

Guidelines for verification of achievement of hepatitis B control target through immunization in the WHO South-East Asia Region

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Acronyms

cMYP	comprehensive multi-year plan
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HepB	hepatitis B vaccine
HepB1	first dose of hepatitis B vaccine
HepB3	third dose of hepatitis B vaccine
ITAG	Immunization Technical Advisory Group
Penta1	first dose of pentavalent vaccine
Penta3	third dose of pentavalent vaccine
RVAP	Regional Vaccine Action Plan, 2016-2020 (of World Health Organization's Regional Office for South-East Asia)
SEAR	South-East Asia Region (of World Health Organization)
SEA REP	South-East Asia Region Expert Panel for Verification of Hepatitis B Control
SEARO	World Health Organization's Regional Office for South-East Asia
WHO	World Health Organization

1. Background of hepatitis B control

Globally, 257 million people are living with chronic hepatitis B virus (HBV) infections. Of these, 39 million (15% of the global number) live in the World Health Organization (WHO) South-East Asia Region (SEAR)¹, representing 2% of the Region's total population. It is estimated that 296 000 people die annually of hepatitis B in the Region². Most of these deaths are from liver cirrhosis and liver cancer, the consequences of chronic HBV infection.

Prevention of HBV infections relies on (i) three-dose hepatitis B vaccine (HepB) for infants, (ii) prevention of mother-to-child transmission of HBV with birth dose vaccine and other approaches which will be adopted by the Region in the near future, such as routine testing and treatment of pregnant women, (iii) blood, injection and surgical safety, and (iv) harm reduction for people who inject drugs. Prevention works and is documented as being cost-effective. There is a new generation of highly effective medicines available for treating chronic HBV infections and lifelong treatment can suppress HBV replication. Economic analysis in several countries indicates that population-based approaches to test for and treat HBV would also be cost-effective.

1.1 Hepatitis B control through immunization

The risk of progression to chronic HBV infection is inversely related to the age at infection. Chronic HBV infection develops in 90% of infants infected before 1 year of age, in 25-50% of children infected at 1-5 years of age and in 5-10% of persons infected after 5 years of age.³ Hepatitis B can be prevented by a safe and effective vaccine. Over 95% of healthy infants develop protective antibody after the primary series of the vaccine and remain protected against the virus for at least 30 years.³ Since perinatal or early postnatal transmission is the most important source of chronic HBV infection, a birth dose of HepB should be given as soon as possible after birth, ideally within 24 hours. Although effectiveness declines progressively in the days after birth, a late birth dose given 7 or more days after birth can still be effective in preventing horizontal transmission and therefore remains beneficial. WHO recommends that all infants receive the late birth dose during the first contact with healthcare providers at any time up to the time of the next dose of the primary schedule. The birth dose should be followed by 2 or 3 additional HepB doses to complete the primary series.³

¹ World Health Organization, 2017. Global and Country Estimates of immunization coverage and chronic HBV infection. Available at <http://whohbsagdashboard.com/#global-strategies>

² World Health Organization, 2018. Global Health Estimates (2016). Available at http://www.who.int/healthinfo/global_burden_disease/en/

³ World Health Organization, 2017. Hepatitis B vaccine position paper. Available at <http://apps.who.int/iris/bitstream/handle/10665/255841/WER9227.pdf?sequence=1>

All countries in the South-East Asia Region have included HepB in the national immunization schedule. Eight countries have introduced the HepB birth dose.

Country	HepB given at	HepB3 introduction (year)	HepB birth dose introduction (year)
Thailand	B, 2, 4, 6 months	1992	1992
Maldives	B, 2, 4, 6 months	1993	1993
Bangladesh	6, 10, 14 weeks	2003	No birth dose
Bhutan	B, 6, 10, 14 weeks	1997	2011
Indonesia	B, 2, 3, 4, 18 months	1997	2003
Nepal	6, 10, 14 weeks	2002	No birth dose
DPR Korea	B, 6, 10, 14 weeks	2003	2003
Myanmar	B, 2, 4, 6 months	2003	2016
Sri Lanka	2, 4, 6 months	2003	No birth dose
Timor-Leste	B, 6, 10, 14 weeks	2007	2016
India	B, 6, 10, 14 weeks	2007	2007
All countries use pentavalent vaccine (diphtheria-tetanus-pertussis (DTP)-Haemophilus influenza b (Hib)- HepB), except Thailand which uses DTP-HepB and Timor-Leste which uses DTP-Hib-HepB-inactivated polio vaccine (IPV). B: birth; HepB3: third dose of HepB			
Source: WHO and UNICEF JRF 2018			

The prevalence of chronic hepatitis B among children is expected to be substantially reduced in countries that have maintained high hepatitis B vaccination coverage.

Since 1992, a series of WHO resolutions on hepatitis B prevention have been adopted by the World Health Assembly. These resolutions urge Member States to include HepB in their national immunization schedules and to scale up the effort to prevent and treat viral hepatitis. In 2015, the 2030 Agenda for Sustainable Development was adopted by the United Nations General Assembly. This Agenda included combating hepatitis as a development priority under Target 3.3 of the 2030 Agenda for Sustainable Development.⁴ In 2016, the World Health Assembly passed a resolution to adopt the Global Health Sector Strategy on Viral Hepatitis, 2016-2021, which set the goal of eliminating viral hepatitis as a public health threat by 2030 by targeting a prevalence of less than 0.1% among children by that year.⁵ The Strategy organizes priority actions under five strategic directions; (i) information for focused action; (ii) interventions for impact; (iii) delivering for equity; (iv) financing for sustainability and (v) innovation for acceleration.

Among its impact and service coverage targets, a key measure of hepatitis B control in the Global Health Sector Strategy on Viral Hepatitis, 2016-2021 is

⁴ United Nations General Assembly resolution A/RES/70/1 – Transforming our world: the 2030 Agenda for Sustainable Development. Available at http://www.un.org/ga/search/view_doc.asp?symbol=A/RES/70/1&Lang=E.

⁵ World Health Organization. Global Health Sector Strategy on Viral Hepatitis, 2016-2020. 2016. Available at <http://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/>

reaching a prevalence of $\leq 1\%$ of hepatitis B surface antigen (HBsAg) among children aged 5 years in 2020 as a proxy to the 30% reduction in incidence aimed at in the Strategy. This target is also reflected in the Regional Action Plan for Viral Hepatitis in South-East Asia, 2016–2021 (endorsed by the Regional Committee in 2017) and recommended in 2016 by the SEAR Immunization Technical Advisory Group (ITAG)⁶. Strategic objectives and a monitoring framework are included in the Regional Vaccine Action Plan 2016-2020 (RVAP)⁷.

The main strategic objectives in RVAP, to accelerate hepatitis B control, articulated in Goal 6, are:

- Achieving high levels of the third dose of HepB (HepB3) coverage among children through routine immunization.

Strengthening routine immunization systems to ensure that high levels of HepB3 coverage in children aged < 1 year is the most important strategy for controlling hepatitis B. Based on the estimated burden of disease, modelling suggests that a minimum HepB3 coverage of 90% is needed to reduce chronic infection to $< 1\%$ among children. Since all of the SEAR countries use combination vaccines, this coverage is in line with the Global Vaccine Action Plan indicator of achieving coverage with the third dose diphtheria-tetanus-pertussis containing vaccine $> 90\%$.⁸

- Timely administration of the first dose of HepB within 24 hours of birth (birth dose).

In countries with intermediate (2-7%) and high endemicity ($\geq 8\%$) of chronic hepatitis B, perinatal transmission contributes to the majority of chronic infections. Post-exposure prophylaxis with HepB birth dose dramatically reduces the risk of infection. Receipt of the first dose beginning ≤ 24 hours after birth among infants of highly infectious mothers (those positive for hepatitis B e antigen) in a three- or four-dose schedule provides higher protection (70-95%) than if the first dose is given after one week (50-57%)⁹. Consequently, delivery of the HepB birth dose within 24 hours of birth for all newborn infants is the preferred strategy.

- Catch-up immunization of older children.

The strategy of catch-up immunization of older children is recommended for those countries which have already demonstrated sustained high vaccination coverage among infants through routine immunization,

⁶ World Health Organization, 2016. WHO South East Asia Regional Immunization Technical Advisory Group (SEAR-ITAG). Report of the Seventh Meeting SEAR-ITAG. New Delhi, India, 7-10 June 2016 Available at http://www.searo.who.int/immunization/documents/sear_itag_2016.pdf

⁷ World Health Organization, 2017. South-East Asia Regional Vaccine Action Plan 2016-2020. Available at <http://apps.who.int/iris/handle/10665/272397>

⁸ World Health Organization. Global Vaccine Action Plan 2011-2020. Available at https://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/

⁹ Accessed at www.cdc.gov/vaccines/pubs/pinkbok/hepB.html

including timely birth dose, and which have additional financial and human resources for enhanced hepatitis B control.

➤ Immunization of high risk adult population groups.

The immunization of high risk adult population groups should only be prioritized after infant routine immunization and catch-up/patch-up campaigns for older children have reached high coverage. Vaccination of high risk adults will not have a significant impact on burden of chronic hepatitis B in the population because, although incidence of acute symptomatic hepatitis B is highest among adolescents and adults, the risk of developing chronic HBV infection and subsequent liver disease is low among adults compared to that among infants and children.

The WHO Regional Office for South-East Asia supports countries in implementing the RVAP strategies and monitors the progress towards hepatitis B control targets. The SEAR ITAG advises on operational aspects of strengthening hepatitis B control and reviews the achievement of control targets by Member States and at the Regional level.

The achievement of the hepatitis B control target in 2020 is primarily assessed by hepatitis B prevalence among children measured through serologic surveys and immunization coverage. WHO has published technical guidelines to support countries in conducting nationally representative serologic surveys to evaluate the impact of hepatitis B immunization programmes^{10 11}. A reference manual on conducting national cluster surveys which provides guidance on designing and implementing national surveys was published in 2018.¹²

By the end of 2018, national hepatitis B serologic surveys to assess the impact of immunization following vaccine introduction had been conducted in Bangladesh, Bhutan, Nepal and Thailand in the WHO SEAR.

This document provides overall guidance on verifying a country's achievement of the hepatitis B control target through immunization. Data and indicators to be used for verification and the verification procedures to be followed are described in the following sections as well as the actual process to be followed. Tools to support the verification process are annexed to this document.

2. Criteria for verification and indicators

The main evidence needed for verification is low prevalence of chronic hepatitis B among vaccinated cohorts of children and proof of high and sustained HepB immunization coverage in the population. These findings can be demonstrated in the following ways and are considered essential criteria for verification:

¹⁰ World Health Organization, 2011. Documenting the impact of Hepatitis B immunization: best practices for conducting a serosurvey. Available at <http://apps.who.int/iris/handle/10665/70808>.

¹¹ World Health Organization, 2011. Sample design and procedures for hepatitis B immunization surveys: a companion to the WHO cluster survey reference manual.

¹² World Health Organization. 2018. Vaccination Cluster Survey: Reference Manual. Available at http://www.who.int/immunization/documents/who_ivb_18.09/en/

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- Prevalence of HBsAg among children: at least one source of nationally representative data from children 5 years of age or older born after the nationwide implementation of universal hepatitis B infant immunization.
 - Coverage of HepB birth dose (where applicable) and HepB3 at national and subnational levels for at least 5 years with coverage levels in line with the RVAP targets. Additional data may be required to review coverage before and after impact assessment surveys.

Additional supplementary information may be required as multiple lines of evidence will be considered and should be congruent in indicating that the target has been achieved.

- Other sources of information should be provided, if measures have been implemented and data are available:
 - Antenatal screening of HBV and prophylaxis for infants born to HBsAg-positive mothers (especially for countries that have not introduced the birth dose). Relevant information may include:
 - National policies and guidance on antenatal HBV screening.
 - Coverage of antenatal screening and prevalence of HBsAg among pregnant women.
 - Timely birth dose coverage among infants born to HBsAg-positive mothers.
 - Availability and coverage of hepatitis B immunoglobulin for infants born to HBsAg-positive mothers.
 - Data from post-vaccination serologic testing.
 - Surveillance for acute hepatitis, especially among children.

2.1 Seroprevalence of HBsAg among cohorts born after national implementation of hepatitis B vaccination

Surveillance based on symptomatic disease provides important information about trends in acute infections as well as risk factors for infection. However, most acute hepatitis B cases, especially those in children, are asymptomatic, which limits the use of surveillance data to estimate disease burden. Serosurveys are therefore necessary to understand the prevalence of infection and to document and plan for effective prevention methods. One of the key requirements for validation will be the analysis of seroprevalence rates of HBV infection markers, and every country should undertake at least one seroprevalence survey of HBsAg based on a representative sampling of population cohorts born after the nationwide implementation of the universal hepatitis B immunization programme and after continuously sustaining high coverage with HepB3 (and HepB birth dose if available).

According to the WHO guidelines *Documenting the impact of hepatitis B immunization: best practices for conducting a serosurvey*,¹³ the most appropriate study design is a cross-sectional survey of a nationally representative population. To document HepB impact, countries should survey children ≥ 5 years of age who had an opportunity to be vaccinated and have passed through the period of highest risk of chronic infection. School-based sampling is the most appropriate if school attendance among the target age group for the survey is at least 95%. Otherwise, countries can use community-based sampling. WHO recommends complex survey sampling (for example, a stratified multistage cluster sample with random selection at each stage). This methodology is described in detail in the *Sample design and procedures for Hepatitis B immunization surveys: A companion to the WHO cluster survey reference manual*.¹⁴

Key thresholds for verification and precision are as follows:

- The point estimate of HBsAg seroprevalence should be less than 1%.
- The upper bound of the 95% confidence interval should not go beyond 1%.

Further criteria for a valid serosurvey for the purpose of verification are included in Annex 1.

2.2 Hepatitis B immunization coverage

Since the serosurvey measures the prevalence of chronic hepatitis B among particular birth cohorts that were included in the survey, it can be assumed that, with sustained hepatitis B immunization coverage, younger cohorts will not have higher HBsAg prevalence than the surveyed older cohorts. Countries should provide data showing HepB3 and HepB birth dose coverage.

Immunization coverage data will be analyzed at national, provincial and district levels, as well as for specific sub-populations whose infant cohorts may not be reached by routine immunization. If evidence suggests that certain communities have a high prevalence of chronic hepatitis B, for example certain ethnic groups, it is highly desirable to have information on immunization coverage in these communities.

Immunization coverage data from administrative sources should be corroborated by data from surveys, for example, immunization coverage surveys, Demographic Health Surveys, or Multiple Indicator Cluster Surveys. Countries could also supplement information on data quality from data quality assessments or audits, or immunization programme reviews.

With immunization as the main and most cost-effective prevention strategy in hepatitis B control, several immunization targets have been endorsed by Member

¹³ World Health Organization (2011). *Documenting the impact of immunization: best practices for conducting a serosurvey*. Available at <https://www.technet-21.org/en/library/main/5089-documenting-the-impact-of-hepatitis-b-immunization-best-practices-for-conducting-a-serosurvey>

¹⁴ World Health Organization. (2011). *Sample design and procedures for Hepatitis B immunization surveys: a companion to the WHO cluster survey reference manual*. World Health Organization. Available at <https://apps.who.int/iris/handle/10665/70876>

States in South-East Asia. The Global Vaccine Action Plan and the RVAP set the target of reaching 90% national coverage and 80% coverage in every district for all vaccines in the national immunization programme^{15 16}. Additionally, the target of reaching 90% coverage with HepB3 and the HepB birth dose to prevent mother-to-child transmission by 2030 has been adopted (among other approaches) in the Global Health Sector Strategy on Viral Hepatitis 2016-2021. The Regional Viral Hepatitis Action Plan has set as targets that, by 2020, all Member States that have the policy of a HepB birth dose have reached 90% coverage with it and 95% coverage with HepB.¹⁷ For verification purposes the targets of the RVAP will be applied.

2.3 Other sources of information if available

Antenatal screening for HBV: WHO recommends that all countries include a HepB birth dose in the national immunization schedule. For countries that have not introduced a universal birth dose, it is recommended to provide evidence that high coverage of antenatal screening of HBV and high coverage with a HepB birth dose among infants born to HBsAg-positive mothers have been achieved. Countries should also provide information on national policies or guidance on antenatal screening of HBV and prevention of perinatal HBV transmission, if hepatitis B immunoglobulin is available and the coverage of hepatitis B immunoglobulin. Countries may also supplement this information with studies on post-vaccination serologic testing of infants born to HBsAg-positive mothers.

Surveillance for acute hepatitis: In paediatric cohorts, surveillance for acute infection is not able to detect the impact of childhood immunization programmes because children infected with HBV are frequently asymptomatic. However, data from this type of surveillance can guide vaccination strategies that a country may be considering for high risk adult populations.

3. The verification procedure

3.1 Constitution of the verification panel

The Regional Director of the WHO SEAR appoints a panel of independent experts with expertise in hepatitis B control, epidemiology, immunization, surveys, statistics and other relevant fields, working in different institutions in various countries. Current membership, terms of reference, conflict of interest and confidentiality policies are outlined in Annex 5. Panel members serve on an honorary basis in the capacity of a WHO temporary advisor. Upon receiving a request from a country for verification, the WHO Secretariat to the SEAR Expert Panel for Verification of

¹⁵ World Health Organization. Global Vaccine Action Plan 2011-2020. Available at http://www.who.int/immunization/global_vaccine_action_plan/en/

¹⁷ WHO Regional Office for South-East Asia. 2017. Regional Action Plan for Viral Hepatitis in South-East Asia: 2016-2021. Available at <http://www.searo.who.int/entity/hepatitis/viral-hepatitis-action-plan.pdf?ua=1>

Hepatitis B Control (SEA REP) will establish a Regional verification team consisting of one chair and 2 other members from the SEA REP. The chair will coordinate communication between team members and will summarize the recommendations from the team. All aspects of the SEA REP will be supported by the WHO Secretariat in the Immunization and Vaccine Development Unit of WHO's Regional Office for South-East Asia.

3.2 Initiation of verification

Once confident that the target has been achieved based on an internal evaluation, the country can request initiation of the Regional verification process. The country may form an internal team to assemble and review the serosurvey and immunization coverage data as well as other information. After this internal assessment, the country may submit a formal request for verification accompanied by the completed verification data package and supporting documents, including a report, to WHO's Regional Office for South-East Asia. Please see Annex 2 for instructions on preparing a verification data package and Annex 3 for the template for the report.

3.3 Verification process

The Regional verification team will perform a detailed desk review of the data submitted in the verification package. The desk review can be done from a distance by members of the verification team working at their places of residence. Discussions will be carried out by e-mail or teleconference. A visit to the country requesting verification or to the WHO office may be undertaken if necessary. The verification team may contact the country's focal person for verification if additional information or clarification is needed.

The Regional verification team will examine evidence in each country on a case-by-case basis following the criteria and indicators laid out in this document. Some criteria may be adjusted by the panel taking into account the country context, for example, subnational variations of hepatitis B epidemiology, other interventions to reduce the risk of HBV infection and demographic characteristics. The review team may also take additional information into consideration, including information derived from its own literature review. A tool for evaluating country verification data and an outline of reference points for evaluation criteria are included in Annex 4.

The Regional verification team will reach its conclusion by consensus and present this conclusion to the SEA REP for a final conclusion. The SEA REP will submit a report to the Regional Director detailing whether the country has reached the target of reducing chronic hepatitis B prevalence among children to $\leq 1\%$, with justification for its finding.

3.4 Report on verification results

The Regional Director will send an official letter to the country informing the country of the verification decision. The WHO Regional Office will report to the ITAG and the WHO Regional Committee as to the countries that have been verified

and may feature these achievements in a news release or other form of communication.

3.5 Maintaining verification status

If a country has been verified to have achieved the target of $\leq 1\%$ HBsAg in children 5 years of age or older, conclusions as to whether verification status has been maintained should be made by the national immunization advisory group based on review of the HepB coverage data submitted each year in the WHO/United Nations Children's Fund Joint Reporting Forms on Immunization and the WHO SEARO IVD Annual EPI Reporting Form and reported to the ITAG. Every 3 to 5 years such data review should be also be performed by the SEA REP.

3.6 Future updating of the verification guidelines

While this version of the guidelines has been established with inputs from SEA REP members and presented to the ITAG for endorsement, there may be future need for reconsideration and modifications based on developments in hepatitis B control. Proposed revisions of the guidelines will require approval by the SEA REP.

Annex 1: Criteria for a valid Hepatitis B Surface Antigen (HBsAg) serosurvey for the purpose of verification

Representativeness: the survey should be nationally representative. Ideally the survey should be a household-based survey using probability sampling. Sample methods which may introduce bias should not be considered for verification although convenience samples or hospital-based samples may be considered as part of pooled evidence. If school enrollment is almost universal (i.e., >95%), conducting a school-based survey may be logistically efficient and satisfies requirements. If school enrollment is not high enough, a household-based survey is recommended as it will ensure that all children in the eligible age group have a chance to be selected. Convenience samples are generally not accepted as the main evidence for verification. However, if the country has strong evidence showing representativeness of the data and is able to supplement the survey with other evidence that very low prevalence has been achieved, the country may be considered by the verification panel. In some situations, especially when no national but several subnational surveys have been conducted, evidence other than a nationally representative survey may be taken into consideration.

Precision: the survey should have a sample that is large enough to generate the estimate of the 95% confidence interval with a total width narrower than 1% (i.e., a half width of 0.5%). When using methods that generate asymmetrical confidence intervals,¹⁸ it is acceptable that the upper limit of the confidence interval be slightly greater than +0.5%, and the lower limit of the confidence interval be slightly narrower than -0.5%, with the total width within 1%.

Age group: the target age group for the survey should be 5 years of age and older, as children in this age group have passed through the period when the risk of infection is the highest. Testing children under the age of 5 years may underestimate the prevalence of chronic hepatitis B, as some children may still be infected and develop chronic hepatitis B as they grow older.

Seromarkers: HBsAg is the seromarker indicating chronic hepatitis B virus (HBV) infection and the testing of HBsAg is required for verification. While clinical diagnosis of chronic hepatitis B is made with two positive HBsAg test results at least 6 months apart, in cross-sectional surveys (especially surveys among children), the prevalence of chronic hepatitis B can be defined as the prevalence of HBsAg-positive cases at a single point in time, as most children develop chronic hepatitis B after infection. Testing of antibodies to HBsAg has been used to provide additional information on the percentage of children immune to HBV and should be considered if available. The prevalence of antibodies to HBsAg should be interpreted with caution as the titers of antibodies to HBsAg among vaccinated children may drop below detectable levels over the years, but children remain protected against HBV through anamnestic responses. Antibodies to hepatitis B core

¹⁸ The Wilson confidence interval with continuity correction is recommended for sample size calculation, as it has better probability coverage than the Wald confidence interval when the prevalence is below 1%. A program written in R has been developed for sample size calculation that can be obtained from the WHO Regional Office for South-East Asia. The survey data should be analyzed using methods that account for the complex survey design.

antigen can be included in the testing as an indication of past infections. Further information is available in: *Epidemiology and Prevention of Vaccine-Preventable Diseases - The Pink Book: Course Textbook - 13th Edition (2015)*.⁸

Ethical standards: the survey protocol should be reviewed by an ethics review committee or a research review committee prior to survey implementation. If the survey receives funding from the World Health Organization (WHO), review by the organization's Research Ethics Review Committee is required. The survey should be implemented in compliance with the approved protocol.

Quality assurance of laboratory procedures: countries should be able to implement proper quality control and quality assurance of laboratory procedures. WHO has a prequalified laboratory-based enzyme immunoassay as well as rapid tests for HBsAg. The list of WHO-prequalified tests can be found on the WHO's website.¹⁹ If countries choose to use other assays, the sensitivity and specificity of these assays should be evaluated. WHO may facilitate proficiency testing of such assays or re-testing of some of the specimens. Surveys using rapid tests with established sensitivity and specificity are acceptable for verification. Rapid tests offer several advantages, including lower costs, minimal or no need for laboratory and cold chain infrastructure, and small specimen volume requirements (only a few drops of blood). Some rapid tests may be used with capillary blood collected by finger stick, thus avoiding venepuncture. Please refer to the instructions of the manufacturers for acceptable specimen types and specimen volumes. As of July 2018, two rapid tests have been prequalified by WHO.

¹⁹ WHO list of prequalified in vitro diagnostic products. Available at http://www.who.int/diagnostics_laboratory/evaluations/PQ_list/en/

Annex 2: Instructions for countries that request verification of achievement of the target of hepatitis B control through immunization

Steps	Details
1. Prepare verification package	<p>A. Complete verification report (Annex 3)</p> <p>B. Attach data or graph on national and subnational hepatitis B vaccination coverage (third dose of hepatitis B vaccine (HepB3) and hepatitis B vaccine (HepB) birth dose, ideally since the start of the programme but at least for the past 5 years. Please specify if HepB birth dose is given within 24 hours of birth, or within and after 24 hours of birth, and provide data on both, as applicable.</p> <p>C. Attach a report of the serologic survey on the prevalence of chronic hepatitis B infection (indicated by hepatitis B surface antigen (HBsAg)) among children. This can be an existing published report or an unpublished report that details the following information:</p> <ul style="list-style-type: none"> i. Objectives of the serologic survey ii. Methods - including sampling methods (target ages, geographic areas and sample selection method), sample size assumptions (if sample size has been calculated) including design effect, time period of participant enrolment/specimen collection, exclusion criteria if any, laboratory test used, testing algorithm and quality assurance procedures. If the survey is school-based, please include the percentage of children attending school. iii. Results - including HBsAg prevalence and confidence intervals by age and, if possible, by gender, geographic region, race/ethnicity, urban/rural, socioeconomic status and vaccination status including </ ≥24 hours birth dose. The percentage of invalid tests and the survey response rate should also be included. If possible, include comparison of demographic characteristics between individuals refusing to participate and those participating in the study. iv. Discussion - including whether the survey represents the vaccinated cohorts of the country, especially with regard to possible groups at high risk of infection (e.g., certain minority groups) and study limitations. <p>D. Attach a report – if data are available - of antenatal HBV screening coverage and HBsAg prevalence. This is particularly important if the country has not introduced the birth dose for all infants.</p> <p>E. Attach any other supporting documents that the country would like to submit, including ones reporting optional data.</p> <p>F. Discuss limitations of the data as applicable.</p>

<p>2. Initiate verification</p>	<p>A. Contact the Immunization and Vaccine Development Unit of the WHO Regional Office for South-East Asia to assist with the process of verification.</p> <p>B. Send a letter from the Ministry of Health to the Regional Director for the WHO South-East Asia Region (SEAR) which includes the following:</p> <ul style="list-style-type: none"> i. a statement of interest in initiating the verification process; ii. the name and contact information for the person who will be the country's contact person during the verification process <p>The report to document verification (see Annex 3) and supporting documents provided to be considered for verification of achievement of regional hepatitis B control goals should be enclosed.</p>
<p>3. Assist review team, if needed</p>	<ul style="list-style-type: none"> i. A team of 3 experts from the regional verification panel will be convened to review the verification package. During this process the contact person should be available for any clarification that may be requested by the panel. ii. The review team should be in touch with the country contact person within 4 weeks at the latest from the time of receipt of the letter with a request for clarification, if this is needed. iii. A letter will be written from the SEA REP to the Regional Director for the WHO SEAR. The Regional Director will inform the country of the panel's decision as per established protocols.

Annex 3: Report to document verification of achievement of Regional hepatitis B control target through immunization

Country: _____

Date: _____

Contact Name and Affiliation: _____

E-mail Address: _____ Telephone No: _____

Section I. Background on country, immunization systems, policies and other control measures for hepatitis B

1. Live births: _____ in year _____ (Source: _____)
2. Percentage of births in health facilities: _____ % (Source: _____)
3. Percentage of births attended by a skilled practitioner: _____ % (Source: _____)
4. Primary school enrolment: _____ % (Source: _____)
5. Do you provide universal hepatitis B vaccination? Yes No
6. If yes, what type of universal hepatitis B vaccination? [*Multiple answers possible*]
 - All children <1 year of age receive 3 doses of hepatitis B vaccine (HepB)
 - All newborns receive birth dose of HepB followed by 2-3 additional doses
 - Birth dose administered only to newborns who are at high risk of infection
Please specify which newborns are considered to be at high risk:

 - Other Please specify: _____

7. Universal hepatitis B vaccination schedule history:

Schedules	Year	Nationwide (yes/no)	Age birth dose	Age 1 st dose	Age 2 nd dose	Age 3 rd dose	Age 4 th dose (if applicable)
First introduced							
Revision 1							
Revision 2							

8. Specify recommended timing of HepB birth dose in national policy (*for countries that administer birth dose to all newborns*): <24 hours after birth 1-7 days after birth other not defined

9. Catch-up hepatitis B vaccination: Yes No

If yes, indicate years and age groups that received catch-up vaccination (add a page if needed):

Year(s): _____ Age(s): _____ # targeted: _____ Coverage: _____ (%)

Year(s): _____ Age(s): _____ # targeted: _____ Coverage: _____ (%)

Section II. Hepatitis B immunization coverage data

10. Please provide national vaccination coverage data for at least the last 5 years (complete table with 'n.a.' if data are not available):

Year	HepB birth dose coverage ¹ (%)		First dose of HepB (HepB1) / First dose of pentavalent vaccine	Third dose of HepB (HepB3) / Third dose of pentavalent vaccine	Indicate data source (World Health Organization/United Nations Children's Fund, administrative)	HepB3 / Penta3 coverage survey ⁴ (%)
	Timely ²	Total ³				

			(Penta1) coverage (%)	(Penta3) coverage(%)		

¹ Only for countries that implement universal newborn vaccination

² Timely HepB birth dose is defined as receipt within 24 hours of birth

³ Total HepB birth dose is defined as any HepB birth dose administered

⁴ Include report if coverage survey data is available (Coverage Evaluation Surveys, Multi Indicator Cluster Surveys, Demographic Health Surveys etc)

11. If national coverage figures are <90% for particular year(s), please describe reason(s) below or provide report:

12. Are there known groups of people or geographic areas with low coverage? If yes, please list these below and provide the plan for improving HepB coverage in these groups or areas:

13. Provide subnational data on HepB birth dose¹ and HepB3 coverage data for the last 3-5 years (if available, data can be provided in another format):

% Districts in coverage brackets	Year:		Year:		Year:		Year:		Year:	
	HepB birth dose ¹	HepB3	HepB birth dose ¹	HepB3	HepB birth dose ¹	HepB3	HepB birth dose ¹	HepB3	HepB birth dose ¹	HepB3
<50%										
50-79%										
80-89%										
90-94%										
≥95%										
Unknown										

¹ Only for countries that implement universal newborn vaccination

14. Alternatively, attach provincial and district-level administrative or official coverage of HepB birth dose, HepB1 and HepB3 from the past 3-5 years as in Annual EPI Reporting Form Table 2A and 2B.

15. If subnational coverage figures are <80% for a particular year(s), please describe reason(s) below or provide a report providing justification:

Section III. Hepatitis B vaccination of high risk groups

16. Hepatitis B vaccination provided to health care workers? Yes No

17. Hepatitis B vaccination provided to high risk groups (e.g., people who inject drugs, sex workers, etc.) Yes No

If yes, specify which risk groups, and, if possible, service delivery model:

**Section IV. This section refers to optional information which can be provided if such activities are implemented and data available
Screening of pregnant women for hepatitis B surface antigen (HBsAg) and prevention of perinatal infection among infants who are at high risk of infection**

18. Do you implement universal screening of pregnant women for HBsAg? Yes No

a. If no, do you implement selective screening? Yes No

- If yes, specify: _____

19. Data for screening of pregnant women for at least 3 years (if available, data can be provided in another format):

Year	Total number of pregnant women	Total number of pregnant women screened for HBsAg during pregnancy	Total number of pregnant women that tested positive for HBsAg

20. **For countries that do not implement universal newborn vaccination:** data for hepatitis B vaccination of newborns who are at high risk of infection for at least 3 years (if available, data can be provided in another format):

Year	Timely HepB birth dose coverage in newborns who are at high risk of infection (%)	Completed vaccination (HepB3) coverage among those children (%)	Testing for HBsAg 1-2 months after completion of hepatitis B vaccination series ¹ (% HBsAg positive)

¹ If available

21. Additional services routinely provided to prevent perinatal transmission of hepatitis B virus (check all that apply):

Hepatitis B immunoglobulin for newborns who are at high risk of infection

Please specify newborns at high risk: _____

Antiviral treatment of pregnant women

Please specify what pregnant women receive treatment: _____

Other, specify: _____

No additional activities

22. Any other information considered relevant for the verification review; this may also include information on other hepatitis B control strategies such as measures to ensure blood and injection safety

Section V. HBsAg serosurvey data among cohorts born after introduction of universal hepatitis B vaccination (SURVEY REPORT REQUIRED). Please complete this section for each survey for which the data are submitted and provide the relevant report(s).

23. Survey year: _____

24. Geographic scope of the survey: National Subnational Other, specify: _____

25. Sampling base: General population/community Healthcare centers Schools
Other, specify: _____

26. Survey design: Probability sample: simple random Probability sample: cluster Classification survey
 Convenience sample Other, specify: _____

27. Hepatitis B virus markers: HBsAg only HBsAg with other tests* (*Provide algorithm and data*):

*Please also refer to WHO guidelines on hepatitis B and C testing, 2017

28. Test kit: Commercially available ELISA kit, specify brand: _____
 Point-of-care, rapid test, specify brand: _____
 Other, specify: _____

29. HBsAg prevalence estimate of survey age groups¹ born after introduction of universal hepatitis B vaccination²:

HBsAg point prevalence (%)	95% Confidence interval	Age group (years)	Sample size

¹ Please ensure that HBsAg point prevalence for children aged 5 years is included, if available.

² Table can be extended to report national and regional estimates if available.

30. Comment on findings, if any, in specified sub-populations:

31. Study limitations:

Section VI. Sustainability

32. Funding source for HepB (check all that apply):

- Self-funded (country) Gavi, the Vaccine Alliance Other (specify): _____

33. Please describe plans to sustain or improve hepatitis B immunization coverage:

(Optional: if preferable, attach the hepatitis B immunization section of the relevant multi-year plan or other strategic documents / plans)

Section VII. Expert consultation

Optional: Please list the areas of hepatitis B control for which the country would like the Regional expert panel on hepatitis B control verification to provide comments/recommendations:

Annex 4: Tool for evaluating country verification data

Country:

Date:

Programme categories	Programme elements	Not compliant/ weak	Compliant/ acceptable	Advanced	Suggestions and comments
Immunization systems and policy	Vaccination schedule				
	Timely birth dose				
	Nationwide vaccination programme				
	Vaccination coverage monitoring systems				
	Optional: Perinatal hepatitis programme	X			
	Optional: Catch-up strategies				
	Optional: High risk groups				
	Summary comments on systems and policy				
Coverage	National HepB3 coverage last 5 years				
	Timely birth dose coverage last 5 years (where applicable)				
	National HepB1 vs. HepB3 coverage (drop out)				

	District HepB3 coverage last 3-5 years				
	Quality of coverage data				
	Summary comments on coverage				
Serologic survey	Conducted after 5 years of high coverage				
	Relevant age groups targeted				
	Population sampled				
	Sampling design				
	Laboratory quality assurance and procedures				
	Use of standard HBsAg test kit				
	HBsAg prevalence =				
	Estimate of precision =				
	Summary comments on survey				
Sustainability	Plans for sustainability				
	Hepatitis B control in comprehensive multi-year plan (cMYP) (immunization)				

Conclusion on 2020 control target:

Observations and recommendations (related to verification):

Observations and recommendations on technical programme aspects including sustainability

To national programme:

To ITAG:

Outline of reference points for evaluation criteria

Programme categories	Programme elements	Not compliant / weak	Compliant / acceptable	Advanced
Immunization systems and policies	Vaccination schedule	Unacceptable schedule based on World Health Organization (WHO) hepatitis B vaccine (HepB) vaccine position paper ²⁰	Infancy schedule based on WHO HepB vaccine position paper	Infancy schedule plus other immunization strategies
	Timely birth dose	Birth dose >24 hours after birth or no birth dose	Documented birth dose within 24 hours if birth	Birth dose integration with Maternal Child Health visit/health education
	Nationwide vaccination programme	HepB programme starting < 5 years ago and no birth dose	HepB programme for ≥5 years and (where in national schedule) birth dose for ≤3 years	HepB and (where in national schedule) birth dose programme ≥5 years
	Vaccination coverage monitoring systems	No monitoring system	HepB3 and (where in national schedule) birth dose coverage monitored at national and district level	HepB3 and (where in national schedule) birth dose coverage monitored at district level by gender and risk populations
	Optional: Catch-up vaccination strategies	Review and comment		
	Optional: Vaccinating high risk groups	Review and comment		
	Optional: Perinatal hepatitis B programme (e.g., screening, offering hepatitis B immunoglobulin, treatment)	Review and comment		
Immunization coverage	National HepB3 coverage last 5 years	Consistent HepB3 coverage <90% for the last 5 years	Consistent HepB3 coverage ≥90% for last 5 years	Consistent HepB3 ≥95% for the last 5 years

	National timely HepB birth dose coverage last 3 years	Consistent coverage of birth dose <90% for last 3 years	Consistent birth dose coverage between 90 and 95% for last 3 years	Consistent birth dose $\geq 95\%$ for last 3 years
	District HepB3 coverage	<80% HepB3 coverage in all districts	$\geq 80\%$ HepB3 coverage in all districts	$\geq 90\%$ HepB3 coverage in all districts
	District HepB birth dose coverage	<80% HepB birth dose coverage in all districts	$\geq 80\%$ HepB birth dose coverage in all districts	$\geq 90\%$ HepB birth dose coverage in all districts
	National HepB1 vs. HepB3 coverage	$\geq 5\%$ dropout between HepB1 and HepB3	<5% dropout between HepB1 and HepB3	<3% dropout between HepB1 and HepB3
	Quality of coverage data	Administrative coverage data only	Administrative and coverage survey data available but not completely consistent	Administrative and coverage survey data available and consistent
Serological surveys	Time at which survey conducted relative to HepB coverage	Survey before 5 years of acceptable coverage	Survey after 5 years of acceptable coverage	Multiple surveys conducted after 5 years of acceptable coverage
	Relevant age groups targeted	Children <5 years of age	Children ≥ 5 years of age who were born during period of national vaccination	Survey includes multiple cohorts of children aged ≥ 5 years who were born during period of national vaccination
	Population sampled	Special population; not representative	Special population; documented to be representative (e.g., school survey with data showing high levels of school enrolment) -General population	Multiple surveys in general and special populations

²⁰ World Health Organization, 2017. Hepatitis B vaccine position paper. Available at <http://apps.who.int/iris/bitstream/handle/10665/255841/WER9227.pdf?sequence=1>

	Sampling design	-Convenience sample* -Probability sample, subnational	-Probability sample, nationally representative -Census with high response rate -Classification survey	Nationally representative probability sample, stratified by geographic area
	Laboratory quality assurance and procedures	-Laboratory quality assurance not reported -Laboratory procedures not well defined	-Key procedures described (e.g., storage, handling, retesting of specimens with equivocal test results) -Known reputable laboratory -Using rapid diagnostic tests that have been evaluated by a reputable laboratory	Plus external quality control (retesting of selected specimens at reference laboratory)
	Standard HBsAg test kit	Tests of unknown or low sensitivity	Tests of documented high sensitivity	WHO prequalified test kits
	Point prevalence of HBsAg	>1%	≤1%	<0.1% (elimination target)
	Estimate of precision	Upper bound of 95% CI >1.5%, or total width of the 95% CI wider than 1%	Upper bound of 95% CI <1%, or by statistical testing, the prevalence is significantly lower than 1% ($p < 0.05$)	
Sustainability	Sustainability of hepatitis B vaccination programme	No plans for sustainability	Programme sustainable based on implementation for past 5 years and plans in place to sustain or improve programme to achieve ≤1% goal	Vaccine self-funded; with national budget line item
		Hepatitis B control through immunization not specified in cMYP	cMYP has specific targets on hepatitis B control through immunization	cMYP crosslinked with national hepatitis B control strategy

*Convenience samples are generally not acceptable for verification; however, if a country can show with strong evidence that the sample is representative, these data will be considered.

Annex 5: World Health Organization (WHO) South-East Asia Regional Expert Panel for Verification of Hepatitis B Control (SEA REP)

Terms of reference

- 1) Conduct desk reviews of the information submitted by the countries for verification of the Regional hepatitis B control goal as per protocol established in the WHO Regional Office for South-East Asia (SEARO) *Guidelines for verification of achievement of hepatitis B control target in the South-East Asia Region*.
 - a. Conduct visits to countries and WHO offices, as required
- 2) Participate in technical meetings organized by WHO SEARO, as required.
- 3) Make recommendations to the Regional Director for the WHO South-East Asia Region as to whether the target of reducing chronic hepatitis B prevalence to <1% among children ≥ 5 years old has been achieved.

The Immunization and Vaccine Development Unit of WHO SEARO will serve as Secretariat to the SEA REP.

Conflicts of interest and confidentiality

- When the SEA REP is formed, and at the start of each SEA REP meeting, members should complete a WHO declaration of interest form and a confidentiality agreement.
- All members will be experts in areas relevant to hepatitis B control, serving in their own capacity, and will not represent the interests of a particular group or stakeholder. Members will refrain from promoting the policies and views and products of the organization/institution for which they work.
- All background documents, papers, presentations and reports presented to the SEA REP shall be treated as confidential and may not be publicly disclosed or used by members without prior approval.
- As a WHO advisory body, neither the SEA REP as a whole, nor individual members, can speak or act on behalf of WHO, or attend meetings on behalf of WHO without prior consent from the Immunization and Vaccine Development Unit of SEARO. SEA REP members may not share any information or make presentations on topics related to the SEA REP without prior approval by the Immunization and Vaccine Development Unit of SEARO.

- SEA REP members will not be remunerated for their participation in the SEA REP; however, SEARO will cover travel expenses related to participation in SEA REP meetings in accordance with WHO policy.

Operational procedures

- Interaction between the Secretariat, SEA REP members and the Chairperson of the SEA REP will take place throughout the year. In-person meetings of the SEA REP will be conducted on an as-needed basis and planning begin at least three months prior. Meetings may also be held by teleconference.
- Representatives of countries as well as external experts may be invited to attend meetings if and when appropriate.
- In preparation for each meeting, the agenda and necessary relevant documents will be circulated in advance.
- A summary report of the SEA REP meetings will be circulated for comments and endorsement within two weeks of the meeting. SEA REP members will be required to respond within two weeks after receiving the communication.
- When review teams have completed the desk data review for verification of the Regional hepatitis B control goal through immunization, the SEA REP will discuss and approve the report submitted by the review team either at a meeting or through exchange of e-mails or other means of communication.
- SEA REP members will not participate in the review team of their own country.

Current membership

Dr Supamit Chunsuttiwat (Chairperson)	Bangkok, Thailand	Ministry of Public Health
Professor Rakesh Aggarwal	Puducherry, India	Jawaharlal Institute of Postgraduate Medical Education and Research
Dr Chris Morgan	Melbourne, Australia	Burnet Institute
Professor Win Naing	Yangon, Myanmar	University of Medicine
Professor Arunasalam Pathmeswaran	Colombo, Sri Lanka	University of Kelaniya
Dr Md. Shamsuzzaman	Dhaka, Bangladesh	Ministry of Health and Family Welfare
Dr Dilip Sharma	Kathmandu, Nepal	National Academy of Medical Science
Dr Rania Tohme	Atlanta, USA	US Centers for Disease Control and Prevention

Annex 6: Template letter - invitation to verification

Subject: Invitation to initiate verification of achieving the Regional target of hepatitis B control through immunization

In 2016, the Regional Immunization Technical Advisory Group recommended the target of reducing chronic hepatitis B to $\leq 1\%$ among children by 2020 measured through prevalence of hepatitis B surface antigen among 5-year old children. This target is also used in the Global Health Sector Strategy on Viral Hepatitis, 2016-2021 (endorsed by the World Health Organization (WHO) World Health Assembly) as proxy to the 30% reduction in incidence aimed at in the Global Health Sector Strategy on Viral Hepatitis as well as in the Regional Action Plan for Viral Hepatitis in South-East Asia, 2016 – 2021 (endorsed by the Regional Committee in 2017).

The verification process consists of a desk review of country data by an independent panel of experts who will advise WHO regarding reaching the target. It is important to document the achievement of verification and gain further commitment to strengthen public health programmes. I would therefore greatly appreciate knowing your interest in initiating the verification process.

Verification consists of the following steps:

- first, the Ministry of Health submits a data and information package to WHO containing the information required for verification, including a request to initiate the process;
- second, WHO convenes a verification team composed of 3 independent experts who are members of the Regional verification panel;
- third, the verification team conducts a review of the data and information package, liaises with the Ministry of Health in case additional information is needed, and informs WHO of its recommendation. Further instructions are enclosed for your information.

If you have any questions, [SEARO-IVD contact person] is available to provide assistance.

(see WHO protocol for appropriate closing in formal letters)