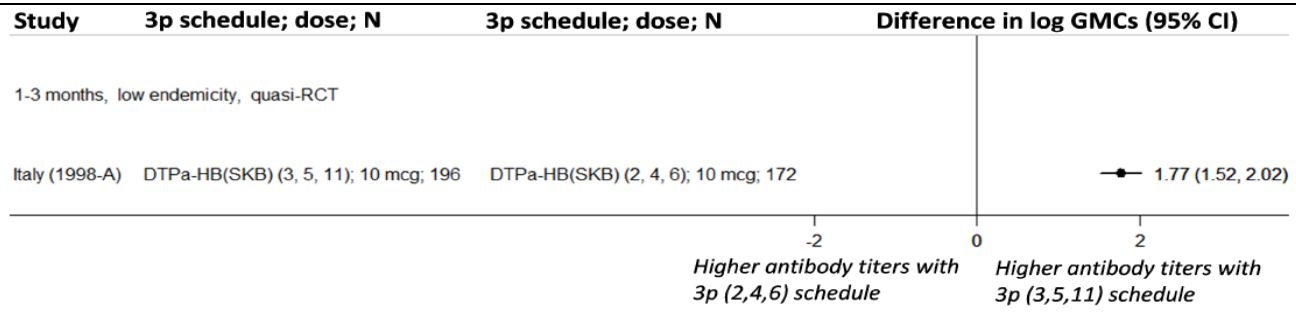
***Patients and setting*: Infants in Italy and Turkey**
***Comparison:* Different intervals, 3 primary doses (3p)**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		bo+3p (Alternative interval, months)	bo+3p (Main interval, months) – the schedule for main was 1,2,3; 2,3,9 or 2,4,6)		
HBsAg seroprevalence	None of the included studies assessed this outcome.	Not measured.	Not measured.	5 Studies, 869 participants	Not estimable
Anti-HBs seroprotection	All studies reported vaccine intervals above one month. It is uncertain whether there are any differences in seroprotection among the different vaccine schedules assessed, because the available evidence is of very low quality.	Low endemicity, blood sampling 1-3 months after last vaccine			⊕OOO VERY LOW [1,2]
		196/196	171/172	1.01 (0.99 to 1.02) 1 Quasi-RCT, 368 participants	
		188/190 (87.37%)	47/50 (94.0%)	1.05 (0.98 to 1.13) 1 Cohort study, 240 participants	
		Low endemicity, blood sampling > 36 months after last vaccine			
		166/172	39/49	1.21 (1.05 to 1.40) 1 Cohort study, 221 participants	
		Moderate endemicity, blood sampling 1-3 months after last vaccine			
		19/20	20/20	0.95 (0.83 to 1.09) 1 Quasi-RCT, 40 participants	
		Moderate endemicity, blood sampling 12-24 months after last vaccine			
		18/20	20/20	0.90 (0.76 to 1.07) 1 Quasi-RCT, 40 participants	
GMCs of anti-HBs	A 3,5,11 months vaccine schedule may result in higher antibody concentrations compared to a 2,4,6 months schedule, but the evidence is of low quality.	Not reported	Not reported	Difference in log GMCs (95% CI) 1.77 (1.52 to 2.02), corresponds to a GMC ratio of 5.87 (4.57 to 7.54) 1 Quasi-RCT, 368 participants	⊕⊕OO LOW [1]

[1]Downgraded 2 points for serious risk of bias (including quasi-RCTs and cohort studies)
[2]Downgraded 1 point for serious imprecision

10.1.2 Forest plots and summaries per outcome: Recombinant DNA HBV vaccines, same schedules, different intervals (all ≥ 1 month)

***Patients and setting*: Infants in Italy and Turkey**
***Comparison:* Different intervals, 3 primary doses (3p)**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection All studies reported vaccine intervals above one month. It is uncertain whether there are any differences in seroprotection among the different vaccine schedules assessed, because the available evidence is of very low quality.		⊕OOO VERY LOW
GMCs of anti-HBs A 3,5,11 months vaccine schedule may result in higher antibody concentrations compared to a 2,4,6 months schedule, but the evidence is of low quality.		⊕⊕OOO LOW

10.1.3 Summary of Findings: Recombinant DNA HBV vaccines, same schedules, different intervals (all ≥1 month)

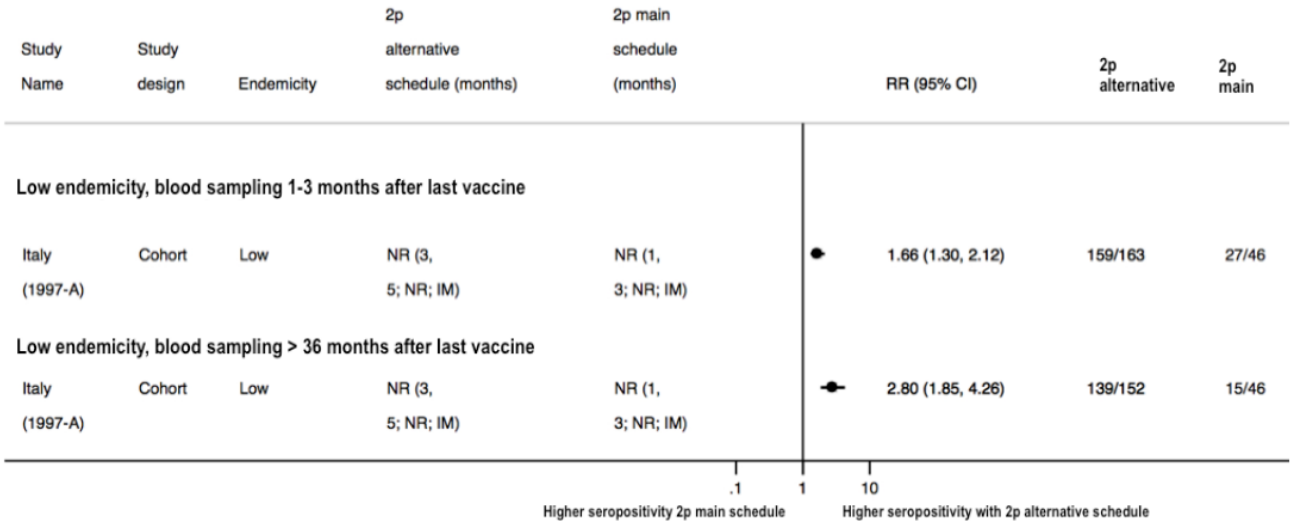
***Patients and setting*: Infants in Italy**
***Comparison:* Different intervals, 2 primary doses (2p)**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		2p, Alternative schedule (3, 5 months)	2p, Main schedule (1,3 months)		
HBsAg seroprevalence	This outcome was not assessed by the included study.	Not measured.	Not measured.	1 Cohort, 209 participants	Not estimable
Anti-HBs seroprotection	It is uncertain whether 3,5 months vaccine schedule results in higher seroprotection compared to 1, 3 months schedule, because the available evidence is of very low quality.	Low endemicity, blood sampling 1-3 months after last vaccine			
		159/163 (97.55%)	27/46 (58.70%)	1.66 (1.30 to 2.12) 1 Cohort study, 209 participants	⨁◯◯◯ VERY LOW [1,2]
		Low endemicity, blood sampling > 36 months after last vaccine			
		139/152 (91.45%)	15/46 (32.61%)	2.80 (1.85 to 4.26) 1 Cohort study, 198 participants	
GMCs of anti-HBs	This outcome was not assessed by the included study.	Not measured.	Not measured.	1 Cohort, 209 participants	Not estimable

[1]**Observational studies begin at low-quality evidence**
[1]**Downgraded 1 point for serious risk of bias**

10.1.3 Forest plots and summaries per outcome: Recombinant DNA HBV vaccines, same schedules, different intervals (all ≥ 1 month)

***Patients and setting*: Infants in Italy**
***Comparison:* Different intervals, 2 primary doses (2p)**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection It is uncertain whether 3,5 months vaccine schedule results in higher seroprotection compared to 1, 3 months schedule, because the available evidence is of very low quality.		⊕OOO VERY LOW

Bibliographic references

1. Qing L, Shuchen D, Qirong Z, et al. The comparison in efficacy between single use of HBV vaccine of different dosages and combined use of HBV vaccine and HBIG of different dosages. [Chinese]. *Acta Academiae Medicinae Shanghai* 1992; **19**(6): 448-52.
2. Mittal SK, Rao S, Kumari S, Aggarwal V, Prakash C, Thirupuram S. Simultaneous administration of hepatitis B vaccine with other E.P.I. vaccines. *Indian J Pediatr* 1994; **61**(2): 183-8.
3. Jain AK, Mittal SK, Ramji S, Chakravarti A. Hepatitis B vaccine in the EPI schedule. *Indian J Pediatr* 2005; **72**(8): 661-4.
4. Girisha KM, Kamat JR, Nataraj G. Immunological response to two hepatitis B vaccines administered in two different schedules. *Indian J Pediatr* 2006; **73**(6): 489-91.
5. Belloni C, Orsolini P, Martinetti M, et al. Control of hepatitis B: evaluation of two different vaccinal schedules in newborns from HBsAg negative mothers. *New Microbiol* 1993; **16**(3): 237-44.
6. Da Villa G, Pelliccia MG, Peluso F, Ricciardi E, Sepe A. Anti-HBs responses in children vaccinated with different schedules of either plasma-derived or HBV DNA recombinant vaccine. *Res Virol* 1997; **148**(2): 109-14.
7. Giammanco G, Moiraghi A, Zotti C, et al. Safety and immunogenicity of a combined diphtheria-tetanus-acellular pertussis-hepatitis B vaccine administered according to two different primary vaccination schedules. Multicenter Working Group. *Vaccine* 1998; **16**(7): 722-6.
8. Moulia-Pelat JP, Spiegel A, Martin PM, et al. A 5-year immunization field trial against hepatitis B using a Chinese hamster ovary cell recombinant vaccine in French Polynesian newborns: results at 3 years. *Vaccine* 1994; **12**(6): 499-502.
9. Artan R, Erol M, Velipasaoglu S, Yegin O. The effect of concurrent use of hepatitis B and Bacille Calmette-Guerin vaccination on anti-hepatitis B response. *Saudi Med J* 2004; **25**(12): 1939-42.
10. Goldfarb J, Baley J, Medendorp SV, 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**(1): 18-22.

Cochrane

Targeted Update

Immunogenicity of recombinant DNA HBV vaccines: booster vaccination

Included studies

Australia 2001-A (RCT)[1]
Australia, Belgium, Spain, Sweden 2005 (RCT-cohort)[2,3]
Australia, Belgium, Ukraine 2007 (RCT-cohort)[4,5]
Italy 1997-B (Cohort)[6]
South Africa 2013 (RCT)[7]
Thailand 1992-B (RCT-cohort)[8,9] (reports 2 studies)

What's new

Latest search was performed: **June 2016**

There is no evidence of a difference in seroprotection rates when a booster dose was given in both groups being compared. There is some evidence that 4p doses plus a booster gives higher antibody concentrations (GMCs) than 3p plus a booster.

When a booster dose was compared with no booster dose, there is some evidence that a booster dose gives a higher proportion of seroprotection and higher levels of antibody concentrations (GMCs) at longer follow up periods of up to 15 years.

There is no evidence of the effects of booster vaccination on clinical and safety outcomes.

Trusted evidence.
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Background

In 1992, the WHO set a goal for all countries to integrate hepatitis B virus (HBV) vaccination into the Expanded Program on Immunization (EPI). Currently the WHO does not recommend a booster dose.

Objectives

To evaluate whether the administration of booster doses of recombinant DNA hepatitis B vaccines induces higher levels of seroconversion (from antibody negative to antibody positive) to hepatitis B surface antigen (anti-HBs), presented as the absolute levels of antibodies (GMCs) and the percentage levels of antibody to hepatitis B surface antigen (anti-HBs) with a threshold of ≥ 10 IU/ml, and clinical outcomes.

Search methods

Search strategies were developed specifically for each database. We searched The Cochrane Library, latest issue; MEDLINE (January 1946 to June 2016); EMBASE (January 1980 to June 2016); and CINAHL (January 1981 to June 2016). We also searched the metaRegister of Controlled Trials (mRCT) (http://www.controlled-trials.com/mrct/) in June 2016.

Selection criteria

Two reviewers independently screened and selected studies, discrepancies were resolved in consultation with a senior reviewer. Randomised controlled trials and prospective observational studies of children vaccinated with any licensed recombinant DNA hepatitis B vaccine, measuring immunological or clinical outcomes, were included. We also included retrospective studies from 2012.

Data collection and analysis

Two reviewers extracted data independently, discrepancies were resolved in consultation with a senior reviewer. Risk ratios were calculated for binary outcome data. For continuous data, values were log-transformed and presented as GMCs. Meta-analysis for most comparisons could not be performed because of lack of data.

Main Results

We included 8 studies (2 RCTs, and 6 cohort studies), published between 1992 and 2016. Five of the cohorts began as an RCT, and the booster was given to a non-random sample of participants five years after primary vaccination.[3,5,9,10]

The risk of bias was unclear or low for the included RCTs and moderate or high for included cohort studies.

Three studies compared 3p and 1 booster with 2p and 1 booster; one study compared the effect of 1 or 2 boosters after 3p; two studies compared booster vaccination with no booster vaccination); and two studies 3p plus booster versus 4p plus booster.

There is no evidence of a difference in seroprotection rates when a booster dose was given in both groups being compared. There is some evidence that 4p doses plus a booster gives higher antibody concentrations (GMCs) than 3p plus a booster.

When a booster dose was compared with no booster dose, there is some evidence that a booster dose gives a higher proportion of seroprotection and higher levels of antibody concentrations (GMCs) at longer follow up periods of up to 15 years.

There is no evidence of the effects of booster vaccination on clinical and safety outcomes.

Implications and conclusions

There is limited confidence in the evidence about the effects of receiving different numbers of primary doses plus booster doses on the outcomes of HBsAg and anti-HBs seroprotection. A booster dose, when compared to no booster, appears to give higher rates of seroprotection, as well as higher levels of antibody concentrations.

14.1.1 Summary of Findings: Recombinant DNA HBV vaccines, booster vaccination

***Patients and setting*: Children and adolescents in Australia, Belgium, Spain, Sweden, USA and Ukraine**
***Comparison:* 3 primary doses + 1 booster (3p+1B) vs. 2 primary doses + 1 booster (2p+1B)**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		3p+1B	2p+1B		
Anti-HBs seroprotection	Data were available from three cohorts of adolescents:	Post-booster (one month after the two-year booster dose, subset of participants, not randomised)			
(Adolescents)	(1) In one of them adolescents, 11-15 years, received a booster dose two years after being randomised. (2) In two of them children 6-11 years were randomised, and a sub-sample received a booster dose 5 years after. Data could only be analysed for the adolescents cohort, but there was no evidence of a difference in seroprotection between schedules post-booster immunization. In all studies anti-HBs antibody concentration ≥10 mIU/mL was ≥ 94%.	64/68 (94.11%)	51/51 (100%)	0.94 (0.88, 1.01) 1 subset non-RCT, 119 participants	⨁⨁◯◯ LOW [1]

[1]Not downgraded (observational studies begin at low quality)

Forest plot not shown for this comparison; studies USA 2001-A[10]; Australia, Belgium, Spain, Sweden 2005[2,3]; Australia, Belgium, Ukraine 2007[4,5]

14.1.2 Summary of Findings: Recombinant DNA HBV vaccines, booster vaccination

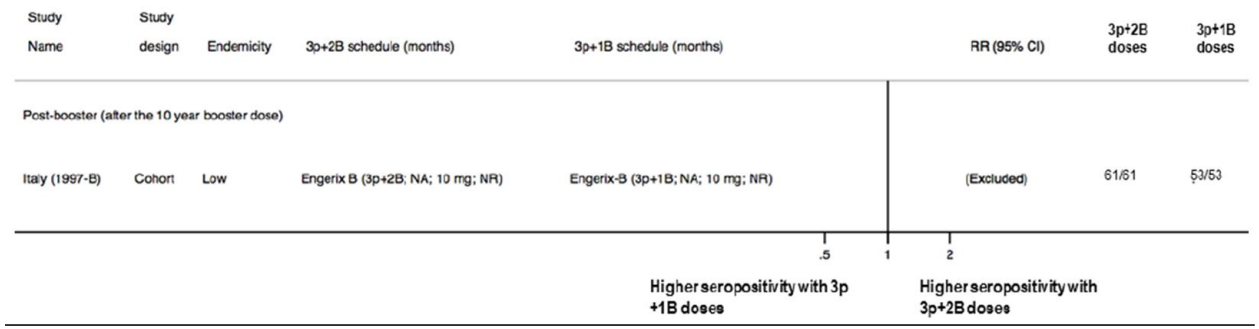
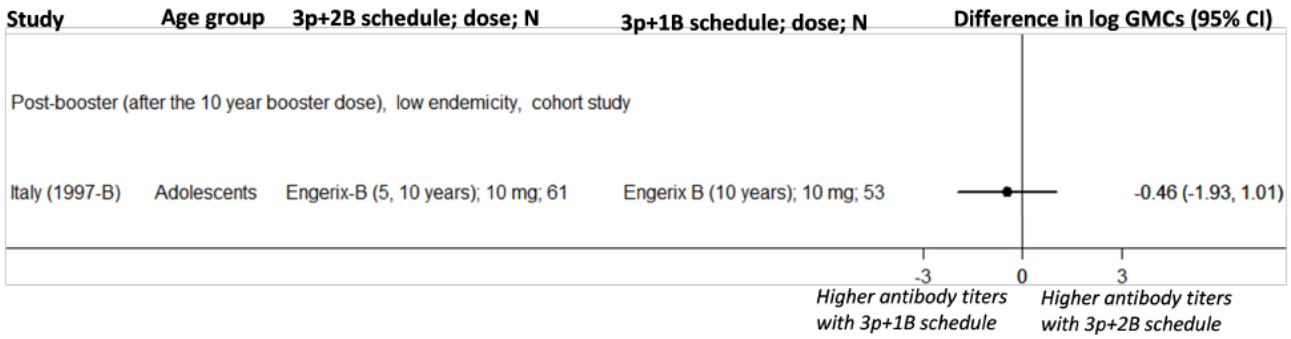
***Patients and setting*: Children in Italy**
***Comparison:* 3 primary doses + 1 booster (3p+1B) vs. 3 primary doses + 2 booster (3p+2B) (different number of booster doses)**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		(3p+1B)	(3p+2B)		
HBsAg seroprevalence	The included study did not report this outcome.				
Anti-HBs seroprotection	All participants were seropositive for anti-HBs 1-3 months post the second booster immunization.	Post-booster (after the ten-year booster dose)			⊕OOO VERY LOW [1,2]
		53/53	61/61	RR=1 1 Cohort study, 114 participants	
GMCs of anti-HBs	There was no evidence of a difference in antibody concentrations (GMCs) between 3p+1B and 3p+2B schedules ten years after the primary vaccination.	NR	NR	Difference in log GMCs (95% CI) -0.46 (-1.93 to 1.01) 1 Cohort study, 114 participants	⊕OOO VERY LOW [1,2]

[1]**Observational studies begin at low quality**
[2]**Downgraded 1 point for imprecision (low number of participants)**
NR – not reported

14.1.2 Forest plots and summaries per outcome: Recombinant DNA HBV vaccines, booster vaccination

***Patients and setting*: Children in Italy**
***Comparison:* 3 primary doses + 1 booster (3p+1B) vs. 3 primary doses + 2 booster (3p+2B) (different number of booster doses)**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection All participants were seropositive for anti-HBs 1-3 months post the second booster immunization.		⊕OOO VERY LOW
GMCs of anti-HBs There was no evidence of a difference in antibody concentrations (GMCs) between 3p+1B and 3p+2B schedules ten years after the primary vaccination.		⊕OOO VERY LOW

14.1.3 Summary of Findings: Recombinant DNA HBV vaccines, same schedules, booster vaccination

***Patients and setting*: Children in Thailand**
***Comparison:* Booster dose vs. no booster dose**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Booster dose	No booster dose		
HBsAg seroprevalence	Outcome not reported by the two included studies.	NR	NR	1 Cohort study, 161 participants 1 RCT, 87 participants	Not estimable
Anti-HBs seroprotection	1 Cohort study, outcome measured at multiple time points; *Comparison: 4 primary doses plus 1 booster dose (4p+1B) vs. 4 primary doses without a booster dose (4p)* After the booster vaccination, higher seroprotection was found for the 4p+1B schedule at 15 years.	**Pre-booster**			⨁⨁⨁◯ VERY LOW [1,2]
		87/97	63/64	RR 0.91 (0.85 to 0.98)	
		12-24 months (after booster)			
		88/90	61/63	RR 1.01 (0.96 to 1.07)	
		24-36 months (after booster)			
		82/84	55/58	RR 1.03 (0.96 to 1.10)	
		>36 months (after booster)			
		77/79	54/56	RR 1.01 (0.95 to 1.08)	
		15 years (after booster)			
		47/56	23/36	RR 1.39 (1.05 to 1.84)	
	A subset of a randomised trial, outcome measured at multiple time points; *Comparison: 3 primary doses plus 1 booster dose (3p+1B) vs. 3 primary doses without a booster dose (3p)* After booster immunization, higher seroprotection was found in the 3p+1B schedule at 24-36 months, 15 years and > 36 months.	**Pre-booster**			⨁⨁◯◯ LOW [2,3]
		34/43	38/44	0.92 (0.75 to 1.11)	
		12-24 months (after booster)			
		35/38	30/40	1.23 (1.00 to 1.50)	
		24-36 months (after booster)			
		33/37	29/41	1.26 (1.01 to 1.58)	
		>36 months (after booster)			
		30/32	23/34	1.39 (1.08 to 1.78)	
		15 years (after booster)			
		16/19	11/25	1.91 (1.18 to 3.10)	
GMCs of anti-HBs	1 Cohort study, outcome measured at multiple time points; *Comparison: 4 primary doses plus 1 booster dose*	**Pre-booster (5 year)**			⨁⨁⨁◯ VERY LOW [1,2]
		NR	NR	Difference in log GMCs (95% CI) -1.23 (-1.75 to -0.71),	

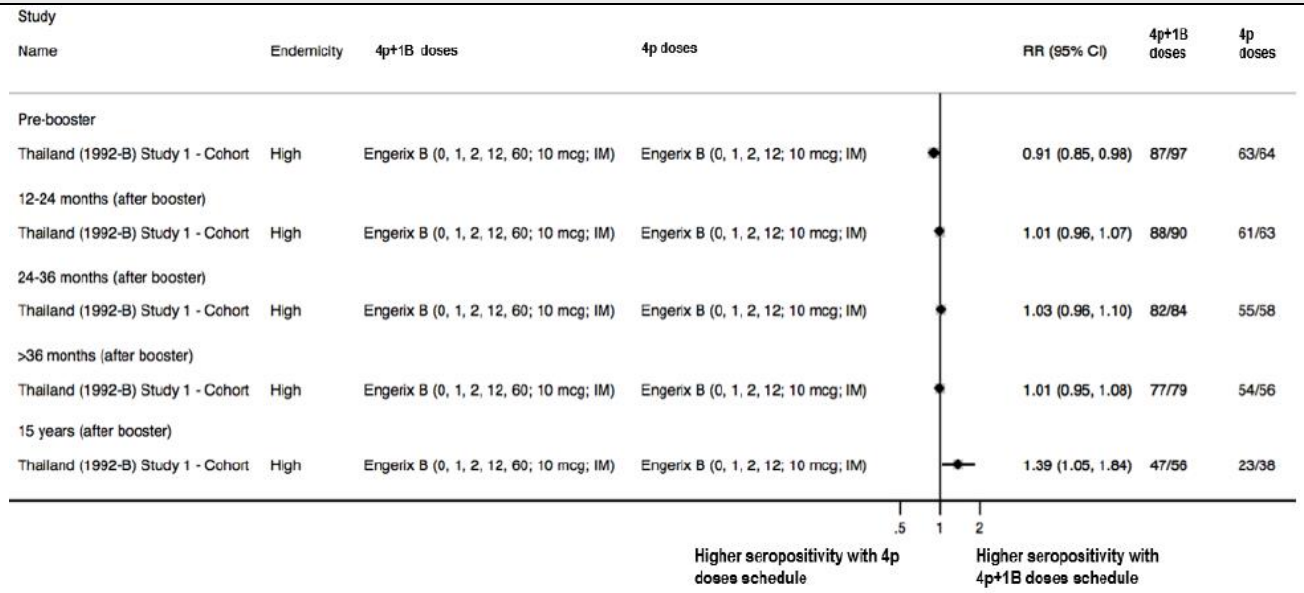
Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Booster dose	No booster dose		
	(4p+1B) vs. 3 primary doses without a booster dose (3p) GMCs were higher for the group receiving a booster dose (4p+1B) at 12-24 months post booster. This effect was continued up to 15 years after the booster dose.			Corresponds to a GMC ratio of 0.29 (0.17 to 0.49)	
		12-24 months (after booster)			
		NR	NR	Difference in log GMCs 1.96 (1.35 to 2.58), Corresponds to a GMC ratio of 7.10 (3.86 to 13.20)	
		24-36 months (after booster)			
		NR	NR	Difference in log GMCs 1.96 (1.33 to 2.58)	
		> 36 months (after booster)			
		NR	NR	Difference in log GMCs 1.65 (1.02 to 2.29)	
		> 36 months (15 years after booster)			
		NR	NR	Difference in log GMCs 1.03 (0.34 to 1.73)	
	A subset of a randomised trial, outcome measured at multiple time points; *Comparison: 3 primary doses plus 1 booster dose (3p+1B) vs. 3 primary doses without a booster dose (3p)* After booster immunization, GMCs were significantly higher for the group receiving a booster dose (3p+1B). This effect was continued up to 15 years after the booster dose.	**Pre-booster (5 years)**			⊕⊕OO LOW [2 3]
		NR	NR	Difference in log GMCs (95% CI) -0.05 (-0.68 to 0.59)	
		12-24 months (after booster)			
		NR	NR	Difference in log GMCs 2.84 (1.95 to 3.72), Corresponds to a GMC ratio of 17.12 (7.03 to 41.26)	
		24-36 months (after booster)			
		NR	NR	Difference in log GMCs 2.86 (1.98 to 3.74)	
		> 36 months (after booster)			
		NR	NR	Difference in log GMCs 2.18 (1.35 to 3.01)	

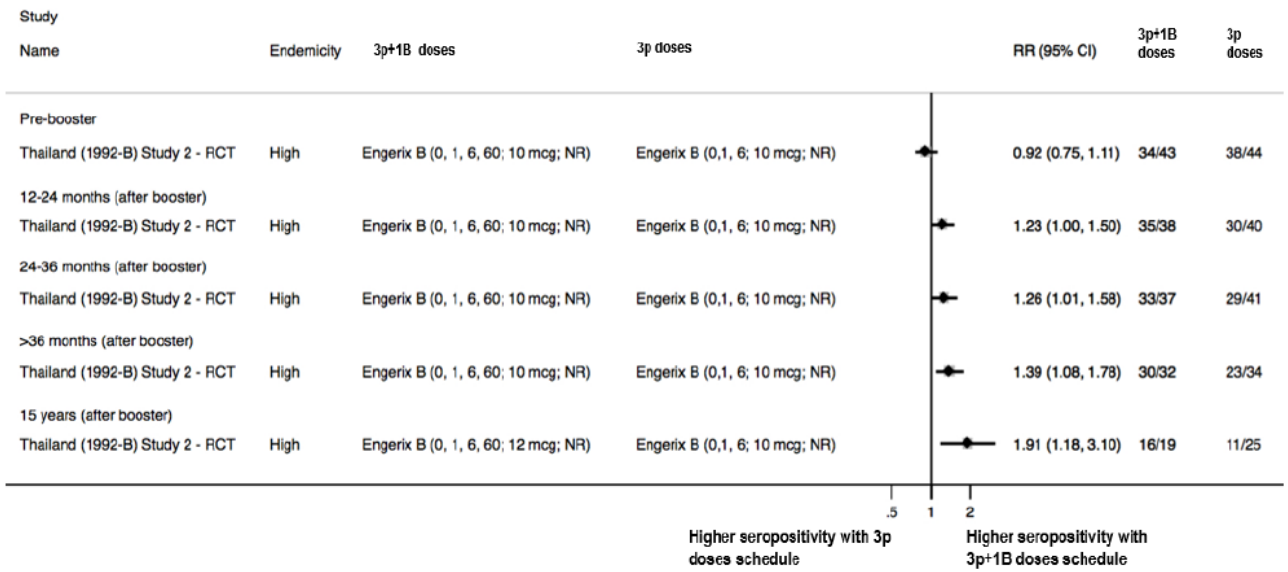
Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		Booster dose	No booster dose		
		> 36 months (15 years after booster)			
		NR	NR	Difference in log GMCs 1.96 (0.97 to 2.95)	

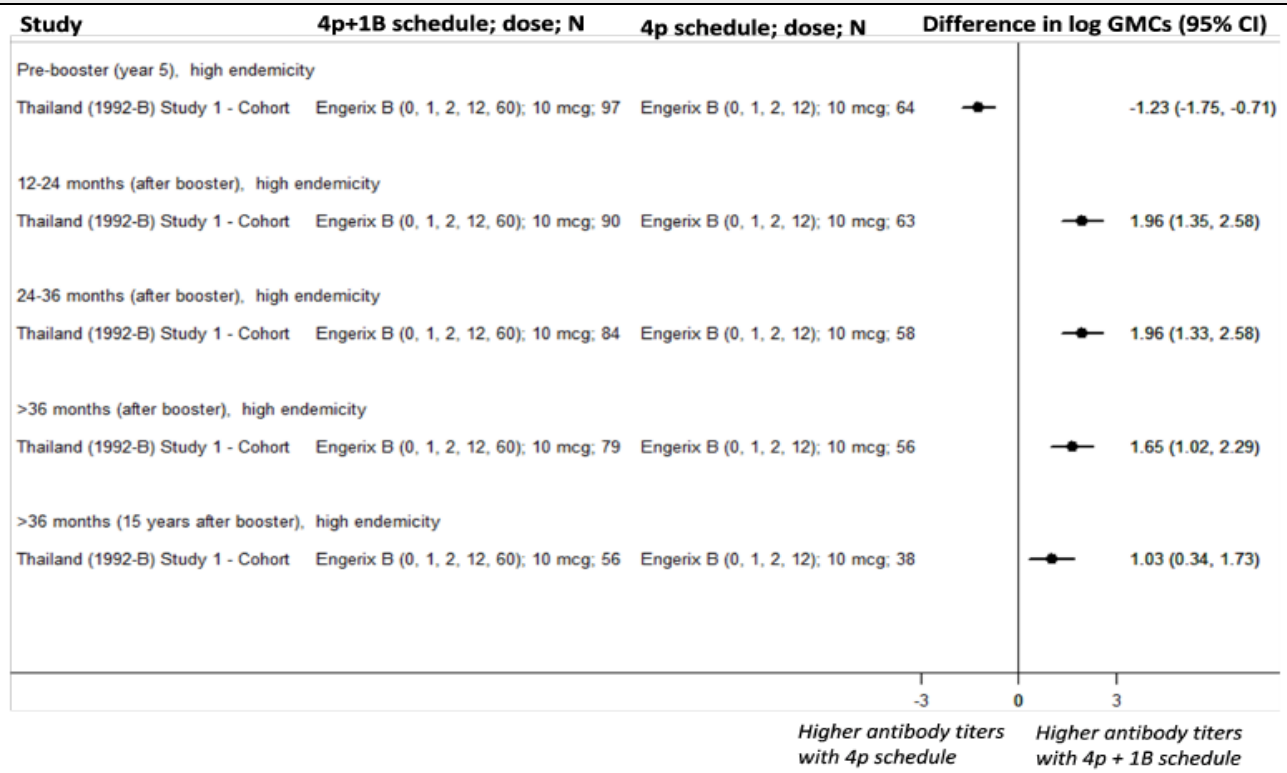
[1]Observational studies begin at low quality
[2]Downgraded 1 point for serious imprecision (small sample size)
[3]Downgraded for risk of bias (non-random comparison)
NR – Not Reported

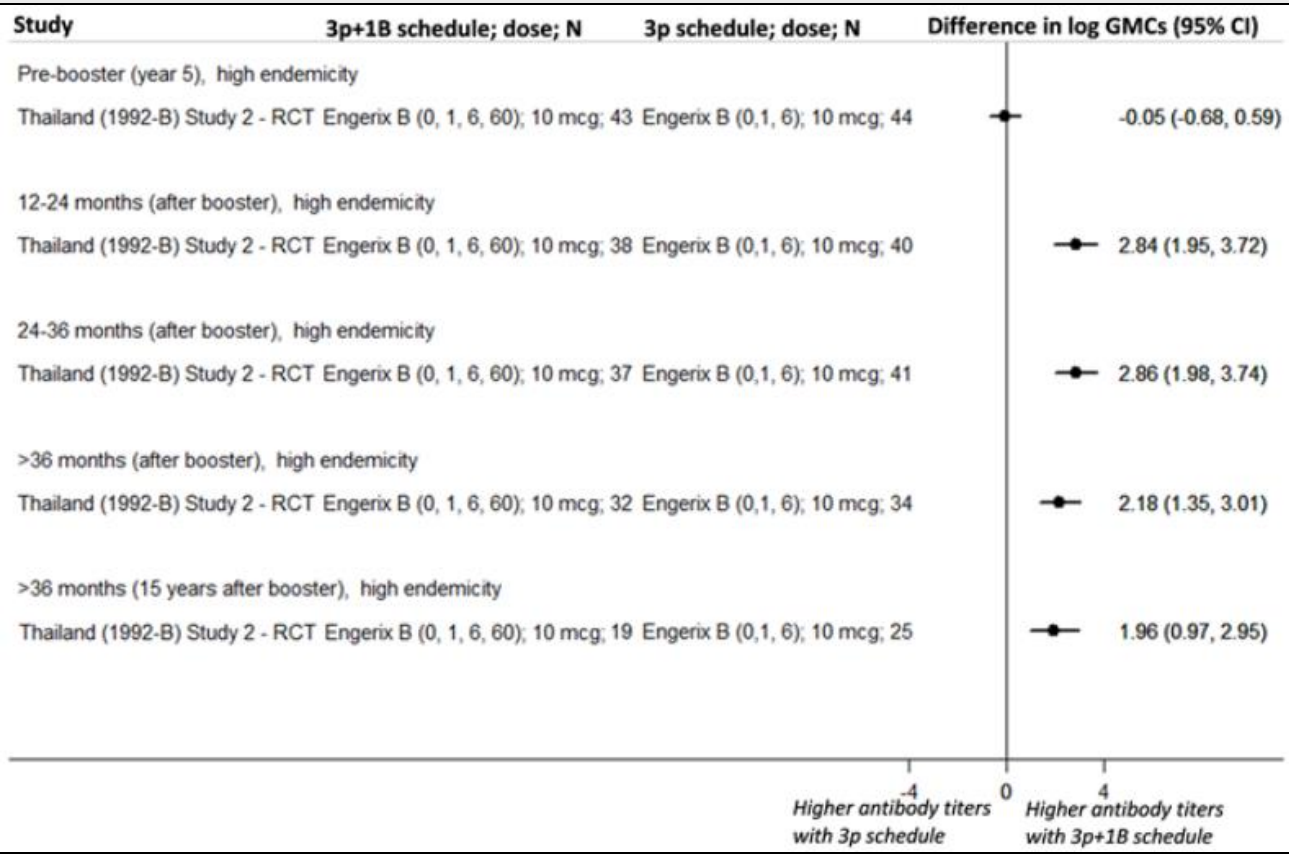
14.1.3 Forest plots and summaries per outcome: Recombinant DNA HBV vaccines, same schedules, booster vaccination

***Patients and setting*: Children in Thailand**
***Comparison:* Booster dose vs. no booster dose**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection After the booster vaccination, higher seroprotection was found for the 4p+1B schedule at 15 years.		⊕⊕⊕O VERY LOW

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection After booster immunization, higher seroprotection was found in the 3p+1B schedule at 24-36 months, 15 years and > 36 months.		⊕⊕OO LOW

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
GMCs of anti-HBs GMCs were higher for the group receiving a booster dose (4p+1B) at 12-24 months post booster. This effect was continued up to 15 years after the booster dose.		⊕⊕⊕O VERY LOW

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
GMCs of anti-HBs After immunization, GMCs were significantly higher for the group receiving a booster dose (3p+1B). This effect was continued up to 15 years after the booster dose.		⊕⊕OO LOW

14.1.4 Summary of Findings: Recombinant DNA HBV vaccines, booster vaccination

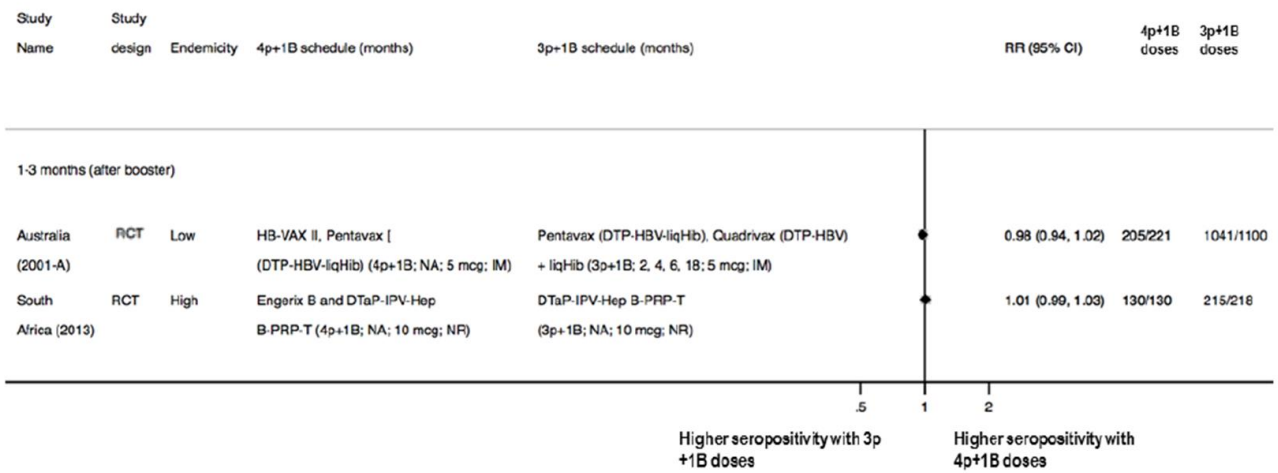
***Patients and setting*: Children in Australia and South Africa**
***Comparison:* 3 primary doses + 1 booster dose (3p+1B) vs. 4 primary doses + 1 booster dose (4p+1B)**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		4p+1B	3p+1B		
HBsAg seroprevalence	None of the two included studies reported this outcome.	Not reported.	Not reported	1 RCT, 348 participants 1 Cohort study, 1321 participants	Not estimable
Anti-HBs seroprotection	There was no evidence of a difference in seroprotection between schedules 1-3 months after booster immunization.	1-3 months after booster vaccination			⊕⊕⊕O MODERATE[1]
		205/221 (92.76%)	1041/1100 (94.64%)	RR 0.98 (0.94 to 1.02) 1 RCT, 1321 participants	
		130/130 (100%)	215/218 (98.6%)	RR 1.01 (0.99 to 1.03) 1 RCT, 348 participants	⊕⊕⊕O MODERATE[1]
GMCs of anti-HBs	Antibody concentrations (GMCs) were higher 1-3 months after booster vaccination.	1 RCT, 348 participants 1-3 months (after booster vaccination)			⊕⊕⊕O MODERATE[1]
		Not reported.	Not reported.	Difference in log GMCs (95% CI): -2.27 (-2.70 to -1.85), Corresponds to a GMC ratio of 0.10 (0.07 to 0.16) 1 RCT, 348 participants	

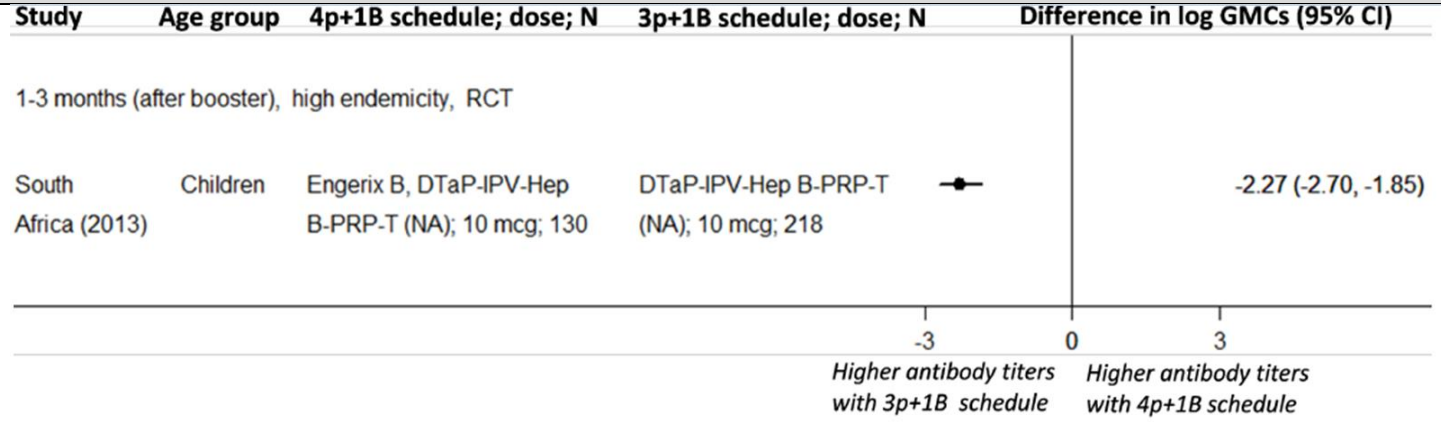
[1]**Downgraded 1 point for serious risk of bias – includes cohort study**

14.1.4 Forest plots and summaries per outcome: Recombinant DNA HBV vaccines, booster vaccination

Patients and setting: Children in Australia and South Africa
Comparison: 3 primary doses + 1 booster dose (3p+1B) vs. 4 primary doses + 1 booster dose (4p+1B)

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection There was no evidence of a difference in seroprotection between schedules 1-3 months after booster immunization.		1-3 months after booster ⊕⊕⊕O MODERATE ⊕⊕⊕O MODERATE

Outcome and	Forest plot	Certainty of the evidence

summary of results		(GRADE)
GMCs of anti-HBs Antibody concentrations (GMCs) were higher in the 3p+1b schedule 1-3 months after booster vaccination.		⊕⊕⊕O MODERATE

Bibliographic references

1. Nolan T, Hogg G, Darcy MA, Skeljo M, Carlin J, Boslego J. A combined liquid Hib (PRP-OMPC), hepatitis B, diphtheria, tetanus and whole-cell pertussis vaccine: controlled studies of immunogenicity and reactogenicity. *Vaccine* 2001; **19**(15-16): 2127-37.
2. Roberton D, Marshall H, Nolan TM, et al. Reactogenicity and immunogenicity profile of a two-dose combined hepatitis A and B vaccine in 1-11-year-old children. *Vaccine* 2005; **23**(43): 5099-105.
3. Marshall H, Nolan T, Diez Domingo J, et al. Long-term (5-year) antibody persistence following two- and three-dose regimens of a combined hepatitis A and B vaccine in children aged 1-11 years. *Vaccine* 2010; **28**(27): 4411-5.
4. Heron L, Selnikova O, Moiseieva A, et al. Immunogenicity, reactogenicity and safety of two-dose versus three-dose (standard care) hepatitis B immunisation of healthy adolescents aged 11-15 years: a randomised controlled trial. *Vaccine* 2007; **25**(15): 2817-22.
5. Van Damme P, Moiseeva A, Marichev I, et al. Five years follow-up following two or three doses of a hepatitis B vaccine in adolescents aged 11-15 years: a randomised controlled study. *BMC Infect Dis* 2010; **10**: 357.
6. Resti M, Azzari C, Mannelli F, Rossi ME, Lionetti P, Vierucci A. Ten-year follow-up study of neonatal hepatitis B immunization: are booster injections indicated? *Vaccine* 1997; **15**(12-13): 1338-40.
7. Madhi SA, Koen A, Cutland C, Groome M, Santos-Lima E. Antibody persistence and booster vaccination of a fully liquid hexavalent vaccine coadministered with measles/mumps/rubella and varicella vaccines at 15-18 months of age in healthy South African infants. *Pediatr Infect Dis J* 2013; **32**(8): 889-97.
8. Poovorawan Y, Sanpavat S, Pongpunglert W, et al. Long term efficacy of hepatitis B vaccine in infants born to hepatitis B e antigen-positive mothers. *Pediatr Infect Dis J* 1992; **11**(10): 816-21.
9. Poovorawan Y, Chongsrisawat V, Theamboonlers A, Bock HL, Leyssen M, Jacquet J-M. Persistence of antibodies and immune memory to hepatitis B vaccine 20 years after infant vaccination in Thailand. *Vaccine* 2010; **28**(3): 730-6.
10. Cassidy WM, Watson B, Ioli VA, Williams K, Bird S, West DJ. A randomized trial of alternative two- and three-dose hepatitis B vaccination regimens in adolescents: antibody responses, safety, and immunologic memory. *Pediatrics* 2001; **107**(4): 626-31.

Cochrane

Targeted Update

Immunogenicity of recombinant DNA HBV vaccines: catch-up vaccination

Included studies

Australia, Belgium, Spain, Sweden 2005 (RCT)[1]
Australia, Belgium, Ukraine 2007 (RCT)[2]
Belgium 1999 (RCT)[3]
Belgium, Czech Republic 2002 (RCT)[4]
China 1986-A (RCT)[5]
India 2002 (RCT)[6]
Italy 1998-B (RCT)[7]
Philippines 2005 (RCT)[8]
Turkey 2005 (RCT)[9]
USA 2001-A (RCT)[10]

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Latest search was performed: **June 2016**

There may be no difference in the proportion of children and adolescents becoming seroprotected 1-3 months post-vaccination when 2 primary catch-up doses are compared with 3 primary catch-up doses; these results remained consistent after a longer follow up period of 12 years.

There is some evidence indicating that catch-up vaccination schedules with 3 doses were associated with higher antibody concentrations (GMCs) at 1-3 months post-vaccination and at longer follow up periods, when compared with 2 primary catch-up doses.

Results indicate there may be little or no difference in rates of serious adverse events when comparing 2 doses with 3 doses in children and adolescents.

There is no evidence of the effects of catch up vaccination in clinical outcomes.

Background

In 1992, the WHO set a goal for all countries to integrate hepatitis B virus (HBV) vaccination into the Expanded Program on Immunization (EPI). The WHO recommends a catch-up vaccination for children in areas with low coverage, as well as for age-specific cohorts and people with risk factors for acquiring HBV infection.

Objectives

To evaluate whether the administration of different numbers of doses of catch-up vaccination of recombinant DNA HBV vaccines induces higher levels of seroconversion (from antibody negative to antibody positive) to hepatitis B surface antigen (anti-HBs), presented as the absolute levels of antibodies (GMCs) and the percentage levels of antibody to hepatitis B surface antigen (anti-HBs) with a threshold of ≥ 10 IU/ml, and clinical outcomes.

Search methods

Search strategies were developed specifically for each database. We searched The Cochrane Library, latest issue; MEDLINE (January 1946 to June 2016); EMBASE (January 1980 to June 2016); and CINAHL (January 1981 to June 2016). We also searched the metaRegister of Controlled Trials (mRCT) (http://www.controlled-trials.com/mrct/) in June 2016.

Selection criteria

Two reviewers independently screened and selected studies, discrepancies were resolved in consultation with a senior reviewer. Randomised controlled trials and prospective observational studies of children vaccinated with any licensed recombinant DNA HBV vaccine, measuring immunological or clinical outcomes, were included. We also included retrospective studies from 2012.

Data collection and analysis

Two reviewers extracted data independently, discrepancies were resolved in consultation with a senior reviewer. Risk ratios were calculated for binary outcome data. For continuous data, values were log-transformed and presented as GMCs. Meta-analysis for most comparisons could not be performed because of lack of data.

Main Results

We included 10 studies (10 RCTs), published between 1986 and 2016.

The risk of bias was high for 3 included RCTs.

Most studies compared 3 primary dose catch-up schedules with 2 primary dose catch-up schedules. One study compared 4 primary dose catch-up schedules with 3 primary dose catch-up schedules.

There may be no difference in the proportion of children and adolescents becoming seroprotected 1-3 months post-vaccination when 2 primary catch-up doses are compared with 3 primary catch-up doses; these results remained consistent after a longer follow-up period 12 years. At 22 years in one study, seroprotection was higher with 3p than with 2p; however, follow-up was very low (<20%), and it is not possible to draw conclusions on this results.

There is some evidence indicating that catch-up vaccination schedules with 3 doses were associated with higher antibody concentrations (GMCs) at 1-3 months post-vaccination and at longer follow-up periods when compared with 2 primary catch-up doses.

Results suggest little or no difference in rates of serious adverse events when comparing 2p vs. 3p schedules in children and adolescents. There is no evidence of the effects of catch up vaccination in clinical outcomes.

Implications and conclusions

There is limited confidence in the evidence about the effects of catch-up vaccination in children and adolescents on the outcomes of HBsAg and anti-HBs seroprotection. Catch-up vaccination schedules containing 3 primary doses appear to be associated with higher antibody concentrations (GMCs) when compared with catch-up vaccination schedules containing 2 primary doses.

13.1.1 Summary of Findings: Recombinant DNA HBV vaccines, catch up vaccination

***Patients and setting*: Children and adolescents in Australia, China, Pakistan, USA, Belgium, Czech Republic, India, Turkey and Ukraine**
***Comparison:* Recombinant DNA HBV vaccines, 3 primary doses versus 2 primary doses**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		3 primary doses (3p)	2 primary doses (2p)		
HBsAg seroprevalence	One study in a high endemicity region, comparing three dose (0, 1, 6 months) versus two dose (0, 1 month) schedule. None of the participants were HBsAg positive in serology performed at 5, 12 and 22 years after vaccination.	0 events	0 events	Relative effect 1. 1 RCT, 201 participants	⨁⨁◯◯ LOW [1,2]
Anti-HBs seroprotection	Results from most studies suggest little or no difference in seroprotection among schedules. However at 22 years seroprotection was higher with 3p than with 2p; however, the follow-up was very low.	1-3 months after last vaccination (Low, Moderate and High endemicity)			
		Results not pooled; see Forest plot for individual study results		Results not pooled; see Forest plot for individual study results 8 RCTs Number participants varied, range 91 to 664.	⨁⨁◯◯ LOW [1,2]
		6-22 years' follow-up (Low and High endemicity)			
		Results not pooled; see Forest plot for individual study results		Results not pooled; see Forest plot for individual study results 5 RCTs Number participants varied, range 34 to 307.	
GMCs of anti-HBs	A 0, 1, 6 months schedule probably leads to	Children: Low endemicity, 1-3 months post vaccination			

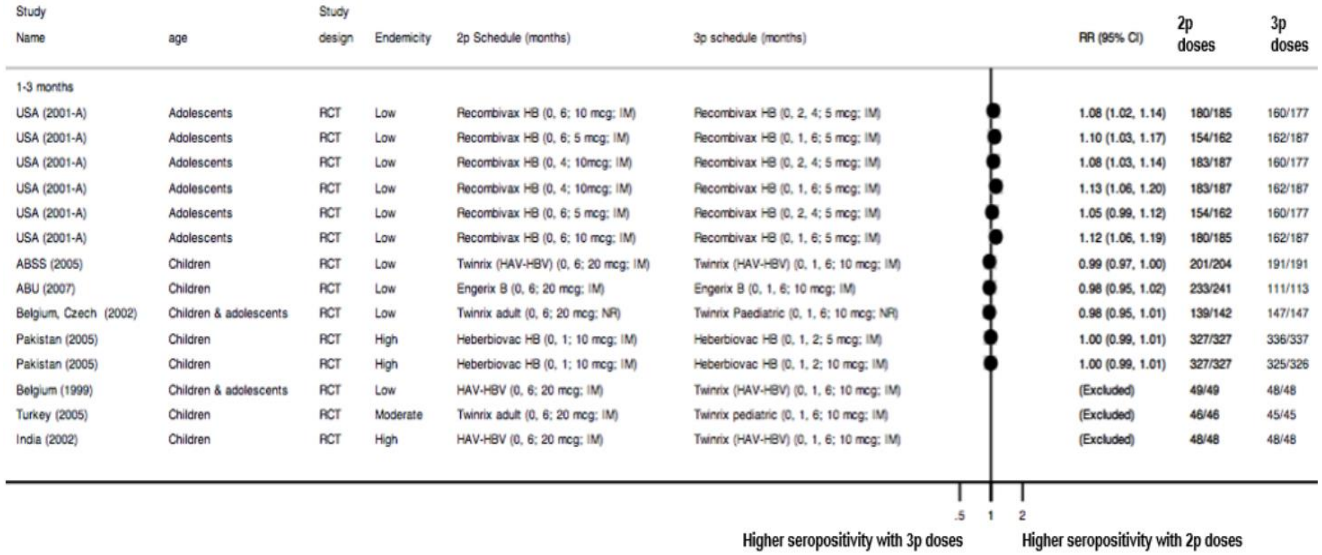
Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		3 primary doses (3p)	2 primary doses (2p)		
	slightly higher antibody concentrations compared to a 0, 6 months schedule.	Not reported.	Not reported.	Difference in log GMCs (95% CI): -0.74 (-1.15 to -0.33), Corresponds to a GMC ratio of 0.48 (0.32 to 0.72) 2 RCTs, 749 participants	⊕⊕⊕O MODERATE[1]
		Children: Low endemicity, > 36 months			
		Not reported.	Not reported.	Difference in log GMCs (95% CI): -0.64 (-1.07 to -0.20) 1 RCT, 206 participants	
	A 0, 1, 6 months schedule may lead to little or no difference in antibody concentrations compared to a 0, 6 months schedule.	Children: Moderate endemicity, 1-3 months post vaccination			⊕⊕OO LOW[1,2]
		Not reported.	Not reported.	Difference in log GMCs (95% CI): -0.64 (-1.49 to 0.21) 1 RCT, 91 participants	
	A 0, 1, 6 months schedule probably leads to slightly higher antibody concentrations compared to a 0, 6 months schedule.	Children: High endemicity, 1-3 months post vaccination			⊕⊕⊕O MODERATE[1]
		Not reported.	Not reported.	Difference in log GMCs (95% CI): **0, 1 month (10 mcg) vs. 0, 1, 2 months (5 mcg):** -0.27 (-0.39 to -0.15) 1 RCT, 664 participants **0, 1 month (10 mcg) vs. 0, 1, 2 months (10 mcg):** -0.51 (-0.62 to -0.40) 1 RCT, 653 participants	
	A 0, 1, 6 months schedule may lead to little or	Children and adolescents: Low endemicity, 1-3 months post vaccination			⊕⊕OO

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		3 primary doses (3p)	2 primary doses (2p)		
	no difference in antibody concentrations compared to a 0, 6 months schedule.	Not reported	Not reported	Difference in log GMCs (95% CI): -0.13 (-0.47 to 0.21) 2 RCTs, 396 participants	LOW[1,2]
		Children and adolescents: Low endemicity, 12-24 months post vaccination			
		Not reported	Not reported	Difference in log GMCs (95% CI): 0.06 (-0.32 to 0.45) 2 RCTs, 250 participants	

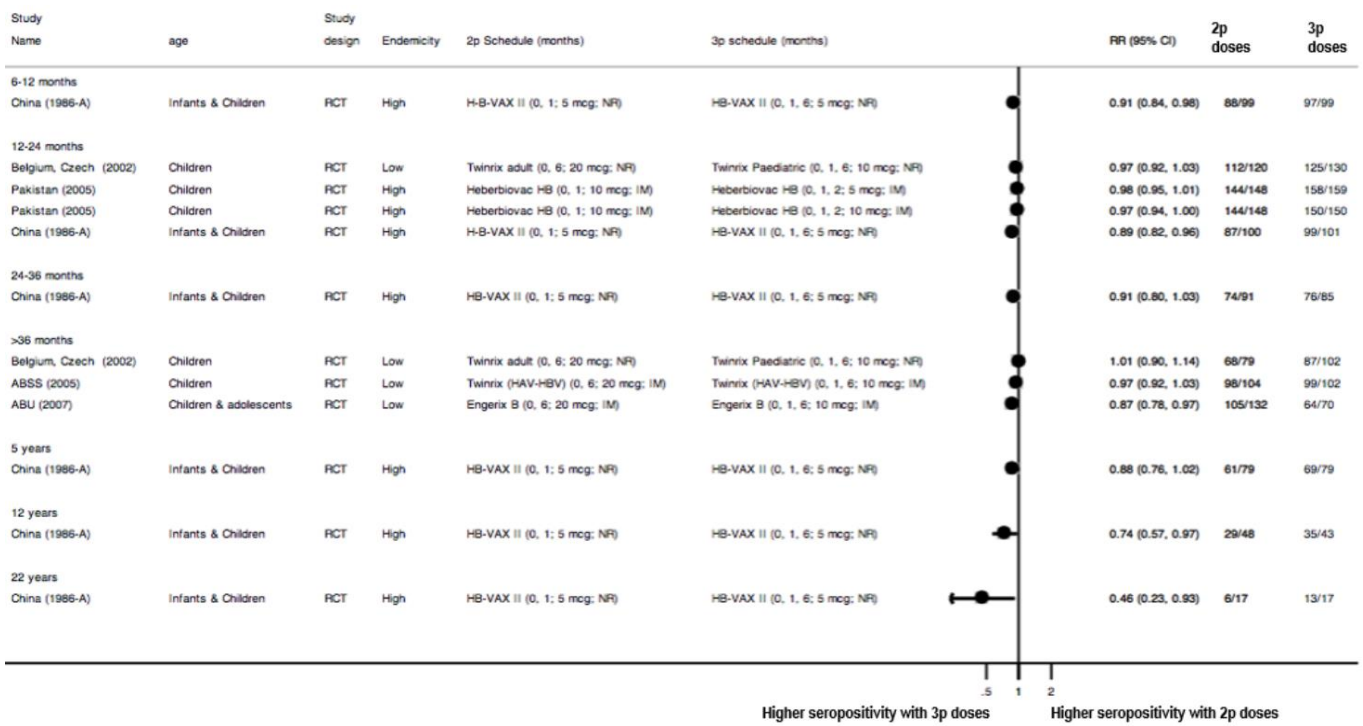
[1]Downgraded 1 point for serious risk of bias
[2]Downgraded 1 point for serious imprecision

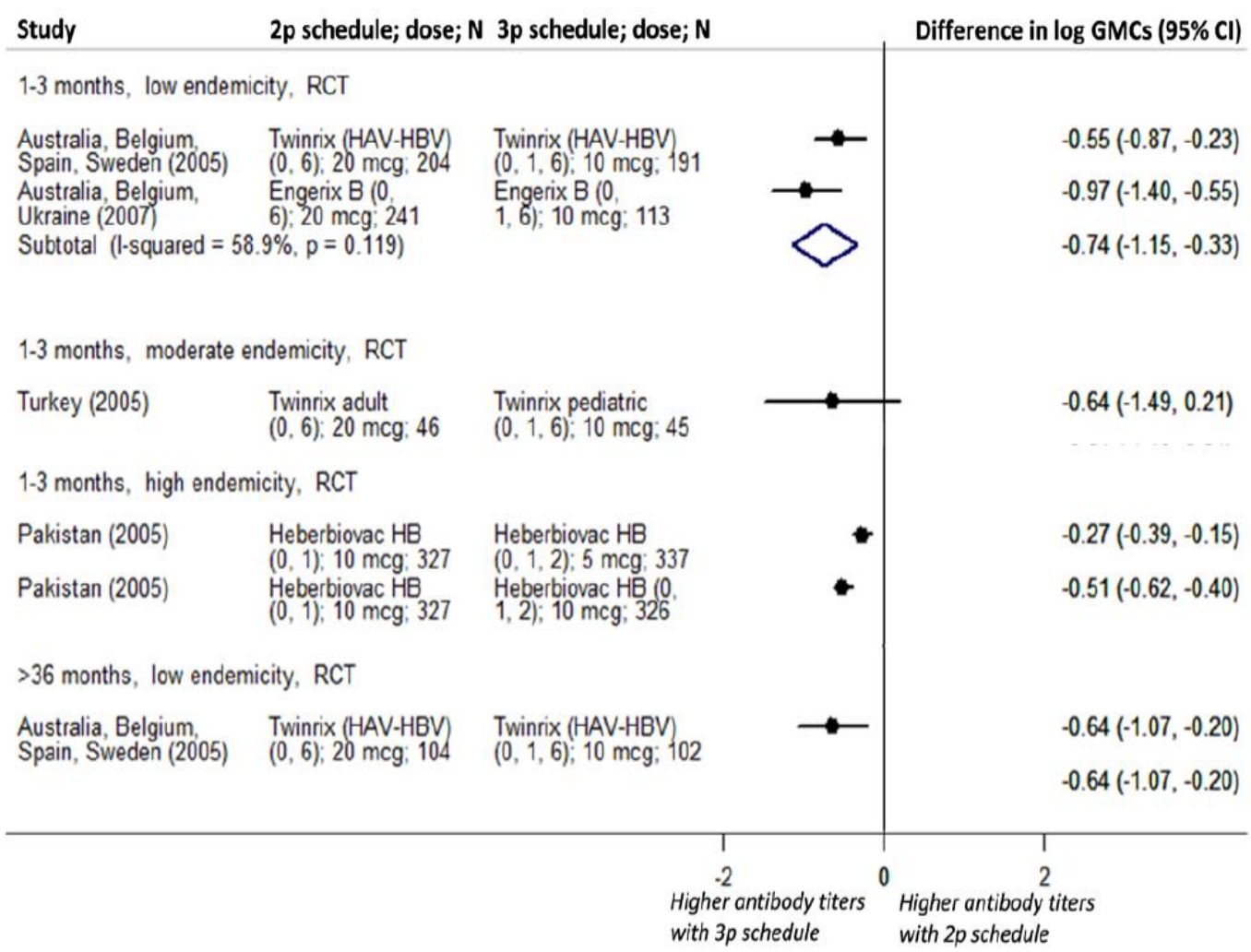
13.1.1 Forest plots and summaries per outcome: Recombinant DNA HBV vaccines, catch up vaccination

***Patients and setting*: Children and adolescents in Australia, China, Pakistan, USA, Belgium, Czech Republic, India, Turkey and Ukraine**
***Comparison:* Recombinant DNA HBV vaccines, 3 primary doses versus 2 primary doses**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection *1-3 months after last vaccination (Low, Moderate and High endemicity)* Results from most studies suggest little or no difference in seroprotection among schedules.		⊕⊕OO LOW

Study Name	age	Study design	Endemicity	2p Schedule (months)	3p schedule (months)	RR (95% CI)	2p doses	3p doses
1-3 months								
USA (2001-A)	Adolescents	RCT	Low	Recombivax HB (0, 6; 10 mcg; IM)	Recombivax HB (0, 2, 4; 5 mcg; IM)	1.08 (1.02, 1.14)	180/185	160/177
USA (2001-A)	Adolescents	RCT	Low	Recombivax HB (0, 6; 5 mcg; IM)	Recombivax HB (0, 1, 6; 5 mcg; IM)	1.10 (1.03, 1.17)	154/162	162/187
USA (2001-A)	Adolescents	RCT	Low	Recombivax HB (0, 4; 10mcg; IM)	Recombivax HB (0, 2, 4; 5 mcg; IM)	1.08 (1.03, 1.14)	183/187	160/177
USA (2001-A)	Adolescents	RCT	Low	Recombivax HB (0, 4; 10mcg; IM)	Recombivax HB (0, 1, 6; 5 mcg; IM)	1.13 (1.06, 1.20)	183/187	162/187
USA (2001-A)	Adolescents	RCT	Low	Recombivax HB (0, 6; 5 mcg; IM)	Recombivax HB (0, 2, 4; 5 mcg; IM)	1.05 (0.99, 1.12)	154/162	160/177
USA (2001-A)	Adolescents	RCT	Low	Recombivax HB (0, 6; 10 mcg; IM)	Recombivax HB (0, 1, 6; 5 mcg; IM)	1.12 (1.06, 1.19)	180/185	162/187
ABSS (2005)	Children	RCT	Low	Twinrix (HAV-HBV) (0, 6; 20 mcg; IM)	Twinrix (HAV-HBV) (0, 1, 6; 10 mcg; IM)	0.99 (0.97, 1.00)	201/204	191/191
ABU (2007)	Children	RCT	Low	Engerix B (0, 6; 20 mcg; IM)	Engerix B (0, 1, 6; 10 mcg; IM)	0.98 (0.95, 1.02)	233/241	111/113
Belgium, Czech (2002)	Children & adolescents	RCT	Low	Twinrix adult (0, 6; 20 mcg; NR)	Twinrix Paediatric (0, 1, 6; 10 mcg; NR)	0.98 (0.95, 1.01)	139/142	147/147
Pakistan (2005)	Children	RCT	High	Heberbiovac HB (0, 1; 10 mcg; IM)	Heberbiovac HB (0, 1, 2; 5 mcg; IM)	1.00 (0.99, 1.01)	327/327	336/337
Pakistan (2005)	Children	RCT	High	Heberbiovac HB (0, 1; 10 mcg; IM)	Heberbiovac HB (0, 1, 2; 10 mcg; IM)	1.00 (0.99, 1.01)	327/327	325/326
Belgium (1999)	Children & adolescents	RCT	Low	HAV-HBV (0, 6; 20 mcg; IM)	Twinrix (HAV-HBV) (0, 1, 6; 10 mcg; IM)	(Excluded)	49/49	48/48
Turkey (2005)	Children	RCT	Moderate	Twinrix adult (0, 6; 20 mcg; IM)	Twinrix pediatric (0, 1, 6; 10 mcg; IM)	(Excluded)	46/46	45/45
India (2002)	Children	RCT	High	HAV-HBV (0, 6; 20 mcg; IM)	Twinrix (HAV-HBV) (0, 1, 6; 10 mcg; IM)	(Excluded)	48/48	48/48

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Anti-HBs seroprotection *6-22 years follow-up (Low and High endemicity)* Results from most studies suggest little or no difference in seroprotection among schedules.		⊕⊕OO LOW

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
GMCs of anti-HBs *Children: Low endemicity, 1-3 & > 36 months post vaccination* A 0, 1, 6 months schedule probably leads to slightly higher antibody concentrations compared to a 0, 6 months schedule.		⊕⊕⊕O MODERATE
Children: Moderate endemicity, 1-3 months post vaccination A 0, 1, 6 months schedule may lead to little or no difference in antibody concentrations compared to a 0, 6 months schedule.		⊕⊕OO LOW
Children: High endemicity, 1-3 months post vaccination A 0, 1, 6 months schedule probably leads to slightly higher antibody concentrations compared to a 0, 6 months schedule.		⊕⊕⊕O MODERATE
Children and adolescents: Low endemicity, 1-3 & 12-24 months post vaccination A 0, 1, 6 months schedule may lead to little or no difference in antibody concentrations compared to a 0, 6 months schedule.		⊕⊕OO LOW

13.1.2 Summary of Findings: Recombinant DNA HBV vaccines, catch up vaccination

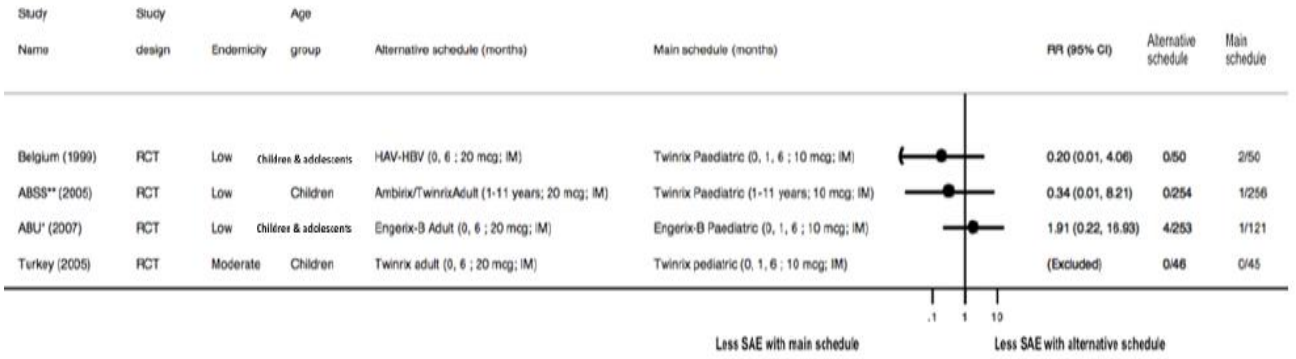
***Patients and setting*: Children and adolescents in Australia, Belgium, Sweden, Spain, Turkey, USA and Ukraine**
***Comparison:* Recombinant DNA HBV vaccines, clinical outcomes for studies comparing 2p vs. 3p schedules**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		2p (Alternative schedule, months)	3p (Main schedule, months)		
Serious adverse events	Results suggest little or no difference in rates of adverse events between schedules in children and adolescents.	Results not pooled; see Forest plot for individual study results.		Results not pooled; see Forest plot for individual study results. 4 RCTs, 1075 participants	⊕⊕OO LOW [1,2]

[1]**Downgraded 1 point for serious risk of bias**
[2]**Downgraded 1 point for serious imprecision**

13.1.2 Forest plots and summaries per outcome: Recombinant DNA HBV vaccines, catch up vaccination

***Patients and setting*: Children and adolescents in Australia, Belgium, Sweden, Spain, Turkey, USA and Ukraine**
***Comparison:* Recombinant DNA HBV vaccines, clinical outcomes for studies comparing 2p vs. 3p schedules**

Outcome and summary of results	Forest plot	Certainty of the evidence (GRADE)
Serious adverse events Results suggest little or no difference in rates of adverse events between schedules in children and adolescents.		⊕⊕OO LOW

13.1.3 Summary of Findings: Recombinant DNA HBV vaccines, catch up vaccination

***Patients and setting*: Children in Italy**
***Comparison:* Recombinant DNA HBV vaccines, 4 primary doses vs. 3 primary doses**

Outcome	Plain language summary	Absolute effect		Relative effect (95% CI) Nº of participants & studies	Certainty of the evidence (GRADE)
		4 primary doses	3 primary doses		
Anti-HBs seroprotection	One study conducted in a low endemicity area provided data comparing a four dose (0, 0.5, 1, 2 months) with a three dose schedule (0, 1, 6 months). All of the included participants were seroprotected at 1-3 months after vaccination.	100%.	100%.	Relative effect measure 1. 1 RCT, 24 participants	⨁⨁◯◯ LOW[1,2]

[1]**Downgraded 1 point for unclear risk of bias**
[2]**Downgraded 1 point for serious imprecision**

Forest plot not shown, as all participants seroconverted. Study reference Italy 1998-B[7].

Bibliographic references

1. Roberton D, Marshall H, Nolan TM, et al. Reactogenicity and immunogenicity profile of a two-dose combined hepatitis A and B vaccine in 1-11-year-old children. *Vaccine* 2005; **23**(43): 5099-105.
2. Heron L, Selnikova O, Moiseieva A, et al. Immunogenicity, reactogenicity and safety of two-dose versus three-dose (standard care) hepatitis B immunisation of healthy adolescents aged 11-15 years: a randomised controlled trial. *Vaccine* 2007; **25**(15): 2817-22.
3. Van Herck K, Van Damme P, Collard F, Thoelen S. Two-dose combined vaccination against hepatitis A and B in healthy subjects aged 11-18 years. *Scand J Gastroenterol* 1999; **34**(12): 1236-40.
4. Levie K, Beran J, Collard F, Nguyen C. Long term (24 months) follow-up of a hepatitis A and B vaccine, comparing a two and three dose schedule in adolescents aged 12-15 years. *Vaccine* 2002; **20**(19-20): 2579-84.
5. Lai CL, Yeoh EK, Chang WK, Lo VW, Ng LN. Use of the hepatitis B recombinant DNA yeast vaccine (H-B-VAX II) in children: two doses vs. three doses of 5 micrograms regime; an interim report. *J Infect* 1986; **13 Suppl A**: 19-25.
6. Guptan RC, Thakur V, Safary A, Sarin SK. Immunogenicity and reactogenicity of a combined high dose hepatitis A and hepatitis B vaccine, compared to that of Twinrix in healthy Indian children. *Vaccine* 2002; **20**(16): 2102-6.
7. Li Volti S, Caruso-Nicoletti M, Biazzo F, et al. Hyporesponsiveness to intradermal administration of hepatitis B vaccine in insulin dependent diabetes mellitus. *Arch Dis Child* 1998; **78**(1): 54-7.
8. Gatchalian S, Reyes M, Bernal N, et al. A new DTPw-HBV/Hib vaccine is immunogenic and safe when administered according to the EPI (Expanded Programme for Immunization) schedule and following hepatitis B vaccination at birth. *Hum* 2005; **1**(5): 198-203.
9. Kurugol Z, Mutlubas F, Ozacar T. A two-dose schedule for combined hepatitis A and B vaccination in children aged 6-15 years. *Vaccine* 2005; **23**(22): 2876-80.
10. Cassidy WM, Watson B, Ioli VA, Williams K, Bird S, West DJ. A randomized trial of alternative two- and three-dose hepatitis B vaccination regimens in adolescents: antibody responses, safety, and immunologic memory. *Pediatrics* 2001; **107**(4): 626-31.

HBV vaccination among low birth weight children (LBW)

Summary of evidence

August 2016

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PART 1 – Updated review on evidence on HBV vaccination among low birth weight children (LBW) published data up to August 2016

Prepared for: Initiative for Vaccine Research, World Health Organization
Prepared by: Fernando de la Hoz Restrepo
August, 2016

Low birth weight is an important factor leading to a decreased immunological response to HBV vaccine. Currently, the WHO position paper recommends that children with birth weight lower than 2,000 grams should be vaccinated at birth and then should receive three additional doses according to the national scheme. However the recommendation did not discriminate between babies at high or low risk of HBV vertical transmission. (WHO, Hepatitis B vaccines. WHO position paper, 2009)

A systematic review commissioned by WHO searched studies addressing issues of HBV vaccine effectiveness with different schedules in different populations. It covered studies published up to 2012. Only one clinical trial was included. It compared immunogenicity (at two weeks after final dose) from different schedules among LBW and normal weight babies. The main finding was that newborn with LBW would have better immunogenicity to HBV vaccine if the first dose is given at one month of age. Three observational studies included in the same review reached similar conclusions even after longer periods of follow up (up to three years). (WHO, Safety and efficacy from randomized controlled trials and observational studies of childhood schedules using Hepatitis B vaccines, 2015)

From 2012 to 2016 only 2 additional references were found. One from Taiwan assessed the national policy on LBW`s HBV vaccination, which considers the weight (not the age) at which LBW children should receive the first dose of HBV vaccine. LBW children in Taiwan born to HBsAg+/HBeAg+ mothers receive a dose of HBIG at birth but the first dose of Hepatitis B vaccine is delayed until they reached a weight of at least 2,000 grs. Children born to HBsAg negative mothers do not receive HBIG and first dose of vaccine is applied using the same criteria. Chen et al followed for several years 25 children born to HBsAg/HBeAg positive mothers and 130 born to HBsAg negative mothers. None of the LBW, vaccinated according to the policy, was infected or carrier. However, this was a retrospective cohort with more than 50% of losses to the sample size of the potential eligible cohort which limits its external validity. (Chen C, 2014)

The other one was a study conducted in Brazil with only 8 LBW children. They claimed that no difference in seroprotection was found between term and preterm infants or normal weight vs. LBW infants. However it was not clear from the paper which vaccination scheme was used in the study. (Miralha A, 2013)

In conclusion, available evidence indicates that in high endemic areas children should be vaccinated against HBV following the current WHO recommendation. For low endemic areas an alternative approach may be discussed at SAGE, i.e vaccinating LBW children after one month of age.

References:

Chen C, C. H. (2014). Weight based policy of hepatitis B vaccination in very low birth weight infants in Taiwan: A retrospective cross sectional study. *Plos One , 9* (3), e 92271.

Miralha A, M. A. (2013). Response to the complete hepatitis B vaccine regimen in infants under 12 months of age: a case series. *Brazilian J of Infect Dis , 17* (1), 82-85.

WHO. (2009). Hepatitis B vaccines. WHO position paper. *Weekly Epidemiological Record , 84* (40), 405-19.

WHO. (2015). *Safety and efficacy from randomized controlled trials and observational studies of childhood schedules using Hepatitis B vaccines.* Geneva.

Part 2. Safety and efficacy from randomized controlled trials and observational studies of childhood schedules using Hepatitis B vaccines

Prepared for: Initiative for Vaccine Research, World Health Organization
Prepared by: Enhance Reviews Ltd
July, 2015

1 LOW Birth Weight

One randomized trial and three observational studies reported on the effect of recombinant DNA vaccines in low-birth weight infants. The studies compared different vaccine schedules including giving a birth dose to very low-birth weight (1000-2000 g), low-birth weight (≥2000 g) and normal weight infants (Table 7).

Table 1| Summary of study characteristics: Pre-term infants that received different schedules of recombinant DNA HBV vaccine on which a birth dose was administered

Study name/ Endemicity	Infants status#	Study characteristics / risk of bias	Reported results	Study conclusions
China 1992-B[1](40) **High**	1.Mixed 2.NR 3.NR	Observational study: Pre-terms infants received 3 vaccine schedules: 1. Engerix-B (10 mcg) at 0 months OR at 1000g, 1 month later, 3 months later, IM. 2. Engerix-B (10 mcg) at 2000g, 1 month later, 3 months later, IM. 3. Engerix-B (10 mcg) at 0, 1, 3 months, IM. Risk of bias: 2/8	Seroprotection rates (Anti-HBs) titre ≥ 10 mIU/ml) and GMTs as measured by enzyme immunoassay at 4-6 weeks after final dose: **GROUP 1 (N=57)** / **GROUP 2 (N=42)** / **GROUP 3 (N=43)** **SEROPROTCTION RATE (%) (P=.0012)**: 78.9 (66.1, 78.9) / 90.5 (77.4, 97.3) / 100 (91.7, 100) **HBSAB (95% CI) (P=.0007)**: 61 (27, 138) / 262 (101, 680) / 679 (265, 1742)	The final seroprotection rates and GMCs of the pre-term infants were significantly lower than that of full-term infants.
Israel 2002(41) **Low**	1.Negative 2.NR 3.±1463 g	Observational study: Pre-term infants received 3 vaccine schedules: 1. IPV + Engerix-B (10 mcg) at 0, 1, 6 months, IM – pre-terms. 2. Engerix-B (10 mcg) at 2000g, 1 month later, 6 months later, IM. 3. IPV + Engerix-B (10 mcg) at 0, 1, 6 months, IM, full-	Seroprotection rates (HBsAb titre ≥ 10 IU/ml) and GMTs as measured by radioimmunoassay at 3 years after final dose: **GROUP 1** / **GROUP 2** / **GROUP 3** **SEROPROTECTION RATE (%)**: 54.4 / 92.5 / 71.8 **GMC (IU/L) MEAN (SD)**: 14.2 (11.1) / 119 (4.8) / 32.7 (9.2)	Delaying vaccination of premature infants against hepatitis B until a weight of 2000 g was reached results in a significantly higher percentage of children with antibody levels and a

[1]Study based in Hong Kong

<table>
<tr><th>Study name/ Endemicity</th><th>Infants status#</th><th>Study characteristics / risk of bias</th><th>Reported results</th><th>Study conclusions</th></tr>
<tr><td></td><td></td><td>term infants

Risk of bias: 3 /8</td><td>Group 1 vs 2: p<.001; Group 2 vs 3: p<.05</td><td>significantly higher GMC as compared to early-vaccinated preterm and full-term infants.</td></tr>
<tr><td>Taiwan 1997(42)

High</td><td>1.Negative

2.NR

3.No</td><td>Observational study: Pre-term infants received 2 vaccine schedules:
1. Infants < 2000 g- HB-VAX-II (5 mcg) at 1, 2, 7 months.
2. Infants < 2000 g and > 2500 g- HB-VAX-II (5 mcg) at 0, 1, 6 months.
Mode of administration not reported.

Risk of bias: 4/8</td><td>All blood samples tested negative for both HBsAg and hepatitis B core antibodies (anti-HBc) at 3 months post-final dose of the vaccine.

Seropositivity rates (HBsAb titre > 10 units/litre) and GMTs as measured by radioimmunoassay at 3 months after final dose:

Seropositivity Rate (%) | GMC (95% CI)
Group A 95 | 257 (155-426)
Group B 90 | 194 (116-323)</td><td>The final seropositive rate and the GMT of hepatitis B surface antibody between the two groups were not significantly different. Preterm infants can be given hepatitis B vaccines using one of the two different schedules described here, at a cut-off birth weight of 2000 g.</td></tr>
<tr><td>USA 1997-A(43)

Low</td><td>1.NR

2.NR

3.NR</td><td>RCT: Low birth weight infants
1. Early Immunization, Low Birth Weight Group- Recombivax HB (2.5 mcg) at 0, 1, 6 months IM.
2. Early Immunization, Normal Birth Weight Group- Recombivax HB (2.5 mcg) at 0, 1, 6 months IM.
3. Late Immunization, Low Birth Weight Group- Recombivax HB (2.5 mcg) at 1, 2, 7 months IM.
4. Late Immunization, Normal Birth Weight Group- Recombivax HB (2.5 mcg) at 1, 2, 7 months IM.

High risk of bias.</td><td>Seroprotection rates (HBsAb titre > 10 units/litre) as measured by AUSAB and EIA at 2 weeks after final dose:

SEROPOSITIVITY (%)
GROUP 1 66
GROUP 2 69
GROUP 3 90
GROUP 4 100</td><td>This study suggests that hepatitis B vaccine can be given to infants with birth weights of < 1500 g at 1 month of age. Use of an age-for-immunization schedule may be more practical to implement than use of weight as an indicator for immunization</td></tr>
</table>

 # Infants status refers to 1. Mother' HBsAg and HBeAg status; 2. whether HBIG was given; 3. Mean (or median) birth weight

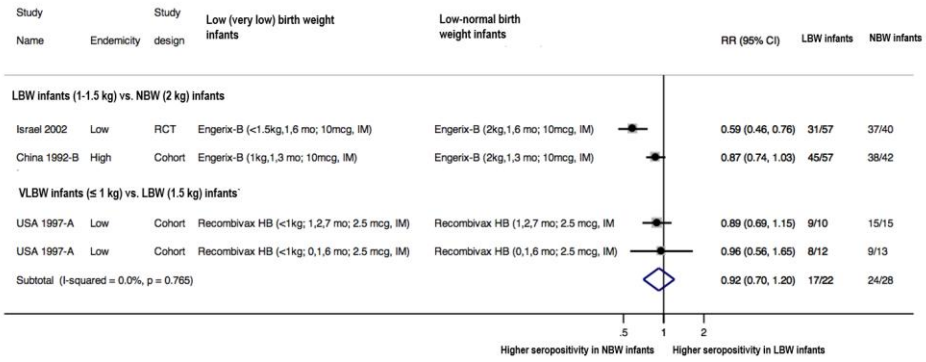
1.1 Anti-HBs (seroprotection)

Israel 2002, a cohort in a low endemicity region, compared a 0, 1, 6 months schedule beginning when infants weighed less than 1.5 kg vs. 2 kg (Figure 24). This study showed higher seroprotection in infants who began vaccination at 2 kg measured at three years after the final dose (N=97, RR 0.59, 95% CI 0.46, 0.76). The mean age at first dose in each group was not reported.

China 1992-B, a cohort study in a high endemicity region (Hong Kong), compared a 0, 1, 3 month schedule beginning when infants weighed 1 kg vs. 2 kg. Again, the mean age at first dose in each group was not reported. Results at 4-6 weeks showed no difference in the rates of seroprotection (Figure 24).

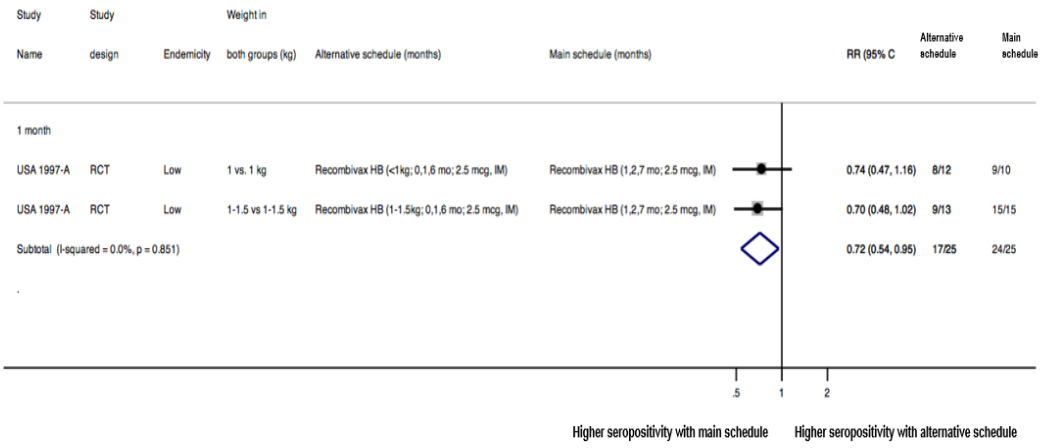
USA 1997-A was an RCT in a low endemicity country, which stratified infants by birth weight (1 kg and 1 to 1.5 kg) and then randomised them to two different schedules (0, 1, 6 months and 1, 2, 7 months). We were able to compare the birth weights for each schedule, although this is not a randomised comparison (Figure 24). No difference was found between 1 kg and 1-1.5 kg for either a 0, 1, 6 month schedule or a 1, 2, 7 month schedule. The mean weight at which the infants received the first dose in the 1, 2, 7 month schedule was not reported.

Figure 1| Forest plot of difference in anti-HBs seroprotection proportions for low birth weight infants given HBV vaccination at different birth weights



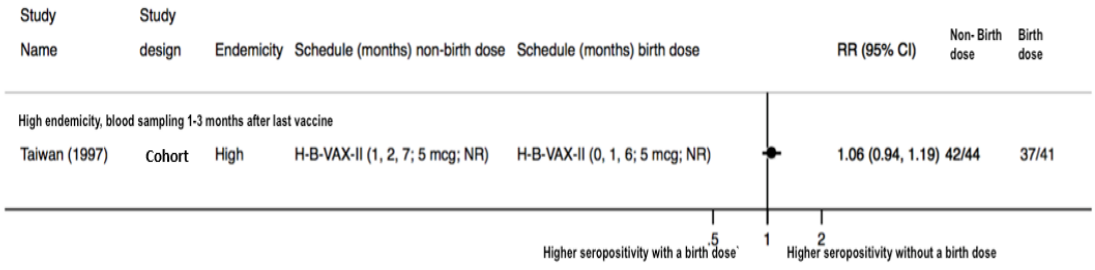
For the randomised comparison in USA 1997-A, in which infants were stratified by birth weight (1 kg and 1 to 1.5 kg) and then randomised them to two different schedules (0, 1, 6 months and 1, 2, 7 months), no difference in seroprotection was found between schedules for infants 1 kg or 1-1.5 kg at two weeks after the final dose, (Figure 25).

Figure 2| Forest plot of difference in anti-HBs seroprotection proportions for low birth weight infants given HBV vaccination at different ages at first dose



Taiwan 1997 was a cohort study in a high endemicity country, which vaccinated pre-term infants to two different schedules depending on their birth weight: those below 2000g were given a 1, 2 , 7 month schedule (although their mean weight at 1 month was not reported) and those weighing 2000-2500 g received a 0, 1, 6 month schedule (Figure 26). No difference in seroprotection was found between the schedules.

Figure 3| Forest plot of difference in anti-HBs seroprotection proportions for pre-term infants given HBV vaccination at different ages at first dose according to their birth weight



2 Comments on study methodology and risk of bias

The risk of bias (RoB) of each included randomized and quasi-randomized trial was assessed using the RoB tool by two independent reviewers and the consensus ratings are presented Appendix D. The methodological quality of each included cohort study was assessed using the Newcastle Ottawa Scale (NOS) by two independent reviewers and the consensus ratings are presented in Appendix E. A summary of the overall quality trends by study design is presented below.

Randomized and Quasi-randomised Controlled Trials

Of the 19 randomized controlled trials (RCTs) and quasi-randomized controlled trials (nRCTs), eight trials [Argentina (2011), China (1998-B), China (2003), Egypt (1995), Ivory Coast (2008), Netherlands (1993-A), Philippines (2005), Turkey (2004-A)] were

rated as having high risk of bias (RCTs = 5; nRCTs = 3), nine trials [China (1992-C), Netherlands (1993-B), Netherlands (1994-B), Philippines (2008), Philippines (2007), South Africa (2013), Taiwan (1983-A), USA (2002-A), USA (2002-B)] were rated as having an unclear risk of bias (RCTs = 7; nRCTs = 2), and two RCTs were considered to have a low risk of bias.

Cohort Studies

Data were prospectively collected in seven cohort studies [China (1992-B), Japan (1989), Israel (2002), South Africa (1991), USA (1997-A), Taiwan (1997), Turkey (2010)]. Overall, the methodological quality of the cohort studies was low to moderate (median score =4 stars; IQR: 2-7).

Part 3. Should hepatitis B vaccine be used for prevention of hepatitis B virus infection in LBW infants?- Evidence used to inform the SAGE recommendations in April 2009

Hepatitis B vaccination of LBW infants

http://www.who.int/wer/2009/wer8440.pdf?ua=1

Some infants born prematurely with low birth weight (<2000 g) may not respond well to vaccination at birth.[42] However, by 1 month of chronological age, premature infants, regardless of their initial weight or gestational age at birth, are likely to respond adequately.[43]

42 Losonsky GA et al. Hepatitis B vaccination of premature infants: a reassessment of current recommendations for delayed immunization. Paediatrics, 1999, 103:E14.

43 Saari TN. Immunization of preterm and low birth weight infants. Pediatrics, 2003, 112:193–198. (American Academy of Pediatrics Committee on Infectious Diseases).

Hepatitis B vaccination in adults with HIV infection.

Due to shared routes of transmission HIV/HBV co-infection is not infrequent in areas of high and low endemicity (Okwen M, 2014). In the pre HAART era several studies showed that HIV/HBV coinfection may increase the likelihood of more severe outcomes of HBV infection. (Thio C, 2002) (Hadler S J. F., 1991) .

Hepatitis B vaccination is the most effective preventive intervention against infection with HBV and its complications, even in HIV infected patients. (Landrum M, 2011) However, immune response to HBV vaccines is poor among HIV infected subjects. (Ni J, 2013) . Currently, the WHO position paper recommends that HIV infected adults should be vaccinated as soon as possible with the standard dose (three doses containing 20 ug of HBsAg). No recommendation is given on the use of higher amounts of HBsAg or incrementing the number of injections. (WHO, 2009). A search of the literature was done in order to identify recent studies that may have the potential to change or modify the current practices of HBV vaccination recommended by WHO for adults infected with HIV.

We found a recent systematic review and meta-analysis addressing the long term immune response of vaccines in HIV infected children and adults. (Kernéis S, 2014). They included observational and experimental studies addressing persistence of antibodies for more than 6 months after the last dose. Twelve studies on hepatitis B were available with follow up times from 15 to 112 months, 6 in adults. As observed in figure 1 there is no clear difference in seroprotection length between different doses. After 3 doses of 40 ug, 71% of primary responders remain with seroprotection titers after 1 year, 33% to 61% after year 2, and 40% after year 5.

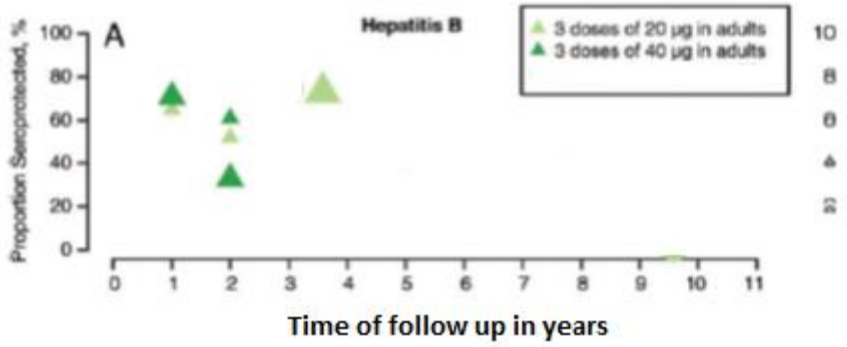
The meta-analysis predicted the proportion of adults with protective titters after 2 or 5 years of vaccination using higher vs standard doses. After 2 years of immunization only 38% of adults would remain with protective titters. Double doses would not improve maintenance of seroprotection compared to standard doses (41% vs 50% respectively). Figures 2 and 3. They recommended that Anti HBs titres should be measured every year among adults living with HIV.

A Cochrane review (Okwen M, 2014) attempted to address the impact of HBV vaccination on prevention of morbidity and mortality in HIV positive patients. They only included clinical trials in the search and just one was found. It described HBV vaccination in 26 participants with HIV infection followed for 3 years on a monthly basis. Most participants lost immunity when ART was stopped. They were unable to test whether HBV vaccine was better than placebo to prevent HBV infection and complications. They conclude the evidence was insufficient to support any recommendation on HBV vaccination use for HIV persons.

An unpublished systematic review from WHO, (Wakefield V, 2014), found several small clinical trials assessing the effectiveness of Hepatitis B vaccine among HIV infected people. They used different vaccination schemes, sites of administration, vaccine adjuvants, HBsAg dose, or number of injections. The outcome in all of them was immunogenicity since most followed patients for less than 12 months. The main conclusion was that HIV infected adults vaccinated with three or four doses using double amount of antigen (40 ug) had a higher peak of antibodies. However, follow up was

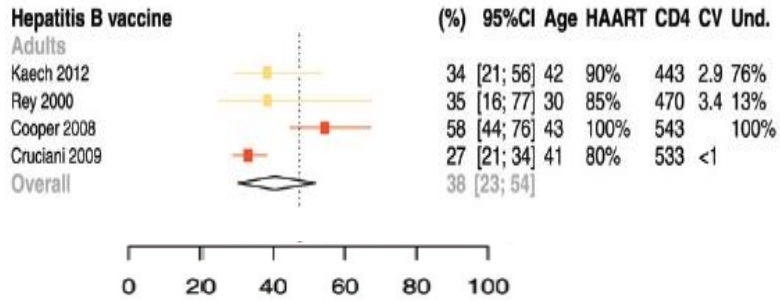
limited to 6 to 12 months after the last dose. One of the trials with the highest quality, double blind RCT, did not found differences between standard doses and double doses.

Figure 1. Percent of individuals with protective levels of Anti HBs in relation to time elapsed since last dose.



Source: (Kernéis S, 2014)**.**

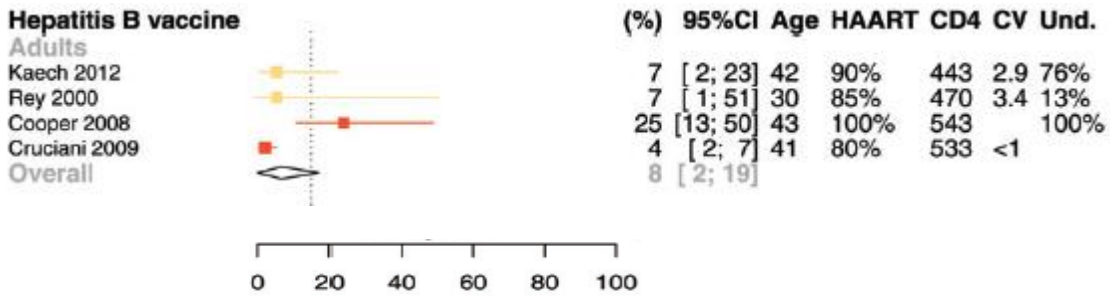
Figure 2. Predicted proportion of adults with protective antibodies after 2 years follow up.



Yellow bars represent titters for 3 doses with 20 ug. Red bars represent titters for 3 doses with 40 ug

Source: (Kernéis S, 2014)**.**

Figure 3. Predicted proportion of adults with protective antibodies after 5 years follow up.



Source: (Kernéis S, 2014)**.**

In conclusion, there is no strong evidence to change current WHO recommendation for one recommending to vaccinate HIV infected adults with double dose. Recommending periodical monitoring of anti HBs titres may be discussed at SAGE.

References

(n.d.).

Diop-Ndiaye H, T.-C. C. (2008). Hepatitis B C and delta virus in HIV 1 senegalese patients at HAART initiation (retrospective study). *J Med Virol, 80*, 1332-6.

Hadler S, F. D. (1986). Long term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. *N Engl J Med, 315*, 209-14.

Hadler S, J. F. (1991). Outcome of hepatitis B virus infection in homosexual men and its relation to prior human immunodeficiency virus infection. *J Infect Dis, 163*(3), 454-9.

Kernéis S, L. O. (2014). Long-term Immune Responses to Vaccination in HIV-Infected Patients: A Systematic Review and metaanalysis. *CID, 58*(8), 1130-8.

Landrum M, H. K.-C. (2011-55). Hepatitis B Vaccination and Risk of Hepatitis B Infection in HIVInfected. *AIDS, 24*(4), 54.

Lee HC, K. N. (2008). Seroprevalence of viral hepatitis and sexually transmitted diseases among adults with recently diagnosed HIV infection in Southern Taiwan 2000-5. *J Formoss Med Assoc, 107*, 404-1.

Ni J, X. Y. (2013). Does increased hepatitis B vaccination dose lead to a better immune response in HIV-infected patients than standard dose vaccination: a meta-analysis? *International Journal of STD & AIDS , 24*, 117–122.

Okwen M, R. S. (2014). Hepatitis B vaccination for reducing morbidity and mortality in persons with HIV infection. *Cochrane database for systematic reviews*(10), 1-24. doi:10.1002/14651858

Owolabi L, I. A. (2014). Prevalence and Burden of Human Immunodeficiency Virus and Hepatitis B Virus Co-infection in Nigeria: A Systematic Review and Meta-Analysis. *J Aids Clin Res, 5*(6), 308.

Thio C, S. E. (2002). HIV1 Hepatitis B virus and risk of liver related mortality in the multicentere cohort study (MACS). *Lancet, 360*, 1921-26.

Wakefield V, B. S. (2014). *A systematic review of the effectiveness of vaccination strategies against hepatitis B in people with HIV.* Geneve: World Heallth Organization.

WHO. (2009). Hepatitis B vaccines. WHO position paper. *Weekly Epidemiological Record, 84*(40), 405-19.

Long protection of Hepatitis B vaccination

Summary of evidence

August 2016

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PART 1 – Updated review on evidence on long term protection of HBV vaccination published data up to August 2016

Prepared for: Initiative for Vaccine Research, World Health Organization
Prepared by: WHO Secretariat
August, 2016

From 2008 to 2016 25 additional references were found.

Table A: Long-term outcomes of hepatitis B vaccination from cohort studies

Prospective Cohorts

Reference	Population	Endemic HBV Level	Comment	Age at Vax; Schedule (Months)	Vax Type-No. Doses	F/U Period (Years)	Initial No. Subjects	No. of Subjects F/U	Vax Record	Previous Booster	Anti-HBs ≥10 mIU/mL % (n/n)	Natural Boost Anti-HBs % (N/N)[1]	Sub-clinical HBV-Anti-HBc % (n/n)	Chronic HBV % (n/n) HBsAg
(Zhu, Liu et al. 2011)	Qidong, China	High	Vaccine trial, RCT	<24hrs 0,1,6	Plasma-3	10	806	806	Study	None	37% (301/806)	6% (48/806)	6.7% (27/404) at 24 yr F/U	1.0% (4/404) at 24 yr F/U
						20		804			33% (265/804)	16.66% (134/804)		
						24		404			30% (121/404)	NA		
(Qu, Chen et al. 2014) (Chen, Qu et al. 2016)	Qidong, China	High	Vaccine trial, RCT	<24hrs 0,1,6	Plasma-3	Median 25.3	38,366	21,770 ages 19-28 6559 for a-HBS	Study	No	33% (459/1410)	NA	NA	1.83% (315/17,204)
										Yes, Engerix-B 11-14 years	45% 2341/5150			

(Poovorawan, Chongsrisawat et al. 2011)	Thailand	High	Vaccine trials	0, 1,2,12	Recom-4	20	222	109	Study	63% at age 5 years	NA	10.0% first decade 10.7% second decade	22.0% (24/109)	None (2/24 transient HBsAg-or HBV +)
(Poovorawan, Chongsrisawat et al. 2013)	Thailand	High	Vaccine trials	0, 1,2,12	Recom-4	20	25	25	Study	Not boosted	64%[2] (16/25)	NA	NA	NA
(McMahon, Bruden et al. 2005)	Alaska Native American, USA	Intermediate	Persons in 15 villages	>6 months-50 years; 0,1,6 months	Plasma-3	15	1578	783	Study	8% 78/967 at 11 yrs	66 517/783	7.9% (62/783 at year 15)	1.0% (5/493, plus 3 transient HBc +)	None
(McMahon, Dentinger et al. 2009)						22		493		Not at 15yrs but 8% at 11yrs	60 298/473			
(Bruce, Bruden et al. 2016)[3]			Persons in 12/15 villages	Age min 30 years 0,1,6 months		30		192		33% boosted at 22 year follow up	48 210/435	NA	2/5 remained anti-HBc +	None
(But, Lai et al. 2008)	Hong Kong, China	High	Children of HBV positive families	3 months-11 years; mean 5.4 years:	Plama-2 5 ug	22	105	23	Study	No	35.3% (6/17)	27 subjects	~1.9% (1/~52, year 11)	None
					Plasma-3	22	106	30		No	76% (13/17)	24 subjects	~1.6% (1/~63 at year 9)	None

				0,1 0,1,6 0,1,6	5 ug Recomb-3 10 ug	22	107	32		No	52.4% (11/21)	21 subjects	~3.3 (1/~30 at year 17)	None
(Lin and Wong 2013)	Hong Kong, China	High	Infants of HBsAg-positive mothers	0,1,6 2,3,8 0,1,2	Plasma-3	30	1044 without HBV at year 3	246	Study	No	37.4 % (92/246)	NA	9% (97 during 30 years)	None
(Ni, Chang et al. 2012)	Taipei, Taiwan	High	Retrospective cohort	At birth 0,1,6	Plasma-3	25	3332	475 *above 25 yrs only	Study	NA	61% (291/475)	NA	12.4% (59/475) * a-HBC and a-HBS *over 25yrs	7.7% (37/475)[4] * over 25 yrs
(Mendy, Peterson et al. 2013)	The Gambia	High	Cross sectional	<5yrs NA	Plasma- 3 or 4 Recomb-3	24	1508	1276	Study	No	17.8 %[5]	NA	25% (77/309) in 20 to 29 yrs old	1.6% (5/304) in 20 to 29 yrs old
(Peto, Mendy et al. 2014)[6]	The Gambia	High	Cross sectional	NR	NR	Up to 31 yrs, not well specified	753	255 fully vaccinated, 23 partially vaccinated	Study	NA	NA	NA	→27% (70/255) in vaccinated → 56% (267-475) in unvaccinated	→ 0.8% (2/255) in fully vaccinated → 17.9% (4/23) in partially vaccinated →12.4% (59/475) in unvaccinated
(Wang, Shen	5 areas	High	Cross-sectional-	Dose 1 of 3 doses = 3-	Plasma	13-23	6772	1720	Study	NA	NA	NA	6.39% overall	3.2 %

et al. 2015)	China		2009	30 days										(55/1720)
				Dose 1 of 3 doses <24 hours				5052			41.7% (2106/5052)			1.58% (80/1052)
(Wu, Zhuang et al. 2011)	Xi'an city, China	High	F/U RTC	5-9 years, doses; 0, 1, 6	Plasma-3	23	128	23	Study	Yes, 11 years post vax	38% (9/23)	NA	16% (13/81)	None
								40	Study	None	75% (30/40)	NA		None
(Chan, Ngai et al. 2014)	Hong Kong, China	High1	Prospective study	At birth 0, 1, 6	Unknown-3	17-23, mean 19	NA	212	Self-questionnaire	No	19 40/212	NA	1% 2/212	1% 2/212

TABLE B: Declines in anti-HBs with or without response to booster (challenge) dose of hepatitis B vaccine
Serosurvey with or without response to booster dose

Reference (No.)	Population	Endemic HBV Level	Design	Age at Vax; Schedule (Months)	Vax Type-No. Doses	F/U Period (Years)	Subjects No.	Booster/ "Challenge" Dose Vaccine Type	Age at current Booster or Serology	Previous Booster Age (Years)	Anti-HBs ≥10 mIU/mL % (n/n)		Sub-clinical HBV-Anti-HBc % (n/n)	Chronic HBV % (n/n) HBsAg
											Pre-boost[3]	Post-Boost		
(Avdicova, Crasta et al. 2015)	Slovakia			3, 5, 11-12	Hexavalent	10-11yrs	95	Engerix-B	Mean 11.3 (11-12) years	NA	48.4% (46/95)	96.8% (91/94)	NA	NA
					Engerix-B[8]	10-11yrs	89			NA	58.4% (52/89)	98.9% (88/89)	NA	NA
(Bagheri-Jamebozorgi, Keshavarz et al. 2014)	Rafsanjan, Iran		Healthy adults at health centers, retrospective cohort	<48 hours, 1.5, 9	Recomb-3	20	300	Recombinant, Heberbiovac	20 yrs	NA	37% (111/300) [9]	97.1%	0/300	0/300
(Chaouch, Hachfi et al. 2016)	Tunisia	Intermediate	Cross-sectional (2012)	3,4,9 months	Recomb-3	17	703	No Access	14.3 (12-17) years	No Access	69% (485/703)	No Access	0.3%(2/703)	NA
(Chaves, Fischer et al. 2012)	Palau, Western Pacific		Cross-sectional	<7 days	Recomb-3	10	75	Recombivax 5mcg	11	None	21% (16/75)	85% (64/75)	0.5% (1/193)	NA
						15	53		15.8		8% (4/53)	74% (39/53)		

(Middleman, Baker et al. 2014)	Houston, USA	Low	44 pediatric medical practices	<7 days, 3	Recomb-3	16-19	180	Engerix-B 10 or 20 ug	Mean 16.9 years	NA	16.7%	90.4%[10]	0/180	NA
				≥ 4 weeks completed by 12 months			240		Mean 17.4 years	NA	33.9%	93.9%[10]	0/240	NA
(Ni and Chen 2010)	Taiwan	High	Retrospective cohort	At birth, 0,1,2,12 or 0,1,6	Plasma Hevac B-4 Or Recomb HBVAXII-3 Or Engerix-3	15	113 (from HBsAg neg mother)	Not specified	15	NA	37.6% (43/113)	96.7% (109/113)	3.7%	1.2%
(Poovorawan, Chongsrisawat et al. 2012)[11]	Thailand	High	Convenience: Maternal HBsAg/HBeAg positive	0, 1,2,12	Recomb-4	20	19	Recomb	20	5[12]	84.5% 16/19	100%	NA	23.1% (30/130)
							25			None	44.0% (11/25)	93.1%		
(Teoharov, Kevorkyan et al. 2013)	Bulgaria		Cross sectional?	At birth 0, 1, 6	Engerix and Euvax-3	5	53	Engerix-B	Approx 5, 10, 15 yrs old, NR	NA	15.4% (8/53)	100% (3/3)	0.7% (1/141)	0.7% (1/141)
						10	52				44.2% (23/52)	100% (11/11)		
						15	36				38.9% (14/36)	100% (9/9)		

(van Damme, Kafeja et al. 2011)	Belgium		Retrospective cohort	At birth 0, 6	Ambirix-2	10	120	N=6 (10 mg dose) N=19 (20 mcg)	17	NA	31.67% 38/120	100% 25/25	NA	NA
(Van Der Meeren, Behre et al. 2016)[9]	Germany		Convenience: 10 health centers	Infancy	Recomb-3	15-16	303	Engerix-B 10 ug	15.3 years	None	65.4% (292)	97.9% (292)	0.6% (2/292)	NA

Footnotes:

1: Defined as spike in a-HBS antibodies without intervention (vaccine, boost)

2: Booster dose offered only to subjects with anti-HBs >100 mIU/mL.

3: No previous booster dose of hepatitis B vaccine

4: Most infections attributed to perinatal transmission

5: 27% of persons with initial anti-HBs >999 mIU/mL had anti-HBs ≥10 mIU/mL at 20 years.

6: This study reports prevalence of HBV infection up to 31 yrs only, no a-HBS antibodies

7: Indication for challenge or booster dose was anti-HBs <10 mIU/mL unless otherwise stated.

8: Vaccines either DTPa-HBV-IPV/hib or DTPa-IPHib-HBV.

9: Assessed response at 4 weeks post-booster.

10: Assessed response to booster dose at 13-15 days

11: Infants born to HBsAg and HBEsAg +ve mother

Abstracts:

Avdicova, M., et al. (2015). "Lasting immune memory against hepatitis B following challenge 10-11 years after primary vaccination with either three doses of hexavalent DTPa-HBV-IPV/Hib or monovalent hepatitis B vaccine at 3, 5 and 11-12 months of age." Vaccine **33**(23): 2727-2733.

BACKGROUND: The combined hexavalent diphtheria-tetanus-pertussis-hepatitis B-inactivated poliomyelitis - Haemophilus influenzae type b conjugate vaccine (Infanrix hexa; DTPa-HBV-IPV/Hib: GlaxoSmithKline Vaccines) induces robust responses to the HBV component when administered at 3, 5 and 11-12 months of age. We assessed long term HBV antibody persistence 10-11 years after primary vaccination in infancy. METHODS: Antibody persistence and immune memory were assessed post-primary vaccination at 3, 5, 11-12 months with DTPa-HBV-IPV/Hib, or monovalent HBV vaccine (Engerix B, GlaxoSmithKline Vaccines) co-administered with DTPa-IPV/Hib (Infanrix-IPV/Hib, GlaxoSmithKline Vaccines) in 185 children aged 11-12 years. Blood samples were collected before and 1 month after a challenge dose of Engerix B (10mug dose). RESULTS: 10-11 years after primary vaccination the percentage of subjects with persisting anti-HBs antibody concentrations >/=10mIU/ml was 48.4% in the DTPa-HBV-IPV/Hib group and 58.4% in the DTPa-IPV/Hib+HBV group. After the HBV challenge dose, the percentage with anti-HBs >/=100mIU/ml increased from 14.7% to 93.6% in the DTPa-HBV-IPV/Hib group and 19.1% to 94.4% in the DTPa-IPV/Hib+HBV group. Anti-HBs GMCs increased by at least 187-fold in each group. An anamnestic response (>/=4-fold increase in initially seropositive or anti-HBs concentration >/=10mIU/ml in initially seronegative subjects) was observed in 96.8% and 96.6% of subjects in the DTPa-HBV-IPV/Hib and DTPa-IPV/Hib+HBV groups, respectively. No serious adverse events occurred that were considered related to challenge vaccination. CONCLUSION: Administration of HBV as part of a combination vaccine or as a monovalent vaccine induced long lasting immune memory against HBV in children primed at 3, 5 and 11 months of age. Antibody persistence and immune memory were similar, suggesting that protection afforded by DTPa-HBV-IPV/Hib and monovalent HBV vaccines, is likely to be of similar duration. The administration of HBV challenge dose 10-11 years after the 3, 5, 11-12 months primary schedule induced strong anamnestic responses and was well tolerated. This study is registered at http://www.clinicaltrials.govNCT01138098.

Bagheri-Jamebozorgi, M., et al. (2014). "The persistence of anti-HBs antibody and anamnestic response 20 years after primary vaccination with recombinant hepatitis B vaccine at infancy." Hum Vaccin Immunother **10**(12): 3731-3736.

Hepatitis B (HB) vaccine induces protective levels of antibody response (anti-HBs>/=10 mIU/mL) in 90-99% of vaccinees. The levels of anti-HBs antibody decline after vaccination. The aim of this study was to evaluate the persistence of anti-HBs antibodies and immunologic memory in healthy adults at 20 years after primary vaccination with recombinant HB vaccine. Blood samples were collected from 300 adults at 20 years after primary HB vaccination and their sera were tested for anti-HBs antibody by ELISA technique. A single booster dose of HB vaccine was administered to a total of 138 subjects, whose anti-HBs antibody titer was <10 mIU/mL. The sera of subjects were re-tested for the anti-HBs antibody levels at 4 weeks after booster vaccination. At 20 years after primary vaccination 37.0% of participants had protective levels of antibody with geometric mean titer (GMT) of 55.44+/-77.01 mIU/mL. After booster vaccination, 97.1% of vaccinees developed

protective levels of antibody and the GMT rose from 2.35+/-6.49 mIU/mL to 176.28+/-161.78 mIU/mL. 125/138 (90.6%) of re-vaccinated subjects also showed an anamnestic response to booster vaccination. At 20 years after primary vaccination with HB vaccine, low proportion of the subjects had protective levels of antibody. However, the majority of the re-vaccinated subjects developed protective levels of anti-HBs and showed an anamnestic response after booster vaccination. Additional follow-up studies are necessary to determine the duration of immunological memory.

Bruce, M. G., et al. (2016). "Antibody Levels and Protection After Hepatitis B Vaccine: Results of a 30-Year Follow-up Study and Response to a Booster Dose." Journal of Infectious Diseases.

Background. The duration of protection in children and adults resulting from hepatitis B vaccination is unknown. In 1981, we immunized a cohort of 1578 Alaska Native adults and children from 15 Alaska communities aged ≥6 months using 3 doses of plasma-derived hepatitis B vaccine.Methods. Persons were tested for antibody to hepatitis B surface antigen (anti-HBs) levels 30 years after receiving the primary series. Those with levels <10 mIU/mL received 1 booster dose of recombinant hepatitis B vaccine 2–4 weeks later and were then evaluated on the basis of anti-HBs measurements 30 days after the booster.Results. Among 243 persons (56%) who responded to the original primary series but received no subsequent doses during the 30-year period, 125 (51%) had an anti-HBs level ≥10 mIU/mL. Among participants with anti-HBs levels <10 mIU/mL who were available for follow-up, 75 of 85 (88%) responded to a booster dose with an anti-HBs level ≥10 mIU/mL at 30 days. Initial anti-HBs level after the primary series was correlated with higher anti-HBs levels at 30 years.Conclusions. Based on anti-HBs level ≥10 mIU/mL at 30 years and an 88% booster dose response, we estimate that ≥90% of participants had evidence of protection 30 years later. Booster doses are not needed.

But, D. Y., et al. (2008). "Twenty-two years follow-up of a prospective randomized trial of hepatitis B vaccines without booster dose in children: final report." Vaccine **26**(51): 6587-6591.

Long-term immunogenicity and efficacy of HBVvaccination with different regimens of HBV vaccines (A: 2-dose recombinant vs. B: 3-dose recombinant vs. C: 3-dose plasma-derived vaccines) without booster dose were examined in 318 Chinese children. Geometric mean titer (GMTs) of anti-HBs of group A subjects was significantly lower than that of groups B and C subjects at years 1, 5, 10 and 15. At year 22, the proportion of subjects with anti-HBs > or = 10 mIU/mL for groups A, B and C were 35.3%, 76.5% and 52.4%, respectively ($p < 0.05$ between groups A and B) in 55 subjects. In the 22 years study period, none was found to be HBsAg positive, and 72 subjects had > or = 1 episodes of anamnestic response. In conclusion, the 3-dose regimens have a better long-term immunogenicity. In terms of protection against HBV infection, the 2-dose and 3-dose vaccines had equal efficacies.

Chan, P. K. S., et al. (2014). "Response to Booster Doses of Hepatitis B Vaccine among Young Adults Who Had Received Neonatal Vaccination." PLoS One **9**(9).

BACKGROUND: Newborns who have received hepatitis B immunization in 1980s are now young adults joining healthcare disciplines. The need for booster, pre- and post-booster checks becomes a practical question. AIMS: The aim of this study is to refine the HBV vaccination policy for newly admitted students in the future. METHODS: A prospective study on medical and nursing school entrants to evaluate hepatitis B serostatus and the response to booster doses among young adults. FINDINGS: Among 212 students, 17–23-year-old, born after adoption of neonatal immunization, 2 (0.9%) were HBsAg positive, 40 (18.9%) were anti-HBs positive. At 1 month after a single-dose booster for anti-HBs-negative students, 14.5% had anti-HBs <10 mIU/mL, 29.0% and 56.5% were 10–100 and >100 mIU/mL, respectively. The anti-HBs levels were significantly higher for females than males (mean [SD]: 431 [418] vs. 246 [339] mIU/mL, P = 0.047). At 2–4 month after the third booster dose, 97.1% had anti-HBs >100 mIU/mL and 2.9% had 10–100 mIU/mL. CONCLUSIONS: Pre-booster check is still worthwhile to identify carriers among newly recruited healthcare workers born after adoption of neonatal immunization. A 3-dose booster, rather than a single dose, is required for the majority to achieve an anti-HBs level >100 mIU/mL, as memory immunity has declined in a substantial proportion of individuals. Cost-effectiveness of post-booster check for anti-HBs is low and should be further evaluated based on contextual specific utilization of results.

Chaouch, H., et al. (2016). "Impact and long-term protection of hepatitis B vaccination: 17 years after universal hepatitis B vaccination in Tunisia." Epidemiol Infect: 1-11.

Hepatitis B virus (HBV) vaccination has been part of the Expanded Programme of Immunization (EPI) in Tunisia since 1995. The aim of this study was to evaluate, for the first time, the impact of mass vaccination in Tunisia 17 years after this programme was implemented, and in parallel, assess the long-term persistence of anti-HBs antibody in the vaccinated Tunisian population. A total of 1422 students were recruited (703 vaccinated, 719 non-vaccinated). HBV seromarkers were checked. None of the students from either group had positive HBsAg. The overall prevalence of anti-HBc was 0.8%. A Significantly higher prevalence of anti-HBc was noted in unvaccinated students than in vaccinated (1.4% vs. 0.3%, P = 0.02). The overall seroprotection rate (anti-HBs titre 10 mIU/ml) was 68.9% in vaccinated subjects. Seroprotection rates and geometric mean titres decreased significantly with increasing age, reflecting waning anti-HBs titre over time. No significant difference was detected between seroprotection rates and gender or students' area of origin. Incomplete vaccination was the only factor associated with an anti-HBs titre <10 mIU/ml. This study demonstrates the excellent efficacy of the HBV vaccination programme in Tunisia 17 years after its launch. However, a significant decline of anti-HBs seroprotection has been observed in 15-year-old adolescents which places them at risk of infection. Additional studies are needed in hyperendemic regions in Tunisia.

Chaves, S. S., et al. (2012). "Persistence of long-term immunity to hepatitis B among adolescents immunized at birth." Vaccine **30**(9): 1644-1649.

The long-term duration of recombinant hepatitis B vaccine-induced immunity among persons vaccinated starting at birth is still not well understood. Waning of vaccine-induced immunity could leave young adults at risk of hepatitis B virus infection due to behavioral or occupational exposures. We followed a cohort of children immunized starting at birth with a 3-dose regimen of recombinant hepatitis

B vaccine (5 mcg, 2.5 mcg, 2.5 mcg). They were challenged with a booster dose of the hepatitis B vaccine 10 and 15 years after vaccination to assess anamnestic response as a measure of persistence of protection. Among 108 participants who had lost protective antibody levels against hepatitis B, the majority (>70%) had an anamnestic response to the booster dose; response rates did not decline significantly between 10 and 15 years follow-up periods. A high antibody concentration following primary vaccination was independently associated with an anamnestic response later on in life. Nonetheless, ~20-30% of participants were unable to mount an immune response after boosting. Hepatitis B revaccination might be required for persons vaccinated starting at birth if opportunities for hepatitis B virus exposure exist. Future vaccine recommendations should be based on studies ascertaining protection against clinically significant disease.

Chen, T., et al. (2016). "[Long-term efficacy of neonatal hepatitis B vaccination against chronic hepatitis B virus infection and chronic liver disease: a cross-sectional study based on Qidong Hepatitis B Intervention Study]." Zhonghua Liu Xing Bing Xue Za Zhi **37**(1): 64-67.

OBJECTIVE: To evaluate the long-term protection efficacy of neonatal hepatitis B vaccination on chronic hepatitis B (CHB) and liver fibrosis and cirrhosis in adults. METHODS: From January to October, 2013, a cross-sectional study was conducted among the participants from Qidong Hepatitis B Intervention Study (QHBIS), who were selected through stratified random sampling. The detections of serum alanine aminotransferase (ALT), HBsAg, anti-HBs, anti-HBc, HBeAg, and anti-HBe were conducted and ultrasonography on liver, gallbladder and spleen was performed for them. The positive rates of each serologic markers, the prevalence of active CHB and liver fibrosis and cirrhosis were calculated, the gender specific differences between vaccination group and control group were compared with Chi-square test. RESULTS: A total of 4 421 participants aged (25.59+/-1.84) years in vaccination group and 3 880 participants aged (26.61+/-2.24) years in control group were surveyed. The positive rates of HBsAg, anti-HBs, anti-HBc, HBeAg and anti-HBe were 2.38%, 37.73%, 3.78%, 0.57% and 2.15% in vaccination group, and 9.02%, 29.41%, 16.83%, 2.73% and 8.87% in control group, respectively, the differences between two groups were statistically significant (all P<0.05). The prevalence of active CHB and liver fibrosis and cirrhosis were 0.45% and 0.16% in vaccination group, 1.29% and 0.39% in control group, the differences between two groups were statistically significant (P<0.05). The active CHB prevalence was lower in females than in males in both vaccination group and control group (P<0.05). The liver fibrosis and cirrhosis prevalence was lower in females than in males in control group (P<0.05); whereas, no statistical significant difference in liver fibrosis & cirrhosis prevalence between males and females was found in vaccination group (P>0.05). CONCLUSIONS: Protection conferred by neonatal hepatitis B vaccination could last to marrying age. The gender specific difference in protection efficacy needs further study.

Lin, A. W. and K. H. Wong (2013). "Long-term protection of neonatal hepatitis B vaccination in a 30-year cohort in Hong Kong." J Hepatol **59**(6): 1363-1364.

McMahon, B. J., et al. (2005). "Antibody levels and protection after hepatitis B vaccination: results of a 15-year follow-up." Ann Intern Med **142**(5): 333-341.

BACKGROUND: The duration of protection afforded by hepatitis B vaccination is unknown. OBJECTIVE: To determine antibody persistence and protection from

hepatitis B virus (HBV) infection. DESIGN: Prospective cohort study. SETTING: 15 villages in southwest Alaska. PARTICIPANTS: 1578 Alaska Natives vaccinated at age 6 months or older. INTERVENTION: During 1981-1982, participants received 3 doses of plasma-derived hepatitis B vaccine. This cohort was followed annually over the first 11 years, and 841 (53%) persons were tested at 15 years. MEASUREMENTS: Antibody to hepatitis B surface antigen (anti-HBs), markers of HBV infection, and testing to identify HBV variants. RESULTS: Levels of anti-HBs in the cohort decreased from a geometric mean concentration of 822 mIU/mL after vaccination to 27 mIU/mL at 15 years. Initial anti-HBs level, older age at vaccination, and male sex were associated with persistence of higher anti-HBs levels at 15 years when analyzed by a longitudinal linear mixed model. After adjustment for initial anti-HBs level and sex, those vaccinated at age 6 months to 4 years had the lowest anti-HBs level at 15 years. Asymptomatic breakthrough infections were detected in 16 participants and occurred more frequently in persons who did not respond to vaccination than those who responded (P = 0.01). Among infected persons with viremia, 2 were infected with wild-type HBV and 4 had HBV surface glycoprotein variants, generally accompanied by wild-type HBV. LIMITATIONS: The loss of participants to follow-up at 15 years was 47%. However, characteristics of persons tested were similar to those of persons lost to follow-up. CONCLUSIONS: Hepatitis B vaccination strongly protected against infection for at least 15 years in all age groups. Antibody levels decreased the most among persons immunized at 4 years of age or younger.

McMahon, B. J., et al. (2009). "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 **200**(9): 1390-1396.

BACKGROUND: The duration of protection in children and adults (including health care workers) resulting from the hepatitis B vaccine primary series is unknown. METHODS: To determine the protection afforded by hepatitis B vaccine, Alaska Native persons who had received plasma-derived hepatitis B vaccine when they were >6 months of age were tested for antibody to hepatitis B surface antigen (anti-HBs) 22 years later. Those with levels <10 mIU/mL received 1 dose of recombinant hepatitis B vaccine and were evaluated on the basis of anti-HBs measurements at 10-14 days, 30-60 days, and 1 year. RESULTS: Of 493 participants, 60% (298) had an anti-HBs level >or=10 mIU/mL. A booster dose was administered to 164 persons, and 77% responded with an anti-HBs level >or=10 mIU/mL at 10-14 days, reaching 81% by 60 days. Response to a booster dose was positively correlated with younger age, peak anti-HBs response after primary vaccination, and the presence of detectable anti-HBs before boosting. Considering persons with an anti-HBs level >or=10 mIU/mL at 22 years and those who responded to the booster dose, protection was demonstrated in 87% of the participants. No new acute or chronic hepatitis B virus infections were identified. CONCLUSIONS: The protection afforded by primary immunization with plasma-derived hepatitis B vaccine during childhood and adulthood lasts at least 22 years. Booster doses are not needed.

Mendy, M., et al. (2013). "Observational study of vaccine efficacy 24 years after the start of hepatitis B vaccination in two Gambian villages: no need for a booster dose." PLoS One **8**(3): e58029.

OBJECTIVES: To determine the duration of protection from hepatitis B vaccine given in infancy and early childhood and asses risk factors for HBV infection and chronic infection. METHODS: In 1984 infant HBV vaccination was started in two Gambian villages. Cross sectional serological surveys have been undertaken every 4 years to determine vaccine efficacy. In the current survey 84.6% of 1508 eligible participants aged 1-28 years were tested. A spouse study was conducted in females (aged 14 years and above) and their male partners. RESULTS: Vaccine efficacy against chronic infection with hepatitis B virus was 95.1% (95% confidence interval 91.5% to 97.1%), which did not vary significantly between age groups or village. Efficacy against infection was 85.4% (82.7% to 87.7%), falling significantly with age. Concentrations of hepatitis B antibody fell exponentially with age varying according to peak response: 20 years after vaccination only 17.8% (95% CI 10.1-25.6) of persons with a low peak response (10-99 mIU/ml) had detectable HBs antibody compared to 27% (21.9% to 32.2%) of those with a high peak response (>999 mIU/ml). Time since vaccination and a low peak response were the strongest risk factors for HBV infections; males were more susceptible, marriage was not a significant risk for females. Hepatitis B DNA was not detected after infection, which tested soley core antibody positive. An undetectable peak antibody response of <10 mIU/ml and a mother who was hepatitis B e antigen positive were powerful risk factors for chronic infection. CONCLUSIONS: Adolescents and young adults vaccinated in infancy are at increased risk of hepatitis B infection, but not chronic infection. Married women were not at increased risk. There is no compelling evidence for the use of a booster dose of HBV vaccine in The Gambia.

Middleman, A. B., et al. (2014). "Duration of protection after infant hepatitis B vaccination series." Pediatrics **133**(6): e1500-1507.

BACKGROUND: Little is known about duration of protection after the infant primary series of hepatitis B (HB) vaccine in settings of low HB endemicity. This study sought to determine the proportion of adolescents immunized as infants who had protective titers of antibody to hepatitis B surface antigen (anti-HBs) before and after a challenge dose of vaccine. METHODS: US-born 16- through 19-year-olds who received a recombinant HB vaccine 3-dose series initiated within 7 days of birth (group 1) or at >/=4 weeks of age (group 2) and completed by 12 months of age were enrolled. Participants had serologic testing before and 2 weeks after randomization to receive a challenge dose of 10 microg or 20 microg of Engerix-B. Baseline and postchallenge levels of anti-HBs were compared by group, challenge dosage, and demographic and behavioral characteristics. RESULTS: At baseline, 24% had protective anti-HBs levels of >/=10 IU/mL; 92% achieved protective levels after challenge dose. Although group 1 had a lower proportion of seroprotection at baseline, group and challenge dosage were not associated with postchallenge proportion of seroprotection. Being in group 2, higher test dosage, higher baseline geometric mean titer, and nonwhite race were associated with significantly higher geometric mean titer after challenge dose. CONCLUSIONS: More than 90% of study participants immunized against HB as infants exhibited a seroprotective response to a challenge dose of vaccine. Duration of protection from the primary infant HB vaccine series extended through the adolescent years in the setting of low HB endemicity.

Ni, Y. H., et al. (2012). "Minimization of hepatitis B infection by a 25-year universal vaccination program." J Hepatol **57**(4): 730-735.

BACKGROUND & AIMS: Hepatitis B virus (HBV) infection was hyperendemic in Taiwan before the implementation of the universal infant hepatitis B immunization program, which was launched in 1984. Five previous seroepidemiologic surveys were conducted at 0, 5, 10, 15, and 20 years after the launch of the vaccination program. METHODS: We enrolled 3332 subjects younger than 30 years of age, with approximately 100 of them in each age cohort. Subjects were recruited voluntarily from schools and other institutions in Taipei, as in previous surveys. HBV seromarkers included hepatitis B surface antigen (HBsAg) and antibodies to HBsAg (anti-HBs) and hepatitis B core antigen (anti-HBc). HBV DNA levels were measured in anti-HBc positive/HBsAg negative subjects (anti-HBc only). RESULTS: The HBsAg, anti-HBs, and anti-HBc seropositive rates were very different between subjects born after the program in 2009 and the baseline group in 1984 (0.9% vs. 10%, 55.9% vs. 24.5%, and 7.0% vs. 28%, respectively). In this 6th survey, we showed that HBsAg prevalence further decreased in the vaccinated cohorts. A positive maternal HBsAg status was found in 86% of vaccine failures. Serum HBV DNA was detected in 4.2% (6/142) of anti-HBc positive/HBsAg negative subjects, with a low level of HBV DNA. All of these six subjects' HBV were genotype C. CONCLUSIONS: The universal infant HBV immunization program in Taiwan has completed its 25-year follow-up and its efficacy in young adults is clear. The continued decrease in HBsAg prevalence suggests that the elimination of HBV infection is becoming a reality.

Ni, Y. H. and D. S. Chen (2010). "Hepatitis B vaccination in children: the Taiwan experience." Pathol Biol (Paris) **58**(4): 296-300.

The world's first nationwide hepatitis B virus (HBV) universal vaccination program for infants was launched in Taiwan in July, 1984. All infants received three to four doses plasma or recombinant HBV vaccines. In addition, infants of HBeAg-positive mothers received 0.5ml of hepatitis B immunoglobulin within 24hours after birth. The vaccination coverage rate is as high as 97%. Seroprevalence of hepatitis B surface antigen (HBsAg) declined from 9.8% (prevaccination period) to 0.6% in children in Taipei City after 20years of mass vaccination. The seropositive rates for HBsAg, antibody to HBsAg, and antibody to hepatitis B core antigen were 1.2%, 50.5%, and 3.7%, respectively, in those born after the vaccination program (<20years old) in 2004. In line with the decrease of chronic HBV infection, the incidence of hepatocellular carcinoma (HCC) also decreased in children in Taiwan. From 1981 to 1994, the incidence of HCC in 6- to 9-year-olds declined from 0.52/100,000 for those born between 1974 and 1984 to 0.13 for those born between 1984 and 1986 ($p<0.001$). We extended the observation to 2000, the incidence of HCC per 100,000 children declined from 0.54 to 0.20. The prevalence of a determinant mutants (amino acids 121-149 of HBsAg) in Taiwanese carrier children was 7.8% (eight out of 103) in 1984, increased to 19.6% (10 out of 51) in 1989, peaked at 28.1% (nince out of 32) in 1994, and remained stationary at 23.1% (three out of 13) and about 25% in 1999 and 2004, respectively; it was higher in those fully vaccinated compared with those not vaccinated. The other group of subjects who are susceptible to vaccine failure is the immunocompromized hosts. We observed some de novo HBV infection in children after liver transplantation. Despite of the success of hepatitis B immunization, childhood chronic HBV infection and HCC were not eliminated by the universal vaccination program. Among those HBsAg carriers born after the vaccination program, 89% of their mothers were found to be positive for HBsAg, indicating the importance of maternal transmission. This was also true in the mothers of children with HCC, of them 96% were HBsAg

positive. After two decades of universal infant HBV vaccination, we found this program provides long-term protection for up to more than 20years, and a universal booster is not required for the primary HBV vaccinees before adulthood. Mother-to-child transmission, although largely diminished, is still the main cause for immunoprophylaxis failure. The emergence of escape mutant did not impose increased risk of chronic infection at present. Nevertheless, development of new vaccines may overcome the vaccine failure.

Peto, T. J., et al. (2014). "Efficacy and effectiveness of infant vaccination against chronic hepatitis B in the Gambia Hepatitis Intervention Study (1986-90) and in the nationwide immunisation program." BMC Infect Dis **14**: 7.

BACKGROUND: Gambian infants were not routinely vaccinated against hepatitis B virus (HBV) before 1986. During 1986-90 the Gambia Hepatitis Intervention Study (GHIS) allocated 125,000 infants, by area, to vaccination or not and thereafter all infants were offered the vaccine through the nationwide immunisation programme. We report HBV serology from samples of GHIS vaccinees and unvaccinated controls, and from children born later. METHODS: During 2007-08, 2670 young adults born during the GHIS (1986-90) were recruited from 80 randomly selected villages and four townships. Only 28% (753/2670) could be definitively linked to their infant HBV vaccination records (255 fully vaccinated, 23 partially vaccinated [1-2 doses], 475 not vaccinated). All were tested for current HBV infection (HBV surface antigen [HBsAg]) and, if HBsAg-negative, evidence of past infection (HBV core-protein antibody [anti-HBc]). HBsAg-positive samples (each with two age- and sex-matched HBsAg-negative samples) underwent liver function tests. In addition, 4613 children born since nationwide vaccination (in 1990-2007) were tested for HBsAg. Statistical analyses ignore clustering. RESULTS: Comparing fully vaccinated vs unvaccinated GHIS participants, current HBV infection was 0.8% (2/255) vs 12.4% (59/475), $p < 0.0001$, suggesting 94% (95% CI 77-99%) vaccine efficacy. Among unvaccinated individuals, the prevalence was higher in males ($p = 0.015$) and in rural areas ($p = 0.009$), but adjustment for this did not affect estimated vaccine efficacy. Comparing fully vaccinated vs unvaccinated participants, anti-HBc was 27.4% (70/255) vs 56.0% (267/475), $p < 0.00001$. Chronic active hepatitis was not common: the proportion of HBsAg-positive subjects with abnormal liver function tests (ALT > 2 ULN) was 4.1%, compared with 0.2% in those HBsAg-negative. The prevalence of antibodies to hepatitis C virus was low (0.5%, 13/2592). In children born after the end of GHIS, HBsAg prevalence has remained low; 1.4% (15/1103) in those born between 1990-97, and 0.3% (9/35150) in those born between 1998-2007. CONCLUSIONS: Infant HBV vaccination achieves substantial protection against chronic carriage in early adulthood, even though approximately a quarter of vaccinated young adults have been infected. This protection persists past the potential onset of sexual activity, reinforcing previous GHIS findings of protection during childhood and suggesting no need for a booster dose. Nationwide infant HBV vaccination is controlling chronic infection remarkably effectively.

Poovorawan, Y., et al. (2013). "Long-term anti-HBs antibody persistence following infant vaccination against hepatitis B and evaluation of anamnestic response: a 20-year follow-up study in Thailand." Hum Vaccin Immunother **9**(8): 1679-1684.

Hepatitis B vaccine has been available worldwide since the mid-1980s. This vaccine was evaluated in a clinical trial in Thailand, conducted on subjects born to hepatitis B

surface antigen positive and hepatitis B e-antigen positive mothers and vaccinated according to a 4-dose schedule at 0, 1, 2 and 12 mo of age and a single dose of hepatitis B immunoglobulin concomitantly at birth. All enrolled subjects seroconverted and were followed for 20 y to assess the persistence of antibody to the hepatitis B surface antigen (anti-HBs) (NCT00240539). At year 20, 64% of subjects had anti-HBs antibody concentrations>/=10 milli-international units per milli liter (mIU/ml) and 92% of subjects had detectable levels (>/=3.3 mIU/ml) of anti-HBs antibodies. At year 20, subjects with anti-HBs antibody titer<100 mIU/ml were offered an additional dose of hepatitis B virus (HBV) vaccine to assess immune memory (NCT00657657). Anamnestic response to the challenge dose was observed in 96.6% of subjects with an 82-fold (13.2 to 1082.4 mIU/ml) increase in anti-HBs antibody geometric mean concentrations. This study confirms the long-term immunogenicity of the 4-dose regimen of the HBV vaccine eliciting long-term persistence of antibodies and immune memory against hepatitis B for up to at least 20 y after vaccination.

Poovorawan, Y., et al. (2012). "Persistence and immune memory to hepatitis B vaccine 20 years after primary vaccination of Thai infants, born to HBsAg and HBeAg positive mothers." Hum Vaccin Immunother **8**(7): 896-904.

This study assessed antibody persistence and immune memory to hepatitis B vaccine 20 y after priming with a recombinant hepatitis B virus (HBV) vaccine during infancy. Infants were vaccinated according to a 0, 1, 6 mo schedule with or without simultaneous administration of hepatitis B immunoglobulin (HBIg). Half of the subjects enrolled received an interim booster dose at year 5 (boosted) group, whereas the other half of the subjects enrolled did not (unboosted group). Antibody persistence was assessed until year 20. Immune memory was assessed by administration of a final HBV vaccine challenge dose at year 20 in a second study. At year 20, anti-HBs antibody concentration >/= 10 mIU/ml rates and GMCs were higher among subjects in the boosted group (84.2% [16/19]; 95%CI: 60.4-96.6) when compared with those in the unboosted group [44.0% (11/25)]; 95% CI: 24.4-65.1). After the HBV vaccine challenge dose at year 20, anti-HBs anamnestic response for subjects in the unboosted and boosted groups was observed in 93.1% (95% CI: 77.2-99.2) and 100% (95% CI: 76.8-100) of subjects, respectively. The mean anti-HBs antibody concentration (GMC) was 562.0 mIU/ml (292.5-1079.7 mIU/ml) post administration of the challenge dose; this is a 28.5 fold increase from the pre- to post-challenge dose administration at year 20. This study demonstrates persistence of anti-HBs antibodies and presence of immune memory following hepatitis B vaccination for up to at least 20 y in Thailand. Immune memory was demonstrated for virtually all subjects, regardless whether they received they had received the additional HBV dose or not. The challenge dose at year 20 was well tolerated and a robust response was demonstrated. ClinicalTrials.gov Identifier: NCT00240526, NCT00774995.

Poovorawan, Y., et al. (2011). "Evidence of protection against clinical and chronic hepatitis B infection 20 years after infant vaccination in a high endemicity region." J Viral Hepat **18**(5): 369-375.

Vaccination against hepatitis B virus (HBV) immediately after birth prevents neonatal infection by vertical transmission from HBV carrier mothers. There is an ongoing debate whether infant vaccination is sufficient to protect against infection

when exposed to HBV later in life. We studied 222 Thai infants born to HBsAg -/+ and HBeAg -/+ mothers who were vaccinated with recombinant hepatitis B vaccine at 0-1-2-12 months of age. A subset of 100 subjects received a booster dose at age 5 years. Blood samples collected yearly for 20 years were examined for anti-HBs antibodies and serological markers of hepatitis B infection (anti-HBc, HBsAg, and in selected cases HBeAg, anti-HBe, HBV DNA). During the 20-year follow-up, no subject acquired new chronic HBV infection or clinical hepatitis B disease. During the first decade, possible subclinical breakthrough HBV infection (anti-HBc seroconversion) was only observed in subjects born to HBsAg +/HBeAg + mothers (6/49 [12.2%]). During the second decade, breakthrough HBV infections were detected in all groups (18/140 [12.8%]). Increases in anti-HBs concentrations that were unrelated to additional HBV vaccination or infection were detected in approximately 10% of subjects in each decade. Primary infant vaccination with a recombinant hepatitis B vaccine confers long-term protection against clinical disease and new chronic hepatitis B infection despite confirmed hepatitis B exposure.

Qu, C., et al. (2014). "Efficacy of neonatal HBV vaccination on liver cancer and other liver diseases over 30-year follow-up of the Qidong hepatitis B intervention study: a cluster randomized controlled trial." PLoS Med **11**(12): e1001774.

BACKGROUND: Neonatal hepatitis B vaccination has been implemented worldwide to prevent hepatitis B virus (HBV) infections. Its long-term protective efficacy on primary liver cancer (PLC) and other liver diseases has not been fully examined. METHODS AND FINDINGS: The Qidong Hepatitis B Intervention Study, a population-based, cluster randomized, controlled trial between 1985 and 1990 in Qidong, China, included 39,292 newborns who were randomly assigned to the vaccination group in which 38,366 participants completed the HBV vaccination series and 34,441 newborns who were randomly assigned to the control group in which the participants received neither a vaccine nor a placebo. However, 23,368 (67.8%) participants in the control group received catch-up vaccination at age 10-14 years. By December 2013, a total of 3,895 (10.2%) in the vaccination group and 3,898 (11.3%) in the control group were lost to follow-up. Information on PLC incidence and liver disease mortality were collected through linkage of all remaining cohort members to a well-established population-based tumor registry until December 31, 2013. Two cross-sectional surveys on HBV surface antigen (HBsAg) seroprevalence were conducted in 1996-2000 and 2008-2012. The participation rates of the two surveys were 57.5% (21,770) and 50.7% (17,204) in the vaccination group and 36.3% (12,184) and 58.6% (17,395) in the control group, respectively. Using intention-to-treat analysis, we found that the incidence rate of PLC and the mortality rates of severe end-stage liver diseases and infant fulminant hepatitis were significantly lower in the vaccination group than the control group with efficacies of 84% (95% CI 23%-97%), 70% (95% CI 15%-89%), and 69% (95% CI 34%-85%), respectively. The estimated efficacy of catch-up vaccination on HBsAg seroprevalence in early adulthood was 21% (95% CI 10%-30%), substantially weaker than that of the neonatal vaccination (72%, 95% CI 68%-75%). Receiving a booster at age 10-14 years decreased HBsAg seroprevalence if participants were born to HBsAg-positive mothers (hazard ratio [HR] = 0.68, 95% CI 0.47-0.97). Limitations to consider in interpreting the study results include the small number of individuals with PLC, participants lost to follow-up, and the large proportion of participants who did not provide serum samples at follow-up. CONCLUSIONS: Neonatal HBV vaccination was found to significantly decrease HBsAg seroprevalence in childhood through young

adulthood and subsequently reduce the risk of PLC and other liver diseases in young adults in rural China. The findings underscore the importance of neonatal HBV vaccination. Our results also suggest that an adolescence booster should be considered in individuals born to HBsAg-positive mothers and who have completed the HBV neonatal vaccination series. Please see later in the article for the Editors' Summary.

Teoharov, P., et al. (2013). "Immune memory and immune response in children from Bulgaria 5-15 years after primary hepatitis B vaccination." Pediatr Infect Dis J **32**(1): 51-53.

BACKGROUND: Bulgaria adopted the World Health Organization recommendation of routine universal infant vaccination against hepatitis B in 1991. Nevertheless, only a few studies evaluated the protection after the vaccination against hepatitis B, especially in children. The objective of this study was to investigate the duration of protection against hepatitis B in children aged 5-15 years after primary immunization, by measuring the immune and anamnestic immune response and possible breakthrough infections. METHODS: A total of 141 children (aged 5-17 years) were recruited randomly and divided into 3 groups, approximately 5 years (group 1), 10 years (group 2) and 15 years (group 3) after primary immunization with a recombinant hepatitis B vaccine; they were tested for hepatitis B markers: hepatitis B surface antigen anti-hepatitis core antibody and antibodies to hepatitis B surface antigen (anti-HB). A booster dose of vaccine was administered to 23 children with titers of anti-HBs antibodies below the threshold considered to be protective (<10 mIU/mL). Anti-HBs concentrations and geometric mean concentration (GMC) were determined before and 21-28 days after the booster vaccination. RESULTS: Protective anti-HBs antibodies were detected in 95 of 141 (67.4 %) tested children, with a GMC of 63.57 mIU/mL. The seroprotection rate and GMC by groups was respectively: 84.6% and GMC of 76.05 mIU/mL in group 1; 55.8% and GMC of 58.1 mIU/mL in group 2; and 61.1% and GMC of 50.33 mIU/mL in group 3. Hepatitis B surface antigen and anti-hepatitis core antibody were found in 1 of the 141 subjects (0.7%). Of the remaining 140 children, 95 had anti-HBs >/=10 mIU/mL, and anti-hepatitis core antibodies were not detected. A booster dose of hepatitis B vaccine was administered to 23 of 45 (51%) children with anti-HBs <10 mIU/mL. Anamnestic immune response was shown in 100% of the children: the GMC was 337.38 mIU/mL and protective antibodies ranged between 15 and 955 mIU/mL. CONCLUSION: The study demonstrates the presence of immune memory and protection 5-15 years after the initial course of newborn immunization with recombinant vaccines against hepatitis B.

van Damme, P. M. D. P., et al. (2011). "Long-term Immunogenicity and Immune Memory After Two Doses of the Adult Formulation of a Combined Hepatitis A and B Vaccine in Children 1 to 11 Years of Age." Pediatric Infectious Disease Journal **30**(8): 703-705.

Long-term persistence of antibodies against hepatitis A and B (anti-HAV and anti-HBs) were evaluated in 1- to 11-year-old children following 2 doses (0, 6 months) of hepatitis A and B vaccine. Ten years postvaccination, all subjects were anti-HAV seropositive (>=15 mIU/mL), 81.7% had anti-HBs antibody concentrations >=10 mIU/mL. All subjects with anti-HBs concentrations <10 mIU/mL, mounted a vigorous anamnestic response to an HBV vaccine challenge dose indicating the presence of immunologic memory against hepatitis B., (C) 2011 by Lippincott Williams & Wilkins, Inc.

Van Der Meeren, O., et al. (2016). "Immunity to hepatitis B persists in adolescents 15-16 years of age vaccinated in infancy with three doses of hepatitis B vaccine." Vaccine **34**(24): 2745-2749.

OBJECTIVE: Vaccination of infants against hepatitis B virus (HBV) using hepatitis B vaccine is effective in preventing the infection during early childhood and there is a growing evidence of long-term protection. So far, no need for a booster dose has been identified in healthy subjects; however further follow-up continues to determine the exact duration of protection. We evaluated antibody persistence and immune response to a hepatitis B vaccine challenge dose in children aged 15-16 years, previously vaccinated with 3-doses of the same vaccine in infancy (third dose received before 18 months of age). METHODS: A single hepatitis B vaccine challenge dose containing 10mug hepatitis B surface (HBs) antigen was administered to adolescents aged 15-16 years. Blood samples were taken before and one month after the challenge dose to measure anti-HBs antibodies using a chemiluminescence immunoassay. Solicited local and general symptoms, as well as unsolicited and serious adverse events were recorded after the challenge dose. RESULTS: 303 subjects were enrolled, of whom 302 and 293 subjects formed the total vaccinated and according-to-protocol cohorts, respectively. Pre-challenge, 65.4% (95% CI: 59.6-70.9) subjects were seroprotected (anti-HBs antibody concentration >/=10mIU/mL). One month post-challenge, 97.9% (95% CI: 95.6-99.2) were seroprotected, while 90.8% (95% CI: 86.8-93.8) had anti-HBs antibody concentrations >/=100mIU/mL. The post-challenge geometric mean concentration (GMC; 4134.9 [95% CI: 3114.2-5490.1]) was 150-fold higher than the pre-challenge GMC. Overall, 96.9% (95% CI: 94.2-98.6) subjects mounted an anamnestic response. The safety and reactogenicity profile of the hepatitis B vaccine challenge dose was consistent with previous experience. CONCLUSIONS: Immunity to hepatitis B persists in 15-16 year old adolescents following primary vaccination in infancy. TRIAL REGISTRATION: http://www.clinicaltrials.govNCT01847430.

Wang, F., et al. (2015). "The long-term efficacy, 13-23 years, of a plasma-derived hepatitis B vaccine in highly endemic areas in China." Vaccine **33**(23): 2704-2709.

OBJECTIVE: To evaluate the long-term effectiveness of the plasma-derived hepatitis B vaccine that has been applied widely in five areas of China where HBV prevalence was highly endemic. METHOD: A cross-sectional investigation was conducted in 2009 at five HBV surveillance sites around China. The target study subjects of 6772 were born between 1986 and 1996 and received plasma-derived HBV vaccine. Serum samples were collected to test for HBV markers using the microparticle enzyme immunoassay. RESULTS: The number of participants enrolled was 6772. The average hepatitis B surface antigen (HBsAg) prevalence was 2.01%. The birth dose group included 5052 children. In this group, the average positive rates of HBsAg and hepatitis B core antibody (anti-HBc) were 1.58% and 6.39%, respectively, and these values declined gradually from 1986 to 1996. The positive rates of anti-hepatitis B surface antibody (HBs) and the geometric mean concentration (GMC) of anti-HBs-positive subjects were 41.69% and 115.8mIU/ml. CONCLUSION: The long-term effectiveness of the plasma-derived hepatitis B vaccine still provided protection 13-23 years after vaccination. It seems that a booster dose is not necessary. Enhancing the rate of the birth dose within 24h is one of the most important measures to prevent and control HBV infection.

Wu, Q., et al. (2011). "Antibody levels and immune memory 23 years after primary plasma-derived hepatitis B vaccination: results of a randomized placebo-controlled trial cohort from China where endemicity is high." Vaccine **29**(12): 2302-2307.

> The duration of protection of hepatitis B vaccine remains incompletely understood. To assess the long-term protection provided by a primary vaccine series, the current study again recruited all subjects of a previous randomized placebo-controlled trial cohort 23 years after vaccination. Two hundred and sixty-one healthy children aged 5-9 years living in a highly HBV-endemic country were enrolled in the primary trial and received three doses of plasma-derived vaccine or placebo. The primary placebo receivers who did not receive any immunization against hepatitis B were used as non-vaccinated controls in the current study. After eliminating the interference of an early booster dose and vaccines outside the study, 48.1% (39/81) vaccinees still maintained anti-HBs titers >/= 10 mI U/mL at Year 23, higher than 34.7% (26/75) in non-vaccinated controls (P=0.088). 75-100% of vaccinees with anti-HBs titer <10 mI U/mL at Year 23 in different sub-groups divided according to early immune backgrounds developed a rapid and robust antibody anamnestic response after a booster dose, highly significantly different from non-vaccinated controls who received the same dose of vaccine (7.5%, P<0.01). No case of clinically significant HBV infection was found in the primary cohort during the whole 23 years, but 10 transient HBsAg seroconversions in the primary placebo group and one in the primary vaccine group were determined. Anti-HBc positive rate obviously tended to be lower in vaccinees compared with non-vaccinated controls at Year 23. These results suggest a persisting immune memory and certain protection for 23 years after primary vaccination in children living in highly HBV-endemic areas. Clinically insignificant infections, which cannot be avoided and may often occur in vaccinees, play a positive role in the maintaining of immunity to HBV. Booster doses should be unnecessary for more than 20 years after a full primary immunization in children (as catch-up vaccination) and, also likely, in newborns living in highly HBV-endemic areas.

Zhu, C. L., et al. (2011). "Presence of immune memory and immunity to hepatitis B virus in adults after neonatal hepatitis B vaccination." Vaccine **29**(44): 7835-7841.

> Neonatal vaccination against hepatitis B virus (HBV) infection was launched in the 1980s in Qidong, China, where HBV and hepatocellular carcinoma were highly prevalent. Presence of immune memory and immunity against HBV in adults needs to be clarified. From a cohort of 806 who received plasma-derived Hep-B-Vax as neonates and were consecutively followed at ages 5, 10, and 20 years, 402 twenty-four-year-old adults were recruited for booster test. Among them 4 (1%) were found to be HBsAg(+), 27 (6.7%) were HBsAg(-)anti-HBc(+), 121 (30.2%) were HBsAg(-)anti-HBc(-)anti-HBs(+), and 252 (62.4%) were HBsAg(-)anti-HBc(-)anti-HBs(-). Of them, 141 subjects with HBsAg(-)anti-HBc(-) were boosted with 10-mug recombinant HBV vaccine on day-0 and 1-month. The conversion rates of anti-HBs >/= 10 mIU/ml on D10-12 and 1-month post-booster were 71.4% and 87.3% respectively in the vaccinees who were anti-HBs(+) at age 5, higher than in those who were anti-HBs(-) at age 5, 57.5% and 80.0% respectively, but no statistically significant. After the second dose of booster, all subjects with anti-HBs(+) at age 5 had anti-HBs >500 mIU/ml. However, 6/40 subjects, with anti-HBs(-) at age 5, had anti-HBs <10 mIU/ml, geometric mean concentration was 3.6 (95% CI 2.0-7.7). Of the subjects received booster, 44 subjects were determined the presence of T cell immunity on

D10-12, 41 had HBsAg-specific T cells detectable, including 7/10 subjects whose anti-HBs were <10 mIU/ml 10-12 days post-booster. Among 27 HBsAg(-)anti-HBc(+) subjects, 19 had detectable serum HBV-DNA, and an "a" epitope mutation was found in 1/5 HBV isolates. One subject who was anti-HBc(+) at age 20 converted into HBsAg(+) 4 years later. The adults received neonatal HBV vaccination had immune memory and immunity against HBV infection. However, 31.9% of neonatal HBV vaccinees who responded weakly at an early age might be susceptible to HBV infection after childhood.

Part 2. Long-term protection provided by Hepatitis B vaccine and the need for booster dose: a meta-analysis.

Poorolajal et al, 2010

Prepared for: Initiative for Vaccine Research, World Health Organization
Prepared by: WHO Secretariat
August, 2016

This meta-analysis aimed to estimate long-term immunity induced by HB vaccines and the possible need of a booster dose.

Regions studied were classified into

1. regions with low endemicity (prevalence of HBV infection <2%)
2. regions with intermediate endemicity (prevalence of HBV infection 2-7%)
3. regions with high endemicity (prevalence of HBV infection is >7%)

Studies included: RCTS and prospective cohorts addressing long term (5 years follow-up ormore) HB vaccine immunogenicity.

Participants: of any age.
Exclusion criteria for participants

1. were not screened for serologic markers of HBV infection (HBsAg and anti-HBc) before vaccination
2. born to HBsAg carrier mothers
3. had predisposing factors for immunodeficiency such as HIV positive or hemodialysis.

Schedule: 3 or 4 dose irrespective of type, dosage, route or site injection.

Results: 22 studies included 20 in English and 2 in Chinese. 42 independent cohorts with overall 11,090 participants.

Table 1 shows that eight transient HBsAg seroconversion occurred among 11,090 in different periods of post-vaccination follow-up but no one become chronic carrier. The only chronic carrier state in these individuals occurred 6 months after the first dose of

vaccine suggesting that the infection was present before protective effect of HB vaccine could be established.

The overall cumulative incidence of HBV breakthrough infection 5 to 20 years in vaccinated participants was 0.007 (95%CI 0.005 to 0.010). The Chi² test for subgroup differences revealed no statistically significant differences between cumulative incidence among strata (p=0.06).

Table 1
Summary of studies results.

Stratum	Study	Fu (year)	Design	Part	Age (year)	Region	Vaccine	*N*	NF	CCS	HBsAg+	Anti-HBc+
1	But [19]	5	RCT	GP	1–11	High	RV	104	63	0	0	0
	But [19]	5	RCT	GP	1–11	High	PDV	104	64	0	0	0
	Chadha [20]	5	Cohort	HCW	37.5	Inter	PDV	18	18	0	0	0
	Durlach [21]	5	Cohort	HCW	22–55	Low	RV	292	175	0	0	0
	Gilca [22]	5	Cohort	GP	8–10	Low	RV	377	283	0	0	0
	Goh [23]	5	Cohort	HCW	19–21	High	PDV	240	100	0	0	1
	Joshi [24]	5	Cohort	HCW	21–40	Inter	RV	78	65	0	0	No data
	Lai [25]	5	RCT	GP	1–11	High	RV	106	63	0	0	0
	Lai [25]	5	RCT	GP	1–11	High	PDV	107	64	0	0	0
	Mintai [26]	5	Cohort	GP	13–15	High	PDV	95	95	0	0	9
	Wainwright [27]	5	Cohort	GP	1–65+	High	PDV	1581	1114	0	0	4
	Yuen [28]	5	RCT	GP	1–11	High	RV	99	63	0	0	0
	Yuen [28]	5	RCT	GP	1–11	High	PDV	104	64	0	0	0
	Zhang [29]	5	Cohort	GP	13–15	High	PDV	95	85	0	0	9
Total	–	5	–	–	–	–	–	3400	2316	0	0	23
2	Goh [23]	6	Cohort	GP	18–21	High	PDV	293	190	0	2	4
	Van Herck [30]	8	Cohort	GP	23.3	Low	RV	132	40	0	0	0
	Xu [31][a]	9	RCT	GP	5–9	High	PDV	126	101	0	1	16
	But [19]	10	RCT	GP	1–11	High	RV	104	55	0	0	1
	But [19]	10	RCT	GP	1–11	High	PDV	104	56	0	0	0
	Chadha [20]	10	Cohort	HCW	37.3	Inter	RV	18	16	0	0	0
	Durlach [21]	10	Cohort	HCW	33–40	Low	RV	292	114	0	0	2
	Gilca [22]	10	Cohort	GP	8–10	Low	RV	377	277	0	0	0
	Patel [32]	10	Cohort	GP	Infants	High	PDV	192	192	0	0	14
	Wainwright [33]	10	Cohort	GP	1–65+	High	PDV	1581	1059	0	2	13
	Yuen [28]	10	RCT	GP	1–11	High	RV	99	55	0	0	1
	Yuen [28]	10	RCT	GP	1–11	High	PDV	104	56	0	0	0
Total	–	6–10	–	–	–	–	–	3422	2211	0	5	51
3	Gabbuti [34]	11	Cohort	GP	12	Low	RV	480	228	0	0	0
	Xu [35][a]	11	RCT	GP	5–9	High	PDV	126	84	0	1	28
	Liu [36]	12	Cohort	GP	Infants	High	PDV	688	424	0	5	No data
	But [19]	15	RCT	GP	1–11	High	RV	104	37	0	0	1
	But [19]	15	RCT	GP	1–11	High	PDV	104	36	0	0	0
	Liao [37]	15	RCT	GP	1–3	High	PDV	308	52	1	1	No data
	McMahon [38]	15	Cohort	GP	1–65+	High	PDV	1436	783	0	6	16
	Yuen [39]	15	RCT	GP	1–11	High	RV	99	37	0	0	1
	Yuen [39]	15	RCT	GP	1–11	High	PDV	104	36	0	0	0
Total	–	11–15	–	–	–	–	–	3449	1717	1	13	46
4	Alavian [40][a]	16	Cohort	HCW	19–49	Inter	RV	200	113	0	0	30
	Yuen [39]	18	RCT	GP	1–11	High	RV	99	30	0	0	1
	Yuen [39]	18	RCT	GP	1–11	High	PDV	104	33	0	0	1
	But [19]	20	RCT	GP	1–11	High	RV	104	22	0	0	1
	But [19]	20	RCT	GP	1–11	High	PDV	104	24	0	0	1
Total	–	16–20	–	–	–	–	–	611	222	0	0	34

FU: follow-up; Part: participants; *N*: number of participants at start of follow-up; NF: number of participants at final follow-up; CCS: chronic carrier state; RCT: randomized clinical trial; GP: general population HCW: health care worker; Low: low endemicity; Inter: intermediate endemicity; High: high endemicity; RV: recombinant vaccine; PDV: plasma-derived vaccine.

[a] Outlier.

Conclusions: The results from this meta-analysis show that protection provided by HB vaccine persists for at least two decades in the great majority of immunocompetent adequately vaccinated individuals. Three doses of HB vaccine ensure a good protection against infection for up to 20 years. However, additional longer-term studies should be conducted to explore vaccine efficacy and the need of booster doses in different subgroups of the population.

Part 3. What is the duration of protection of Hepatitis B vaccines- Evidence used to inform the SAGE recommendations in April 2009

Duration of Protection

http://www.who.int/wer/2009/wer8440.pdf?ua=1

The higher the peak anti-HBs concentrations following immunization the longer it usually takes for antibody levels to decline to ≤10 mIU/ml.[23] A number of long term follow-up studies from various epidemiological settings have confirmed that HBsAg-carrier status or clinical HBV-disease rarely occurs among successfully vaccinated individuals even when the anti-HBs concentrations decline to ≤10 mIU/ml over time.[20, 36, 37] Even an absent anamnestic response following booster vaccination may not necessarily signify susceptibility to HBV in such individuals.[38] A study conducted in China, Province of Taiwan, [39] showed that immunization remained highly efficacious in reducing the HBsAg positivity rate 15–18 years after a 4-dose series of infant vaccination, despite 63.0% of vaccinees having no protective anti-HBs; and anti-HBs remained undetectable in 28.7% (158/551) of participants after a booster dose. Similarly, a randomized controlled trial in the Gambia showed that vaccination during early childhood can provide long-lasting protection against HBsAg carriage, despite the fact that 15 years after vaccination, fewer than half of the vaccinees had detectable anti-HBs antibody titres.[40] Furthermore, observational studies have shown the effectiveness of a primary series of hepatitis B vaccine in preventing infection up to 22 years post vaccination of infants.[41]

[23] Floreani A et al. Long-term persistence of anti-HBs after vaccination against HBV: an 18 year experience in health care workers. Vaccine, 2004, 22: 607–610.
[20] Jack AD et al. What level of hepatitis B antibody is protective? Journal of Infectious Diseases, 1999,179:489–492.
[36] Banatvala JE, Van Damme P. Hepatitis B vaccine–do we need boosters? Journal of Viral Hepatitis, 2003, 10:1–6.
[37] Yuen MF et al. 18-year follow-up study of a prospective randomized trial of hepatitis B vaccinations without booster doses in children. Clinical Gastroenterology and Hepatology, 2004, 2:941–945.
[38] Hammitt LL et al. Hepatitis B immunity in children vaccinated with recombinant hepatitis B vaccine beginning at birth: a follow-up study at 15 years. Vaccine, 2007, 25:6958–6964.
[39] Lu CY et al. Humoral and cellular immune responses to a hepatitis B vaccine booster 15–18 years after neonatal immunization. Journal of Infectious Diseases, 2008, 197:1419–1426.
[40] van der Sande MA et al. Long-term protection against carriage of hepatitis B virus after infant vaccination. Journal of Infectious Diseases, 2006, 193:1528–1535.
[41] Grading table III with key references. Conclusion: (i) high-quality evidence to support effectiveness of a primary series of hepatitis B vaccine to prevent any HBV infection at 15 years post-vaccination of infants; (ii) high-quality evidence to support effectiveness of a primary series of hepatitis B vaccine to prevent chronic HBV infection at 15 years post-vaccination of infants; (iii) low-quality evidence to support effectiveness of a primary series of hepatitis B vaccine to prevent HBV infection at up to 22 years post-vaccination of infants. For additional information, see: http://www.who.int/immunization/hepb_grad_duration.pdf