WORLD HEALTH ORGANIZATION

REGIONAL OFFICE FOR THE WESTERN PACIFIC

WESTERN PACIFIC REGIONAL PLAN FOR HEPATITIS B CONTROL THROUGH IMMUNIZATION

Manila, Philippines
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WESTERN PACIFIC REGIONAL PLAN FOR HEPATITIS B CONTROL THROUGH IMMUNIZATION

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SUMMARY

Worldwide, an estimated 350 million people have chronic hepatitis B virus (HBV) infections. In spite of being home to only 28% of the global population, the WHO Western Pacific Region bears a disproportionate burden of HBV-related mortality and morbidity, accounting for almost half of all chronic hepatitis B infections worldwide. With an estimated 160 million chronic HBV carriers living in the Region, hepatitis B is responsible for almost 890 deaths per day, a mortality rate comparable to that of tuberculosis. With few exceptions, most countries were estimated to have a chronic HBV infection rate of more than 8% before the introduction of vaccination. Of the 278 000 estimated deaths caused by HBV infection in the Region, nearly all were consequences of chronic infection, mostly decades after the initial infection at birth or in early childhood. Hepatitis B is, therefore, an important regional public health priority.

Universal childhood immunization with three doses of hepatitis B vaccine in the first year of life has been proven to be the most effective strategy for prevention and control of hepatitis B. In 2002, the WHO Western Pacific Region became the first WHO Region to achieve the distinction of having infant hepatitis B immunization included in the national immunization programmes (NIPs) of all its Member States. Striving to build upon the gains achieved in immunization systems during the poliomyelitis eradication initiative, the Region has adopted hepatitis B control through universal childhood immunization as one of the pillars for strengthening immunization service delivery systems. In September 2005, the Western Pacific Region became the first WHO Region to set a time-bound goal of reducing chronic HBV infection rates to less than 2% among five-year-old children by 2012.

For countries to achieve that goal, the key programmatic strategies will be:

- Strengthen routine immunization services to achieve and sustain at least 85% coverage (preferably 90%) with three doses of hepatitis B vaccine by one year of age in each birth cohort. At least 80% coverage to be achieved in each district.
- Establish a system to deliver a timely scheduled birth dose (within 24 hours of birth), with the target to reach at least 80% of births at each subnational level and at the national level.
- Institute catch-up immunization for older children, the first priority being children under five years of age, followed by those aged six to 15 years born before the start of vaccination, where resources allow and where infant immunization programmes, including delivery of a timely birth dose, are relatively mature.
- Institute immunization for high-risk population groups as the next priority after immunization of infants and younger children. However, immunization for health workers, among the high-risk population groups, can be taken as a priority along with infant immunization programmes because of the operational ease of identifying and accessing this population group.
- Achieve predictable financing for hepatitis B vaccine for at least the next three years on a continuous rolling basis to avoid any disruptions in the programme.
- Carry out advocacy and social mobilization activities.
- Include a hepatitis B control plan as an integral part of the multiyear plan for immunization programmes.

Monitoring of hepatitis B immunization programmes is carried out primarily through coverage assessment, including monitoring of the percentage of newborn infants receiving a timely birth dose. The impact of vaccination programmes on HBV-related disease cannot be monitored like other vaccine-preventable diseases through regular disease surveillance because of the large number of asymptomatic infections, especially among children, the long time-lag before complications develop from chronic infection, and the fact that those complications are not exclusively caused by HBV. Therefore, the impact should be assessed through HBsAg seroprevalence surveys, along with regular monitoring of vaccine coverage rates. Countries should undertake at least one serosurvey in vaccinated cohorts to validate the impact expected from reported vaccine coverage rates.

GLOSSARY

Anti-HBs	antibodies to the surface antigen of hepatitis B virus.
BCM	baby of carrier (HBsAg-positive) mother
Carrier	person with long-term (chronic) HBV infection.
DTP	diphtheria-tetanus-pertussis vaccine—a combination product of the three vaccines that protect against the three diseases
DTP3	third dose of diphtheria-tetanus-pertussis vaccine
DTP-HepB	combination of vaccines that protects against diphtheria, pertussis, tetanus and hepatitis B
DTP-HepB3	third dose of DTP-HepB—the final one in the series. For monitoring this should be considered as the HepB3 dose, even if a birth dose is given making it the fourth dose of hepatitis B vaccine.
EPI	Expanded Programme on Immunization
GAVI	Global Alliance for Vaccines and Immunization
Anti-HBc	antibodies to hepatitis B core antigen (HBcAg)—a protein found in the core of the virus
HBeAg	hepatitis B 'e' antigen—indicates greater infectivity in chronic infection
HBIG	hepatitis B immunoglobulins
HBsAg	hepatitis B surface antigen—a protein from the coat of the virus. A positive test for HBsAg indicates active HBV infection. The immune response to HBsAg provides the basis for immunity against HBV, and HBsAg is the main component of HepB.
HBV	hepatitis B virus
HCC	hepatocellular carcinoma, or primary liver cancer—a major complication of chronic HBV infection, usually fatal
HepB	hepatitis B vaccine (can be plasma-derived or recombinant)
HepB0	first dose of hepatitis B vaccine given within 24 hours. HepB0 will be same as HepB1 if all the first doses are given within 24 hours of birth.
HepB3	third and final dose of HepB— three doses are recommended for protection
Hib	*Haemophilus influenzae* type B
NIP	national immunization programme
Plasma-derived HepB	hepB manufactured from the plasma of HbsAg+ carriers by extracting the HBsAg
Recombinant HepB	hepB manufactured from a genetically modified yeast or mammalian cell with the gene to produce HBsAg
RED	reaching every district (RED)
Seroprevalence	percentage of a population positive for a specific antibody (e.g. to HBsAg) or antigen (e.g. HBsAg)
TAG	Technical Advisory Group

1 INTRODUCTION

1.1 Purpose and focus of the plan

Worldwide, an estimated 350 million people have chronic hepatitis B infections. In spite of being home to only 28% of the global population, the WHO Western Pacific Region is estimated to bear a disproportionate burden of HBV-related mortality and morbidity, accounting for almost half of all chronic hepatitis B infections worldwide. With an estimated 160 million chronic HBV carriers living in the Region, hepatitis B is responsible for almost 890 deaths per day, a mortality rate comparable to that of tuberculosis. With few exceptions, most countries were estimated to have a chronic HBV infection rate of more than 8% before the introduction of hepatitis B vaccine. Hepatitis B is, therefore, an important regional public health priority.

Striving to build upon the gains achieved in immunization systems during the poliomyelitis eradication initiative, the Western Pacific Region has adopted hepatitis B control through immunization as one of the pillars for strengthening immunization service delivery systems. Following the recommendation of the second expert working group meeting on hepatitis B, held in Tokyo, Japan, in June 2002, the WHO Regional Office for the Western Pacific published the first Regional Plan for Hepatitis B Control in January 2003. A third expert working group meeting was held in Tokyo in March 2007.

This second, updated version of the Regional Plan for Hepatitis B incorporates the recommendations made by the WHO Regional Committee for the Western Pacific at its 57th session, in September 2005; the 16th Technical Advisory Group (TAG) meeting, held in June 2006; and the third expert working group meeting on hepatitis B, held in March 2007.

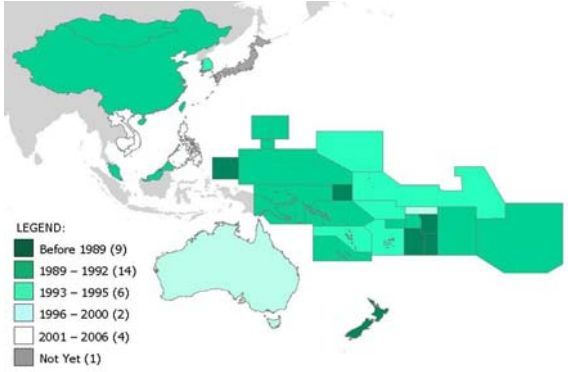
The Plan provides an update on the progress made since 2003, regional goals, programmatic strategies and sub-indicators, and a plan for monitoring and evaluation of achievement of the hepatitis B control goal. The document not only provides an overall plan of action for the Western Pacific Regional Office, but can also be adapted by individual Member States to prepare their national plans of action.

1.2 Control options: Immunization and non-immunization

Universal infant immunization with three doses of hepatitis B vaccine, with the first dose provided within 24 hours of birth, is the most cost-effective prevention and control strategy. This strategy provides the earliest possible protection to future birth cohorts and reduces the pool of chronic carriers in the population. Catch-up immunization of children born before introduction of vaccine and immunization of adults at high risk for HBV infection are additional preventive strategies that can help to protect older birth cohorts not yet exposed or infected.

Non-immunization control options include ensuring the safety of blood and blood products through regular screening of donors, promotion of safe sex and ensuring injection safety. These control strategies will have positive public health benefits, not only in terms of hepatitis B control, but also for other bloodborne infections, such as HIV/AIDS. Notwithstanding the merits of these additional strategies, however, this Plan focuses specifically on hepatitis B control through immunization.

Figure 1. Year HepB vaccine routinely offered to all infants



1.3 Progress made in the Western Pacific Region since 2003

Figure 1 illustrates the years in which hepatitis B vaccination was first offered to all infants in the various countries of the Region.

Since the publication of the last Regional Plan in 2003, substantial progress has been made in implementation of universal infant vaccination starting at birth, as presented in Box 1. By the end of 2006, all but one[i] Member States in the Region were providing hepatitis B immunization for all infants nationwide and had included a birth dose in their official immunization schedules. Reported coverage for HepB3 is generally the same as for DTP3 in most countries, although data quality remains a concern. The financing for vaccines included in national immunization schedules varies throughout the Region, but all countries offer HepB on the same basis as other EPI vaccines.

Please see Annex 4, Table 4 for additional information on the non-infant immunization policies currently being followed in Member States.

Box 1: Progress made since the last regional plan (2003)

- ⇨ China greatly expanded hepatitis B vaccination coverage with GAVI support. In 2005, a national law was passed abolishing user fees for all immunizations offered as part of EPI. The Government took over the full financing of hepatitis B vaccines after GAVI support ended in 2006.
- ⇨ Cambodia and the Lao People's Democratic Republic expanded DTP-HepB vaccination nationwide with GAVI support in 2004 and 2005, respectively.
- ⇨ In 2005, Mongolia changed its hepatitis B vaccination schedule, with provision of the birth dose within 24 hours of birth, replacing its earlier policy of within 24 to 48 hours.
- ⇨ In 2006, the Philippines passed an administrative order to change the hepatitis B immunization schedule, with a birth dose within 24 hours being introduced and 100% of funding being committed for procurement of hepatitis B vaccine until the end of 2010.
- ⇨ Viet Nam integrated hepatitis B vaccination into its EPI with provision of hepatitis B vaccine nationwide by 2003. GAVI support ended in the middle of 2007 and the Government has made a commitment to complete financing of hepatitis B vaccine from domestic resources. In addition, Viet Nam is slowly changing its policy on the birth dose. The current schedule provides for the first dose within 24 hours of birth compared with its earlier policy of within seven days of birth.

Background information about HBV, the consequences of HBV infection, and HBV epidemiology can be found in Annex 1; the estimated disease burden for the 2005 surviving birth cohort in Annex 2; and information on HepB vaccine in Annex 3. More information is available from various sources including WHO guidelines,[1] and from the Internet, including: the United States Centers for Disease Control and Prevention (CDC), Atlanta, website at www.cdc.gov/ncidod/diseases/hepatitis/b/index.htm; www.immunize.org/hepb/index.htm; www.hepnet.com/hepb.html; www.hepb.org; and www.hepatitisb.org. A training resource for hepatitis B is available at: http://www.path.org/vaccineresources/files/HBV_training_module_CVP.pdf .

[i] Japan has hepatitis B vaccination included in the national immunization schedule, but it is provided only to high-risk infants born to HBsAg-positive mothers.

2 REGIONAL GOAL, STRATEGIES AND SUB-INDICATORS

2.1 The regional hepatitis B control goal

Each child counts. Hence, the ultimate goal of the WHO Regional Office for the Western Pacific is to protect each and every child from HBV infection. Time-bound realistic goals are needed, however, to guide the programme. In September 2005, during its 56th session, the WHO Regional Committee for the Western Pacific unanimously adopted the regional hepatitis B control goal[ii] of reducing chronic HBV infection rates (as measured by HBsAg seroprevalence) among children aged five years to less than 2% by 2012[iii].

Box 2: Why was the hepatitis B control goal set up in terms of HBsAg seroprevalence and not in terms of visible disease outcomes?

Most of the current vaccine-preventable diseases (e.g. diphtheria, pertussis, measles, polio, tetanus, *Haemophilus influenzae* type B (Hib) etc.):

- are acute in nature: The impact of the vaccination programme is immediately visible in the same year on the symptomatic disease burden in the age group targeted for vaccination (e.g. infants).
- have distinct clinical signs and symptoms (except Hib): This results in syndromic surveillance of relatively high sensitivity (e.g. Acute flaccid paralysis for poliomyelitis; and fever and rash for measles) and allows good monitoring of the disease burden through syndromic surveillance, at least in the early stages of the vaccination programme, even when laboratory capacity is inadequate (although adequate laboratory capacity will be needed in the advanced stage—elimination or eradication—of the programme).

However, none of the above criteria apply to hepatitis B. Infants, the key target group for hepatitis B immunization programmes, rarely develop symptomatic disease (e.g. acute hepatitis, chronic hepatitis B, liver cirrhosis and hepatocellular carcinoma) immediately following HBV infection. Nevertheless, infants and younger children are highly prone to HBV infection from perinatal and horizontal transmission, and are more likely than adults to become chronically infected with HBV. These children are, not only likely to die from cirrhosis or liver cancer in their 30s to 50s, but also serve as an infectious pool to sustain the transmission of HBV infection among the general population.

Hence, surveillance for symptomatic hepatitis B disease among children (as practised for other vaccine-preventable diseases) is unlikely to show any impact of the vaccination programme unless and until there is a highly sensitive surveillance system with laboratory support that can show trends in relatively rare events, such as acute hepatitis among children. The first indicator to be affected by a vaccination programme is the seroprevalence of HBsAg among children, as fewer and fewer children will become infected. Hence, the hepatitis B goal was set in terms of reduction in chronic HBV infection as evidenced by a decrease in the seroprevalence of serological markers (HBsAg) rather than a reduction in the incidence of acute hepatitis or cirrhosis or hepatocellular carcinoma, which would take several decades.

[ii] The regional goal for hepatitis B control was setup along with the regional goal for measles elimination, constituting the twin regional goals of the Expanded Programme on Immunization.

[iii] The Resolution number for endorsement of twin regional goals of hepatitis B control and measles elimination was WPR/RC56/SR/8.

The final goal, however, remains achieving a chronic HBV infection rate of less than 1%, as outlined in the earlier Regional Plan in 2003, although the date and time-frame for this has not been decided. Countries that have already achieved the interim milestone of <2% prevalence need to strive for the final regional goal of <1% or an even a more challenging goal (e.g. elimination of HBV transmission).

Box 3: Why was the goal set among five-year-old children?

Children have a 90% chance of developing chronic HBV infection if infected initially at birth, a 30% chance if infected between the ages of one and five years, and only a 5% to 10% chance if infected after five years of age. In settings hyperendemic for hepatitis B, as is the case in most countries of the Western Pacific Region, most chronic infections are acquired by age five. Goldstein and colleagues* estimated that in 75% of all HBV-related deaths, infection is acquired before five years of age. As most chronic HBV infections are also acquired by age five, measuring the goal among children aged five years or older will take into account the complete exposure period when the risk of horizontal transmission and likelihood of becoming chronically infected are highest. Setting the goal among children under five years of age may overestimate the impact of vaccination programmes if some of the children who are uninfected and unprotected at the time of evaluation later become infected by age five and become chronically infected with HBV.

* Goldstein ST et al. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. *International Journal of Epidemiology*, December 2005, 34: 1329-1339.

2.2 Specific strategies and sub-indicators

In order for countries to achieve the time-bound regional goal of reducing chronic HBV infection rates to less than 2% among five-year-old children by 2012, eight specific strategies are recommended:

(1) Strengthening routine immunization services to achieve sustained high coverage with three doses of hepatitis B vaccine among infants

(2) Universal provision of the first dose of hepatitis B vaccine within 24 hours of birth to prevent mother-to-child transmission

(3) Catch-up immunization of older children

(4) Immunization of high-risk adult population groups

(5) Promotion of self-reliance in hepatitis B vaccine financing

(6) Ensuring vaccine potency by avoiding inadvertent vaccine freezing

(7) Advocacy and social mobilization

(8) Inclusion of hepatitis B control strategies in the multiyear plan for EPI

Strategy 1: Strengthening routine immunization services to achieve sustained high coverage with three doses of hepatitis B vaccine among infants

Strengthening routine immunization services in order to immunize at least 85%, and ideally 90%, of each birth cohort with three doses of hepatitis B vaccine before the age of one year is the most important strategy for hepatitis B control. [Please see Box 5 and Table 2 for the rationale for hepatitis B vaccine coverage levels.]

Sub-goal : Minimum HepB3 coverage of 85% by 2007 and 90% by 2008, with at least 80% coverage in all the districts.

Sub-indicators:

(1) Percentage of infants immunized with three doses of vaccine by age one year at national level and at each subnational/district level

(2) Percentage gap between DTP3 and HepB3 coverage (goal is to reduce the gap to less than 5%)

(3) Percentage drop-out rates from HepB1 to HepB3 (goal is to have drop-out rates of less than 10%)

(4) Synchronization of hepatitis B schedule with DTP dose: Y/N

(5) Inclusion of hepatitis B vaccination in the definition of children fully immunized: Y/N

Activities:

- Use tools, such as microplanning, the RED strategy[iv], improved supervision at all levels, better logistics and inventory management of vaccines and injection supplies to streamline and strengthen routine immunization services to reach each and every child.

- Include HepB3 coverage among infants as an indicator to monitor the performance of routine immunization services.

- Rationalize immunization schedules by scheduling hepatitis B vaccination at the same time as other vaccines to reduce the number of visits needed, which in turn will increase the likelihood of children being fully immunized. Table 1 shows the recommended schedule for HepB and DTP in the Western Pacific Region. Several countries are still scheduling a separate visit for HepB vaccination (Table 1, Annex 4).

It has been observed in some countries, even those with the same schedule for DTP and hepatitis B vaccination, that fewer vaccination sessions are organized for HepB than for DPT (e.g. DTP sessions may be organized four days a week and a HepB session only once a week, forcing mothers to bring children twice). This is ostensibly to reduce the wastage rate for the more expensive hepatitis B vaccine. However, this practice may reduce the vaccine coverage rates for HepB. Procuring smaller vaccine vials (one- or two-dose vials) may be a better alternative to reduce vaccine wastage. In addition, smaller vaccine vials will discourage service providers to schedule fewer vaccination sessions for hepatitis B.

[iv] Please refer to the WHO website at http://www.who.int/immunization_delivery/systems_policy/red/en/index.html for more information on the 'reaching every district' strategy

Table 1: Recommended schedules of HepB and DTP in the Western Pacific Region.

Age*	Monovalent vaccine		Combination vaccine
	DTP	HepB	
At birth (within 24 hours)		HepB birth	HepB-birth
6 weeks	DTP1	HepB2	DTP-HepB1
10 weeks	DTP2		DTP-HepB2
14 weeks	DTP3	HepB3	DTP-HepB3

*Ages given are flexible, with the recommended ages being the earliest possible. Immunization programmes should emphasize vaccination at birth and completing the HepB series by six months of age.

Strategy 2: Universal provision of the first dose of hepatitis B vaccine within 24 hours of birth to prevent mother-to-child transmission

Protecting children against perinatal infection is a high priority as almost 30% to 40% of chronic infections may be acquired perinatally in the Region. The baby of an HBsAg-positive (carrier) mother has a 70% to 90% risk of infection if the mother is HBeAg-positive, and a 5% to 20% (~10%) risk if she is HBeAg-negative. Post-exposure prophylaxis with hepatitis B vaccine immediately after birth (birth dose) dramatically reduces the risk of infection. There are limited data on when a birth dose is too late to protect the newborn infant. However, receipt of the first dose beginning ≤12 hours after birth among infants of highly infectious mothers (HBeAg-positive) in a three- or four-dose schedule provides higher protection (70% to 95%) than if the first dose is given after one week (50% to 57%).[1, 5-7] Protective efficacy of 75% was found in one group of infants of HBeAg-positive mothers who received vaccine alone in week two.[5]

Given the importance of early protection, timely delivery of the first dose of vaccine within 24 hours of birth[v] (referred to as the birth dose) for all newborn infants is the preferred strategy. Where resources allow, HBIG (passive immunity) may be given in addition to the vaccine to children born to hepatitis B positive mothers..[vi] However, the option for HBIG is conditional on the existence of comprehensive antenatal screening programmes for hepatitis B, and will be of limited value in settings with poor antenatal coverage.

The birth dose should ideally be given within 24 hours of birth, as it is likely that the earlier the vaccine is given, the earlier the neutralizing antibodies will form, and the more likely that infection will be prevented. However, the birth dose may be of value in preventing perinatal infection even if given later, and it should be given on first possible contact, if missed at birth[vii].

By 2006, a birth dose (either targeted or universal) within 24 hours of birth[viii] had become part of the immunization schedule in all Member States of the WHO Western Pacific Region. Japan, New Caledonia, New Zealand, Wallis and Futuna, however, provide a birth dose only to those infants born to HBsAg-positive mothers. Most of the other countries have

[v] Provides active immunity as opposed to the time-limited, passive immunity provided by HBIG.

[vi] However, some studies suggest HBIG offers only limited marginal protection over and above that provided by hepatitis B vaccine alone.

[vii] Please refer to WHO 2006 publication, *Preventing mother-to-child transmission of hepatitis B: Operational field guidelines for delivery of birth dose of hepatitis B vaccine*, for detailed instructions if the child first comes into contact with the health system later than 24 hours after birth.

[viii] Some countries specify within 12 hours of birth (e.g. Malaysia, Republic of Korea).

a policy for universal birth dose, while some provide HBIG in addition to hepatitis B vaccine if the mother is positive for HBsAg[ix].

Box 4: Why is the universal birth dose for all newborn infants recommended rather than a targeted approach for infants born to HBsAg-positive mothers?

In most of the developing countries in the Western Pacific Region, a targeted approach providing a birth dose of hepatitis B vaccine only to those infants born to HBsAg-positive mothers would be very difficult to implement for the following reasons:

- access to and provision of antenatal care is poor ;
- the antenatal care may be provided by health workers or health facilities not equipped to carry out HBsAg testing ;
- there may be a lack of financing for laboratory testing (the financing required for testing may equal that required for the infant immunization programme);
- there may be a lack of systematic linkages between antenatal care records and the care delivery site; and/or
- there may be a lack of financing for HBIG.

Considering these constraints, substantial investment may be required to implement a targeted birth dose strategy in developing countries. However, this investment may not be justified (rather efforts may be better spent increasing immunization coverage at birth) as the approach offers no additional benefits to those expected from a policy of universal birth dose coverage, especially since the additional protection offered by HBIG, compared with vaccine alone, is only marginal. On the other hand, a policy of universal infant vaccination beginning at birth provides additional benefits in terms of a 'safety net', not only for prevention of perinatal infection, but also against subsequent horizontal transmission from household contacts or other sources. In addition, administration of a birth dose has been associated with higher rates of on-time completion of the hepatitis B vaccine series and, in certain settings, improved completion rates for all other infant vaccines.

However, despite policies for universal birth dose coverage, in countries with a substantial number of births occurring outside the health facilities, birth dose provision has, in practice, remained limited to facility-based births, at most[x].

[ix] Currently, Australia, Brunei Darussalam, Guam, Hong Kong (China), Japan, Macao (China), Malaysia, New Caledonia, New Zealand, the Republic of Korea and Singapore have universal antenatal screening programmes for hepatitis B and provide HBIG in addition to hepatitis B vaccine to babies of all HbsAg-positive mothers (only HBeAg-positive mothers in Singapore). Several hospitals in China also provide HBIG, although neither antenatal screening for hepatitis B nor provision of HBIG are official policies.

[x] For example, the proportion of births outside health facilities is 62% in Cambodia, 79% in the Lao People's Democratic Republic and 44% in the Philippines.

Box 5: What is the minimum coverage required with timely birth dose and with HepB3 to achieve the interim regional goal of <2%?

This will depend on HBsAg prevalence among pregnant women, as well as on assumptions about vaccine efficacy in preventing perinatal transmission (70%-95%); vaccine efficacy in preventing infections at other ages (95%); the risk of perinatal transmission for infants born to HBsAg-positive mothers (a 70%-90% risk in HBeAg-positive mothers, and a 10% risk in HBeAg-negative mothers); and the risk of exposure to infection by age five. The modelling also assumes that the distribution of infection risk and the probability of receiving vaccine are independent of each other and distributed equally among the population. In countries with about an 8% baseline HBsAg seroprevalence rate and assuming an HBeAg seropositivity rate of 30% among HBsAg-positive women, the minimum coverage required for the birth dose and for HepB3 in the most conservative scenario will be 67% and 85%, respectively, while the same under the least conservative scenario will be 44% and 85%. Countries with higher HBsAg prevalence among pregnant women will require higher coverage levels to achieve the goals (see Annex 5 for more details on the model used to calculate the minimum vaccine coverage levels required to reach the hepatitis B control goals.).

Sub-indicators:

(1) The official immunization schedule of the country includes a HepB birth dose within 24 hours: Y/N.

(2) The percentage of newborn infants given a birth dose within 24 hours of birth, for health-facility births and for home births.

(3) The percentage of public delivery hospitals (secondary- and tertiary-level) with systems to provide a timely birth dose.

(4) The percentage of private delivery hospitals with systems to provide a timely birth dose.

(5) The percentage of lowest-level health centres with systems to provide a timely birth dose.

(6) A system to deliver a timely birth dose for home births: Y/N.

(7) A system to monitor the on-time delivery of the birth dose at all administrative levels: Y/N.

Table 2: Estimates of minimum vaccine coverage required to achieve the regional goal of less than 2%							
Most conservative scenario[xi]						Least conservative scenario[xii]	
Birth-dose efficacy 70%		Birth-dose efficacy 80%		Birth-dose efficacy 90%		Birth-dose efficacy 90%	
Birth-dose coverage%	HepB3%	Birth-dose coverage%	HepB3%	Birth-dose coverage%	HepB3%	Birth-dose coverage%	HepB3%
60%	90%	50%	90%	50%	90%	30%	90%
70%	85%	60%	85%	60%	80%	40%	80%
80%	80%	70%	80%	70%	75%	50%	75%

Activities[xiii]:

- Develop and implement systems to deliver and monitor the provision of timely birth doses in all health facilities, as well for home births as far as possible.
- Issue standing orders for all health facilities that provide maternity services to give hepatitis B vaccine to newborn infants as soon as possible after birth, preferably within 24 hours. This should include establishing systems for hepatitis B vaccine supply and storage (in or out of the cold chain) in these health facilities.
- Promote the use of hepatitis B vaccine out of the cold chain to increase coverage with the birth dose in health facilities with no continuous cold chain and for home births[xiv].

As hepatitis B vaccine is relatively heat-stable and retains its potency even after storage out of the cold chain[xv], this may be especially useful for the timely provision of a birth dose, provided the vaccine is not frozen. The addition of the most thermo-stable variety of vaccine vial monitors (VVM[xvi]), which are now available for most UNICEF-procured vaccines, provides a new opportunity to use these vaccines after exposure to ambient temperature for several days or even weeks. In addition, the availability of monovalent hepatitis B vaccine in prefilled single-dose injection devices (e.g. Uniject™) can facilitate the administration of the vaccine by birth attendants to infants delivered at home.[6]

[xi] The most conservative scenario assumes the highest rates of infection transmission (a 90% risk of perinatal infection among HBeAg-positive women, and a 6% chronic infection rate by age five years), and the lowest vaccine efficacy in preventing perinatal infection (70%).

[xii] The least conservative scenario assumes the lowest rates of infection transmission (a 70% risk among babies of HBeAg-positive women, and a 5% chronic infection rate by age five years) and the highest vaccine efficacy (90% of perinatal infection)

[xiii] Please consult *Preventing mother-to-child transmission of hepatitis B: Operational field guidelines for delivery of birth dose of hepatitis B vaccine*, published by the WHO Western Pacific Regional Office.

[xiv] Please refer to *Preventing mother-to-child transmission of hepatitis B: Operational field guidelines for delivery of birth dose of hepatitis B vaccine* for detailed instructions for out-of-cold-chain use of hepatitis B vaccine.

[xv] On the other hand, freezing the vaccine destroys its potency, making it ineffective.

[xvi] VVM of varying stability are available and provide assurance that cumulative heat exposure has not exceeded the limit for that vaccine. VVM30, the most thermo-stable variety out of four types of available VVM, is currently recommended for hepatitis B vaccine. At 37º Celsius, 95% of these VVMs will reach discard point before 30 days and 5% after day 30.

Strategy 3: Catch-up immunization of older children

The first priority is protecting infants through routine immunization services. The strategy of catch-up immunization for older children is recommended only for those countries with relatively mature infant vaccination programmes that have additional financial and human resources for enhanced hepatitis B control. In the event of limited human and financial resources, the first priority always has to be ensuring sustained high rates of infant immunization, including timely birth dose. Any extension of immunization for older children should be based on careful epidemiological and economic analysis, and may include:

- children under five years who missed immunization as infants ('patch-up');and
- children up to a specified age born before hepatitis B vaccine started to be offered ('catch-up').

When considering immunization strategies for older children, the first priority will be providing catch-up and patch-up of children under the age of five years, as these are most likely to acquire chronic HBV infection following exposure to HBV infection and sustain the infectious pool in the population (please see Annex 1). For example, in a country that had introduced a nationwide infant immunization programme three years previously, the first priority age-group for a catch-up campaign would be four-five-year-olds. The second priority group would be the population aged six to 15 years. It is up to each country to prioritize other groups for publicly funded immunization.

Catch-up campaigns have already been undertaken in several countries in the Region, including American Samoa, Australia, French Polynesia, Macao (China), Niue, Palau, the Republic of Korea, Singapore, Tokelau, Vanuatu and Wallis and Futuna[xvii]. Malaysia has started a catch-up campaign for older school children enrolled in public schools born before the start of nationwide hepatitis B vaccination in September 2006, while China is planning to organize a 'patch-up' campaign for children under five years of age who missed routine vaccination in 2007. Hong Kong (China) has been organizing a patch-up immunization programme for schoolchildren aged 10 to 13 years who were previously unimmunized, as identified on school-entry check-up, on a regular basis.

In a country with an immunization check-up at elementary-school entry, a patch-up immunization programme can be organized on an ongoing basis by ensuring immunization of those children found to be unimmunized at the time of entry.

Sub-indicators:

(1) All children under-five years of age have been provided with an opportunity for vaccination at least once (either through routine immunization or through catch-up campaigns): Y/N.

(2) The percentage coverage achieved in the catch-up campaign for the eligible population.

(3) Immunization is offered to children found to be unimmunized on school-entry check-up: Y/N.

[xvii] Some countries and areas with small populations, such as American Samoa and Palau, undertook catch-up vaccination programmes for the entire population in the same year as they introduced routine immunization for infants.

Strategy 4: Immunization of high-risk adult population groups

The immunization of high-risk adult population groups should be prioritized after infant immunization and catch-up/patch-up campaigns for older children.

High-risk adult groups include contacts of HBsAg-positive persons, sex workers, health workers, injecting drug users and frequent recipients of blood/plasma transfusions.

Incidence of acute HBV infection is highest among adolescents and adults, although the risk of developing chronic HBV infection is low compared to that among infants and children. Vaccination programmes targeting high-risk adult groups can be difficult to implement, primarily because of problems in identifying and vaccinating persons engaged in high-risk activities before they become infected [7]. Health care workers are often unaware of groups at high risk of acquiring HBV infection and may not identify such clients during routine health care visits. Currently, there is only limited vaccination of susceptible household and sexual contacts of HBsAg-positive persons identified in screening programmes for blood donors in most Member States in the Region.

Health care workers constitute a well-identified and accessible group at increased risk of HBV infection, and vaccination for them may not require much programmatic effort. Hepatitis B vaccination of health care workers appears to have resulted in a substantial decrease in the rate of the disease in this group[8]. The 16th TAG meeting recommended that regulations be developed in Member States to ensure vaccination of all health workers. Hence, vaccination programmes for health workers may be started at the same time as infant immunization. All health workers should be offered mandatory free vaccination at job entry. A catch-up campaign may be conducted in the beginning to immunize all clinical health workers, followed by regular immunization on job entry.

If resources allow, pre-vaccination screening may be conducted by testing anti-HBc, and all anti-HBc-negative health workers should be offered the complete three-dose vaccination schedule normally given at at 0, 1 and 6 months. However, if there are limited resources, pre-vaccination screening can be waived and all health workers offered vaccination. The results of screening for HBV infection either at the time of job entry or otherwise, should not be used to discriminate against health workers or exclude them from their jobs.

Subgoal : All countries providing free vaccination to all the health workers as a matter of policy by 2012

Sub-indicators:

(1) The country has an official policy requiring and providing hepatitis B vaccination for all the health workers: Y/N.

(2) All clinical health workers have been provided with at least one opportunity to be vaccinated with hepatitis B vaccine: Y/N.

Strategy 5: Promotion of self-reliance in hepatitis B vaccine financing

Many countries in the Region (e.g. Cambodia, China, the Lao People's Democratic Republic and Viet Nam) introduced hepatitis B vaccine with GAVI support, which either ended in 2006 or will end by 2010. Although China and Viet Nam have developed plans for switching to domestic funding, hepatitis B vaccination programmes are still at risk in other countries after GAVI support ends. In addition, in many other countries, financing is either unpredictable and not secured in the regular budget or is highly dependent on external donors. In such scenarios, all efforts should be made with national governments to ensure regular, predictable funding for hepatitis B vaccine. These efforts may include either negotiating for a line-item for procurement of hepatitis B vaccine in the annual health budget or coordinating donor support for vaccine supplies through such mechanisms as intercountry coordination committees.

A high vaccine wastage rate is another significant barrier to financial sustainability in many countries. As hepatitis B vaccine is relatively expensive, and the combination (DTP-HepB) vaccine even more so, the amount of vaccine currently being wasted in many countries may be sufficient to immunize half of the birth cohort each year. Improvements in vaccine logistics and management, as well as better planned immunization sessions can considerably reduce vaccine wastage without compromising immunization coverage, as shown by the experience in many countries (such as Viet Nam). The key step is having a clearly defined process for monitoring vaccine wastage and identifying the different types of wastage.

Another key strategy to reduce vaccine wastage, as well increase coverage, is to opt for smaller vial formulations (one- to two-dose vials). The savings from the consequent reduction in vaccine wastage from higher dose vials may very well offset the marginally higher price for smaller-dose vials and the need to expand cold chain space. The smaller-dose vial may also reduce the tendency on the part of health workers to deny immunization to children on the grounds of few children being present in a session and hence may have a positive impact on coverage. In addition, it will have a positive impact on the quality of immunization, considering the often less-than-optimal practice of using multi-dose vials (e.g. handing aspirating needle, contamination risk, etc.).

Sub-indicators:

(1) The country provides free hepatitis B vaccinations to all the infants as part of the national immunization programme: Y/N.

(2) The country has predictable and secure financing for hepatitis B vaccine for at least the next three years on a rolling basis: Y/N.

(3) The percentage of vaccine wasted (both closed vial and open vial wastage).

Strategy 6: Ensuring vaccine potency by avoiding inadvertent vaccine freezing

Hepatitis B vaccine is very freeze-sensitive. Hence, health workers should be trained regularly on the correct way to store the vaccine and the importance of preventing it from freezing. All supervision visits should include checking for vaccine freezing.

To prevent freezing during air transport, vaccine manufacturers should follow the guidelines for international packaging and shipment of vaccines.[9] Any temporary storage period during customs clearance should be kept to a minimum. The condition of the vaccines on arrival, including the state of freeze indicators, should be assessed and recorded for every shipment.

To prevent freezing during storage in cold rooms, it is necessary to ensure that:

(1) the refrigeration unit's plume of cold air close to the evaporator, has free flow;
(2) the evaporator is fitted with a mesh cage to prevent vaccine being stored in the danger zone;
(3) ceiling-mounted units are positioned in the centre of circulation aisles;
(4) the air outlets in ceiling-mounted units are directed away from any shelving; and
(5) alarms are fitted to continuous/intermittent temperature recording/monitoring devices.

To prevent freezing during storage in cold climates:

(1) Permanently heat the vaccine store.
(2) Heat the cold room (+2°C to +8°C cold rooms should be fitted with frost-protection heater circuits, unless the space in which the cold room is housed is permanently heated and the heating system is 100% reliable.)

To prevent freezing in refrigerators:

(1) Do not store freeze-sensitive vaccines within 20cm of an ice-lined refrigerator's base.
(2) Keep the thermostat at a setting to ensure +8°C at the hottest time of day.

Many temperature-monitoring studies have indicated that vaccine shipments are more likely to be frozen during transportation than while in storage at a health facility. Hence, special attention is needed to ensure that vaccine is not frozen while being transported.

To prevent freezing during vaccine transport:

(1) Condition icepacks before loading a cold box.
(2) Use cold packs (not frozen).
(3) Use warm packs in extremely cold climates.
(4) Use heated vehicles or transport.
(5) Avoid the cold (do not leave the cold boxes outdoors and/or in unheated rooms)

Tools to detect freezing:

(1) Continuous/intermittent temperature recording, especially for storage facilities.
(2) Vaccine arrival report (Documenting the freeze indicator status on vaccine arrivals).
(3) Freeze Watch/Stop Watch/Shake test.

Sub-indicators:

(1) Supervisory checklists at all levels include checking for freezing of hepatitis B and other freezing-prone vaccines: Y/N.

(2) EPI training programmes at all levels include a session on prevention and testing for freezing of hepatitis B vaccine: Y/N.

(3) A special temperature-monitoring study has been undertaken at least once in the last five years: Y/N.

(4) The percentage of vaccine shipments found frozen on arrival at the first national level.

Strategy 7: Advocacy and social mobilization

Advocacy and social mobilization are important for immunization programmes in general, but particularly for hepatitis B because there is:

- no external manifestation for most HBV infections among children;
- no clinical manifestation of chronic HBV infection until serious sequelae develop;
- an insidious onset and a very long time before onset of chronic sequelae ;
- a lack of recognition that HBV is responsible for long-term sequelae; and
- few directly recognizable deaths (e.g. from fulminant hepatitis B).

Advocacy is a process for raising awareness, especially among decision-makers and service providers, to ensure that the service (hepatitis B immunization) is available to all children. Monitoring and improving the knowledge of health workers is an important part of improving the coverage and quality of immunization services.

Increasing awareness of the importance of HBV as a cause of disease and death in the community is the key activity. Another critical aspect is showing the impact of immunization in preventing that disease burden. As nearly all disease prevention will occur several decades after delivery of immunization in that cohort, special advocacy efforts are needed.

Social mobilization is the process of ensuring that parents take up an available service (hepatitis B immunization). It is similar to advocacy, but has different target audiences (primarily parents) and is focused on getting children to the point of service delivery.

For both advocacy and social mobilization, the foundation is good science and finding the effective and appropriate media to get the messages across. A range of media should be used to deliver the messages, including community volunteers and health workers, as well as the mass media.

Sub-indicators:

(1) The EPI has developed key messages to increase awareness among parents and health workers of how to prevent HBV transmission: Y/N.

(2) The immunization and maternal and child health training programmes for health workers include materials for raising awareness about hepatitis B: Y/N.

Strategy 8: Inclusion of hepatitis B control strategies in the multiyear plan for EPI

The national multiyear plans for immunization (MYP) should include plans for hepatitis B control, incorporating above strategies and sub-indicators. The goals and targets for each of the above strategies should be clearly defined, taking the local context into account.

Sub-indicators:

(1) The MYP of the country contains operational strategies and goals for hepatitis B control: Y/N.

3 MONITORING AND EVALUATION

The rationale for setting up the hepatitis B control goal in terms of seroprevalence of HBsAg among five-year-old children rather than in terms of incidence of new infections or overt disease outcomes has already been explained. The regular monitoring and evaluation of the hepatitis B vaccination programme towards achievement of hepatitis B control goals should take into account:

- vaccine coverage data;
- at least one source of representative data on HBsAg seroprevalence among children of five years or older born after the nationwide implementation of universal hepatitis B infant immunization; and
- acute or chronic hepatitis B surveillance data [optional—may be useful to evaluate the impact of catch-up campaigns for older children and immunization programmes targeting adult populations].

Some of these indicators have already been listed to monitor various programmatic processes and strategies. This section focuses more, in terms of monitoring and evaluation of the programme, on the outcome indicator—i.e. chronic HBV infection rates as measured by HBsAg seroprevalence rates among children of five years or older.

3.1 Hepatitis B vaccine coverage rates

Vaccine coverage rates since the implementation of nationwide hepatitis B vaccination should be analysed. As frequent serological surveys are not feasible, vaccine coverage rates serve as a good interim proxy for programme performance, as vaccine efficacy is well known, although programmatic errors (e.g. vaccine freezing, incorrect immunization schedules, high drop-out rates, etc.) may result in a less than optimal response. Hence, vaccine coverage should be monitored regularly at the national and subnational/district levels.

The key indicators that should be monitored at least annually, and preferably on quarterly basis include:

- the percentage of infants having received three doses of hepatitis B vaccine (HepB3 %);
- the percentage of newborn infants given the first dose within 24 hours of birth (HepB0%);
- drop-out rates from the first dose to the third dose [(HepB1-HepB3)/HepB1] to measure the completeness of hepatitis B immunization; and
- the percentage difference between DPT3 and HepB3 coverage or the ratio of DPT3 to HepB3 (DPT3/HepB3).

Corroboration of the administratively reported HepB3 coverage data:

Although routinely collected administrative data should be used for regular monitoring, those data should be corroborated with household surveys periodically to detect any major problems. The household survey may be a stand-alone immunization survey (e.g. WHO-recommended 30-cluster survey) or conducted as part of other wider household surveys (e.g. a demographic and health survey, a multiple-indicator cluster survey or a national health survey, etc.). Most household surveys target children aged 12 to 23 months at the time of the survey to calculate the immunization coverage in the year preceding the survey.

What if the data are from children younger than five years?

Children younger than five years of age have not yet passed through the complete exposure period, and some of those children who are currently uninfected and unimmunized may subsequently acquire chronic HBV infection. Hence, the seroprevalence estimates in this age group may underestimate the eventual seroprevalence in this cohort.

3.2 Evidence for seroprevalence of hepatitis B markers: Cross-sectional seroprevalence surveys

Although immunization coverage data can suggest the approximate impact on HBV chronic infection rates, it needs to be validated at least once, as there are programmatic factors that can affect the impact of vaccination. The key programmatic factors that can lead to a less than anticipated impact on the outcomes include: reduced vaccine potency due to freezing; delays in administration of the birth dose; and inequities in immunization coverage, with children at higher risk of HBV infection having less chance of getting vaccinated. However, considering the special efforts required for serosurveys, these should not be undertaken unless and until immunization coverage (both HepB3 and HepB0) has been sustained at high-enough levels for at least five years.

Analysis of the seroprevalence rates of different HBV infection markers, especially for HBsAg among children of five years or older born after the start of universal infant vaccination, will be one of the key strategies to evaluate the hepatitis B vaccination programme, as explained in previous sections. Every country should undertake at least one HBsAg seroprevalence survey based on a representative sampling of population cohorts of children at least five years old[xviii] born after the nationwide implementation of the infant hepatitis B immunization programme. Additional age groups, such as one-year-old children, may be sampled to measure the impact on perinatal transmission, where resources allow.

Can the seroprevalence data be from children older than five years?

Yes. For example, if the HBsAg rate is demonstrated to be less than 2% among children aged six to 10 years in a country that introduced vaccine more than 10 years previously and has achieved sustained high coverage with HepB3 (i.e. the coverage in last five years is the same as in the previous five years), the country will be deemed to have achieved the interim regional goal of <2%. It is not necessary to have the seroprevalence data from children of exactly five years of age.

3.3 Overall guidelines for conducting a serosurvey

Representativeness of the estimates:

Ideally, the seroprevalence survey should be population-based (household survey or school-based survey). Guidelines for undertaking a representative sample survey are being prepared by WHO, including advice on sample sizes and the selection process[10]. However, convenience sampling (e.g. testing of children admitted to a hospital, etc.) may be more practical and cheaper, and will be able to provide representative estimates, especially in small

[xviii] As most chronic infections are acquired by age five, sampling children of five years or older will take into account the complete exposure period when the risk of horizontal transmission and the likelihood of becoming a chronic carrier are highest.

countries with only one or two health facilities catering to all children. If convenience sampling is used, it should be ensured that results are not likely to be biased, especially in the direction of underestimation.

Appropriate sample size:

The accuracy of the estimate should be within ±0.5%[xix]. The sample size should be adequate to show with 95% confidence HBsAg prevalence of <2%.

Standard laboratory procedures:

Standard laboratory procedures with proper quality assurance should be used. Serological assays are commercially available for all markers of hepatitis B and the majority rely on enzyme-linked immunosorbent assay (ELISA) tests, which are quite sensitive and specific. Proper documentation of the quality assurance of the laboratory procedures should be ensured during the serosurvey. The diagnosis of HBV infection or assessment of immunity to HBV requires laboratory detection of HBsAg and anti-HBs, respectively. Testing for anti-HBc may provide estimates of the resolved infection and natural immunity after infection in the past, besides providing estimates of life-time risk of HBV infection (please see the table below). The minimum requirement for the evaluation will be valid estimates of HBsAg. From a public health point of view, HBeAg testing among children is not useful and should be avoided in population-based surveys.

Antigen/antibody	**Interpretation**	**Indication**
HBsAg	Potentially infectious person—presents weeks before to several months after onset of symptoms and persists in chronic infection	Infection
HBeAg	Replication of virus and high infectivity	Infectivity
Anti-HBs	Immune to HBV (vaccine or past infection)	Immunity
Total anti-HBc	Acute, chronic or past infection	Exposure
IgM anti-HBc	Acute infection	Acute infection

Use of rapid field tests:

In areas without the laboratory capacity and in other resource-constrained settings, the testing may be done with rapid-strip field tests, which offer several advantages for undertaking a serosurvey: they are low cost; they need for only minimal training and laboratory infrastructure; they require only a drop of blood as opposed to venepuncture; they have no cold chain requirements; and there is no specimen handling. They also offer immediate results, with the potential for counselling, referral and immunization of contacts. Some of these tests have also been validated for their sensitivity and specificity in field settings[11] [12]. However, since the sensitivity of rapid field tests may be lower than that of standard ELISA tests (about 90%-92%), the results should be adjusted slightly upwards, according to the documented sensitivity of the tests.

3.4 Acute and chronic hepatitis B surveillance

Acute hepatitis B represents only a small part of the overall disease burden due to hepatitis B, and the probability of acute HBV infection being symptomatic is much higher

[xix] However, such sample sizes may be difficult to achieve in countries and areas with smaller populations, where other special statistical methods should be used, including applying finite population corrections.

among adults than among children—the target of immunization programmes. Hence, the impact of infant immunization programmes on overall acute hepatitis B rates may not be visible within five years, as acute hepatitis B cases among children will comprise a very small proportion of the total. To see the impact on acute hepatitis B within five years of a vaccination programme among children under five years of age would require a highly sensitive surveillance system. In addition, it would require a well-developed laboratory system that can test for multiple seromarkers of hepatitis B[xx] and distinguish between different hepatitis viruses, as acute hepatitis B is clinically indistinguishable from hepatitis caused by other hepatitis viruses (A, C, D and E).

Considering these issues, trend data on acute hepatitis incidence, especially among children less than 10 years of age, if available, should be used only to supplement vaccination-coverage and seroprevalence data.

Notwithstanding the limited utility of acute hepatitis B surveillance in assessing the impact of infant immunization programmes, where resources allow, countries are encouraged to set up laboratory-based acute viral hepatitis surveillance systems, especially in sentinel sites, as an additional means of:

- monitoring the impact of older children, adolescent or adult immunization programmes in countries where such immunization programmes are in place;
- identifying the disease burden among adults and identifying risk groups who should be offered immunization in countries that are considering introducing immunization programmes for adolescents and adults[xxi]; and
- quantifying the burden due to different hepatitis viruses, especially due to hepatitis A, which may help countries to assess the need for hepatitis A prevention and vaccination strategies. Similarly, quantification of viral hepatitis due to hepatitis C or E may provide information on problems with the blood transfusion system, injection drug use, or injection safety in health care settings in the country.

3.5 Incidence and mortality due to chronic hepatitis B disease

Most countries do not routinely collect data on chronic liver disease. Hence these data are not normally available, except in countries with cancer registries and reliable mortality statistics. Similar issues with respect to acute hepatitis B also apply to the use of data on incidence and mortality due to chronic hepatitis, cirrhosis and liver cancer. Hence, these data, if available, may be used to supplement other data to monitor the performance of the programme. In addition, these data may provide important information to evaluate the cost-effectiveness of the vaccination programme.

[xx] If the only test used is for HBsAg, it will not differentiate acute from chronic infection.

[xxi] However, the existing evidence shows that efforts to vaccinate persons in the major risk groups have had limited success due to difficulties in health care workers being able to identify such groups during normal health care visits and vaccinate them before they indulge in the high-risk behaviour exposing them to infection.

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ANNEX 1: HEPATITIS B VIRUS

History

Hepatitis transmitted through serum was first documented during a smallpox immunization campaign in 1883. McCallum proposed the term hepatitis B for 'serum' hepatitis in 1947, as opposed to hepatitis A, spread by the oro-faecal route. The hepatitis B surface antigen (HBsAg) was first identified in the liver of an Australian aborigine in 1967 (initially called Australia antigen).

Virology

Hepatitis B virus (HBV) is a DNA virus, with a core antigen (HBcAg) surrounded by a coat containing surface antigen (HBsAg). The immune response to HBsAg provides the basis for immunity against HBV. Antibodies to HBcAg (anti-HBc) indicate infection—IgM anti-HBc indicates recent infection and usually disappears within six month, while IgG anti-HBc persists for life and indicates past infection. Antibodies to HBsAg (anti-HBs) only appear after clearance of HBsAg or after immunization. The presence of HBsAg for more than six months is defined as chronic HBV infection (or carriage). The presence of a third antigen, HBeAg, indicates a high degree of infectivity (i.e. actively replicating virus).

Transmission

HBV enters the body parenterally or through small breaks in the skin or mucosal linings. The virus is found in the blood and body fluids in acute or chronic infection. Blood and fluids become less infectious as they dry on exposure to air. The greatest spread is between young children, probably related to contact with skin sores and small breaks in the skin, and from household contacts (including adults). The virus is also passed from mother to baby as a result of blood exposures during childbirth. The baby of an HBsAg-positive mother has a 70%-90% risk of infection if the mother is HBeAg-positive, and about a 10% risk if HBeAg-negative. Providing post-exposure prophylaxis by immunizing the child with a first dose of hepatitis B vaccine within 24 hours of birth reduces the risk by 70%-95%. Studies suggest that breastfeeding by an HBsAg-positive mother does not increase an infant's risk for acquisition of HBV infection[1] .

Sexual contact, non-sterile (shared or re-used without sterilization) injections, and any other way of passing body fluids can lead to infection. HBV is not spread through the air or in food. The incubation period before seroconversion varies from six weeks to six months, and is usually three to four months.

Outcomes of infection

The initial infection is referred to as acute HBV infection; it may be either symptomatic (acute hepatitis B) or asymptomatic. The outcomes of acute HBV infection are either (1) chronic HBV infection (carriage) or (2) immunity.

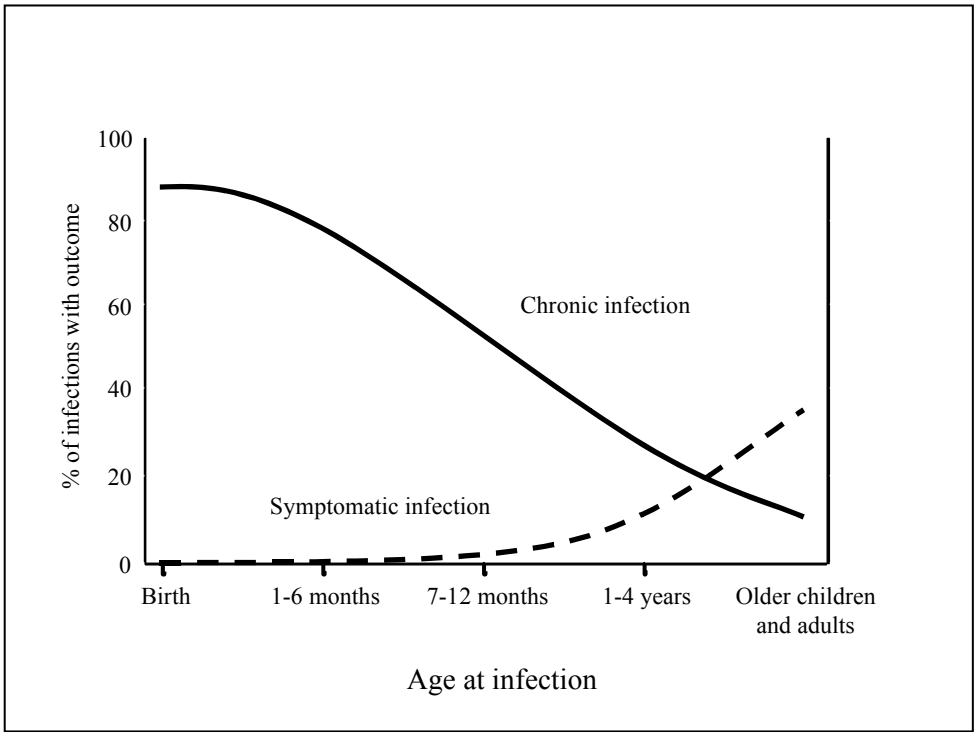
Chronic HBV infection (carriage): Usually with no symptoms, the virus remains in the liver, where it eventually (after decades) can cause liver cancer or cirrhosis, leading to premature death in up to 25% of chronically infected persons. The major HBV-related disease burden is from these consequences of chronic infection.

Acute HBV infection*:* An acute illness lasting several weeks, with loss of appetite, weakness, nausea, vomiting, abdominal pain, jaundice (yellow skin or eyes), dark urine, skin rashes and joint pain. The person usually recovers with no long-term effects, but 1%−2% will die from fulminant hepatitis (mortality increases with age).

The age at which a person becomes infected with HBV is the main factor determining the outcome (see Figure 1). The risk of chronic HBV infection drops from about 90% in the first six months of life, to about 30% by the age of five years and 10% by the age of

15 years.[2] It is unusual (2%-5%) for those infected in later adult life to develop chronic infection. Fewer than 10% of children less than five years old and only 30%-50% of adults develop symptomatic acute hepatitis B after infection.[3]

Figure 1. Outcome of hepatitis B virus infection by age at infection



Source: *Introduction of hepatitis B vaccine into childhood immunization services. Management guidelines, including information for health workers and parents* [WHO/V&B/01.31]. Geneva, World Health Organization, 2001.

Escape mutants

During the past decade, there have been occasional reports in the literature of persons infected with HBV variants and mutants. Some persons infected with HBV mutants are HBsAg-negative; infection is detected with molecular techniques such as polymerase chain reaction. Even with high levels of antibody, some persons have been infected with such 'escape mutants'. Despite apparent increases in reports, the prevalence of HBV escape mutants is low, and it is not yet clear whether these escape mutants are of public health importance. Ongoing monitoring is needed to assess their implications.

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ANNEX 2: DISEASE BURDEN

The actual data on mortality and morbidity related to hepatitis B are limited in most of the countries in the Region, especially the developing countries, due to very limited laboratory support and poor surveillance systems. Some countries have undertaken special studies to assess how many of the total deaths caused by cirrhosis and hepatocellular carcinoma (HCC) can be attributed to HBV. In New Zealand, an estimated 100 deaths per year are attributable to chronic HBV infection[1], or about 0.3% of all deaths, even although overall rates of carriage are relatively low.

Disease burden as estimated by seroprevalence of different hepatitis B markers

Considering the limited availability of data on actual disease outcomes and the technical and financial constraints on setting up well-functioning surveillance systems in the majority of countries to collect that data, most of the time the disease burden due to hepatitis B is reported in the form of HBsAg seroprevalence, as measured in cross-sectional surveys or from sentinel serosurveillance of special population groups, such as blood donors, migrants and pregnant women. Available data on HBsAg prevalence show a wide range of values among countries and even within some countries. The results of a limited review undertaken for this Plan were pooled to provide an estimate of prevalence. The estimates from some countries may be biased upwards, as most of the studies have been undertaken in higher-risk populations (e.g. in New Zealand). The pooled estimate was then used together with other estimates (including official country estimates) and a 1997 WHO estimate to provide a 'best estimate' of pre-vaccine HBsAg prevalence for each country (Table 3, Annex 4).

Where there was an assessment of impact for vaccinated children, seroprevalence was reduced by over 85%, with the exception of Mongolia, which had an estimated decline of only 50% [2] (Table 3, Annex 4).

Modelling the HBV- related mortality and morbidity from seroprevalence data

A model developed by WHO estimates the current global burden at 360 million chronically HBV-infected people, 5.7 million HBV-related cases and 520 000 deaths per year[3]. Approximately 45% of the world's population lives in areas where chronic HBV infection is highly endemic ($\geq$ 8% of the population is HBsAg-positive); 43% live in areas of intermediate endemicity (2−7% HBsAg-positive); and 12% in areas of low endemicity (<2% HBsAg-positive).

Over half of the annual deaths (278 000) occur in the Western Pacific Region, which accounts for only about 28% of the global population. It should be noted that these estimates are lower than previous estimates as they take into account competing mortality and exclude people with chronic HBV infection who die prematurely from unrelated causes.

The model estimates that 92% of the morbidity is from acute hepatitis, 6% from HCC and 2% from cirrhosis, globally. In contrast, 69% of HBV-related deaths are from HCC (with or without cirrhosis), 21% from cirrhosis and 10% from acute hepatitis. Overall, it is estimated that 15%-25% of people with chronic HBV infection die prematurely from HCC or cirrhosis caused by the infection[4 5 6].

A mathematical model has been developed by the United States Centers for Disease Control and Prevention (CDC) to estimate country, regional and global hepatitis B disease burdens. The inputs in the model include HBsAg and HBeAg prevalence among women of child-bearing age; risk of infection by age five years, as measured by seroprevalence of anti-HBc among five-year-old children; and the seroprevalence of anti-HBc among the population $\geq$30 years old [7]. This model estimates that, in 2000, 620 000 persons died worldwide from HBV-related causes, of which 325 000 (52% of global deaths) of those deaths were estimated to have occurred in the Western Pacific Region. In the surviving birth cohort for 2000, the

model estimates that worldwide, without vaccination, 64.8 million would have become infected with HBV, 9.7 million would have become chronically infected, and 1.4 million would have died from HBV-related disease. In the Western Pacific Region, similar figures for the surviving birth cohort for 2000 are estimated to be 19.2 million HBV infections (29.8% of the global total); 3.2 million chronically infected (33% of the global total); and 581 000 HBV-related deaths (41.4% of the global total).

Comparison with disease burden due to other common infectious diseases

The relative importance of hepatitis B in the Region, as well as the potential for control, is illustrated by comparing the estimates of measles deaths in 1999. As a result of successful immunization programmes, it is estimated that measles deaths have been reduced by over 95%, and only about 2% of global measles deaths now occur in the Region (about 20 000 of the global total of 875 000 measles deaths). In contrast, the Region has over half of the estimated HBV-related deaths, at 278 000 per year.

However, mortality just represents the tip of the iceberg. The total morbidity in terms of acute and chronic hepatitis B cases exceeds the morbidity caused by any other vaccine-preventable disease against which a vaccine has been included in the schedule. Almost 2.7 million cases of acute hepatitis B are estimated to occur in China alone, in addition to 300 000 cases of chronic hepatitis B and hepatocellular carcinoma.

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ANNEX 3: HEPATITIS B VACCINE

History and types of vaccine

HBsAg is the main component of hepatitis B vaccine. Plasma-derived HepB, available from 1982, uses HBsAg from the blood of people with chronic HBV infection. Recombinant vaccines became available in 1986, using HBsAg derived from yeast cells (and now also mammalian cells) that are genetically modified by inserting (recombining) the gene coding for HBsAg protein. Recombinant vaccine is currently the most commonly used vaccine type. In both types of vaccines the HBsAg is joined to an aluminium salt to increase its immunogenicity. The vaccine can also contain a preservative (e.g. thiomerosal)

In 1992, WHO recommended the integration of HepB into NIPs by 1995 for countries with an HBsAg prevalence of 8% or more and for all countries by 1997[1]. By the end of 2005, 158 (83%) of the 191 WHO Member States had done so.

Combination vaccines

Hepatitis B vaccine is now available as tetravalent (DPT-HepB) and pentavalent vaccine (DPT-HepB-Hib). The combination vaccines reduce the number of injections required to complete the vaccination schedule. However, the birth dose of hepatitis B vaccine can only be given as monovalent hepatitis B vaccine, as DTP is not recommended before the age of four weeks. Currently, only a few countries in the Region are using combination vaccines, such as Cambodia, the Lao People's Democratic Republic, Malaysia and Mongolia. However, more countries may introduce combination vaccines as many plan to introduce Hib vaccine. The relatively higher current price of combination vaccines (DTP-HepB, which had a 2005 price of US$1.25 per dose is over five times the average price of monovalent hepatitis B vaccine) is a barrier to wider uptake of combination vaccines. However, this situation may improve in the future with multiple manufacturers producing these vaccines.

Vaccine efficacy

Hepatitis B vaccine, both plasma-derived and recombinant, is remarkably effective, with no important differences in the efficacy of the different types. Clinical trials in high-risk groups have shown immunogenicity of 85%-95% and virtually complete protection in those who developed antibody levels of ≥ 10mIU/ml (considered the protective level).

At least 95% of infants, children and adolescents develop protective antibody levels after three doses of vaccine. The response rate drops with age from 90% for adults under 40 years to about 70% for those aged 60 years. Smoking, obesity, HIV infection and chronic disease are additional factors that may reduce the response rate.

Vaccine schedules

In the initial trials, vaccine was given as three doses at 0, 1, and 6 months. Hence, most manufacturers tend to recommend this schedule. However, hepatitis B vaccine has been shown to be immunogenic using a wide range of schedules[2]. In general, three doses given at intervals of at least four weeks (but not more than two months between doses one and two), are recommended. Please refer to Table 1 for the recommended schedules in the Western Pacific Region.

Although antibody levels decline after immunization, immune memory is maintained and booster doses do not appear to be needed to maintain immunity for the duration of the follow-up studied to date[3]. Therefore, booster doses are not currently recommended by WHO and other experts[4].

Vaccine safety

Anaphylaxis is the only known serious reaction to hepatitis B vaccine. However, the risk of anaphylaxis is estimated at 1 per 600 000 doses. Even minor reactions (fever and local inflammation) are relatively rare.

Since its first use, there have been concerns about the potential for infection from plasma-derived vaccines. However, there is no evidence to support such concerns and the intense purification and sterilization procedures have been proved safe and efficient in preventing transmission of bloodborne viruses like HIV. Previous concerns about an association between HepB and an increased risk of demyelination (e.g. multiple sclerosis) have proved unfounded.

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ANNEX 4: STATUS OF HEPATITIS B IN COUNTRIES OF THE WESTERN PACIFIC REGION AT THE END OF 2005

Table 1: Current and historic use of hepatitis B vaccine in national immunization programme

Country/Area	First Year in NIP	Year recommended for infants (part or whole country)	Year routinely offered all infants	Potential for less visits	HepB1	HepB2	HepB3	Booster (s)	BCM - extra doses	Public vaccine to: School children, Health workers, Contacts, Others#	Oldest full cohort offered protection (year born)	Birth dose % given within 24h	Births % In hospital	Birthds % HW attended (in or out of hospital)	HBiG given to BCMs (public)
	History of NIP			Schedule - infants & use in others								Birth Dose			
American Samoa	1986	1986	1987	Y	0	1m	12m			#	1986	100	100	100%	Y#
Australia	1997	2000	2000		0	2m	4m	6/12m#		S	~1984		98	99	Y
Brunei	1983	1988	1988	Y	0	1m	6m			H.C	1988		99	100	Y
Cambodia	2001	2001	2005		6w	10w	14w				2005		6	38%	N
China	1992	1992	1992	Y	0	1m	6m				1992	80		67	N
Cook Islands	1989	1989	1989	Y	0	1m	6m				1989		100	100	Y
Micronesia FS	1989	1989	1989		0	2m	6m	12m		S.H#	~1980	80	80	90	Y
Fiji	1989	1995	1995	Y	0	2m	5m				1989	22	97	99	Y#
French Polynesia	1990	1990	1990	Y	0	1m	6m			S	~1980	97	n/a	100%	Y
Guam	1989	1990	1990		0	2m	6m		#		1990	99			Y
Hong Kong (China)	1984	1988	1988	Y	0	1m	6m			S.H.O.	1986	99	100%	100	Y
Japan	?	N	N		#	#	#						99	100	Y
Kiribati	1995	1995	1995		0	6w	14w				1995		32%		N
Lao PDR	2001	2001	2004		6w	10w	14w				2004		11	21%	N
Macao (China)	1984	1989	1989	Y	0	1m	6m	5y		S.H.#	1981		100	100	Y
Malaysia	1989	1989	1989	Y	0	1m	5m			H.#	1989	94	94	97	N
Mariana Islands	1989	1990	1990		0	6w	6m			S.H.#	1983		100	100%	Y
Marshall Islands	1988	1988	1993		0	2m	6m						72	85%	N
Mongolia	1987	1987	1991	Y	0	2m	8m				1987	90#	99	99%	N
Nauru	1983	1984	1985	Y	0	1m	6m	5y			1985		100	100	Y#
New Caledonia	1989	1989	1989	Y	2m	3m	9m		#	C.H.#	1990	100	96	96	**Y**
New Zealand	1985	1988	1988		6w	3m	5m		0	S.C.H#	1984		98	99	Y
Niue	1986	1986	1986	Y	0	4w	6m			H#	1979		100	100%	Y
Palau	1988	1988	1988		6w	4m	12m		0		1988				
Papua New Guinea	1989	1989	1989		0	1m	3m			H	1989			45%	Y
Philippines	1991	1992	not yet		6w	10w	14w			#	2007		34	56	N
Republic of Korea	1984	1995	1995	Y	0	1m	6m				1985		98	98	Y
Samoa	1990	1990	1990		0	6w	14w				1990		80	90	N
Singapore	1985	1987	1987	Y	0	1m	5m		12m	H.C	1987		100	100	Y
Solomon Islands	1990	1990	1991		0	2m	4m				1991				N
Tokelau	1997	1997	1997	Y	0	6w	5m			#	<1997		100	100	N
Tonga	1988	1988	1998		0	6w	5m			#	1988		93	94	N
Tuvalu	1993	1993	1993	Y	0	6w	9m				1993		100	100	Y
Vanuatu	1993	1993	1993		0	6w	14w				1993		37	53	Y
Viet Nam	1997	1997	2003		0	2m	4m				2003	32	10	70	N
Wallis and Futuna	1992	1992	1992	Y	2m	3m	9m						100	100	Y

Y = Yes

N= No

NR - Not reported

- See supplementary information

Annex 4

Table 2: Hepatitis B vaccine coverage and source of vaccine funding and procurement

Country/Area	1999	2000	2001	2002	2003	2004	2005	HepB coverage close to DTP3	2003 DTP3%-HepB3%	2004 DTP3%-HepB3%	2005 DTP3%-HepB3%	Local Production	Donor funding	UNICEF procurement
	HepB3 coverage(%) <1 yr old							Integration				Vac Source		
American Samoa	91	81		96	89		80		5	NR	7		100%	
Australia			94	94	95	95	94	Y	-2	-3	-2.5		0	
Brunei	93	100	100	ND		100	99.8	Y	=	=	=		0	
Cambodia	ND	NR	NR	NR	NR	ND		= =	NA	-8.3	7.9		100%	Y
China	NR	ND	92.4	95.8	96.7	98.7	84.3	N	NR	NR	NR	100%	~15%	
Cook Islands	90	98	93	93	93	100	100		1.5	0.2	2.2		0	Y
Fiji			93	78	92	72.9	75	Y	3	=	=		0	Y
French Polynesia	95	97	95	96	98		97.2	Y	2	-1.6	=		0	Y
Guam	99	94	84	78	77	85	88		1	ND	1.6		100%	
Hong Kong	88	89	89	85	85.6	95	95	Y	11	2	-1.6		0	
Japan			NR	NR				=	-0.9	=	=	100%	0	
Kiribati	82	90	85	100		66.6	84.9		NR	NR	NR		0	Y
Republic of Korea		93	89	92	91	91.6	99	N R	ND	-3.2	-6	100%	0	
Lao PDR	NR		.	4	50	45	49	=	ND	ND	ND		100%	Y
Malaysia	90.7	93.3	95	93.1	90.9	93.8	91.5	Y	=	=	=		0	
Macao	92	91	90	91	91	86.4	87.5	Y	7.8	0.4	3.8		0	
Micronesia	77	87	81	89	89	80	91		=	3.8	4.7		100%	Y
Mongolia	84	94	94	94	95	95	98.7	Y	3	-2	3		100%	Y
Marshall Islands	80	38	76	77	74	72	89	N	3	3.9	0.3		100%	Y
New Caledonia	73							Y	-6	-8	-12		0	?
New Zealand	89	90	90	ND			87	Y	NR	NR	NR		0	
Niue	100	100	100	100		100	86	Y	ND	ND	2		0	Y
Mariana Islands	96	89			93	89	89	Y	ND	=	-1		100%	
Nauru	62	58.3	95	75		75	80	Y	-1	-2	-16		0	Y
Palau	96	96	100	100	100	98	98		ND	5	=		100%	
Philippines	NR	3	80	31	ND	43	44	N	NR	34	35		0	Y
Papua New Guinea	54	57	41	60	67	60	62.9	N	1	2	-1.9		~70%	Y
Singapore	96	97	95	95	95	94	96	Y	1	1	=		0	
Samoa	99	96	98	98	97	70	60	Y	-3	-2	3		0	Y
Solomon Islands	62	73	78	68	78	72	73	Y	-5	8	5		100%	Y
Tokelau	100	100	100		70	99	100	Y	-29	=	=		0	Y
Tonga	93	97	96	95	93.1	99.2	99.4	Y	5.2	0.1	-0.5		0	Y
Tuvalu	93	78	99	99	95	98	79	Y	-2	=	14		0	Y
Vanuatu	75	75	69		56		70	N	-7	ND	-4		0	Y
Viet Nam	82	94	96	65	78	94.2	93.7	=	22. 2	2	0.9	~15%	~85%	Y
Wallis and Futuna	100	100	100	100	100			Y	=	ND	ND		100%	

Note: "HepB3 coverage close to DTP3" judgement by national authority.

Annex 4

Table 3: Estimates of hepatitis B seroprevalence, impact of immunization and plans

Country/Area	Best Estimate (WPRO)	WPRO estimate in 1997	Official pre-vaccine estimate	Estimate (95% CI) from available studies of pre-vaccine % HBsAg+	Representative population sample	Blood donors	Ante-natal tests	Impact of vaccine assessed	HBV carriage % change (vaccinated children)	Request help to monitor HBsAg+	Acute hepatitis B data	Acute cases % change post-vaccine	National Plan	Help requested: Advice; Review programe; National plan; Serosurvey, Training
	Pre-vaccine HBsAG+ (%)							Impact assessment						
American Samoa	7	7	7	5.7(4-7)	6			Y			Y	N	Y	T
Australia	<1	0.5									N		Y	
Brunei	5	8		5.2(5-6)		5					Y	?	Y	S
Cambodia	9	12				9					N		Y	
China	10	12	10	11(10-11)				Y	~90%		N	NR	Y	R
Cook Islands	10	10									Y	?	Y	R
F.S. Micronesia	15	12	15		15		10	Y	~85%		N		Y#	
Fiji	11	11		10 (8-12)				Y	90%		N		Y	S.N.T.
French Polynesia	3	10	3				3						NR	
Guam	4	4												
Hong Kong (China)	10	2	10				10#	Y	89%		Y	17%	Y	
Japan	2	2	2	1(0.5-1.2)		0.5		Y			Y		Y	
Kiribati	29	31		29(25-32)		15		Y	86%		NR		Y	N
Lao PDR	8	12				>10	6				N		N	N
Macao (China)	11	12	11				10				Y	49	Y	A
Malaysia	5	5	3-14	5(4-6)							N		Y	T
Mariana Islands	5	5									N		N	S
Marshall Islands	12	2									N		N	
Mongolia	10	14	10-39	9(7-10)				Y	~50%		Y	64%	Y	
Nauru	20		40	15(12-17)							Y	?		A
New Caledonia	6	8		9(7-10)				Y			Y	?	Y	
New Zealand	<1	1	<1	7(7-8)#	1	1					Y	-85%	N	
Niue	8		8	12(10-13)							N		Y	
Palau	20	12	20											
Papua New Guinea	8	20		7(6-8)							N		Y	
Philippines	9	10	9	8(7-8)			9				N	-	N	A
Republic of Korea	5	12		4(4-5)		7					Y		Y	
Samoa	6	8		6(4-8)									Y	
Singapore	5	12	5	5(5-6)				Y	100%		Y		Y	
Solomon Islands	21	20		21(20-23)							y		N	
Tokelau													Y	S
Tonga	18	20		18(15-20)				Y	66%		N		Y	
Tuvalu	15						15#				N		Y	A
Vanuatu	21	19		21(19-23)				Y	81%		N		N	S
Viet Nam	14	12	17	10(9-11)							N		Y	N
Wallis and Futuna	8	8						Y	100%				Y	A

Y= Yes NR= Not reported

N= No # = See supplementary information

NR = Not reported

WPRO = WHO Western Pacific Regional Office

Please report any additional data on pre-vaccine seroprevalence and impact to WPRO/EPI

Annex 4

Table 4: Supplementary information calculate data in Tables 1-3

	Vaccine use in infants	Others given (public) vaccine	HBsAg+, acute disease and Vaccine Impact	National Plan
American Samoa	BCM given HBIG within 7 days of birth; HepB3 at 6mo; tested at 12mo	All under 21 year olds; others tested then immunized if susceptible	Acute hep B shows no impact from immunization - no data provided	Health education, idenitifying cases, and testing household contacts
Australia	Two schedules (depends on vaccine used): 0,2,4,6mo or 0,2,4,12mo. Combination vaccine used in most states. No monitoring birth dose timeliness	Catch-up programme for 10-13 year old children	No comprehensive data on HBsAg prevalence; limited data show: 0.1-0.2% in Europeans; 3-9% in indigenous populations	Infant immunization and disease notification
Brunei Darussalam		Health workers. Household and other contacts of carriers		Routine EPI + antenatal and blood screening; follow-up of carriers
Cambodia	Phasing in DTP-HepB over 4 years, starting in 2001. Birth dose will be piloted in 2 places in 2002	No	HBsAg serosurvey in pilot province in 2001: 9-17mo: 3%; 4-5yr: 5%; 13-15yr: 8%; 20-35yr: 11%	National plan proposed in 2001
China	Birth dose – 80% in first 48hrs of life (1999 survey); but only 67% health worker attendance at birth (ranging from 16% in Tibet to 98% in Beijing). Policy of HBIG for BCM being considered – will not be free		9.9% HBsAg+ (40% HBeAg+) in cross-sectional national survey of 60,000; now <1% in vaccinated children	Target of >85% coverage by 2006, monitor coverage, use sero-survey and pilot acute surveillance
Mariana Is., Northern	BCM given HBIG within 12 hours of birth –all babies born in hospital	Travellers, students, health workers and police officers		
Cook Islands		Students		Routine vaccine use and increase target age group.
Micronesia, F.S.	All children born in the 4 hospitals get birth dose of vaccine within 24 hours. Policy to give HBIG to BCM, but not been available for several years. Vaccine funded by CDC USA	Health workers, student travelling abroad, adults and by request. Required for college and high school entry	2-6 yr olds HBsAg+ reduced from 15% (1988) to 2.5% (2000). Study: HBsAg+ 0% if birth dose; 5% if did not get birth dose	No formal plan, but annual grant request to CDC fills that function
Fiji	Vaccine introduced in 1989, but not well established because of cost and erratic supply until 1995 (Pacific HepB project). HBIG given since 1995, but not consistently because of cost to Govt. F$38.55	Health workers at risk of exposure	Best pre-vaccine estimate: 11% HBsAg+ (1980). 1997 study HBsAg+: 9-24mo old (vaccinated): 0.7%; 9-12yr old (unvacinated): 6.9%; mothers of infants of 6.6%	Immunization for infants and high risk groups, screen blood, test pregnant mothers
French Polynesia		Previously unimmunized 11 yr olds.	Antenatal tests (1997-99): 2.5% HBsAg+.	
Guam	BCM given vaccine at 0,1,6 mo			
Hong Kong (China)	Nearly all newborns (>99%) get birth doses before discharge from hospital, but no data on timeliness. Survey data higher than administrative data for HepB3 as latter does not include some doses given in private sector	Health worker in public service, renal dialysis patient. Since 1998, patch-up for schoolchildren aged 10 – 13 years	Pre-vaccine: 9.6% HBsAg+ (blood donors and inpatients); 2001 estimate of 8.8%. Continuing sero-surveys and follow-up studies of vaccinated babies to monitor impact. Data on acute cases available only since 1989 (one year after start of immunization)	Responsibility of scientific working group (annual report porivded)
Japan	Infant immunization only for BCM: HBIG given within 48 hr and at 2-3 mo after birth; vaccine given at time of second HBIG, seocnd dose 1mo later; third dose 3mo after first dose (HBIG and vaccine covered by health insurance since 1995)	Voluntary vaccination for non-risk population	Blood donors: 0.46% HBsAg+, and 424 acute HepB cases reported in 2000	Prevention of transmission from carrier mothers to infants since 1995
Kiribati	No data on timeliness of birth dose, but usually witihin 24 hours of birth	No	Current best estimate is 20-30%, 25% in one school	No national plan
Lao P.D.R.	Phasing in DTP-HepB over 3 years, starting in 2001.	No	Data on acute hepatitis not good.	National plan only for introducing vaccine.
Macao, SAR	Only BCMs given vaccine from 1984; all newborns from 1989; 4th dose added in 1996. HBIG for BCM within 12 hrs of birth since 1984 in public and since 1988 in private (no fees). No data on timeliness of birth dose of vaccine; but most imminized on second morning of life	Under 12yr olds; high risk groups (health worker, household contact, on haemodialysis or who need regular blood products, intravenous drug user, disabled people living in nursing homes), security force recruits, susceptible blood donors	Pre-vaccine official estimate 11% HBsAg+; now 8.5%. Acute HepB cases declined from was 24.5 (1986-1988) to 8.8 per 100,000 (1999-2000). Antenatal tests in 2001 found HBsAg+ reduced from 10%(born 1965-1971) to 5% (born 1982-86)	Integation of HepB vaccine; monitor with serosurveys in young people and children
Malaysia		Health workers at risk; IV drug users; blood donors		National plan not comprehensive, but aime to accelerate control
Marshall Islands	Birth dose given within first 8 hours in most cases	No		No national plan

	Vaccine use in infants	Others given (public) vaccine	HBsAg+, acute disease and Vaccine Impact	National Plan
Mongolia	Survey of infants born in 1998-1999: 97% of urban and 90% of rural infants received first dose within 4 days of birth. Schedule changed (from 0,1,6mo to 0,1,8mo) to maintain higher antibody levels	No	Pre vaccine estimates of HBsAg+: 9.8% (1978) and 14-39% (1989). In vaccinated children 6-7% (estimated 2-3 fold reduction)	Developing new infectious diseases control programme including viral hepatitis control
Nauru	HBIG given to BCM -when available,			
New Caledonia	Changed from 4- to 3-dose schedule in 1996; abolished boosters in 1998. BCM given vaccine at 0, 1, 6 mo and HBIG at birth given before leaving maternity clinic	Household contacts, health workers, renal failure and dialysis patients	75% reduction in carriage among vaccinated; infection (Anti-HBcAg) decreased from ~ 50% (born before 1990) to 8% in those born in 1991-92	Free compulsory vaccination, with plans to monitor and accelerate control; schedule and catch-up under review
New Zealand	Started in 1985 for BCM only, then babies in high risk district in 1987, then all infants (using low dose vaccine given in four doses) in 1988; full dose recombinant vaccine from 1989 (three doses). Schedule change in 1996 with HepB3 moved form 15 mo to 5mo	Household and sexual contacts. All children under 5yrs in 1988, and from 1990 all under 16yrs are eligible but not activley offered vaccine	Pre-vaccine HBsAg+: 0.4% in Europeans and 4% in Maori (adult workers); 9% in school children in high risk area. Acute hep B cases notified decreased from 600 cases in 1980s to 78 in 2000 (but earlier data may have included carriers as well as acute cases)	No formal plan – but immunization, IVDU needle programme, donor screening, and community screening in north island. Plan to monitor coverage in national immunization register
Niue		Catch-up programme for children born 1979-1985. Plumbers, hospital staff, and if prescribed by doctor		Compulsory immunisation of all infants
Palau				
Papua New Guinea	Schedule from 2,4,6 mo to 0,1,3 mo. HBIG only in some locations (no fee)	Health workers		Part of EPI plan
Philippines	Vaccine introduced in 1991, but funding only adequate for 40% of population; progressively increased but no vaccine in 1998 and 2000 due to lack of funds	When there is remaining vaccine from an open vial	Best estimate 9.2% HbsAg+ , 20.7% HbeAg+ (1984 antenatals)	No national plan. Plan to conduct serosurvey in infants
Republic of Korea	HBIG given within 12 hours of birth with first dose	No	1988 national survey: 5.6% male, 4.4% female HBsAg+. Data on acute HepB cases only from sentinel surveillance started in 1999; 410 cases identified in 2001 from sentilnel sites . Blood donor information shows 70% decline in HBsAG+ donor registered between 1983-1998 (7% to 2%)	Prevent vertical transmission and improve vaccine coverage. Plans to monitor impact using sentinel surveillance and coverage
Samoa		No.		National plan using prevention like other communicable disease control –immunize all infants at birth
Singapore	Started in1985 for BCM; for all infants from 1987	Health workers (tested first); contacts of cases	1998-99 study: HBsAg 5% in unvaccinated; 0% in vaccinated. Acute cases reduced from 243 (9.5 per 100,000 in 1985) to 46 (1.4 per 100,00 in 2000), and in under 15 yr olds reduced from 10 per year to 0	Part of EPI plan.
Solomon Islands				
Tokelau	Birth dose given in first 24 hrs	Catch up for those not covered in 1997 campaign	Serosurvey in 1999 found no cases	
Tonga		Those who migrate to USA, and Latter Day Saints Missionaries		No details
Tuvalu		No	14.5% HBsAg+ (antenatals and seafarers)	Continue and improve immunization through education programmes
Vanuatu		Catchup for 0-5 yrs for all vaccines including HepB	Best estimate from Ambae, 8.2% of 352 women HBsAg+	Part of EPI plan
Viet Nam	Birth dose to be given in first three days of life, but many births not attended in remote areas	No	Pre-vaccine survey (Thanh Ho province) found 17% HBsAg+	Action plan for introduction (2002-2006), coverage survey in 2003 to monitor impact
Wallis and Futuna Is.	HBIG (but not vaccine) given to BCM	Children born before year vaccine introduced -1992	Impact on HBsAg+: 0% under 5 yrs, 3.7% in 5-10 yrs, 3.8% in 10-15 yrs, and 8.2% in 15-20 yrs	

ANNEX 5: MATHEMATICAL MODEL TO ESTIMATE THE VACCINE COVERAGE REQUIRED TO ACHIEVE THE GOAL OF <2% SEROPREVALENCE AMONG FIVE-YEAR-OLD CHILDREN

Objectives of the model

Although all efforts should be made to immunize each and every child (every child counts!), this model tries to calculate the expected levels of HBsAg seroprevalence at five years of age at different vaccine coverage levels or, alternatively, the minimum vaccine coverage levels required to reach a particular seroprevalence goal. The model produces two outputs—the HepB0 coverage required and the HepB3 coverage required to reach a particular seroprevalence goal. However, one of the outputs has to be fixed/known in the model to calculate the other output. Example for, the model allows calculation of the HepB0 coverage level required at a given HepB3 coverage rate to reach a particular seroprevalence goal.

As in other mathematical models, the outcomes are very much dependent on the assumptions entered into the model, and the actual results may be different if some of the assumptions used in the model are not true or if the model fails to take into account other important parameters that may affect the outcomes. In addition, the model may be more sensitive to violation of certain assumptions than others.

Basic assumptions

(1) The probability of mother-to-child transmission at birth is 70% to 90% among women who are HBeAg-positive and 10% among women who are only HbsAg-positive.

(2) 75% of chronic HBV infections are acquired by five years of age from perinatal transmission and from horizontal transmission from child to child or from other household contacts. For example, if an 8% HBsAg-positive rate is assumed among antenatal women, it is assumed that 75% of these chronic infections (i.e. 6%) were acquired by age five, in the absence of actual empirical data on chronic infection rates from children aged five years.

(3) The protective efficacy of vaccine alone, if given within 24 hours of birth, in preventing perinatal transmission will vary from 70% to 95%.

(4) The protective efficacy of a three-dose vaccine schedule in preventing post-perinatal transmission is 95%.

(5) The risk of becoming a chronic HBV carrier if infected at birth is 90%.

(6) In the absence of antenatal screening, the probability of receiving a timely birth dose is the same for HBsAg-positive women and HBsAg-negative women.

(7) The probability of receiving vaccination and being exposed to HBV infection are independent of each other. That is, the population sub-groups that are at high risk of hepatitis B infection are not less likely to be vaccinated than the population subgroups at lower risk of infection.

(8) Children who receive a timely birth dose also get a complete series of vaccinations.

Assumptions most likely to be violated:

Rural-urban differences and gender differences in chronic HBV infection rates have been noted in almost all countries where serosurveys have been conducted, with rates in rural areas demonstrated to be much higher than in urban areas. Although some of the differentials observed in China and Mongolia may reflect differentials in vaccination coverage in urban and rural areas, the differences in the case of Cambodia were observed in the absence of a

vaccination programme, reflecting probable differences in prevalence and exposure to risk factors for HBV infection.

If the population subgroups where new birth cohorts have the highest risk of exposure to infection are least likely to be vaccinated, then the impact of a national vaccination programme may be less than is estimated by the model.

Table 1: Rural-urban differences in HBsAg-seroprevalence rates in selected countries

Country	Rural (%)	Urban (%)	Total (%)	Year and age group of survey
Mongolia	7.7	3.0	5.2	2005, 7-12 years
China	8.3	2.1	5.2	2002, 1-12 years
Cambodia*	8.5	3.4	3.4	2006, 5 years old

* In Cambodia, the distribution is by remote/least-developed region and most-developed region, rather than by rural and urban.

Data to be entered into the model

The model uses a hypothetical cohort of 100 children, as the objective is not to calculate the total disease burden but the percentage vaccination coverage required to reach a particular goal in terms of HBsAg seroprevalence.

(1) The percentage of pregnant women positive for HBsAg. In most countries, data from pregnant women may not be available. Hence, data may be entered from women (men) in the age group 15-49 years old.

(2) The percentage of HBsAg-positive pregnant women who are positive for HBeAg. In most countries, data from pregnant women may not be available. Hence, data may be entered from women (men) in the age group 15-49 years old. If no such data are available, it is recommended to use a figure of 30%, based on review of results obtained from different countries in the Region.

Basic formulas used

(1) Number of children (X_b) who will be become chronic carriers due to acquisition of infection at the time of birth:

$X_b = X$* 90% (a_s*30%*%risk of transmission among HBeAg +ve women)+a_s(1-30%).10%)*(1-vaccine efficacy%*HepB0%)

Where X equals the total birth cohort (will be entered as 100), a_s is the proportion of antenatal women positive for HBsAg. HepB0 is the first dose of vaccine provided within 24 hours of birth (referred to as the birth dose in rest of the paper), and 90% indicates the risk of becoming a chronic HBV carrier among children who might be infected at the time of birth. The figure of 30% in the first and second bracket indicates the proportion of HBsAg-positive pregnant women who may also be positive for HBeAg, while the 10% in the third bracket indicates the risk of transmission of infection to newborn infants among women who are only positive for HBsAg.

(2) Number of children (X_h) that will become chronic carriers due to acquisition of infection after birth to age five years from horizontal transmission: This calculation step assumes that 75% of all chronic HBV infections are acquired by age five.

X_h =(X*0.75*(a_s)- X_b)*(1-VE%*Hep3%)*

(3) Total carrier rate at age five in %= (X_b+ X_h)/X*100.

The main outputs

The HepB0 coverage required to achieve a less than 2% goal (say 1.99%) at a given Hepb3 coverage rate will be equal to (Xb+(Xh*(1-VEh*Hepb3) -1.99)/(Xb*VEb) , where VEh is the vaccine efficacy in preventing horizontal transmission of infection and VEb is the vaccine efficacy in preventing vertical transmission of infection.

The HepB3 coverage required to achieve a less than 2% goal (1.99) at a given HepB0 coverage rate will be equal to ((Xb- (Xb *100*VEb*HepB0%)+Xh-1.99)/(Xh*VEh).

Calculations

The model was applied to China.

Two sets of large, representative national data are available from China that provide information on HBsAg positivity among women in the child-bearing age group. As per a national survey conducted in 1992, 8.25% of women in the age group (15-49 years) tested positive for HBsAg (N=21 000). The HBeAg-positivity rate among this age group (both sexes) was 25.3%. However, the HBeAg rate decreases rapidly by age, from 50+ % in <15 years of age to 40% in 15-19 years, 33% in 20-24 years and down to 12% in 40-49 years old.

In another nationwide survey, conducted in 2002, 8.45% women in the age group 15-49 years tested positive for HBsAg (n~11 000), although no HBeAg testing was done. Hence, HBsAg prevalence rates are comparable across the two surveys, and are not statistically different.

An HBsAg rate of 8.45% among antenatal women, 25.3% of whom are positive for HBeAg, was, therefore, entered into the model. However, since the HBeAg rate declines with age and most child bearing in China is limited to the age group 20-34 years, a higher rate of 30% was used in scenario 2.

	Description	Formula used	Middle scenario to achieve less than 2%	Most conservative scenario to achieve less than 2%	Least conservative scenario to achieve less than 2%	Middle scenario to achieve less than 1%
A.	Total number of children		100	100	100	100
B.	HBsAg-positive rate among women*		0.0845	0.0845	0.0845	0.0845
C.	HBeAg-positive rate among women**		0.3	0.3	0.3	0.3
D.	Rate of perinatal transmission among HBeAg-positive rate		0.8	0.9	0.7	0.9
E.	Rate of perinatal transmission among women positive only for HBsAg		0.1	0.1	0.1	0.1
F.	Protective efficacy of birth dose		0.8	0.7	0.9	0.8
G.	Protective efficacy of HepB3		0.95	0.95	0.95	0.95
H.	Risk of becoming chronic carrier if infected at birth		0.9	0.9	0.9	0.9
I.	On-time birth dose coverage		**0.5**	**0.5**	**0.5**	**0.95**
J.	HepB3 coverage among infants		**0.85**	**0.85**	**0.85**	**0.95**
K.	% of children infected at birth in the absence of vaccination	**(B*C*D)+[B*(1-C)*E]**	0.026195	0.02873	0.02366	0.02873
L.	Children becoming chronic HBV carriers in the absence of vaccine in a birth cohort of 100 (Xb)	**100*K*H**	2.35755	2.5857	2.1294	2.5857
M.	Children becoming chronic HB carriers in the presence of a timely birth dose vaccination at particular OT coverage level	**L(1-*F*I)**	1.41453	1.680705	1.17117	0.620568

N.	Percentage risk of becoming chronic carrier of HBV due to horizontal transmission after birth to age five in the absence of vaccination (Ch)	**(B*0.75)-(L/100)**	0.0398	0.037518	0.042081	0.037518
O.	Children becoming chronic carriers in the absence of any vaccination due to horizontal transmission (Xh)	**N*100**	3.98	3.75	4.21	3.75
P.	Children becoming chronic carriers due to horizontal transmission at a given HepB3 coverage level	**O*(1-G*J)**	0.77	0.72	0.81	0.37
Q.	**HepB0% required to reach a goal of less than 2% at a particular Hepb3 coverage level**	**[L+P-1.99)/(L*F)**	**0.60**	**0.73**	**0.50**	**0.46**
R.	**Hep3 coverage required to reach a goal of less than 2% at a particular OT coverage level**	**[M+O-1.99)/(O*G)**	**0.90**	**0.97**	**0.85**	**0.67**
S.	**HepB0% required to reach a goal of less than 1% at a particular HepB3 coverage level**	**[L+P-0.99)/(L*F)**	**1.13**	**1.28**	**1.02**	**0.95**
T.	**Hep3 coverage required to reach a goal of less than 1% at a particular OT coverage level**	**[M+O-0.99)/(O*G)**	1.16	1.25	1.10	0.95

The above model implies that, under the most conservative scenario (with the highest possible transmission rate of 90% among HBeAg-positive women and the lowest documented birth dose efficacy of 70% in preventing chronic HBV infection), if the HepB3 coverage level is 85%, 73% coverage with HepB0 is required to reach the goal of less than 2%. Alternatively, at 50% HepB0 coverage, 97% coverage is needed with HepB3. In the least conservative scenario, (lowest perinatal transmission rate of 70% and highest vaccine efficacy of 90% at birth), at the 85% HepB3 coverage level, the OT birth dose coverage required will be 50%.

For certification purposes, vaccination coverage thresholds will be established as required under the most conservative scenario, although the certification panel can relax them or make them stricter depending upon the local circumstances in a country.

Accuracy of the data

Modelling is just that, and cannot completely account for the complex interactions that may occur in the environment that may affect the epidemiology of the transmission of infection. Some of the potential factors are listed below:

Herd immunity: The model does not take into account the effect of herd immunity, especially the fact that by reducing the number of chronically HBV-infected children at birth, the overall pool of people with chronic HBV infections will reduce, reducing the risk of horizontal transmission as well. While modelling the impact of herd immunity would be too complex, ignoring its effect will lead to overestimation of the vaccination coverage required to meet an HBsAg seroprevalence goal.

Improvement in injection safety, socioeconomic life-style: Both these factors will also lead to a reduced risk of horizontal transmission. Ignoring the effect of these factors will also lead to overestimation of the vaccination coverage required to reach a particular HBsAg seroprevalence goal.