EXPANDING THE POTENTIAL OF THE HEPATITIS B VACCINES BY OPTIMIZING THE IMMUNIZATION SCHEDULES AND DELIVERY STRATEGIES

A. POLICY QUESTIONS AND OVERALL CONCLUSIONS

A safe and effective vaccine against hepatitis B has been available since 1982. The vaccine has also been associated with reductions in the incidence and mortality from hepatocellular carcinoma (HCC) in time series analyses. By 2015, 185 (95%) of countries worldwide had introduced the hepatitis B vaccine with 97 (49%) countries having introduced the recommended birth dose. WHO has estimated that 84% of infants received at least three doses of Hepatitis B containing vaccine in 2015 and 39% of newborns received the birth dose.

Number of doses
Evidence available supports current recommendation of at least 3 doses of vaccine. The current recommendation is that the birth dose should be followed by 2 or 3 doses to complete the primary series. In most cases, one of the following 2 options is considered appropriate: (i) a 3-dose schedule of hepatitis B vaccine, with the first dose (monovalent) being given at birth and the second and third (monovalent or combined vaccine) given at the same time as the first and third doses of DTP vaccine; or (ii) 4 doses, where a monovalent birth dose is followed by 3 monovalent or combined vaccine doses, usually given with other routine infant vaccines.

For recombinant DNA vaccines there is no difference in the proportion of infants becoming seroprotected 1-3 months post-vaccination with a birth dose followed by 3 primary doses (b0+3p) vs. a birth dose followed by 2 primary doses (b0+2p). Also, the proportion seroprotected between a birth dose followed by 3 primary doses (b0+3p) vs. no birth dose + 3p doses is similar. For all other comparisons, schedules with a higher number of doses seem to increase the rate of seroprotection, but these results were 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.

Age at administration of first dose
Current recommendation is that all infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours. There is moderate quality evidence to support the effectiveness of hepatitis B vaccine given within 24 hours of birth to prevent hepatitis B infection.

Interval between doses
Current recommendation is that the birth dose should be followed by 2 or 3 doses with a minimum interval of 4 weeks. Available evidence is inconclusive regarding the differences in immunogenicity for various intervals between doses (e.g. 4 or 8 weeks apart). For recombinant DNA and plasma vaccines there is a higher proportion of infants becoming seroprotected 1-3 months post-vaccination with 1-3 months or 1-2-7 months schedules when compared to 3-5 and 1-3-10 months schedules respectively; this evidence is based on few studies of limited quality. There is very low quality evidence that recombinant DNA vaccine given in the 3-5-11 months schedule resulted in higher antibody concentrations (GMCs) measured 1-3 months post vaccination when compared to a 2-4-6 months schedule.

This summary includes

Booster dose
There is no evidence to support the need for a booster dose of hepatitis B vaccine in routine immunization programmes. For recombinant DNA HBV vaccines, there is low quality evidence on higher immunogenicity, however, the clinical relevance of these findings is unknown. The comparison of 3 or 4 primary vaccination schedules with an additional booster dose at 5 years of age vs. no booster added showed a very low quality evidence indicating higher proportion of seroprotection of a booster dose of recombinant DNA vaccine given 5 years after 3 or 4 primary doses when compared to no booster in children, this effect last for at least 3 years. There was also a very low quality evidence indicating that a booster dose of recombinant DNA vaccine given 5 years after 4 primary doses gives higher antibody concentrations (GMCs) measured 1-15 years post vaccination.

Catch up vaccination
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.

Immunization of LBW newborns
Current recommendation is that preterm infants should be vaccinated at birth and subsequently enters the national hepatitis B vaccination schedule. However, if an infant's birth weight is <2000 g, the vaccine dose given at birth should not be counted towards the primary series and 3 additional doses should be given according to the national vaccination schedule. Current data suggest that all babies should have a birth dose whatever their birth weight and those with a low birth weight should start their primary series of vaccination 1 month later or soon later after the birth dose (e.g. at the age of the national recommended schedule for the first dose).

Immunization of HIV infected population
There is no reason to change the current WHO recommendation of vaccination of HIV positive individuals as early as possible. There is no clinical evidence on the benefits of providing an additional dose or a dose with higher titre to HIV infected individuals. Higher titre doses do not result in longer term protection compared to standard doses.

What is the impact of the vaccination programme in the hepatitis B epidemiology?
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 and suggests no need for a booster dose.[1] A study in the Gambia[2] found that 60.9% of the children who became chronic carriers despite having been fully vaccinated had HBsAg-positive mothers and none received the birth dose. These findings suggest the importance of interrupting mother to mother transmission to reduce the HBV-related burden.

Several clinical trials have shown that a timely birth dose may reduce by 60 to 80% the likelihood to become a chronic HBsAg carrier compared to no birth dose. A model estimated the burden of HBV in terms of HBV-attributable acute

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and chronic disease outcome, and the impact of the global vaccination efforts at reducing HBV related disease, both at the current time, and into the future.

Does the available evidence support flexibility in the requirement for cold chain storage of Hepatitis B monovalent vaccines in order to expand the delivery of the birth dose?

Since access to the birth dose may be hampered by an important proportion of deliveries at home or limited cold chain in peripheral health, a review of published data and manufacturers' data assessed the thermostability of Hepatitis B monovalent vaccine. Existing data indicates that most hepatitis B vaccines are heat stable and have been found to maintain immunogenicity after exposure to temperatures of up to +45°C for one week and temperatures up to +37°C and +41°C for several weeks. Field experience suggest that there maybe programmatic advantages in keeping hepatitis B vaccine in ambient temperatures at service delivery points for a priori determined periods (e.g. one week), especially as a strategy for reaching home births. This indicates that these vaccines would be able to meet the CTC storage of at least 3 days at at least 40°C and these manufacturers should be encouraged to seek on-label extended controlled temperature chain.

Annex 1 includes conclusions and recommendations of the ad-hoc expert consultation on Hepatitis B vaccines (1-2 September 2016).

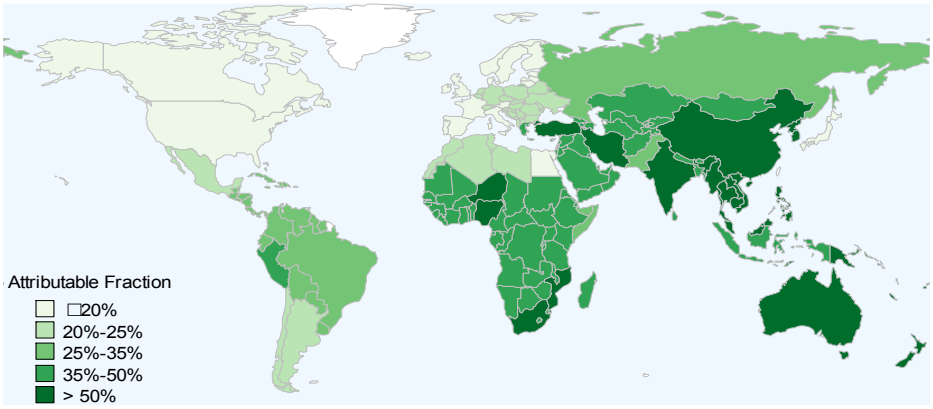
Type of evidence: randomized clinical trials (RCTs), observational studies, mathematical model estimates
Quality: Varies across studies. Not formally assessed for the mathematical model.
Caution: For some of the comparisons discussed the evidence is considered low quality because there is a limited number of trials or because they are afflicted with high risk of bias.

B. KEY FINDINGS

Burden of HBV disease

A systematic review estimated the global burden of liver cancer attributable to HBV and HCV. The estimation proceeded in three steps: 1) extrapolation of prevalence estimates to countries without data; 2) calculation of country-specific AF by combining estimates of prevalence and relative risk; 3) combination of AF with estimates of cancer burden and aggregation to regional estimates of cancer attributable to HBV and HCV. HBV and HCV are responsible for 72% of liver cancer cases worldwide, with wide geographical variations in the attributable fraction. For further information refer to WHO HBV burden 2016 document.

Figure 1: Estimated fraction of liver cancer attributable to Hepatitis B by country
Plummer et al 2016[3]



Epidemiology of Hepatitis B infection

Assessment of the global and regional prevalence of HBV carriage.
In September 2015, the United Nations General Assembly adopted the 2030 Agenda for Sustainable Development. A goal is to eliminate viral hepatitis as a public health threat by 2030. The target for 2020 is a 1% prevalence of HBsAg among children[4].
A systematic review of published seroprevalence data that also considered the date of Hepatitis B vaccine introduction, was used to update the global estimates of hepatitis B surface antigen seroprevalence [5]. Table 1 below depicts the countries according to the proportions seropositive in children. It is important to note that for some countries the data is from nationally representative surveys, while for others data is from local samples. Control of early childhood transmission of Hepatitis B control have had important advances in several regions around the world. The Western Pacific is the region where it has been documented more extensively using national serosurveys. Among the most populated countries in the area, only Philippines and Papua New Guinea remain with more than 2% of HBsAg in children under 5 years. Some small territories still lack adequate information. In Eastern Mediterranean, most countries have met the goal of less than 2% of HBsAg, some have been confirmed using national or local serosurveys in children and others, because national general prevalence do not support a higher prevalence in children. That is the case of Bahrain, Iran, Kuwait and others. That is also the case for South East Asia where only Nepal has a national serosurvey. However local studies from other lower intermediate endemic countries, like India and Bangladesh, supports that prevalence in children is decreasing. In Africa, most countries do not have enough information on prevalence among vaccinated children. In some of them, local studies show that prevalence in children born after vaccine introduction is going down.Europe and Americas are regions where infection in early childhood are low. In addition many countries in Europe and almost all in Latin America have been vaccinating for two or three decades. Some countries in both regions lack enough data to be classified and therefore should be encouraged to conduct additional studies.

Table 1a: Preliminary estimates of levels of endemicity in children < 5 years of age by WHO region using published literature[5]

WHO Region	Countries with HBsAg prevalence < 1% in children < 5 yrs	Countries with HBsAg prevalence 1-2% in children < 5 yrs	Countries with HBsAg prevalence > 2% in children < 5 yrs	Countries with no data
Western Pacific	China*, Macao*, Hong Kong*, Malaysia*, Mongolia*, Rep of Korea*, Am Samoa*, Australia*, Brunei*, Cook Islands*, Japan*, New Zealand*, Palau*,	Tonga*, Cambodia*, Fiji*, Lao PDR*, Marshall Is*, N Mariana Is*, Vietnam*,	Papua New Guinea*, Kiribati*, Philippines*, Samoa*, Solomon Is*, Vanuatu*	Fr Polynesia, Guam, Micronesia, Nauru, N Caledonia, Niue, Tokelau, Tuvalu, Wallis and Futuna
Africa	Uganda**, Cameroon**, Burkina Fasso**, Gambia*, Senegal**, Seychelles¶, South Africa*	Tanzania**, Rwanda**, Madagascar¶, Kenya¶, Burundi¶, Algeria¶, Cape Verde¶,Ethiopia¶, Eritrea¶,		Nigeria, Ghana, Niger, Angola, South Sudan, Mozambique, Zimbabwe, Malawi, Namibia, Botswana, Swaziland, Congo, Guinea, Guinea Bissau, Equatorial Guinea, Sierra Leona, Cote d´Ivoire, Togo, Benin,
Eastern Mediterranean	Bahrain¶, Iran¶, Jordan¶, Kuwait¶, Lebanon¶, Libya*, Morocco¶, Oman*, Palestine¶, Qatar*, Saudi Arabia¶, , Tunisia¶, United Arab Emirates¶, Egypt*	Syria¶, Afghanistan**, Iraq¶, Yemen**, Djibouti¶	Somalia¶, Pakistan¶,Sudan¶,	
South East Asia	Nepal*, Sri Lanka¶, Bangladesh*, India**¶, Indonesia**	, Thailand**		Bhutan, Myanmar,
America	USA*, Canada¶, Mexico*, Peru**, Venezuela**,Costa Rica¶, Panama¶, Colombia**, Ecuador¶, Argentina¶, Brazil**, Uruguay¶, Paraguay¶, Cuba¶,Guatemala¶, Nicaragua¶,			Haiti, Belize, Dominican Republic, Jamaica, Surinam
Europe	Austria¶, Belgium¶, Bosnia¶, Czek Rep¶, Denmark¶, France¶, Germany¶, Greece¶, Hungary¶, Iceland¶, Ireland¶, Israel**, Lithuania¶, Netherlands¶, Norway¶, Poland¶, Portugal¶, Serbia¶, Slovakia¶, Slovenia¶, Spain¶, Switzerland¶, Ukraine¶, UK¶, Turkey¶, Russia¶, Italy**, Bulgaria**	Azerbaijan¶, Cyprus¶,	Tajikistan, Albania**	Romania, Moldova, Kyrgyzstan, Kosovo, Kazakhstan, Belarus, Georgia

* based on national seroprevalence surveys
** based on local seroprevalence studies
¶ based on general prevalence studies

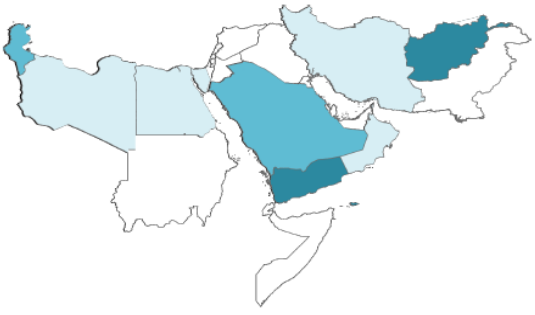
Figure 1b: Countries with evidence of HBsAg prevalence among vaccinated cohorts.

AFRO			
Country	Year of Vaccine Introduction	Prevalence	Reference
< 1%			
Uganda	2002	0%	Teshale 2015
Senegal	2004	0.3%	Bekondi 2015
South Africa	1995	0.4%	Schoub 2002
Burkina Faso	2006	0.5%	Ouedraogo H 2013
Cameroon	2005	0.7%	Cuille 2013
1-2 %			
Rwanda	2002	1%	Orikiiriza 2015
Tanzania	2002	1%	Muro 2013
Nigeria	2004	1.3%	Odusanya 2005
Gambia	1995	<1.5%	Peto 2014
Ghana	2002	1.5%	Dassah 2015
2-5 %			
Central Africa Republica	2008	5%	Cuille 2013

AMRO			
Country	Year of Vaccine Introduction	Prevalence	Reference
< 1%			
Peru	2005	0%	Cabezas 2014
Brazil	1998	<1%	Ximenez 2015
1-2 %			
Bolivia	2000	5% AntiHBc (1% HBsAg)	Masuet-Aumatell C 2013
2-5 %			
Colombia	1994	2%	De la Hoz 2008

EURO			
Country	Year of Vaccine Introduction	Prevalence	Reference
< 1%			
Tajikistan	2002	<1%	Khetsuriani 2015
1-2 %			
Bulgaria	1991	1%	Kevorkyan 2015
2-5 %			
Uzbekistan	2001	2%	Kurbanov 2010

EMRO			
Country	Year of Vaccine Introduction	Prevalence	Reference
< 1%			
Iran	1993	0%	Saffar H 2014
Egypt	1992	0.5%	Salama I 2013
Oman	1990	0.5%	Al Awaidy 2013
Libya	1998	< 1%	Daw 2014
1-2 %			
Tunisia	1995	1%	Chaouch H 2016
Saudi Arabia	1989	< 1.5%	Al Humayed 2016
2-5 %			
Yemen	1999	2.7%	Sallam 2012
Afghanistan	2006	3.6%	Tanju I 2014



SEARO			
Country	Year of Vaccine Introduction	Prevalence	Reference
< 1%			
Bangladesh	2005	0%	Paul 2012
Indonesia	2003	0%	Utsumi 2014
Nepal	2005	0.1%	Raj Upreti 2014
India	2011	0.15%	Aggarwal 2014
1-2 %			
Thailand	1992	1%	Posuwan 2016

WPRO			
Country	Year of Vaccine Introduction	Prevalence	Reference
< 1%			
Cook Islands	1989	0%	Wiesen2016
Macao	1989	0%	Wiesen2016
Palau	1988	0%	Wiesen2016
Guam	N/A	0%	GuamHealth Dpt2015
Niue	1986	0%	NiueHealth Dpt 2015
Brunei Darussalam	1988	0.1 %	Wiesen2016
American Samoa	1986	0.2%	Wiesen2016
New Zealand	1985	0.2%	Wiesen2016
China	1992	0.3 %	Wiesen2016
Malaysia	1989	0.3%	Cheang 2013
Singapore	1987	0.3%	Wiesen2016
Australia	2000	0.4%	Gidding 2007
Republic of Korea	1995	0.4%	Wiesen2016
Mongolia	1991	0.5%	Wiesen2016
Philippines	1992	<0.5%	Balangue-Tundag 2015
Hong-Kong	1988	0.8%	Wiesen2016
Wallis and Futuna	N/A	0.9%	Wiesen2016
1-2%			
Mongolia	1991	1%	Ochirbat 2008
Singapore	1987	1%	Ang 2013
Fiji	1995	1.3%	Tsukakoshi 2015
Cambodia	2006	1.5%	Bunsoth 2013
Laos	2004	1.7%	Xeuatongsa 2014
2-5 %			
Papua NG	1989	1.4-3.2%	Kitau 2015
Marshall I and Micronesia	1988	1.8%-2.5%	Bialek 2010
Laos	2004	2%	Komada 2015
VietNam	2003	2.2%	Wiesen2016
Laos	2004	3%	Black 2014
Kiribati	1995	3.3%	Patel 2016
Malaysia	1989	5%	Hudu 2013*

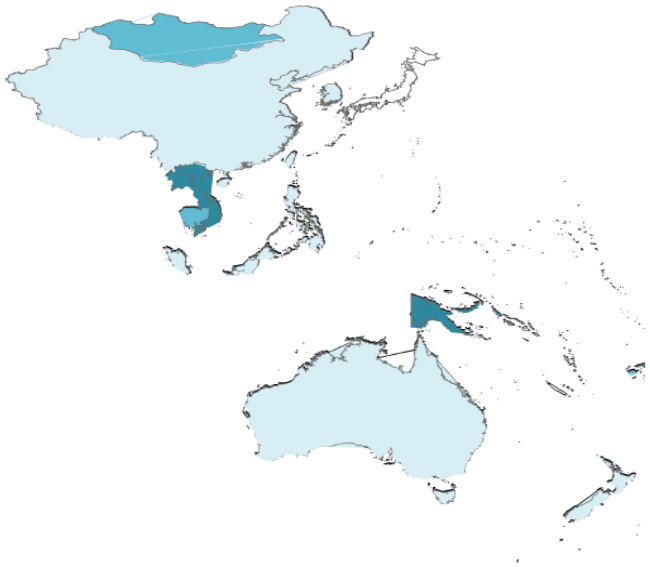


Figure 1A continuation

Global and country-specific estimates

Modelling of HBV infection seroprevalence globally [6].
The objective was to generate and provide up to date estimates on the global, regional and national prevalence of chronic HBV infection measured by HBsAg prevalence in sera. This work is part of a wider study on estimating the impact of hepatitis B vaccination. The model benefits from inputs from a number of systematic reviews on HBV vaccine efficacy and on surface antigen (HBsAg) carriage. The statistical and modelling component of the work consists of three related subcomponents: (1) Estimation of the pre- and post-vaccination country-specific prevalence of HBsAg by age and sex using spatially explicit statistical models. This uses the systematic review of HBsAg prevalence and uses Bayesian statistical methods to infer estimates for settings (and age groups) where data are currently missing; (2) Country-specific estimates of the impact of HBV vaccination on severe HBV-related disease (in particular liver cancer and cirrhosis) using a static model. The model uses data from the HBsAg review and WHO data on HBV vaccine coverage by birth cohort. It takes account of horizontal and perinatal infection in childhood and has been fitted to data from a number of sources on progression to severe outcomes. It also takes account of past and projected future demographic changes to estimate the number of deaths prevented by HBV vaccination by country; (3) Detailed estimates of the impact of vaccination, including the indirect (herd immunity) impact are made using data from three countries with high quality pre- (and post-) vaccination data on HBsAg prevalence and HCC (China, The Gambia and South Korea). See detailed report in supplemental information online.

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

WHO Recommendations for Routine Immunization[7]
Since perinatal or early postnatal transmission is an important cause of chronic infections globally, all infants should receive their first dose of hepatitis B vaccine as soon as possible (<24 hours) after birth even in low-endemicity countries. The primary hepatitis B immunization series conventionally consists of 3 doses of vaccine (1 mono-valent birth dose followed by 2 monovalent or combined vaccine doses at the time of DTP1 and DTP3 vaccine doses). However, 4 doses may be given for programmatic reasons (e.g. 1 monovalent birth-dose followed by 3 monovalent or combined vaccine doses with DTP vaccine doses), according to the schedules of national routine immunization programmes. Premature low birth weight (<2000g) may not respond well to vaccination at birth. However, by 1 month of chronological age, premature infants, regardless of their initial weight or gestational age at birth, are likely to respond adequately. Therefore, doses given to infants <2000g should not be counted towards the primary series. (http://www.who.int/immunization/policy/Immunization_routine_table2.pdf)

Available evidence suggest that the current recommendations do not need to be adjusted. A systematic review by Soares et al[8] included 72 studies (92 references) covering immunological and clinical outcomes (HBsAg, anti-HBs, anti-HBc, chronic HBV infection, serious adverse events, and all cause-mortality) for the following comparisons: timing of birth dose, number of doses after the birth dose, different intervals used for the same number of doses, timing of booster doses. All analyses were stratified by endemicity and time point of blood collection: regional endemicity has not directly impacted the results presented for any of the comparisons. Many studies were of poor methodological quality as reported.

There is a high flexibility of schedule possible in terms of number of doses and spacing provided the first two doses were delivered in early life.

Effect of number of doses of Hepatitis B vaccine on selected outcomes:

Available evidence suggest that the current recommendations do not need to be adjusted. A systematic review [8] found that schedules with a higher number of doses seems to increase the rate of seroprotection for b0+3 v 3p and b0+1p v b0+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 clinical effectiveness provided for a higher number of doses against chronic hepatitis B carriage. There was no difference in the number of serious adverse events when comparing different schedules. There was no data available on the effect of hepatitis B vaccination and all-cause mortality. The quality of evidence for these comparisons is very limited.

Table 2: Summary of findings per outcome of the number of doses of recombinant DNA HBV vaccine

Outcome of interest	Number of doses		
	Birth dose + 3p vs birth dose + 2p	**Birth dose + 3p vs 3p**	**3 primary vs 2 primary doses**
HBsAg seroprevalence	**Very low quality evidence**. One RCT[9] and one cohort[10 11]study provided data for multiple time points. Both studies were in high endemicity areas. Mothers in both studies were HBeAg + and were HBsAg + in one study. 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.	None of the included studies assessed this outcome.	There were no studies found that assessed this outcome
Anti-HBs seroprotection	**Moderate quality evidence from RCTs** Three RCTs [9 12 13]provided data on this comparison. Mothers were HBsAg and HBeAg positive in one study. There is probably little or no difference between b0 + 3p vs. b0 + 2p recombinant DNA HBV vaccines on Anti-HBs seroprotection at 1-3 months, 3-6 months or 6-12 months post vaccination. **Very low quality evidence** Three cohort studies [10 11 14 15 16 17 18 19] showed no evidence of a difference in seroprotection rates between schedules at 1-3 months after immunization, 6-12 months and 24-36 months. One study [14-18] 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. However, results are consistent with RCTs.	**Low endemicity – very low quality evidence** One low endemicity cohort study[20] , found no evidence of a difference in seroprotection rates between a birth dose + 3p compared to a 3p doses. **Moderate endemicity - low quality evidence** one moderate endemicity quasi-RCT [21] found no evidence of a difference in seroprotection rates between a birth dose + 3p compared to a 3p doses. **High endemicity – moderate quality evidence** Three high endemicity RCTs[22 39 23] found marginally statistically significant higher seroprotection rates (RR 1.05, 95%CI 1.02-1.07) between a birth dose + 3p compared to a 3p doses	**Very low quality from cohort studies** One cohort study[24] in a low endemicity area found that there was no difference in seroprotection rates at 1-3 months after immunization; at >36 months.

Outcome of interest	Number of doses		
	Birth dose + 3p vs birth dose + 2p	**Birth dose + 3p vs 3p**	**3 primary vs 2 primary doses**
GMCs of anti-HBs	**Very low quality evidence** Two RCTs [25] [13,19] and one cohort study [14-18] 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.	**Moderate quality evidence** Two RCTs [38] [21] from low and moderate endemicity areas and two RCTs [39] [22] from high endemicity areas found that the birth dose + 3 primary doses schedules probably improves GMCs compared to 3 primary doses only.	**Low quality evidence** One RCT [13] in high endemicity area and one cohort study [24] in a low endemicity area found no significant difference in the antibody concentrations (GMCs) 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.

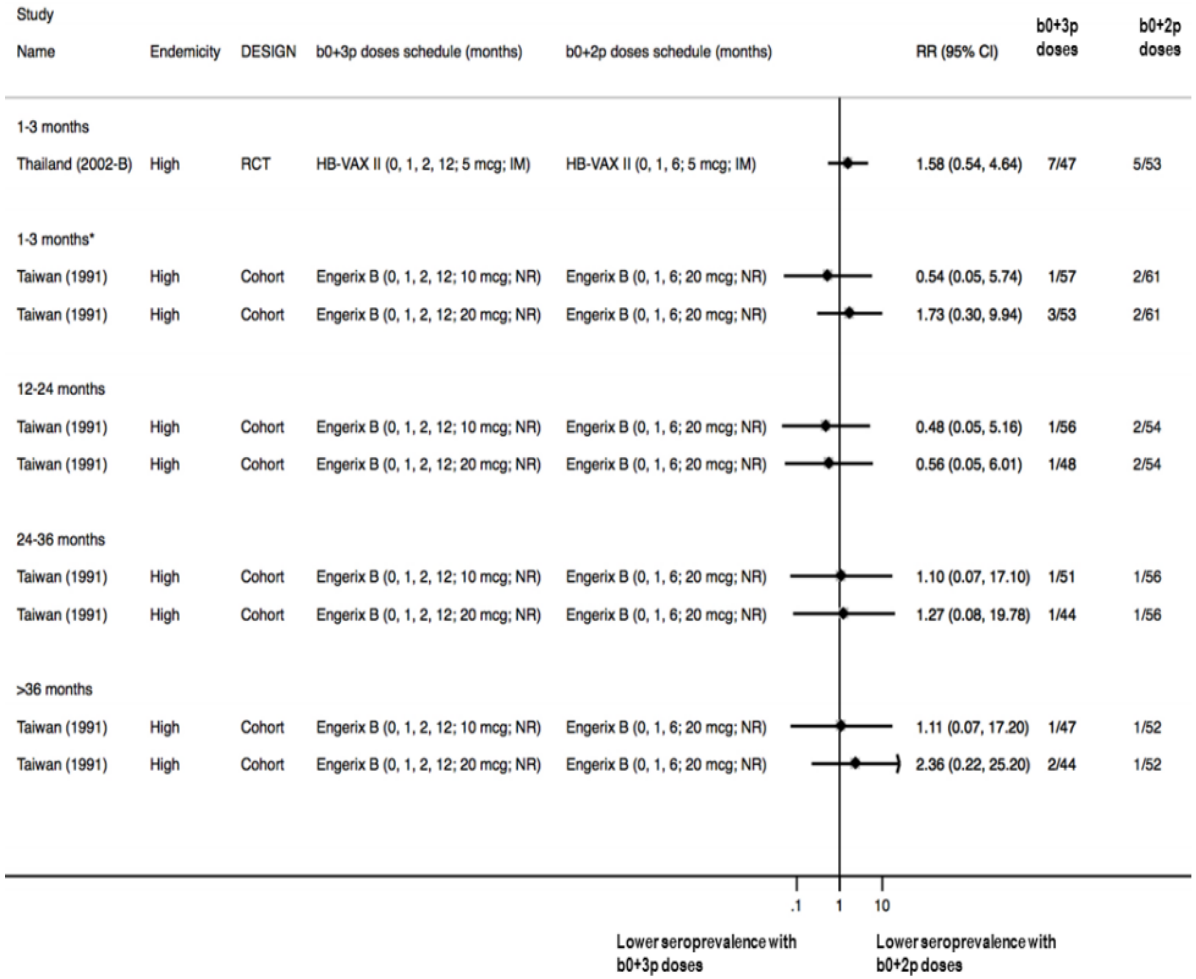


Fig 2: Forest plot of difference in HBsAg seroprevalence between birth dose + 3p vs. birth dose + 2p

Available evidence suggest no difference in prevalence for various schedules compared.

Forest plots for anti-HBs seroprotection and GMCs of anti-HBs available in the Targeted Update: immunogenicity of recombinant DNA HBV vaccines: difference in the number of doses.

Effect of timing of first dose of Hepatitis B vaccine on selected outcomes

One RCT[26] of moderate quality evidence comparing recombinant DNA HBV vaccine at 0, 1, 2 and 14 months vs placebo among children born to HBsAg positive mothers found anti-HBs antibodies in protective titers in 76.7% of children aged 4-5 months after the third dose.
Another four RCTs[27 28 29 30 31 32] of moderate quality evidence using plasma derived vaccine compared a birth dose + 3p doses or a birth dose + 2p versus placebo concluded that HB vaccine should be provided to all newborn infants at risk of perinatal hepatitis B infections as soon as possible after birth.

Table 3: **Summary of findings per outcome of timing of the first dose of recombinant DNA HBV vaccines**

Outcome of interest	Timing of first dose		
	Birth dose (at ≤ 24 h) vs no birth dose	**Birth dose at 0 to 3 days vs no birth dose**	**Birth dose given ≤ 2 weeks vs no birth dose**
HBsAg seroprevalence	**Very low quality evidence** One quasi-RCT[33] in a high endemicity region compared this schedule with a birth dose given < 24 h with schedules that did not include the birth dose; blood sampling was collected 3-6 months after immunization. The mothers of infants were HBsAg +, some of the included mothers were also HBeAg +. There was some evidence of lower seroprevalence rates in vaccine schedules without a birth dose, but this is based in a single study with high risk of bias.	**Moderate quality evidence** A cohort study[34] in children who received HBIG within 12 h of birth and 3 doses of vaccine at 0, 1, and 6 months reported that 2.3% of children were HBsAg +. Mothers were HBsAg + Evidence suggests that a delay in the initial dose of vaccine was associated with an increased risk of carriage. One RCT[35] assessing plasma vaccine in a low endemicity area with blood sampling at 1-3 months after vaccination showed no evidence of a difference in seroprevalence rates between vaccine schedules. Mothers were HBsAg and HBeAg +, HBIG was used in addition to the vaccine. An observational study [34] in children receiving their first dose of hepatitis B at 1-3 days, 4-7 days, 8-61 and ≥62 days showed a strong relationship between time of first dose and chronic infection with a 3.3 OR (95%CI 1.3-8.2) for each unit increase in age.	There were no studies found that assessed this outcome
Anti-HBs seroprotection	**Very low quality evidence** Seven RCTs [36 37 38 39 40 41 42 43] and two quasi-RCTs [21 33] provide data on seroprotection rates. Six studies were in high endemicity areas, two were in a low, and one a moderate endemicity area. Mothers in one study [33] were HBsAg + (some were also HBeAg +); in the remaining studies mothers were either negative or their status was not reported. Meta-analysis was possible for three RCTs form high endemicity areas in which no difference in serprotection rates was	**Low quality evidence** Two RCTs [22 44 45 46] provided data on seroprotection rates comparing schedules with a birth dose given 0 to 3 days with no birth dose, with blood sampling at 1-3 months. One study [45, 46] was in high endemicity area and another [44,45,46] in low endemicity area. The mothers in one study were HBsAg + and some were also HBeAg +; in the other study mothers were negative or their status was not reported. Studies showed no difference in seroprotection	**Very low quality evidence** One RCT[47], one quasi-RCT[48] and one cohort study[49] provided data on seroprotection rates comparing four schedules with a birth dose given up to two weeks after birth with schedules that did not include a birth dose, with blood sampling at 1-3 months after immunization. The mothers in one study were HBsAg and HBeAg positive, and HBIG was used in addition to the vaccine; in the remaining studies the mothers were negative or their status was not reported. There was no

Outcome of interest	Timing of first dose		
	Birth dose (at ≤ 24 h) vs no birth dose	**Birth dose at 0 to 3 days vs no birth dose**	**Birth dose given ≤ 2 weeks vs no birth dose**
	observed at 1-3 months after vaccination (RR 0.97 95%CI 0.95-0.98) There was no evidence of a difference in seroprotection rates between schedules except for one study which showed higher seroprotection (RR 1.12, 95% CI 1.01, 1.25) without a birth dose at 12-24 months post vaccinations. We are uncertain about the effect of birth dose versus no birth dose, because the evidence is of very low quality.	rates between vaccine schedules.	evidence of a difference in seroprotection rates between vaccine schedules for the RCT and quasi-RCT. A cohort study showed higher seroprotection rates without a birth dose (2, 3, 6 months vs. 0, 1, 3 months schedules; RR 1.27, 95% CI 1.07, 1.51).
GMCs of anti-HBs	**Low quality evidence** Four RCTs [36,37, 38, 40, 39] and one quasi RCT [21] provided data on GMCs comparing this schedule at 1-3 months post vaccination. Two studies were in high endemicity areas, two were in a low and one in a moderate endemicity area. None of the studies reported that mothers were HBsAg or HBeAg +. All studies found a higher antibody titres with a birth dose (<24 h) compared to schedules without a birth dose. For two studies from low endemicity areas the pooled GMC ratio was 0.49 (95% CI 0.37-0.66). One study [21] from a moderate area found higher antibody titres with a birth dose schedule (GMC ratio 0.50 95%CI 0.36-0.70) We are uncertain of the effect of a birth dose compared to no birth dose schedule.	**Moderate quality evidence** One RCT [22] in a high endemicity area were the mothers were all negative for HBsAg found higher antibody titres with a birth dose, at 1-3 months after vaccination. Birth dose given at 0 to 3 days of life probably leads to higher antibody concentrations.	**Very low quality evidence** One RCT [47] 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 [48] reported data at 1-3 and 12-24 months after immunization, and results showed no difference in log GMCs for the compared schedules.

Fig 3: Forest plot of diference in HBsAg seroprevalence between first dose of recombinant DNA HBV vaccine given within 24 h vs no birth dose

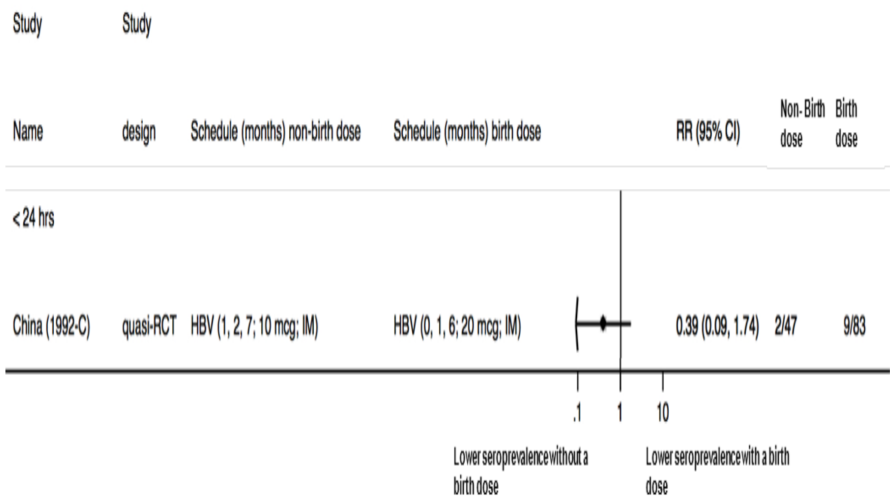
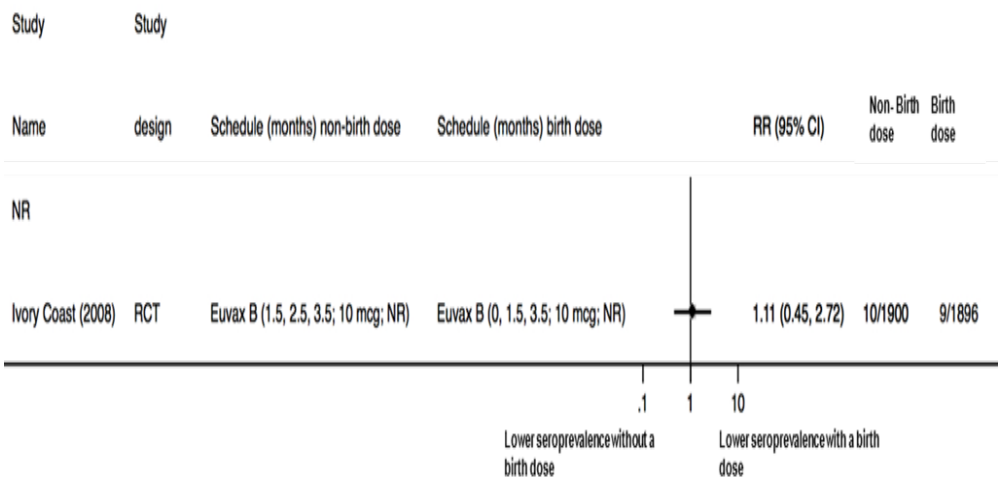


Fig 4: Forest Plot of difference in HBsAg seroprevalence between first dose of recombinant DNA HBV vaccine given in the first month of life vs no birth dose



Very limited evidence suggests lower seroprevalence rates in vaccine schedules without a birth dose compared to birth dose given < 24h.
Very limited evidence suggest no difference in seroprevalence rates between birth does given at "0 months", exact timing not reported compared to no birth dose.

Forest plots for anti-HBs seroprotection and GMCs of anti-HBs available in the Targeted Update: Immunogenicity of recombinant DNA HBV vaccines: timing of first dose.

Effect of the interval between doses of recombinant DNA HBV vaccines on selected outcomes

There is 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 is 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 with a 2,4,6 months schedule, but the evidence is of low quality.8

Table 4: Summary of findings per outcome of interval between doses of recombinant DNA HBV vaccines

Outcome of interest	Interval between doses		
	Same schedules, different intervals (all ≥ 1 m) Birth dose + 2 p	**Same schedules, different intervals (all ≥ 1 m) 3 p**	**Same schedules, different intervals (all ≥ 1 m) 2p**
HBsAg seroprevalence	None of the included infants were HBsAg positive in serology performed 1-3 months after vaccination in both studies.	There were no studies found that assessed this outcome	There were no studies found that assessed this outcome
Anti-HBs seroprotection	**Low quality evidence and very low quality evidence** Three RCTs[50 51 52] and three quasi-RCTs[53 54 55]found no difference among comparisons, although our confidence in the findings is limited because of small samples and flaws in the conduct of included studies**.**	**Very low quality evidence** Two quasi-RCTS[56 48] and one cohort study [24] conducted in low and moderate endemicity areas found no significant difference in seroprotection among the different vaccine schedules All studies reported vaccine intervals above one month. .	**Very low quality evidence** A cohort study [24] in low endemicity area found higher seroprotection rates in a 3,5 months vaccine schedule compared to 1, 3 months schedule.
GMCs of anti-HBs	**Low quality evidence** *Low endemicity* Two RCTs[57 51] conducted in low and in high endemicity arear found no difference in antibody concentrations in 0,1,6 months vaccination schedule compared to 0,1,2 months schedule at 12-24 months after vaccination.	**Low quality evidence** A single quasi-RCT [56] provided data on GMCs comparing 3,5,11 months to a 2,4,6 months schedule. The 3, 5, 11 schedule gave higher antibody concentration at 1-3 months post vaccination	There were no studies found that assessed this outcome

Forest plots for anti-HBs seroprotection and GMCs of anti-HBs available in the Targeted Update: Immunogenicity of recombinant DNA HBV vaccines: same schedule, different intervals.

Effect of booster dose of Hepatitis B vaccine on selected outcomes

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.[8]

Table 5: Summary of findings per outcome of booster of recombinant DNA HBV vaccines

Outcome of interest	Booster dose	
	3 primary doses + 1 booster (3p+1B) vs. 2 primary doses + 1 booster (2p+1B)	**Booster vs no booster**
HBsAg seroprevalence	There were no studies found that assessed this outcome.	There were no studies found that assessed this outcome
Anti-HBs seroprotection	**Low quality evidence** Two cohort studies[58 59 60] and one RCT[61 62] conducted in low endemicity region found no evidence of a difference in seroprotection rates between schedules at pre-booster immunization. After booster immunization all three studies reported 100% anti-HBs seroprotection	**Very low quality evidence** 1 Cohort study [14 17] and one RCT [14 17] in Thailand (high endemicity), compared 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. **Low quality evidence** A subset of a randomised trial [14 17], outcome measured at multiple time points compared 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.

Outcome of interest	Booster dose	
	3 primary doses + 1 booster (3p+1B) vs. 2 primary doses + 1 booster (2p+1B)	**Booster vs no booster**
GMCs of anti-HBs	There were no studies found that assessed this outcome	**Very low quality evidence** 1 Cohort study [14 17] , outcome measured at multiple time points; Comparison: 4 primary doses plus 1 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. **Low quality evidence** A subset of a randomised trial [14 17], 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.

Forest plots for anti-HBs seroprotection and GMCs of anti-HBs available in the Targeted Update. Immunogenicity of recombinant DNA HBV vaccines: booster dose.

A systematic review assessed the benefits and harms of a booster dose hepatitis B vaccination, more than five years after the primary vaccination, for preventing hepatitis B virus (HBV) infection in healthy individuals previously vaccinated with the hepatitis B vaccine, and with hepatitis B surface antibody levels (anti-HBs) below 10 mIU/mL.[63] and concluded that individuals adequately vaccinated in a 3-dose or 4- dose schedule do not require additional booster dose. Another systematic review[64] assessing the benefits and harms of booster dose hepatitis B vaccination, more than 5 years after primary vaccination for preventing HBV infection in healthy individuals previously vaccinated with the hepatitis B vaccine, and with hepatitis B surface antibody (anti-HBs) levels below 10mIU/ml. They found no eligible randomised clinical trials fulfilling the inclusion criteria for the review. A third review[65] examined literature and insights regarding the need for booster doses against hepatitis B published since 2002, starting from the article by Banatvla et al. Investigators concluded that there was no need for boosters in immunologically potent persons as long as a full course was adequately administered that respected the recommended timelines, as evidenced by studies conducted up to 20 years after the original immunization course.

Effect of catch up vaccination of Hepatitis B vaccine on selected outcomes

A systematic review assessed the benefits and harms of catch up vaccination of hepatitis B vaccines 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. The clinical implications are unknown.
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.[8]

Table 6: Summary of findings per outcome of catch up vaccination of recombinant DNA HBV vaccines

Outcome of interest	Catch up vaccination
	3 primary doses vs 2 primary doses
HBsAg seroprevalence	**Low quality evidence** One RCT[66] in a high endemicity region, compared 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.
Anti-HBs seroprotection	**Low quality evidence** Nine RCTs [58 59 61 67 68 69 70 71 72] with a higher dose of vaccine in the 2p schedule, apart from one comparison in Pakistan and two comparisons in USA. *1-3 months after last vaccination (Low, Moderate and High endemicity)* - Results from most studies suggest little or no difference in seroprotection among schedules *6-22 years follow-up (Low and High endemicity)*- Results from most studies suggest little or no difference in seroprotection among schedules.
Anti-HBs	**Moderate quality evidence**. Two RCTs [59 61] from a low endemicity region found that a 0, 1, 6 months schedule gave higher antibody concentrations at 1-3 months post vaccination compared to the 0, 6 months schedule. **Low quality evidence** One RCT [70] in a moderate endemicity region found that a 0, 1, 6 months schedule may lead to little or no difference in antibody concentrations at 1-3 months post vaccination compared to the 0, 6 months schedule. **Moderate quality evidence** One RCT [68] in a high endemicity region found that a 0, 1, 6 months schedule probably leads to slightly higher antibody concentrations at 1-3 months post vaccination compared to the 0, 6 months schedule. **Low quality evidence** One RCT [59] in children and adolescents in a low endemicity region found that a 0, 1, 6 months schedule probably may lead to little or no difference in antibody concentrations at 1-3 months post vaccination compared to the 0, 6 months schedule

Forest plots for anti-HBs seroprotection and GMCs of anti-HBs available in the Targeted Update: Immunogenicity of recombinant DNA HBV vaccines: catch-up vaccinations

Effect of birth dose of Hepatitis B vaccine started at different birth weights on selected outcomes

A systematic review assessed 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). [8]

Table 7: Summary of findings per outcome of recombinant DNA HBV vaccines in 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 of interest	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			⊕⊕⊕O 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			⊕⊕⊕O 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			

Outcome of interest	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		
		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

Table 8: Summary of findings per outcome of recombinant DNA HBV vaccines in 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 of interest	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	⨁⨁⨁◯ 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 for anti-HBs seroprotection available in the Targeted Update: Immunogenicity of recombinant DNA HBV vaccines: timing of first dose.

Evidence shows the reduced immunogenicity of vaccination in low birth weight infants. However delaying vaccination would leave the babies at risk. It is therefore recommended that all babies should have a birth dose whatever their birth weight and those with a low birth weight should start their primary schedule of vaccination 1 month later.

HIV infected population:

A systematic review and meta-analysis assessed the long term immune response of vaccines in HIV infected children and adults.[73] The review 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 of them in adults. As observed in figure 5 there is no clear difference in seroprotection length between vaccines with different titres composition. After 3 doses of HBV containing 40 ug of antigen, 71% of primary responders have seroprotective level titers one year after vaccination, 33% to 61% after year 2, and 40% after year 5. Despite the slightly higer titer in the 40 ugrs group, over time titres become comparable to those receiving a HBV with 20 ugrs. Therefore, administering a higher titre HBV to this group does not seem to improve maintenance of seroprotection compared to standard doses (41% vs 50% respectively). Figures 6 and 7.

Figure 5. Percent of individuals with protective levels of Anti HBs in relation to time elapsed since last dose

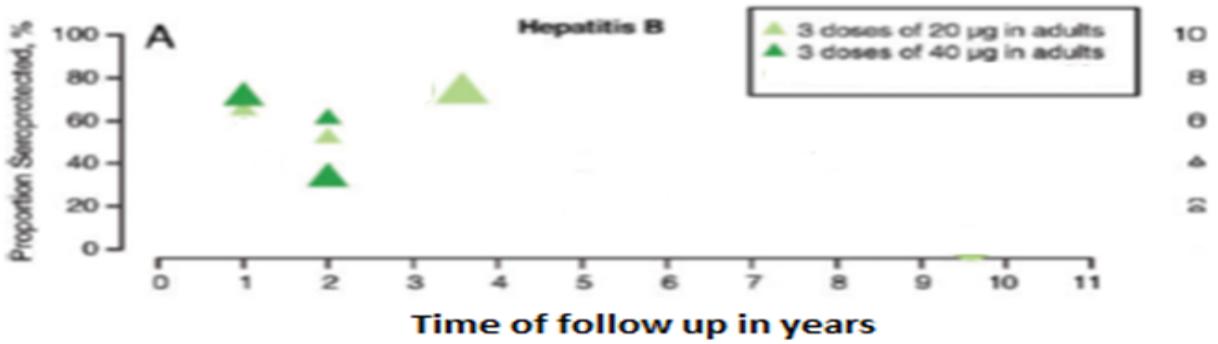


Figure 6: Predicted proportion of adults with protective antibodies after 2 years follow up

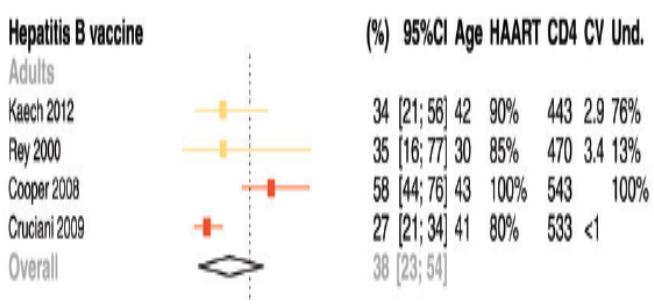
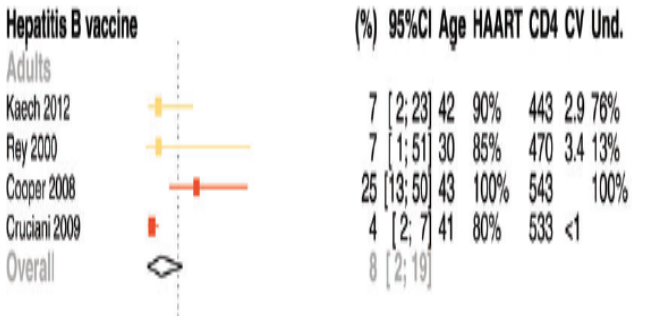


Figure7 : Predicted proportion of adults with protective antibodies after 5 years follow up.



A Cochrane review [74] evaluated the impact of HBV vaccination on prevention of morbidity and mortality in HIV positive patients and included only clinical trials. Only one RCT 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. Therefore the evidence is insufficient to support any recommendation on HBV vaccination use for HIV persons.

Another systematic review[75], 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.

In conclusion, there is no strong evidence to change current WHO recommendation on vaccination of HIV positive population at any age. Recommending periodical monitoring of anti HBs titres may be discussed at SAGE.

Long term protection

A meta-analysis[76] assessed the long-term immunity induced by HB vaccines and the possible need of a booster dose. 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.

Vaccination of Health Care Workers

Hepatitis B virus (HBV) infection is a well-recognized occupational risk for health-care workers (HCW) and HCW trainees with blood and body fluid exposures.[77] Because of their contact with patients or infective material from patients, susceptible health-care workers (HCW) are at considerably greater risk for exposure to and transmission of HBV than the adult population as a whole.([77] [78]) The risk for HBV infection is greatest among HCW with exposures to blood or body fluids from patients who are hepatitis B e antigen (HBeAg) positive, a marker of high HBV replication and viral load. ([79]) HBV is stable, remaining infectious on environmental surfaces for at least 7 days, and is transmissible in the absence of visible blood.([80], [81]) HCW do not recognize all exposures to potentially infectious blood and body fluids, or contaminated environments.([82], [83], [84] [85] [86] [87]) Even if exposures are recognized, HCW often do not seek post-exposure prophylactic management.([88]) Optimal use of hepatitis B vaccine safeguards the health of workers and provides greater protection for patients from becoming infected through exposure to infected workers or contaminated environments. [89]

Does the available evidence support flexibility in the requirement for cold chain storage of Hepatitis B monovalent vaccines in order to expand the delivery of the birth dose?

Thermostability of hepatitis B vaccines

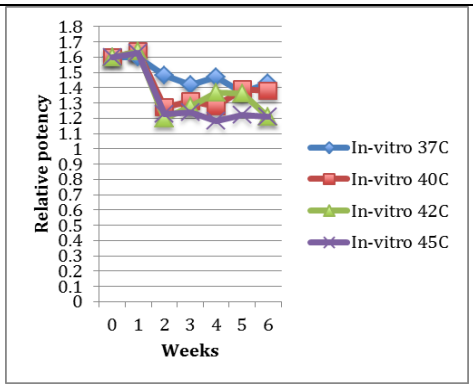
Introduction: In many resource-poor countries, a substantial percentage of births may occur outside of health care facilities. Lack of access to vaccine in cold storage may reduce birth-dose hepatitis B vaccine (HBV) coverage and thus place infants at risk of perinatal transmission. One mechanism to address this issue would be to allow vaccine to be out of the cold chain at the point of delivery, but few manufacturers have pursued an on-label indication for storage at >8^{o}C (known as the extended controlled temperature chain [ECTC]), including the World Health Organization (WHO) CTC programmatic approach allowing for vaccine to be stored at 40^{o}C for three days.

Methods: Thermostability data was obtained from eight of nine monovalent WHO prequalified HBV manufacturers. A systematic literature review was conducted to identify studies in which HBV was stored outside the cold chain.

Results: Eight manufacturers provided in-vitro potency results following storage at 37^{o}C for four weeks, and all met minimum lot release specifications, with an average decrease in potency of 16%. Four manufacturers assessed in-vitro potency after 1 to 4 weeks storage at 45^{o}C, and five assessed in-vivo potency after storage at 37-45^{o}C and all met minimum specifications as well. The systematic literature review identified four controlled field studies that evaluated an out-of-the-cold-chain approach; no differences were seen in GMTs or seroconversion between children who received vaccine in intervention versus non-intervention communities. Similarly, two experimental studies in humans and three in animals supported HBV thermostability over a four-week period.

Conclusions: Since an important proportion of deliveries at home or limited cold chain in peripheral health facilities may hamper access to the birth dose, a review of published data and manufacturers' data assessed the thermostability of Hepatitis B monovalent vaccine. Existing data indicates that most hepatitis B vaccines are heat stable and have been found to maintain immunogenicity after exposure to temperatures of up to +45°C for one week and temperatures up to +37°C and +41°C for several weeks. Field experience suggest there maybe programmatic advantages in keeping hepatitis B vaccine in ambient temperatures at service delivery points, especially as a strategy for reaching home births.

Figure 8a 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).



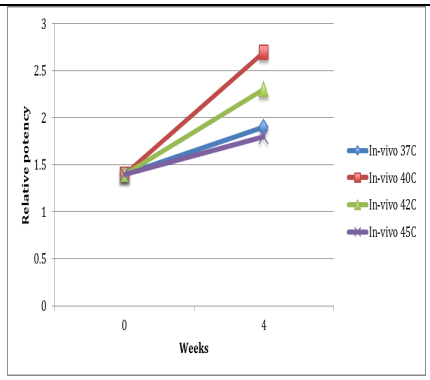
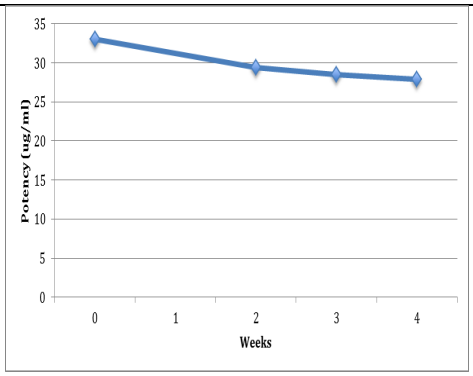


Figure 8b. In-vivo relative potency of manufacturer A monovalent hepatitis B vaccine, exposed to different temperatures for different time periods. Minimum release and end of shelf-life relative potency upper 95% confidence limit of estimated relative potency >=1.0. Data provided by manufacturer.

Figure 9a. 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 not specified but manufacturer indicated data confirmed stability to 4 weeks. Data provided by manufacturer and based on in-house potency test. Values represent averages of two different lots.



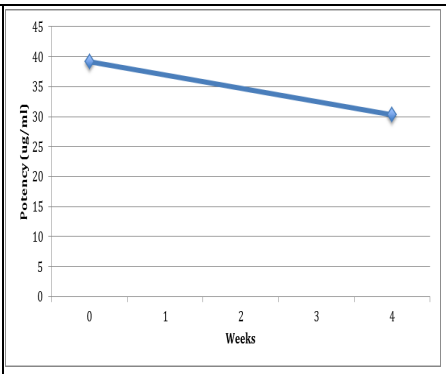
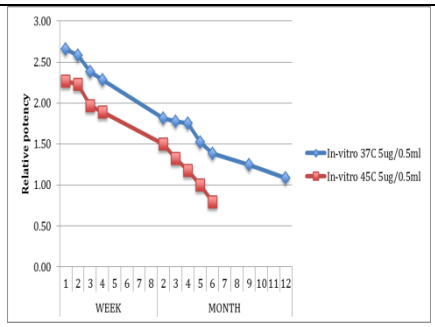


Figure 9b. In-vivo relative potency of manufacturer B monovalent hepatitis B vaccine, exposed to 37°C for 4 weeks. Minimum release and end of shelf-life relative potency not specified but manufacturer indicated data confirmed stability to 4 weeks. Data provided by manufacturer and based on in-house potency test. Values represent averages of two different lots.

Figure 10a. Study 1: 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.



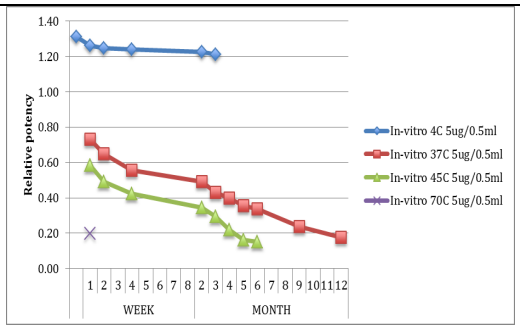
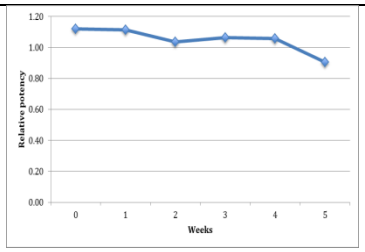


Figure 10b. Study 2: in-vitro relative potency of manufacturer C monovalent hepatitis B vaccine, exposed to different temperatures for different time periods. Minimum release and end of shelf-life relative potency >=0.50. Data provided by manufacturer. Values represent averages of three different lots.

Figure 11a. In-vitro relative potency of manufacturer D monovalent hepatitis B vaccine, exposed to 37°C 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.



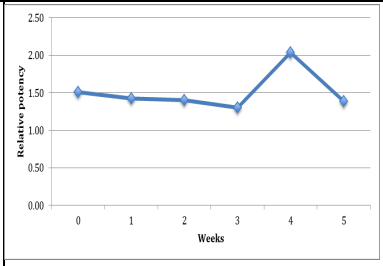
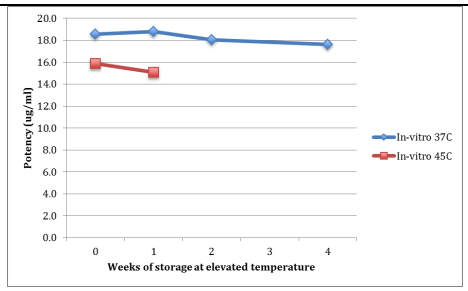


Figure 11b. In-vivo relative potency of manufacturer D monovalent hepatitis B vaccine, exposed to 37°C for 5 weeks. Minimum release and end of shelf-life relative potency upper 95% confidence limit of estimated relative potency >=1.0. Data provided by manufacturer and based on in-house potency test. Values represent averages of three different lots.

Figure 12a. In-vitro relative potency of manufacturer E monovalent hepatitis B vaccine, exposed to 37oC for 4 weeks and 45 oC 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 37oC and three lots at 45 °C



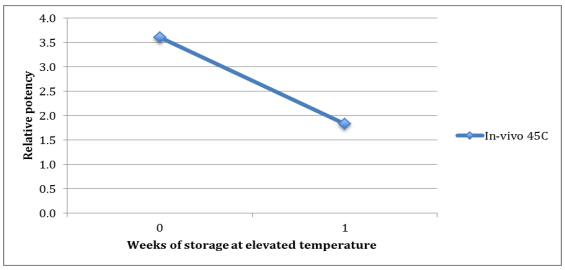


Figure 12b. In-vivo relative potency of manufacturer E monovalent hepatitis B vaccine, exposed to 45oC for 1 week. Minimum release and end of shelf-life relative potency upper 95% confidence limit of estimated relative potency >=1.0. Data provided by manufacturer and based on in-house potency test. Values represent averages of three different lots.

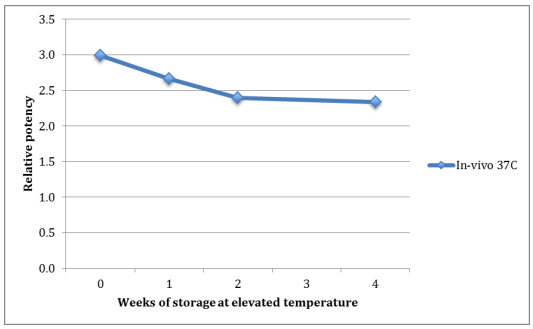


Figure **13**. In-vivo relative potency of manufacturer F monovalent hepatitis B vaccine, exposed to 37°C for 4 weeks. Minimum release and end of shelf-life relative potency upper 95% confidence limit of estimated relative potency >=1.0. Data provided by manufacturer and based on in-house potency test. Values represent averages of three different lots.

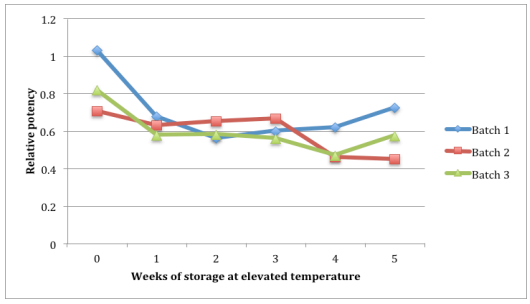
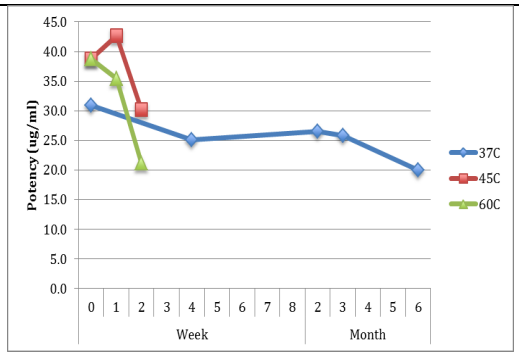


Figure **14**. In-vivo relative potency of manufacturer G monovalent hepatitis B vaccine, exposed to 37°C for 5 weeks. Minimum release and end of shelf-life relative potency >=0.56. Data provided by manufacturer and based on in-house potency test. Individual batch values are presented to demonstrate variation in meeting minimum specification.

Figure 15a. 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.



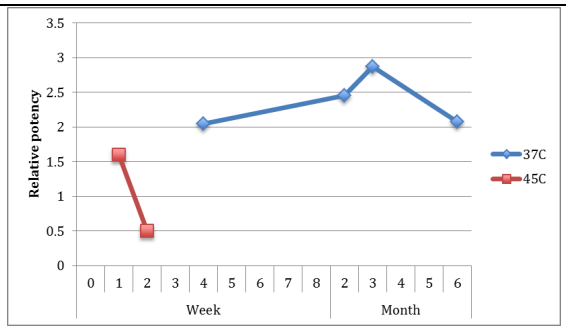


Figure 15b. In-vivo relative potency of manufacturer H monovalent hepatitis B vaccine, exposed to 37°C for 6 months (average value for testing of 7 lots) and 45°C for 2 weeks (average value of 3 lots),. Minimum release and end of shelf-life relative potency upper 95% confidence limit of estimated relative potency >=1.0. Data provided by manufacturer.

Barriers to introduce the Hepatitis B birth dose. Ensuring that all infants receive a dose of hepatitis B vaccine within 24 hours of birth requires implementation of specific programmatic measures. Increasing the number of infants born in facilities or attended by trained health staff would improve birth dose coverage. Ensuring that there is coordination between immunization services and maternal health services is important so that vaccine is available at the place of delivery or immediately after birth. Expanding vaccine management systems and innovative outreach to provide vaccine for home births [90] will ensure that hepatitis vaccine is available in settings where births take place. Efforts to develop new heat-stable and freeze-stable hepatitis B vaccine will aid these attempts. In addition, health promotion efforts aimed at parents and training aimed at providers are needed to increase awareness about the importance of administering hepatitis B vaccine within 24 hours of birth.[91] A large list of potential barriers for birth dose delivery was found. Barriers arising from health services in developing countries included: low coverage of institutional birth, poor performance of outreach vaccination activities, logistical constriction for cold chain in rural and remote areas, out of pocket costs, and false contraindications. Potential barriers from health care users included most frequently: concerns about health effects, false contraindications, married category of mothers and mother's education. In developed countries barriers included confusion about reimbursement procedures and immigration status of mothers. No specific study for barriers impairing hepatitis B birth dose delivery was found in the Eastern Mediterranean region. New ways to deliver hepatitis B vaccines to neonates being born at home should be envisaged if the goal of eliminating perinatal transmission of hepatitis B is to be achieved.

Table 9. Barriers for timely hepatitis B birth dose in Western Pacific Region Community based studies

Author	Year published	Country	Study setting	Population studied	Reasons 1	Reasons 2	Reasons 3	Reason 4	Reason 5
Mao	2013	Cambodia	Community	General	Maternal education	Birth at home			
Cui	2006	China	Community	General	Birth at home				
Zhou	2009	China	Community	General	Birth at home	Parent awareness on HBV	Ethnic minority	Parents concern on adverse effect	
Patel	2014	Philippines	Community	General	Birth at home				
Murakami	2008	Vietnam	Community	General	Vaccine storage	Pregnancy tracking performance	Conflicting guidelines at hospitals	Private maternity services	Low birth weight
Murakami	2014	Vietnam	Community	General	Media report on adverse effects				

Table 10. Barriers for timely hepatitis B birth dose in Western Pacific Region. Hospital based studies

Author	Year published	Country	Population studied	Reasons 1	Reasons 2	Reasons 3	Reason 4	Reason 5	Reason 6
Sahhar	2015	Australia	high risk	Care by obstetritian					
Kang	2014	China	high risk	Low birth weight	Prematurity				
Keuatvongsa	2013	Laos	General	Vaccine outage	False contraindications	Health workers training	Limited outreach services		
Wiesen	2016	New Guinea	General	Health workers training/ supervision	Quality of outreach services	HB vacc available in facility	Vaccination in weekends	Birth at home	Mother knowledge of HBV
Patel	2014	Philippines	General	Out of pocket Cost	False contraindications	HW training	Vaccine availability	Private providers	Birth at home
Sobel	2011	Philippines	General	Trained staff	Standing order for HB admon	Copy of HB vacc policy in health facility			

Table 11. Barriers for hepatitis B birth dose in AMRO Region

Author	Year published	Country	Study setting	Population studied	Reasons 1	Reasons 2	Reasons 3	Reason 4	Reason 5
Bascom	2007	Puerto Rico	Hospital	General	Month of delivery	Birth weight			
Dayan	2001	USA	Hospital	high risk	Mother age	Hospital	Being less educated	Being single	
Aiken	2001	USA	Hospital	Managers	Reimbursement	Outreach inconvenience			
Thomas	2002	USA	Hospital	high risk	Thimerosal				
Cabana	2002	USA	Hospital	Managers	Thimerosal				
Clark	2004	USA	Hospital	Managers	Thimerosal				
Cooper	2005	USA	Hospital	HW	Tracking hospital immunizations	High cost	reimbursing	parents unwilling	Safety concerns
Zhao	2011	USA	Community	General	2 or + providers	Public/private provider	Mother Married status	Mother education	
Myers	2015	USA	Hospital	General	Marital status	Race			

Table 12. Barriers for hepatitis B birth dose in EURO Region

Author	Year published	Country	Study setting	Population studied	Reasons 1	Reasons 2	Reasons 3
Sloan	2005	UK	Hospital	high risk	Year of birth	antenatal booking	Maternal serologic al status
Giraudon	2009	UK	Hospital	high risk	London sector of residence	Command of english	

Table 13. Barriers for hepatitis B birth dose in SEARO Region

Author	Year publish	Country	Study setting	Population studied	Reasons 1	Reason 2	Reason 3	Reason 4	Reason 5
Alexander	2013	India	Hospital	high risk	Birth outside				
Lahariya	2013	India	Community	General	Fear of vaccine wastage	HW poor knowledge			
Creati	2007	Indonesia	Community	General	policy weakness	limited transport	poor communica tion	cold chain	HW training

Social and demographic factors related to timely birth dose in The Gambia are described by Miyahara for The Gambia. Living in rural areas was the most important risk factor for no receiving a birth dose (OR=6,1 CI 3.2-11.8).

In addition, information provided by the African Regional Office and the South-East Regional Office provides further insight on the countries progress and expressed barriers to the introduction of the Hepatitis B vaccine birth dose. Data on the following questions was collected:
1. Have the NITAG's recommended the introduction of the hepatitis B vaccine birth dose
2. What are the main barriers to the introduction of the birth dose?
3. What are the recommendations to overcome these barriers?

According to the information provided by the AFRO region, 10 of 47 countries have introduced the hepatitis B birth dose in their immunization schedule. Among the nine countries that provided HepB-BD in their vaccination schedule in 2015, coverage was <80% in three (Angola at 19%, Mauritania at 51% and Nigeria at 43%), between 80-95% in four (Botswana and Namibia at 87%, Cap Vert at 93% and Sao Tome at 91%), and >95% in two (Algeria and The Gambia). In Sierra Leone, the EPI Technical Committee (TCC) has recommended the introduction of Hepatitis B birth **dose** for 2018. Niger is planning to introduce the birth dose in 2019. In Mauritius the hepatitis B birth dose is given to babies whose mothers are HBV infected. The number of life births estimated for the AFRO region in 2015 was 35 380 279[92] . The number of life births in the countries that have no yet introduced the birth dose was 26 966 573 in 2015 [92]. The proportion of life births taking place in homes ranges from 8% in the Congo to 89% in Ethiopia.[93] Data from the World Bank shows that the range of births attended by skilled health staff in AFRO is 15.5% in Ethiopia to 99.2% in Mauritius.[94] Among the 37 countries that have not yet introduced the birth dose, 10 had an established NITAG and three had recommended the birth dose introduction into the national schedules. One country, Cameroon is pending approval of the 2017 budget to purchase the birth dose.
The most common mentioned barriers in the AFRO region to introduce the birth dose are the lack of funding for the birth dose programmes, the percentage of births that take place outside health facilities, the insufficient disease burden data, the vaccine storage facilities and access to cold chain and the central policies and guidelines.

Currently 7 of 11 countries in the SEAR have the hepatitis B birth dose in their national schedule; one country introduced it in February 2016. Among the six countries that provided HepB-BD in their vaccination schedule in 2015, coverage was <80% in two (Bhutan at 78% and India at 44%), between 80-95% in one (Indonesia), and >95% in three (DPRK, Maldives, and Thailand). Bangladesh, Myanmar, Sri Lanka, and Nepal do not provide a HepB-BD, though both Myanmar and Nepal may reconsider full or partial introduction of the birth dose as part of their national control strategies. Indonesia is using Uniject outside of cold chain and Timor Leste will do so for home deliveries or in places far from health centers. The barriers for introduction of the birth dose are the lack of funds, as there is no Gavi support for the birth dose, insufficient disease burden data, the use of out of the cold chain (OCC) and/or future

controlled temperature chain (CTC). The actions points suggested to overcome these barriers were advocacy for government budget allocation, conduct seroprevalence surveys, conduct country pilot studies on the use of the OCC and contribute to the capacity building of NITAGs and national regulatory authorities (NRAs). The SEAR region also provided information on the barriers to achieving high coverage. Those included the number of home deliveries without skilled birth attendance, the lack of awareness and/or training among health staff at birthing facilities (incomplete integration in newborn care packages, false contraindications, fear of adverse events following immunization (AEFI), weak coordination between MCH and EPI), challenges in the vaccine supply (presentation and availability, access, management like open vial policy), incomplete participation of the private sector.

Economic Evaluation of Hepatitis B vaccination

Economic evaluations of *Hepatitis B* vaccine: systematic review of the literature[95]

The objective was to systematically review the evidence for economic evaluations of HBV vaccination in LMICs.

Key findings included: (1) Since the introduction of HBV only 19 CEA studies in LMICs have been identified; (2) HBV vaccination in LMICs has favorable cost-effective results in almost all published studies using per GDP per capita cost-effectiveness thresholds; (3) This systematic review highlights that vaccine price, prevalence of HBV, discount rate, cost component, wastage rate of vaccine, and vaccine efficacy are the key drivers and play influential role in the decision to implement HBV immunization program in LMIC and; (4) In addition to cost-effectiveness results, decision makers should consider feasibility, affordability and sustainability of vaccination programs to ensure equitable access of vaccine when deciding whether to include HBV vaccination in national immunization program.

Out of 19 studies, 18 studies considered HBV vaccination cost-saving or cost-effective intervention, while only one study showed that it was unlikely to be cost-effective. Five of the six studies investigating birth dose HBV vaccination showed that it was cost-effective.

Most studies conducted one-way sensitivity analysis. Probabilistic sensitivity analysis (PSA) was conducted in eight studies. The most reported influential parameters were prevalence of HBV (7 of 19 studies), vaccine price (7 of 19 studies), discount rate (6 of 19 studies), cost component (4 of 19 studies), wastage rate of vaccine (3 of 19 studies), and vaccine coverage (2 of 19 studies).

In conclusion studies are overwhelmingly favourable with the exception of one study in India which did not find a birth dose cost effective. There was a paucity of studies and none of them used transmission models and modern methods. New studies would be valuable, particularly to NITAGs tasked with developing national policies.

For further information refer to the document: Hepatitis B Vaccination: An Updated Systematic Review of Economic Evaluations in Low and Middle Income Countries.

Table 14: Economics evaluation of Hepatitis B vaccination in LMICs

Study	Country	Type of economic analysis	Model	Perspective	Sponsor	Immunization approach*	Effectiveness measure	Threshold
Hall, 1993	The Gambia	CEA	None	Society	Department for Co-operation and Development of the Ministry of Foreign Affairs of Italy. The vaccine for the study was donated by Merck, Sharp, and Dohme.	Universal	Death averted	US$2750 (year 1979)
Liu, 1995	China	CBA	Static model: Decision tree	Society	N/A	Universal	BCR	N/A
Edmunds, 2000	Ethiopia	CEA, CMA	None	Healthcare	University of Warwick's Research and Training Development Fund. Wellcome Health Services Research Fellowship.	N/A	Per fully vaccinated child	N/A
Hu, 2001	China	CUA	Static model: Decision tree	Society	N/A	Targeted*	DALY	N/A
Aggarwal, 2003	India	CUA	Static model: Markov	Society	N/A	Universal	LYG, QALY	GNP per capita (US$440 for year 1999)
Prakash, 2003	India	CUA	Static model: Decision tree	Society	N/A	Universal	DALY	N/A
Adibi, 2004	Iran	CEA	Static model: Decision tree	Society and Healthcare	Research Center for Gastroenterology and Liver Disease, Shaheed Beheshti University of Medical Sciences, Tehran, Iran	Targeted*	Per chronic infection prevented	GDP per capita (US$1641 for year 2002)
Sahni, 2004	India	CBA, CUA	Static model: -	Society	The Canadian International Development Authority (CIDA)	Universal	QALY	GNP per capita (US$466 for year 2001)
Griffiths, 2005	Mozambique	CUA	Static model: -	Society	N/A	Universal	QALY	GNP per capita (US$210 for year 2001)
Vimolket, 2005	Thailand	CEA	Static model: Decision tree	Society	The Center of Excellence Research Fund, Chulalongkorn University; and the Thailand Research Fund, Senior Research Scholar.	Universal	Per case adverted	N/A
Kim, 2007	The Gambia	CUA	Static model: -	Society and Healthcare	Supported in part by a Harvard Graduate Society Fellowship.	Universal	DALY	GDP per capita (US$300 for year 2002)
Hutton, 2010	China	CEA	Probability tree and Markov	Societal	N/A	Catch-up program	Death, HBV infections averted, and QALYs	GDP per capita (US$2,500 for year 2008)
Guo, 2012	China	CEA HBIG	N/A	N/A	The National Nature Science Foundation of China	N/A	DALY averted	N/A
Klingler, 2012	Mozambique	CEA	Markov	Payer	N/A		DALY averted	GDP per capita (US$441 for year 2008)
Tu, 2012	Vietnam	CEA	Decision tree and Markov	Societal, healthcare, and payer	The Dutch Higher Education Foundation (NUFFIC)	Universal	LYG and QALY	GDP per capita (US$440 for year 2002)

Study	Country	Type of economic analysis	Model	Perspective	Sponsor	Immunization approach*	Effectiveness measure	Threshold
Lu, 2013	China	CEA, CUA	Decision tree and Markov	Societal and healthcare payer	N/A	Universal	New infections, HCC, deaths, LYG, and QLAY	GDP per capita (US$1,136 for year 2002)
Jia, 2014	China	CEA	Decision tree and Markov	Societal	National Health and Family Planning Commission and Minister of Science and Technology	Catch-up program	QLAY	GDP per capita (US$5,414 for year 2013)
Zheng, 2015	China	CBA	Decision tree	Direct and Societal	The Chinese Ministry of Science and Technology Program for Important Infectious Diseases Control and Prevention	Screening based vaccination for 21-59 years old	NPV, BCR	BCR ≥1
Chen, 2016	China	CBA	Decision tree and Markov	Direct and Societal	The Chinese Ministry of Science and Technology Program for Important Infectious Diseases Control and Prevention	Combine with one dose of HBIG for infants with HBsAg +ve mothers	NPV, BCR	BCR ≥1

* Universal = Immunization given to the whole general population or to all within a certain age group of the population (newborns, adolescents, adults, and so on), Targeted and catch-up = Immunization programs selectively targeting individuals at risk of hepatitis B virus
BCR: Benefit cost ratio; CBA: Cost–benefit analysis; CEA: Cost–effectiveness analysis; CMA: Cost–minimization analysis; CUA: Cost–utility analysis; DALY: Disability-adjusted life year; GNP: Gross national product; GDP: Gross domestic product; HBIG: Hepatitis B immunoglobulin; HCC: Hepatocellular carcinoma; QALY: Quality-adjusted life year; LYG: Life year gained; N/A: Not applicable; NPV: Net present value.

Table 15: Vaccine coverage, efficacy duration, price, discounting, and results

Study	Vaccine coverage	Vaccine efficacy /protection duration	Vaccine price per dose (US$)*		Discounting rate (%)		Results (US$, at costing year)
			Price	Costing year	Cost	Effect	
Hall, 1993	10%-15%	99% (95%CI 91-100)	3	1998	6	N/S	**Cost-effective** US$150-200 per death averted
Liu, 1995	100%	50% (HBsAg+ by 3 doses of 10μg) 90% (HBsAg+ by 3 doses of 30μg) 90% (HBsAg-)	6.53 (for 3 doses of 10μg) 12.37 (for 3 doses of 30μg)	1990	-	-	**Cost saving** With screening 30μg X3 for HBsAg+ and 10μg X3 for HBsAg-: BCR = 42.41 30μg X3 for HBsAg+ and no vaccination for HBsAg-: BCR = 48.01 Without screening 10μg X3 for both HBsAg+ and HBsAg-: BCR = 43.64
Edmunds, 2000	60%	N/A	0.35-1.69	1996	6	N/S	**Cost-effective** US$7.83 per fully vaccinated child (Extrapolate the cost-effectiveness in terms of outcome measure such as life years gained relative to The Gambia)
Hu, 2001	100%	90%	2.97	2001	3	-	**Cost-effective** Without screening: CER = 392.7 With screening: CER = 251.9
Aggarwal, 2003	75% (40% - 95%)	95%	3	2002	3	0	**Cost-effective** US$16.27/LYG and US$13.22/QALY
Prakash, 2003	52%	95%	0.75	1993	3	0 or 3	**Cost-effective**

Study	Vaccine coverage	Vaccine efficacy /protection duration	Vaccine price per dose (US$)*		Discounting rate (%)		Results (US$, at costing year)
			Price	Costing year	Cost	Effect	
							US$27.36/DALY
Adibi, 2004	100%	N/A	4.8	2003	3	0	**Cost-effective** US$202 per chronic infection prevented (no HBcAb screening) US$197 per chronic infection prevented (with HBcAb screening)
Sahni, 2004	N/A	100%	4.2	2001	3	0	**Not cost-effective** US$2909/QALY (US$8894/ discounted QALY)
Griffiths, 2005	80% (70% - 85%)	95% (90% - 99%)	0.27 for monovalent vaccine and 1.2 for DTP-Hepatitis B	2001	3	0 or 5	**Cost-effective** Undiscounted US$436 per death averted, US$15/DALY (monovalent), and US$36/DALY (combination vaccine) Discounted US$1833 per death averted, US$19/DALY (monovalent),, and US$47/DALY (combination vaccine)
Vimolket, 2005	N/A	N/A	3.75	2004	N/S	N/S	**Cost-effective** US$2201 per case averted (screen for HBsAg, then vaccination) US$464 per case averted (screen for HBsAg, HBeAg, then vaccination) US$152 per case adverted (universal vaccination) (Based on funds presently available in Thailand, universal vaccination should certainly be continued)
Kim, 2007	94% (85% - 100%)	95% (90% - 100%)	0.32	2002	3	3	**Cost-effective** US$28/DALY (societal perspective) US$47/DALY (healthcare perspective)
Hutton, 2010	100% (catch up for those who missed newborn vaccination)	95%	0.34	2008	3	3	**Cost-saving**
Guo, 2012	N/A	N/A	30.93, HBIG	N/A	N/A	N/A	**Cost-effective** US$118.61/DALY averted
Klingler, 2012	55%	88%	0.71	2008	3	3	**Cost-effective** US$250.95/DALY averted
Tu, 2012	70%	84%	1	2008	0 or 3	0 or N/S	**Cost-effective** US$4.52/LYG and US$3.77/QALY
Lu, 2013	84.3% for HepB3 and 66.1% for timely HepB1	66% (HBsAg+ HBeAg+) 73% (HBsAg+ HBeAg-) 95% (HBsAg- HBeAg-)	3.6, vaccination cost	2008	3	3	**Cost-saving**
Jia, 2014	100% (catch up for those who missed newborn vaccination)	N/A	0.34	2013	3	0 or N/S	**Cost-effective**
Zheng, 2015	50% for direct vaccination and 75% for screening based vaccination	93% (21-29 years) 89% (30-39 years) 80 (40-49 years) 70 (50-59 years)	0.76	2014	3	3	**Cost saving for young adults (21-39 years)** Without screening: direct BCR = 1.06, societal BCR = 1.42 With screening: direct BCR = 1.19, societal BCR = 1.73 **Not cost saving for middle aged adults (40-59 years)** Without screening: direct BCR = 0.59, societal BCR = 0.59 With screening: direct BCR = 0.68, societal BCR = 0.43
Chen, 2016	99.6% for HepB3 and 95.88% for timely birth dose	83.1% for vaccine only and 91.0% for vaccine+HBIG (HBSAg+ HBeAg+)	0.5	2013	3	3	**Cost saving** HepB+HBIG compared with HepB vaccination without HBIG: direct BCR = 0.4, and societal BCR = 2.7

*The Campbell and Cochrane Economics Methods Group (CCEMG) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre) Cost Converter (http://eppi.ioe.ac.uk/costconversion/default.aspx)
CBA: Cost–benefit analysis; CEA: Cost–effectiveness analysis; CMA: Cost–minimization analysis; CUA: Cost–utility analysis; DALY: Disability-adjusted life year; QALY: Quality-adjusted life year; LYG: Life year gained; N/A: Not applicable, N/S: Not specified

Prevention of mother-to-child-transmission (PMTCT)

A review assessed the effect of the use of antivirals in pregnancy to reduce hepatitis B viral load and reduce perinatal transmission. It was undertaken as part of scope of work for 2015 WHO Guidelines on Prevention, Care and Treatment of persons with chronic hepatitis B infection. A proportion of infants born to HBsAg-+ve mothers acquire HBV despite HBV vaccination; together with growing evidence suggesting that maternal treatment with nucleo(s)tide analogue therapy in 3rd trimester of pregnancy plus vaccine /HBIG for infant may further reduce HBV transmission to the infant. 35 studies were identified (12 RCTs, 19 observational studies and two systematic reviews).

No formal recommendation on use of antivirals for PMTCT was made for 2015 HBV guidelines because: (1) Current limited and low quality evidence base with 3 ongoing (and one completed but unpublished) trials due to report in 2015–2016; (2) Overall, data limited for comparisons of different antivirals, and suitable data were identified only for three different antivirals: lamivudine, telbivudine and tenofovir; and (3) Lack of consensus as to the programmatic implications of a policy of more widespread antiviral use in pregnancy, given very limited access to HBV viral load assays.
There are plans within GHP to update the systematic review on effectiveness data to include additional trials, especially those with tenofovir, and to also seek additional programmatic experience to inform feasibility: (e.g. Access to HBV DNA, HBsAg quantification, HBeAg; Implementation of HBsAg testing and coverage in antenatal clinic setting; Prevalence of HBeAg + and high HBV DNA in different regions/settings and Access to TDF). There is currently no recommendation from the Global Hepatitis Programme. The evidence would be reviewed again in 2017.

Introducing this intervention would potentially require antenatal screening with some measure of viral load. The programmatic requirements of such an approach are likely to be considerable and it would be good to develop documentation of what these might be prior to guidance on use.

It is important to map the proportion of HBsAg positive women of childbearing age who were HBeAg positive and/or HBV DNA positive. This information might be required by region or country (for example there appears to be a marked difference in HBeAg prevalence between China Asia and AfricaSub-Saharan Africa).

Countries that have introduced hepatitis B birth dose
http://www.who.int/immunization/monitoring_surveillance/data/en/

List of WHO Prequalified hepatitis B containing vaccines and licensed schedules:
http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html

Number of births occurring at home: http://www.who.int/maternal_child_adolescent/epidemiology/profiles/maternal/en/

Births attended by skilled health staff (% of total): http://data.worldbank.org/indicator/SH.STA.BRTC.ZS

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World Health Organization

Initiative for Vaccine Research
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Annex 1:

Ad-hoc expert consultation on optimizing the hepatitis B vaccination schedule

1–2 September 2016

Conclusions and recommendations (28/09/2016)

Disclaimer: This document has been prepared to inform SAGE deliberations on HBV vaccination schedules. The content of this document includes the conclusions and proposed recommendations by a group of HBV and immunization experts. However, these conclusions and recommendations will only become WHO recommendations if and when SAGE endorses them.

Objectives

- To discuss and review the evidence on hepatitis B vaccine to inform SAGE discussions on optimal schedules and delivery strategies. Evidence will include:
  - Global hepatitis B seroprevalence systematic review.
  - Immunogenicity and efficacy of selected hepatitis B vaccine schedules.
  - Effect of hepatitis B vaccination among immunosuppressed populations
  - Literature review on the thermostability of the hepatitis B vaccines
  - Review of barriers to implement the birth dose.
  - Current and anticipated impact of various vaccination schedules at reducing HBV related disease.

- To outline the conclusions and recommendations that will be presented for SAGE's consideration
  - What are the optimal immunization schedules for hepatitis B vaccines for infants living in different epidemiological settings?
  - Do persons at high risk of inadequate immune response should receive different schedules?
  - What is the incremental effectiveness of implementing a hepatitis B vaccine birth dose (e.g. immunological and clinical outcomes)?
  - Does the available evidence support flexibility in the requirement for cold chain storage of hepatitis B containing vaccines to expand the delivery of the birth dose?

Summary

1. Welcome and Introductions. Dr Okwo-Bele opened the meeting with a presentation summarising the current status of global immunisation highlighting the issues for hepatitis B vaccination.

   Dr Hall then noted that this meeting was to address the questions and evidence that should be presented to the SAGE meeting in October.

   Dr Okwo-Bele's presentation had highlighted the tremendous success in the Western Pacific Region (WPR) in hepatitis B control. In continuation, Dr Joe Woodring from Manila presented the situation of that Region.

2. **Updated on hepatitis B Control – WPR experience.** In his presentation, Dr Woodring highlighted a number of key issues which had facilitated WPRO success: Political commitment, leadership by the Regional Office, recruitment

of expertise globally and formation of an Expert Resource Panel, individual country analyses of issues and their solutions, an emphasis on the birth dose delivery either through deliveries in health institutions or by delivering vaccine outside the cold chain where appropriate and health worker education and vaccination policy. Dr Woodring summarized the progress towards the regional control goal of ≤1% of chronic hepatitis b infection. He also discussed the strategies to improve the birth dose coverage and presented the results of two out of the cold chain pilot studies. Concerns were raised regarding the wastage of vials in one of the study sites. However it was clarified that the pilots used one and 10-dose vials and that the wastage as reduced when the 10-dose vials were not counted.

3. Review of **re-analysis of the HBsAg prevalence.** Professors Edmunds and de la Hoz each presented aspects of a large database re-analysis of prevalence data compiled by Dr Ott and her team. Professor Edmunds described the techniques that he was using to provide estimates for areas with no data available and Prof de la Hoz described the descriptive analysis separating out studies before and after the introduction of vaccination.

   Meeting participants noted the value of prevalence data for mathematical modelling exercises and as feedback to the countries themselves. However they noted how sparse post-vaccination data was especially countries outside of the WPR. It was also recommended that antenatal surveys are conducted as they reflect pre-vaccination carriage prevalence for countries with introduction in the last decade as well as they show the probability of perinatal transmission. It was also suggested to generate a data extraction tool to obtain the data points for the future surveys.

4. Review of the **efficacy, effectiveness and safety** from randomized controlled trials and observational studies of childhood schedules using hepatitis B vaccines. Dr Karla Soares-Weiser presented an update of her previous systematic review of the immunogenicity and safety of hepatitis B vaccination schedules. She noted a great paucity of recent studies and that many of the studies in the review were of poor methodological quality as reported.

   The meeting noted that the possible schedule are highly flexible in terms of numbers of doses and spacing provided between the various doses delivered early in life.

   Data on boosters and long term protection were discussed and it was concluded that the evidence doesn't contradict the current WHO recommendations. It was suggested to note to SAGE that the decline in antibody titre or waning antibodies (anti-HBs) does not imply "loss of clinical protection" as evidenced by increases in anti HBsAg titres following a booster dose (Middleman AB et al 2014; Spradling PR, et. al. Infect Control Hosp Epidemiol. 2015). In addition, the critical point to

eliminate hepatitis B is preventing perinatal transmission as most of chronic carriers are attributable to mother-to-infant-transmission (Shimakawa et al 2105.)
It was also suggested to provide a GRADE summary table with the studies on long-term protection and the systematic review.
The need for continued surveillance was highlighted.

5. Special populations – **Low birth weight**. Dr Henao Restrepo provided a summary of the evidence on vaccination and low birth weight babies. This clearly showed the reduced immunogenicity of vaccination in this group. However, the group noted that delaying vaccination would leave the baby at risk. The participants therefore recommended that all babies should have a birth dose whatever their birth weight and those with a low birth weight should start their primary schedule of vaccination 1 month later. Vaccinating all infants at birth ensures that all babies have some protection in case of positive, unknown or false negative maternal antigen status or exposure in the first month of live.

6. Special populations – **HIV infected persons**. The group had previously discussed an expert review commissioned and undertaken by British Medical Journal Clinical Evidence Group in 2014 and presented by Dr Easterbrook at a previous meeting which concluded a double dose (40 ug) HBV vaccine at 0, 1, 6 months was more clinically effective than the standard regimen with 20 ug in those HIV positive. A further search conducted by Professor de la Hoz in both children and in adults addressed the medium to long term effects of vaccination. This review found that the increase in antibody following higher concentration vaccine was short-lived. It also found that there was no evidence available on the protective effects of vaccine-induced antibody in those HIV positive.
   The group concluded that there was no strong evidence to change the current WHO recommendation on vaccination of HIV positive population at any age. Recommending periodical monitoring of anti HBs titres may be discussed at SAGE. Clearly additional research on this issue is needed.

7. **Hepatitis B and hepatitis C attributable liver cancer.** Dr Plummer presented a recently published analysis that assessed the fraction of primary liver cancer by area that could be attributed to HBV and to HCV. This emphasised the large number of cases from these causes in East Asia and in Africa. The group noted the great value of this for advocacy and suggested the possibility of age-stratified analyses to particularly look at potentially preventable cases in the younger ages groups.

8. **Mathematical model.** John Edmunds presented two types of mathematical models. First, a static model using the global prevalence review looking at the likely impact of vaccination country by country. Second, a transmission model applied to data from China, South Korea and The Gambia looking at the long

term (over the next century) impact of the hepatitis B vaccination programmes on cirrhosis and primary liver cancer incidence.

The group noted that vaccine alone will not lead to a reduction in persons with disease until the second half of the century. The group noted that this illustrated the continuing need for treatment of existing carriers, cirrhosis and liver cancer.

The model also illustrated the flexibility of the vaccine schedule in as much as the modelling results of any schedule showed a similar estimated impact.

The group noted that the model did not show an early impact because of the population growth which is expected in many countries. However it also noted that data from China clearly showed that the population under ten there is effectively and "infection free generation".

9. **Evaluation of hepatitis B Vaccination.** Dr Raymond Hutubessy then presented a review of cost effectiveness studies of hepatitis B vaccination in low and middle income countries.

   The group noted that these were overwhelmingly favourable with the exception of one study in India which did not find a birth dose cost effective.
   It also noted that there was a paucity of studies and that none of them used transmission models and modern methods. It was therefore felt new studies would be valuable, particularly to NITAGs tasked with developing national policies.

10. **Prevention of mother to child transmission.** Dr Philippa Easterbrook presented evidence on the use of antivirals in pregnancy to reduce hepatitis B viral load and reduce perinatal transmission that was undertaken as part of scope of work for 2015 WHO Guidelines on Prevention, Care and Treatment of persons with chronic hepatitis B infection. A proportion of infants born to HBsAg +ve mothers acquire HBV despite HBV vaccination; together with growing evidence suggesting that maternal treatment with nucleo(s)tide analogue therapy in 3rd trimester of pregnancy plus vaccine/HBIG for infant may reduce HBV transmission to the infant. 35 studies were identified (12 RCTs, 19 observational studies and two systematic reviews).
    She emphasised that no formal recommendation on use of antivirals for PMTCT was made for 2015 HBV guidelines because: (i) Current limited and low quality evidence base with 3 ongoing (and one completed but unpublished) trials due to report in 2015–2016; (ii) Overall, data limited for comparisons of different antivirals, and suitable data were identified only for three different antivirals: lamivudine, telbivudine and tenofovir; and (iii) Lack of consensus as to the programmatic implications of a policy of more

widespread antiviral use in pregnancy, given very limited access to HBV viral load assays.
Dr. Easterbrook highlighted plans within GHP to update the systematic review on effectiveness data to include additional trials, especially those with tenofovir, and to also seek additional Programmatic experience to inform Feasibility: (eg. Access to HBV DNA, HBsAg quantification, HBeAg; Implementation of HBsAg testing and coverage in antenatal clinic setting; Prevalence of HBeAg + and high HBV DNA in different regions/settings and Access to TDF).

The group noted that this intervention would potentially require antenatal screening with some measure of viral load. The programmatic requirements of such an approach are likely to be considerable and the group felt it would be good to develop documentation of what these might be prior to guidance on use.

The group also noted that mapping of the proportion of HBsAg positive women of childbearing age who were HBeAg positive and/or HBV DNA positive by region or country would be useful (for example there appears to be a marked difference in HBeAg prevalence between Asia and Sub-Saharan Africa).

Cost effectiveness analyses would be valuable.

11. **Hepatitis B birth dose coverage.** Dr de la Hoz presented the results of a systematic review on the barriers to implement a birth dose. Among the main barriers perceived by the countries in the AFRO and SEARO regions were the funding for birth dose programmes, the births occurring outside the health facilities, the lack of data on the disease burden, issues on the vaccine storage and cold chain and the central policies and guidelines. This was in agreement with the literature review that in addition noted the health workers' poor knowledge on HBV.

    Presentations were made by SEARO and AFRO verbally on the issues that they perceived being obstacles to improving hepatitis B vaccine coverage.

    In discussion these obstacles were categorised into:
    - Policy/political, coordination challenges between EPI and the Ministries of Health, rationale, advocacy and support for introduction of the birth dose, policy updates, establish and/or reinforce NITAGs.
    - Operational, technical support to reach home deliveries, benefits of the use of the out of the cold chain
    - Monitoring: data on country coverage and introduction, fear of Adverse events after immunization , data on seroprevalence

The group noted that the definition of birth dose needed to be clarified as it varied across countries and studies. The group also suggested the drafting of a document to support the introduction of the hepatitis b birth dose.

12. **Stability of hepatitis B vaccine.** Since an important proportion of deliveries at home or limited cold chain in peripheral health may hamper access to the birth dose, Dr Brad Gessner presented a review of published data and manufacturers' data that assessed the thermostability of hepatitis B monovalent vaccine. Existing data indicates that most hepatitis B vaccines are heat stable and have been found to maintain immunogenicity after exposure to temperatures of up to +45°C for one week and temperatures up to +37°C and +41°C for several weeks. Field experience suggest there maybe programmatic advantages in keeping hepatitis b vaccine in ambient temperatures at service delivery points, especially as a strategy for reaching home births.

13. **CTC process to on-license us of hepatitis B birth dose in a CTC.** Dr Petit presented on the regulatory process required for pre-qualification of a vaccine, concerns raised by the CTC working group under IPAC regarding OCC off-label vaccine use and a survey of countries in AFRO and WPRO on their desire for a CTC- compatible hepatitis B birth dose vaccine.

    The group noted that a CTC pre-qualified vaccine might be more expensive, though so far only one manufacturer has provided this information. The group further noted that and that several countries were already using the vaccine OCC, though except for Indonesia, only on a pilot basis. It proposed that SAGE recommends encouraging CTC pre-qualification whilst recommending the use of vaccine off label for OCC. However, the question was raised how much scientific background and detail was required by SAGE to make a sound and sufficiently informed decision regarding off-label use, and to define the conditions for OCC usage, in terms of temperature and time. It was further recommended to contact those manufacturers who have shared their thermostability data, so as to encourage them to apply for CTC licensure.

14. **Preparing for SAGE discussions.** The group discussed the questions to be put to SAGE they were:

    - Do the current recommendations require any change?
    - What is the impact of the vaccination programme in the hepatitis b epidemiology?

- Does the available evidence support flexibility in the requirement for cold chain storage of hepatitis B monovalent vaccine in order to expand the delivery of the birth dose?

15. Next steps

a. WHO Secretariat to summarize the evidence presented at the meeting and to produce the background document for SAGE.
b. WHO Secretariat to write a short document on antiretroviral therapies.
c. WHO Secretariat to produce an overview of the different interventions for different demographic/epidemiological settings.