WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR THE WESTERN PACIFIC

GUIDELINES FOR CERTIFICATION OF ACHIEVEMENT OF HEPATITIS B CONTROL GOAL IN THE WESTERN PACIFIC REGION

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EXECUTIVE SUMMARY

The certification for achievement of the hepatitis B control goal in the World Health Organization (WHO) Western Pacific Region will be based on HBsAg positive rates among children 5 years or older, born after the start of a nationwide infant vaccination programme.

At least one representative serosurvey is required to document the HBsAg rates among the birth cohorts born after the start of nationwide vaccination, preferably among children 5 years or older. The point estimates of HBsAg seroprevalence among children 5 years or older have to be less than 2% and less than 1% for certification for interim and final hepatitis B control goal, respectively. The accuracy of the estimates of HBsAg should be within ±0.5% with 95% confidence.

Even though vaccination coverage data will not be used as primary criteria for certification, the certification panel will assess the vaccination coverage data carefully and make vaccine coverage recommendations for maintaining the certification status and for achieving better control. Estimated vaccine coverage levels required to achieve the goal of less than 2% and 1% HBsAg seroprevalence have been calculated using a mathematical model. Assuming an average HBsAg positive rate of 8% among pregnant women, HepB3 coverage has to be at least 85% and timely birth dose coverage has to be at least 65%. However, the required coverage levels will be higher in countries with higher baselines HBsAg positive rates

If a country achieves less than 2% HBsAg seroprevalence rate among children 5 years or older, but the vaccine coverage levels in the last 5 years have been lower than suggested by the mathematical model, or if the vaccine coverage levels have been declining among the younger cohorts, then the country will be certified having achieved the regional goal, provided it presents a plan to increase the vaccine coverage levels as well as a plan to achieve the final hepatitis B control goal of <1% chronic HBV rate.

The methodologies described in the document including thresholds for various indicators are for overall guidance of the certification group to be established to oversee the certification process and have to be interpreted in the context of each country.

The procedure for the certification has also been defined. The process borrows elements from the processes set up for the certification of polio eradication and for validation of maternal and neonatal tetanus elimination (MNTE). The WHO Regional Office for the Western Pacific will establish an expert resource panel, from which a three-to four-member certification panel will be constituted when a request for certification is received from a country. The certification panel will review all the documents for HBsAg seroprevalence and vaccine coverage data to certify the country. The certification results will be reported to the WHO Regional Committee for the Western Pacific and will be published in the Weekly Epidemiological Record—a WHO publication, regularly.

GLOSSARY

Anti-HBs	antibodies to the surface antigen of hepatitis B virus
Anti-HBc	antibodies to hepatitis B core antigen (HBcAg) – a protein found in the core of the 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 protects against the three diseases
DTP3	The third dose of diphtheria-tetanus-pertussis vaccine
DTP-HepB	A combination vaccine that protects against diphtheria, pertussis, tetanus and hepatitis B
DTP-HepB3	The 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
FIC	fully immunized child – a child that has received all the recommended vaccines by a specified age (usually by 12 months)
GAVI	Global Alliance for Vaccines and Immunization
GCC	Global Certification Commission
HBeAg	hepatitis B 'e' antigen –indicates greater infectivity in chronic infection
HBIG	hepatitis B Immunoglobulins
HBsAg	hepatitis B surface antigen: a protein from the virus coat. 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	HepB birthdose –the first dose of HepB vaccine administered within 24 hrs of birth
HepB1	The first HepB dose which includes both HepB0 and the first dose given after 24 hours of birth. HepB1 should ideally be equal toHepB0 where all infants receive their first dose within 24 hours of birth
HepB3	The third and final dose of HepB – three doses recommended for protection
Hib	*Haemophilus influenzae* type B
NIP	national immunization programme

MNTE	maternal and neonatal tetanus elimination
RCC	Regional Commission for the Certification of Poliomyelitis Eradication
Seroprevalence	Percentage of a population positive for a specific antibody (e.g. to HBsAg) or antigen (e.g. HBsAg)

1 SETTING UP OF THE HEPATITIS B CONTROL GOAL IN THE WESTERN PACIFIC REGION BACKGROUND AND RATIONALE

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

Universal childhood immunization with three doses of hepatitis B vaccine in the first year of life, has proven to be the most effective strategy to control hepatitis B. In 2002, the Western Pacific became the first WHO region to achieve the distinction of having hepatitis B immunization included in the national immunization programmes (NIP) of all its Member States[1]. Striving to build upon the gains achieved in immunization systems during the poliomyelitis eradication initiative, the Region has adopted hepatitis B control through universal infant immunization as one of the pillars for strengthening immunization service delivery systems.

In September 2005, the Western Pacific became the first WHO region to set a time-bound goal of reducing chronic HBV infection rates to less than 2% among 5 year-old children by 2012. This 2012 goal is an interim milestone on the path to achieving the final regional goal of less than 1% HBsAg prevalence among 5 year-olds, although the date and timing 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 or even a more challenging goal (e.g. elimination of HBV transmission).

The rationale of setting the hepatitis B control goal in terms of seroprevalence of HBsAg among children 5 years old rather than in terms of incidence of new infections or overt disease outcomes has been explained in the regional plan for hepatitis B control[2] and in Annex 3 dealing with different questions and answers.

This document provides overall guidance on how to monitor and certify the achievement of the regional goal among its Member States. The following sections describe data and indicators to be used for certification of the interim and final goals, and the certification procedures to be adopted.

[1] However, Japan continues to provide hepatitis B immunization to infants born only to HBsAg positive mothers, though on a nationwide basis.

[2] Western Pacific Region, WHO. 2007. Western Pacific Regional plan for hepatitis B control through immunization. Philippines, Manila, 2007 (manuscript under finalization).

2 CERTIFICATION INDICATORS AND THRESHOLDS

The certification thresholds described below are for the purpose of overall guidance only and are not prescriptive. The certification panel will have to assess the requirements in the context of each country. It may make the thresholds stricter or waive/exempt some of the requirements for the purposes of certification, but it will have to provide technical justification for any departures/exemptions.

2.1 Certification Indicators

The assessment of the achievement of the hepatitis B control goals will take into account the following data:

- at least one source of representative data on seroprevalence of HBsAg among children 5 years or older born after the nationwide implementation of universal hepatitis B infant immunization;
- hepatitis B vaccine coverage data to assess the maintenance and sustainability of the certification status; and
- acute or chronic hepatitis B surveillance data (optional, especially if available among children).

2.1.1 Seroprevalence of HBsAg

One of the key requirements for certification will be the analysis of seroprevalence rates of different HBV infection markers, especially for HBsAg among children 5 years or older, born after the start of universal infant vaccination. Every country should undertake at least one seroprevalence survey of HBsAg based on representative sampling of population cohorts of children at least 5 years old[3] born after the nationwide implementation of an infant hepatitis B immunization programme.

Can the seroprevalence data be from children older than 5 years?

Yes. For example, if HBsAg rate is demonstrated to be less than 2% among children 6 to 10 years of age in a country that introduced vaccine more than 10 years ago and achieved sustained high coverage with HepB3 (i.e. the coverage in last five years is same as previous five years) will deemed to have achieved the goal. It is not necessary to have the seroprevalence data from children exactly 5 years old.

[3] As most chronic infections are acquired by age 5, sampling children 5 years or older will take into account the peak exposure period when the risk of horizontal transmission and likelihood of becoming a chronic carrier are the highest.

What if the data are from children younger than 5 years?

Children younger than 5 years of age have not yet passed through the complete exposure period, and some of them who are currently negative may get infected and become carriers. Hence, the seroprevalence estimates in this age group may underestimate the eventual seroprevalence that may be achieved in this cohort at age 5 years. In this event, a lower target of seroprevalence (e.g. less than 1.5% rather than 2% for the interim goal; and less than 0.8% rather than 1% for the final goal) may be set to certify the achievement of the goal.

Another possibility is to use a combination of HBsAg and anti-HBs among children younger than 5 years as required indicators for certification process.

2.1.1.1 Thresholds for seroprevalence of HBsAg for certification of interim hepatitis B control goal of <2% prevalence among 5 year olds:

- the point estimate for the seroprevalence of HBsAg should be less than 2%; and
- the accuracy of the estimate should be within ±0.5%.

Thresholds for seroprevalence of HBsAg for certification of final hepatitis B control goal of <1% prevalence among 5 year olds:

- the point estimate for the seroprevalence of HBsAg should be less than 1%; and
- the accuracy of the estimate should be within ±0.5.

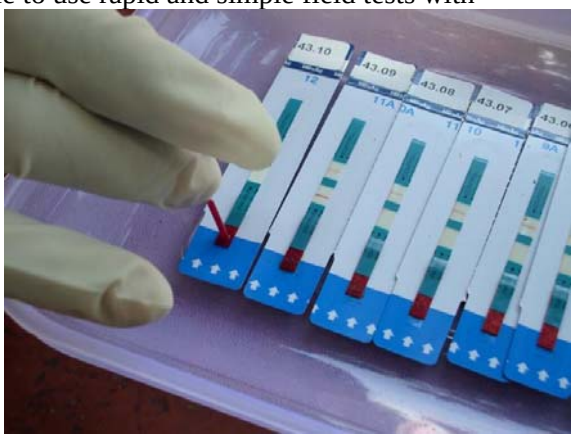
However, it must be noted that these thresholds are for overall guidance only and should not be taken as prescriptive. Some smaller countries, such as many Pacific island countries and areas, have very small birth cohorts (less than 500 births each year), and in these cases it may be difficult to achieve the 95% confidence interval within ±0.5%. Finite population correction should be applied in these cases to calculate the sample.

2.1.1.2 Criteria for considering a serosurvey valid for the purpose of certification:

- *Representativeness of the estimates*: Ideally, the seroprevalence survey should be population based, though the units of sampling may be households or schools (especially in countries where school enrolment rates are almost universal) depending upon the country context. WHO Headquarters is preparing the guidelines for undertaking a representative sample survey, including advice on sample sizes and the selection process. However, convenience sampling (e.g. testing of children admitted in a hospital, etc.) may be more practical and less expensive and will be able to provide representative estimates in some settings, such as in small countries with only one or two health facilities catering to all the children. If the convenience sampling is used, the country should be able to clearly demonstrate that results are not likely to be biased, especially in the direction of underestimation. Countries should be able to produce proper documentation showing representativeness of the data.
- A*ppropriate sample size*: The accuracy of the estimate should be within ±0.5%. The sample size should be adequate to show with 95% confidence the target HBsAg prevalence of <2% or <1%, whichever is applicable.
- S*tandard laboratory procedures, including* proper quality control and assurance: Serologic assays are commercially available for all markers of hepatitis B and majority of them rely on enzyme-linked immunosorbent assay (ELISA) tests, which are quite

sensitive and specific. The diagnosis of HBV infection or assessment of immunity to HBV requires laboratory detection of HBsAg and anti-HBs, respectively. Additional testing for anti-HBc may provide estimates of the resolved infection and natural immunity after infection in the past, in addition to providing estimates of life-time risk of HBV infection. The minimum requirement for the certification process will be valid estimates of HBsAg. Countries should be able to produce proper documentation of the quality control and assurance of the laboratory procedures during the serosurvey.

- *Use of rapid field tests*: In areas with limited laboratory capacity and in other resource constrained settings, it will be acceptable to use rapid and simple field tests with established sensitivity and specificity[4]. These tests offer several advantages for undertaking a serosurvey: low cost; minimal requirements for training, specimen handling, and laboratory and cold chain infrastructure; and requirement of only a drop of blood as opposed to venipuncture. However, simple and rapid tests may be inadequate for the purpose of notifying individuals about their HBV infection status especially in the countries with low prevalence of HBV where positive predictive values of the tests may be lower.



[4] Some of these tests have also been validated for their sensitivity and specificity in field setting. Please see World Health Organization. 2004. Hepatitis B surface antigen: operational characteristics (Phase I), Report 2,WHO/Geneva; Lien TX, Tien NTK, Chanpong GF et al, Evaluation of Rapid Diagnostic Tests for the Detection of Human Immunodeficiency Virus Types 1 and 2, Hepatitis B Surface Antigen and Syphilis in Ho Chi Minh City, Vietnam. American Journal of Tropical Medicine and Hygiene 62(2), 301-309 (2000); Hills SL, Hipgrave DB et al, Population-level use of rapid antigen test to assess rates of hepatitis B infection." Unpublished manuscript (2005).

What if HBsAg prevalence in children 5 years and older is <2% but the vaccination coverage levels are lower than that suggested by model to reach <2% HBsAg rate?

Though less than 2% HBsAg prevalence among children 5 years or older would be required for certification, the vaccination coverage levels in the last 5 years will provide information about the maintenance of low HBsAg rates among children born subsequent to birth cohorts among whom HBsAg prevalence was evaluated. Most of the countries in the Region have more than 8% prevalence of chronic HBV infection, and this will require three to four decades of sustained high vaccination coverage, until population cohorts with high chronic HBV infection rates pass out of population. The HBsAg levels lower than 2% among 5 years old or older would reflect immunization services performance five years ago. However, if the vaccination coverage goes down subsequently, there is a risk that the HBsAg seroprevalence levels among younger children may increase again, especially in countries with high baseline chronic HBV infection rates. Proof of sustained high vaccination coverage in the last five years with seroprevalence measurement among children 5 years or older will indicate that even younger children that were not included in the current serosurvey will not have more than 2% HBsAg positive rate. Hence, though the country will be certified on the basis of HBsAg levels, the country has to present plans to increase the vaccine coverage required to maintain less than 2% HBsAg rate and to achieve the final regional goal of less than 1% HBsAg rate.

2.1.2 Hepatitis B vaccine coverage rates

Since the hepatitis B vaccine efficacy is known for prevention of perinatal and horizontal infection of hepatitis B, a mathematical model can be used to project vaccine coverage rates (HepB0 and HepB3) required to reduce the chronic HBV infection rate to a particular level. Hence, the vaccine coverage data will provide an indication to countries about whether or not they have achieved the hepatitis B control goal and whether they should conduct a serosurvey. Since the HBsAg serosurvey data will refer to a particular cohort of children (normally 5 years or older), sustained vaccine coverage data among the younger children will provide evidence that the younger cohorts will not have higher chronic HBV infection rates than the cohorts where HBsAg is measured. Vaccine coverage rates will be analysed since the implementation of nationwide hepatitis B vaccination programme or at least for the five years immediately prior to the year in which certification is requested. Vaccination coverage data will be examined at both the national- and first subnational or district level. If a country achieves less than 2% HBsAg seroprevalence rate among cohorts, 5 years or older but the vaccine coverage levels in the last five years have been lower than suggested by the mathematical model, or if the vaccine coverage levels have been declining among younger cohorts, then the country will only be certified as having achieved the regional goal, if it presents a plan to increase the vaccine coverage levels as well as a plan to achieve the final hepatitis B control goal of <1% chronic HBV rate.

Hence, even though vaccination coverage data will not be used as primary criteria for certification, the certification panel will assess the vaccination coverage data carefully and make vaccine coverage recommendations for maintaining the certification status and achieving better control.

The key indicators that will be assessed at time of certification for the last five years, both at the national and at the first subnational or the district level will include:

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

2.1.2.1 Corroboration of the administratively reported HepB3 coverage data

Though routinely collected administrative coverage data will be used for the assessment, the certification panel may like to corroborate the administrative coverage data with data from at least one household survey collected in the same period. The household survey data 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. demographic and health survey, multiple indicator cluster survey, or national health survey, etc.). Most of these household surveys target children 12 months to 23 months old at the time of survey, in order to calculate the immunization coverage in one year preceding the survey. As far as possible, the estimates from administrative data should be within ±5% points of the estimates from the household survey to be acceptable.

In the absence of such survey-based data in the past five years, the certification panel may look for other proof of the quality of administrative data, especially in countries and areas where the quality of vaccine coverage data are perceived to be poor. This proof may be in the form of a data quality audit report or other reports from data quality assessments if carried out in last five years. The data quality audit score should not be less than 0.80 for the administrative estimates to be acceptable.

2.1.2.2 Estimated thresholds for vaccine coverage levels for maintenance of achievement of less <2% goal

Thresholds for vaccine coverage—HepB3 and HepB0—can be calculated using a mathematical model under different assumptions of protective efficacy of vaccine alone in preventing perinatal transmission. The model and the assumptions made therein are presented in Annex 5. The thresholds below refer to the HepB3 and HepB0 levels required assuming the baseline HBsAg seroprevalence of 8% among general adult population, which is the average estimated in majority of the Member States in Western Pacific Region. In addition, the thresholds described below take into account the most conservative scenario (70% protective efficacy of vaccine in preventing the perinatal transmission and 90% transmission rate among HBeAg positive mothers). However, if the exact baseline HBsAg seroprevalence levels are known in a country and are higher than 8%, then the required minimum coverage levels should be calculated using the model presented in Annex 4.

Vaccination coverage thresholds in countries with baseline HBsAg seroprevalence of 8%:

- At least 85% coverage for HepB3 at national level, and at least 80% HepB3 coverage in all the districts or the minimum HepB3 coverage required depending upon the prevalence of chronic HBV infection in its adult population as per the calculation in the model presented in Annex 4.
- At least 65% coverage for HepB0 at both the national and district level or the minimum HepB0 coverage required depending upon the prevalence of chronic HBV infection in its adult population as per the calculation in the model presented in Annex 4.
- Less than 5% difference between reported DPT3 and HepB3 coverage levels.
- Less than 10% drop out rate for HepB3.

Countries should try to meet all the four vaccination coverage thresholds to maintain and sustain the hepatitis B control as certified, though the last two thresholds are more for internal checks in data quality and for quality of the programme.

2.1.2.3 Estimated thresholds for vaccine coverage levels for achieving less than 1% goal:

- At least 95% coverage for HepB3 at the national level, and at least 85% HepB3 coverage in all the districts or the minimum HepB3 coverage required depending upon the prevalence of chronic HBV infection in its adult population as per the calculation in the model presented in Annex 4.
- At least 90% coverage for HepB0 at both the national and district level or the minimum HepB0 coverage required depending upon the prevalence of chronic HBV infection in its adult population as per the calculation in the model presented in Annex 4.
- Less than 5% difference between reported DPT3 and HepB3 coverage levels.
- Less than 5% drop out rate for HepB3.

At the time of certification for achievement of less than 2% goal, countries should submit plans to increase their vaccine coverage to levels required for achieving the less than 1% goal. If certified for the less than 1% goal, then the country should present a plan for sustaining the vaccine coverage levels at the certification level in future.

2.1.3 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 among adults than among children—the target of immunization programmes and the certification process. As acute hepatitis B cases among children will comprise a very small proportion of total acute hepatitis B cases, the impact of infant immunization programmes may not be visible within five years on the overall acute hepatitis B rates. To see the impact on acute hepatitis B rates among children under 5 years of age within five years of vaccination programme would require a highly sensitive surveillance system. In addition, this would require a well-developed laboratory system that can test for multiple seromarkers of hepatitis B[5] and for other hepatitis B viruses, as acute hepatitis B is clinically indistinguishable from hepatitis caused by other hepatitis viruses.

Considering these issues, trend data on acute hepatitis incidence, especially among children less than 10 years of age, if available, will be used only to supplement vaccination coverage and seroprevalence data and will not be a mandatory requirement for the certification of the country for achieving the regional goal.

2.1.4 Incidence and mortality due to chronic hepatitis and other liver diseases

Similar issues with regard to acute hepatitis B also apply to morbidity and mortality due to chronic liver disease. Hence, these data if available will only be used to supplement other data but will not be a mandatory requirement for certification process.

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

2.2 The Certification Procedure

2.2.1 Constitution of expert resource panel

An expert resource panel will be appointed by the WHO Regional Director for the Western Pacific, comprising of 10 to 15 experts recognized in the field of hepatitis B and working in different institutions[6] in various countries. The experts will serve as resource people for the certification panel that will be constituted for a particular country on receipt of a request from that country for certification. All appointments to the expert resource panel will be on honorary and on voluntary basis, though the members will serve in the WHO temporary adviser capacity when called for the certification process in a particular country. The expert resource panel will be shared with all the Member States.

2.2.2 Constitution of certification panel

The certification process will be conducted by a certification panel having three members drawn from the expert resource panel constituted for this purpose. The Regional Office will be responsible for constitution of certification group.

2.2.3 Initiation of the certification process

The certification process will be initiated at the request of a country, once the country expresses confidence based on its own internal evaluation and review process of having met the certification thresholds. Countries may form an internal national expert committee to review the vaccine coverage and seroprevalence data. The country will submit the following documents to the Regional Office with a formal request to carry out the certification:

- the documents showing the detailed methodology and results from a serosurvey done among children 5 years or older;
- the documents showing the vaccination coverage data as reported in the last five years for all the vaccine coverage indicators; and
- the documents for a household vaccination coverage survey done in last five years.

On receiving the request from the country, the Regional Office will initiate the process for constituting a certification group by inviting three members from the expert resource panel constituted for this purpose.

2.2.4 Procedure during certification process

– The three-member certification group will carry out the detailed desk-review of the vaccination coverage data and other seroprevalence data as outlined above. A field visit may be undertaken to the country, if needed.

[6] The institutions can be both United Nations and non-United Nations organizations, including universities and other academic institutes.

- The country will appoint a representative who will serve as a focal point to assist the certification team during the visit and coordinate with various departments and institutions involved in the planning of the visit and during the review.
- The certification group will broadly follow the guidelines provided in this document for the indicators, thresholds and criteria. However, the certification group will critically examine each country on a case-to-case basis taking into account its demographic situation, historical chronic HBV rates, etc., and may relax or tighten some of the requirements for certification. The decision whether the country has achieved the hepatitis B control goal will be taken by consensus and will be fully documented by the certification group.
- The certification group will submit a report detailing whether a country has or has not met the certification thresholds for the interim WPRO goal or the final WPRO goal, the reasons for its finding, and follow-up recommendations.

2.2.5 Reporting of the certification results

The Regional Office will report to the WHO Regional Committee for the Western Pacific each year on the countries that have been certified to have achieved the interim and final hepatitis B control goals. If possible, the results will also be published in Weekly Epidemiological Record (WER) published by WHO.

2.2.6 What will happen after the certification?

Certification for each country will take place only once, if the country is successful in meeting the certification thresholds for the final Western Pacific Regional goal of <1% the first time. However, the procedure may be repeated for countries that failed to meet certification thresholds. Certification may be done for achievement of the interim hepatitis B control goal (<2%) and the final hepatitis B control goal (<1%). Once the certification thresholds are met, the maintenance of the certification status will be ascertained by regular assessment of the vaccine coverage rates reported through mechanisms such as the annual WHO/UNICEF Joint Reporting Forms on Immunization (JRF) or in Regional Technical Advisory Group/EPI managers meetings.

ANNEX 1: CERTIFICATION PROCESS OF POLIO ERADICATION

Based on the experiences of certification of smallpox eradication, the Pan American Health Organization appointed an independent Commission for the Certification of Polio Eradication (ICCPE) in 1990, composed of internationally recognized experts in several health disciplines. At the core of the certification process criteria established by the ICCPE were the requirements for disease- and laboratory-based surveillance activities and performance standards for acute flaccid paralysis (AFP) surveillance, the latter based on several sensitivity studies conducted in the Americas.

In 1995, a year after the Americas were certified polio-free, WHO established the Global Commission for the Certification of Poliomyelitis Eradication (GCC) which developed a blueprint for the Global process (and ultimate decision on the goal) and further developed standard performance indicators for AFP surveillance based on surveillance assessments conducted in almost 30 countries in three WHO Regions.

In concordance with Global requirements, the Western Pacific Regional Office of WHO developed a plan of action for the Regional certification of polio eradication in 1996 for endorsement of the newly appointed Regional Certification Commission (RCC). Major components of the plan, similar to the one used in PAHO, included:

- criteria for certification;
- disease- and laboratory-based surveillance activities;
- performance standards for AFP surveillance;
- additional surveillance activities required in high-risk areas and non-polio-endemic countries;
- special requirements for the certification of the Pacific island subregion;
- documentation required from each country; and.
- a tentative timeline for the certification

The RCC made special efforts to account for special circumstances prevailing in the Region, while at the same time remaining consistent with the standards of the GCC. The RCC also recommended appointment of a national certification committee (NCC) for each country in the Region, along with a sub-regional committee for the 20 Pacific Island countries and areas.

The RCC liaised closely with the Technical Advisory Group (TAG) on the EPI in the Western Pacific Region. The RCC clarified that if all countries provide adequate evidence consistent with the absence of wild poliovirus for three years, under conditions of high quality surveillance, the Region could be certified by the RCC as polio-free (i.e., free of indigenous wild poliovirus transmission). Regular (at least annual) meetings led to Regional certification in 2000. However, annual RCC meeting are continuing since then with clearly defined reporting requirements from each member state. The recommendations from these RCC meetings are reported regularly to the NCCs and NIPs as well as the GCC and Certification of Global polio eradication will be possible only when all Regions have been certified polio-free and all pre- and post-eradication wild poliovirus containment tasks have been completed.

ANNEX 2: VALIDATION PROCESS FOR MATERNAL AND NEONATAL (MNT) ELIMINATION

As neonatal tetanus (NT) cannot be eradicated and control measures must continue forever, the verification of elimination status (defined as less than 1 NT case per 1,000 live births) is a rather "unofficial" process. The validation exercise is initiated by WHO Geneva (in coordination with UNICEF) after National Immunization Programmes (NIP) claim to have reached elimination and is usually conducted about one year after the last vaccination campaigns have taken place, giving the last birth cohort the benefit of these activities. The exercise is usually supported by an experienced consultant.

Community-based conventional surveys were considered impractical for MNT elimination validation because they would require very large sample sizes (e.g. tens of thousands of live births) to measure a low rate of NT mortality. After view and experiences in several countries and settings, the lot quality assessment - cluster survey (LQA-CS) methodology was opted to assess NT mortality to evaluate progress made towards achieving MNT elimination status and validating it once achieved. It has been designed to be used specifically in the end-stages of the programme, when NT is considered small. The method combines lot quality assurance methods with cluster sampling, resulting in relatively small sample size requirements. While assessing the NT mortality rate (MR), the protocol allows for simultaneous data collection on immunization coverage among pregnant women (PW) and child bearing age women (CBAW), as well as on the circumstances surrounding the delivery. In summary, this method is considered the most practical for assessing whether MNT elimination has been achieved; if districts at highest risk are surveyed and “pass”, it is reasonable to assume that other districts (at lower risk) have also achieved MNT elimination.

The fact that the LQA-CS measures NT deaths rather than NT cases has been considered by a group of independent experts as an acceptable limitation. During its meeting in March 2003, the MNTE Ad Hoc Committee recommended that LQA can be used to validate MNT elimination; alternative methods may also be used, based on the agreed upon algorithm and the method would need to be adapted for small populations.

It is important to note that the validation begins much before the conduct of the LQA-CS; with a district data review to support a country’s claim of elimination and identify the weakest districts within that country. If the validation claim cannot be upheld at this stage, the next step is a field visit to review the lowest performing districts. The final step is the LQA in the worst performing districts to either confirm the elimination claim or identify the need for further activities. Confidence in the assumption that the selected districts were bound to be worse off than the non-selected districts is based on the fact that extensive risk assessment of districts using the recommended standard and surrogate quality indicators for MNTE has usually been done before on a regular basis by the NIP and during external visits by WHO and UNICEF.

Assuming that if these poorly performing sampled districts would do better, the non-sample districts would automatically do even better is based on the strategic approach used for MNTE, namely to plan and conduct tetanus toxoid (TT) vaccination based on risk assessment (see above) and implement a combination of routine immunization services (targeting pregnant

women alone or all child bearing age women mainly during antenatal care - ANC) and special campaign activities.

Validation outcomes are then published in the WHO Weekly Epidemiological Record (WER).

ANNEX 3: FREQUENTLY ASKED QUESTIONS AND ANSWERS

Question 1: Why was the hepatitis B control goal set-up in terms of seroprevalence of HBsAg 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: Impact of vaccination programmes 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 relative high sensitivity of syndromic surveillance (e.g. Acute flaccid paralysis for polio; and fever and rash for measles) and allows good monitoring of disease burden through syndromic surveillance at least in the early stages of the vaccination programme even when laboratory capacity is not adequate (though adequate laboratory capacity will needed in advance stage—elimination or eradication—of the programme).

However, none of the above criteria apply to hepatitis B. The 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 transmission and from 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 the infectious pool to sustain the transmission of HBV infection among the population.

Hence the surveillance for symptomatic hepatitis B disease among children (as practised for other vaccine preventable diseases) is unlikely to show an 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 indicator *first* to get affected by vaccination programme, is the seroprevalence of HBsAg among children, as fewer and fewer children will get infected. Hence, the hepatitis B goal was set in terms of reduction in chronic HBV infection as evidenced by decrease in seroprevalence of serological markers (HBsAg) rather than as reduction in the incidence of acute hepatitis or cirrhosis or hepatocellular carcinoma, which would take several decades.

Question 2: **Why was the goal set among children five years old?**

Children have a 90% chance of developing chronic HBV infection if infected initially at birth, a 30% chance if infected between one and five years of age, 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 of the Western Pacific Regional countries, most of the chronic infections are acquired by age five years. Goldstein et al (2005) estimated that in 75% of all hepatitis B related deaths, infection is acquired before five years of age. As most chronic infections are also acquired by age 5, measuring the goal among children 5 years or older will take into account the complete exposure period when the risk of horizontal transmission and likelihood of becoming chronically infected is the highest. Setting the goal among children under 5 years of age may *overestimate* the impact

of the vaccination programmes, if some of the children who are uninfected and unprotected earlier at the time of evaluation become infected by age 5 and become chronically infected with HBV.

ANNEX 4: MATHEMATICAL MODEL TO ESTIMATE THE VACCINE COVERAGE ESTIMATES REQUIRED TO REACH THE REGIONAL HEPATITIS B GOAL

A. Objectives of the model:

Though 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. For example, the model allows us to calculate the HepB0 coverage level required at a given HepB3 coverage rates to reach a particular seroprevalence goal.

As in other mathematical models, the outcomes in the model 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 assumption than other assumptions.

B. 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 the 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 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 5, in the absence of actual empirical data on chronic infection rates from children five years of age.
3) Protective efficacy of vaccine alone, if given within 24 hours of birth, in preventing the perinatal transmission will vary from 70% to 95%
4) Protective efficacy of three-dose vaccine schedule to prevent post-perinatal transmission: 95%
5) Risk of becoming chronic HBV carrier if infected at birth=90%
6) In the absence of antenatal screening, the probability of receiving timely birth dose is the same for HBsAg+ women and for HBsAg-ve 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 immunization.
8) Children who get timely birth dose also get complete series of vaccination.

Assumptions most likely to be violated: The rural-urban differences and the gender differences in chronic HBV infection rates have been noted in almost all the countries where serosurveys have been conducted, with rates in rural areas demonstrated to be much higher than in the urban areas. Though some of the differentials observed in Mongolia and China may reflect differentials in vaccination coverage in the urban and rural areas, the differences in case of Cambodia were observed in the absence of vaccination programme, reflecting probable differences in the prevalence and exposure to risk factors for HBV infection.

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

Table 5A: Rural-urban differences in the 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 old
Cambodia*	8.5	3.4	3.4	2006, children 5 years old

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

C. Data to be entered into the model: The model will use a hypothetical cohort of 100 children, as the objective of the model is not to calculate the total disease burden but the percent vaccination coverage required to reach a particular goal in terms of seroprevalence of HBsAg.

1) Percentage of pregnant women positive for HBsAg: In most the countries, the 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) Percentage of HBsAg positive pregnant women that is positive for HBeAg. In most of the countries, the 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.

D. Basic formulas used:

1) Number of children (X_b) that 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 is 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 birth dose in rest of the paper. 90% indicates the risk of becoming chronic HBV carrier among children who might be infected at the time of birth. The figure of 30% in the first and 2nd bracket indicates the proportion of HBsAg positive pregnant women that may also be positive for HBeAg. 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 5 from horizontal transmission: This calculation step assumes that 75% of all chronic HBV infections are acquired by age 5.

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

3) Total carrier rate age 5 in %= $(X_b + X_h)/X*100$

The main outputs:

HepB0 coverage required to achieve less than 2% goal (say 1.99%) at a given Hepb3 coverage 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

HepB3 coverage required to achieve less than 2% goal (1.99) at a given HepB0 coverage will be equal to **((Xh +(Xb***(1-**VEb*HepB0) -1.99)/(Xh*VEh)**

E**. Calculations**: **We applied the model 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 the year 1992, 8.25% of women in the age group (15-49 years tested positive for HBsAg (N=21,000). The HBeAg positivity among this age group (both sexes) was 25.3%. However, the HBeAg 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 age group 15-49 yrs tested positive for HBsAg (n~11,000), though no HBeAg testing was done.

Hence, HBsAg prevalence are comparable across the two surveys, and not statistically different.

Hence, an HBsAg rate of 8.45% among antenatal women, 25.3% of whom are positive for HBeAg was entered in the model. However, since the HBeAg rate declines with age, and most of

the child-bearing in China is limited to age group 20-34 years old, 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 getting 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 timely birth dose vaccination at paricular OT coverage level	**L(1-*F*I)**	1.41453	1.680705	1.17117	0.620568
N.	Percent risk of becoming chronic carrier of HBV due to horizontal transmission after birth to age 5 in the absence of vaccination (Ch)	**(B*0.75)-(L/100)**	0.0398	0.037518	0.042081	0.037518
O.	Children becoming chronic cariers 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	**O*(1-G*J)**	0.77	0.72	0.81	0.37
Q.	**HepB0% required to reach less than 2% goal at a particular Hepb3 coverage**	**[L+P-1.99)/(L*F)**	**0.60**	**0.73**	**0.50**	**0.46**
R.	**Hep3 coverage required to reach less than 2% goal at a particular OT coverage**	**[M+O-1.99)/(O*G)**	**0.90**	**0.97**	**0.85**	**0.67**
S.	**HepB0% required to reach less than 1% gaol at a particular**	**[L+P-0.99)/(L*F)**	**1.13**	**1.28**	**1.02**	**0.95**

	HepB3 coverage					
T.	**Hep3 coverage required to reach less than 1% goal at a particular OT coverage**	**[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 highest possible transmission rate of 90% among HBeAg positive women, and lowest documented efficacy of 70% of birth dose in preventing the chronic HBV infection), if the HepB3 coverage is 85%, 73% coverage with HepB0 is required for reaching the less than 2% goal in China. Alternatively at 50% HepB0 coverage, 97% coverage is needed with HepB3. In the least conservative scenario (lowest perinatal transmission rate of 70% and the highest vaccine efficacy of 90% at birth), at the 85% HepB3 coverage, the OT birth dose coverage required will be 50%.

For maintenance of certification status or for setting vaccination coverage targets to achieve the final regional goal of less than 1%, the countries should try to establish the vaccination coverage goals as required under the most conservative scenario.

Accuracy of the data: Modelling is just a modelling and can not 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 with reducing 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. However, modelling the impact of herd immunity will be too complex. Ignoring the effect of herd immunity will *over-estimate* the vaccination coverage required to meet an HBsAg seroprevalence goal.

Improvement in injection safety, socio-economic lifestyle: Both these factors will also lead to 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.