Expanding the impact of hepatitis B vaccines

Optimising schedules & delivery strategies

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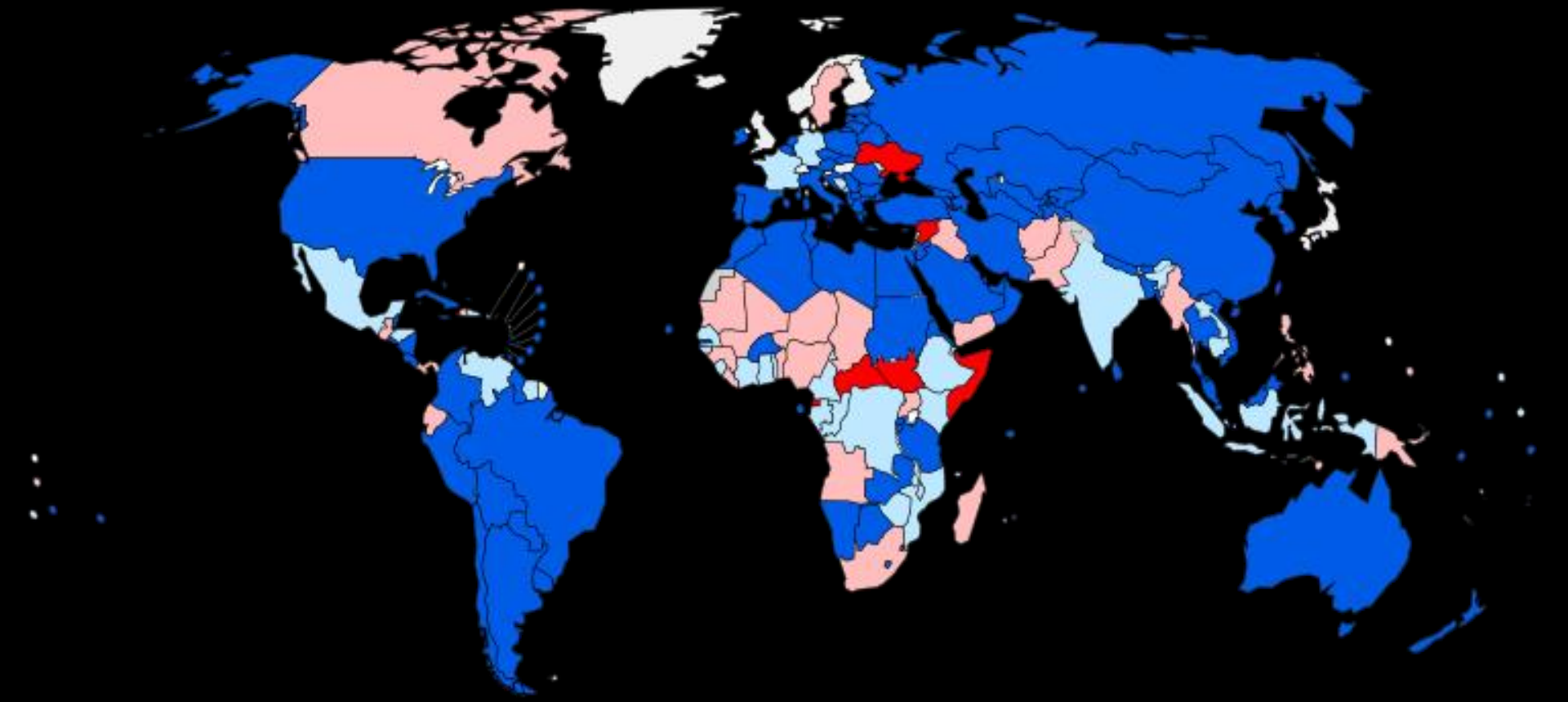
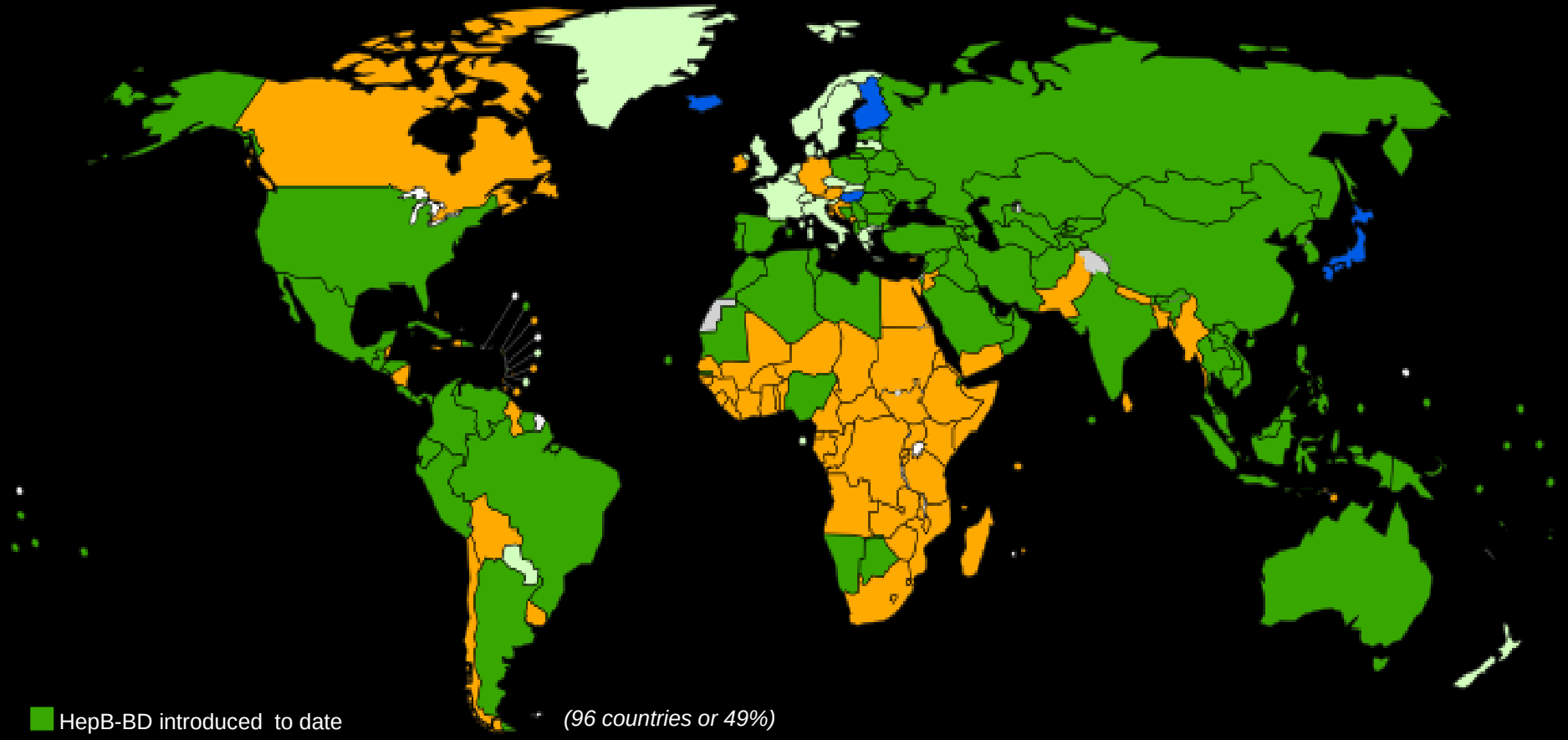
Vaccination coverage with HepB3 in infants, 2015



<50% *(6 countries or 3%)*
50-79% *(30 countries or 16%)*
80-89% *(35 countries or 18%)*
>=90% *(114 countries or 59%)*
Not available / HepB not introduced or no coverage data available *(9 countries or 5%)*
Not applicable

Source: WHO/UNICEF coverage estimates 2015 revision. July 2016. Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization. 194 WHO Member States. Date of slide: 20 July 201 6

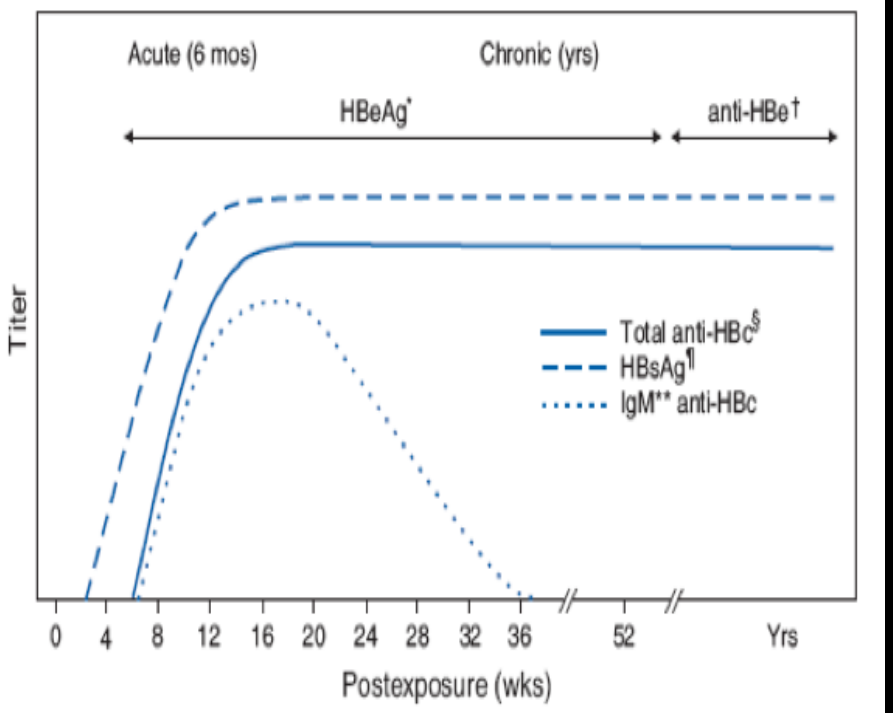
Countries with hepatitis B vaccine birth dose (HepB-BD) in the national immunization programme



- HepB-BD introduced to date *(96 countries or 49%)*
- HepB-BD only for infants born to HBsAG-positive mothers *(22 countries or 11%)*
- HepB in schedule but no HepB-BD *(72 countries or 37%)*
- HepB given only for risk groups or adolescents *(4 countries or 2%)*
- Not available
- Not applicable

Data source: WHO/IVB Databse as at 30 June 2016 and ECDC published data at http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx
194 WHO Member States
Map production Immunization Vaccines and Biologicals (IVB), World Health Organization
Date of slide: 30 June 2016

Typical serological course of acute hepatitis B virus (HBV) infection with progression to chronic HBV infection



* Hepatitis B e antigen.
† Antibody to HBeAg.
§ Antibody to hepatitis B core antigen.
¶ Hepatitis B surface antigen.
** Immunoglobulin M.

Serological marker				Interpretation
HBsAg	Total anti-HBC	IgM anti-HBC	Anti-HBs	
-	-	-	-	Never infected No vaccinated
+	+	-	-	**Chronic infection**
+	+	+	-	Acute infection
-	+	-	+	Recovered from infection; immune
-	-	-	+	Immune (vaccine or natural)

http://www.cdc.gov/mmWr/preview/mmwrhtml/rr5708a1.htm

Does the evidence suggest the need to adjust current Hep B vaccine recommendations?

Elements considered:

1. Need and timing of the first dose.
2. Number of primary doses.
3. Interval between doses.
4. Special populations (HIV – LBW - HCW)
5. Catch up schedules.
6. Booster doses.

Is birth dose important to prevent perinatal transmission?

Role of perinatal transmission on HBV related chronic liver disease in The Gambia

Between 1974 and 2008, serosurveys were repeated in two Gambian villages, and an open cohort of treatment-naive chronic HBV carriers was recruited.

405 chronic carriers (95% genotype E), recruited at a median age of 10.8 years, were followed for a median length of 28.4 years.

Chronic carriage	OR 2.0, 95% CI 1.3 to 3.1
Significant fibrosis	OR 6.4, 95% CI 2.1 to 19.8
Requiring antiviral treatment	OR 8.5, 95% CI 1.8 to 40.9
HBV-related significant fibrosis	54.3%, 95% CI 41.5% to 64.3%
Cases requiring antiviral treatment	63.0%, 95% CI 47.0% to 74.1%

The proportion of chronic carriers attributable to having an HBsAg-positive mother, was 16.0% (95% CI 8.6% to 22.9%)

Source= Shimakawa et al 2015

How protective is a birth dose against HBsAg carriage?

Studies comparing birth dose vs no birth dose

Protection against HBsAg carriage - Plasma vaccine

One RCT (Wong, 1984) compared birth dose (1 hr after birth) vs no birth dose (and no HBIG).

VE of birth dose alone =71%

Another RCT (Grosheidi, 1993) compared birth dose (0-3 days) vs no birth dose. All received HBIG.

No difference with a RR =1.0

Other RCT (Beasley 1983) compared birth dose (0-15 days) vs no birth dose. All received HBIG.

No difference with a RR=1.4 (0.3-5.7)

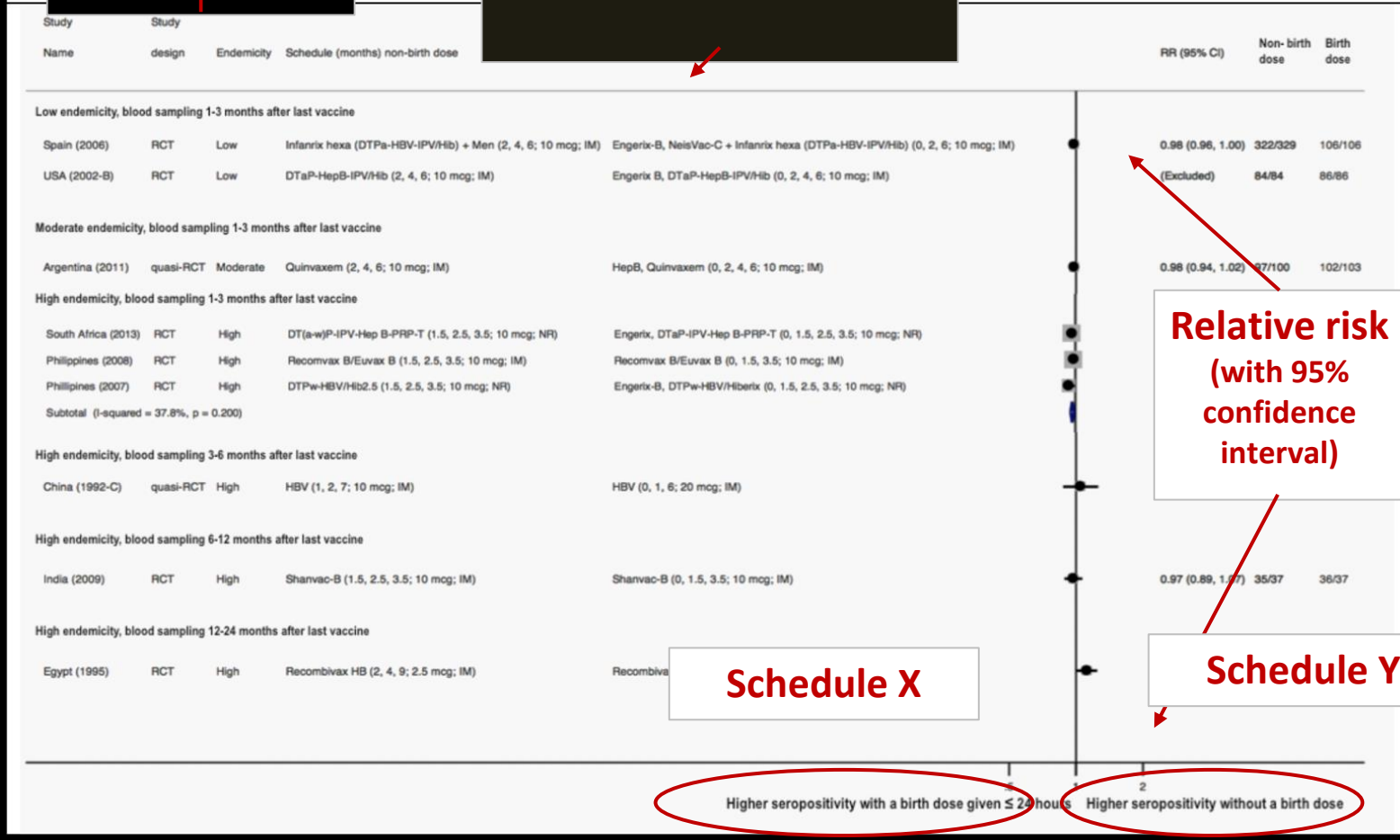
Are there differences in immunogenicity between schedules with birth dose < 24 hours vs schedules without birth dose?

Study, year, design

Schedules being compared

D … s seropr … first dose of recombinant
D … 4 hours

Certainty of the evidence (GRADE)



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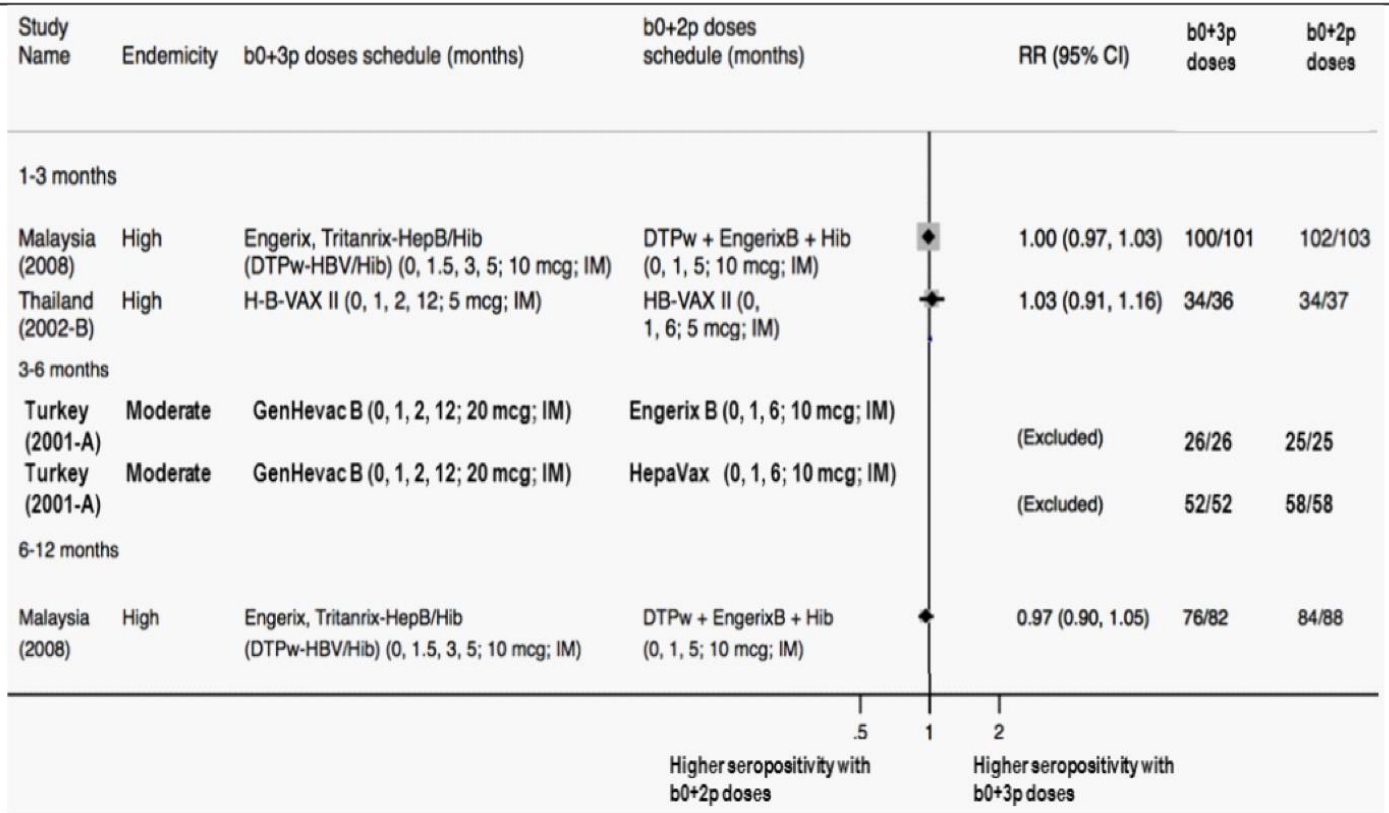
VERY LOW

7 RCTs + 2 QRCTs . Levels of anti-HBs seropositivity similar for both schedules.

Are there differences in immunogenicity between schedules with birth dose followed by 3 or by 2 primary doses?

Difference in Anti-HBs seroprotection proportions between birth dose plus 3 primary doses and birth dose plus 2 primary dose in RCTs

Forest plot



Certainty of the evidence (GRADE)

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MODERATE

No difference in seroprotection rates between schedules .

Does immunogenicity differ between schedules with different intervals between doses?

Difference in anti-HBs seroprotection proportions between two schedules of BD+ 2 p with different intervals between doses

Study Name	Study design	Endemicity	b0+2p alternative schedule (months)	bo+2p main schedule (months)	RR (95% CI)	b0+2p	b0+2p
Low endemicity, blood sampling 1-3 months after last vaccine							
USA (1994-B)	RCT	Low	Engerix-B (0, 1, 6; 10 mcg; IM)	Engerix-B (0, 1, 2; 10 mcg; IM)	1.05 (0.96, 1.15)	50/52	63/69
High endemicity, blood sampling 1-3 months after last vaccine							
Tahiti (1994)	quasi-RCT	High	Genehevac B (0, 1, 12; 20 mcg; IM)	Genehevac B (0, 1, 6; 20 mcg; IM)	1.05 (0.95, 1.15)	31/32	62/67
India (1994)	quasi-RCT	High	Engerix B (0, 1.5, 3.5; 10 mcg; IM)	Engerix B (0, 1, 2; 10 mcg; IM)	1.00 (0.83, 1.20)	25/26	8/8
India (2006)	RCT	High	NR (0, 1, 6; 10 mcg; IM)	NR (0, 1, 2; 10 mcg; IM)	0.81 (0.66, 0.99)	26/34	33/35
India (2005)	RCT	High	NR (0, 1.5, 9; 10 mcg; IM)	NR (0, 1, 6; 10 mcg; IM)	1.01 (0.99, 1.03)	297/300	299/304
High endemicity, blood sampling 3-6 months after last vaccine							
Tahiti (1994)	quasi-RCT	High	Genehevac B (0, 1, 12; 20 mcg; IM)	Genehevac B (0, 1, 6; 20 mcg; IM)	0.87 (0.52, 1.45)	2/2	33/34
China (1992-C)	quasi-RCT	High	HBV vaccine (1, 2, 7; 10 mcg; IM)	HBV vaccine (0, 1, 6 ; 20 mcg; IM)	1.05 (0.87, 1.26)	38/47	64/83
High endemicity, blood sampling 6-12 months after last vaccine							
Tahiti (1994)	quasi-RCT	High	Genehevac B (0, 1, 12; 20 mcg; IM)	Genehevac B (0, 1, 6; 20 mcg; IM)	0.98 (0.80, 1.20)	12/13	15/16
Low endemicity, blood sampling 12-24 months after last vaccine							
Italy (1993-A)	RCT	Low	Engerix B (0, 1, 6; 10 mcg; IM)	Engerix B (0, 1, 3; 10 mcg; IM)	1.01 (0.96, 1.07)	191/201	135/144
Low endemicity, blood sampling >36 months after last vaccine							
Italy (1993-A)	RCT	Low	Engerix B (0, 1, 6; 10 mcg; IM)	Engerix B (0, 1, 3; 10 mcg; IM)	1.12 (0.93, 1.35)	87/117	55/83

Certainty of the evidence (GRADE)

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LOW

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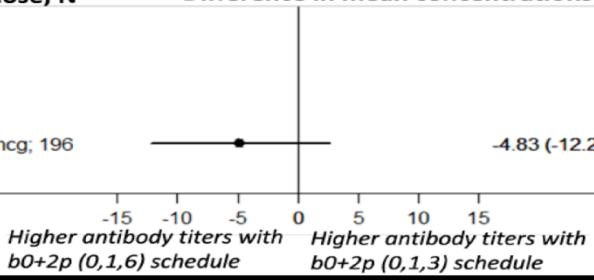
VERY LOW

Difference in GMCs of anti-HBs between two schedules of birth dose followed by 2 primary doses with different intervals between doses

Study	b0+2p schedule; dose; N	b0+2p schedule; dose; N	Difference in mean concentrations (95%)
12-24 months, low endemicity, RCT			
Italy (1993-A)	Engerix B (0, 1, 3); 10 mcg; 137	Engerix B (0, 1, 6); 10 mcg; 196	-4.83 (-12.24, 2.58)



Certainty of the Evidence (GRADE)

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LOW

Summary on effect of birth dose, number of primary doses and intervals between doses

Infants who are infected perinatally had a much higher risk of liver disease.

Protection against HBsAg carriage

Anti –HBs seroprotection

There is no difference in schedules using a birth dose followed by 2 or 3 primary doses

HBsAg seroprevalence

GMCs

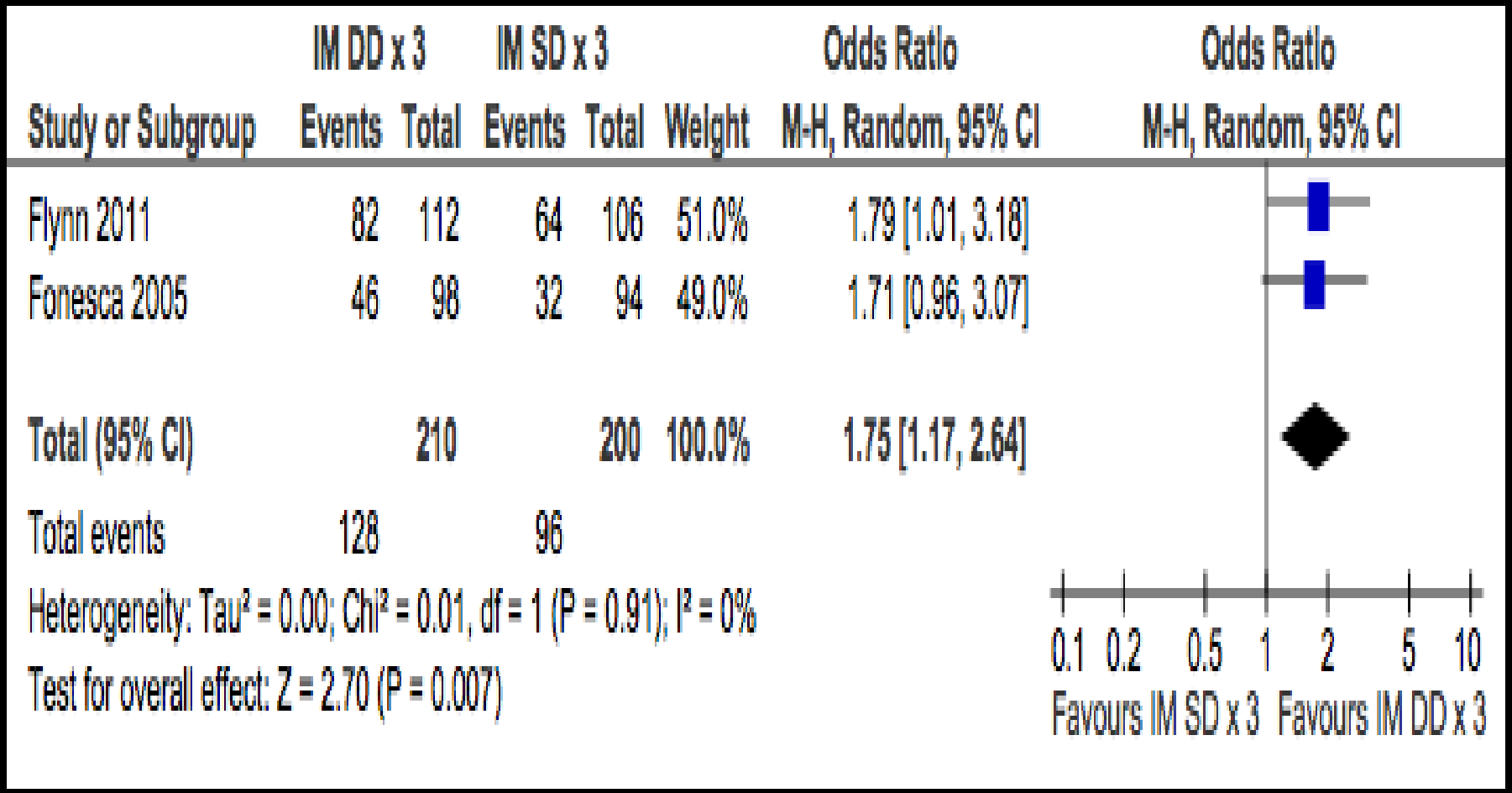
There is no difference in schedules with intervals of 1, 2 or 5 months between primary doses

Anti –HBs seroprotection

Mean concentrations

Do HIV positive people may benefit from additional doses or higher dosage of HBV vaccine?

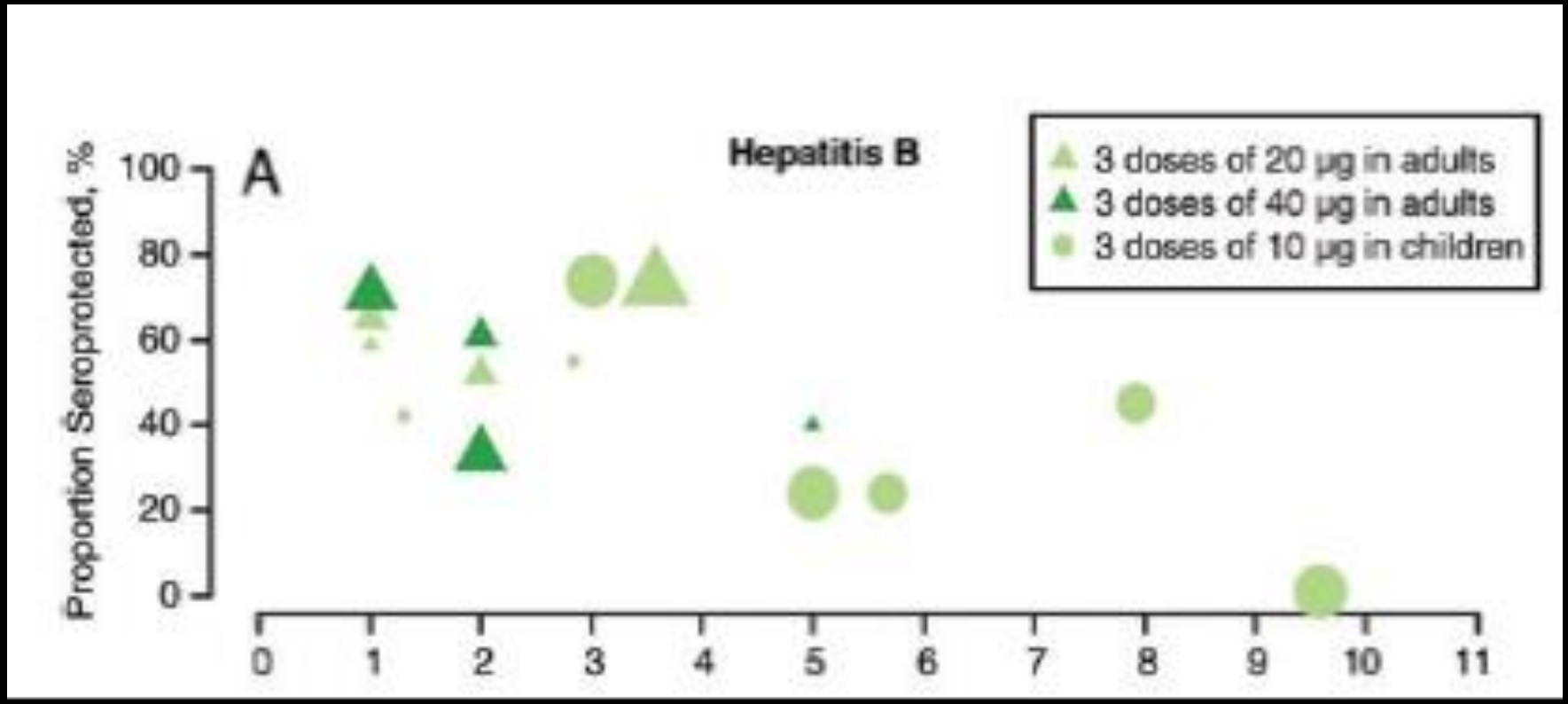
Effect of 3 injections with a double dose (3 doses of 40 µg) of recombinant HBV vaccine vs standard dose (3 doses of 20 µg doses)



Source: Wakefield 2014

Do HIV positives patients need more doses or higher dosage of HBV vaccine?

Percent of individuals with protective levels of anti-HBs in relation to time elapse since last dose

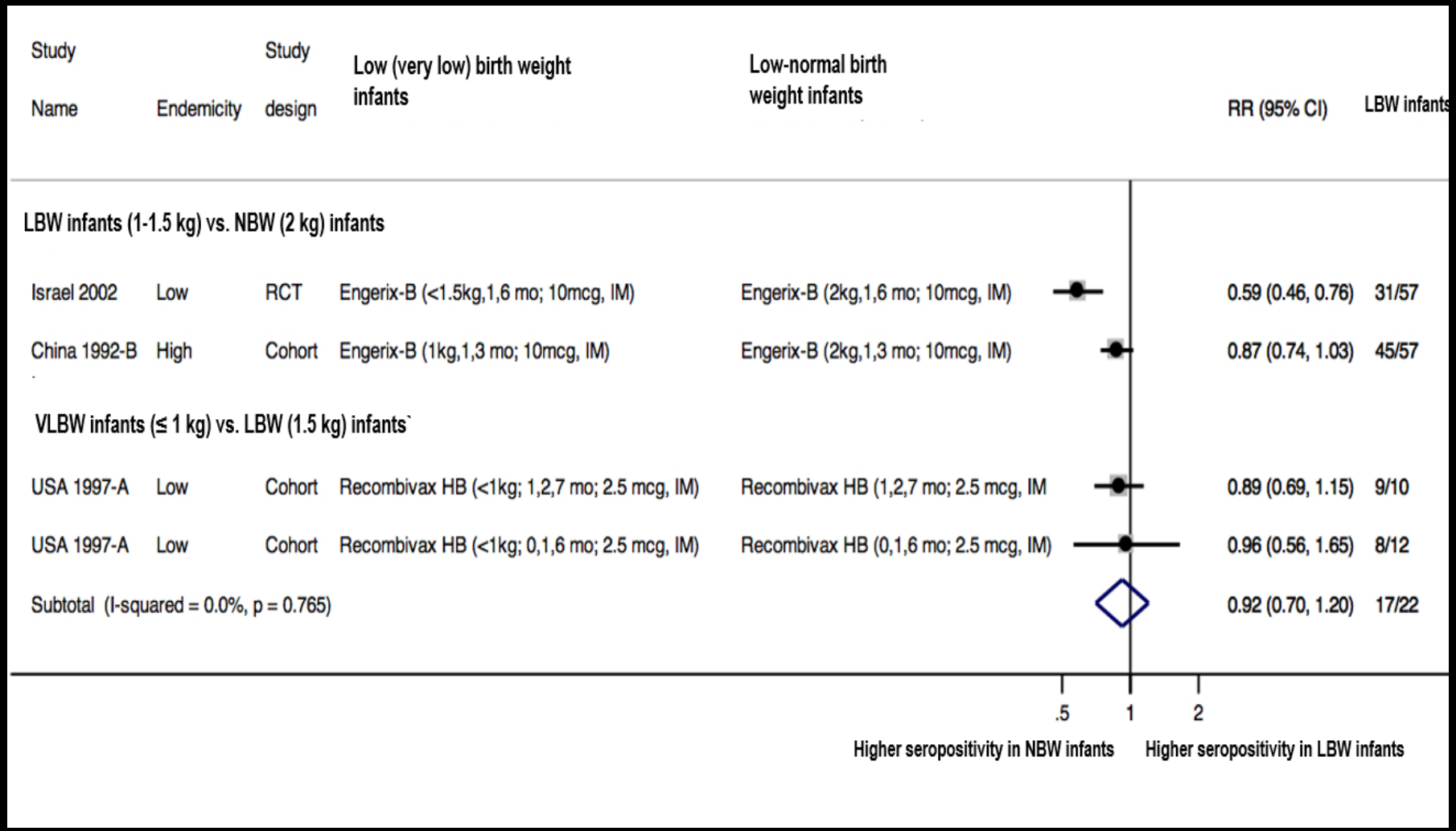


Studies with several years of follow-up do not show benefit for vaccinating HIV infected with higher titres.

Source: Kerneis S 2014

Does recommendation for Hep B vaccination among LBW babies need to be reviewed?

Difference in seropositivity for infants vaccinated at different birth weights



Special populations

Health care workers

HBV infection is a well-recognized occupational risk for HCW.

HBV is stable, infectious on surfaces for at least 7 days.

Transmissible in the absence of visible blood.

HCW do not recognize all exposures.

Even recognized, HCW often do not seek post-exposure prophylaxis.

Hepatitis B vaccine of health care workers safeguards the health of workers

Summary on the effect of Hep B vaccination among special populations

HIV infected individuals

No evidence that higher dosage or additional doses provide better protection, particularly in the long term.

Seroprotection

Low birth weight

No difference in seropositivity between low birth weight and normal birth weight neonates.

Seroprotection

Health care workers:

Hep B vaccination is important for this population

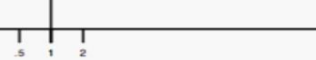
Catch-up vaccination

Difference in anti-HBs seroprotection proportions between 3P and 2P at 1-3 months after immunization

Forest plot

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

Study Name	age	Study design	Endemicity	2p Schedule (months)	3p schedule (months)	RR (95% CI)	2p doses	3p doses
6-12 months								
China (1986-A)	Infants & Children	RCT	High	H-B-VAX II (0, 1; 5 mcg; NR)	HB-VAX II (0, 1, 6; 5 mcg; NR)	0.91 (0.84, 0.98)	88/99	97/99
12-24 months								
Belgium, Czech (2002)	Children	RCT	Low	Twinrix adult (0, 6; 20 mcg; NR)	Twinrix Paediatric (0, 1, 6; 10 mcg; NR)	0.97 (0.92, 1.03)	112/120	125/130
Pakistan (2005)	Children	RCT	High	Heberbiovac HB (0, 1; 10 mcg; IM)	Heberbiovac HB (0, 1, 2; 5 mcg; IM)	0.98 (0.95, 1.01)	144/148	158/159
Pakistan (2005)	Children	RCT	High	Heberbiovac HB (0, 1; 10 mcg; IM)	Heberbiovac HB (0, 1, 2; 10 mcg; IM)	0.97 (0.94, 1.00)	144/148	150/150
China (1986-A)	Infants & Children	RCT	High	H-B-VAX II (0, 1; 5 mcg; NR)	HB-VAX II (0, 1, 6; 5 mcg; NR)	0.89 (0.82, 0.96)	87/100	99/101
24-36 months								
China (1986-A)	Infants & Children	RCT	High	HB-VAX II (0, 1; 5 mcg; NR)	HB-VAX II (0, 1, 6; 5 mcg; NR)	0.91 (0.80, 1.03)	74/91	76/85
>36 months								
Belgium, Czech (2002)	Children	RCT	Low	Twinrix adult (0, 6; 20 mcg; NR)	Twinrix Paediatric (0, 1, 6; 10 mcg; NR)	1.01 (0.90, 1.14)	68/79	87/102
ABSS (2005)	Children	RCT	Low	Twinrix (HAV-HBV) (0, 6; 20 mcg; IM)	Twinrix (HAV-HBV) (0, 1, 6; 10 mcg; IM)	0.97 (0.92, 1.03)	98/104	99/102
ABU (2007)	Children & adolescents	RCT	Low	Engerix B (0, 6; 20 mcg; IM)	Engerix B (0, 1, 6; 10 mcg; IM)	0.87 (0.78, 0.97)	105/132	64/70
5 years								
China (1986-A)	Infants & Children	RCT	High	HB-VAX II (0, 1; 5 mcg; NR)	HB-VAX II (0, 1, 6; 5 mcg; NR)	0.88 (0.76, 1.02)	61/79	69/79
12 years								
China (1986-A)	Infants & Children	RCT	High	HB-VAX II (0, 1; 5 mcg; NR)	HB-VAX II (0, 1, 6; 5 mcg; NR)	0.74 (0.57, 0.97)	29/48	35/43
22 years								
China (1986-A)	Infants & Children	RCT	High	HB-VAX II (0, 1; 5 mcg; NR)	HB-VAX II (0, 1, 6; 5 mcg; NR)	0.46 (0.23, 0.93)	6/17	13/17



Certainty of the evidence (GRADE)

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LOW

Is a booster dose needed?

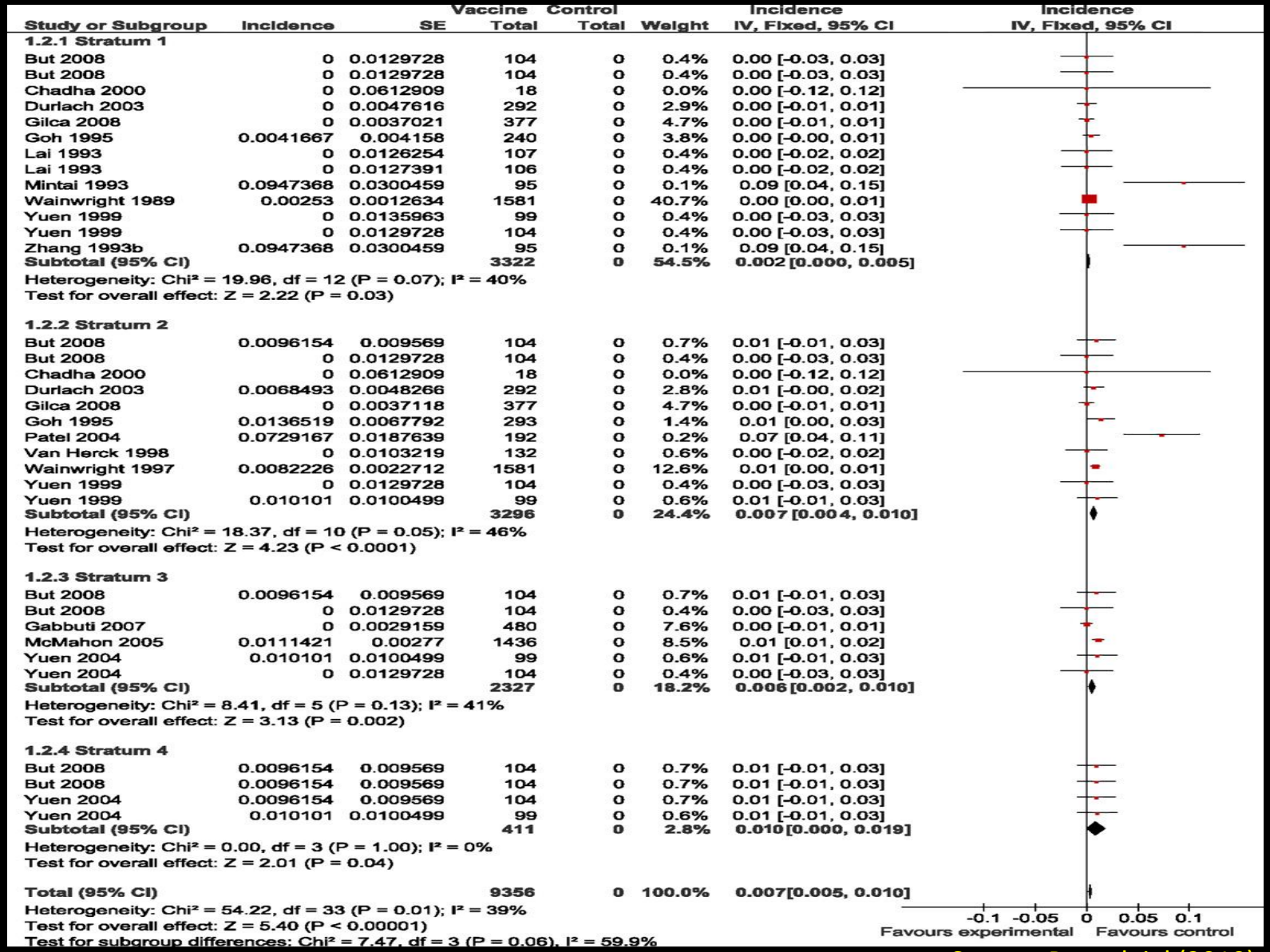
Incidence risk of HBV breakthrough infection

5 yrs

6-10 yrs

11-15 yrs

16-20 yrs



Study or Subgroup	Incidence	SE	Vaccine Total	Control Total	Weight	Incidence IV, Fixed, 95% CI
1.2.1 Stratum 1						
But 2008	0	0.0129728	104	0	0.4%	0.00 [-0.03, 0.03]
But 2008	0	0.0129728	104	0	0.4%	0.00 [-0.03, 0.03]
Chadha 2000	0	0.0612909	18	0	0.0%	0.00 [-0.12, 0.12]
Durlach 2003	0	0.0047616	292	0	2.9%	0.00 [-0.01, 0.01]
Gilca 2008	0	0.0037021	377	0	4.7%	0.00 [-0.01, 0.01]
Goh 1995	0.0041667	0.004158	240	0	3.8%	0.00 [-0.00, 0.01]
Lai 1993	0	0.0126254	107	0	0.4%	0.00 [-0.02, 0.02]
Lai 1993	0	0.0127391	106	0	0.4%	0.00 [-0.02, 0.02]
Mintai 1993	0.0947368	0.0300459	95	0	0.1%	0.09 [0.04, 0.15]
Wainwright 1989	0.00253	0.0012634	1581	0	40.7%	0.00 [0.00, 0.01]
Yuen 1999	0	0.0135963	99	0	0.4%	0.00 [-0.03, 0.03]
Yuen 1999	0	0.0129728	104	0	0.4%	0.00 [-0.03, 0.03]
Zhang 1993b	0.0947368	0.0300459	95	0	0.1%	0.09 [0.04, 0.15]
Subtotal (95% CI)			3322	0	54.5%	0.002 [0.000, 0.005]
Heterogeneity: Chi² = 19.96, df = 12 (P = 0.07); I² = 40%						
Test for overall effect: Z = 2.22 (P = 0.03)						
1.2.2 Stratum 2						
But 2008	0.0096154	0.009569	104	0	0.7%	0.01 [-0.01, 0.03]
But 2008	0	0.0129728	104	0	0.4%	0.00 [-0.03, 0.03]
Chadha 2000	0	0.0612909	18	0	0.0%	0.00 [-0.12, 0.12]
Durlach 2003	0.0068493	0.0048266	292	0	2.8%	0.01 [-0.00, 0.02]
Gilca 2008	0	0.0037118	377	0	4.7%	0.00 [-0.01, 0.01]
Goh 1995	0.0136519	0.0067792	293	0	1.4%	0.01 [0.00, 0.03]
Patel 2004	0.0729167	0.0187639	192	0	0.2%	0.07 [0.04, 0.11]
Van Herck 1998	0	0.0103219	132	0	0.6%	0.00 [-0.02, 0.02]
Wainwright 1997	0.0082226	0.0022712	1581	0	12.6%	0.01 [0.00, 0.01]
Yuen 1999	0	0.0129728	104	0	0.4%	0.00 [-0.03, 0.03]
Yuen 1999	0.010101	0.0100499	99	0	0.6%	0.01 [-0.01, 0.03]
Subtotal (95% CI)			3296	0	24.4%	0.007 [0.004, 0.010]
Heterogeneity: Chi² = 18.37, df = 10 (P = 0.05); I² = 46%						
Test for overall effect: Z = 4.23 (P < 0.0001)						
1.2.3 Stratum 3						
But 2008	0.0096154	0.009569	104	0	0.7%	0.01 [-0.01, 0.03]
But 2008	0	0.0129728	104	0	0.4%	0.00 [-0.03, 0.03]
Gabbuti 2007	0	0.0029159	480	0	7.6%	0.00 [-0.01, 0.01]
McMahon 2005	0.0111421	0.00277	1436	0	8.5%	0.01 [0.01, 0.02]
Yuen 2004	0.010101	0.0100499	99	0	0.6%	0.01 [-0.01, 0.03]
Yuen 2004	0	0.0129728	104	0	0.4%	0.00 [-0.03, 0.03]
Subtotal (95% CI)			2327	0	18.2%	0.006 [0.002, 0.010]
Heterogeneity: Chi² = 8.41, df = 5 (P = 0.13); I² = 41%						
Test for overall effect: Z = 3.13 (P = 0.002)						
1.2.4 Stratum 4						
But 2008	0.0096154	0.009569	104	0	0.7%	0.01 [-0.01, 0.03]
But 2008	0.0096154	0.009569	104	0	0.7%	0.01 [-0.01, 0.03]
Yuen 2004	0.0096154	0.009569	104	0	0.7%	0.01 [-0.01, 0.03]
Yuen 2004	0.010101	0.0100499	99	0	0.6%	0.01 [-0.01, 0.03]
Subtotal (95% CI)			411	0	2.8%	0.010 [0.000, 0.019]
Heterogeneity: Chi² = 0.00, df = 3 (P = 1.00); I² = 0%						
Test for overall effect: Z = 2.01 (P = 0.04)						
Total (95% CI)			9356	0	100.0%	0.007 [0.005, 0.010]
Heterogeneity: Chi² = 54.22, df = 33 (P = 0.01); I² = 39%						
Test for overall effect: Z = 5.40 (P < 0.00001)						
Test for subgroup differences: Chi² = 7.47, df = 3 (P = 0.06), I² = 59.9%						

Source: Poorolajal (2010)

Summary on vaccination for catch up and booster dose

Catch up schedules:

Consideration should be given adjust the number of doses recommended (2 or 3 doses)

Booster doses:

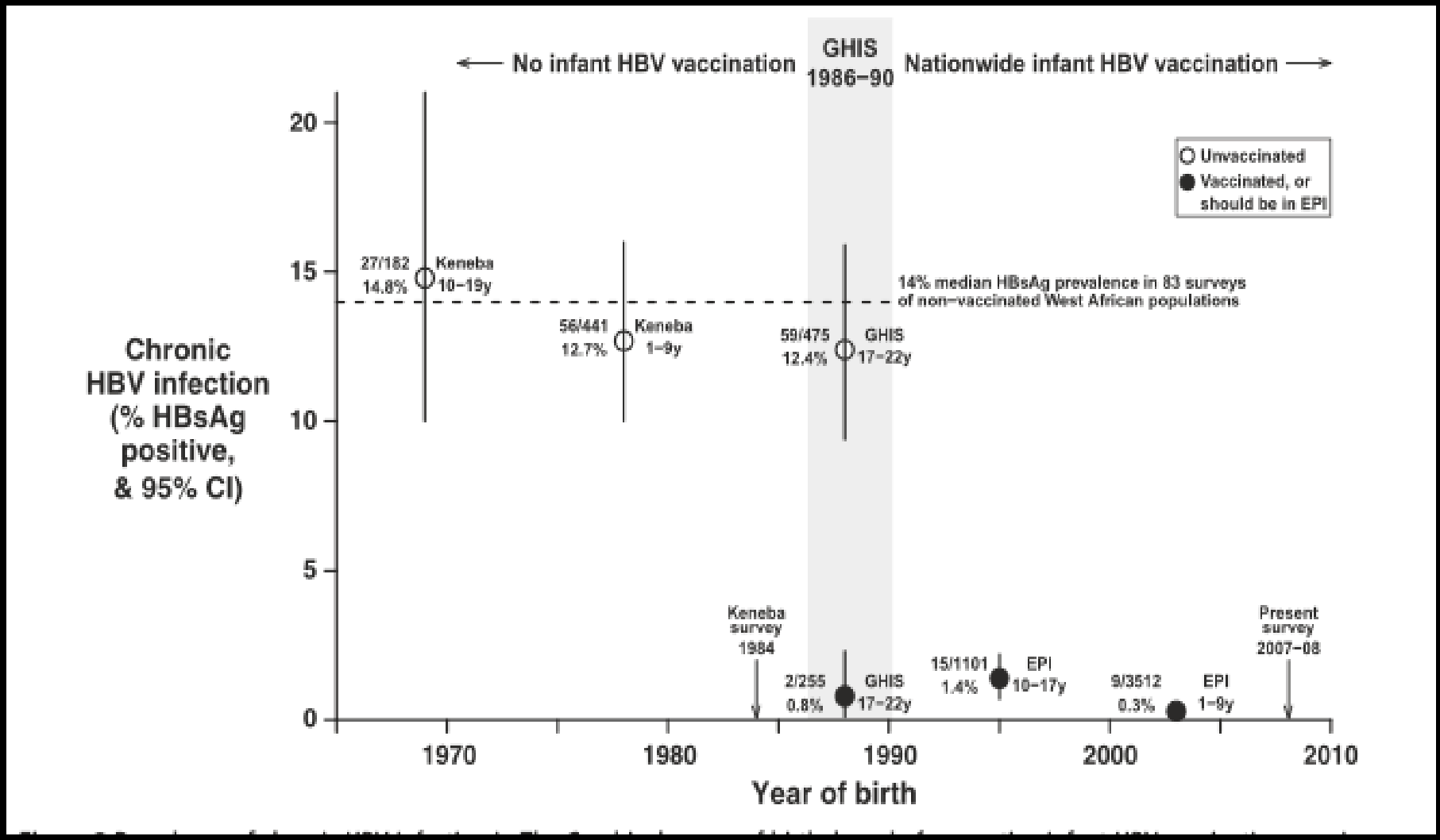
No evidence supporting the use of a booster dose.

2. What is the impact of Hep B vaccination programmes on HBV epidemiology ?

Elements considered:

1. HBV epidemiology (The Gambia, Western Pacific countries, Alaska Eskimos communities)
2. Liver cancer (China)
3. Economic analysis of Hep B vaccination

Long term protection of the Hep B vaccination program in The Gambia.



Source= Peto et al 2014

Impact of Hep B vaccination programme in children < 5 years. Western Pacific Region. 2015

Country/area	Pre-vaccination (%)		Post-vaccination			
	Median	(Min, Q1, Q3, Max) or original data[a]	Year	Age	Prevalence (%)	Number of lives saved[f]
Verified to have met the 2017 goal of less than 1%						
American Samoa	11.0[d]	11.0 [10]	2011	4–9 y	0.2 [11][d]	559
Australia	0.9[c]	0.0, 0.5, 1.3, 2.0 [12]	2002	1–9 y	0.4 [12][c]	8706
Brunei Darussalam	4.5[e]	(1.9, 3.6, 5.3, 10.5) [13,14]	2011	8–10 y	0.1 [11][d]	1984
China	8.8[b]	8.5, 8.6, 8.9, 10.5 [15]	2014	1–4 y	0.3 [11][b]	5,505,879
Cook Islands	17.4[e]	14.7, 20.0 [16,17]	2012	7 y	0.0 [11][d]	6991
Hong Kong SAR (China)	9.3[e]	(8.5, 9.0, 10.1, 11.3) [18]	2009	12–15 y	0.8 [11][b]	39,901
Macao SAR (China)	10.4[b]	7.2, 8.7, 12.15, 12.18 [19]	2003	6–9 y	0.0 [11][b]	2585
Malaysia	2.9[e]	1.4, 1.8, 3.9, 5.2 [20–23]	2009	9–10 y	0.3 [11][b]	189,942
Mongolia	10.3[e]	7.0, 10.1, 10.4, 12.0 [24–26]	2009–2010	4–6 y	0.5 [27][b]	13,420
New Zealand	1.8[b]	1.2, 1.8, 1.9 [28]	2005–2007	6–10 y	0.2 [29][c]	4738
Palau	13.5[b]	9, 13, 14, 16 [30]	2008	5–7 y	0.0 [11][d]	3302
Republic of Korea	3.9[b]	(2.0, 2.8, 4.1, 5.1) [31]	2013	10–18 y	0.4 [31][b]	234,167
Singapore	4.2[b]	3.8, 4.1, 4.3, 4.5 [32]	2008–2010	1–17 y	0.3 [32][c]	15,116
Post-vaccination representative serosurvey conducted						
Fiji	4.1[e]	(0.5, 1.6, 6.9, 12.0) [33–35]	2008	6 m–5 y	0.0 [34][c]	13,868
French Polynesia	10.5[b]	(7.6, 10.0, 12.7, 13.9) [36]	2013–2014	6–7 y	0.0 [11][b]	2742
Guam	4.5[e]	4, 5 [37,38]	2015	6 y	0 [11][d]	761
Japan	1.1[e]	(0.89, 0.94, 1.3, 1.4) [39]	2009	5–9 y	0.0 [39][e]	11,328
Kiribati	32[e]	(15.1, 27.5, 33.9, 36.2) [35,37,40]	2014	5–9 y	3.3 [41][b]	2103
Lao People's Democratic Republic	5.4[e]	(1.7, 3.1, 7.6, 9.7) [42,43]	2012	5–9 y	1.7 [42][b]	22,269
Marshall Islands	12.8[e]	9.5, 16.0 [37,44]	2007	5–9 y	1.8 [44][b]	230
Niue	10.5[e]	(4.2, 7.5, 13.5, 18.1) [45,46]	2015	5–12 y	0 [11][d]	24
Northern Mariana Islands	7.0[b]	5, 7, 8 [30]	2014	6 y	0.0 [11][d]	247
Papua New Guinea	14.0[e]	(7.9, 11.9, 36.8, 46.0) [47,48]	2012–2013	4–6 y	2.3 [49][b]	42,153
Tokelau	ND	ND	2014	6–12 y	0.0 [11][d]	41
Tonga	14.9[e]	11.1, 18.6 [35]	2004–2007	6–59 m	0.8 [50][c]	1711
Viet Nam	12.0[e]	(5.7, 10.0, 18.2, 24.7) [51–60]	2011	5–7 y	2.2 [61][b]	523,868
Wallis and Futuna	27.9[e]	27.9 [62]	2012	9–11 y	0.9 [63][d]	249

From Wiesen E, Diorditsa S, Li X. Progress towards hepatitis B prevention through vaccination in the Western Pacific, 1990–2014. Vaccine. 2016 May 27;34(25):2855-62.

Control of hepatitis B among Alaska Natives

1578 Alaska Native adults and adolescents (15 communities) aged ≥6 months received 3 doses of plasma derived hepB vaccine.

Tested for antibody to hepatitis B surface antigen (anti-HBs) levels 30 years after primary series.
Booster of recombinant vaccine to those with anti-HBs<10 mIU/mL 2–4 weeks later
Re-evaluated for anti-HBs levels 30 days after the booster.

243 persons (56%) responded to the original primary and did not received additional doses during the 30-year period,

- 125/243 (51%) had anti-HBs level ≥10 mIU/mL.
- 75 /85 (88%) with < 10mlIU/ml responded to a booster dose (anti-HBs ≥10 mIU/mL) at 30 days.
- Initial anti-HBs level after the primary series correlated with higher anti-HBs levels at 30 years.

Based on anti-HBs level at 30 years and an 88% booster dose response concluded that ≥90% of participants had evidence of protection 30 years later. Booster doses are therefore not needed

Bruce 2016.

Control of hepatitis B among Alaska Natives

Table 2. Prevalence of hepatitis B virus infection and immunity among Alaska Natives in study villages, Bristol Bay, Alaska, 1993.

Age, years	Total population	No. (%) in study sample	HBsAg positive		No. (%) HBeAg positive[a]	Resolved infection[b]	
			No. (%)[c]	95% CI		No. (%)[c]	95% CI
0–5	271	121 (45)	0	0–3	0	1 (1)	0–5
6–10	282	150 (53)	0	0–2	0	3 (2)	0–6
11–15	203	118 (58)	9 (8)	4–14	6 (67)	20 (17)	11–25
16–20	141	60 (43)	11 (18)	10–30	3 (27)	18 (30)	19–43
21–25	156	62 (40)	13 (21)	12–33	0	25 (40)	28–54
26–30	185	92 (50)	20 (22)	14–32	1 (5)	28 (30)	21–41
Total	1238	603 (49)	53 (9)	7–11	10 (19)	95 (16)	13–19

NOTE. HBsAg, hepatitis B surface antigen; HBe, hepatitis B e antigen; CI, confidence interval.

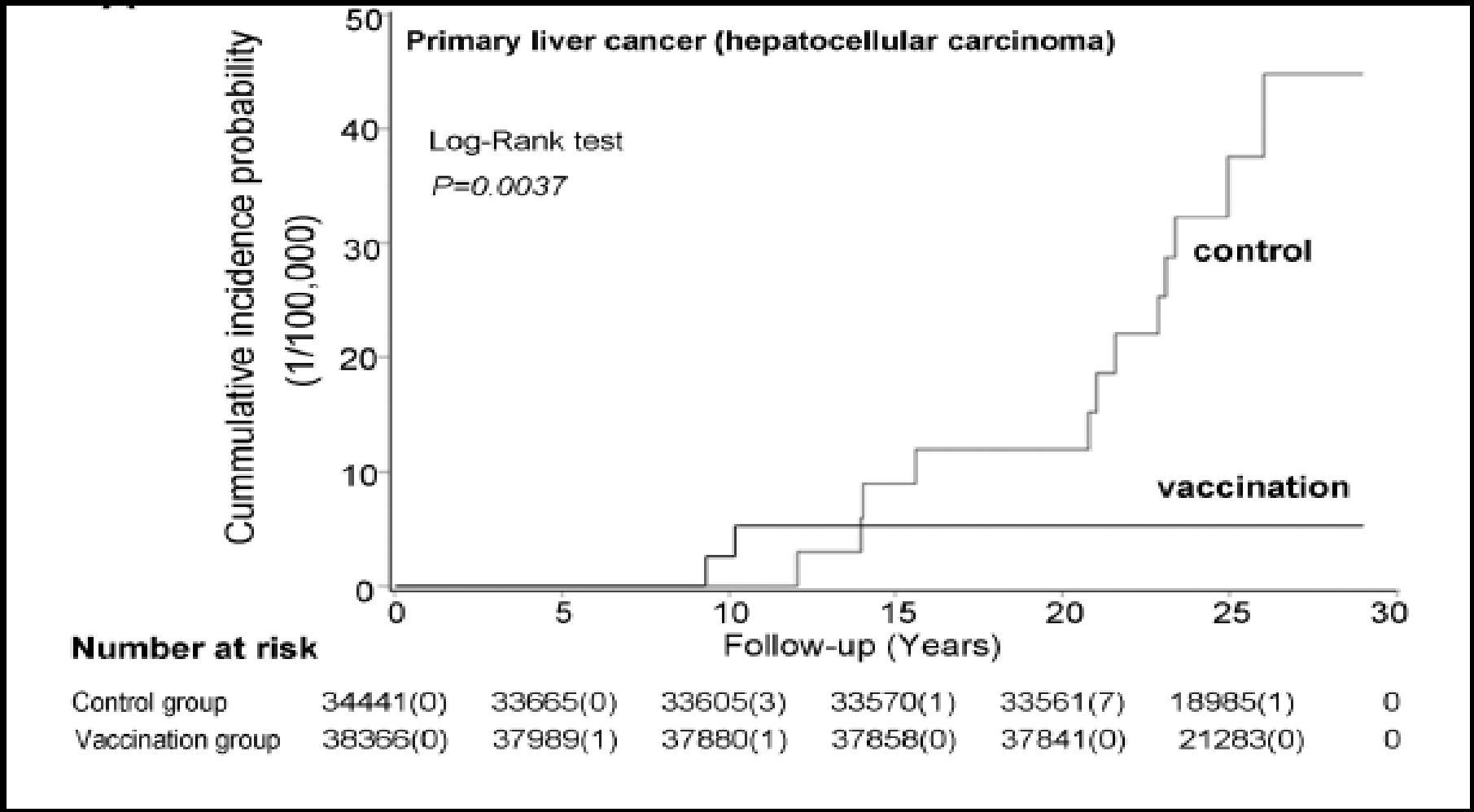
[a] Percentages calculated with HBsAg-positive subgroup ($n = 53$) as denominator.

[b] Positive for antibody to hepatitis B core antigen (anti-HBc) and antibody to hepatitis B surface antigen (anti-HBs) (8 persons were anti-HBc positive and anti-HBs negative; 1, 16–20; 1, 21–25; and 6, 26–30 years old).

[c] Percentage for each age group calculated with total study number for that age group as denominator.

Harpaz 2000. Elimination of new chronic hepatitis B virus infection: Results of the Alaska Immunization program. JID;181:413

Efficacy of neonatal Hep B vaccination on liver cancer over 30 year follow up in China (Qidong Hep B intervention trial)



Source= Qu et al 2014. Plos Med 11 (12)

VE: 84% (CI95% 23-97%)

Systematic review of economic evaluation of Hep B vaccine in LMICs

Since introduction of Hep B vaccine 19 CEA studies

14 Asia

China (8), Vietnam (1), India (3), Thailand (1), Iran (1)

5 Africa

The Gambia (2), Mozambique (2), Ethiopia (1)

Vaccination approach

Universal (12)

Targeted (4)

Not specified (3)

18/19 studies considered Hep B vaccination cost saving or cost effective. Only one study reported it was unlikely to be effective.

5/6 studies that considered the birth dose reported it was cost effective.

Vaccine price, prevalence of HBV infection, cost component, wastage rate and efficacy assumptions are key drivers.

Source= Soakaew et al. In publication

Summary on the impact of Hep B vaccination programs and economic evaluation

Long term protection:

Strong evidence on long term impact Hep B vaccination.

Impact demonstrated on chronic HBsAg carriage and hepatocellular cancer

Economic analysis

Hep B vaccination was considered cost saving and cost effective intervention

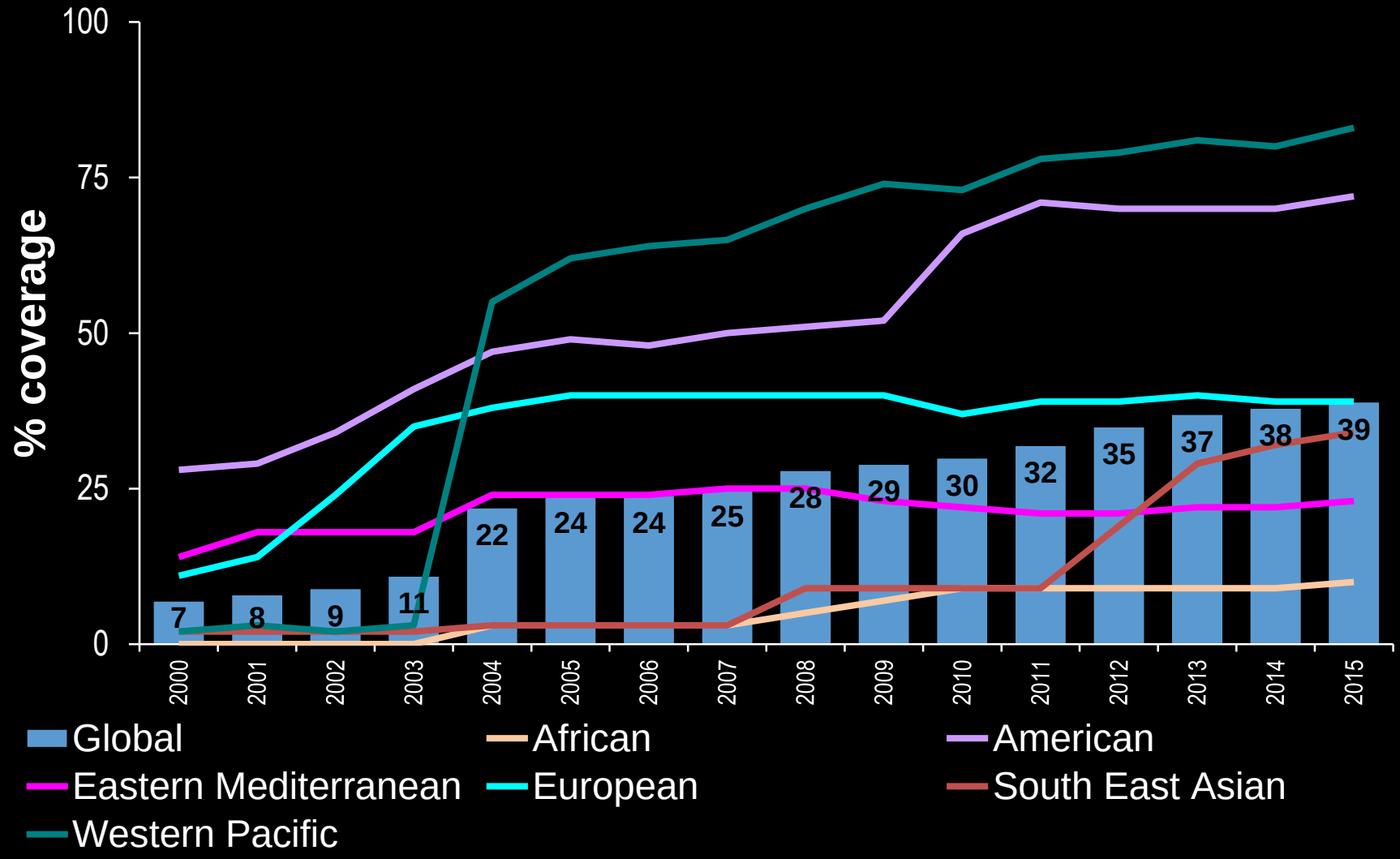
CEA analysis on birth dose should be considered for regions where it has not been introduced.

Does the evidence support flexibility in the cold chain requirement for monovalent Hep B vaccine?

Elements considered:

1. Barriers for birth dose introduction and coverage
2. Thermostability of Hep B monovalent vaccines

Global & Regional HepB birth dose coverage 2000-2015,



Source: WHO/UNICEF coverage estimates 2015 revision. July 2016
Immunization Vaccines and Biologicals, (IVB), World Health Organization.
194 WHO Member States. Date of slide: 20 July 2016.

% of births in health facility by country in Africa (UNICEF 2015)

> or = 90	8 countries
80-89	6 countries
70-79	6
60-69	7
50-59	8
<50	9

Source=UNICEF 2015

Barriers to the introduction of the Hep B birth dose Survey in selected WHO Regional offices

AFRO and SEARO Regions

Most common barriers	Proposed actions to overcome barriers
Funding not available	Partners being supportive of birth dose delivery Advocacy with MoH to identify resources/budget allocation
Births outside health facilities	Strength outreach activities to vaccinate newborns outside the health facilities
Vaccine storage/cold chain	Cold chain adequacy Conduct country pilot studies on OCC
Insufficient local disease burden data	Conduct seroprevalence surveys
Capacity to develop national policies and guidelines	Capacity building for NITAGs and NRAs

Reported barriers to the introduction of the Hep B birth dose
Findings from literature review. Community based surveys

Western Pacific	AFRO	AMRO	SEARO
Birth at home	Birth at home	Conflicting guidelines. Public vs private providers	HW poor knowledge on HBV
Vaccine storage cold chain	Performance of outreach services	Birth at home	HW´s fear of vacccine wastage.
Conflicting guidelines on birth dose. Private vs public services		Out of pocket cost	Cold chain and other vaccine management logistic weakness
Performance of outreach services			

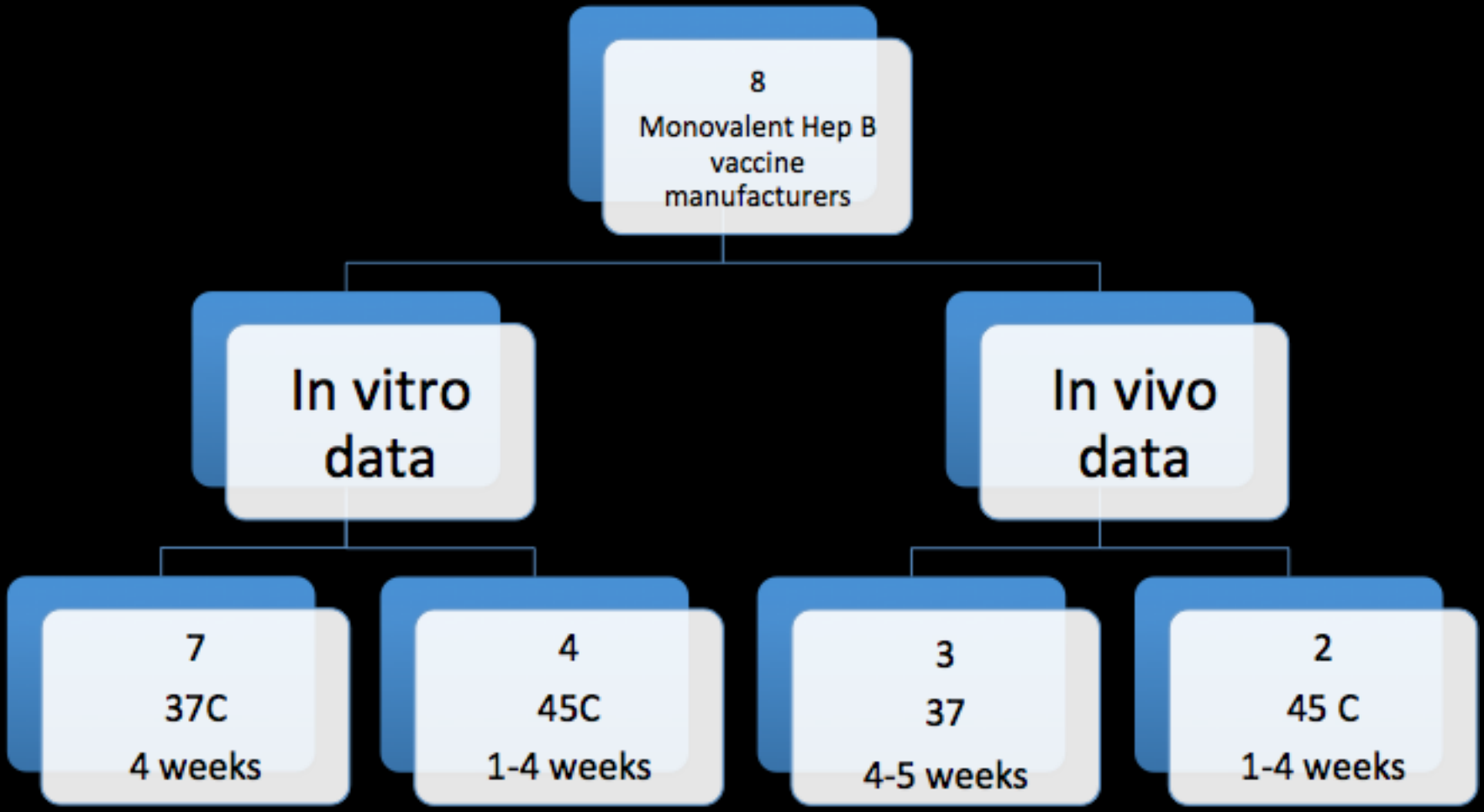
Source= De la Hoz et al 2016

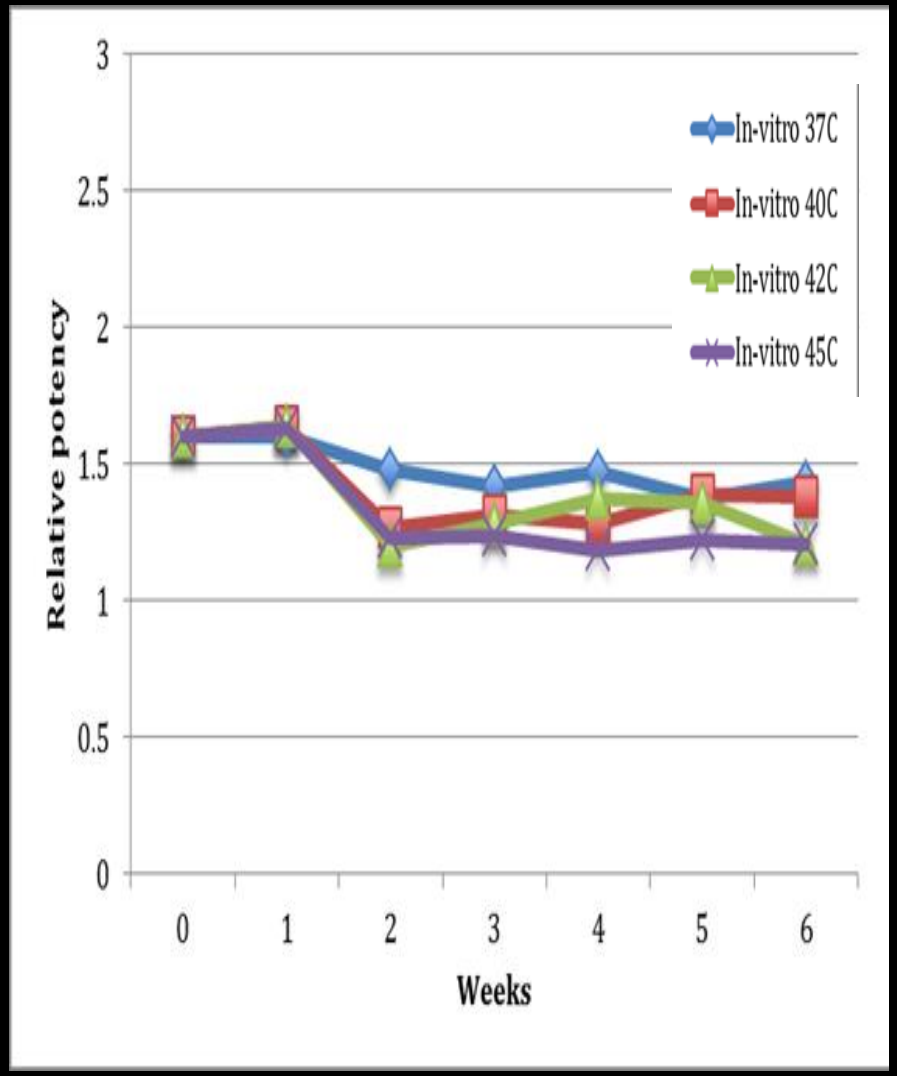
Thermostability of HBV monovalent vaccines

- Review of data from manufacturers.
- Systematic review.

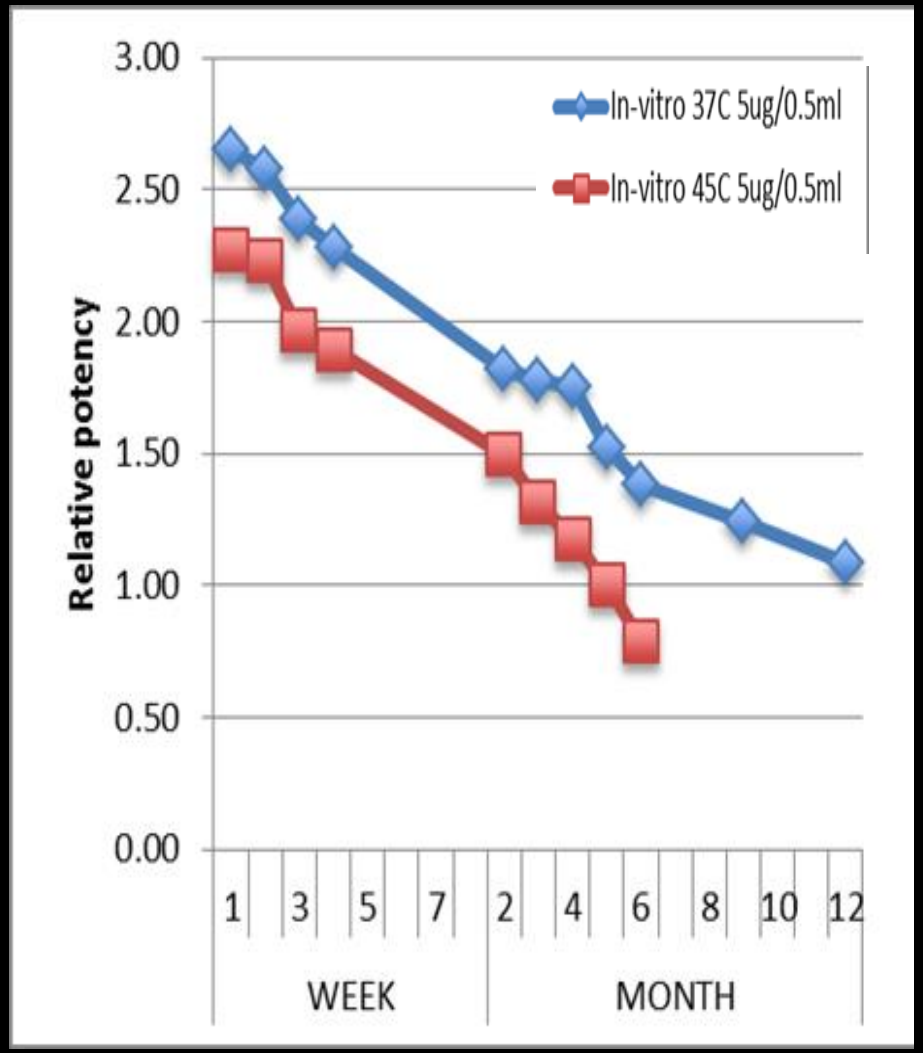
  Clinical trials and field studies assessing immunogenicity (differences in GMT) in children vaccinated with vaccine out of the cold chain
- Review of previous published reviews, reports and guidelines

Thermostability of HBV monovalent vaccines
Review of data from manufacturers

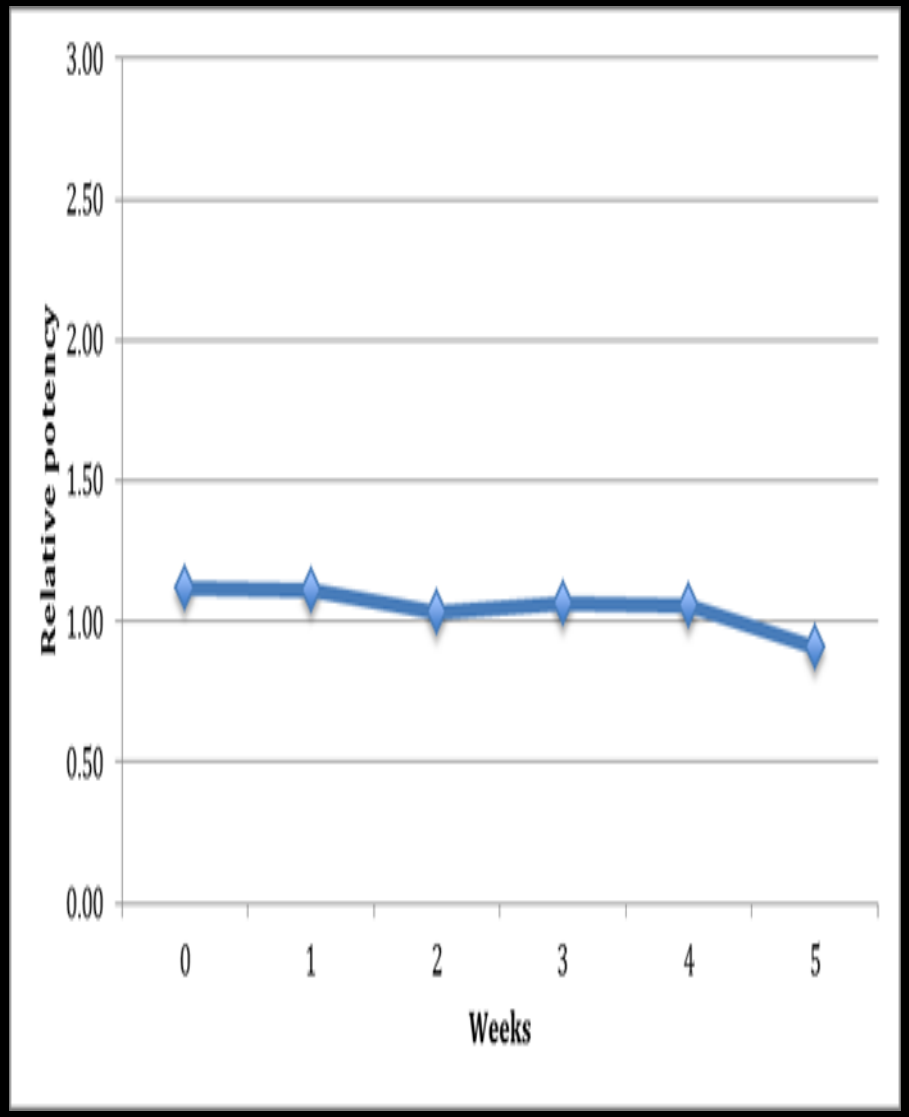




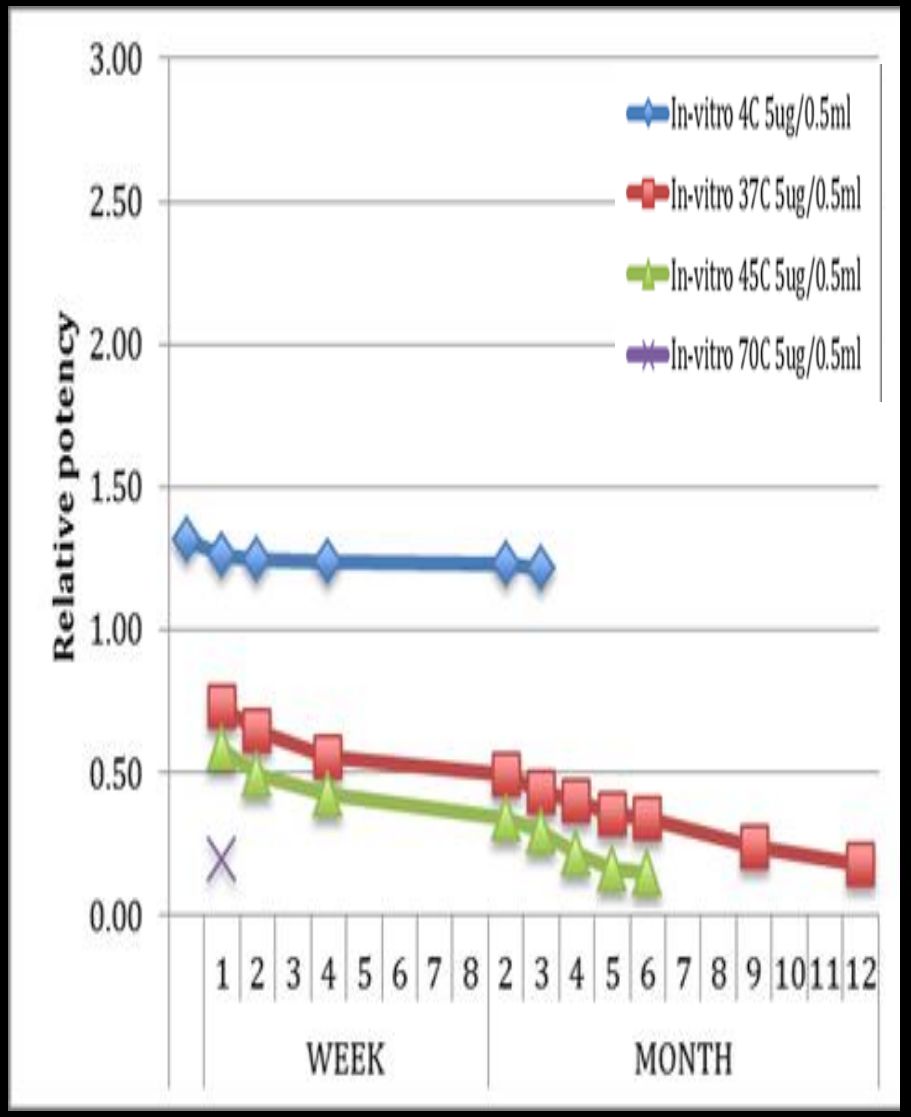
In-vitro relative potency of manufacturer A monovalent hepatitis B vaccine, exposed to different temperatures for different time periods. Minimum release and end of shelf-life relative potency >=0.45. Data provided by manufacturer and results based on Murex test kit (Diasorin).



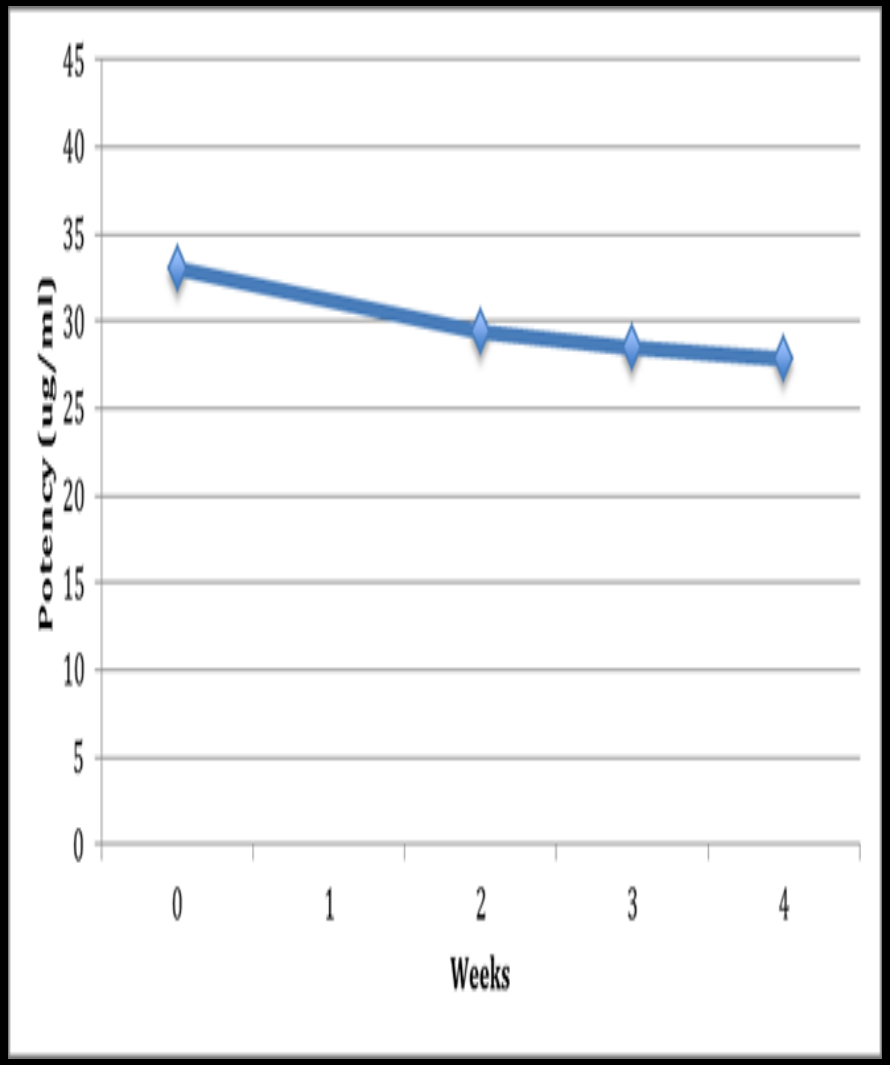
In-vitro relative potency of manufacturer C monovalent hepatitis B vaccine, exposed to different temperatures for different time periods. Minimum release and end of shelf-life relative potency >=0.50. Data provided by manufacturer. Values represent averages of two different lots.

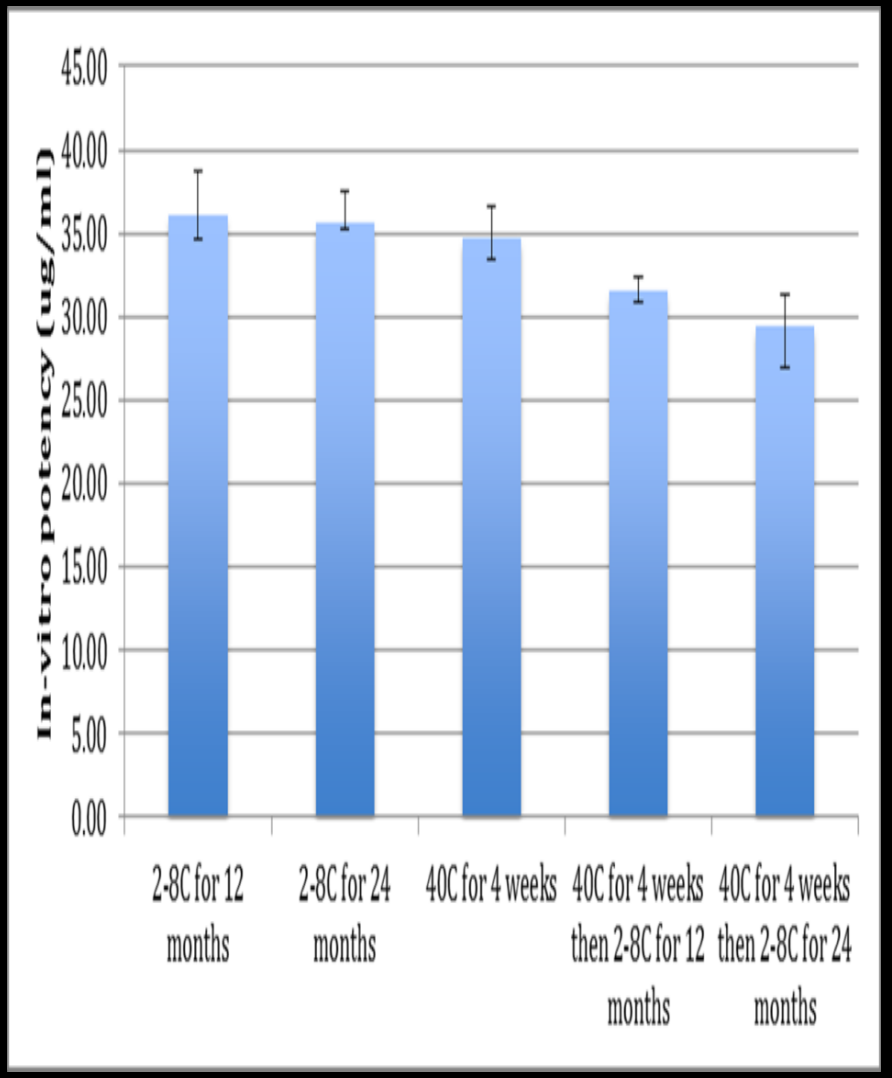


In-vitro relative potency of manufacturer D monovalent hepatitis B vaccine, exposed to 37ºC for 5 weeks. Minimum release and end of shelf-life relative potency >=0.80. Data provided by manufacturer and based on in-house potency test. Values represent averages of three different lots.



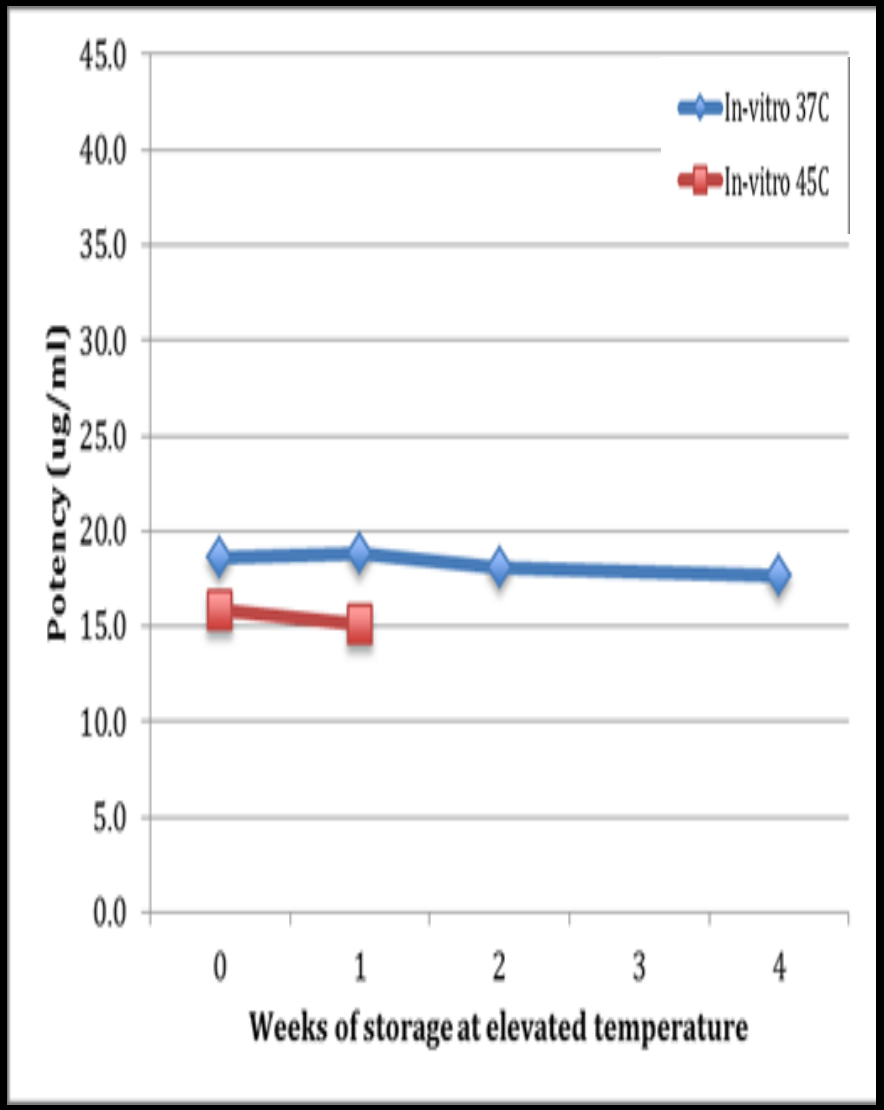
- in-vitro relative potency of manufacturer C monovalent hepatitis B vaccine, exposed to different temperatures for different time periods. Minimum release and end of shelf-life relative potency >=0.50. Data provided by manufacturer. Values represent averages of three different lots.



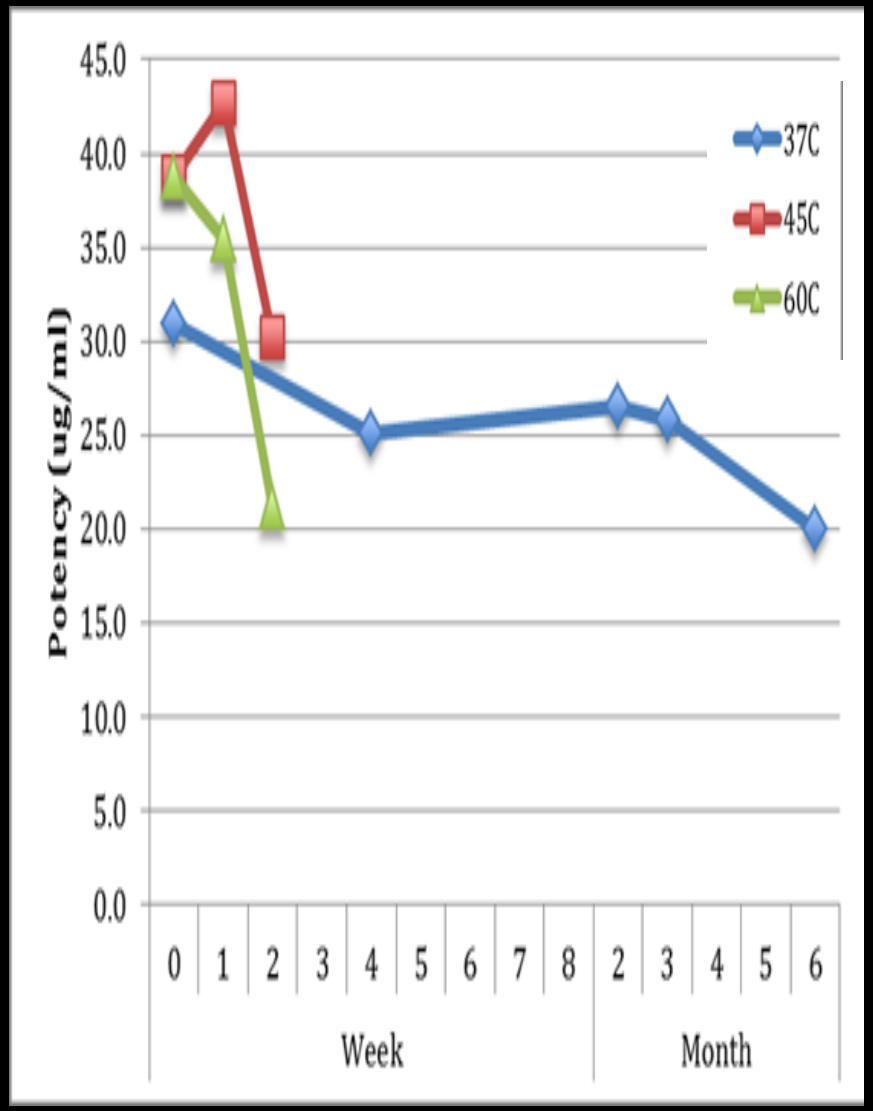


- In-vitro relative potency of manufacturer B monovalent hepatitis B vaccine, exposed to 37°C for 4 weeks. Minimum release and end of shelf-life relative potency >= 20ug/ml. Data provided by manufacturer and based on in-house potency test. Values represent averages of two batches.

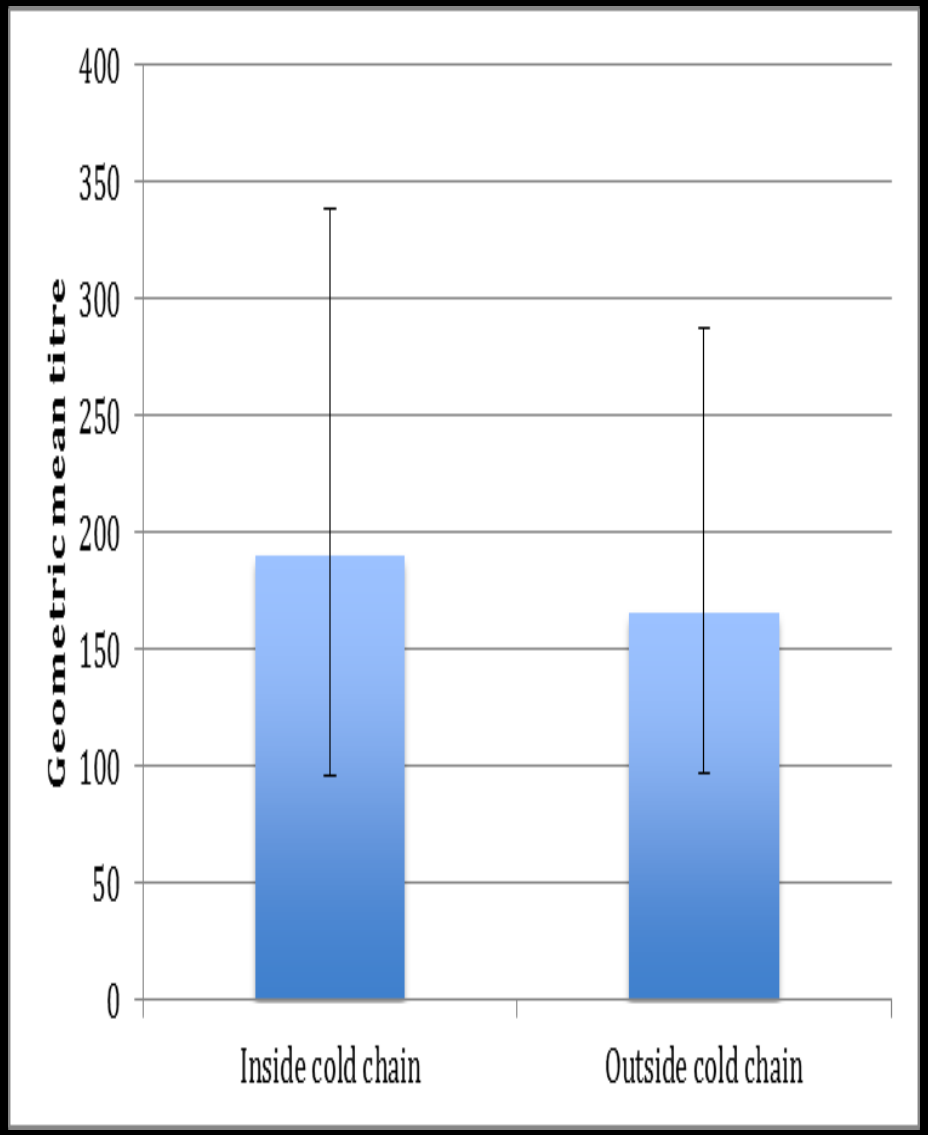
In-vitro relative potency of manufacturer B monovalent hepatitis B vaccine, exposed to different temperatures and times. Minimum release and end of shelf-life relative potency >=20 ug/ml. Data provided by manufacturer and based on in-house potency test. Values represent averages of three different lots and error bars show maximum and minimum values.



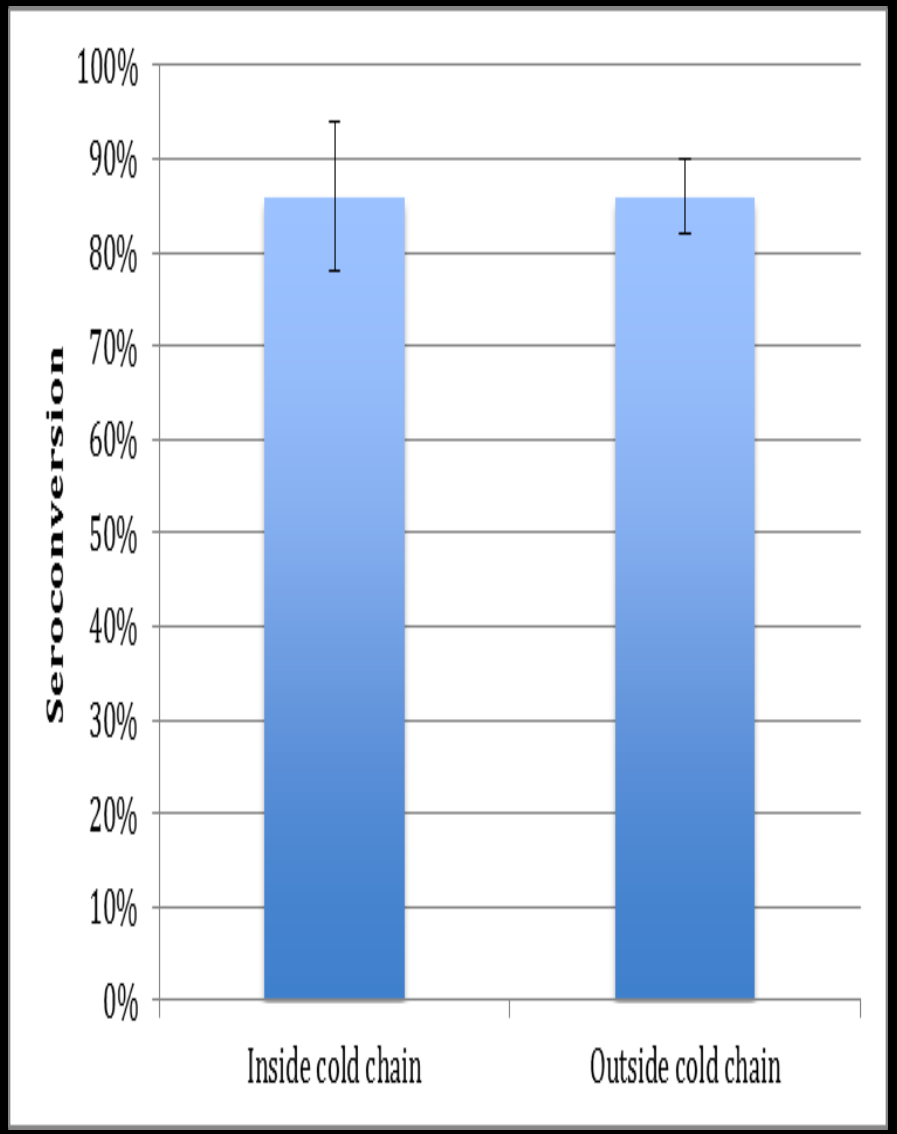
In-vitro relative potency of manufacturer E monovalent hepatitis B vaccine, exposed to 37°C for 4 weeks and 45 °C for 1 week. Minimum release and end of shelf-life relative potency 15-25 ug/ml. Data provided by manufacturer and based on in-house potency test. Values represent averages of four different lots at 37°C and three lots at 45 °C.



In-vitro relative potency of manufacturer H monovalent hepatitis B vaccine, exposed to 37°C for 6 months (average value for testing of 10 lots), 45°C for 2 weeks (average value of 2 lots), and 60°C for 2 weeks (average value of 2 lots). Minimum release and end of shelf-life relative potency 15 ug/ml. Data provided by manufacturer.



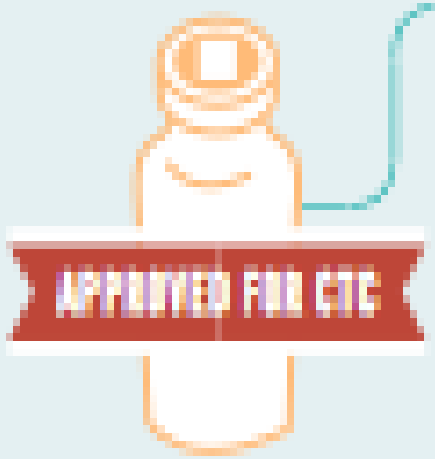
- Average geometric mean titres from four community-based studies that delivered childhood hepatitis B vaccine after storage inside or outside the cold chain. Error bars show range of values.

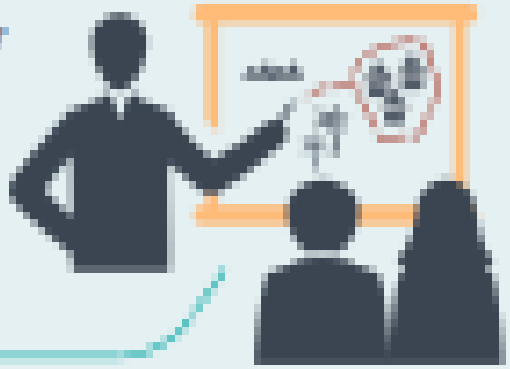


Average seroconverson from four community-based studies that delivered childhood hepatitis B vaccine after storage inside or outside the cold chain. Error bars show range of values.

WHAT IS A CONTROLLED TEMPERATURE CHAIN (CTC)?

A controlled temperature chain is an optional method of transporting and storing vaccines in carriers **without ice packs** up to a specific number of days before the vaccines are administered. It is only recommended for vaccines **officially labeled for this use** where a pronounced need is apparent and **training and supervision** are provided. Vaccines carried in a CTC must be monitored using a vaccine vial monitor (VVM) and peak temperature threshold indicator (PTTI) to indicate exposure to heat.





HOW DO **CTC** AND **ECTC** RELATE TO EACH OTHER?

Traditional Cold Chain

2°C to 8°C

8°C and higher →

ECTC

EXTENDED CONTROLLED TEMPERATURE CONDITIONS

Regulatory requirements for licensure

Apply to thermostable vaccines that are able to tolerate **any specified temperature above 8°C** for **any specified number of days**

Independent of specific programmatic requirements

CTC

CONTROLLED TEMPERATURE CHAIN

Programmatic strategy for field implementation

40°C and higher →

Applies to thermostable vaccines that are able to tolerate temperatures of **at least 40°C** for a **minimum of three days**

WHO provides support through **guidance, training**, and **supervision**

HOW ARE VACCINES APPROVED FOR CTC?

Not all vaccines can be used in a CTC. To be used in a CTC, four conditions should be met:

1

[illegible]

The vaccine must undergo and pass stability testing.

2

NATIONAL REGULATORY AUTHORITY

Appropriate regulatory authorities must license the vaccine for CTC use with a label that specifies the conditions of use.

3

WHO

The vaccine must be prequalified by the World Health Organization.

4

[illegible]

The government of the country where the vaccine will be used must give its consent in advance.

APPROVED

- THERMOSTABLE
- LICENSED
- PRE-QUALIFIED
- APPROVED

ECTC model

ECTC model is based on a single exclusion at an ECTC temperature (e.g., 40C) at the end of the dating period. Return to cold storage after ECTC exposure is not contemplated.

We calculate release potency needed to maintain potency above a clinically justified end-expiry potency value based on:

- Assay variability (estimated)
- Rates of potency decay at different temperature (e.g., 365 days at 4-8, followed by up to 5 days at ECTC temperature
- Errors in these estimates

Usually, having more available data on assay precision or from stability tests allows for more time at ECTC temperature (because more data reduces error terms in the calculation)

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION Geneva, 12 to 16 October 2015
Guidelines on the stability evaluation of vaccines for use under extended controlled temperature conditions

Preliminary analysis

- We analyzed 3 vaccines, which had >1 lot with data at a temperature > 37°C
- Manufacturers may have more data that could provide better estimates of assay variability or of stability at typical 4-8°C storage temperature, which could improve ECTC results
- Additional data at higher temperatures could also improve confidence in these estimates
- **These are preliminary analyses, and have not been subjected to regulatory review**

Preliminary statistical analysis of vaccine stability

Vaccine	SE of assay (log potency) estimate	Slope: log potency change/day (SE, # of lots) in parentheses			Increase over end expiry potency for 1 yr storage at 4-8°C	Increase over end expiry potency for 5 days at 37°C	Increase over end expiry potency for 5 days at ECTC temp
		4-8°C	37°C	ECTC temp: 45°C (40°C for vaccine B)			
A	.035	0 (2.5E-5, 13 lots)	-.0009 (.0008, 4 lots)	-.003 (.002, 3 lots)	15%	1.4%	4.7%
B	.025	-8E-5 (1.1E-4, 10 lots)	-.003 (.0009, 9 lots)	-.005 (.001, 6 lots)	28%	3.9%	9%
C	.02	0 (2E-4, 6 lots)	-.001 (.0003, 6 lots*)	-.003 (.0007, 6 lots*)	33%	2.1%	4.8%

*Lot poolability criteria were not met at 37C and 45C for vaccine C

Conclusions

- These analyses are not comprehensive and would need to be considered in the context of each manufacturer's release model and may need to consider other factors (e.g., poolability, representativeness of data with limited lots).
- Nonetheless, even with limited data, 5 days at ECTC temperatures could likely be supported with only modest (5-9% of end-expiry potency) increases in vaccine potency for these vaccines
- Existing filling models may already provide this leeway for some of these vaccines

Summary on the thermostability of hepatitis B vaccine

An important proportion of deliveries take place at home and there are places with limited cold chain in peripheral health facilities.

Existing data indicates that hepatitis B vaccines are heat stable and found to maintain immunogenicity after exposures of up to 45C for one week and 37C and 41C for several weeks

Field experience suggest there are programmatic advantages in keeping hepatitis B vaccine in ambient temperatures at service delivery points, in certain settings.

Even with limited data, 5 days at ECTC temperatures could likely be supported with only modest increases in vaccine potency for these vaccines (maybe already cover in the over the end period potency increases)

Thank you