Guidance for country validation of viral hepatitis elimination and path to elimination

World Health Organization

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Guidance for country validation of viral hepatitis elimination and path to elimination: technical report

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Acronyms and abbreviations

ALT	alanine aminotransferase
ANC	antenatal care
APRI	aspartate aminotransferase-to-platelet ratio index
ART	antiretroviral treatment
CDAF	Center for Disease Analysis Foundation
CHB	chronic hepatitis B
DAA	direct-acting antiviral (drug)
DBS	dried blood spot
EMTCT	elimination of mother-to-child transmission (of hepatitis B)
EPI	Expanded Programme on Immunization
EQA	external quality assessment
GHSS	Global Health Sector Strategy (on viral hepatitis)
GVAC	Global Validation Advisory Committee
GVS	Global Validation Secretariat
HB PMTCT	hepatitis B prevention of mother-to-child transmission
HBeAg	hepatitis B e antigen
HBIg	hepatitis B immunoglobulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCVAb	HCV antibody
HCVcAg	hepatitis C virus core antigen
HepB-BD	hepatitis B birth dose
HepB3	three doses of hepatitis B vaccine
IHME	Institute for Health Metrics and Evaluation
LDSS	low dead-space syringe
LMICs	low- and middle-income countries
MCH	maternal and child health

MSM	men who have sex with men
MTCT	mother-to-child transmission
NAT	nucleic acid test
NSP	needle–syringe programme
NTD	neglected tropical disease
NVS	National Validation Secretariat
NVTF	National Validation Task Force
OST	opioid substitution therapy
PMTCT	prevention of mother-to-child transmission
PTE	Path to Elimination
PVST	post-vaccination serological testing
PWID	people who inject drugs
RDT	rapid diagnostic test
RVC	Regional Validation Committee
RVS	Regional Validation Secretariat
RVTF	Regional Validation Task Force
SDGs	Sustainable Development Goals
SRA	stringent regulation authority
STI	sexually transmitted infection
SVR	sustained virological response
UHC	universal health coverage
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organization
WUENIC	WHO and UNICEF Estimates of National Immunization Coverage

Glossary

Attributable fraction (AF)	In this document, the surrogate measurement used to estimate the AF for HBV or HCV is the proportion of patients with decompensated cirrhosis or HCC that have been diagnosed with chronic hepatitis infection due to HBV or HCV, respectively. This surrogate measure is considered to be a close approximation to the AF because of the strength of the association between HBV/HCV infection and cirrhosis/hepatocellular carcinoma.
Chronic hepatitis B virus (HBV) infection	Persistence of hepatitis B surface antigen (HBsAg) for at least six months.
Chronic hepatitis C virus (HCV) infection	The presence of viraemia (HCV RNA or HCV core antigen [HCVcAg]) in association with positive serology for HCV antibody
Cirrhosis	An advanced stage of liver disease characterized by extensive liver scarring secondary to prolonged inflammation of the liver (F4 in the METAVIR scoring system)
Compensated cirrhosis	Cirrhosis without symptoms or signs of decompensation
Decompensated cirrhosis	Cirrhosis with symptoms and/or signs of decompensation. The main clinical features are portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy, and liver insufficiency (jaundice).
Elimination as a public health problem	As a result of deliberate efforts, reduction of disease incidence, prevalence, morbidity or mortality to a level below which the public health burden is considered negligible. The target level is generally defined globally by WHO. When reached, continued action is required to maintain the reduction. Documentation of independent confirmation of elimination as a public health problem is called “validation”.
Enzyme immunoassay (EIA)	Laboratory-based serological immunoassays that detect antibodies, antigens, or a combination of both
HBV DNA	HBV viral genomes that can be detected and quantified in serum by nucleic acid testing (NAT)
Hepatitis B control	Refers to attainment of regional HepB-BD and childhood vaccination programme threshold, impact assessment for seroprevalence goal and verification and monitoring by the relevant immunization technical advisory group(s) (TAG). It does not include maternal HBsAg screening, prophylaxis or treatment where eligible.

HCV antibody	Antibody to HCV, which can be detected in the blood usually within two to three months of HCV infection or exposure
HCV core antigen (HCVcAg)	Nucleocapsid peptide 22 of HCV, which is released into the plasma during viral assembly and can be detected from early on and throughout the course of infection
HCV RNA	HCV viral genomes that can be detected and quantified in serum by nucleic acid testing (NAT)
HCV sustained virological response (SVR)	Undetectable HCV RNA in the blood 12 weeks after treatment completion. SVR 12 is considered equivalent to a cure for HCV infection.
Hepatocellular carcinoma (HCC)	Primary cancer of the liver arising from the hepatocytes and may be a complication of chronic hepatitis B or C infection
Hepatitis B surface antigen (HBsAg)	HBV envelope protein often produced in excess and detectable in the blood in acute and chronic HBV infection
Hepatitis B e antigen (HBeAg)	Viral protein found in the high replicative phase of HBV. HBeAg is usually a marker of high levels of replication with wild-type virus but is not essential for viral replication.
Nucleic acid testing (NAT)	A molecular technology, for example, polymerase chain reaction (PCR) or nucleic acid sequence-based amplification (NASBA) that can detect very small quantities of viral nucleic acid (RNA or DNA), either qualitatively or quantitatively
Path to Elimination (PTE)	Path to Elimination (PTE): A set of criteria for recognition of substantial progress in countries towards EMTCT of HIV, syphilis and HBV, as well as towards HBV and/or HCV as a public health problem.
Rapid diagnostic test (RDT)	Immunoassays that detect antibodies or antigens and can give a result in less than 30 minutes. Most RDTs can be performed with capillary whole blood collected by finger-stick sampling, but now also oral fluid sampling.
Spontaneous viral clearance	Clearance of HCV infection without treatment
Steatotic liver disease (SLD)	Includes a range of liver disease processes, previously known as fatty liver disease including alcoholic and non-alcoholic fatty liver disease

Executive summary

In 2016, the World Health Assembly adopted the Global Health Sector Strategy (GHSS) 2016–2021 on viral hepatitis, which for the first time called for the elimination of viral hepatitis B and C infection as a public health problem by 2030 (defined as a 90% reduction in incidence [95% for HBV and 80% for HCV] and 65% reduction in mortality) compared to the 2015 baseline. The subsequent GHSS 2022–2030 brought together HIV, viral hepatitis and STI elimination goals in an integrated strategy and expanded the concept of elimination of viral hepatitis. The strategy defines absolute impact targets and programmatic targets for 2025 and 2030, and provides the foundation for criteria for country validation of elimination and path to elimination.

In 2021, WHO developed an interim guidance and a framework for countries and other stakeholders seeking validation of elimination of viral hepatitis as a public health problem, in the general population, with a specific focus on the hepatitis B virus (HBV) and the hepatitis C virus (HCV). The guidance was developed in partnership with a range of different stakeholders through two global consultative meetings. These reviewed the feasibility of use of absolute impact targets as a standardized approach to validate elimination rather than the relative reduction targets originally defined in the 2016–2021 GHSS on viral hepatitis. Selection of elimination targets and criteria were supported by scientific evidence and comprehensive literature reviews as well as a WHO-commissioned survey of 28 countries to gain critical insights for the development of the interim guidance.

The 2021 guidance provided a global framework for the processes and standards for validation of elimination with the goals of placing hepatitis elimination efforts within a public health perspective; building national capacity (addressing different country contexts, including differences due to various levels of endemicity); implementing control and elimination programmes efficiently; and, motivating countries to take rapid and appropriate action toward viral hepatitis elimination.

A series of country implementation pilots, were conducted between June 2021 and May 2022 in seven countries across the six WHO regions, namely, Brazil, Egypt, Georgia, Mongolia, Rwanda, Thailand, and the United Kingdom to evaluate the feasibility and acceptability of the different approaches used to measure the impact and programmatic targets for elimination. The pilots provided a unique opportunity to field-test the elimination criteria and the validation tools as well as address some key questions to inform the revised guidance.

This second version and updated *Guidance for country validation of viral hepatitis elimination and the path to elimination,* building on the 2021 interim guidance incorporates the lessons and feedback from the implementation pilot studies as well as experiences from a range of other countries. It includes for the first time, the development of the global criteria for a path to elimination (PTE) for hepatitis B and C as public health problems. This path has been developed to recognize a clear progression and significant national effort towards implementing key programmatic interventions in countries that may not yet be in a position to achieve the impact targets of elimination.

This updated version also includes changes, clarifications and new guidance on processes and alternative measurement approaches for country validation of elimination. These have been developed in partnership with stakeholders through a global consultation in April 2023 (the third in this series) that brought together over 40 experts, policy-makers and representatives from 15 ministries of health. The 2030 elimination targets and recommendations for direct measurement of impact targets using country collected data are unchanged. Box 1 summarizes the revisions and updates in this second version (2023 edition) of the **WHO *Guidance for country validation of viral hepatitis elimination and path to elimination***

Box 1. What's new in the 2023 edition of the *WHO Guidance for country validation of viral hepatitis elimination and path to elimination*

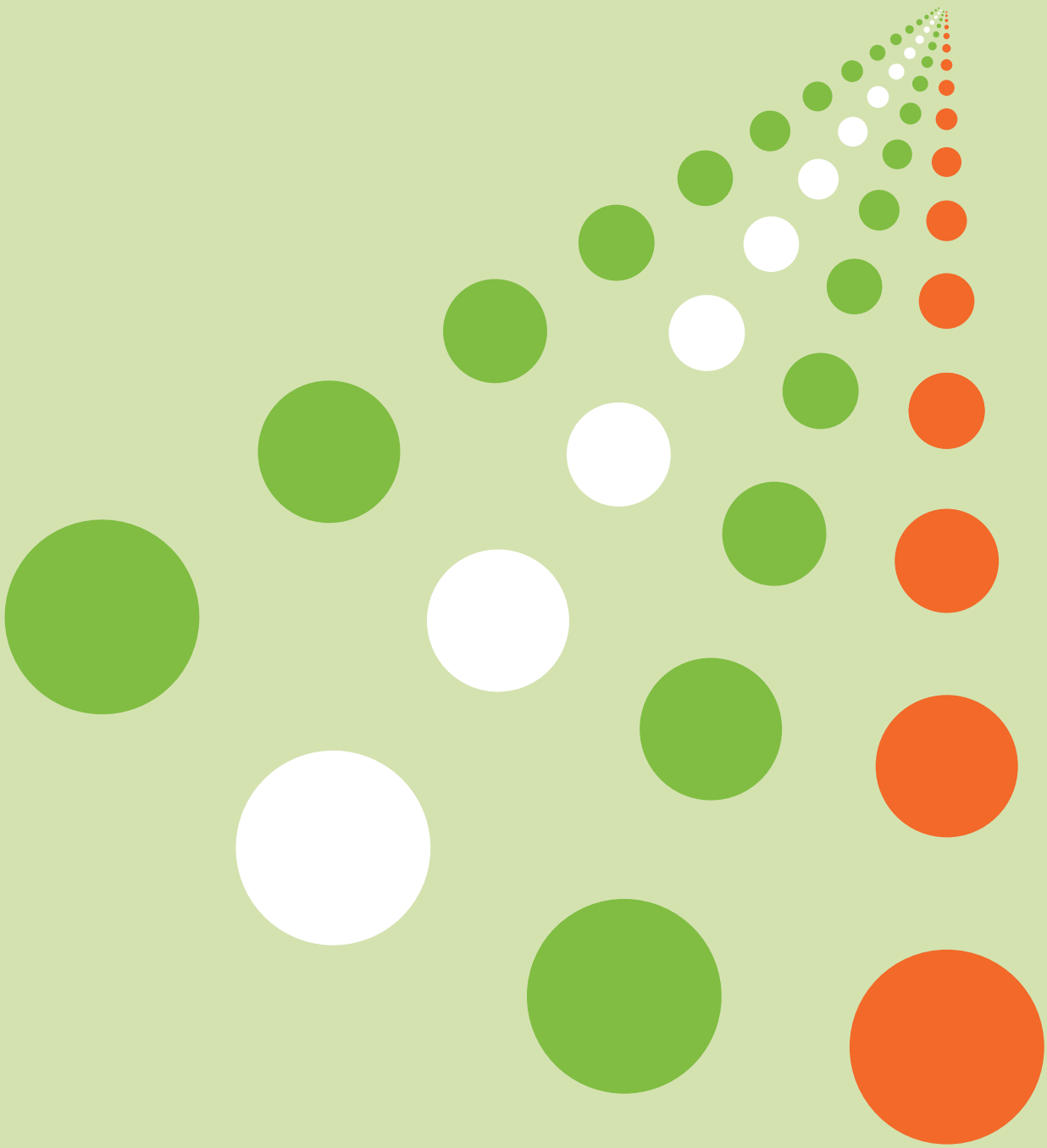
This 2023 version maintains the 2030 elimination targets as well as the empirical measurements of HBV and HCV absolute impact targets. This second and updated version includes criteria for the path to elimination as well as changes, clarifications and new guidance on criteria, path to elimination (PTE) processes and measurement approaches for country validation of the elimination of viral hepatitis. These include the following:

1. The major new addition is the criteria to support validation for a path to hepatitis B and C elimination as a public health problem, in the general popuation, to recognize major progress in countries that do not yet meet full validation criteria (Chapter 6). This complements the existing path to elimination for mother-to-child transmission (EMTCT) of HBV.
2. Modifications have been made to align with the Global Health Sector Strategies (GHSS) (2022–2030), including the incorporation of the 2025 and 2030 targets.
3. The major technical chapters (Chapters 4 and 5) have been revised and updated to highlight the requirement for validation of hepatitis B and C as public health problems through the achievement of incidence and mortality, as well as, optimal programme coverage.
4. Inclusion of an alternative method of measuring the impact of prevention of mother-to-child transmission (PMTCT) of hepatitis B. Namely, in countries with a high coverage of maternal hepatitis B surface antigen (HBsAg) testing and post-vaccination serological testing (PVST), they can use integrated maternal and perinatal data to assess both the impact and programme targets for the EMTCT of hepatitis B without the need for additional serosurveys (Chapter 3).
5. New alternative methods of measuring HCV incidence and inclusion of key programme data, including injection safety and/or harm reduction.
6. For mortality, the focus is now on a combined mortality rate of less than 6/100 000. Additionally, measurement options for attributable fraction for hepatitis-related liver disease and mortality have been expanded.
7. The critical utility of mathematical modelling in both assessment of progress and validation is emphasized throughout the document to complement the use of empirical data, with the support for a WHO modelling reference group for hepatitis.
8. The care cascade for HBV and HCV has been updated with clear definitions and programmatic measurement methods.
9. The process of country validation and governance has been revised (*see* Annex 2) and the validation tools have been updated.

For full validation of elimination, a country will need to demonstrate achievement of the impact (incidence and mortality reduction) alongside the programmatic targets, ensuring that all populations have been reached with equitable services. For path to elimination (PTE), countries will need to achieve programme coverage targets (according to relevant tiers), a process that will promote national programme expansion, wide country engagement, as well as, document progress towards achieving elimination of HBV and/or HCV. Both approaches require documentation of high quality data sources, good laboratory processes, accessible health-care programmes, and adherence to the principles of human rights, equity, gender equality and community engagement in access to hepatitis services. To achieve these targets, countries must support high-quality national programmes and a comprehensive system for surveillance, with systematic documentation of achieving and maintaining programme targets for at least 2 years.

This document provides standardized guidance for achieving WHO validation of elimination of viral hepatitis, the tools utilized for assessment, as well as the necessary governance structures. Countries are encouraged to pursue elimination of both viral hepatitis B and C as public health problems, but may choose to apply for one of the four certification options in a phased approach to be officially recognized by WHO for the elimination of mother-to-child transmission of HBV, or elimination of HBV and/or HCV as a public health problem. Chapters 1 and 2 provides the background to the key WHO strategies and guidelines and recommended interventions, as well as, guiding principles and an overview of the validation process. Chapters 3–5 outline technical considerations of identification and measurement of impact and programme targets for HBV and HCV as public health problems. Chapter 6 defines the criteria for validation of a PTE for viral hepatitis B and C recognizing progress towards elimination without the need to demonstrate achievement of HBV or HCV incidence or mortality impact targets. It lays the foundation for validation of disease elimination through a step-wise progression towards attainment of complete validation of elimination criteria. It serves to promote an iterative expansion of programmes and strengthen measurement systems to support attainment of 2030 elimination goals. Annexes 1–6 address implementation considerations for countries to assess the sustainability of their response, as well as, other tools to support country self-assessment, and the key elements of the national elimination dossier report.

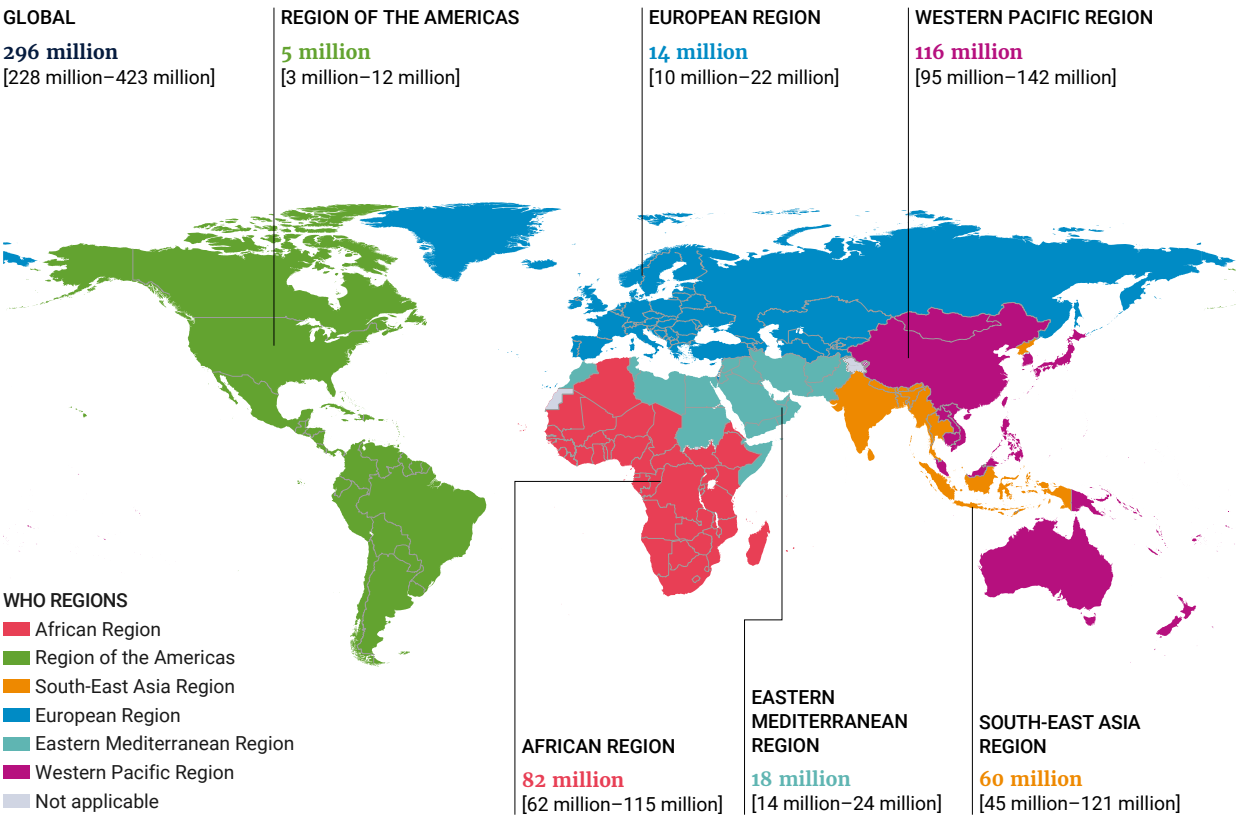
Chapter 1.
Introduction and background



1.1 Epidemiology of viral hepatitis B and C infection

Hepatitis B virus (HBV) infection. The World Health Organization (WHO) estimates that in 2019, 296 million persons, or 3.8% of the population, were living with chronic hepatitis B virus (HBV) infection in the world (Fig. 1.1) *(1)*. The African and Western Pacific regions accounted for over half (67%) of those living with HBV globally, with South-East Asia accounting for 20% and lower burdens across Europe (6%) and the Americas (2%). In 2015, the estimated global prevalence of HBV infection in people living with HIV was 7.6%, and 2.7 million persons were coinfected with HBV and HIV *(2)*. Most of the people currently living with HBV infection were born before the hepatitis B vaccine was widely available and used in infancy *(3)*.

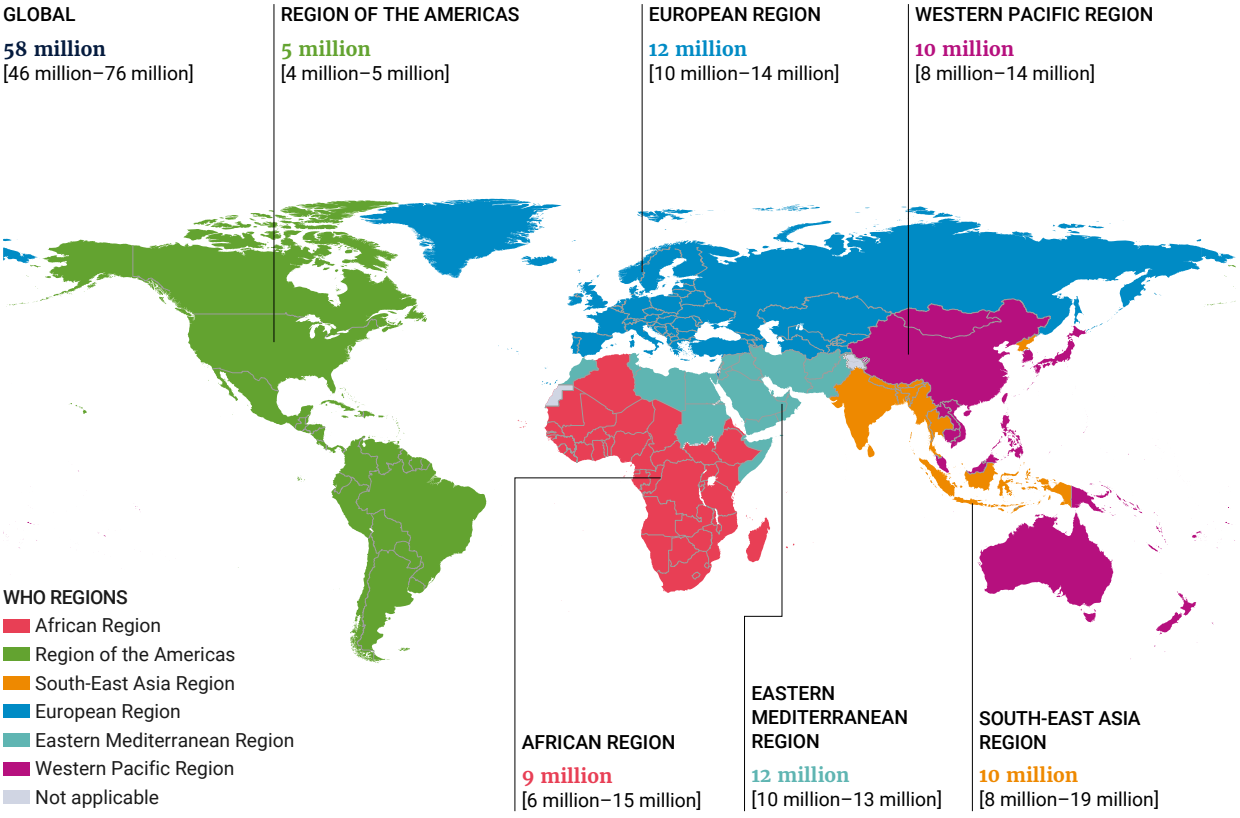
Fig. 1.1 Global status of chronic hepatitis B virus infection by WHO region, 2019 *(4)*



WHO has also estimated that the prevalence of chronic HBV infection among children under 5 years of age fell from 4.7% in the pre-vaccine era of the mid-1990s to 0.9% in 2019 *(1)*. The remaining infections are in neonates or infants, which occur through transmission from the mother at birth prior to vaccination, or early childhood transmission through close contact with other infected young children and infected adults in the household. Estimates show that about 1.5 million people newly acquire HBV infection each year, despite the availability of a highly efficacious vaccine *(1)*.

Hepatitis C virus (HCV) infection. WHO estimated that in 2019, 58 million persons were living with hepatitis C virus (HCV) infection in the world, accounting for 0.75% of the population *(1)*. Of those living with HIV, 2.3 million persons also had HCV infection, of which 1.2 million were people who inject drugs (PWID) *(5,6)*. HCV infection is unevenly distributed across the world. The European (22%), South-East Asia (20%) as well as the Eastern Mediterranean (17%) regions are the most affected, but there are variations in prevalence across and within countries (Fig. 1.2). Unsafe health-care procedures and injection drug use were the leading causes of new HCV infections, though health-care-related new HCV infections are decreasing following global action to address safe injections. In 2019, there were 1.5 million new infections, with one third of new HCV infections occurring in the Eastern Mediterranean Region *(1)*.

Fig. 1.2 Burden of chronic hepatitis C viraemic infection by WHO region, 2019 *(4)*

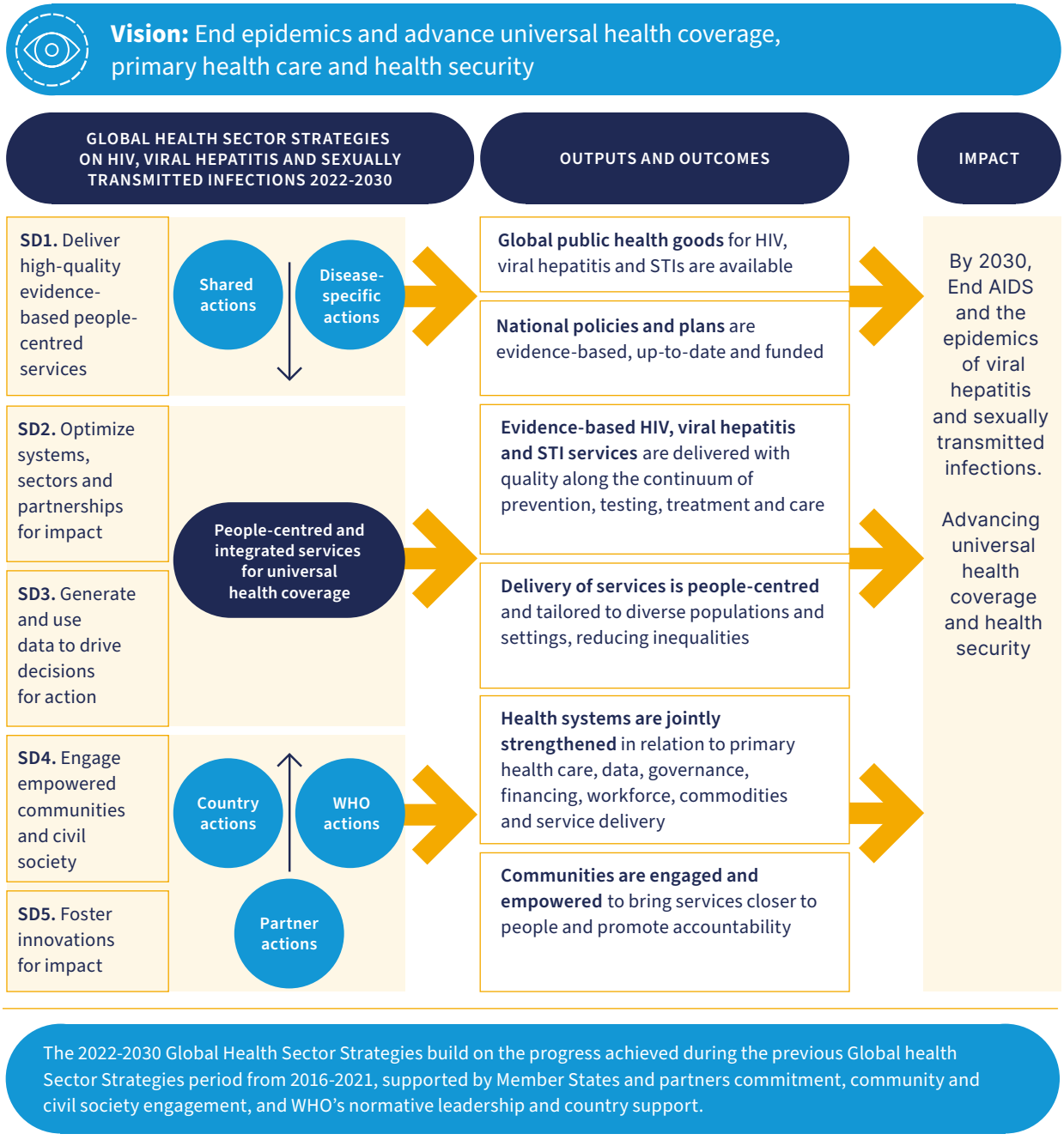


WHO estimated that, in 2019, viral hepatitis B and C were together responsible for 1.1 million deaths, mainly due to cirrhosis and hepatocellular carcinoma (HCC) *(4)*, with 821 000 HBV-related deaths and 288 000 HCV-related deaths *(1)*. Unless more people with HBV and HCV infection are diagnosed and treated, the number of deaths due to viral hepatitis will continue to increase *(4,7)*.

1.2 Global health sector strategies on viral hepatitis (2022–2030)

The *Global health sector strategies on HIV, viral hepatitis and sexually transmitted infections, 2022–2030 (7)* noted by the World Health Assembly in 2022, share a common vision to end the epidemics and advance universal health coverage (UHC), primary health care and health security. Five strategic directions guide actions across all three strategies, reflecting synergy in the responses to HIV, viral hepatitis and sexually transmitted infections (STIs). For viral hepatitis, it builds upon the global framework laid out in the 2016 *Global health sector strategy for viral hepatitis* with the vision of a world where transmission of viral hepatitis is halted and everyone living with viral hepatitis has access to safe, affordable and effective prevention, diagnosis, care and treatment. As described in Fig. 1.3, this vision could be achieved through five strategic directions; and under the key principle of promoting a public health approach and achieving UHC.

Fig. 1.3 Strategic directions linked to outputs to end epidemics in the *Global health sector strategies on HIV, viral hepatitis and STIs 2022–2030 (7)*



Source: GHSS 2022–2030 *(7)*.

The strategies aim to end AIDS and the epidemics of viral hepatitis and STIs by 2030 through joint action in areas of convergence while maintaining disease specificities focused on interventions and innovations aligned with the goals of the 2030 Agenda for Sustainable Development and WHO's General Programme of Work.

The global impact and programmatic targets for viral hepatitis guide the development of national targets and apply to everyone at risk of or living with viral hepatitis infection.

1.3 Key interventions for the prevention, diagnosis, treatment and care of viral hepatitis

This section provides a summary of WHO-recommended key prevention, diagnosis, treatment and care interventions and services (Table 1.1).

Table 1.1 Key interventions to address viral hepatitis with the GHSS on viral hepatitis and global targets (2022–2030)

			Targets	
Interventions	**Indicator**	**2020 baseline**	**2025**	**2030**
1. Hepatitis B vaccination	HepB3 vaccine coverage	90%	90%	90%
2. HBV PMTCT[a]	Hep B timely birthdose vaccine coverage	50%	70%	90%
3. Blood safety	Donations screened with quality assurance	95%	100%	100%
4. Injection safety	Proportion of safe injections	95%	100%	100%
5. Harm reduction	Syringes & needles distributed/ PWID/year	200	200	300
6. Testing services	% HBV-infected diagnosed	30%	60%	90%
	% HCV-infected diagnosed	30%	60%	90%
7. Treatment	% diagnosed with HBV on treatment	30%	50%[b]	80%[b]
	% diagnosed with HCV on treatment	30%	50%[c]	80%[c]

HepB-BD: hepatitis B birth dose vaccine; HepB3: three doses of hepatitis B vaccine; PMTCT: prevention of mother-to-child transmission; PWID: person who injects drugs

Source: WHO, including commissioned work, United Nations, UNICEF

a Interventions to prevent mother-to-child transmission of HBV

b Of those eligible for treatment. Around 20–30% of persons living with HBV infections may develop progressive liver disease or HCC and are eligible for treatment with nucleoside analogue therapies;

c For HCV, all are eligible for treatment according to WHO guideline

1.3.1 Hepatitis B vaccination and prevention of mother-to-child transmission of HBV

Most of the global burden of chronic hepatitis B virus (CHB) infection can be attributed to mother-to-child transmission (MTCT) of HBV at the time of, or shortly after, birth or in early childhood from infected children and adults through horizontal transmission. Such perinatal infections lead to a high rate of chronicity, and these individuals may remain viraemic for decades *(8)*.

WHO recommends universal immunization of infants, with at least three doses of the hepatitis B vaccine (HepB3), and timely hepatitis B birth dose (HepB-BD) vaccination (as soon as possible after birth, preferably within 24 hours) *(3)*. Since 1992, WHO has recommended inclusion of the hepatitis B vaccine in the Expanded Programme on Immunization (EPI) *(3)*. High coverage of the timely HepB-BD, given within 24 hours of birth, and completion of the infant hepatitis B vaccine series are the most important interventions for reducing MTCT of HBV as well as early childhood transmission and achieving the HBV elimination goals.

The **infant hepatitis B vaccine series** should be completed through administration of two or three additional doses of hepatitis B-containing vaccine, each separated by at least four weeks, according to the national infant immunization schedule.[1,2] Completion of the infant hepatitis B vaccine series leads to immunological protection and prevention of infection in >95% of children *(3)*. The Immunization Agenda 2030 *(9)* sets an ambitious, overarching global vision and strategy for vaccines and immunization programmes for the decade 2021–2030 with a focus on coverage and equity, with a commitment that everyone everywhere should have equal access to vaccines. This is critical in meeting the timely HepB-BD and HepB3 coverage targets.

Since 2020, WHO has recommended that hepatitis B surface antigen (HBsAg)-positive pregnant women at high risk of transmitting the virus to their infants due to high HBV DNA level (≥200 000 IU/mL) receive peripartum antiviral tenofovir prophylaxis from the 28th week of pregnancy until at least delivery to prevent mother-to-child transmission (PMTCT) of HBV *(10)*. This recommendation is likely to provide expanded options for women in low- and middle-income countries (LMICs) in the 2023 update of the hepatitis B treatment guidelines. This recommendation is in addition to the three-dose hepatitis B vaccination in all infants (starting with timely HepB-BD). In a number of settings (mostly high- and high-middle-income countries), hepatitis B immunoglobulin (HBIg) may also be used to further reduce the risk of MTCT of HBV.

1.3.2 Harm reduction interventions

Globally, it is estimated that there are 14.8 million PWID. 2.6 million PWID are living with HIV, 5.78 million with hepatitis C and 1.2 million are living with both hepatitis C and HIV *(6)*. Further, it is estimated that 23–39% of new HCV infections occur among people who currently inject drugs *(11)*.

Harm reduction measures recommended by WHO *(12)* include distribution of sterile needles and syringes (including low dead-space syringes [LDSS] *(14)*) to PWID and opiate agonist therapy (OAT) for people who are dependent on opiates. Needle and syringe distribution and OAT programmes should be provided with high coverage to effectively prevent HCV and HIV transmission *(15,16)*, but globally coverage remains inadequate *(17)*.

1.3.3 Prevention of viral hepatitis infections in health-care settings

Unsafe injections within health-care and community settings and transfusion of contaminated blood and blood products continue to be important modes of HBV and HCV transmission in some countries and settings. Infection prevention by improving blood safety and instituting universal safe injection practices are core interventions in the GHSS for the elimination of viral hepatitis. WHO recommends the use of sterile single-use needles and syringes for all medical injections and has published guidance on standard procedures for effective sterilization and decontamination of medical devices *(18)*. WHO also supports the procurement of safety-engineered injection devices with a sharps injury protection feature (SIP) or the use of injection devices with a reuse prevention feature (RUP) *(19)*.

WHO also recommends that 100% of donated blood should be screened for bloodborne infections (HBV, HCV, HIV and syphilis) to avoid transfusion-related transmission *(20)* and has developed a global *Action framework to advance universal access to safe, effective and quality-assured blood products 2020–2023 (21)*.

1.3.4 Testing for hepatitis B and C infection

WHO issued comprehensive testing guidelines for hepatitis B and C in 2017 *(22)*, with some further updated recommendations in the 2022 HCV guidelines and forthcoming 2023 HBV guidelines. Focused testing for hepatitis B or C infection is recommended for individuals from populations most affected by HBV or HCV infection. These include those who are either part of a population with a higher seroprevalence (e.g. mobile/migrant populations from countries with high/intermediate endemicity, and certain Indigenous populations), or who have a history of exposure to, or high-risk behaviours for HBV or HCV infection (e.g. PWID, people in prisons and other closed settings, men who have sex with men [MSM] and sex workers, people living with HIV, their partners, family members and children of people living with CHB). Routine testing of all pregnant women for HBsAg, HIV and syphilis in antenatal clinics is also recommended. In settings with a ≥2% or ≥5% seroprevalence of HBsAg or anti-HCV, respectively (depending on the country context regarding epidemiology or hepatitis surveillance infrastructure), it is recommended that all adults have routine access to and be offered testing (i.e. a general population testing approach). Overall, these different testing approaches should make use of existing facility-based services such as antenatal clinics, refugee or migrant clinics, HIV and TB clinics, or chronic care clinics for diabetes/hypertension, as well as, community-based testing opportunities and programmes. In addition,

1 Three doses of hepatitis B vaccine are sufficient to induce immunity. However, for programmatic reasons, the monovalent HepB-BD may be followed by three additional doses in national routine infant immunization schedules:
i) three-dose schedule: three doses of hepatitis B vaccine, the monovalent HepB-BD followed by two doses (monovalent or as part of a combined vaccine) given at the same time as the first and third doses of DTP-containing vaccine;
ii) four-dose schedule: four doses of hepatitis B vaccine, with the monovalent HepB-BD followed by three doses (monovalent or combined vaccine), usually given with other routine infant vaccines.

2 The HepB3 vaccination coverage indicator measures the third dose of hepatitis B vaccine, whether or not a fourth dose is given.

the 2030 global testing target is that 90% of those living with viral hepatitis B or C infection will have been diagnosed – making close to universal screening necessary to reach this target.

Screening for HBsAg and HCV antibody (HCVAb) should be carried out with a serological assay (in either a rapid diagnostic test [RDT] or laboratory-based immunoassay format) that meets minimum quality, safety and performance standards *(22)*. The hepatitis C virus self-testing guideline *(23)* recommends self-testing as an additional testing option to reach people who might not otherwise test using existing services. Chronic HCV infection can be confirmed by using either a laboratory-based quantitative or qualitative HCV RNA nucleic acid test (NAT) assay or a point-of-care assay *(22,24)*. HBV DNA measurement is based on either a laboratory-based quantitative or qualitative nucleic acid test assays (NAT). The use of point-of-care NAT assay are being increasingly documented and will be explored in the upcoming revision of the HBV guidelines scheduled for 2023.

1.3.5 Treatment and monitoring of chronic hepatitis B

Antiviral treatment for HBV infection (mainly lifelong) with tenofovir or entecavir induces sustained viral suppression and thus reduces the risk of HBV-related complications such as decompensated liver cirrhosis and HCC, especially in those with advanced liver disease. Without treatment, an estimated 20%–30% of people with chronic HBV infection will develop cirrhosis and are at risk of decompensated cirrhosis and HCC. In 2015, WHO issued comprehensive guidelines for the prevention, care and treatment for chronic hepatitis B *(25)*, and prioritized treatment of individuals with cirrhosis or, in the absence of cirrhosis, in adults with persistently abnormal alanine aminotransferase (ALT) levels and evidence of high-level HBV replication (HBV DNA >20 000 IU/mL) *(25)*. Where HBV DNA testing was not available, treatment could be considered based on persistently abnormal ALT levels alone. Continued monitoring is necessary for all persons with chronic hepatitis B infection whether on treatment or not, including regular screening for HCC detection. Updated recommendations for diagnosis, treatment and service delivery for HBV will be launched in late 2023. It is anticipated that there will be substantial expansion of treatment eligibility and simplification of service delivery to promote a comprehensive public health response.

1.3.6 Treatment of hepatitis C

Treatment of hepatitis C using direct-acting antivirals (DAAs) with attainment of sustained virological response (SVR) after 12 weeks post-treatment (SVR12) – "cure" – has been shown to substantially reduce the incidence of HCC by an estimated 85%, liver-related mortality and all-cause mortality by 75% in individuals with cirrhosis *(26)* and close to 70% in those without cirrhosis *(27)*. WHO HCV guidelines recommended offering treatment to all individuals – adults, adolescents and children – diagnosed with HCV infection who are 3 years of age or older, irrespective of disease stage, using one of three pangenotypic DAA drug regimens (sofosbuvir/daclatasvir, sofosbuvir/velpatasvir, and glecaprevir/pibrentasvir) *(24,28,29)*. The length of treatment varies according to the presence or absence of cirrhosis, although SVR12 is achieved in ≥90% of individuals*(29)*. HIV coinfection does not reduce the effectiveness of HCV DAA pangenotypic therapy *(29)*. The guidelines also recommended HCV testing and treatment at decentralized sites, including at primary care level and at harm reduction sites and in prison settings. These can be provided by non-specialist doctors and nurses as well as specialists to promote access.

1.4 Progress on the global response and key updates

Since the adoption of the GHSS on viral hepatitis in 2016 *(30)*, there have been major developments in the global hepatitis landscape and response relevant to the elimination of viral hepatitis. These include key WHO guidelines and updates, and other initiatives, a new global strategy for 2022–2030 in 2022 *(3,4,7,10,12,22,24,25,29)*, national and programmatic expansion, and simplified service delivery platforms, especially for hepatitis C. The *Progress report on HIV, viral hepatitis and sexually transmitted infections, 2021: accountability for the global health sector strategies 2016–2021 (4)* provided the assessment of implementation of the first GHSS on viral hepatitis, and builds on the 2019 mid-term assessment *(31)*.

1.4.1 National responses and programmatic initiatives

- DAAs have revolutionized treatment since 2016. Cure (SVR12) can be achieved in more than 90% of cases with pangenotypic regimens. There has been great progress in reducing DAA prices, diagnostic and treatment costs. Treatment costs remain a key barrier to treatment expansion in certain countries *(32)*.
- In 2016, only 15 countries had comprehensive national action plans for viral hepatitis. By 2019, around 124 countries had national action plans or they were in development. WHO encourages countries to cost their national response to facilitate resource planning and allocation.
- Global coverage of HepB-BD has continued to increase, with 45% of countries meeting the target in 2022, despite the COVID-19 pandemic, while HepB3 reached 84% in 2022, just below prepandemic levels (33).

1.4.2 WHO guidelines

- Key clinical guidelines developed include the 2015 Hepatitis B prevention, treatment and care guidelines *(25)* with a major update ongoing in 2023, four updates of the HCV guidelines and most recently in 2022 *(24)*, hepatitis B and C testing guidelines in 2017 *(22)*, with HCV self-testing guidance in 2021 *(23)* and antiviral prophylaxis guidelines for PMTCT of hepatitis B *(10)*.
- The updated consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations in 2022 *(12)* outlines a public health response for five key populations (MSM, trans- and gender-diverse people, sex workers, PWID and people in prisons and other closed settings). Key populations face particular social, legal, structural and other contextual factors that both increase vulnerability to HIV, viral hepatitis and STI and limit access to health and other essential services. These consolidated guidelines present and discuss new recommendations and consolidate a range of person-centred recommendations and guidance from existing guidelines *(12)*.
- Consolidated strategic information guidelines for viral hepatitis, 2019 provides a simplified framework for surveillance, monitoring and evaluation *(34)*. An update is planned for early 2024.

1.4.3 Other elimination initiatives

Elimination of mother-to-child transmission of HIV, syphilis and Hepatitis B virus – (known as triple elimination)

- Since 2016, WHO has promoted an integrated approach to the elimination of mother-to-child transmission (EMTCT) of infectious diseases pioneered by the joint effort of the Pan American Health Organization, the WHO Office for the Region of the Americas *(35)*, and the Regional Office for the Western Pacific *(36)*.
- In 2017, the Pan American Health Organization published the *Framework for elimination of mother-to-child transmission of HIV, syphilis, hepatitis B, and Chagas – "EMTCT Plus" (35)*, which includes region-specific impact and programme targets for all four diseases, followed by a progress report in 2019 and inclusion in the 2019 Integrated Sustainable Framework for the Elimination of Communicable Diseases in the Americas *(37)*. At the same time, the Regional Committee for the Western Pacific endorsed the *Regional framework for the triple elimination of mother-to-child transmission of HIV, hepatitis B and syphilis in Asia and the Pacific, 2018–2030 (38)*. Both regional frameworks are aligned with the existing global and regional strategies, action plans and goals for reproductive, maternal, newborn and child health, and control of HIV, hepatitis and STI.
- In 2021,WHO published the Global guidance on criteria and processes for validation: elimination of mother-to-child transmission of HIV, syphilis and Hepatitis B virus, third edition (39). Triple elimination is now a key shared intervention across these diseases in the 2022 *Global health sector strategies on HIV, viral hepatitis and STIs (7)*.

The WHO integrated framework for disease elimination

- Today, at least 30 diseases have been assigned global targets for elimination or eradication by WHO (Table 1.2). Prompted by the Pan American Health Organization EMTCT Plus initiative, WHO is developing an overall framework to facilitate elimination of multiple diseases at the same time, including viral hepatitis, in a holistic, coordinated, comprehensive and sustainable manner, and adopting a people-centred approach within the context of UHC. The Framework aims to guide actions at country, regional and global levels to achieve greater efficiency, equity and impact through cross-programme synergies. It will focus on those diseases and health conditions where elimination or eradication commitments have been made and provides the rationale for multidisease elimination, promotes greater standardization of definitions, and criteria and validation processes for disease elimination. It also provides guidance on the integration of disease elimination efforts, including those for viral hepatitis, into broader national health planning and programming.

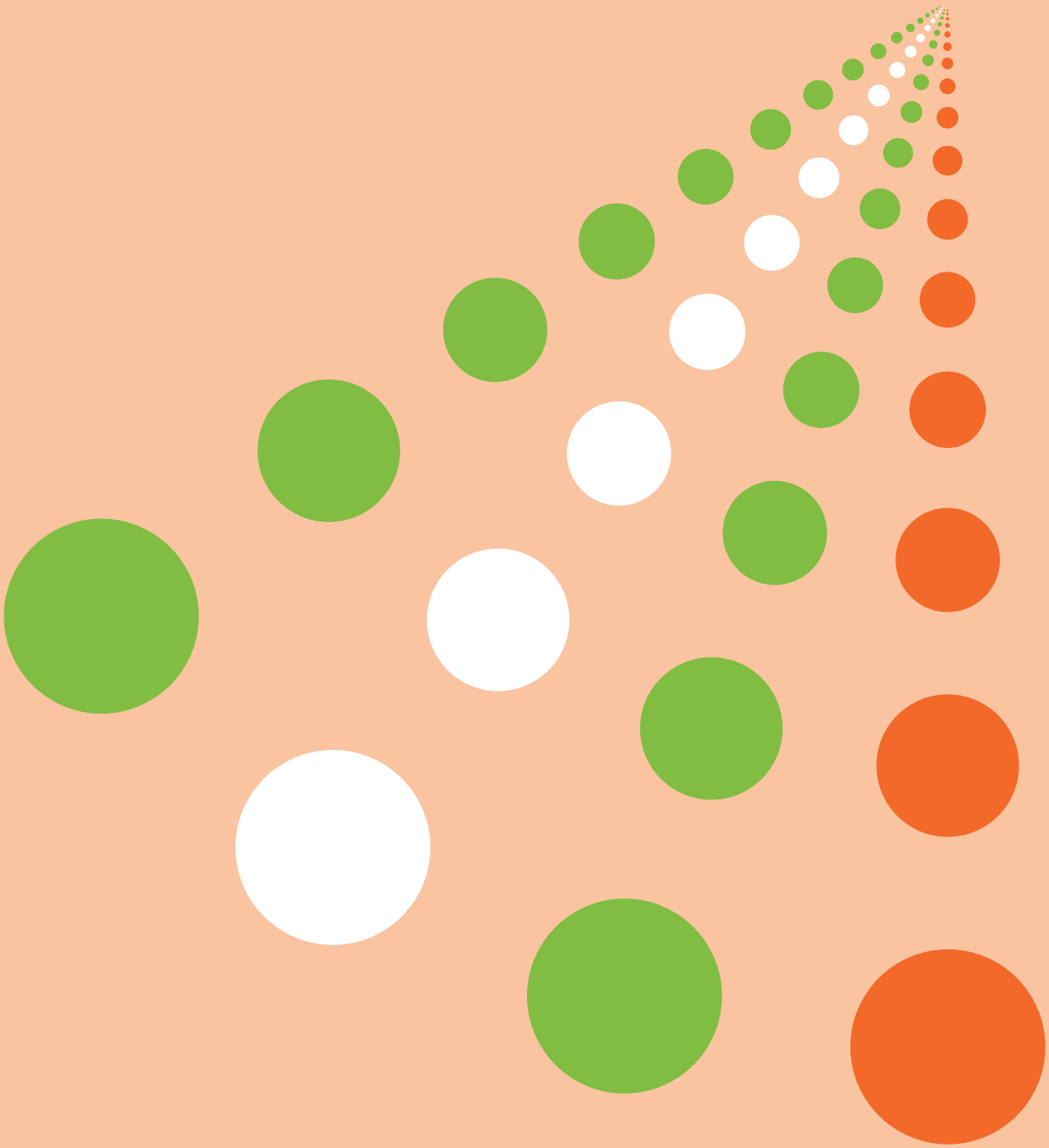
Table 1.2 Diseases with global elimination targets

Goal	Diseases targeted
Eradication	Dracunculiasis; malaria; polio; yaws
Elimination of transmission	Human African trypanosomiasis (HAT) (gambiense); leprosy; measles, onchocerciasis, rubella (including congenital rubella syndrome [CRS])
Elimination as a public health problem	Cervical cancer; Chagas disease; cholera; gonorrhoea; hepatitis B & C; HIV; HAT (rhodesiense); leishmaniasis (visceral); lymphatic filariasis; maternal and neonatal tetanus; meningitis; rabies; schistosomiasis; soil-transmiited helminthiasis/ strongyloidiasis; syphilis; trachoma; TB; vector-borne diseases (including chikungunya, dengue, Japanese encephalitis and Zika virus disease); yellow fever

Source: Interim guidance for country validation of hepatitis elimination. Geneva: WHO; 2021:11.

Chapter 2.

Elimination of viral hepatitis: principles and practice



2.1 Guiding principles in the validation of elimination of viral hepatitis

This chapter focuses on the guiding principles for validation of elimination, key recommended components in the development and implementation of an evidence-based national viral hepatitis action plan and summarizes the approaches to country validation of elimination of viral hepatitis as a public health problem.

The overarching guiding principle in achieving elimination of viral hepatitis is that of a public health approach, which aims to provide the maximum health benefit for the largest number of people within the available resources. The approach, placing people at the centre, promotes standardization and simplification of interventions and services, with a focus on decentralization, integration and coordination with other disease categories and community engagement.

The validation process stresses such a broad but person-centred approach as central to achieving elimination at the country level. Additional principles include the following:

- **Promotion of universal health care adopts a harmonized and integrated approach to triple elimination** of MTCT of HIV, syphilis and hepatitis B virus (together with other conditions, such as Chagas disease in the Region of Americas), ensuring the health of mothers through comprehensive care of women, quality maternal and child health services, care of infants, reduction in preventable adverse birth outcomes and leveraging existing HBV immunization initiatives.
- **Adaptation to the country context** effectively addresses disease epidemics – through primary health care in particular – in each unique population, setting and context, reflecting important variations in disease burden and epidemic dynamics across different countries and regions.
- **Country-led: the process places a strong emphasis on country accountability** and promotes country stewardship in setting national targets and designing its own pathway towards elimination.
- **Respects human rights and promotes equity in access and community engagement:** elimination criteria must be achieved in a manner that protects and respects human rights and promotes equity. It recognizes the central role of civil society and affected communities in implementing community-led and community-owned elimination programmes for viral hepatitis with their involvement in the validation process.

2.2 The national planning process

National planning of the domestic hepatitis response is the building block from which validation of the elimination of viral hepatitis can ultimately be achieved. Therefore, the national planning process should be informed by a comprehensive assessment of the national situation regarding disease epidemiology and dynamics, population characteristics and country context, health system capacity and multisectoral national response to viral hepatitis. The process should be guided by setting national impact and programmatic targets that are consistent with the global approach to elimination and targets of the GHSS 2022–2030 on viral hepatitis and are ideally presented as absolute thresholds aligned to this guidance.

The national strategy should be operationalized through a fully costed national viral hepatitis action plan, which defines the core interventions and resources needed to achieve national elimination targets. A well-developed investment case, which demonstrates the value of taking a disease elimination approach, in support of implementation of the national hepatitis elimination strategy, is a powerful tool for advocacy and resource mobilization.

The Ministry of Health (MoH) should be responsible for implementing the national viral hepatitis action plan, and coordinating efforts across the public, community and private sectors and with other relevant government sectors. A strong civil society is key to an effective national hepatitis response, providing a legitimate and authentic voice to those affected by viral hepatitis. In some cases, it would also provide a range of services, particularly for vulnerable and marginalized populations. Civil society should be engaged in all aspects of national planning, implementation and accountability.

The *WHO Guidance for national strategic planning for HIV, viral hepatitis and sexually transmitted infections* and *Guide to conducting programme reviews for HIV, viral hepatitis and sexually transmitted infections* (WHO 2023) and the *Manual for the development and assessment of national viral hepatitis plans* provides guidance to countries on key components of a national plan and its integration into the broader national health response *(40)*.

In addition, *the WHO UHC compendium (41)* is a tool that can assist countries in selecting the most appropriate package of interventions and services for inclusion in their national hepatitis elimination plan, as countries plan for leveraging existing programmes, services and health insurance schemes and expansion of domestic funding as part of their national response.

2.2.1 Monitoring and evaluation

The validation process will require the measurement and documentation of the impact (incidence and mortality) and programmatic targets (prevention and care), and implementation considerations for elimination of viral hepatitis. This process relies principally on the availability of high-quality national programmes and a comprehensive system for surveillance, with systematic documentation of reaching the proposed impact and programme targets and maintaining programme targets for a total of at least two years. National viral hepatitis action plans should include a monitoring and evaluation framework that describes how the specific programmatic and impact targets and indicators of the national response will be continuously measured and assessed. Most countries have existing arrangements for monitoring and evaluation of the wider national health sector response, which can be modified to also include that for viral hepatitis. In 2019, WHO published the *Consolidated strategic information guidelines for viral hepatitis (34)*, which summarizes and simplifies the overall approach proposed by WHO to collect, analyse, disseminate and use strategic information on viral hepatitis at local, subnational, national and international levels. The data systems needed to report against the core indicators of the monitoring and evaluation framework for viral hepatitis should also capture those data necessary to report progress towards elimination in the validation process.

Data sources should include the following:

1. **nationally representative viral hepatitis surveillance (acute and chronic infection), including** surveillance for the prevalence of chronic infections ideally through biomarker surveys, data on testing for viraemic infection and treatment, surveillance for incident chronic HCV infections, as well as acute viral hepatitis (not only acute jaundice), which reflects new acute infections;
2. **vital statistics or surveillance of cause-specific mortality for both viruses;**
3. **programme data or health-care facility surveys; routine data from the EPI and programmes** for PMTCT, injection safety and harm reduction for prevention activities; surveillance for infections transmitted in health-care settings (e.g. through surgery, transfusion, dialysis, endoscopy); data from patient registers or databases to monitor the cascade of diagnosis and treatment.

Further details regarding data sources for national programming and validation can be found in the *Consolidated strategic information guidelines for viral hepatitis*, which provide a simplified framework for viral hepatitis surveillance, monitoring and evaluation *(34)*. This document is expected to be updated in late 2023.

2.3 Approaches to the country validation of elimination of viral hepatitis B and C as a public health problem

2.3.1 Introduction

This section summarizes the approaches to country validation of elimination of viral hepatitis as a public health problem. It provides practical guidance on implementation, including the use of targets set in this guidance and the relevant measurement indicators in the WHO monitoring and evaluation framework for viral hepatitis B and C *(34)* based on the results framework. To be validated, the different criteria and targets, the rationale for their use and the respective approaches to measurement are detailed in Chapters 3–6 and summarized in Table 2.1. Absolute impact targets, aligned to and as defined by the GHSS on viral hepatitis 2016–2021 *(30)* allows standardization across all settings and are used for WHO validation of viral hepatitis elimination.

Table 2.1 Summary of impact and programmatic targets for country validation of elimination of HBV and HCV infection as a public health problem

Elimination targets	HBV infection as a public health problem		HCV infection as a public health problem	
2030 GHSS relative reduction targets (compared to 2015)	**Incidence** 95% reduction	**Mortality** 65% reduction	**Incidence** 80% reduction	**Mortality** 65% reduction
HBV- and HCV-specific absolute prevalence, incidence and mortality targets	**HBV EMTCT** ≤0.1% HBsAg prevalence in ≤5 year olds[b, c, e] *Additional target:* ≤2% MTCT rate (where targeted HepB-BD used)[f]	**Annual mortality[d]** (combined HBV/HCV) ≤6/100 000	**Annual incidence[e]** (HCV) ≤5/100 000 ≤2/100 (PWID)	**Annual mortality[d]** (combined HBV/HCV) ≤6/100 000
Programmatic targets[a]	**Countries with universal hepatitis B vaccine birth dose (HepB-BD)** ≥90% HepB3 vaccine coverage ≥90% timely HepB-BD coverage[g]	**Testing and treatment** ≥90% people with HBV diagnosed ≥80% of people diagnosed with HBV and eligible for treatment are treated [h]	**Testing and treatment** ≥90% people with HCV diagnosed ≥80% of people diagnosed with HCV are treated[h]	
	Countries with targeted timely HepB-BD ≥90% HepB3 vaccine coverage ≥90% coverage of those infants at risk with targeted timely HepB-BD ≥90% coverage of maternal antenatal HBsAg testing ≥90% coverage with antivirals for those eligible	**Prevention** 100% safe injections[i] 100% blood safety	**Prevention** 100% safe injections[i] 100% blood safety 300 needles/syringes/PWID/year[j]	

EMTCT: elimination of mother-to-child transmission; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HepB-BD: hepatitis B birth-dose vaccine; HepB3: three doses of hepatitis B vaccine; PWID: people who inject drugs

a All targets must be achieved and maintained for at least 2 years.
b Childhood prevalence at ≤5 years of age is a proxy for HBV incidence.
c The ≤0.1% HBsAg prevalence can be measured among either 5 year olds, 1 year olds, those aged 1–5 years according to existing country surveillance and data collection activities. For those regions and countries with a long history of high Hep B vaccination coverage and which already conduct school-based serosurveys, there could be flexibility in conducting serosurveys in older children >5 years.
d To reach the desired global mortality reduction, the GHSS defined a combined mortality threshold for both HBV and HCV of <6/100 000/year. Previously, the use of different thresholds for HBV or HCV (≤4/100 000 and ≤2/100 000, respectively) based on global epidemiology was described but has been shown to vary significantly according to diverse regional and national epidemiology of both viruses. The current preference is to use a combined threshold to define the mortality target at the country level.
e The assessment of incidence is largely based on reduction in new chronic rather than acute infections.
f The ≤2% MTCT rate is an additional target to ≤0.1% HBsAg prevalence among ≤5-year-old children in countries that provide targeted timely HepB-BD or low-prevalence settings where there may be sub-populations with high HBsAg prevalence.
g Timely HepB-BD is defined as within 24 hours of birth.
h Initiation of short-term curative treatment for HCV infection (SVR12), and generally lifelong antiviral therapy for HBV to maintain long-term HBV DNA viral suppression
i An alternate measure is that 90% of syringes procured have autodisable function.
j An alternate target in countries with opioid epidemics is opioid agonist treatment coverage among PWID ≥40%.

2.3.2 Criteria for elimination of viral hepatitis B and C as a public health problem according to country options for certification

Countries will be officially and globally recognized for validation of elimination of hepatitis B and C by WHO for one of the four options given in Table 2.2: EMTCT of HBV, elimination of HBV and/or HCV as a public health problem, or both. Each of these options also has a path to elimination (PTE) approach that is intended to recognize clear progression and significant national effort based on attaining specific programmatic milestones. *See* Chapter 6 for gold, silver and bronze criteria on the PTE.

Table 2.2 Options for validation of elimination of viral hepatitis B and C as a public health problem

Options for validation of elimination	Impact indicators	Programme indicators
HBV EMTCT **(as part of triple elimination[a] of HIV, syphilis and HBV, or HIV and HBV)**	Annual HBV incidence[b] and MTCT rate[c] (additional target) in countries with targeted timely HepB-birth dose (HepB-BD)	Hepatitis B vaccine birth dose and infant vaccination coverage for newborns and infants HBV antenatal testing and antiviral prophylaxis coverage
HBV as a public health problem (including HBV EMTCT)	Annual HBV incidence (HBV EMTCT) and HBV mortality[d]	Coverage of prevention, testing and treatment
HCV as a public health problem	Annual HCV incidence and HCV mortality[d]	Coverage of prevention, testing and treatment
Elimination of both HBV (including HBV EMTCT) and HCV as public health problems	All of the above	All of the above

a Countries can choose HIV, or HIV and syphilis, or HIV and syphilis and hepatitis B.
b The prevalence of hepatitis B surface antigen (HBsAg) in children aged ≤5 years of age is used as a surrogate indicator of the cumulative incidence of chronic hepatitis B.
c The ≤2% MTCT rate is an additional target to ≤0.1% HBsAg prevalence among ≤5-year-old children in countries that provide targeted timely HepB-BD or low-prevalence settings where there may be sub-populations with high HBsAg prevalence.
d Whatever option is chosen by a country, a combined mortality impact target is used (for both HBV and HCV).

The criteria for country validation of HBV EMTCT, or HBV and/or HCV elimination as a public health problem require the attainment of the relevant **HBV and/or HCV impact targets (incidence and mortality)** and **programme targets** (*see* Table 2.3), as well as the documentation of implementation considerations, as set in this guidance (Annex 1). It is recognized that attainment of the incidence and mortality targets may occur at different times, as it may take much longer for mortality to drop following an incidence reduction. Programmatic targets should be achieved and maintained for at least two years, and in a manner consistent with international human rights considerations.

Data systems that are needed to inform strategic information on viral hepatitis for validation of elimination include serosurveys; surveillance for chronic viral hepatitis infections and sequelae; and programme data documenting prevention, testing and treatment, which include the cascade of care *(34, 40, 42)*. However, mathematical models can usefully complement the empirically collected data in several areas to determine attainment of the country elimination target.

Table 2.3 Indicators and data sources for impact targets repetition

Targets	Preferred measurement indicators	Data sources and approaches to measurement
I. HBV incidence: impact target and measurement indicators		
<0.1% prevalence of HBsAg in ≤ 5 year olds[a]	% HBV infections in ≤5 year olds[a] MTCT rate ≤2%[b]	*See* Box 3.6 • National serosurvey • Post-vaccination serological testing (PVST) survey for MTCT rate • Programmatic data[c] • Modelled estimates based on programmatic data and existing biomarker survey
II. HCV incidence: impact target and measurement indicators		
Annual incidence of new HCV infections ≤5/100 000 general population **AND** ≤2/100 in people who inject drugs (PWID)	Number of new HCV cases per 100 000 population **AND** Number of new HCV cases per 100 PWID	*See* section 5.3 • Prospective and retrospective cohort studies • Modelled estimates using serial serosurveys and programmatic data
iii. HBV and/or HCV mortality: impact target and measurement indicators		
Annual crude mortality rate of HBV- and HCV-related deaths ≤6/100 000 population	Number of deaths caused by HCV and/or HBV infection per 100 000 population	*See* sections 4.2, 5.2 and Annex 6 • Data from vital registration of deaths from cirrhosis and HCC and cancer registries (HCC reporting) • Surveillance for sequelae in sentinel centres • Modelled estimates using epidemiological and other empirical data.

HCC: hepatocellular carcinoma; HBsAg: hepatitis B surface antigen; MTCT: mother-to-child transmission; PWID: people who inject drugs

a The ≤0.1% HBsAg prevalence can be measured among either 5 year olds, 1 year olds or those aged 1–5 years, according to existing country surveillance and data collection activities. For those regions and countries with a long history of high Hep B vaccination coverage (e.g. Region of the Americas), and that already conduct school-based serosurveys, there is flexibility to conduct serosurveys in older children >5 years.

b Countries that provide targeted timely HepB-BD, and where vertical transmission continues due to specific populations of pregnant women with a high HBsAg prevalence, e.g. Indigenous populations or other higher-risk vulnerable populations, are required to show both ≤0.1% HBsAg prevalence among ≤5-year-old children and an MTCT rate of ≤2%.

c Routine programmatic date from EPI and other EMTCT programmes can be complemented and confirmed by mathematical modelling to strengthen the process of country validation

The implementation considerations for elimination (Annex 1) provide guidance on assessing the quality of strategic information systems and data; laboratory systems, diagnostics and medicines; quality of clinical services and programmes, including vaccination, and the principles of human rights, equity, gender equality and community engagement relevant to the elimination of viral hepatitis (*see* country-level checklist for implementation considerations in Annex 4) as recommended by WHO. Additionally, a set of WHO tools and templates are available to support country self-assessment and development of national elimination report (HBV and HCV toolkits). see Annex 3.

2.3.3 Path to elimination option for HBV EMTCT and hepatitis B and/or C

The path to elimination (PTE) of HBV EMTCT option is a single set of criteria based only on programmatic targets established in 2021. See section 3.2.3 in Chapter 3 for gold, silver and bronze criteria on the PTE. The PTE of EMTCT of hepatitis B seeks to recognize high-burden countries with an HBsAg prevalence >1% among ≤5 year olds and/or with a general population prevalence >5%, which have made significant progress in implementing key hepatitis B vaccination interventions and some progress with antenatal HBV testing and antiviral prophylaxis for eligible women, but which may not yet be in a position to achieve the full incidence impact targets for HBV EMTCT.

The PTE option for viral hepatitis B and C as public health problems is now added as an option (chapter 6, tables 6.2 and 6.3). It recognizes the attainment of milestones of progress towards elimination, which are similar to the framework used for PTE for EMTCT of hepatitis B. The criteria comprise high programme coverage without the need to demonstrate achievement of HCV or HBV impact targets, namely, the absolute thresholds for viral hepatitis mortality and incidence.

2.3.4 Governance approaches to elimination

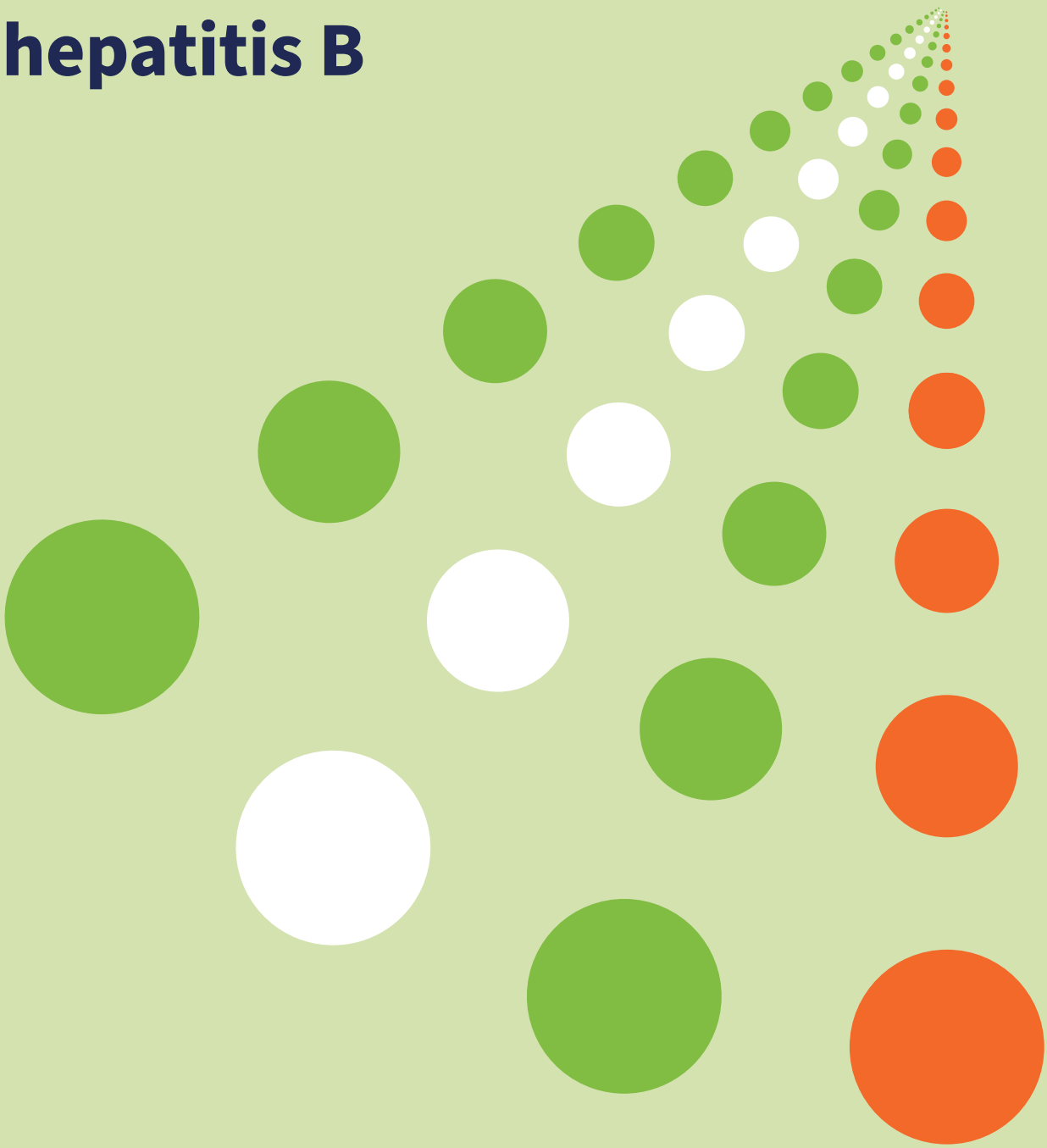
Governance of the elimination of hepatitis B and/or C as a public health problem as well as EMTCT of HBV will be guided by relevant committees and secretariats at the national, regional and global levels, as proposed in the route illustrated in Fig. 3.1 and Annex 2 (Fig. A2.1). This route is aimed at the efficient use of human resource capacity at the national and regional levels for assessing the elimination of hepatitis B or C infection. To assess country reports for validation, regions should have the required expertise in relevant disease areas, including immunization, viral hepatitis and health systems strengthening. The assessment process for the PTE of viral hepatitis as a public health problem is completed at the regional level, unless a WHO regional office specifically requests global-level engagement for higher-level advocacy.

If a country opts to be validated only for the HBV EMTCT component of its viral hepatitis strategy, applications could be channelled through the existing regional and global processes (GVAC) originally designed for dual validation of EMTCT of HIV and syphilis. This pathway has now been strengthened to address all the various validation options, including validation of hepatitis B and/or C as a public health problem.

Countries that have been validated for achieving the elimination of viral hepatitis as a public health problem will be assessed every 5 years for maintenance of validation (this will be every 3 years for countries certified for PTE).

Chapter 3.

Validation of elimination of mother-to-child transmission of hepatitis B



3.1 Background

In the absence of preventive interventions, MTCT at the time of or shortly after birth and early childhood transmission account for most of the burden of CHB infection, because the majority of perinatal infections lead to chronic infection. Incident hepatitis B infections in adolescents and adults seldom progress to chronic infections *(3)*. The risk of developing CHB decreases from around 90% of infected neonates born to hepatitis B e antigen (HBeAg)-positive mothers to 30% among children infected between the ages of 1 and 4 years, and less than 5% among those infected as adults,*(3, 43)* The prevalence of HBsAg in children aged 5 years is therefore used as an overall proxy for new HBV infections from vertical and/or early horizontal transmission and is also used as a surrogate target of the cumulative incidence of CHB infections. The GHSS (2022–2030) on viral hepatitis includes an HBsAg prevalence target in children of ≤1% by 2020 and ≤0.1% by 2030. In addition, most WHO regions have established interim regional targets for hepatitis B control *(44–48)*.

Countries can apply for full validation or PTE of HBV EMTCT to demonstrate elimination of the predominant route of HBV transmission. Both of these options can be pursued within the context of triple elimination of MTCT of HIV, syphilis and hepatitis B. Countries may also choose to apply for validation of the broader HBV elimination as a public health problem, in the general population. This approach will include attainment of HBV EMTCT targets as well as mortality and programme targets related to prevention, testing and treatment of hepatitis B.

This chapter outlines criteria for validation of the elimination of HBV EMTCT at the country level, as well as programme coverage targets. It provides a range of options for countries to measure these impact and programme targets according to the available surveillance data and capacity.

3.2 Elimination of mother to child transmission of hepatitis B

Early childhood and mother-to-child transmission predominantly cause new chronic infection, although there are several other routes of HBV transmission such as blood transfusion and unsafe injections (*see* section 5.4). This section outlines the criteria for the validation of reduction of hepatitis B transmission with a focus on EMTCT of HBV. It defines indicators as well as targets and provides measurement tools for use in assessing and validating EMTCT of hepatitis B, ideally within the triple elimination framework. It also provides options for countries to measure or estimate transmission according to specific country contexts, given the differences in HBV epidemics across WHO regions, and heterogeneity in available quality surveillance data and national capacity for gathering such data. It also outlines a process for recognition of a country's progress on their journey towards achieving elimination in settings where, because of a particularly high HBsAg prevalence, the country may not yet be able to achieve the impact targets for HBV EMTCT.

3.2.1 Triple elimination of mother-to-child transmission of HIV, syphilis and Hepatitis B virus infection

Over the past decade, WHO policy recommendations have increasingly integrated health-care interventions to support person-centred care. In 2014, WHO first launched criteria and processes for validation of EMTCT of HIV and syphilis, known as "dual elimination" *(49)*, and established the GVAC for EMTCT of HIV and syphilis the following year. In 2020, WHO launched the first guidelines on PMTCT of hepatitis B and use of antiviral prophylaxis *(10)*. In 2021, hepatitis B was included in the dual elimination initiative in addition to HIV and syphilis and referred to as "triple elimination". Triple elimination has expanded to most WHO regions with an increasing number of countries adopting it as a national policy and include global targets for 2030 of zero new HIV infections in infants, elimination of congenital syphilis as a public health problem, and ≤0.1% prevalence of HBsAg among children aged 5 years. Global guidance on validation of elimination of HIV, syphilis and hepatitis B was launched in 2021 *(39)*.

Triple elimination targets can be achieved only when access to quality reproductive, maternal and child health-care services is ensured and used by all women, children and their families. Mother-to-child or vertical transmission of HIV, hepatitis B and syphilis can be effectively prevented and eliminated by similar strategies among people of reproductive age, including by antenatal screening for HIV, syphilis and HBV, syphilis treatment of mothers and their infected infants, HBV and HIV antiviral treatment or HBV prophylaxis for eligible mothers, and HBV infant prophylaxis (including birth dose vaccination). The funding and organization of antenatal care (ANC) services and programmes at global and national levels provides an opportunity for integrated service delivery to optimize programme efficiencies, deliver quality patient-centred care and improve outcomes *(50)*. The validation framework for triple elimination is described in detail in the *2021 Global guidance on criteria and processes for validation: elimination of mother-to-child transmission of HIV, syphilis and hepatitis B virus (39)*.

3.2.2 Impact targets and rationale for validation of EMTCT of hepatitis B virus

To achieve validation of the elimination of MTCT of HBV, it is necessary to demonstrate the attainment of a set of impact targets, as shown in Box 3.1.

Box 3.1 Impact targets for validation of elimination of MTCT of HBV

Countries that provide **universal HepB-BD** to all neonates should have achieved the following **impact target** for validation of EMTCT of hepatitis B:

- ≤0.1% HBsAg prevalence among the ≤5-year-old birth cohort (and older children)[a]

Countries that provide **targeted timely HepB-BD** only should have achieved an additional **impact target** for validation of EMTCT of hepatitis B:[b]

- ≤0.1% HBsAg prevalence among the ≤5-year-old birth cohort (and older children)

and

- Maternal–child transmission rate of ≤2%.[a]

[a] The ≤0.1% HBsAg prevalence can be measured among either 5 year olds, 1 year olds or those aged 1–5 years, according to existing country surveillance and data collection activities. For those regions and countries with a long history of high Hep B vaccination coverage (e.g. Region of the Americas), and that already conduct school-based serosurveys, there is flexibility to conduct serosurveys in older children >5 years.

[b] Countries that provide targeted timely HepB-BD, and where vertical transmission continues due to specific populations of pregnant women with a high HBsAg prevalence, e.g. Indigenous populations or other higher-risk vulnerable populations, are required to show both ≤0.1% HBsAg prevalence among ≤5-year-old children and an MTCT rate of ≤2%.

EMTCT: elimination of mother-to-child transmission; HepB-BD: hepatitis B birth dose; HBsAg: hepatitis B surface antigen; MTCT: mother-to-child transmission

Box 3.2 Rationale for the impact targets

Universal HepB-BD – HBsAg prevalence ≤0.1% in 1–5 year olds and older children

In the absence of preventive interventions, MTCT at the time of, or shortly after, birth accounts for most of the global burden of CHB infection, because a large proportion of these perinatal infections lead to chronic infection. The prevalence of HBsAg in ≤5 year olds captures new infections from both these transmission routes and is therefore a proxy of true CHB incidence. It is recognized that the measurement of HBsAg prevalence in 5 year olds only reflects the impact of an intervention from five years earlier. Therefore, there is flexibility for countries to include a broader age grouping of those 1–5 years of age or 1 year old to measure this indicator using representative serosurveys. It is also recognized that conducting surveys in children <5 years of age may be challenging in certain countries. Since many countries already conduct school-based hepatitis B serosurveys (e.g. in the Western Pacific Region), or among vaccinated cohorts across a wider age range (e.g. in the European Region), there could be flexibility to use these existing serosurveys in older children >5 years (as well as ≤5 years), especially if there are long-established programmes where programmatic evidence of high infant vaccination coverage has been maintained over several years. This will capture the impact on both vertical and horizontal transmission.

The GHSS 2030 targets of 95% reduction in new chronic hepatitis B infections is equivalent to ≤0.1% prevalence of HBsAg in ≤5 year olds based on modelled outputs from China *(51)*.

Attainment of this target is feasible. In 2020, for example, based on modelled data from the Center for Disease Analysis, 52/119 countries *(52)* were estimated to be already at ≤0.1% HBsAg prevalence (one country in the WHO African Region, 10 in the Eastern Mediterranean, 23 in Europe, 13 in the Americas, five in the Western Pacific, but none yet in the South-East Asia Region *(53)*. They are therefore candidates for validation of achieving the HBsAg prevalence impact target for EMTCT of hepatitis B. Based on actual serosurvey data, there are eight countries/territories in the Western Pacific Region that have an HBsAg prevalence <0.1% and one country in South-East Asia with a prevalence of 0.05%.

Box 3.2 (continued) Rationale for the impact targets

This guidance expands the cohort for measurement of this indicator to ≤5 year olds or 1 year olds, as well as to older children >5 years to provide countries (especially those with a long history and programmatic evidence of high sustained coverage of HepB-BD and infant vaccination) with greater flexibility in validation of elimination.

Targeted HepB-BD – HBsAg prevalence ≤0.1% in ≤5 year olds and mother-to-child transmission rate of ≤2%

The MTCT rate of ≤2% is an **additional** target for countries that provide targeted timely HepB-BD, and where it is recognized that there is still continuing vertical transmission due to specific subpopulations of pregnant women with high HBsAg (e.g. among Indigenous populations or migrant populations from high HBsAg-prevalence countries).

The MTCT rate measures the proportion of HBsAg-positive infants (numerator) among those infants exposed (denominator), i.e. infants of HBsAg-positive mothers. Calculation of this transmission rate requires both high-level coverage (>90%) of antenatal HBsAg testing to identify positive mothers, and PVST of exposed infants at 9–12 months of age to identify infected infants. It is recognized that some countries providing targeted timely HepB-BD, which do not currently have the required data collection systems and linkages between programmes in place to capture this target, will need to develop this capacity.

The MTCT target threshold of ≤2% is based on a modelled output MTCT rate from one country, China, predicting attainment of ≤0.1% HBsAg prevalence in 5 year olds by 2030 using the combined strategy of targeted timely HepB-BD plus at least two additional doses of hepatitis B vaccine and HBIg at very high coverage (>95–99%) *(54)*. The relationship between MTCT rate and ≤0.1% HBsAg prevalence requires confirmation through modelling in other countries. Although the MTCT target of ≤2% was not specified in the GHSS targets for 2030 *(30)*, it was included in the WHO Regional Action Plan for Viral Hepatitis in the Western Pacific *(48)*.

CHB: chronic hepatitis B infection; EMTCT: elimination of mother-to-child transmission; HepB-BD: hepatitis B birth dose; HBsAg: hepatitis B surface antigen; MTCT: mother-to-child transmission; PVST: post-vaccination serological testing

3.2.3 Programmatic targets for validation of EMTCT of HBV

Box 3.3 Programmatic targets for validation of EMTCT of HBV

Universal HepB-BD

Countries that provide **universal HepB-BD** to all neonates should have achieved and maintained both of the following programmatic targets for at least two consecutive years:

- **≥90% coverage of HepB3 vaccination**
- **≥90% coverage of HepB-BD**

Note: a target of ≥80% coverage of HepB-BD and HepB3 in all provinces or subnational areas can support evidence of equity of EMTCT of HBV in those countries with universal timely HepB-BD but is not essential for validation of elimination.

Targeted timely HepB-BD

Countries that provide **targeted timely HepB-BD** only to offspring of HBsAg-positive mothers should have achieved and maintained the following programmatic targets for at least 2 years:

- **≥90% HepB3 vaccine coverage**
- **≥90% coverage of infants at risk with targeted timely HepB-BD**
- **≥90% coverage of antenatal testing for HBsAg among pregnant women**
- **≥90% coverage with antivirals for those HBsAg-positive pregnant women eligible for prophylaxis or treatment (plus coverage of HBV-exposed babies with HBIg, if available).**

Box 3.4 Rationale for programmatic targets

The GHSS on viral hepatitis sets programme coverage targets for the most important preventive interventions (≥90% of infants with three or more doses of vaccination and ≥90% of neonates who receive HepB-BD vaccination within 24 hours of birth), but also for screening at least 90% of pregnant women and treating at least 90% of those eligible for countries using targeted timely HepB-BD. Global models have estimated that achievement of these programme coverage levels in vaccination, testing and treatment targets in the applicable birth cohort would likely result in a country achieving the impact targets.

A minimum period of 2 years for attainment of the indicators for vaccination coverage is required to ensure continuous programme performance. Of note, generally for vaccination, a five-year period of sustainability is required to be able to measure the impact by serosurveys *(55)*.

Universal HepB-BD

Achievement of **≥90% hepatitis B third-dose infant vaccination coverage and ≥90% HepB-BD vaccination coverage** are aligned with the GHSS global programmatic targets, based on modelling of coverage required to reach the impact targets. These targets are also consistent with the WHO Global Vaccine Action Plan *(56)* and the new Immunization Agenda 2030 *(9)*.These vaccine coverage indicators are annually estimated by WHO and the United Nations Children's Fund (UNICEF) in assessment of the Joint Reporting Form *(57)* and as a hepatitis core indicator (C3a) *(34)*. By 2019, 51 of 95 countries (where data are available) were estimated to have ≥90% timely HepB-BD coverage, and 117 of 186 countries (where data are available) were estimated to have coverage of the HepB3 vaccine dose of ≥90%, and 75 at ≥95%. It is noted that the WHO regions of the Americas and the Western Pacific have set regional coverage of HepB-BD and HepB3 targets at ≥95%.

≥80% coverage of HepB3 vaccination in all provinces or subnational areas is consistent with the Global Vaccine Action Plan coverage goal for 2020 *(56)*. Because of heterogeneity in coverage and population distribution, a country can achieve 90% nationally, but fail to reach remote populations. By ensuring 80% coverage at subnational levels, the immunization programme aims to achieve equity throughout the country.

Targeted timely HepB-BD

If national policy is for targeted timely HepB-BD, then indicators with coverage targets are needed, which address interventions in both the newborns of HBsAg-positive mothers (HepB3 and HepB-BD) as well as in the mothers (HBsAg testing in mothers and antivirals for those eligible).

For the **offspring of HBsAg-positive mothers, the same 90% coverage** of HepB3 and HepB-BD as for universal HepB-BD applies.

The ≥90% coverage of HBsAg testing of pregnant women is an essential programmatic target only in countries that offer targeted timely HepB-BD to infants of high-risk mothers. The high coverage serves to ensure the identification of high-risk mothers and exposed infants for interventions and is broadly consistent with the ≥95% testing coverage required for EMTCT of HIV and syphilis, in which testing and treatment of infected mothers is the only intervention to prevent MTCT.

The ≥90% coverage of the use of antivirals in eligible HBsAg-positive pregnant women (including with a high HBV DNA level (>200 000 IU/mL) or HBeAg positivity (plus **HBIg in HBV-exposed infants,** if available) is an additional indicator based on the 2020 WHO PMTCT recommendations for the use of antivirals in HBsAg-positive pregnant women *(10)*. This is lower than the coverage levels set for antiretroviral therapy (ART) and syphilis treatment for HIV and syphilis elimination, respectively, because for hepatitis B, the availability of vaccines (HepB-BD and infant vaccination) is the most effective intervention for PMTCT of hepatitis B; thus, maternal testing and the use of antivirals are additional interventions.

CHB: chronic hepatitis B infection; EMTCT: elimination of mother-to-child transmission; HepB3: three doses of hepatitis B vaccine; HepB-BD: hepatitis B vaccine birth dose; HBIg: hepatitis B immune globulin; HBsAg: hepatitis B surface antigen; MTCT: mother-to-child transmission; PMTCT: prevention of mother-to-child transmission

3.3 Criteria for path to elimination: recognizing progress towards HBV EMTCT

There is considerable heterogeneity in the epidemiology of hepatitis B across different countries and in the implementation and coverage of key interventions for EMTCT, especially HepB-BD and infant vaccination interventions. Many countries have made considerable progress in scaling up infant hepatitis B vaccination for PMTCT of hepatitis B, with or without HepB-BD vaccination. However, it is estimated in 2023 that 41 countries remain above the 2020 target of ≤1% HBsAg prevalence in 5-year-olds, most in the WHO African Region, which is characterized by high endemicity of hepatitis B infection, suboptimal coverage of routine infant vaccination, low coverage of HepB-BD, and limited availability of in vitro diagnostic infrastructure and commodities (including HBIg). In addition, in many settings, out-of-health facility birthing compounds challenges in delivering the HepB-BD. A number of Pacific Island countries in the Western Pacific Region also have a high hepatitis B prevalence, a general lack of health infrastructure and supply chain issues, including challenges in cold chain management.

In 2017, to recognize the challenges in achieving EMTCT of HIV and syphilis in high-burden countries, particularly those in the African Region, and the considerable progress made in some countries, the GVAC established a set of criteria for countries as they progress along the "path to elimination". The PTE for hepatitis B was developed in line with this framework and is particularly applicable to high-HBsAg prevalence countries that are still improving coverage for hepatitis B infant and HepB-BD vaccination, such as in the African Region. This is important, given the opportunity for low-income countries to access funding for introduction of HepB-BD through the investment strategy of Gavi, the Vaccine Alliance*(58)*. An overview of the approach for hepatitis B can be found in Fig. 3.1.

The PTE involves a three-tier system (gold, silver and bronze), which recognizes different stages of progress toward elimination. Each tier is defined by attainment of increasing levels of service coverage of key interventions for PMTCT of hepatitis B through infant and childhood vaccination and testing of pregnant women. Moving to a higher tier brings a country progressively closer to the ultimate elimination target of ≤0.1% HBsAg prevalence in 5 year olds, given that achievement of HepB-BD and HepB3 vaccination coverage, together with antenatal testing and antiviral prophylaxis, will ultimately result in the elimination of MTCT of HBV.

A country seeking validation for being on the PTE will have the opportunity of being recognized for significant efforts towards EMTCT of hepatitis B and organize a consultative process to further develop its national strategy to reach elimination in the coming years. The validation process is conducted at the regional level and is outlined in Chapter 6 and will follow the same procedure as a country requesting validation for EMTCT of hepatitis B (Table 3.1).

Table 3.1 Indicators and targets for path to elimination of HBV EMTCT

Indicators for the assessment of progress on the path to elimination of MTCT of hepatitis B in countries with an HBsAg prevalence >1% among ≤5 year olds and/or with general population prevalence exceeding 5%		
	Impact targets	**Programme targets[a]**
The gold level recognizes where a country has implemented:		
GOLD TIER	Not necessary	• ≥90% coverage of hepatitis B 3rd dose infant vaccination • ≥90% coverage of universal timely hepatitis B birth dose • Antenatal hepatitis B surface antigen (HBsAg) testing coverage ≥30%
The silver level recognizes where a country has implemented:		
SILVER TIER	Not necessary	• ≥90% coverage of hepatitis B 3rd dose infant vaccination • ≥50% coverage of universal timely hepatitis B birth dose • Antenatal HBsAg testing available in public sector
The bronze level recognizes where a country has implemented:		
BRONZE TIER	Not necessary	• ≥90% coverage of hepatitis B 3rd dose infant vaccination • Implementation of universal timely hepatitis B birth-dose policy

a Programme targets should be achieved for 2 years.
Requirement for high coverage at the district level: e.g. ≥80% coverage in all districts for HepB3 in all tiers and ≥80% coverage in all districts for HepB-BD in gold tier and ≥50% for timely targeted HepB-BD in all districts for the silver tier.

Box 3.5 Rationale for the path to elimination

The PTE seeks to recognize countries that have made significant progress in implementing key hepatitis B vaccination interventions alongside antenatal testing and antiviral prophylaxis for eligible women, but that may not yet be in a position to achieve the elimination impact target of ≤0.1% HBsAg prevalence in ≤5 year olds. This may be because of a current high HBsAg prevalence and limited implementation of universal HepB-BD vaccination. Countries with an estimated HBsAg prevalence in 5 year olds of ≥1% are eligible to seek validation for the PTE as it is recognized that it takes time to expand programmatic coverage to an extent that it will reduce prevalence from >1% to ≤0.1%.

A key principle is that each tier of the PTE represents *a milestone of progress* towards elimination, where validation of elimination is the ultimate goal.

The cost of measurement of the impact indicator of HBsAg prevalence in ≤5 year olds through a national survey may be an impediment to monitoring and achieving progress towards elimination. Hepatitis B vaccination is highly efficient in preventing MTCT of hepatitis B and if the coverage levels in the gold, silver and bronze tiers have been attained, then this would result in countries being able to achieve elimination in future years. For these reasons, PTE criteria require achieving programmatic coverage targets only as countries progress to measuring impact targets.

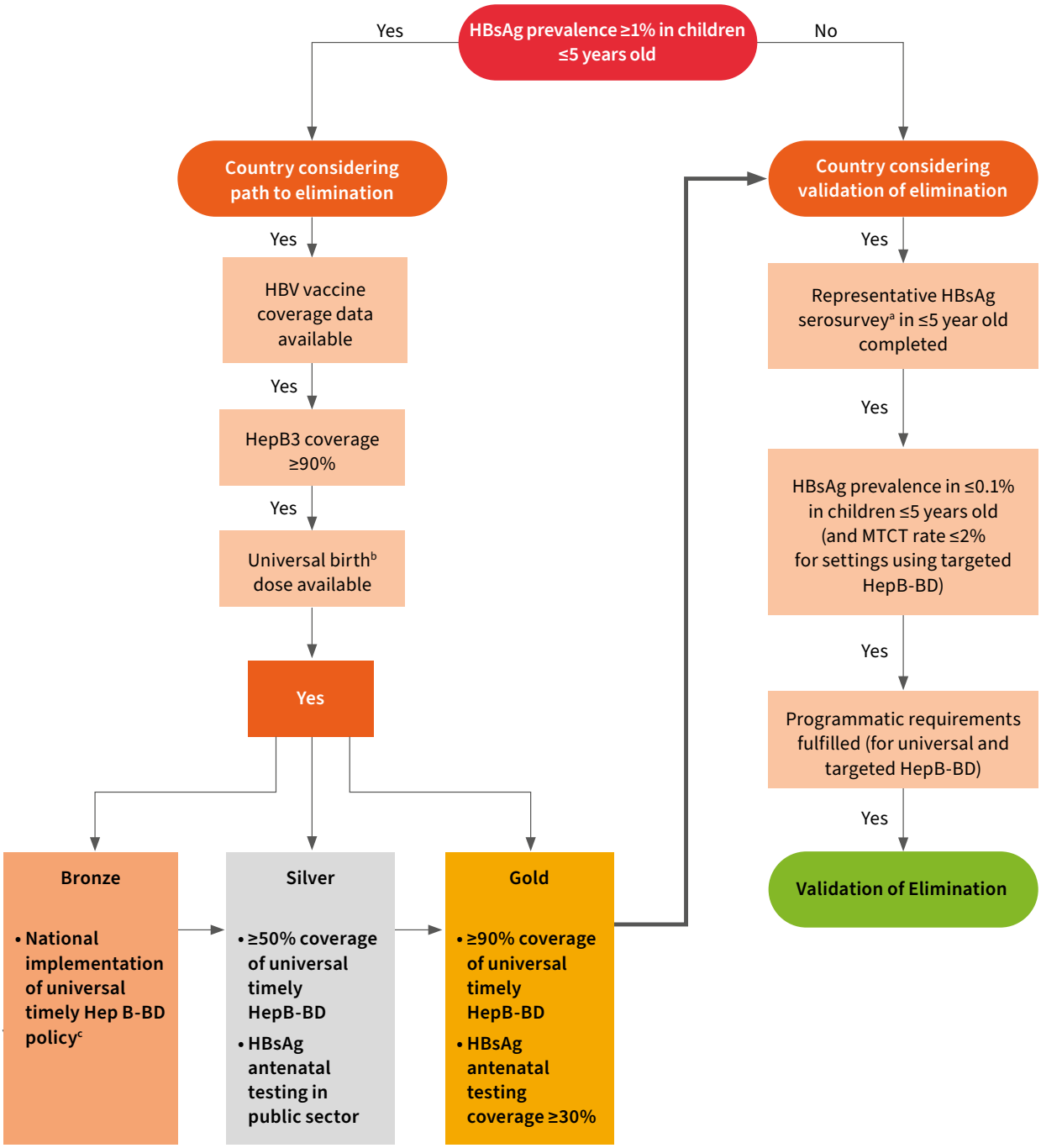
The indicators for the PTE reflect the critical role of HepB-BD and infant vaccination in eliminating MTCT of HBV.

- The bronze level recognizes where a country has implemented a universal HepB-BD policy as a first critical step towards EMTCT.
- The silver level of HepB-BD coverage of ≥50% recognizes the attainment of the 2020 milestone target for HepB-BD coverage in the GHSS *as well as antenatal HBsAg testing in the public sector.*
- The gold level of HepB-BD coverage of ≥90% recognizes the attainment of the 2030 service coverage target for HepB-BD coverage in the GHSS; it further introduces the importance of HBsAg testing in pregnant women within the triple elimination framework.

Other programmatic indicators are not included in the PTE process, as the aim is to use a set of simplified indicators that are routinely measured in most countries. Other measures such as the use of tenofovir and/or HBIg are not routinely captured in many countries (Fig. 3.1).

EMTCT: elimination of mother-to-child transmission; GHSS: Global health sector strategy; HepB-BD: hepatitis B birth dose; HBIg: hepatitis B immune globulin; HBsAg: hepatitis B surface antigen; MTCT: mother-to-child transmission

Fig. 3.1 Summary schematic of approach to validation of hepatitis B EMTCT and path to elimination for countries



B3: three doses of hepatis B vaccine; BD: birth dose; EMTCT: elimination of mother-to-child transmission; HBsAg: hepatitis B surface antigen

a Alternative approach to measurement of HBV EMTCT targets using routine data and complemented by modeling in countries with strong integrated national surveillance systems

b Countries with targeted HepB-BD are required to show ≥ 90% coverage of maternal ANC testing and should apply for full validation of HBV EMTCT.

c This means that (i) country has a national policy (ii) and services are implemented in at least several public health services at every provincial/sub-national level.

3.4 Approaches to measuring HBV incidence as part of EMTCT of HBV

3.4.1 Measurement of impact indicator(s) for validation of EMTCT of hepatitis B

The preferred approach is for countries to collect person-level empirical data, i.e. a national survey on HBsAg seroprevalence (single or multiphase) in children aged ≤5 years (and also older children, as appropriate) (Box 3.6). As an alternative, in countries with high programme coverage and highly developed integrated HBV surveillance systems for both maternal and neonatal data, these data may be used to generate evidence of attainment of the goal, as described in Box 3.6. If these are not feasible, a mathematical modelling process of the impact indicator using available representative empirical data may be considered. Triangulation of methods is recommended.

Box 3.6 Measurement of childhood prevalence of HBsAg in ≤5 year olds

A. Preferred approach: measurement of childhood HBsAg prevalence in ≤5 year olds

The preferred approach is to directly measure a proxy for chronic HBV incidence (i.e. childhood HBsAg prevalence in ≤5 year olds) with national-level biomarker surveys among young children. This is the recommended gold standard by WHO in ≤5 year olds for monitoring progress towards hepatitis B control targets, but requires large sample sizes in settings that have a low prevalence *(55)* The focus should be on obtaining the best possible representative prevalence estimates with narrow confidence intervals in the 1–5-year-old age cohort. The advantage of measuring HBsAg prevalence in this age group is that it also captures the effects of interventions on mother-to-child as well as early horizontal transmission. There is therefore flexibility for countries to include the convenience of an age group of 1–5 years or a narrower age range such as 1 year old (to capture the impact of recent interventions, though there are logistical and cost constraints in undertaking serosurveys in a younger cohort aged 1 year, with requirement for household surveys and venous sampling).

Given that many countries already conduct school-based hepatitis B serosurveys or among vaccinated cohorts across a wider age range, there is flexibility to use these existing serosurveys in older children >5 years, especially if there is a long history and programmatic evidence of high sustained hepatitis B vaccine birth dose and infant vaccination coverage. This will also capture the impact on both vertical and horizontal transmission.

The technical challenges of conducting a nationally representative biomarker survey increases as countries approach the ≤0.1% goal, and the required sample size to achieve confidence estimates can be very large and indeed costly. This can be minimized through complementing such serosurveys with other focused surveys targeting high-risk geographical areas or subpopulations likely to have a higher prevalence (e.g. children from particular population groups or migrant communities) or based on programmatic indictors such as HepB3 and HepB-BD and prevalence in pregnant women or women of reproductive age, multiphase methodology surveys or integrating into existing national surveys for other disease areas such as the Demographic and Health Surveys and AIDS Indicator Surveys.

Nevertheless, conducting **multiphase methodology serosurveys** *(59)* (to reduce the required sample size and increase the power of the serosurvey to confirm elimination) does require strong programmatic data, adequate demographic data and a robust knowledge of the various geographical and population risk factors associated with hepatitis B as well as close to universal engagement of pregnant women by health services.

For countries with a small population size such as the islands in the Pacific and the Caribbean, it may be actually easier to do a national survey and validate elimination. A finite population correction factor (FPC) can be calculated when estimating the required sample size. Even for verification of control, an FPC was applied to generate the sample size due to the small size of the population in those islands *(60,61)*.

Box 3.6 (continued) Measurement of childhood prevalence of HBsAg in ≤5 year olds

B. Additional approach: measurement of the MTCT rate through follow up of HBV-exposed infants in settings using Hep B targeted timely birth dose vaccination (Box 3.2)

Measurement of the additional indicator and target of an MTCT rate of ≤2% may be indicated in countries using targeted timely HepB-BD where there are subpopulations with still high prevalence and so continuing vertical MTCT of hepatitis B (e.g. among Indigenous populations or migrant populations from high-HBsAg prevalence countries). It may also be considered in settings where population-based serosurveys may not be feasible.

Note: The MTCT rate is calculated as the proportion of infants with CHB infection, i.e. HBsAg-positive infants (numerator) of those infants exposed (denominator), i.e. infants of HBsAg-positive mothers. Calculation of this transmission rate requires both high-level coverage (>90%) of antenatal HBsAg testing to identify positive mothers, and post-vaccination serological testing (PVST) of exposed infants at 9–12 months of age to identify infected infants. *Note:* some countries such as China recommend PVST at 7–9 months of age. The WHO policy on hepatitis B vaccination recommends that PVST[a] should be carried out at least 1–2 months after administration of the last dose of the hepatitis B vaccine series when the antibody response is greatest *(3)*. Several scenarios are possible. The exposed infant may be: (i) infected with HBV; (ii) uninfected and have responded adequately to the hepatitis B vaccine series; or (iii) uninfected but may not have responded to the hepatitis B vaccine and needs to be revaccinated.

It is recognized that some countries providing targeted timely HepB-BD, which do not currently have the required data collection systems and linkages between programmes in place to capture this target, will need to develop this capacity.

[a]Routine PSVT testing for immunity is not necessary, but is recommended in the context of HBV elimination in low-prevalence settings where it serves as a tool to estimate EMTCT of HBV.

C. Alternate approach: use of routine programmatic data to estimate HBsAg prevalence in ≤5 year olds (with modelled estimates)

Where countries can demonstrate sustained high HBsAg testing coverage of pregnant women (>90%) in the presence of PVST in exposed infants and the availability of standardized strong monitoring and evaluation (M&E) and integrated strategic information systems, the use of routine data for assessing both impact (HBsAg prevalence among the ≤5-year and MTCT rate) and programme targets for EMTCT of HBV is possible without the need for additional serosurveys. This method can be complemented and confirmed by mathematical modelling to strengthen the process of country validation.

CHB: chronic hepatits B infection; EMTCT: elimination of mother-to-child transmission; GHSS: Global health sector strategy (on viral hepatitis); HepB3: three doses of hepatitis B vaccine; HepB-BD: hepatitis B birth dose; HBsAg: hepatitis B surface antigen; MTCT: mother-to-child transmission

3.4.2 Measurement of programmatic indicators

Indicators for hepatitis B vaccination coverage are based on routinely collected programme data, which are collated through the WHO and UNICEF Estimates of National Immunization Coverage (WUENIC). While the final estimates are informed by data from national authorities and may differ from the reported data, they constitute an independent technical assessment by WHO and UNICEF of the likely true coverage *(57)*. For district-level coverage (where necessary), vaccine administrative coverage data can be used or available data from immunization coverage surveys that are powered to provide district-level estimates.

Timely HepB-BD estimates are produced for vaccination given within 24 hours after birth. The timeliness component of HepB-BD administration is required; however, previous surveys and administrative data either do not appropriately collect or report on the strict timing for administration. As a result, WHO and UNICEF estimates for HepB-BD have been overestimated historically, especially for countries with low rates of "institutionalized" births in health facilities *(57)*.

Testing coverage of pregnant women can be captured through national data reporting systems for the maternal and child health programme. While many countries collect and report antenatal HIV and syphilis testing data, national surveillance of hepatitis B testing and reporting on pregnant women and their viral loads lags behind. Countries are encouraged to include hepatitis B testing in HIV and syphilis testing programmes and follow this up with integrated data collation and reporting.

Data on the use of antivirals and HBIg during pregnancy should be collected and reported through national data collection systems for maternal and child health and antenatal programmes.

3.4.3 Using mathematical modelling alongside empirical data to determine attainment of the elimination targets

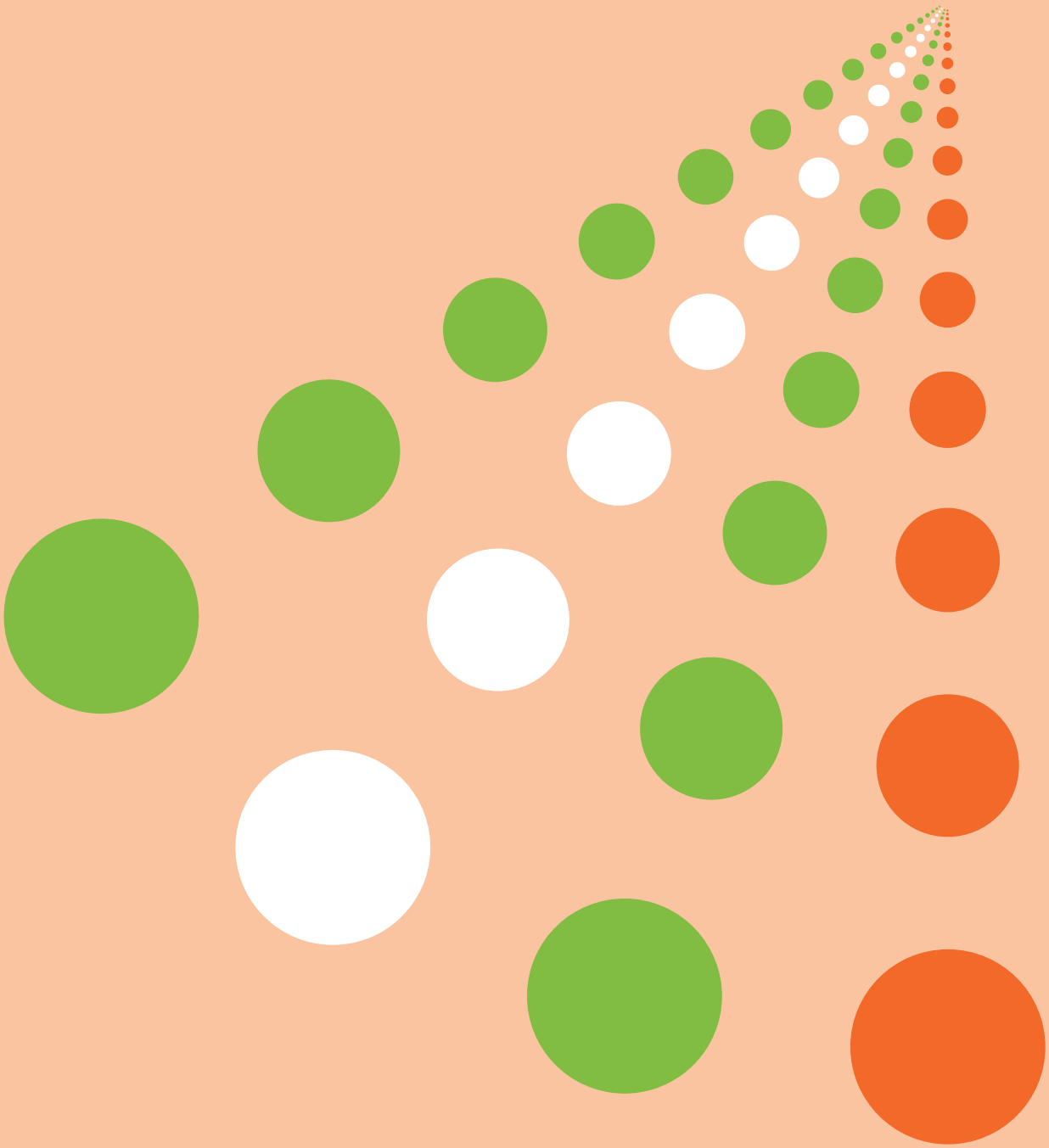
As detailed throughout this section and in Annex 5, mathematical modelling is a powerful tool that can offer new insights and identify data gaps in countries' progress towards the elimination of HBV transmission and mortality. However, modelling is not a substitute for the collection of data. Where national empirical data are of sufficient quality and coverage, mathematical models may be useful to assess the progress of countries towards the achievement of the impact targets for perinatal and horizontal hepatitis B elimination and constructing the HBV cascade of care to support achievement of programme targets. Models may also be used to project the potential impact of additional preventive (including immunization), diagnostic and treatment interventions on the 2030 targets for elimination.

To determine if a country has achieved elimination, modelling could be used in the following specific applications:

- to set country-specific targets for programmatic coverage that can be used to guide a strategic response;
- to utilize programmatic data to determine whether it is likely that elimination has been reached in any particular place. This could also inform the commissioning of a biomarker survey. The general assumption is that where global targets for programmatic coverage indicators have been reached then elimination is also likely to have been reached. However, this relies on assumptions made in the course of various modelling exercises, which may not apply to all epidemiological contexts. In addition, there would need to be assurance of high-quality programmatic data and robust reporting systems if this methodology was to be adopted;
- to establish whether measurement of the MTCT rate may alone be sufficient to establish whether elimination has been reached, and to "convert" a measurement of MTCT to an estimate of the likely incidence rate for the whole population;
- to establish the necessary design of a biomarker survey and to "convert" a measure of HBV prevalence into an estimate of the likely incidence rate for the whole population. The standards for the calculation of these indicators for HBV EMTCT, comparable to the approach used for the Spectrum model for HIV *(62)*, remain to be determined.

Chapter 4.

Validation of elimination of hepatitis B as a public health problem



4.1 Background

Hepatitis B is an important global health problem with an estimated 296 million people living with CHB and 1.5 million new chronic infections in 2019. It is also a leading cause of death is a leading cause of death, causing an estimated 0.8 million deaths annually *(1)*. About 96% of deaths due to viral hepatitis are attributable to the complications of chronic HBV (66%) and HCV (30%) related decompensated cirrhosis and HCC. A key goal of the national elimination programme is to reduce HBV transmission as well as the liver related mortality. Mother to child and early childhood infections are the predominant routes of HBV transmission. The prevalence of HBsAg in children is a proxy for new chronic infections from vertical and/or early horizontal transmission, and is used as a surrogate target of the cumulative incidence of CHB infections. The GHSS established coverage targets for HBV preventive interventions (three or more doses of HBV vaccine for 90% of infants, and timely HepB-BD vaccination for at least 90% of neonates, i.e. within 24 hours of birth, as the most important interventions for reducing MTCT of HBV as well as early childhood transmission (see chapter 3). In addition to childhood vaccination and timely HepB-BD vaccination, WHO recommends the screening of pregnant women and administration of antiviral prophylaxis and/or antiviral treatment *(9)* where eligible, in order to further reduce the perinatal transmission rates of HBV. Within the broader context of HBV elimination as a public health problem, WHO also recommends implementation of other intervention including safe injections and blood products and harm reduction measures to prevent inadvertent hepatitis transmission.

In people living with chronic hepatitis B, progressive liver disease may occur over several decades. Antiviral treatment for HBV infection (mainly lifelong) with tenofovir or entecavir induces sustained viral suppression and reduces disease progression and the risk of mortality from HBV-related complications. The GHSS also established coverage targets for diagnosis (diagnosis of 90% of people infected with HBV) and treatment (antiviral treatment of 80% of people who are diagnosed and eligible for treatment. Without treatment, an estimated 20–30% of people with chronic HBV are at risk of HBV-related complications such as decompensated cirrhosis and HCC, especially those with advanced liver disease.

Countries can apply for validation of Hepatitis B elimination as a public health problem (demonstrating achievement of incidence, mortality and programme targets), or any of the three tiers of PTE, which recognize countries with significant programmatic coverage of HBV prevention interventions (HBV EMTCT, injection and blood safety) as well as testing and treatment.

This chapter focuses on the criteria for the assessment of reduction in liver-related mortality due to chronic viral hepatitis. It also provides guidance for countries to measure or estimate mortality rates according to specific country contexts, available surveillance system and capacity for gathering accurate and adequate data.

4.2 Impact indicators and targets for HBV elimination

Validation of hepatitis B elimination as a public health problem, requires achievement of incidence (including HBV EMTCT), mortality and programme targets. The impact indicators and targets for HBV EMTCT, as the predominant route of hepatitis B transmission are fully described in chapter 3. The criteria for validation of elimination of HBV as a public health problem is shown in table 4.1. HBV mortality is a core component of this approach and includes interventions of testing and treatment represented in the cascade of care as well as prevention approaches common to other blood borne diseases.

Table 4.1 Criteria for validation of elimination of HBV as a public health problem

Criteria*	Data sources and approaches to measurement
HBV incidence (HBV EMTCT)	• National biomarker survey, post-vaccination serological testing (PVST) survey for MTCT rate, triangulation of data (including from immunization and ANC programmes), modelled estimates (based on programme data or existing biomarker surveys), WHO modelled estimates of HBsAg prevalence.
HBV prevention interventions	• Prevention programmes records- including HepB-BD and childhood vaccination, MCH records, Injection safety facility surveys, DHS population surveys, records from procurement of engineered devices, blood transfusion services and harm reduction programmes (NSP, OAT), population size estimates for PWID and opioid dependent people.
HBV mortality	• Data from vital registration of deaths from cirrhosis and HCC and cancer registries (HCC reporting), surveillance for sequelae in sentinel centres, modelled estimates (using existing epidemiological or programme data).
HBV cascade of care	• Testing and treatment programme records including hepatitis testing service records, laboratory registers, logbooks and reporting forms at facility and community levels, EMR/electronic information systems.

* For validation, attainment of the impact (incidence and mortality) is accompanied by a set of programmatic targets linked to service delivery which need to be maintained for 2 years to show consistency in the programmatic response. Evidence of quality of data sources, laboratory processes, health care programmes as well as adherence to principles of principles of equity, gender equality, human rights and community engagement are important implementation considerations.

To validate a reduction in hepatitis B mortality to support elimination of viral hepatitis as a public health problem, it is necessary to demonstrate attainment of a combined absolute threshold for mortality of ≤6/100 000 per year for both HBV and HCV at the country level by 2030 (Box 4.1). In addition, countries need to demonstrate achievement of the core programmatic targets, as shown in Box 4.3.

Box 4.1 Impact targets for validation of reduction in viral hepatitis mortality

Countries should have achieved the following impact target for validation with regard to viral hepatitis mortality.

A combined hepatitis B- and C-related mortality rate of ≤6/100 000 per year by 2030

The calculation of different mortality targets for HBV and HCV alone based on the global contribution of HBV and HCV to global mortality may differ significantly from the national epidemiology and is therefore no longer recommended for country-level validation.

Box 4.2 Rationale for absolute mortality indicators of chronic viral hepatitis

The GHSS for viral hepatitis states that global HBV- and HCV-related mortality should be reduced from 1.4 million deaths in 2015 to less than 500 000 by 2030 (i.e. a 65% relative reduction for both viral hepatitis B and C). Global population projections for 2030 are around 8.6 billion, and so the absolute 2030 mortality rate that would equate to the 500 000 deaths is calculated as 5.9/100 000 for HBV and HCV combined, rounded to a crude mortality rate of 6/100 000 population.

A differential absolute mortality threshold derived from this calculation was previously proposed to reflect the relative contribution of HBV and HCV to liver- related global mortality (66% and 30%, respectively) is equivalent to 4/100,000 and 2/100,000 for HBV and HCV per year. Lessons from the elimination pilots in 7 countries, as well as other country experience show that these differential thresholds may not be relevant or practical at the country level as the relative contribution of HBV and HCV may vary considerably from one country to another, depending on the national epidemiological context.

Additional concerns in application of differential absolute thresholds for hepatitis B and C mortality is related to (i) the lack of reliable mortality data in many countries, and (ii) widely divergent global population growth and age distribution, for estimation of global projection for 2030 mortality rate.

The preferred approach for estimating country mortality is therefore to use a combined crude mortality rate of ≤ 6/100 000. Additional justification are noted below:

- In the majority of countries, with a few exceptions, either hepatitis B or C virus predominates, and the other virus does not represent a public health problem and would therefore not significantly impact the mortality rate.
- The overarching goal is to eliminate both hepatitis B and C, so every country is encouraged to monitor mortality from HBV and HCV, regardless of which virus is prioritized for elimination.
- Surveillance systems in place for one virus should be able to monitor both, and detect any expected or unexpected change (e.g. migration from countries with high HBV endemicity, or recent opioid epidemics that would affect HCV transmission in PWID).

This combined mortality target implies that the documentation of mortality reduction should be obtained for both viruses. It is recognized that attainment of the incidence and mortality targets may occur at different times, as it may take substantially longer for mortality to fall following a reduction in incidence. The long latency from the impact of treatment on mortality in contrast to incidence is well recognized, especially for hepatitis B where treatment is currently limited to viral suppression and often requires life long therapy.

4.2.1 Programmatic targets for validation of HBV elimination

Programmatic targets for validation of hepatitis B elimination are shown in table 4.1. It includes prevention interventions for safe blood transfusion, injection safety and EMTCT as well as diagnosis and treatment. In the near- to medium term, mortality is influenced by the proportion of people living with HBV that are diagnosed and treated (Box 4.3).

Box 4.3 Programmatic targets for validation of HBV elimination as a public health problem

Countries should have achieved and maintained for at least 2 years the following programmatic targets for validating the elimination of HBV mortality:

Testing and treatment

- **≥90% of persons with chronic hepatitis B infection diagnosed**
- **≥80% of persons diagnosed with chronic hepatitis B virus infection treated**

Prevention

- **100% of blood units screened for HBsAg**
- **100% safe injections in health-care settings**

* Programmatic targets for HBV EMTCT are shown in box 3.3.

Box 4.4 Rationale for the programmatic targets

The GHSS for viral hepatitis established hepatitis B programme coverage targets for preventive interventions (immunization, blood and injection safety), diagnosis (diagnosis of 90% of people with chronic HBV infection), and treatment (antiviral treatment of 80% people who are diagnosed are receiving antiviral treatment). This was partially based on global mathematical models, which showed that achievement and maintenance of optimal coverage thresholds would result in a country achieving the impact targets for incidence and mortality *(30)*.

National and cohort data show that attainment of high coverage of prevention, testing and treatment interventions has an impact on mortality. The most important determinant of mortality, in the short- to medium term, is access to early diagnosis and effective antiviral treatment to prevent disease progression to cirrhosis and reduce development of HCC and liver-related deaths. For HBV, this is long-term antiviral treatment with tenofovir (or entecavir) to achieve sustained suppression of HBV DNA below detectable levels *(25)*.

For prevention, the programmatic targets of HBV vaccination, blood safety and injection safety are consistent with guidance in these areas of WHO global agreements and guidance (*see* sections 5.4.2 and 5.4.3). Lessons from the country elimination pilots illustrate various challenges with measuring safe injection coverage using population level DHS surveys or health care facility-assessment. The use of bioengineered (autodisable) devices and evidence of procurement of these commodities for use in the public sector is considered an alternative indicator for injection safety.

4.3 Approaches to measurement of indicators and targets for viral hepatitis B mortality

There is a paucity of quality data on liver-related mortality due to HBV, particularly in LMICs, and challenges in generating complete country-specific empirical datasets for HBV- and/or HCV-related mortality (among deaths due to HCC and decompensated cirrhosis).

There are several potential approaches and methodologies that can be used for measuring and monitoring mortality due to HBV-related liver conditions in countries. Countries should review and identify the most appropriate option according to their epidemiological profile, health system context, and availability and quality of surveillance data. The advantages and disadvantages of the different options are summarized in Boxes 4.5 and 4.6. Where possible, a relatively standardized methodology should be used across multiple countries as described below.

4.3.1 Measurement of the impact indicators for validation of mortality due to viral hepatitis

The capacity for assessing mortality rates varies widely across the world: some countries (or jurisdictions within countries) have good HBV testing levels, sophisticated public health surveillance systems, and notification registries that allow data linkage with, for example, hospitalizations, cancer and death registries. At the other end of the spectrum, many countries, particularly low-income ones, have low screening levels, and lack the capacity to monitor liver-related deaths, even from HCC, at the population level.

Direct measurement of liver-related mortality

The optimal approach to measuring the absolute mortality indicator is through direct measurement of liver-related deaths due to HBV infection.

The measurement of an absolute decline in mortality requires the capacity to estimate and monitor the number of liver-related deaths due to HBV infection. Options for empirical data-based direct mortality monitoring include death certification, cancer registries and sentinel clinics. However, for many settings, this would require significant changes in coding practices, and even the format of the death certificate, which often lack cause specific or aetiological diagnosis.

Indirect measurement of liver-related mortality

There are several alternative methodologies that can support the estimation of a national mortality rate, where direct measurement is not possible.

A. Use of sentinel networks of clinical sites for estimation of the attributable fraction

The use of clinic-based sentinel networks in countries provides a mechanism for monitoring cases of HCC as well as decompensated cirrhosis in the absence of a formal registry, and the attributable fraction (AF) of cases due to HBV and HCV. This population-specific caseload can then be extrapolated to the national level and applied to the national mortality estimate to provide an national estimate of HBV- and HCV-related mortality (Box 4.5 and annex 6).

Using sentinel networks, the generation of national estimates of hepatitis-related mortality requires three separate steps:

Step 1: In selected representative sentinel centres, estimation of the fraction of patients with decompensated cirrhosis and HCC whose disease is attributable to HBV and HCV (AFs).

Step 2: Estimation of the mortality envelope from cirrhosis and HCC: this estimation would be based on data derived from vital statistics and cancer registries, where available and of sufficient quality;

Step 3: To apply these AFs to the mortality envelope derived from vital statistics to estimate national mortality due to viral hepatitis sequelae.

In addition, to assess and improve the quality of vital statistics (the mortality envelope) – critical for public health systems to track hepatitis-related mortality – countries may consider the following options (non-exhaustive):

- Mortality from cirrhosis and HCC in selected sentinel centres, as described below and in Annex 6, can be measured and compared to data corresponding to the same geographical area as reported in the national vital statistics database.
- Unexpected or unexplained geographical or temporal variations in cirrhosis/HCC mortality can then be investigated.
- Triangulation can be done with other available robust data sources such as cancer registries, national databases of notifiable diseases, or cohorts of patients chronically infected with HBV (if available).

Countries could consider moving progressively toward the freely available ICD-11 coding.[3]

3 ICD 11 coding allows (i) digital platform and recording; (ii) automatic prompting to etiological factors (e.g. mandatory post coordination for cirrhosis automatically asks for certain aetiologies, including viral hepatitis); (iii) internal quality control; and (iv) integration with other databases (hospital, notifiable diseases, etc.).

Box 4.5 Rationale for measuring and monitoring the viral hepatitis attributable fraction among all cases with HCC and cirrhosis

Deaths related to hepatitis B infections are mostly due to decompensated cirrhosis and HCC, but accurately measuring mortality is challenging as death certificates often do not capture the underlying disease (e.g. viral hepatitis infections or other causes of chronic liver disease such as heavy alcohol consumption or steatotic liver disease [SLD]). Most countries have not yet established a clear system for generating national estimates of mortality resulting from the sequelae of chronic HBV and HCV infection.

WHO has developed a protocol to assist sentinel centres (e.g. hepatology or gastroenterology units) to estimate the proportion of people with HBV- and HCV-related cirrhosis and HCC. This proportion can be used to estimate the fractions of these sequelae attributable to HBV and HCV infection and to then generate national HBV and HCV mortality rates. The WHO protocol provides detailed methodology on sampling procedures and data collection, as well as guidance on data analysis, data ownership and ethical considerations *(63)*. A simplified protocol to collect the minimum set of data needed to generate national AF estimates is shown in Annex 6 and should be adapted to country context.

A major advantage of the use of clinic-based sentinel networks is that this information has already been utilized by the Institute for Health Metrics and Evaluation (IHME) as part of their global burden of disease modelling approach *(64)*. A further advantage is that a relatively small number of representative sites could be utilized to provide an ongoing surveillance mechanism. Limitations include the fact that the characteristics of cases at larger tertiary centres may not be representative of community caseloads, and referral patterns may vary based on local patterns of comorbidities and primary health care capacity.

To support countries in monitoring mortality from HBV over time at the national level, two independent, complementary datasets should be collected. These are given below:

1. **The proportions of sequelae** (decompensated cirrhosis and HCC) that are attributable to hepatitis B or to other risk factors that are known to cause these sequelae
    a. These AFs vary greatly between countries due to differences in the scale and progression of HBV epidemics over time and to the presence of other risk factors (alcohol, non-alcoholic steatohepatitis [NASH], or other rarer conditions).
    b. Up-to-date AFs are best estimated in selected sentinel centres that diagnose, follow up and treat representative populations of patients with cirrhosis and HCC.
2. **The "mortality envelope"** from chronic liver disease (i.e. cirrhosis and HCC)*
    a. National mortality data are usually available from vital statistics registries, but at the country level their quality needs to be assessed to ensure that all (or an acceptable proportion of) deaths occurring as a consequence of decompensated cirrhosis or primary liver cancer, namely HCC, are captured, whatever the underlying cause.

*This "mortality envelope" is a term that has been developed to define all the different possible causes of death (e.g. HCC) that are potentially related to HBV or HCV as defined by ICD coding or other criteria (e.g. clinical).

B. Use of vital statistics and HCC incidence as a surrogate for liver-related mortality

This approach consists of identifying new HCC cases that can be attributed to either HBV or HCV and is therefore a country-level proxy of liver-related mortality due to HBV and HCV. A linkage with nationally available HBV (and HCV) data is needed, such as cohort, registry, surveillance system, which would then allow indirect measurement of HBV/HCV mortality. This approach requires the availability or establishment of population-based surveillance systems for monitoring people with HBV and HCV infection, as well as linkages between databases of diagnoses and cancer registries for viral hepatitis or hospitalization records of HCC diagnosis (Box 4.6) *(65–69)*.

Box 4.6 Rationale for the use of HCC incidence as a proxy for HBV- and HCV-related cancer mortality

Worldwide, primary liver cancer, which is mostly HCC, is the fifth leading type of cancer and the third leading cause of cancer-related deaths *(70)*. The relative contribution of HBV and HCV infections to HCC varies across different regions. For example, HBV-related HCC is more dominant in Asian (except for Japan) and African countries *(71)*. Poor survival following HCC means that trends in HCC incidence correlate well with trends in HCC mortality *(68,72)*.

The major advantage of using HCC incidence as a surrogate indicator for liver cancer-related mortality is that new HCC cases are often more reliably recorded than decompensated cirrhosis. This is because there is more reliable surveillance for both clinical diagnostic events and deaths due to HCC than for decompensated cirrhosis. The focus for such an indicator and measurement mechanism would be to optimize surveillance mechanisms for monitoring cancer diagnoses and deaths, including those that are HCC related, rather than a broader focus on liver-related mortality due to viral hepatitis. Limitations include: the need for considerable resources to optimize data collection; lack of cancer registries and access to histological data in many countries, as well as data on attributable causes such as HBV and HCV; and that trends in HCC incidence do not always reflect trends in liver-related mortality, particularly in settings where HCC management is improving. In addition, there are concerns that a focus on HCC would underestimate hepatitis-related mortality – for example, in the European Union, HCC-related deaths account for 55% of the mortality burden due to viral hepatitis *(73)*.

4.3.2 Mathematical modelling for estimation of mortality

As detailed throughout this section and in Annex 5, mathematical modelling (although is not a substitute for the collection of data) it is a powerful complementary tool that offers new insights and identifies data gaps in countries' progress towards attaining the mortality reduction component of hepatitis elimination.

While the preferred approach is for countries to collect mortality data directly, i.e. a national death registry, if this is not feasible, a mathematical modelling process of the impact indicator, using available existing representative empirical data or proxy measures, including, but not limited to, HCC incidence and fractions of decompensated cirrhosis or HCC cases attributable to HBV/HCV may be considered. Modelling-based mechanisms have the potential for calibration using epidemiological data and would be suitable whether the target was absolute mortality or relative reduction. Such modelling could be used to model mortality on the basis of sequential measurement of prevalence, or estimation of viraemic prevalence (for HCV) or empirical data from HCC incidence or AF. These modelling approaches allow comparison with empirical data, if available, and could facilitate estimation in settings where there are limited mortality data but sufficient other epidemiological and programmatic data *(74)*.

Modelling data could also be used to predict the impact of testing and treatment programme coverage or other service delivery data on mortality. This option, however, requires access to and ongoing monitoring of primary data for service delivery interventions (particularly antiviral therapy coverage) and then development of models to incorporate these parameters as well as data on other relevant comorbidities (e.g. alcohol use disorder) that affect progression of liver disease.

At present, there are several reasonable approaches to mathematical modelling of viral hepatitis mortality. The use of mathematical modelling to complement empirical data for the estimation of country-level mortality should therefore be clearly described and justified, the important sources of uncertainty reported, and the validity of the model addressed (Box 4.7). Additionally, assumptions should be stated, ascertained and discussed, and sources of parameters and empirical data communicated prior to request for WHO validation.

Box 4.7 Rationale for indirect estimation of viral hepatitis-related mortality using mathematical modelling

Data on death registration or cancer registration are inadequate or of low quality in most countries. The lack of systematic and cause-specific death registries in most countries means that a reliance on direct monitoring of trends in HBV- and HCV-related death notifications would be problematic. In many high- and some middle-income countries, dynamic models of transmission using available programmatic data are commonly used to understand the HBV and HCV epidemics and project the impact of prevention, diagnosis and treatment scale up *(75)*. Bayesian meta-regression and cause-of-death ensemble models (CODEm) have also been used to triangulate between data on multiple indicators and produce estimates of the incidence and prevalence of HBV and HCV and their sequelae, including mortality, and gauge the impact of interventions *(76)*.

The major strength of using mathematical modelling is that there are at least three well-established international modelling groups involved in country-level estimation of hepatits B- and C-related mortality for many years. A potential limitation is the diversity of modelling methodologies that have been used by different countries. The options are for countries to use their own in-country established groups or adapt a preferred international model. In the case of disease progression models, with cofactor (such as alcohol) and treatment impact parameters within the models that are not specific to individual countries, additional country-specific data will be needed to provide context-specific estimates of impact. Likewise, country-level estimates from meta-regression and CODEm provide uncertain estimates for locations where data for one or more indicators are scarce and would need country-specific data for at least some model inputs to obtain sufficient certainty to validate elimination.

4.4 Approaches to measurement of programme indicators for HBV mortality

The GHSS target for diagnosis is that 90% of people living with hepatitis B have been diagnosed by 2030 (Box 4.3) *(7)*. The target for treatment is to treat 80% of people diagnosed with hepatitis B with recommended antivirals, where eligible (Box 4.3). Based on these targets, the hepatitis B cascade of diagnosis and treatment indicators are used to measure progress towards the GHSS targets. For validation of elimination, countries should have attained and sustained the targets for two consecutive years. The following tables provide information on the calculation and disaggregation of the indicators (Tables 4.2 and 4.3).

Table 4.2 Proportion of people living with chronic hepatitis B who have been diagnosed

Target for elimination	≥90% of people living with chronic hepatitis B who have been diagnosed[1]
Indicator	Proportion of people living with chronic hepatitis B (HBsAg positive) who have been diagnosed
Numerator	Number of people living with chronic hepatitis B infection who have been diagnosed with a positive HBsAg test[2]. This is the cumulative number of people ever diagnosed with chronic hepatitis B infection (HBsAg positive) since the defined baseline year[3,4]. *Data sources:* Information may be sourced from specific programme or clinical patient monitoring tools (electronic or paper medical records), hepatitis testing records, laboratory registers, ANC registers, logbooks and reporting forms at facility and community levels.
Denominator	Estimated total number of people living with chronic hepatitis B infection (HBsAg positive) in the defined baseline year[3]. *Data sources.* Information is derived ideally from biomarker surveys[5], but can be derived from nationally representative modelled estimates[6].
Disaggregation	Age, gender, geographical location, higher risk populations, pregnancy status, HIV infection status, Hepatitis Delta co-infection status

1. For validation, a target of ≥90% of people living with chronic hepatitis B who have been diagnosed should be achieved and maintained for at least two consecutive years.
2. The use of quality assured HBsAg assays is important but may vary across countries. Therefore, information on the HBsAg test used should be included in the validation dossier.
3. The defined baseline year is the reference time point (year) for the estimation of the size of the population infected with chronic hepatitis B (estimated from biomarker or from modelling).
4. Programme data on number of people with chronic hepatitis B who have been diagnosed should be cumulatively counted from the defined baseline year. This is intended to reflect the historical testing effort and coverage.
5. The size of the population infected with chronic hepatitis B should be estimated from a nationally representative biomarker survey. Detailed information on the biomarker survey should be provided in the validation dossier to demonstrate that the study population is nationally representative and measures were taken to minimize potential sampling and information bias.
6. Modelling can be used alongside available empiric data to estimate the size of the population infected. For example, prevalence data obtained from a population survey conducted at one point in time may be used estimate prevalence at more recent time point. Such models need to take into account relevant input parameters such as, number of people treated over time, vaccination coverage, HBV incidence and deaths (liver related deaths and background deaths in the general population)

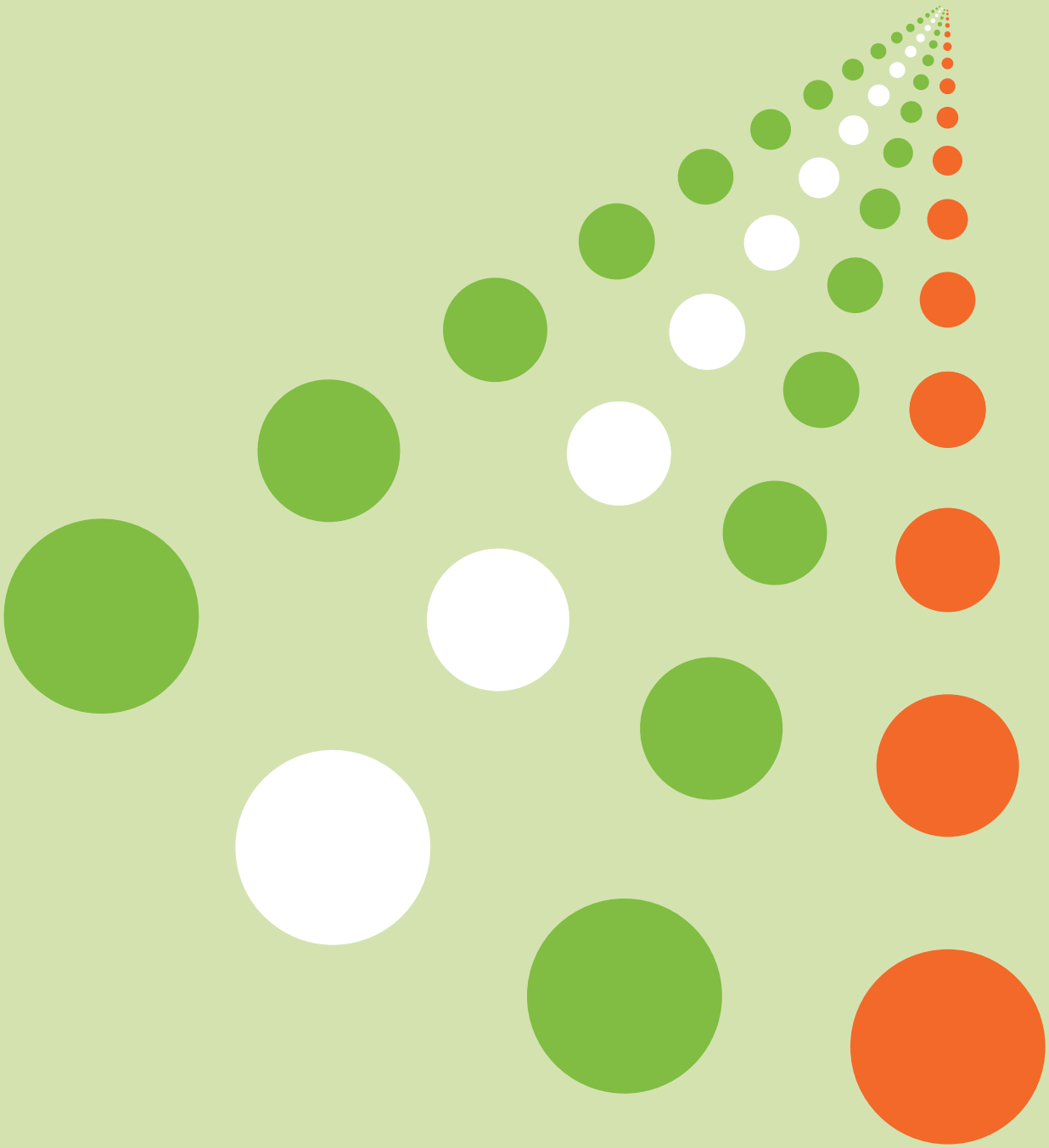
Table 4.3 Proportion of people diagnosed with chronic hepatitis B who have been treated

Target for elimination	≥80% of people diagnosed with chronic hepatitis B infection, who have been initiated on treatment[1]
Indicator	Proportion of people diagnosed with chronic hepatitis B infection, who have been initiated on treatment
Numerator	Number of people diagnosed with chronic HBV infection who have been initiated on treatment[2]. This is the cumulative number of people ever initiated on antiviral treatment since the defined baseline year[3,4]. *Data sources*: Information may be sourced from specific programme or clinical patient monitoring tools (electronic or paper medical records).
Denominator	Number of people living with chronic hepatitis B infection who have been diagnosed with a positive HBsAg test[5]. This is the cumulative number of people ever diagnosed with chronic hepatitis B infection (HBsAg positive) since the defined baseline year[3,4]. *Data sources:* Information may be sourced from specific programme or clinical patient monitoring tools (electronic or paper medical records), hepatitis testing records, laboratory registers, ANC registers, logbooks and reporting forms at facility and community levels.
Disaggregation	Age, gender, geographical location, higher risk populations, pregnancy status, HIV infection status, Hepatitis Delta co-infection status.

1. For validation, a target of ≥80% of those diagnosed with chronic hepatitis B who have been initiated on antiviral treatment should be achieved and maintained for at least two consecutive years.
2. Not all people diagnosed with chronic hepatitis B are eligible for treatment. Treatment eligibility differs across countries and regions and should be defined in accordance with current WHO guideline/regional or national guidelines.
3. The defined baseline year is the reference time point (year) for the estimation of the size of the population infected with chronic hepatitis B (estimated from biomarker or from modelling).
4. Programme data on both: (i) number of people with chronic hepatitis B who have been diagnosed: (ii) number of people diagnosed with chronic hepatitis B infection initiated on antiviral treatment, should be counted cumulatively from the defined baseline year. This is intended to reflect the historical testing and treatment effort and coverage.
5. The use of quality assured HBsAg assays is important but may vary across countries. Therefore, information on the HBsAg test used should be included in the validation dossier.

Chapter 5.

Validation of elimination of hepatitis C as a public health problem



5.1 Background

Hepatitis C is an important global public health problem with an estimated 58 million people living with chronic hepatitis C, 1.5 million new HCV infections and 290 000 deaths annually *(1)*. Highly effective curative treatments are available for HCV infection. In the absence of effective treatment, an estimated 20–30% of people with chronic HCV will develop advanced liver disease and be at risk for decompensated cirrhosis and HCC *(77)*.

A key goal of national hepatitis C elimination programmes is to reduce HCV transmission as well as liver-related mortality to very low levels, such that HCV infection ceases to be a public health problem at the population level. High-level programme coverage of evidence-based prevention, testing and treatment interventions, including safe injections in health-care settings, harm reduction for PWID, as well as access to high coverage of testing, treatment and cure, especially in populations with ongoing high rates of transmission, should result in low levels of HCV incidence and HCV-related mortality.

The epidemiology and drivers of new HCV infections vary markedly between countries and regions and are not well defined in some countries. In some settings, epidemics are predominantly driven by injecting drug use and occur among MSM, while others have more generalized epidemics that affect the general population and often in particular older age groups as a result of poor injection safety and infection control in both formal and informal health care, especially in the past *(4)*. Nevertheless, most countries have epidemic profiles that show mixed HCV transmission. As an example, modelling analysis undertaken in 2019 assessed the degree to which injecting drug use contributes to HCV transmission in different settings *(11)*. Based on these modelled estimates, 31% of countries globally are estimated to have more than 90% of their new infections among PWID; 63% have mixed epidemic dynamics with new infections occurring through unsafe health-care procedures but also from risk behaviours related to injecting drug use; and just 6% of all countries were estimated to have more than 90% of all new infections originating in health-care settings *(11)*.[4]

To accelerate global progress towards elimination, accurate data are required for estimating HCV-related incidence and mortality as well as for programme coverage. The long latency of the impact of prevention and treatment interventions on mortality compared to incidence is well recognized.

Countries can apply for validation of HCV elimination as a public health problem (demonstrating achievement of incidence, mortality and programme targets) or any of the tiers of the PTE (see chapter 6.4 and table 6.3), which recognizes countries that have extensively expanded hepatitis C prevention, diagnosis and treatment programme coverage, while not yet meeting the impact targets for incidence and mortality related to full elimination.

This chapter outlines simplified and updated criteria for validation of the elimination of HCV transmission and reduction in liver-related mortality due to HCV at the country level. It also provides a range of options for countries to measure these targets according to the available surveillance data and capacity.

Table 5.1 Criteria for validation of elimination of HCV as a public health problem:

Criteria*	Data sources and approaches to measurement
HCV incidence	• Direct estimates based on prospective and retrospective design, repeated cross-sectional surveys (in specific populations), modelled estimates (based on existing programme or other empirical data)
HCV mortality	• Data from vital registration of deaths from cirrhosis and HCC and cancer registries (HCC reporting), surveillance for sequelae in sentinel centres, modelled estimates (using existing epidemiological or programme data)
HCV cascade of care	• Testing and treatment programme records including. hepatitis testing service records, laboratory registers, logbooks and programme records at facility and community levels, EMR/electronic information systems
HCV prevention interventions	• Injection safety facility surveys, DHS population surveys, procurement records (for safety engineered injections), records from blood banks, harm reduction programme records (NSP, OAT), population size estimates for PWID, including with opioid dependence.

* For validation, attainment of the impact (incidence and mortality) is accompanied by a set of programmatic targets linked to service delivery which need to be maintained for 2 years to show consistency in the programmatic response.Evidence of quality of data sources, laboratory processes, health care programmes as well as adherence to principles of equity, gender equality, human rights and community engagement are important implementation considerations

4 Note that these country estimates are associated with a level of uncertainty due to limitations in data availability and quality, and representativeness. In addition, viraemic HCV prevalence and population size estimates may alter these analyses.

5.2 Impact and programme indicators and targets

5.2.1 Impact indicators for incidence and mortality

To achieve validation of elimination of HCV, it is necessary to demonstrate that **HCV incidence** rates are below a specified absolute threshold at the national level (Box 5.1). Countries also need to demonstrate achievement of the impact target for mortality (as shown in Box 5.3) and the core programmatic targets (as shown in Box 5.5).

Box 5.1 Impact targets for validation of HCV transmission

Countries should have achieved the following impact targets related to HCV transmission:

- **≤5 new annual HCV infections/100 000 persons**

*This HCV incidence measure should be **representative** of the adult population at country level*

and

- **≤2 new annual HCV infections/100 PWID**

*This HCV incidence measure should be **representative** of the adult PWID population at country level.*

Note:

1. Where direct empirical measurement of HCV incidence based on nationally representative data across the general population or PWID population is not feasible, measurement of incidence can be conducted in highly affected geographical areas (i.e. high baseline HCV prevalence or incidence) and/or in certain PWID population settings at particularly high risk for HCV transmission (e.g. recent injectors).
2. Countries that can demonstrate that injecting drug use is not present in any community across the country need to document only the incidence target in the general adult population.

Box 5.2 Rationale and basis of calculation of the incidence impact targets

Absolute incidence targets are proposed on the basis of the GHSS target of 80% relative reduction in HCV incidence (compared to 2015 baseline): for the following reasons *(30)*:

- They enable direct comparison of progress towards elimination across countries.
- In many countries, baseline estimates of incidence (in 2015) are either unavailable or likely to be inaccurate, with wide confidence intervals. This would mean that relative reduction measures would be rather unreliable. Thus, setting absolute incidence targets reduces the burden on the country for the validation process.
- An absolute incidence impact target has a more direct relationship with the public health burden of HCV in a country, and therefore the goal of elimination of viral hepatitis as "a public health problem".
- An absolute incidence impact target aligns better with absolute validation targets for mortality and EMTCT of HBV.

The calculation of the absolute global incidence rate of ≤5/100 000 new annual infections in the adult general population is based on the 80% reduction in the HCV incidence target (when compared to a 2015 baseline), as outlined in the original GHSS in 2016 (30). Using the WHO-estimated global annual HCV incidence estimate from 2015 of 23.7/100 000 people, the global annual incidence rate would need to decrease in the adult population to around 4.7/100 000 people to meet this target of 80% reduction. To allow for uncertainty in this estimate, this figure has been rounded off to a target of annual incidence of ≤5/100 000 people.

The rationale behind the specific absolute global target of ≤2/100 new annual infections in PWID is based on modelled estimates indicating an annual incidence in 2015 of 8.6/100 PWID (which varies by region from an estimated 4.3 to 12.5 per 100 PWID) (11). An 80% reduction in the annual incidence rate of 8.6 per 100 PWID thus accounts for a global annual HCV incidence of 1.7/100 PWID for validation of elimination, rounded off to 2/100 PWID to account for uncertainty.

There was initial consideration of a proposal for different HCV incidence impact targets for different epidemic scenarios (i.e. concentrated [among PWID], mixed and generalized epidemics [among the general population]). However, two impact targets among PWID and the general population were adopted instead for all countries, regardless of their epidemic profile for the following reasons: (i) the importance of a unified set of indicators across all countries; (ii) the challenges in categorizing countries according to HCV epidemic profiles; and (iii) the fact that the majority of LMICs globally have a mixed epidemic profile with a contribution from both unsafe health-care practices and sharing of needles, syringes and drug paraphernalia among PWID. Demonstrating achievement of both these targets is the optimal approach to achieving and maintaining elimination of HCV transmission as a public health problem. However, it is important for all countries to fully understand the underlying drivers and dynamics of their epidemics and conduct appropriate monitoring and evaluation as they develop their elimination strategy.

To achieve validation of elimination related to **hepatitis C mortality** (to support elimination of viral hepatitis as a public health problem), it is necessary to demonstrate attainment of a specific absolute threshold for combined mortality from viral hepatitis B and/or C of ≤6/100 000 per year at the country level by 2030 (Boxes 5.3 and 5.4). It is recognized that attainment of the incidence and mortality targets may occur over different time periods, as it may take substantially longer for mortality to fall following a reduction in incidence.

Box 5.3 Impact target for validation of mortality

Countries should have achieved the following impact targets related to reduction of viral hepatitis mortality :

Absolute combined hepatitis B- and C-related mortality rate of ≤6/100 000 per year by 2030

Box 5.4 Rationale and basis of calculation of absolute mortality target

The GHSS stated that global HBV- and HCV-related mortality should be reduced from 1.4 million deaths in 2015 to less than 500 000 by 2030 (i.e. 65% for both viral hepatitis B and C). Global population projections for 2030 are ~8.6 billion, and so the absolute 2030 mortality rate that would equate to the 500 000 deaths is calculated as 5.9/100 000 for HBV and HCV combined, rounded to 6/100 000 population.

For validation of HCV elimination, the achievement of the combined crude mortality rate is preferred (in contrast to the differential target threshold for hepatitis B and C (≤4/100 000 and ≤2/100 000, respectively).

The full rationale for adoption of the combined crude mortality rate is provided in section 4.2 and Box 4.2.

5.2.2 Programmatic indicators and targets for validation of hepatitis C elimination

In addition to the above impact targets for validation, countries must demonstrate overall achievement of programmatic targets. These programmatic targets constitute the key interventions for eliminating HCV as a public health problem. Countries must demonstrate that they have achieved and maintained for at least 2 years the following programmatic targets for validating the elimination of HCV as a public health problem (Box 5.5).

Box 5.5 Programmatic targets for validation of HCV elimination

Testing and treatment

- **≥90% of persons with chronic HCV infection diagnosed**
- **≥80% of persons diagnosed with chronic hepatitis C virus infection treated**

Prevention

- **≥300 syringes and needles distributed/PWID/year[a]**
- **100% of blood units screened for bloodborne infections**
- **100% safe injections in health-care settings**

[a] For countries with predominant opioid injecting epidemics, achievement of high coverage OAT (defined as ≥40% of PWID dependent on opioids receiving opioid agonist treatment) as an alternative programmatic target may be used.

Box 5.6. Rationale for the programmatic targets

The GHSS on viral hepatitis established hepatitis C programme coverage targets for preventive interventions (blood and injection safety and harm reduction), diagnosis of people with chronic HCV infection and antiviral treatment of people who are diagnosed with chronic HCV infection This was partially based on global mathematical models, which showed that achievement and maintenance of optimal coverage thresholds would result in a country achieving the impact targets for incidence and mortality *(30)*. The programme coverage targets for validation largely reflect the initial elimination targets from the GHSS 2016–2022 *(7)*.

Harm reduction measures are those recommended by WHO *(12,13)* – distribution of sterile needles and syringes to PWID and OAT for people who are dependent on opiates. High coverage of these has been shown to effectively prevent HCV and HIV transmission *(15,16,78)*. Additional impact can be obtained by the use of low dead-space syringes (LDSS) in needle–syringe programmes (NSP), which have been shown to reduce HCV transmission by 76% compared to regular syringes *(14)*.

Given the complexity of health programming for drug users, the problems with criminalization of the PWID population and the paucity of systematic data, high coverage of OAT (defined as ≥40% of people who inject opioids receiving opioid agonist treatment) may be considered as an *alternative programmatic target by countries – where the target for needle and syringe programming can not be demonstrated or fully documented*.

Programmatic targets for blood safety and injection safety are consistent with WHO global agreements and guidance. Lessons from the elimination pilots conducted in 7 countries (79) highlight the challenges with measuring facility-based safe injection coverage and hence an alternative indicator is included of evidence of procurement of bioengineered (autodisable) devices for public health care (table 5.4, 5.5, 5.6).

5.3. Approaches to measurement of impact indicators.

5.3.1 Measurement of impact indicators for validation of elimination of hepatitis C transmission

HCV incidence. The optimal approach to measuring the absolute HCV incidence target for validation of elimination will be determined by whether the general or specific population incidence can be assessed directly to generate reliable estimates. The target incidence rates to document elimination of HCV transmission (≤5/100 000 new annual HCV infections in the adult population; ≤2/100 new annual HCV infections in PWID) are ideally generated from empirical data sources, which are critical for accuracy in estimating the elimination of new HCV infections.

HCV incidence measurement using empirical data is the preferred approach for validation of the elimination of HCV transmission. Measurement of HCV incidence levels through direct, empirical methods remain key to monitoring progress and assessing the drivers of HCV epidemics.

This section will describe in more detail the different methodological options and their limitations for direct and indirect HCV incidence estimates, including the use of linked cross-sectional surveys *(80,81)* – Box 5.7.

Box 5.7 Measuring indicators for validation of elimination of HCV transmission

Preferred direct measures (general population or PWID)

Method A

Direct estimation of HCV incidence based on prospective design (HCV retesting of persons who initially tested negative for HCVAb or RNA)

This gold-standard method involves ascertaining new HCV cases prospectively among individuals at risk of infection, who are followed up over time; this approach is, however, not efficient if HCV incidence is a rare outcome.

Suitable mainly if: (i) HCV incidence is sufficiently high to balance sample size requirements, and (ii) financial and logistical resources are available to use this approach among a representative population sample. It is important to recognize that this requires registration of people testing negative at baseline with a unique identifier.

Method B

Direct estimation of HCV incidence based on retrospective design (HCV retesting of persons who initially tested negative for HCVAb or RNA). This method consists of using routinely collected health data to ascertain new HCV infection cases among susceptible individuals who receive multiple HCV tests over time as part of routine care. Can be used to estimate primary HCV infection or HCV reinfection.

Suitable only if: (i) HCV incidence is insufficient to justify a prospective study, or (ii) financial and logistical resources are limited and do not allow for nationwide prospective surveillance among a representative sample, and (iii) high-quality and representative data collected through medical records are available.

Method C (mainly applicable to incidence estimates in specific populations with ongoing risk behaviour and HCV exposure)

Direct estimation based on linked repeated cross-sectional surveys. In repeat cross-sectional surveys, a new sample of participants is recruited with each round. If some participants appear in multiple rounds and individual-level data can be linked over time, then these surveys can be used to estimate HCV incidence. This method has been used to estimate HCV incidence (primarily among PWID) in settings such as Canada, Australia, and Greece. There is a limitation in settings or populations with low baseline incidence and/or large populations as very large sample sizes are necessary, and as a small proportion of individuals typically participate in multiple survey rounds. Consequently, this method is likely to be primarily applicable to populations (PWID, MSM) at risk of high incidence of HCV infection.

Alternative approach

Use of serosurveys and programmatic data to estimate HCV incidence in both the general population and PWID (with mathematical modelling)

Given the complexity of measuring incidence in a representative way through direct measurement methods, as well as the fact that new HCV infections are potentially a rare event modelling may use be used to estimate HCV incidence for validation. Robust mathematical modelling can be used under specific conditions to generate HCV incidence estimates. HCV incidence estimates using a mathematical model should be based on prevalence data, further calibrated with programmatic coverage data. Suitable where (i) at least two country-specific prevalence serosurveys are available, and (ii) programmatic data are sufficiently robust as model inputs.

Models should be, peer-reviewed, published and have undergone a validation process against an empirical serosurvey and other empirical data in an independent setting. Model inputs and outputs should be country specific.

5.3.2 Measurement of impact targets for validation of elimination of hepatitis C mortality

As with hepatitis B mortality measurements, there are several potential approaches and methodologies that can be used for measuring and monitoring mortality due to HCV-related liver conditions in countries. The capacity for assessing mortality rates varies widely across the world: some countries (or jurisdictions within countries) have good sophisticated public health surveillance systems, and notification registries that allow data linkage with, for example, hospitalizations, cancer and death registries. These settings, such as in some European countries, Australia and Canada, can both closely monitor trends in HBV- and HCV-related mortality, and use empirical data to validate and adjust mathematical models to estimate and project the impacts of interventions. At the other end of the spectrum, many countries, particularly low and middle income countries, lack the capacity to monitor liver-related deaths, even from HCC, at the population level.

Measurement of liver-related mortality due to HCV

The optimal approach to measuring the absolute mortality indicator is through direct measurement. Direct mortality measurement and monitoring should ideally rely on strong vital statistics (via death certification), which would be able to accurately capture HCV as the underlying cause of death. However, for many settings, this would require significant changes in coding practices, and even the format of the death certificate, which often lack cause specific or aetiological diagnosis.

There are several different alternative methodologies that can support the estimation of a national mortality rate where direct measurement of the national mortality rate is not possible. This includes the use of HCC incidence as a surrogate for liver-related mortality as well as the use of sentinel networks of clinical sites for estimation of AF. The use of clinic-based sentinel networks in countries provides a mechanism for monitoring cases of HCC as well as decompensated cirrhosis in the absence of a formal registry, and the AF of cases due to HCV. This population-specific caseload can then be extrapolated to provide a national estimate of HBV- and HCV-related mortality (Annex 6).

Approaches to estimating HCV mortality are the same mechanisms used for measuring HBV mortality and are fully described in section 4.3. Countries should review and identify the most appropriate option according to their epidemiological profile, health system context, and availability and quality of surveillance data. The advantages and disadvantages of the different options are summarized in box 4.5, 4.6 and 4.7.

5.4 Approaches to measurement of programme coverage targets

5.4.1 Hepatitis C cascade of diagnosis and treatment indicators

The GHSS elimination targets aim for 90% of people living with hepatitis C to be diagnosed and 80% of people diagnosed with hepatitis C to receive curative treatment with recommended antivirals by 2030. Based on these targets, the hepatitis C cascade of diagnosis and treatment indicators are used to measure progress towards the validation targets. Because of the high effectiveness of DAAs in the treatment of HCV, the proportion of persons treated for HCV will be measured for validation, i.e. reporting on the proportion of persons who have attained SVR will not be made necessary. For validation of elimination, countries should have attained and sustained the targets for two consecutive years. The following tables provide information on the calculation and disaggregation of the indicators.

Table 5.2 Proportion of persons living with chronic hepatitis C who have been diagnosed

Target for elimination	**≥90% of people living with chronic hepatitis C who have been diagnosed[1].**
Indicator	Proportion of people living with chronic hepatitis C infection (positive RNA [PCR] or HCV core Ag) who have been diagnosed
Numerator	Number of people living with chronic hepatitis C who have been diagnosed with a positive HCV RNA [PCR] or HCV core Ag[2]. This is the cumulative number of people ever diagnosed with chronic hepatitis C infection (positive RNA [PCR] or HCV core Ag) who have been diagnosed since the defined baseline year[3,4]. *Data sources:* Information may be sourced from specific programme or clinical patient monitoring tools (electronic or paper medical records), hepatitis testing records, laboratory registers, logbooks and reporting forms at facility and community levels.
Denominator	Estimated total number of people living with chronic hepatitis C infection (positive RNA [PCR] or HCV core Ag) in the defined baseline year[3]. *Data sources*. Information is derived ideally from biomarker surveys[5], but can be derived from nationally representative modelled estimates[6].
Disaggregation	Age, gender, HIV status, geographical location, higher risk populations

1. For validation, a target of ≥90% of people living with chronic hepatitis C who have been diagnosed should be achieved and maintained for at least two consecutive years.
2. Chronic hepatitis C infection is defined as the presence of viraemia (HCV RNA or HCV core Ag) in association with positive serology for HCV antibody.
3. The defined baseline year is the reference time point (year) for the estimation of the size of the population infected with chronic hepatitis C (estimated from biomarker or from modelling).
4. Programme data on number of people living with chronic hepatitis C who have been diagnosed should be counted cumulatively from the defined baseline year. The number includes those with resolved infection (cured or naturally cleared) and those who have died. This is intended to reflect the historical testing effort and coverage. Those with re-infection are included but counted once.
5. The size of the population infected with chronic hepatitis C should be estimated from a nationally representative biomarker survey. Detailed information on the biomarker survey should be provided in the validation dossier to demonstrate that the study population is nationally representative, and measures were taken to minimize potential sampling and information bias.
6. Modelling can be used alongside available empiric data to estimate the size of the population infected. For example, prevalence data obtained from a population survey conducted at one point in time may be used estimate prevalence at more recent time point. Such models need to take into account relevant input parameters such as number of people treated/cured over time, HCV incidence and deaths (liver related deaths and other causes of death in the general population).

Table.5.3 Proportion of persons living with HCV treated

Target for elimination	≥80% of people diagnosed with chronic hepatitis C infection who have been initiated on treatment[1] .
Indicator	Proportion of people diagnosed with chronic hepatitis C infection who have been initiated on treatment
Numerator	Number of people diagnosed with chronic hepatitis C infection who have initiated treatment[2]. This is the cumulative number of people ever initiated on antiviral treatment since the defined baseline year[3,4]. *Data sources:* Information may be sourced from specific programme or clinical patient monitoring tools (electronic or paper medical records)
Denominator	Number of people living with chronic hepatitis C who have been diagnosed with a positive HCV RNA [PCR] or HCV core Ag[5]. This is the cumulative number of people ever diagnosed with chronic hepatitis C infection (positive RNA [PCR] or HCV core Ag) who have been diagnosed since the defined baseline year[3,4]. *Data sources:* Information may be sourced from specific programme or clinical patient monitoring tools (electronic or paper medical records), hepatitis testing records, laboratory registers, logbooks and reporting forms at facility and community levels.
Disaggregation	Age, gender, HIV status, geographical location, higher risk populations)

1. For validation, a target of ≥80% of those diagnosed with chronic hepatitis C who have initiated antiviral treatment should be achieved and maintained for at least two consecutive years.
2. Treatment initiation will be defined as initiation of the treatment course with DAAs (typically 12-24 weeks). Because of the high effectiveness of DAAs in the treatment of HCV, reporting on the proportion of people who have attained SVR will not be necessary for validation, although data should be provided if available.
3. The defined baseline year is the reference time point (year) for the estimation of the size of the population infected with chronic hepatitis C (estimated from biomarker or from modelling).
4. Programme data on both: (i) number of people with chronic hepatitis C who have been diagnosed: (ii) number of people diagnosed with chronic hepatitis C infection initiated on antiviral treatment, should be counted cumulatively from the defined baseline year. This is intended to reflect the historical testing and treatment effort and coverage.
5. Chronic hepatitis C infection is defined as the presence of viraemia (HCV RNA or HCV core Ag) in association with positive serology for HCV antibody.

5.4.2 Health-care transmission and injection safety

The WHO Consolidated strategic information guidelines for viral hepatitis (34) outlines the methodology for determining the proportion of safe injections in health-care facilities. This programmatic indicator is expressed as the proportion of injections given with new, sterile syringes and is measured through health-facility or population-level surveys. In the early 2000s, health-care facility assessment was the reference method used to estimate the proportion of injections that were safe. The EPI made extensive use of these health-care facility assessment surveys. However, as vaccination injections improved due to use of autodisable syringes, these surveys were less useful. In some countries, template Demographic and Health Surveys (DHS) include questions on injection practices and can serve as a source of data to evaluate the proportion of unsafe injections in the population.

An *alternative indicator* is the evidence of procurement of bioengineered (autodisable) devices for public sector health care. The indicator to measure against this target is the *proportion of safety-engineered devices* (with RUP or SIP features) procured at the national level and/or at health-facility level if procurement is decentralized. The target is >90% (table 5.4).

Table.5.4 Injection safety indicators

Target	**100% safe health-care injections**
Indicator	Proportion of injections given with new or non-reusable sterile syringes in health-care settings [1,2]
Numerator	Number of sampled health-care facilities where all therapeutic injections are given with new, disposable or non-reusable single-use injection equipment in the reporting year
Denominator	Number of facilities sampled in the reporting year
Alternative Indicator for Injection safety: As not all countries may be able to document and measure health-care injections through facility or population-level surveys, an alternative indicator is provided.	
Target	**90% of health care injection devices procured are safety-engineered**
Indicator	Proportion of safety-engineered devices with RUP features among those procured at national level (or health-facility level if procurement is decentralized) in the reporting year
Numerator	Number of devices/syringes with safety engineered features procured at national or health facility level in the reporting year *Data sources:* Procurement records at national or health facility level
Denominator	Total number of devices/syringes procured at national or health-facility level in the reporting year *Data sources:* Procurement records at national or health facility level

1. This indicator is measured through health facility surveys (facility data).
2. Alternative measurement approach for injection safety.: An alternative approach is to use population surveys DHS estimate the proportion of the last injections received that have been given with a new, unopened package on the basis of individual data. Even though the source of data and measurement differ, estimates of the frequency of reuse of injection equipment from population surveys are often comparable to data from health-facility surveys

5.4.3 Blood safety

The indicator for the proportion of blood units screened for bloodborne diseases is defined as the percentage of blood donations screened for infections such as HIV, HBV, HCV, and syphilis utilizing essential quality-assured processes. The quantifiable aspect of this indicator is the number of blood units that have been screened for these bloodborne diseases within the reporting year (table 5.5). The primary source of these data is derived from programme records *(21)*.

Table 5.5 Blood safety Indicators

Target	100% of blood units screened for bloodborne diseases
Indicator	Proportion of blood units screened
Definition	Proportion of blood donated by donors screened for blood borne infection using quality-assured procedures[1]
Numerator	Number of blood units screened for bloodborne diseases in the reporting year *Data sources:* Programme records
Denominator	Total number of blood units donated in the reporting year.

[1] Policies on blood safety and safe blood transfusion differ across countries. For countries applying for validation of elimination of hepatitis B or hepatitis C, policies on screening for borne diseases should include screening of HBV and HCV. Therefore, detailed information on national policies for blood safety should be included in the validation dossier.

Table.5.6 Harm reduction Indicators

Target	≥300 syringes and needles distributed/PWID/ year
Indicator	Coverage of needle and syringe programmes at population level[1]
Numerator	(a) Number of sterile needles–syringes distributed in the past 12 months by the needle/ syringe programme (NSP) at the end of reporting year or the latest year with available data and can include (b) number of needles/syringes sold to PWID by pharmacies or other outlets in the reporting period[2]. *Data source:* Programme data used to count the number of needles and syringes distributed, including the total number of needles/syringes from both NSPs and pharmacies in the numerator if data are available.
Denominator	Population-size estimate of PWID in relevant geographical area at country level[3]. *Data source:* Estimation of the number of PWID at country level from population size estimation exercises. UNODC publishes estimates of the number of PWID in the World drug report (84). These estimates may be used.
Alternative indicator: In countries with opioid epidemics, an alternative harm reduction indicator is the coverage of opioid agonist maintenance	
Target	**≥40% of PWID receiving opioid agonist therapy**
Indicator	Coverage of opioid agonist maintenance treatment among PWID[4]
Numerator	Estimated number of PWID who are receiving opioid agonist maintenance treatment in the reporting year or the latest year with available data *Data source:* Programme data, OAT programme
Denominator	Estimated number of opioid-dependent PWID in the country in the reporting year or the latest year with available data[5]. *Data source:* size estimation of opioid-dependent PWID.

1. This indicator has the advantage that it needs only programme-level data (and not any individual-level data) that is rather easy to generate and can include data from programme needle stocks.
2. There may be some difficulties in counting needles and syringes and, in some cases, only data on the number of syringes distributed by NSPs but not pharmacy sales are available.
3. Estimating the number of PWID at the country level may present some challenges. Some countries update their size estimates rather regularly whereas for other countries estimates may be less recent. The most recent estimate should be used for this indicator. PWID are defined in many ways, and the estimates should provide ranges or confidence intervals.
4. This indicator can be calculated as well at the programme level. The denominator would then be the number of opioid-dependent PWID accessing services. For validation of elimination and as an alternative indicator, it needs to be measured at the population level. Further information is available at the following *(85–87)*.
5. The population size estimate used as the denominator should be appropriate for the numerator i.e not all opioid agonist therapy recipients have a history of injecting and not all PWID use or are dependent on opioids

5.4.4 Harm reduction

The GHSS target for harm reduction as a core prevention intervention for elimination of viral hepatitis is set at 300 sterile syringe/needles distributed per year per PWID *(7, 34)*. At the population level, this indicator measures the total number of injecting equipment in circulation that might be used by the overall population of PWID, noting that secondary distribution of equipment within networks is a significant source of sterile equipment among PWID and should be included. When measured at the population level with a denominator that is the estimated number of PWID at country level, this indicator allows understanding of the country's progress towards national coverage of needle/syringe programmes for all PWID (table 5.6). It has thus been used as the main programme coverage indicator in the GHSS and interim guidance of WHO since 2015 *(30,82)*.

In countries with opioid epidemics, an alternative indicator is the **coverage of opioid agonist maintenance treatment with the target coverage of** ≥40% of PWID. The **numerator is the number of PWID who are receiving opioid agonist maintenance treatment** in the reporting year (measured through programme records, e.g. OAT registries), while the denominator is the population size estimate of opioid-dependent PWID (table 5.6) *(34,83)*.

5.4.5 Mathematical modelling alongside empirical data for validation of HCV as a public health problem.

As detailed throughout this section and in Annex 5, mathematical modelling is a powerful tool that can offer new insights and identify data gaps in countries' progress towards the elimination of HCV transmission and mortality. Where national empirical data are of sufficient quality and coverage, mathematical models may be useful to assess the progress of countries towards the achievement of the impact targets for hepatitis C elimination and constructing the HCV cascade of care for programme targets. Models may also be used to project the potential impact of additional prevention, diagnosis and treatment interventions necessary to achieve hepatitis C elimination.

Chapter 6.

Path to elimination: recognizing progress toward viral hepatitis elimination

6.1 Background

There is considerable heterogeneity in the epidemiology of hepatitis B and C across different regions, and countries, and even at sub-national level. Some countries that have made significant progress in implementing key hepatitis prevention, testing and treatment interventions may not be able to achieve absolute incidence and mortality targets because of the larger disease burden at baseline. Other factors that impede attainment or measurement of hepatitis impact targets despite significant country efforts include the delay in achieving mortality targets of ≤6/ 100 000/year (due to the long natural history of disease to cirrhosis and HCC) as well as the complexity and cost of demonstrating an absolute annual HCV incidence of ≤5 per 100 000 persons and of ≤2 per 100 people who inject drugs (PWID) for HCV and ≤0.1% HBsAg prevalence in those aged 5 years or less.

Several disease programmes have recognized that disease elimination is a process that requires focused sustained action to reach elimination or eradication targets. The malaria, tuberculosis and cervical cancer (HPV) programmes provide specific examples of approaches and step-wise milestones towards country elimination. The triple elimination initiative for MTCT of HIV, syphilis, and hepatitis B specifically recognize country progression towards elimination in high-burden countries facing greater challenges to meeting elimination goals and absolute targets. It provides a PTE framework with three levels of achievement for which country certification is available. Each level is defined by a set of criteria and indicators that represent the progressive steps towards EMTCT.

Leveraging on the experience from other disease programmes and the EMTCT, as well as lessons learned from the 2022 hepatitis elimination pilots *(39,79)* this chapter defines targets for use in the assessment and certification of a PTE for viral hepatitis B and C- as a public health problem. These targets are developed to recognize progress towards elimination and lay the foundation for validation of disease elimination by encouraging national scale-up and expansion of key programme interventions, promoting the establishment and strengthening of measurement systems (including for hepatitis related incidence and mortality estimation that will be required for full validation).

In alignment with full validation, countries are encouraged to pursue PTE of both hepatitis B and C but may choose to apply for any of the options in a phased manner, i.e. PTE of hepatitis B EMTCT, or PTE of hepatitis B or hepatitis C as a public health problem. A key principle is that each tier of the PTE represents a certifiable milestone of progress towards elimination, where validation of elimination is the ultimate goal. Certification for the PTE will follow a similar procedure as a country requesting full validation of hepatitis B or C. While validation of elimination is documented at the global level, recognition of PTE is completed at the regional level, unless the region specifically requests for global input for higher level advocacy to accelerate national response. The process of WHO recognition is initiated through a desk review, focuses on documentation of programme coverage targets and includes review of the four key areas of implementation considerations (data quality; laboratory and programme quality; equity, gender equality and human rights; and community engagement) (Annex 1). See detailed process of validation and governance in Annex 2.

6.2 Indicators and rationale for the path to elimination for viral hepatitis

The criteria for PTE of hepatitis B and C as a public health problem follows the approach already established for PTE of hepatitis B EMTCT and is mostly based on programme coverage targets without the need to demonstrate achievement of HBV or HCV incidence or mortality impact targets. The GHSS on viral hepatitis sets programme coverage targets for the most important HBV and HCV prevention interventions, and also for diagnosis of 90% of people infected with HBV and/or HCV, and antiviral treatment of 80% of people who are diagnosed and eligible for treatment according to established guidelines (see table 6.1). Global models have estimated that achievement of these synergistic programme coverage levels would likely result in a country achieving the impact targets.

The rationale for PTE is shown in Box 6.1 and serves to promote programme expansion, encourage wide country engagement, and significantly impact incidence and mortality (in the long term). The key programme interventions encompass the prevention, testing and treatment of viral hepatitis and are shown in table 6.1 with further narrative description in 6.2.1 and 6.2.2. (see the definitions for all programme indicators in Chapters 4 and 5).

Table 6.1 Key interventions to address viral hepatitis with the GHSS on viral hepatitis and global targets (2022–2030)

Interventions	Indicator	Targets	
		2025	2030
1. Hepatitis B vaccination	HepB3 coverage	90%	90%
2. HBV PMTCT[a]	HepB vaccine birth dose coverage	70%	90%
3. Blood safety	Donations screened with quality assurance	100%	100%
4. Injection safety	Proportion of safe injections	100%	100%
5. Harm reduction	Syringes & needles distributed/PWID/year	200	300
6. Testing services	% HBV-infected diagnosed	60%	90%
	% HCV-infected diagnosed	60%	90%
7. Treatment	% diagnosed with HBV on treatment	50%[b]	80%[b]
	% diagnosed with HCV on treatment	50%[c]	80%[c]

HepB-BD: hepatitis B birth dose vaccine; HepB3: three doses of hepatitis B vaccine; PMTCT: prevention of mother-to-child transmission; PWID: person who injects drugs

Source: WHO, including commissioned work, United Nations, UNICEF

a Interventions to prevent mother-to-child transmission of HBV

b Around 20–30% of persons living with HBV infections may develop progressive liver disease or HCC and are eligible for treatment with nucleoside analogue therapies;

c For HCV, all are eligible for treatment according to WHO guideline

6.2.1 Hepatitis Prevention programme interventions

- **Hepatitis B vaccination and prevention of mother-child transmission of HBV.** The detailed description for prevention of early-life infection through HBV timely birth-dose and childhood vaccination and other interventions for EMTCT is shown in chapter 3.
- **Blood and injection safety.** The 100% coverage target for injection safety and safe blood transfusion emphasizes the critical importance of these two health sector interventions for every level of validation of elimination for HBV and HCV.
- **Harm reduction coverage targets** for the different tiers of PTE take into consideration the reported complexity of developing high coverage, quality services for the often-criminalized PWID population. To allow continuous engagement with and further improvement of countries in this programme area, the gold tier for PTE gives the option for achieving a moderately high NSP coverage (≥ 150 needles and syringes per PWID per year – see Table 6.3) or proof of doubling of harm reduction service coverage in the previous 2 years. This flexibility will promote programme development with investment and improvements towards full validation.

6.2.2 Hepatitis testing and treatment programme interventions

- Early diagnosis of hepatitis infection is critical for effective treatment and care. Yet globally, less than 10% and 21% respectively of persons with chronic viral hepatitis B or C have been diagnosed. Although effective antiviral agents against viral hepatitis B and curative DAA therapy for C have the potential to dramatically reduce morbidity and mortality, less than 13% have received HCV therapy (less than 2% for HBV) *(4)*.
- The step-wise progression of coverage of diagnosis and treatment from bronze to silver to gold tiers promotes iterative expansion of programmes in line with recommended WHO guidance.
  - The bronze tier is aligned with the already approved 2025 GHSS programme coverage milestones.
  - Each coverage tier is aligned to facilitate ultimate progress to full validation.

Box 6.1 Rationale for the path to elimination for HBV and HCV

The PTE seeks to recognize countries that have made significant progress in implementing key programme interventions but that may not yet be able to achieve the absolute impact targets for HBV and HCV. This may be because of a high HBV/HCV prevalence or incidence and limited availability of data or systems to establish absolute mortality reductions. The establishment or attainment of impact targets (incidence and mortality) for HBV or HCV are not a requirement for the PTE approach.

HBV and HCV programme targets

Adequate coverage of hepatitis B and C prevention, testing and treatment interventions have been shown by modelling to achieve mortality thresholds for the 2030 elimination targets. National and cohort data also show that attainment of high coverage of prevention, testing and treatment interventions have an impact on both incidence and mortality. Each tier of the PTE is defined by attainment of increasing levels of service coverage of key interventions and represents a milestone of progress towards elimination, where validation of elimination is the goal. This step-wise progression serves to encourage national scale-up and expansion of key programme interventions in line with recommended WHO guidance, promote the establishment and strengthening of measurement systems to support attainment of the 2030 elimination goal, foster wide country engagement, and significantly impact incidence and mortality (in the long term).

HBV and HCV impact targets

HBV incidence. The prevalence of HBsAg in children aged ≤5 years is a proxy for new hepatitis B infections from vertical and/or early horizontal transmission and serves as a surrogate target of the cumulative incidence of CHB infections. It is a core component of the full validation of HBV EMTCT, as well as the broader elimination of HBV as a public health problem, but is not a requirement for certification of PTE.

HCV incidence. Evaluation of HCV incidence to assess the effectiveness of interruption of HCV transmission is a core component of the full validation approach. Demonstrating reduction in HCV incidence is not required in the PTE certification tiers for several reasons: (i) the differing epidemiological profiles of disease epidemics in different regions preclude a single measure of PTE; (ii) the need for representative national incidence measurement in general and specific populations is associated with complexity and costs that may deter countries from seeking validation, especially those with a high disease burden or with limited resources.

HBV and HCV mortality. Evaluation of mortality is a vital component of the public health elimination of viral hepatitis as it reflects deaths due to liver cancer and cirrhosis. Given disease latency, countries may require several years to reach the combined elimination mortality rate of ≤6/100000 per year despite attaining and maintaining maximum treatment thresholds. Demonstrating achievement of the impact target related to reduction of mortality is not a requirement for PTE. However, in countries where direct measurement of mortality is not possible, the establishment of national surveillance and sentinel centres for liver disease-related sequelae (HCC and decompensated cirrhosis) assists countries in estimating the AF of HBV- and HCV-related disease which is critical for full validation. This is included as a process indicator for attaining PTE certification in the gold tier. See further rationale in Box 4.5 and a detailed description of the sentinel surveillance programme for hepatitis sequelae in Annex 6.

6.3 Elimination of HBV as a public health problem: path to elimination

A country seeking recognition for significant efforts towards elimination will have the option of EMTCT of hepatitis B (HBV EMTCT only)[5] or to pursue the broader context of elimination of HBV as a public health problem, in the general population.

6.3.1 HBV EMTCT: path to elimination

The PTE for hepatitis B EMTCT primarily applies to high HBV-burden countries that are scaling up hepatitis B vaccine and EMTCT service coverage, such as in the African Region.

Each PTE tier is defined by attainment of increasing levels of service coverage of key interventions for PMTCT of hepatitis B through infant and childhood vaccination and testing of pregnant women (Table 3.1 and 6.2). Moving to a higher tier brings a country progressively closer to the ultimate elimination impact target of ≤0.1% HBsAg prevalence in children ≤ 5 years of age (see Chapter 3 for further details).

6.3.2 Elimination of HBV as a public health problem: path to elimination

The PTE for HBV seeks to recognize countries that have implemented key interventions to reduce HBV transmission and mortality for a comprehensive HBV response. It requires attaining the relevant programmatic thresholds for EMTCT, blood and injection safety targets, as well as identification of cases in the general population. Treatment with antivirals are recommended for eligible HBsAg positive persons to reduce mortality from hepatitis B. Additionally, over the long term, reducing incidence through EMTCT, safe injections and blood transfusions means fewer new infections and ultimately decline in chronic infections and HBV related deaths.

Step-wise progression through the prevention, diagnosis and treatment coverage from bronze to silver to gold tiers will promote an iterative expansion of programmes in line with recommended WHO guidance and the GHSS. The bronze tier is aligned with the already approved 2025 GHSS programme coverage milestones. The silver and gold tiers provide increasing level of service coverage (see table 6.2). The establishment of sentinel centres for liver disease-related sequelae assists countries in estimating the AF of HBV- and HCV-related disease, is critical for ultimately estimating mortality.

5 Preferably in the framework of triple elimination of MTCT

Table 6.2 Path to elimination of HBV as a public health problem (including HBV EMTCT)

PTE tier	Impact targets	Programme targets (Prevention (except EMTCT), testing, treatment)	Programme targets for HBV EMTCT*
The gold level recognizes where a country has implemented:			
Gold tier	N/A	• 100% blood safety • 100% injection safety • ≥80% of people living with chronic HBV are diagnosed • ≥70% of people diagnosed and eligible are treated for HBV • Establishment of sentinel surveillance programme for sequelae of hepatitis[a]	• ≥90% coverage of hepatitis B 3rd dose infant vaccination • ≥90% coverage of universal timely birth dose • Antenatal HBsAg testing coverage ≥30%
The silver level recognizes where a country has implemented:			
Silver tier	N/A	• 100% blood safety • 100% injection safety • ≥70% of people living with chronic HBV are diagnosed • ≥60% of people diagnosed and eligible are treated for HBV	• ≥90% coverage of hepatitis B 3rd dose infant vaccination • ≥50% coverage of universal timely hepatitis B birth dose • Antenatal HBsAg testing (available in public sector)
The bronze level recognizes where a country has implemented:			
Bronze tier	N/A	• ≥95% blood safety • ≥95% injection safety • ≥60% of people living with chronic HBV are diagnosed • ≥50% of people diagnosed and eligible are treated for HBV	• ≥90% coverage of hepatitis B 3rd dose infant vaccination • National implementation of universal timely hepatitis B birth-dose policy.

* HBV EMTCT indicators can be validated independently, or as part of Triple elimination, or as part of the comprehensive HBV response

[a] This is a requirement in countries lacking strong surveillance systems for direct measurement of mortality. A simplified protocol template for establishment of sentinel surveillance is shown in Annex 6. It should be implemented in at least one centre and adapted to the country context.

6.4 Elimination of HCV as a public health problem: path to elimination

The PTE for HCV seeks to recognize countries that have implemented key interventions to reduce HCV transmission and mortality but may not yet have achieved the elimination impact goals due to continued transmission even though at a lower level, or a high initial prevalence of HCV and delays with achieving mortality impact targets.

Although absolute reduction in incidence and mortality remain the impact criteria for validation of hepatitis elimination, the challenges of reaching these thresholds despite the scale up of key interventions to address viral hepatitis as well as the complexity and cost of impact measurements are well recognized, especially in LMICs that bear the highest burden of chronic viral hepatitis.

As with PTE of hepatitis B, step-wise progression through the prevention, diagnosis and treatment coverage from bronze to silver to gold tiers will promote an iterative expansion of programmes in line with recommended WHO guidance and the GHSS. Each tier is aligned with programmatic coverage that will facilitate full validation. The programmatic targets for prevention of HCV are related to reducing transmission in blood transfusion services and promoting the use of safe injection practices. The role of harm reduction is particularly important for HCV; the bronze and silver levels promote the establishment of evidence-based harm reduction interventions, while the gold tier requires an interim coverage or improvement of NSPs to be achieved and evidence of recent (past two years) expansion of national harm reduction coverage. Optimizing these prevention interventions reduces new incident infections, in combination with increased treatment coverage, reduces the pool of HCV infection in a population.

The establishment of sentinel centres for liver disease-related sequelae (HCC and decompensated cirrhosis) assists countries in estimating the AF of HBV- and HCV-related disease, and is required to attain the gold tier.

Table 6.3 Path to elimination of HCV as a public health problem

PTE tier	Impact targets	Programme targets
The gold level recognizes where a country has implemented:		
Gold tier	N/A	• **100% blood safety** • **100% injection safety** • **≥150 needles/syringes/year in PWID[a] (or OAT coverage for PWID >20% in countries with defined opioid epidemics)** • **≥80% of people living with chronic HCV are diagnosed** • **≥70% of people diagnosed with HCV are treated** • **Establishment of sentinel surveillance programme for hepatitis sequelae[b]**
The silver level recognizes where a country has implemented:		
Silver tier	N/A	• **100% blood safety** • **100% injection safety** • **NSP and OAT present in country[c]** • **≥70% of people living with chronic HCV are diagnosed** • **≥60% of people diagnosed with HCV are treated**
The bronze level recognizes where a country has implemented:		
Bronze tier	N/A	• **≥95% blood safety** • **≥95% injection safety** • **NSP is present in the country[c]** • **≥60% of people living with chronic HCV are diagnosed** • **≥50% of people diagnosed with HCV are treated**

a Alternatively, countries can demonstrate a doubling of NSP coverage or OAT coverage (in countries with defined opioid epidemics) in the past 2 years.
b This is a requirement in countries lacking strong surveillance systems for direct measurement of mortality. A simplified protocol template for establishment of sentinel surveillance is shown in Annex 6. It should be implemented in at least one centre and adapted to the country context.
c Present in-country means (i) country has a national policy (ii) and services are implemented in at least one public health service site.

6.5 Elimination of hepatitis B and C as a public health problem: path to elimination

PTE is also possible for the certification for both HBV and HCV as a public health problem. The indicators for this overarching option combine the indicators for both HBV (including EMTCT of hepatitis B) and HCV, as detailed above.

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Annex 1. Implementation considerations

Implementation considerations for validation of elimination are those health systems and related criteria that can be used to determine the feasibility of achieving or sustaining the elimination of viral hepatitis, including for the bronze, sliver and gold tiers of the PTE. These implementation considerations include the quality of strategic information, laboratory processes, diagnostics and medicines, and health-care programmes, as well as adherence to the principles of equity, human rights and community engagement in countries' efforts to achieve elimination. These criteria are assessed by in-country exercises that are completed using the country self-assessment tools for validation of hepatitis elimination which are included in this guidance document.

- The national hepatitis report and dossier for assessment of validation of viral hepatitis elimination should include a chapter on implementation considerations, as described below (see the overall template for a national report in Annex 3).
- A checklist is provided for countries in Annex 4 to facilitate the systematic writing of the chapter on implementation considerations in the national hepatitis elimination report. It is suggested that a country highlights key findings from this checklist in the report's narrative, and that the full checklist is provided in an annex to the report. Several tools for the validation of hepatitis B and C and the path to elimination (Annex 3) are also provided as a resource to guide country self-assessment.
- The regional validation process will include a review and provide feedback on the chapter on implementation considerations in the national hepatitis elimination report as part of the Regional Validation Task Force (RVTF) report. Depending on the context, the validation process can be conducted in-person or virtually by the regional review team with national-level cooperation (the steps of the validation process are detailed in Annex 2).

Implementation considerations are important for the validation of elimination and will be considered during validation and maintenance. A country should be able to demonstrate that it has addressed the recommendations relating to implementation considerations made during the initial validation process.

A1.1 Ensuring the quality of strategic information systems and data

Countries should have a national health management information system that can generate and analyse reliable data necessary for monitoring and assessing progress against the hepatitis elimination criteria and impact and programme targets. Where possible, these data should be collected routinely through the national health management information system, in line with WHO guidance on strategic information for viral hepatitis *(1, 2)* and the global reporting system for hepatitis *(3)*, but with consideration also for data collection from sentinel sites where the national system is weak.

Evidence of data of high quality in the national hepatitis elimination report will be assessed through a review of the national system capacity to provide robust and representative data (and, where appropriate, disaggregated by geographical area and risk groups), particularly related to assessment of the impact indicators for the incidence and mortality of HBV and HCV. It is recognized that while national surveys can provide data of high quality on impact indicators, this may be a challenge for programme-level data, as it is based on routine data collection and sometimes limited geographical coverage.

The assessment should be based on the WHO comprehensive monitoring and evaluation framework for viral hepatitis B and C *(2)* and the WHO Consolidated strategic information guidelines for viral hepatitis: planning and tracking progress towards elimination *(1)* which summarizes the overall approach to collecting, analysing, disseminating and using strategic information on viral hepatitis at local, subnational, national and international levels. It describes the use of strategic information at various stages of the response in the context of strengthening broader health information systems and highlights the 10 core programmatic indicators for the elimination of viral hepatitis.

National hepatitis elimination reports should focus on detailing evidence to support the quality of data sources that provide proof of achievement of elimination. These data points relate specifically to the impact and programmatic indicators described in this guidance. Countries are encouraged to utilize existing data infrastructure on national surveillance and hepatitis (and other diseases) and, where necessary, engage in obtaining additional specific information required for the validation process.

In addition to standard viral hepatitis surveillance data points for impact indicators or programmatic goals, as well as health-care facility surveys, quality data should also be sourced from the EPI for hepatitis B vaccination, alongside HBsAg testing in pregnant women and antiviral prophylaxis in those eligible. In addition, data on prevention interventions, and testing and treatment for hepatitis B and C should be obtained from programme data. These should be able to capture service delivery and outcome data from both the public and private health sectors. Data quality for each of the required global validation impact and process indicators should be assessed by the country for completeness, accuracy, consistency and timeliness. The key requirements for data quality assessment are shown below (Box A1.1).

Box A1.1 Key requirements for data quality assessment

1. Review service delivery and outcomes data from the public and private (and other non-public sectors)
2. Review the functionality of information systems
3. Review indicator definitions and measurements
4. Examine population-level estimates
5. Complete the data quality assessment located in the country self assessment toolkit for validation of hepatitis elimination.

The validation assessment should also consider the national capacity to undertake or commission mathematical modelling for viral hepatitis to model incidence or mortality projected into the future. Through this process, it is possible to estimate progress towards or achievement of the impact indicators for hepatitis elimination, as indicated in the previous sections, where the specific data points are available and nationally representative. The report also provides an opportunity to include reflections on potential limitations of the outputs.

The modelling process is highly technical and requires both empirical data and national consensus on key data inputs and assumptions. In addition to reviewing data inputs, analysis and outputs of the model, the mathematical model and its assumptions used to generate the data for the national validation report should also be subjected to a thorough independent peer-review by the WHO modelling reference group.

The checklist provided in Annex 4 and the country self assessment toolkit for validation of hepatitis elimination, provide further details on the key elements that should be assessed in the area of data quality.

A1.2 Ensuring the quality of diagnostics, laboratory services and medicines

Meeting laboratory standards and ensuring quality standards for medicines are important requirements for the validation of hepatitis elimination.

A1.2.1 Ensuring the quality of laboratory services

Laboratories that contribute data points to the surveillance system and for validation, including serosurveys, and for clinical diagnosis and programme implementation should:

1. Have in place a laboratory quality management system to ensure that hepatitis tests are procured, stored and used in accordance with manufacturers' protocols, supported by robust leadership and governance;
2. Ensure the quality of test kits and procedures: that tests are procured, stored and used according to international standards, such as WHO prequalification or other regulatory equivalent;
3. Ensure the quality of testing: personnel who perform the tests have been trained in accordance with nationally recommended algorithms; and
4. Have a laboratory quality assurance mechanism that is routinely and consistently applied and verified through participation in both external and internal quality assurance programmes for HBV and HCV testing *(4)*.

When point-of-care tests are used, the quality and diagnostic performance of the test kits should be verified in accordance with international standards set by stringent regulators such as the WHO prequalification programme. National reference laboratories should oversee and monitor procurement and storage of the tests and perform routine lot testing to verify satisfactory test kit performance. Laboratory quality management systems should include proficiency testing to ensure the quality of testing and monitor compliance with approved algorithms. The key requirements for laboratory quality assessment are shown in Box A1.2.

Box A1.2 Key requirements for laboratory quality assessment

1. Summarize the quality management system
2. Review testing algorithms and strategies and assess the quality of tests and testing
3. Report on internal quality assurance and control
4. Participate in and report on EQA programme
5. Complete the laboratory quality validation assessment section of the country self assessment toolkit for validation of hepatitis elimination.

A1.2.2 Meeting quality standards for medicines

In terms of ensuring that quality standards are met for medicines, it is important that national testing and treatment guidelines specify which medicines and diagnostic assays should be used. Furthermore, it is important to ensure that medicines used for the treatment of viral hepatitis have been approved and registered by a stringent national authority and included in the national essential medicines list. The checklist provided in Annex 4 provides further details on the key elements that should be assessed in the area of data quality of laboratories and medicines.

A1.3 Ensuring the quality of prevention, diagnosis and treatment services, including that of the vaccination programme

A programme quality assessment is part of the validation process and is an in-country exercise.

The programme components assessed are only those relevant to the elimination of hepatitis B and C as a public health problem. These include the provision of quality-recommended prevention, diagnostic and treatment services for viral hepatitis, liver cirrhosis and liver cancer, accompanied by laboratory and data systems targeted at affected populations for viral hepatitis in both the public and private sectors.

To achieve validation of EMTCT of hepatitis B, and/or HCV or HBV as a public health problem, countries must demonstrate the achievement of the programmatic targets in accordance with the PTE tier or for full validation, which are outlined in the document and provide evidence that high-quality services for hepatitis exist in both the public and private health sectors in both urban and rural areas. These aspects of programme quality will be addressed in the national hepatitis elimination report under the chapter on implementation considerations.

A1.3.1 EMTCT of hepatitis B

For EMTCT of hepatitis B, strengthening the maternal and child health (MCH) and vaccination programmes, and coordinating and linking these to the HIV, viral hepatitis and STI programmes is key *(5)*. The national programme should include comprehensive ANC services, including maternal HBsAg testing, preferably integrated with HIV and syphilis testing and treatment programmes, treatment and care for pregnant women, with chronic hepatitis B, with timely birth-dose vaccination of their newborns. Immunization stakeholders, such as ministries of health, should regularly assess the quality of the national immunization programme, including for hepatitis B birth dose and infant vaccination. Priority should be placed on leveraging these existing efforts and assessments of the national immunization programme to inform about the performance of hepatitis B immunization-related activities and to avoid duplication. Interprogrammatic relationships at the national level should be further developed. This should include an assessment of equity in access to hepatitis B vaccine, with evidence that high-quality services for HBV EMTCT are being delivered at the lower-performing subnational administrative units (e.g. municipalities) and for undeserved communities communities (e.g. migrant populations).

A1.3.2 Prevention of HBV and HCV transmission

Programmatic assessment of interventions to prevent HCV and HBV transmission in adolescents and adults should include the availability and quality assessments of safe injection policies and practices in health facilities, safe blood products, effective harm reduction interventions, such as high coverage of NSPs (potentially with low dead-space needles and syringes) and OAT, and accessible HCV treatment to populations with high HCV incidence and/or prevalence (e.g. PWID and those in closed settings such as prisons).

A1.3.3 Hepatitis testing and treatment assessment

These should include the availability of quality screening (HBsAg and HCVAb), additional and/or confirmatory testing (e. g. HBV DNA, HCVcAg, or HCV RNA) and disease staging (APRI [e.g. aspartate aminotransferase-to-platelet ratio index], elastography) for the general population as well as vulnerable groups – in accordance with WHO testing and treatment guidelines *(6-9)*. There should be evidence of health-sectorwide linkage to hepatitis care and treatment for all individuals diagnosed with viral hepatitis, including blood donors and high-risk populations.

Recommended antiviral treatment for hepatitis B should be limited to those effective medicines with a high barrier to resistance. Pangenotypic DAAs that include pangenotypic combination therapy for hepatitis C and antivirals for hepatitis B should be registered, included in the national guidelines, on the national list of essential medicines, and available through public health systems. Cost should not be a barrier to care and treatment for people living with chronic viral hepatitis. Liver cancer screening using recommended practices should be available to those with cirrhosis, and detection and treatment programmes for liver cancer should be included in the public health system.

The key requirements for programme assessment are shown below and should include national policy, plans, guidelines and protocols as well as programme components pertinent to the elimination strategy, which should be in line with current WHO recommendations (Box A1.3).

Box A1.3 Key requirements for HBV and/or HCV programme assessment.

1. Review relevant national policies, plans, guidelines and protocols
2. Assess evidence that services exist in both public and private (and other non-public sector)
3. Complete the programme validation assessment section of the country self assessment toolkit for validation of hepatitis elimination (including review of low performing administrative units and coverage of relevant subpopulations)

To verify whether services are sufficient in scope, accessibility and quality to sustain the HBV and/or HCV elimination targets, these elements should be reviewed during country and regional assessments.

Assessment of low-performing units and of subpopulations with lowest coverage and access to services

Countries must also provide evidence that, even in the lowest-performing subnational administrative units and among subpopulations with the lowest coverage and the least access to services, there is a concerted effort to deliver high-quality services for HBV and/or HCV elimination. Lowest-performing subnational administrative units may be identified using subnational data and defined in a number of ways. Examples include regions or areas in the country (identified by national or regional validation teams or working groups):

- that perform poorly on relevant health indicators;
- that have the highest disease burden;
- with marginalized or vulnerable populations;
- where some or all of the impact and/or process indicators have not been met.

Countries are encouraged to work with the RVTF and Secretariat (RVTF/ RVS) to determine an appropriate selection process to ensure that the assessment accurately reflects the lowest-performing subnational administrative unit. To be eligible for validation, a country does not have to meet the programmatic targets for elimination in all subnational units, but there must be evidence that performance in subnational units has been reviewed and that substantial efforts are being made to address low-performing units. These efforts should include outreach to underserved, migrant, remote or key populations and those in closed settings. There should be evidence that hepatitis services are being offered, accessed and have achieved success that can be maintained.

The checklist provided in Annex 4 provides further details on the key elements that should be assessed in the area of programme quality.

A1.4 Ensuring community engagement, gender equality, human rights and equity in access to services

Equity, human rights, gender equality and community engagement principles are relevant to the validation and PTE of viral hepatitis. The validation assessment needs to take these principles into consideration.

The concepts of no one being left behind and health equity are central to the WHO GHSS *(10)*, and the broader WHO mission *(11-15)*. WHO guidance on hepatitis reflects equity, human rights, gender equality and community engagement as fundamental principles that impact on countries' effective implementation of action to address viral hepatitis.

With regard to "triple elimination", a key requirement for country validation of EMTCT of HIV, syphilis and HBV is that the interventions to reach impact and programme targets have been implemented in a manner consistent with international, regional and national human rights standards, have engaged the community of women living with HIV and HBV and have taken gender equality into consideration *(16)*. These same principles apply to the elimination of viral hepatitis in general.

Many individuals with chronic HBV and HCV infection are from marginalized or stigmatized populations such as PWID, MSM, people in prison, migrants, Indigenous peoples, and have poor access to health care. WHO guidance recommends a specific focus on these populations regarding access to health care, including to hepatitis services *(7)*.

Concerns that mandatory or coercive approaches might be used among highly affected and vulnerable populations highlight the importance of adequate information, informed consent, appropriate health worker training and rights-based legal frameworks to facilitate access to testing and treatment services *(6, 8)*. Stigma and discrimination among key and vulnerable populations at high risk of HIV, HBV and HCV have been well documented *(17, 18)*. Despite increased access to highly effective HCV treatment, stigma, discrimination and criminalization continue to persist in many parts of the world. For hepatitis B, although there is substantial variation in stigma and discrimination*(19, 20)*, as well as human rights violations across regions and countries, criminalization is less common than with HIV *(17, 18)*

Additionally, gender equality is a very important aspect of public health and viral hepatitis elimination. Gender equality considerations are particularly relevant in the context of vertical transmission of HIV, HBV and syphilis, as gender norms and practices implicitly shape sexual and reproductive health (SRH) and the rights of women, as well as the health outcomes of their children. Promoting and ensuring gender equality can improve the opportunities for women and girls to access the necessary information and services. In addition, providing the opportunity for engagement of young women in health services and offering testing to establish hepatitis B status during or before pregnancy is a critical first step to preventing further MTCT.

The relationship between hepatitis C and gender is complex. In most countries, population prevalence of hepatitis C is higher in males, and increases with age. In addition, there is also a predominance of men among people who use or inject drugs, MSM (by definition), as well as residents of closed settings, such as prisons. Nevertheless, women who use drugs and women in closed settings are especially vulnerable for a variety of reasons – in many countries, sociocultural and economic inequality means that women living with hepatitis C may have poorer access to hepatitis C prevention, diagnosis and treatment services.

National responses should be cognizant of the hepatitis prevention, diagnosis and treatment needs of gender-diverse groups, and support active measures to include these high-risk and marginalized populations in accessing these services.

Fundamentally, the goal of the GHSS is to save lives through global attainment of the incidence and mortality impact targets. Saving lives requires the active participation of people living with and at risk for hepatitis B or C in recommended interventions for the prevention, diagnosis and treatment of hepatitis. The following implementation considerations have been identified as potential barriers to achieving these mortality and incidence reductions and should be assessed and included in national validation reports.

Box A1.4 Key requirements for assessment of equity, human rights, gender equality and community engagement

1. Desk reviews of laws, policies and reports
2. Interview with key stakeholders
3. Organize independent consultation with people living with HBV and/or with lived experience of HCV
4. Organize multi-stakeholder consultation and facilitated dialogue to review the findings
5. Complete validation assessment section for equity, human rights, gender equality and community engagement in country assessment toolkit for validation of elimination.

The checklist in Annex 4 provides further details on key elements that should be assessed in the area of equity, human rights, gender equality and community engagement.

The important issues to be considered in reviewing hepatitis B and C in the context of human rights, assessment of the equity, gender equality, community engagement principles of hepatitis elimination during the validation process obligations are shown in Annex 4 and in the country assessment toolkit for validation of hepatitis elimination.

A1.4.1 Human rights

The important issues to be considered in reviewing hepatitis B and C in the context of human rights obligations in law and practice are as follows:

1. availability of voluntary and accessible viral hepatitis testing and treatment;
2. evidence of confidentiality and privacy of hepatitis B and C testing and treatment;
3. evidence of absence of legal discrimination (for employment status, access to education, housing, social benefits);
4. documentation of stigma-free access to health care, testing and treatment for HBV and HCV in policy and practice;
5. evidence that people living with hepatitis are informed of their status and educated about their medical care;
6. evidence of the absence of drug use, sexual orientation status, incarceration experience, immigration status or profession as a criterion for exclusion from hepatitis testing and treatment;
7. evidence of the possibility of health-care access without disclosure of or discrimination against key population status;
8. decriminalization of populations at risk or most affected by viral hepatitis, including people who use drugs, sex workers, MSM.

A1.4.2 Equity

The goal for delivering for equity – the absence of inequalities in health that are avoidable by reasonable means – is a strategic direction of the GHSS *(10)*. It has a focus on strengthening health and community systems to deliver high-quality services to achieve equitable coverage and maximum impact.

Assessment of the equity principles of hepatitis elimination during the validation process includes the following:

1. evidence that national hepatitis elimination targets and interventions include populations that are most affected;
2. evidence of service decentralization, especially with regard to access to prevention, testing and treatment for vulnerable populations and communities, including outside major urban centres;
3. evidence of the integration of hepatitis services in general health service provision and other services as appropriate – which may include services for HIV, STI, other infectious diseases, MCH, vaccination, migrant health, reproductive health, harm reduction and OAT;
4. evidence of care linkages at different levels of the health system with clear definition of the relative contribution and roles of community services, primary health-care peer workers, referral care and hospital care;
5. evidence of cultural responsiveness in the health-care system and efforts to reduce cultural and language barriers;
6. evidence of disaggregation of data by key variables such as gender, geography and risk groups to enable detection of differences across population groups;
7. evidence of inclusion of core essential hepatitis interventions, medicines, diagnostics and vaccines within the national health benefit package to promote equity of access.

A1.4.3 Gender equality

Gender equality is an additional important aspect of public health and elimination of viral hepatitis.

Assessment of gender equality that supports elimination during the validation process includes the following:

1. evidence of the availability of epidemiological data disaggregated by gender;
2. evidence of disaggregation of programmatic data on hepatitis prevention, diagnosis and treatment services by gender;
3. evidence of the presence of a national policy that includes specific reference to addressing the gender needs of those living with or at risk for viral hepatitis, including transgender populations;
4. evidence of accessible hepatitis testing and treatment services for women;
5. evidence of efforts to address stigma/discrimination for both men and women living with hepatitis.

A1.4.4 Community engagement

The meaningful participation of people living with hepatitis B and C and their families and communities is of critical importance in determining and developing national and subnational policies for affected communities and should be actively promoted. Community engagement is also important and highly relevant for supporting and implementing service delivery.

Community engagement can be assessed through evidence of formal and active national-level participation of affected persons in the development, implementation and evaluation of the national hepatitis responses.

Assessment of community engagement that supports elimination during the validation process includes the following:

1. evidence of affected community representatives in the national hepatitis task force;
2. national hepatitis policy documents explicitly state the active participation of the affected community in hepatitis prevention, diagnosis and treatment services;
3. evidence of peer-led or peer-navigation interventions for hard-to-reach, rural and marginalized populations;
4. government funding for representative groups of the hepatitis-affected community.

Annex 2. Validation of elimination and process of governance

A2.1 Overview

The process of validation of elimination of viral hepatitis as a public health problem aims to confirm a member state's attainment of the impact targets of hepatitis B and C incidence and mortality as detailed in the GHSS, with supporting evidence of adequate programmatic coverage and quality through inclusive and effective implementation of the national elimination response. Additionally, each tier of the PTE represents a certifiable milestone of progress towards elimination, where validation of elimination is the ultimate goal. Important principles to be considered by countries before application for validation or certification for PTE include the following:

- The process is country led.
- Achieving elimination targets for viral hepatitis has been prioritized within the national health strategy and immunization development plans and will contribute to reducing the overall national disease burden.
- Achieving elimination targets is feasible and adequate resources are available or could be mobilized.
- There is support and commitment from key stakeholders, including populations most affected and the broader community.
- The process, achievement and maintenance of validation will act as an incentive for accelerated and intensified action. It will also serve as a strong advocacy tool to generate broad support in addressing the burden of viral hepatitis.
- Validation is meaningful to the country and adds to other national accountability mechanisms to monitor progress against national strategies and commitments.

A2.2 Process of governance and integration within the existing infrastructure for validation of elimination

The validation process for the elimination of viral hepatitis should be integrated as far as possible with existing national monitoring, validation and certification processes, and infrastructure for disease elimination, including that of other communicable diseases (e.g. malaria, vaccine-preventable diseases) and the triple elimination of mother to child or vertical transmission of HIV, syphilis and HBV and future multidisease elimination initiatives to promote greater programme integration, alignment and efficiency.

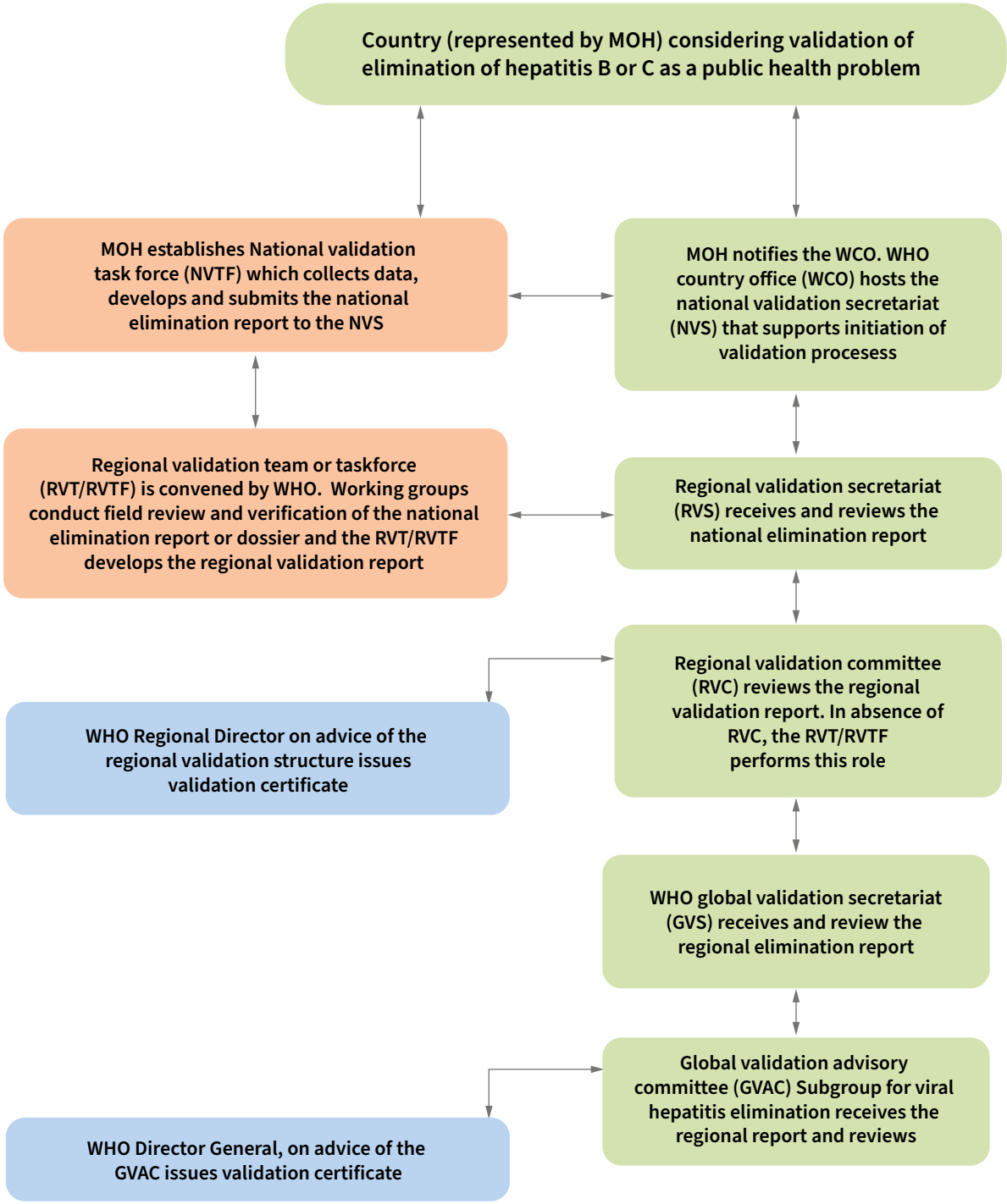
Countries electing to be validated for all components of the elimination of hepatitis B and/or C as a public health problem) will focus on all aspects of the national elimination strategy. Governance of the process will be guided by relevant WHO proposed committees and secretariats at the national, regional and global levels in the triple elimination and viral hepatitis structures, as illustrated in Fig. A2.1. These approaches aim to make efficient use of human resources and capacity. To assess for validation, countries and regions should have the required expertise in those disease areas and health systems aspects, including viral hepatitis. Of note, the process for assessing attainment of the targets on the “path to elimination” of viral hepatitis as a public health problem is completed at the regional level, unless a region specifically requests global-level engagement for higher-level advocacy.

If a country elects to be validated only for the HBV EMTCT component of its viral hepatitis strategy, applications will be channelled through the triple elimination path by independent assessment of regional reports by the GVAC and Regional Validation Committee (RVC), where available, for EMTCT. Notably, this route is currently available to countries opting to be validated for one, two or three infectious diseases to promote integrated validation of EMTCT of HIV, syphilis and HBV. Furthermore, if a country that has been validated for all components of the elimination of hepatitis B as a public health problem and later chooses to seek validation for triple elimination, its validated status for EMTCT of HBV will be recognized (if still valid) without the need for a reassessment.

In addition, if a country elects to be validated for the elimination of hepatitis B or C as a public health problem, applications will be channeled through the GVAC subgroup and undergo independent assessment. Countries that have completed the the verification of HBV control by immunization will need to demonstrate adequate coverage of maternal HBsAg testing and treatment of eligible women to be recognized for validation of HBV EMTCT by the GVAC.

The resources (human and financial) required to support the validation process for hepatitis elimination should be integrated into the national health plan, to optimize the use of existing resources and maximize interprogrammatic efficiencies.

Fig. A2.1 Governance process for the validation of viral hepatitis B and/or C as a public health problem: triple elimination and viral hepatitis route



CO: country office; DG: Director-General; EMTCT: elimination of mother-to-child transmission; GVAC: Global Validation Advisory Committee; NVTF: National Validation Task Force; RVC: Regional Validation Committee; RVTF: Regional Validation Task Force [Corrections needed in the figure]

A2.3 The submission processes

Six steps are required for recognition of the elimination of viral hepatitis through validation by WHO.

1. Request sent to WHO. Once the national government has reviewed its programmes and is confident that it can meet the qualifying criteria, the national government takes the decision to be assessed for validation of elimination and informs the WHO Representative in the Country Office, who then relays the request to the WHO Regional Office. In the absence of a WHO country office, the initial step would commence at the Regional Office. WHO responds by formally communicating the elimination criteria and processes for validation, including the documents necessary to provide clear, convincing evidence that the specific impact and process targets have been met.
2. Formulation and implementation of a validation plan of action, preparation and submission of the national hepatitis elimination report. The national Ministry of Health coordinates the planning and development of a detailed national hepatitis elimination report based on criteria provided by WHO. The Ministry of Health convenes a task force for validation of national hepatitis elimination, as part of broader national disease elimination assessment committees (where one exists), and consistent with WHO guidance. The task force is responsible for synthesizing, reviewing and analysing documentation and other information submitted by the Ministry of Health and other sources to prepare a draft national elimination report. A broad national consultative process should enable inputs into the report from all key stakeholders. The task force submits the report to the Ministry of Health, which then formally submits it to WHO. Throughout the process, WHO provides technical support and facilitates the coordination function of the Ministry of Health. WHO's support is managed through the WHO Country Office.
3. Evaluation by expanded RVTF experts supported by the WHO Secretariat through the regional validation report. The national hepatitis elimination report is submitted by the respective Ministry of Health through the WHO Country Office to the respective WHO Regional Office and on to the Regional Validation Secretariat.
4. The WHO Secretariat convenes a regional validation task force (RVTF) for validation of hepatitis elimination. The RVTF is responsible for reviewing the national report, gathering additional information if required, analysing all relevant inputs and preparing a regional validation report on hepatitis elimination. The WHO Secretariat facilitates the work of the RVTF, including organization of country site visits or virtual review meetings with country counterparts to verify the content of the national report and related documents. The regional report is submitted to the WHO Regional Secretariat, with recommendations as to whether validation of elimination should be granted.
5. Report review by the expanded Regional Validation Committee (if established) for the final decision on approval to be taken. The WHO Secretariat shares the report with the Regional Validation Committee for critical review. Committee members vote on the outcome of the assessment, which is shared with the WHO Secretariat (regional and global). The final regional-level decision to validate the elimination of viral hepatitis as a public health problem is taken by the respective WHO Regional Director.
6. The approval decision is conveyed to WHO headquarters for further action. The GVS reviews the regional report, recommendations and decisions to determine what further action might be required, and to inform global accountability and reporting on hepatitis elimination. The GVS informs GVAC and convenes hepatitis subgroup to review regional elimination report where full- validation is required (or PTE where requested by regional structures). The respective WHO Regional Director and the WHO Director-General communicate the final decision to the national government through an official letter.
7. Optional publication of validation in the WHO Weekly Epidemiological Record. The WHO Secretariat publishes positive decisions in the Weekly Epidemiological Record.

While validation of elimination is documented at the global level, recognition of the PTE is completed at the regional level only, unless the RVS specifically requires that this be escalated to the global level for higher-level advocacy purposes.

A2.4 National level

A2.4.1 The national hepatitis elimination report

The national hepatitis elimination report should have the following elements:

- Executive summary
- Brief description of the overall health system, including financing
- A description of the national viral hepatitis programme
- Methodology and detailed data sources for the required impact and programmatic indicators sufficient to demonstrate proof of achievement of these indicators
- Provision of a response and details of assessment impact
- Provision of a response to all implementation considerations for elimination of viral hepatitis detailed in the implementation considerations document. Reference is made to the national elimination report template in Annex 3.
- Outline of the potential risks and accompanying strategies for sustaining elimination of viral hepatitis.

A full description of and template for the national hepatitis elimination report can be found in Annex 3.

A2.4.2 National Validation Secretariat

The WHO Country Office's role is to support the National Validation Task Force (NVTF) in preparing a national hepatitis elimination report detailing evidence of elimination. The National Validation Secretariat (NVS) is hosted by the WHO Country Office and supports the Ministry of Health in its overall coordination function. It serves as the first point of contact for national stakeholders and as an intermediary between the Ministry of Health, NVTF and regional secretariat. It convenes other key national partners contributing to efforts at hepatitis elimination and associated health issues, including United Nations (UN) agencies. It provides technical support to the Ministry of Health and the NVTF, together with relevant UN and other partners, to assist with assessing the programme for the elimination of hepatitis B or C or both, and then developing and preparing the national validation report.

A2.4.3 National Validation Task Force

The NVTF is established by the Ministry of Health and is responsible for writing the national elimination report and submitting it on behalf of the Ministry of Health through the NVS, and addressing any queries or clarifications regarding the report, including from the RVTF. NVTF members should have the technical expertise to contribute to the national validation report. The following considerations should inform the establishment of the NVTF:

- The NVTF may in the future be a task force of a broader national disease elimination assessment committee that coordinates/oversees assessment of the efforts to eliminate all diseases targeted for elimination in the country.
- The NVTF is a multidisciplinary team comprising a wide cross-section of professionals from various services and programmes, such as reproductive health, MCH, laboratory, health systems, health information (including epidemiology/surveillance/monitoring), immunization, hepatology, and relevant legal and civil society representatives. If the report includes EMTCT (of HBV), at least one individual with expertise in coinfection of HIV or syphilis with HBV should be included to provide linkage and integration to these areas. The WHO Secretariat should provide broader health systems expertise and link the NVTF with other relevant national disease elimination efforts (i.e. for assessing laboratory, disease surveillance and human resources capacity).
- Preference should be given to members with more than one skill set to ensure that all areas are covered, and the group is close to the minimum size. It is expected that the majority of NVTF members would be national experts, but external experts may be considered, particularly from neighbouring countries that have already completed an elimination validation process.
- All NVTF members should sign statements of confidentiality and declarations of interest reviewed by the Ministry of Health or the Secretariat, as necessary, to identify any real or perceived conflicts of interest. Participation should be voluntary and not remunerated by WHO or the Ministry of Health.

A2.5 Regional level

A2.5.1 Regional Validation Secretariat

The role of the WHO Regional Office is twofold: first, to support the NVTF and NVS, as well as the RVTF in their assessment of the national elimination report. Second, it also acts as a conduit for submission of the report to the Regional Director or the Regional Validation Committee and to the global Secretariat to facilitate ultimate final approval and confirmation of the validation of elimination of viral hepatitis. Where validation ends at the regional level, the Regional Validation Secretariat (RVS) is responsible for facilitating congratulatory or other communication from the WHO Regional Director to the country.

The role of the RVS is as follows:

- establishing, convening and coordinating the RVTF;
- supporting the coordination of national validation processes and activities;
- approving and submitting the final elimination reports from the RVTF to the WHO Regional Director or the Regional Validation Committee
- providing communication between regional and national stakeholders and the global level, including communicating the decision of the Regional Director regarding validation or maintenance of validation to the NVS and any request for clarification;
- collaborating with the country to ensure that reports on maintenance of validation are completed every five years and that the report addresses the recommendations made by the RVTF.

A2.5.2 Regional Validation Task Force

The RVTF oversees the validation processes in the region and the establishment of teams or working groups dedicated to the validation process for a specific country. It is responsible for submitting a complete and accurate regional validation report to the RVS, which in turn submits it to the Regional Validation Committee, where it exists. Where the validation process ends at the regional level, the RVTF is responsible for making a recommendation to the Regional Director for communication to the country. The responsible RVTF should be fully integrated as part of the Regional Validation Committee, where it exists.

Steps in the tasks of the RVTF are as follows:

- Review national hepatitis elimination reports from candidate countries, make an assessment of compliance with global-/region-specific minimum criteria, request additional information or clarification.
- Collaborate with the RVS.
- Conduct an in-country or virtual validation visit for an in-depth assessment, supporting the NVTF (joint visit led by WHO, but which includes members of the RVTF).
- Consider the country visit report on hepatitis elimination and assessment of the national elimination report.
- Thereafter, the full RVS will advise whether a candidate country (i) has successfully achieved hepatitis B or C elimination (or both) and can be recommended for validation to the GVS; or (ii) is on the hepatitis B or C PTE (or both) and can be recommended for validation to the Regional Secretariat and subsequently the Regional Director.
- Provide recommendations to a country to support ongoing monitoring and maintenance of validation in coordination and aligned with those of regional advisory bodies.

A2.6 Global level

A2.6.1 Global Validation Secretariat

The GVS is hosted by WHO headquarters and is staffed by the Department of Global HIV, Hepatitis and Sexually Transmitted Infections programmes. The GVS provides coordination, leadership and oversight to the global validation process. The GVS includes representatives from other relevant departments, especially in the areas of blood and injection safety; reproductive, maternal, neonatal, child and adolescent health; and immunization/vaccine-preventable diseases across the communicable and noncommunicable disease spectrum. It works in collaboration with external partners, including other UN agencies (e.g. UNAIDS, UNICEF, United Nations Population Fund [UNFPA], UNITAID and UNODC).

A2.6.2 Global Validation Advisory Committee (GVAC) for triple elimination of mother-to-child transmission of HIV, syphilis and HBV and subgroup for validation of elimination of viral hepatitis as a public health problem

The GVAC is an independent advisory body that provides technical assistance and supports oversight of the validation process for EMTCT of HIV, syphilis and hepatitis B as well as viral hepatitis elimination to determine whether countries' efforts towards achieving elimination meet the global validation criteria. Countries that have achieved hepatitis B immunization goals (HBV control) and have received regional verification by the immunization technical advisory group (TAG) can also apply for validation of HBV EMTCT by GVAC. In these countries, the verification certificate of the immunization TAG or equivalent body will be accepted by GVAC, without the need for re-assessment. Additional evaluation will focus on programmatic coverage of maternal testing and antiviral HBV prophylaxis or treatment where eligible. The validation process will include assessment of HIV and/or syphilis for countries that apply for dual or triple EMTCT elimination.

The GVAC sub-group will provide an independent review of regional hepatitis elimination reports submitted in the context of of hepatitis B and/or C elimination as a public health problem in the general population. The GVAC subgroup will provide assessment of national reports for full validation of Hepatitis B and/or C as a public health problem in the general population. They will also assess PTE of these options based on regional request.

A2.7 Process for the maintenance of validation, revalidation, and reversal of validation

- Countries that have been validated for achieving the elimination of viral hepatitis as a public health problem will be assessed every five years for maintenance of validation (this assessment will be done every 3 years for maintenance of PTE). Consideration should be given to synchronizing revalidation with relevant national programme reviews and revalidation of other related diseases. To be assessed for maintenance of validation, the Ministry of Health is asked to submit a brief report to the respective RVC.
- The WHO Secretariat will work with the RVC to reach one of the following conclusions: maintain validation without recommendations; maintain validation with recommendations; defer maintenance of validation pending requests for clarification or more information from the country or do not maintain validation.

The process for deferring validation, requesting clarification and conflict resolution and mechanisms for appeals will be conducted as published in the governance manual for Validation of elimination of mother-to-child transmission of HIV and syphilis *(21)*.

Annex 3. National elimination report template

The following template can be helpful in structuring the national elimination report.

- Executive summary
- Country context
  - Description of the National Validation Task Force (NVTF) and summary of goals of the review
  - Demography, basic health indicators
  - Country epidemiological profile for viral hepatitis (trends, drivers of infection)
  - Brief description of all levels of the health system, including financing, special population needs- and access, where applicable.
- A description of the viral hepatitis policies and programme, including laboratory services, data management, gender equality, equity in access and community engagement.
- Provision of data, sources, representativeness of data and methodology for the required impact and programmatic indicators sufficient to demonstrate proof of achievement of these indicators
- Provision of a response to all implementation considerations for elimination of viral hepatitis detailed in the chapter on implementation considerations and demonstration of key findings, including consistency of achievements across geographical areas (note Annex 4 checklist)
- Outline of the potential risks and accompanying strategies for sustaining elimination of viral hepatitis.
- The country assessment and the indicator data collection tools serves as a resource for assessing the country preparedness for validation as well as a data collection tool to assess attainment of the targets for impact and programmes.
  - Tools for the Validation of Hepatitis B and C and the Path to Elimination: 2023

Annex 4. Checklist for supporting evidence of implementation considerations for validation of elimination

Note: This checklist provides a concise summary of implementation consideration for validation or elimination and should be used in conjunction with the country validation self assessment toolkits for HBV and HCV. It is provided to facilitate the writing and documentation of the implementation considerations in the national hepatitis elimination report; it is suggested that the full checklist be filled in and used as an annex to the main national elimination report. Depending on the option that is chosen for validation of elimination or PTE, not all items of the checklist apply (e.g. when applying for validation of elimination of HCV as public health problem only, the items on HBV do not apply).

Table A4.1. Checklist for supporting evidence of implementation considerations for validation of elimination

Implementation component	Present (Y/N)	Detailed information on component (e.g. when developed or updated, etc.)	Evidence to support statement and other references
Data quality			
1.1 Country has a standard mechanism/system in place to collect and report on the WHO 10 core programmatic indicators			
1.2 Programmatic indicators are well-defined at the country level and data inputs regularly checked			
1.3 National information system is able to provide disaggregated and representative data relating to hepatitis impact indicators			
1.4 National information system is able to capture service delivery and outcome data from both the public and private health sector			
1.5 National capacity to undertake or commission mathematical modelling using country data for viral hepatitis is available			
1.6 Viral hepatitis case reporting is included in the national surveillance system			
1.7 Surveillance system can differentiate between acute and chronic viral hepatitis cases			
1.8 Attributable fraction of HCC and cirrhosis are estimated on a national level			
1.9 Registry for liver cancer in place			

Table A4.1. (continued) Checklist for supporting evidence of implementation considerations for validation of elimination

Implementation component	Present (Y/N)	Detailed information on component (e.g. when developed or updated, etc.)	Evidence to support statement and other references
1.10 Registry for cirrhosis and/or decompensated cirrhosis in place			
1.11 National registry for chronic viral hepatitis patients established			
2. Laboratory and medicines quality			
2.1 Laboratory quality management system is in line with existing WHO laboratory guidance			
2.2 Internal and external quality assessment (EQA) programmes present			
2.3 National hepatitis reference laboratory oversees the domestic laboratory network and laboratory quality management (including procurement, staff proficiency, etc.)			
2.4 Hepatitis tests and molecular diagnostics are quality assured and WHO prequalified or approved by a relevant regulatory authority			
2.5 Antivirals for hepatitis B treatment are domestically registered and are WHO prequalified or approved by a relevant regulatory authority			
2.6 Direct-acting antivirals for hepatitis C treatment are domestically registered and WHO prequalified or approved by a stringent regulatory authority (SRA)			
3. Quality hepatitis programming, policy and practice			
3.1 National infection control and blood safety policies are consistent with WHO recommendations and implemented accordingly			
3.2 National vaccination programme is consistent with WHO recommendations and implemented accordingly (including assessment of rationale if targeted timely birth dose)			
For elimination of mother-to-child transmission (EMTCT) of hepatitis B, there is evidence of comprehensive antenatal care (ANC) services and timely birth-dose vaccination of their newborns as well as hepatitis B testing and treatment prophylaxis, preferably integrated with HIV and syphilis testing			
3.3 Evidence-based harm reduction interventions (including needle and syringe programming) are implemented in consistent with WHO recommendations			

Table A4.1. (continued) Checklist for supporting evidence of implementation considerations for validation of elimination

Implementation component	Present (Y/N)	Detailed information on component (e.g. when developed or updated, etc.)	Evidence to support statement and other references
3.4 National hepatitis testing and diagnosis algorithms are consistent with WHO recommendations and implemented accordingly			
3.5 National hepatitis B and C treatment protocols are consistent with WHO recommendations and implemented accordingly			
3.6 Hepatitis B vaccination is available for health workers and high-risk and vulnerable populations			
3.7 Hepatitis B testing and treatment are available across the country (all regions and districts) and to vulnerable and high-risk populations (including in prisons) through public health systems			
3.8 Hepatitis C testing and treatment are available across the country (all regions and districts) and to vulnerable and high-risk populations (including in prisons) through public health systems			
3.9 There is evidence of liver cancer screening for eligible persons living with chronic viral hepatitis			
3.10 Hepatitis workforce training (in-person/online training, curriculum and mentorship) is included in national health policies			
3.11 Programmatic indicators and programme quality have been reported from the lowest-performing subnational unit			
4. Human rights			
4.1 Evidence of voluntary viral hepatitis B and C testing and treatment			
4.2 Evidence of confidentiality and privacy of hepatitis B and C status and treatment			
4.3 Evidence of absence of legal discrimination (for employment status, access to education, housing, social benefits)			
4.4 Evidence of stigma-free access to health care and treatment for those with HBV and HCV			
4.5 Evidence that people living with hepatitis are informed of their status and provided adequate counselling			

Table A4.1. (continued) Checklist for supporting evidence of implementation considerations for validation of elimination

Implementation component	Present (Y/N)	Detailed information on component (e.g. when developed or updated, etc.)	Evidence to support statement and other references
4.6 Evidence of the absence of drug use, sexual orientation status, incarceration experience, immigration status or profession as a criterion for exclusion from hepatitis treatment			
4.7 Evidence of health-care access without need for disclosure of or discrimination against key population status;			
4.8. Evidence of decriminalization of populations at risk or most affected by viral hepatitis, including people who use drugs, sex workers, MSM.			
5. Equity			
5.1 Evidence of testing and treatment service decentralization and integration			
5.2 Evidence of disaggregation of programme and epidemiological data by gender and other equity stratifiers			
6. Gender equality			
6.1 Evidence of the presence of national policy that includes specific reference to addressing the gender needs of those living with or at risk for viral hepatitis, including access, and stigma/discrimination			
6.2 Evidence of efforts to address stigma/ discrimination of men and women living with hepatitis			
7. Community engagement			
7.1 Evidence of affected community representatives in the national hepatitis task force			
7.2 National hepatitis policy documents explicitly state the active participation of the affected community in hepatitis prevention, diagnosis and treatment services			
7.3 Evidence of peer-led navigation in hepatitis service delivery for hard-to-reach, rural and marginalized populations			
7.4 Evidence of government support or funding for representative groups of the hepatitis-affected community			

1 Equity stratifiers are those variables that can be measured to identify population subgroups having poorer health or health-care access.

Annex 5. The cross-cutting issue of mathematical modelling to assess progress towards viral hepatitis elimination

While the collection of empirical data is critical for assessing progress towards incidence, mortality and elimination targets, as well as progress of programmatic coverage, it has become clear that mathematical modelling is a critical tool used by countries to assess progress and understand the gaps and strengths of their national hepatitis response. In addition, as outlined in the main document, there have been some initial efforts to validate progress towards elimination using mathematical modelling in combination with national empirical data and programmatic coverage information.

A non-exhaustive summary of the utility of modelling and approaches (key inputs, calibration steps, outputs) in hepatitis elimination efforts is given below:

Benefits of modelling

- Offers new insights and identifies data gaps
- Estimates incidence levels in different populations
- Integrates diverse data sources
- Accounts for uncertainty in parameter estimates
- Predicts the potential impact of different interventions
- Addresses challenges of direct measurement of HBV or HCV incidence or mortality.

Key inputs for mathematical modelling for hepatitis

- Representative epidemiological data on incidence or prevalence of viraemic infection (HCV) and HBsAg prevalence (HBV)
  - Two prevalence values more than 1 year apart can be sufficient as a basis for accurate estimations of incidence and mortality trajectory
- Behavioural data on risk factors and transmission-related behaviours
- Health-care systems data on diagnosis, treatment, and harm reduction programme coverage
- Hepatitis B- or C-related deaths or HCC case incidence or numbers
- Hepatitis B vaccine coverage rates and change over time
- Demographic data and population structure
- Evidence-informed assumptions about transmission dynamics, infectiousness, natural history of infection, disease progression rates, spontaneous clearance, and prevention, testing, and treatment intervention impacts.

Calibration steps for mathematical models for hepatitis

- Estimating key parameters using available data
- Fitting model outputs to country-specific observed, empirical data on hepatitis B or C prevalence and incidence trends
- Conducting sensitivity analyses to assess the robustness of the model under varying parameters and assumptions.

Key outputs of hepatitis models

- Estimated incidence of hepatitis B or C
- Viral hepatitis-related mortality and morbidity
- Economic impact analysis.

Applications of modelling

- Assessing progress towards and validation of viral hepatitis elimination
- Providing insights into hepatitis B or C transmission dynamics
- Evaluating the impact of prevention, diagnosis and treatment strategies
- Identifying potential gaps in data and areas for programmatic improvement
- Supporting viral hepatitis prevention and control efforts by informing policy decisions, especially in populations driving new infections in a country.

Models should be peer-reviewed, published and have undergone an internal validation process against serosurvey and other empirical data in at least one country. Model outputs and inputs should be country specific.

Annex 6. Methods for estimating and monitoring the mortality from cirrhosis and hepatocellular carcinoma attributable to viral hepatitis B and C at a national level

A6.1 Background

In 2016, WHO published the GHSS for viral hepatitis that aims at the elimination of hepatitis B and C as a public health problem by 2030. A reduction in mortality due to HBV and HCV infections is one of the two criteria that the GHSS uses to define elimination. Indeed, one of the two impact targets outlined in the GHSS is related to hepatitis mortality. The GHSS for HIV, viral hepatitis and sexually transmitted infections for the period 2022–2030 and the supporting WHO guidance for country validation of hepatitis elimination includes the use of absolute impact targets to validate elimination at the national level, instead of, although equivalent to, the relative reduction targets originally defined in the 2016 GHSS (10, 22, 23).

While WHO and the Global Burden of Disease (GBD) project have estimated mortality from viral hepatitis at the global level based on modelling approaches using data from published studies, most countries have not yet established a clear system for generating national estimates of mortality due to long-term sequelae from chronic HBV and HCV infections. Deaths related to hepatitis B and C infections are mostly due to decompensated cirrhosis and HCC, but accurately measuring mortality is challenging as death certificates often do not capture the underlying disease (e.g. viral hepatitis infection). Here we propose and describe two independent methods for collection of data, which are complementary. They will support countries to monitor mortality from HBV and HCV over time at the national level. The overarching goal is to set up a long-term surveillance system in the country.

1. **The first is to estimate the proportions of sequelae (cirrhosis and HCC) that are attributable to hepatitis B and C viruses or to other risk factors that are known to cause these sequelae**. These proportions, also referred to as attributable fractions (AFs), vary greatly between countries due to differences in the scale and progression of HBV and HCV epidemics over time and to the presence of other risk factors (alcohol, steatotic liver disease [SLD]), aflatoxin toxicity, or other rarer conditions) in the country population. Up-to-date AFs are best estimated in selected sentinel centres that diagnose, follow up and treat representative populations of patients with cirrhosis and HCC.
2. **The second is to estimate the "mortality envelope" from chronic liver disease (i.e. cirrhosis and HCC)**. This "mortality envelope" is a term that has been developed to define all the different possible causes of death (e.g. HCC) that are potentially related to HBV or HCV as defined by ICD coding or other criteria (e.g. clinical). National mortality data are usually available from vital statistics registries, but their quality need to be assessed to ensure that all (or an acceptable proportion of) deaths occurring as a consequence of decompensated cirrhosis or primary liver cancer, namely HCC, are captured, whatever the underlying cause. This assessment should be done by the country as the accuracy of vital statistics strongly depends on the challenges faced locally.

To assess the quality of vital statistics, one may consider the following options (non-exhaustive):

a. Mortality from cirrhosis and HCC in selected sentinel sites can be measured and compared to data corresponding to the same geographical area as reported in the national vital statistics database.
b. Unexpected or unexplained geographical or temporal variations in cirrhosis/HCC mortality could be investigated.
c. Triangulation with other available robust data sources such as cancer registries or cohorts of patients (if available) may be undertaken.

Applying AF estimates to the mortality envelope derived from vital statistics will enable calculation of national mortality due to viral hepatitis sequelae over time.

In 2019, WHO developed a protocol to support countries in implementing simple studies to collect the data needed to generate national estimates. This protocol, available at: https://www.who.int/publications/i/item/9789241515191 (Annex 3), provides a standardized method to estimate the proportion of patients with cirrhosis and HCC who have HBV and HCV infection in sentinel centres. This template protocol needs to be adapted to a country-specific setting.

An amended and simplified methodological approach is outlined in this short concept note. Two departures from the original protocol need to be highlighted:

- **One of the key suggested changes to the initial protocol is that the AF should be based only on the proportion of patients diagnosed with decompensated cirrhosis (instead of all patients with cirrhosis) and HCC.** The rationale for this change is that patients with decompensated cirrhosis are more likely to die at the cirrhosis stage than patients with compensated cirrhosis. Therefore, the estimated AF in these two groups (decompensated cirrhosis and HCC) will better reflect the underlying cause of death when applied to the mortality envelope.
- **A further suggestion is that a surveillance system should be ultimately developed to allow periodical or continuous collection of data over the years to monitor AF changes due to health policy measures or, in the absence of public health measures, to the natural course of the epidemic in a given country.**

A6.2 Main steps in measuring hepatitis-related mortality

1. To carefully select one or several sentinel centres (see below)
2. To recruit or assess a representative and large enough sample of consecutive patients with decompensated cirrhosis and HCC over a predefined period
3. To assess these patients for the underlying cause of the disease: HBV (also ideally HDV) and HCV chronic infection, as well other non-viral causes, through a review of medical records supplemented, where appropriate, by direct contact (interview/questionnaire) with caregivers
4. To calculate the proportion of patients that have HBV and HCV infection, or other non-viral causes (AFs)
5. To apply these AFs to the mortality envelope derived from vital statistics to estimate national mortality due to viral hepatitis sequelae.

A6.3 Design

A prospective or cross-sectional study design that follows up patients over time and collects real-time information may be easiest to implement as opposed to a retrospective approach that requires a search through different sources to identify data relating to previous patients who may have died, their records hard to locate or whose information may have been lost. However, in some instances, a retrospective approach may be quicker to undertake and may therefore be more feasible, especially if there are challenging ethical considerations (e.g. consent forms for the prospective recruitment of patients), lack of funding, or large sample sizes.

A6.4 Sentinel centres

The selection of sentinel sites requires careful consideration and should include centres that see patients with both decompensated cirrhosis and HCC in sufficient numbers for the required sample size. The selection of sentinel sites should include a prior assessment of the underlying characteristics of patients attending the centre through discussion with local clinicians to avoid centres with major sources of referral bias that would affect the AF and to ensure that data can be collected from all the various departments where patients with decompensated cirrhosis and/or HCC are cared for. While it may be easier and more feasible to collect data from just one sentinel site, representativeness is likely to be improved if data were collected from a few different clinical sites across the country.

A6.5 Population

Any patient with decompensated cirrhosis or HCC seen during the study period. Patients seen several times should be included only once. The inclusion of patients in departments other than hepatology and gastroenterology is important as patients with decompensated cirrhosis or HCC may present with a range of atypical complications (e.g. sepsis, haemorrhage, encephalopathy, etc.).

A6.6 Investigators

Participating centres will identify a team of investigators for the purpose of data collection. A lead will be identified who will be the liaison point for the country lead investigator.

A6.7 Case definitions

Cases are broadly defined using the clinical criteria below, but these criteria should be refined and adapted to the country health-care system:

Decompensated cirrhosis

- A case of decompensated cirrhosis is defined by clinical symptoms (e.g. recurrent or refractory ascites, portal hypertension-related bleeding, hepatic encephalopathy, acute kidney injury and hepatorenal syndrome).

Hepatocellular carcinoma

- A case of HCC is defined using imaging criteria or pathological evidence.

A6.8 Sample size considerations

The sample size will depend upon the **highest expected viral AF** in the sentinel centre and the desired precision for the estimate. The sample size calculation will need to be undertaken separately for decompensated cirrhosis and HCC. For an absolute precision of 5%, it may roughly vary between 70 and 400, depending on the expected highest AF. A local decision may need to be made around the desired level of precision for the estimate and the size of the sample that is reasonable to collect.

Table A6.1 Examples of sample size calculations based on an absolute precision of 5%

Estimated AF*	Estimated sample size	Estimated AF*	Estimated sample size
50%	384	50%	384
40%	369	60%	369
35%	350	65%	350
30%	323	70%	323
25%	288	75%	288
20%	246	80%	246
15%	196	85%	196
10%	138	90%	138
5%	73	95%	73

* Highest expected AF (for HBV or for HCV) in the sentinel centre (use 50% if not sure)

A6.9 Data collection

- For each case, investigators will extract information from the patients' records using a case report form (see enclosed template table that can be locally adapted as necessary).
- Data extracted should include at least age, sex, serological testing showing HBV (possibly HDV) and/or HCV chronic infection, HIV, as well as excessive alcohol consumption, and metabolic syndrome components (diabetes, obesity). Other rare risk factors for cirrhosis or HCC will be aggregated under "other cause".
- As this information is normally collected as part of the assessment of a patient with cirrhosis or HCC under normal clinical practice, no additional data need to be collected for the purpose of the surveillance activity.

A6.10 Expected outcomes

- Improved national mortality estimates (after applying the AF data to the mortality envelope)
- Capacity-building for the ongoing surveillance of HBV and HCV infection among patients with cirrhosis and HCC
- Creation of a community of practice/partnership with clinicians, laboratory, and public health specialists, which could be used for other data collection or research initiatives.

Table A6.2 Minimum set of data to be extracted

General Characteristics				
Centre				
Case ID:				
Date of inclusion (dd/mm/yyyy):		_____/_____/_____		
Age:				
Gender:		☐ Male ☐ Female ☐ Other		
Sequelae				
Decompensated cirrhosis ☐		***Hepatocellular carcinoma** ☐		
Optional: Clinical main symptom (see case definition) and/or APRI score, Fib-4 index		*Optional*: Diagnosis tool (see case definition)		
Possible risk factors/exposures for cirrhosis or hepatocellular carcinoma				
Chronic infection with viral hepatitis viruses (HBV and/or HCV)				
HBV	HBsAg	☐ Positive	☐ Negative	☐ Unknown
	HBV DNA (last available) (IU/mL)			☐ Unknown
	Optional: Currently under treatment	☐ Yes	☐ No	☐ Unknown
	Optional: Treatment regimen	☐ Positive		☐ Unknown
	Optional: HDV test (RNA or Ab)	☐ Positive	☐ Negative	☐ Unknown
HCV	Anti-HCV	☐ Positive		☐ Unknown
	HCV RNA (last available)	☐ Detectable		☐ Unknown
	HCV core antigen	☐ Positive		☐ Unknown
	Optional: Received treatment with DAA	☐ Yes		☐ Unknown
	Optional: Treatment regimen			☐ Unknown
	Optional: Treatment date (dd/mm/yyyy)	Start: _/_/__	End: _/_/__	☐ Unknown

Table A6.2 (continued) Minimum set of data to be extracted.

Other risk factors			
Excessive alcohol consumption, as per local definition	☐ Yes	☐ No	☐ Unknown
Arterial hypertension	☐ Yes	☐ No	☐ Unknown
Fatty liver disease	☐ Yes	☐ No	☐ Unknown
Diabetes, as per local definition	☐ Yes	☐ No	☐ Unknown
Obesity (BMI >25)	☐ Yes	☐ No	☐ Unknown
Other causes (e.g. Wilson disease, haemochromatosis, autoimmune hepatitis, etc.)	☐ Yes	☐ No	☐ Unknown

*If a patient presents with both decompensated cirrhosis and HCC, the patient will be considered as having HCC for the analysis.

Case definitions: To be refined and adapted to the country health-care specificity. Examples provided below	
Decompensated cirrhosis Cases defined by clinical symptoms such as • recurrent or refractory ascites • portal hypertension-related bleeding • hepatic encephalopathy • acute kidney injury • Hepatorenal syndrome	Hepatocellular carcinoma Cases defined using clinical criteria, imaging criteria or pathological evidence

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