World Health Organization

CONSOLIDATED STRATEGIC INFORMATION GUIDELINES FOR VIRAL HEPATITIS

PLANNING AND TRACKING PROGRESS TOWARDS ELIMINATION

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Consolidated strategic information guidelines for viral hepatitis: planning and tracking progress towards elimination

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ABBREVIATIONS AND ACRONYMS

DHIS2	District Health Information System 2 (software)
EPI	Expanded Programme on Immunization
ERC	WHO research Ethics Review Committee
GHSS	Global Health Sector Strategy
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
ICER	incremental cost–effectiveness ratio
Ig	immunoglobulin
SARA	Service Availability and Readiness Assessment
SDG	Sustainable Development Goal

EXECUTIVE SUMMARY

In May 2016, the World Health Assembly endorsed the first Global Health Sector Strategy (GHSS) on viral hepatitis. The GHSS on viral hepatitis calls for elimination of viral hepatitis as a public health threat by 2030 through implementation at sufficient service coverage of five core interventions (hepatitis B immunization, prevention of mother-to-child transmission of hepatitis B virus [HBV], blood and injection safety, harm reduction for people who inject drugs, and testing and treatment).

The WHO monitoring and evaluation framework for viral hepatitis B and C follows a results-based approach that considers context (prevalence of infection), input, output and outcome (including the cascade of prevention, testing and treatment), and impact (incidence and mortality). Data systems that are needed to inform this framework include (i) surveillance for acute hepatitis, chronic infections and sequelae, and (ii) programme data documenting prevention, testing and treatment, which includes the cascade of care.

Collaboration between viral hepatitis and other health programmes (e.g. immunization, communicable disease control including infection control, harm reduction, HIV, tuberculosis, primary care, cancer care) will be needed at the strategic, policy, technical, implementation and data management levels to ensure that strategic information can be collected, transmitted, analysed and used for action without creating new data systems. This will monitor progress towards achieving the viral hepatitis elimination targets and the Sustainable Development Goals (SDGs), as the cumulative incidence of HBV infection in children under 5 years of age is an SDG indicator.

BACKGROUND

The first-ever *Global hepatitis report (1)* published in 2017 indicated that in 2015, 1.34 million persons died from the consequences of viral hepatitis infection. More than 90% of this burden was due to cirrhosis and hepatocellular carcinoma (HCC), which are the sequelae of infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) *(1)*. In May 2016, the World Health Assembly endorsed the 2016–2021 Global Health Sector Strategy (GHSS) on viral hepatitis, which calls for elimination of viral hepatitis as a public health threat by 2030. Elimination is defined as a 90% reduction in new chronic infections and a 65% reduction in mortality, compared with the 2015 baseline *(2)*. Countries now need to develop national goals appropriate to their local epidemiological circumstances and health system capacities.

To eliminate viral hepatitis as a public health threat, the GHSS focuses on five core interventions that need to be implemented at a sufficient level of service coverage (Table 1) *(3,4)*. Four address prevention: (i) three doses of hepatitis B vaccine for infants (2030 target: 90%); (ii) prevention of mother-to-child-transmission of HBV (2030 target: 90%); (iii) blood and injection safety (2030 target: 100%); and (iv) comprehensive harm reduction services for people who inject drugs (2030 target: 300 syringes and needles per person who injects drugs per year). The fifth is about (v) testing and treatment (2030 target: 90% of patients diagnosed and 80% of eligible patients treated) *(2)*. WHO recommends that persons living with HBV infection who meet certain criteria should receive lifelong treatment, whereas persons living with HCV infection should receive short-course curative treatment.

TABLE 1 Global service coverage targets that would eliminate HBV and HCV as public health threats, 2015–2030

Level	Areas	Indicators	Baseline 2015	2020 target	2030 target
Service coverage	**Prevention**	1. Three-dose hepatitis B vaccine for infants (coverage %)	82%	90%	90%
		2. Prevention of mother-to-child transmission of HBV: hepatitis B birth-dose vaccination or other approaches (coverage %)	38%	50%	90%
		3a. Blood safety: donations screened with quality assurance (coverage %)	89%	95%	100%
		3b. Injection safety: use of engineered devices (coverage %)*	5%	50%	90%
		4. Harm reduction (sterile syringe/needle sets distributed per person per year for PWID)	20	200	300
	Testing and treatment	5a. Diagnosis of HBV and HCV (coverage %)	<5%	30%	90%
		5b. Treatment of HBV and HCV (coverage %)	<1%	5 million (HBV) 3 million (HCV)	80% eligible treated
Impact leading to elimination	**Incidence**	Incidence of chronic HBV and HCV infections	6–10 million	–30%	–90%
	Mortality	Mortality from chronic HBV and HCV infections	1.46 million	–10%	–65%

HBV: hepatitis B virus; HCV: hepatitis C virus; PWID: persons who inject drugs

* While the service coverage target is about output (adoption of reuse-prevention injection devices), the C.5 indicator focuses on outcome (provision of safe injections).

AIMS OF THIS DOCUMENT

Scope and purpose

This document 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. It describes the use of strategic information at various stages of the response in the context of strengthening broader health information systems. Strategic information can be defined as data collected at all service delivery and administrative levels to inform policy and programme decisions.

Guidance already available

In 2016, WHO published guidance on strategic information in the field of viral hepatitis, including surveillance *(5)*, and monitoring and evaluation *(6)*. Surveillance describes the epidemiological situation, from new infections, to chronic infections to sequelae that lead to morbidity and mortality *(5)*. Monitoring and evaluation tracks how programmes are performing using a standard framework that measures how inputs turn into outputs, outcomes and impact for viral hepatitis prevention, testing, treatment and care services *(6)*.

Development process

This document does not contain new guidance on strategic information for hepatitis. Rather, following advice from the Viral Hepatitis Strategic Information and Modelling Reference Group *(7)*, the WHO Global Hepatitis Programme summarized, simplified and consolidated the guidance contained in existing documents on surveillance *(5)* and monitoring and evaluation *(6)*, and placed this guidance in the perspective of the national programme development cycle. WHO then pilot-tested a draft of this document during multiple country missions to ensure that it meets the needs of national programme managers.

Use of this document

National programme managers can use this document as an overall high-level guidance on strategic information for viral hepatitis. The document includes three online appendices in the form of template surveillance protocols for acute hepatitis, chronic infections and sequelae, which were developed in collaboration with scientific committees that included experts from the six WHO regions. These received preliminary approval from the WHO research Ethics Review Committee (ERC).

SURVEILLANCE

Understanding how a hepatitis epidemic unfolds in time

Infections with HBV or HCV evolve in three phases. New infections (mostly asymptomatic but sometimes symptomatic in the form of acute hepatitis) may evolve into chronic infections (usually asymptomatic), which may further evolve into sequelae (cirrhosis and HCC) that lead to morbidity and mortality. As there can be more than 20–30 years between infection and mortality, viral hepatitis surveillance needs to capture these three phases to fully describe the epidemiological situation. A description of new, incident infections guides prevention activities. Estimations of current, prevalent infections guide testing and treatment, which would prevent future morbidity and mortality. Current mortality from the sequelae of chronic infections acquired in the past quantifies the baseline burden and evaluates the impact of past interventions. The three components of viral hepatitis surveillance (Table 2) may be implemented by different actors of the public health system. Thus, the programme responsible for viral hepatitis needs to consolidate and triangulate sources of information from these different systems to describe the epidemiological situation of HBV and HCV infection.

Surveillance of acute hepatitis informs incidence and guides prevention

Most new infections with the hepatitis viruses are asymptomatic or undiagnosed. However, capturing a constant fraction of the new infections that are detected because they are symptomatic provides information on trends in acute hepatitis. WHO has published standardized case definitions for surveillance of acute hepatitis (Table 3) *(5)*. These case definitions can be used to differentiate acute hepatitis from newly diagnosed cases of chronic infection (*see* Monitoring the cascade of testing and treatment).

TABLE 2 Surveillance activities needed to describe the epidemiology of viral hepatitis, including hepatitis B and hepatitis C

	Activities that contribute to surveillance for viral hepatitis		
	1. Surveillance for acute hepatitis that reflects new infections	**2. Surveillance for chronic, prevalent hepatitis**	**3. Surveillance for sequelae**
Activities	• Syndromic surveillance in the general population • Event-based surveillance* • Enhanced case reporting (with in-vitro diagnosis and collection of information on risk factors)†	• Regular biomarker surveys	• Combination of data from death certificates, and testing of patients with cirrhosis and HCC for HBV and HCV infection
Population under surveillance	• Persons presenting with acute hepatitis to health-care facilities (discrete onset of symptoms)	• Persons without acute symptoms tested during population surveys	• Persons diagnosed with cirrhosis and HCC
Usual implementer	• Communicable disease surveillance • Communicable disease surveillance (if countrywide) • Hepatitis programme (if sentinel sites)	• Hepatitis programme in coordination with the other actors implementing biomarker surveys	• Vital registration • Sentinel sites caring for patients with cirrhosis and HCC • Cancer registries
Case definitions to use (*see* Table 3)	• Presumptive case of acute hepatitis • Confirmed case of acute hepatitis (by type)	• Chronic HBV and HCV infection • Serological evidence of past or present HCV infection	• Cases of cirrhosis or HCC • Chronic HBV or HCV infection
Objective of the surveillance activity	• Detect outbreaks • Describe trends in type-specific acute hepatitis‡ and identify risk factors	• Estimate the prevalence of infections • Model incidence trends	• Estimate mortality from HBV- or HCV-associated HCC and cirrhosis

HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus

* In-vitro diagnosis needs to be organized on a sample of cases when an outbreak is reported.
† High-quality data (i.e. reliable in-vitro diagnosis, good information on risk factors) from a smaller number of tertiary centres is preferable and more efficient than poor-quality data from many sites.
‡ Surveillance for acute hepatitis cannot be used directly to quantify new infections. The reported number of cases of acute hepatitis needs to be adjusted for the large proportion of asymptomatic cases and underreporting.

TABLE 3 WHO surveillance case definitions for viral hepatitis*

		HAV	HEV	HBV	HCV
Acute hepatitis	**Clinical criteria identifying presumptive cases**	Discrete onset of an acute illness with signs/symptoms of (i) acute infectious illness (e.g. fever, malaise, fatigue) and (ii) liver damage (e.g. anorexia, nausea, jaundice, dark urine, right upper quadrant tenderness, OR raised alanine aminotransferase [ALT] levels more than ten times the upper limit of normal of the laboratory)†			
	Biomarker/ epidemiological criteria to confirm cases	IgM anti-HAV +ve **OR** Epidemiological link with a confirmed case	IgM anti-HEV +ve **OR** Epidemiological link with a confirmed case	IgM anti-HBc +ve‡	HCV RNA +ve **AND** anti-HCV –ve
					OR Seroconversion to anti-HCV§
					OR Anti-HCV +ve **AND** IgM anti-HBc –ve **AND** Anti-HAV IgM –ve **AND** Anti-HEV IgM –ve
Chronic infections	**Confirmed cases only, requiring biomarker criteria**	NA	Rare event, no WHO standard case definition	Person not meeting the case definition for acute hepatitis** **AND**	
				HBsAg +ve††	HCV RNA +ve‡‡ **OR** HCV Ag +ve

Ag: antigen; anti-HAV: antibody against hepatitis A virus; HBsAg: hepatitis B surface antigen; anti-HBc: antibody against hepatitis B core antigen; anti-HCV: antibody against hepatitis C virus; anti-HEV: antibody against hepatitis E virus; HBV: hepatitis B virus; HCV: hepatitis C virus; Ig: immunoglobulin; NA: not applicable; RNA: ribonucleic acid

* Case definitions are for the purpose of reporting and surveillance and may differ from criteria to be used for the management of patients.
† Ten times the upper limit of normal (400 IU/L) is the threshold used by the United States' State and Territorial Epidemiologists (CSTE). Countries may also select lower (more sensitive) or higher (more specific) thresholds.
‡ Hepatitis test panels usually include HBsAg with anti-HBc IgM test (positive predictive value of anti-HBc IgM higher if HBsAg +ve). Specific test/threshold needed to exclude transient appearance of IgM during flares in chronic HBV infection.
§ Among patients tested regularly at short time intervals, seroconversion to anti-HCV suggests a recent HCV infection. Seroconversion to anti-HCV should be followed by a reflex RNA test (when available). Seroconversion indicates a new HCV infection, but acute symptoms are necessary to meet the case definition of acute hepatitis C.
** Person tested in the context of evaluation for a chronic liver disease, a check-up or a survey
†† Most testing strategies would also test for total anti-HBc. The combination of total anti-HBc and HBsAg is more specific for chronic HBV infection than HBsAg alone.
‡‡ Persons who are anti-HCV positive have serological evidence of past or present infection.

Syndromic surveillance uses presumptive case definitions, mostly based on clinical features, for reporting in all health-care facilities. Syndromic surveillance captures undifferentiated, acute viral hepatitis. It is a baseline surveillance standard that is not resource intensive. However, its usefulness is limited to detecting large outbreaks, which are usually outbreaks of hepatitis A or acute hepatitis E. Syndromic surveillance of unspecified acute hepatitis is usually covered under communicable disease surveillance.

Enhanced case reporting uses confirmed case definitions based on a combination of clinical and biomarker criteria, usually in fixed sentinel sites. Enhanced case reporting captures cases of acute hepatitis, by type (i.e. A, B, C, D or E) following in-vitro diagnosis (i.e. immunoglobulin [Ig]M tests), and also collects information on possible exposure. The WHO template protocol for enhanced case reporting is available from the WHO Internet site *(8)*. When captured with case definitions of sufficient specificity (i.e. based on the use of an IgM diagnostic test), cases of acute hepatitis are uniquely informative as they denote recent infection. Hence, collection of information on possible exposures during the referent exposure period (or the incubation period) provides information on sources of infection.

In most high-income countries, enhanced case reporting exists countrywide as part of the communicable disease surveillance system. If the national system for acute hepatitis surveillance is based on syndromic case definitions, enhanced case reporting can be established in a small number of fixed sentinel facilities where there is access to IgM in-vitro diagnosis and staff who can collect information on potential risk factors. Building on universal syndromic surveillance to implement enhanced case reporting allows a description of trends in type-specific acute hepatitis and contributes to the generation of hypotheses regarding the predominant modes of transmission. Enhanced case reporting of acute hepatitis is particularly important in places where the incidence of new HBV or HCV infection remains high (e.g. because of injection drug use or unsafe health care). For HIV, new infections may be followed up over time through longitudinal surveillance *(9)*. For hepatitis, this may not be a good use of resources, given the larger number of infections (about 325 million worldwide *(1)*) and the longer timeline between infection and disease.

Biomarker surveys estimate the prevalence of chronic infections and guide testing and treatment

Regular biomarker surveys are the method of reference to estimate the prevalence of chronic infections in the general population. Reliable estimates of prevalence are key to predicting future mortality from present infections and deciding on a testing approach *(10)*. The WHO template protocol for conducting

biomarker surveys for viral hepatitis is available on the WHO Internet site *(11)*. Viral hepatitis biomarker surveys can be expensive. Hence, they should be implemented along with other health-related population surveys that examine HIV *(12)*, tuberculosis incidence, the impact of hepatitis B immunization *(13)* or chronic diseases. Planning integration of surveillance for HBV and HCV with other health-related surveys ahead of time as part of the objectives of a survey is preferable to testing stored specimens. Testing stored sera may raise methodological issues when specimens are not available from all study participants *(14)*. It can also raise ethical issues. Participants may not have consented to additional testing and those identified with HBV or HCV cannot be linked to care.

Surveillance of chronic infections through regular biomarker surveys may be done by specific programmes or through a central mechanism (e.g. a national centre for research or epidemiology). When population-based surveys are not possible, "data mining" can also be undertaken to collate existing data on HBV or HCV infection (e.g. from blood transfusion services or antenatal clinics) *(5)*. Reporting cases of chronic infection presenting to health-care facilities is a way to monitor testing, treatment and care services (*see* Patient databases on page 12) *(5)*, but cannot be used to estimate the prevalence of chronic infection.

In addition to surveys conducted in the general population, surveys or regular surveillance among specific groups (e.g. people who inject drugs, men who have sex with men, prisoners) can provide information on risk behaviours and the prevalence of infection in these groups *(15)*. This type of surveillance is often conducted in the context of HIV programmes and can be extended to viral hepatitis. The prevalence ratio (the prevalence in specific groups divided by the prevalence in the general population) guides focused testing in specific groups *(10)*. Groups among which the prevalence is not substantially higher than in the general population do not need to be prioritized for subsequent surveillance and/or focused testing. Persons who inject drugs and prisoners are the two groups most likely to have a higher prevalence of HCV infection in most settings *(1)*.

Surveillance for sequelae estimates morbidity and mortality to evaluate impact

Measuring the fraction of cirrhosis and HCC attributable to HBV and HCV infections is key to measuring the impact of hepatitis elimination on morbidity and mortality. The WHO protocol for surveillance of sequelae is available on the WHO Internet site *(16)*. In vital registration systems, viral hepatitis-associated deaths are mostly recorded under deaths from acute hepatitis, cirrhosis or HCC *(17)*. However, certificates documenting cirrhosis or HCC deaths usually do not capture the

etiological causes (e.g. whether the sequela was due to viral infection, alcohol or other causes). For these deaths to be attributed to a cause, attributable fractions must be estimated *(18,19)*. Estimation of the attributable fraction in persons with sequelae can be implemented through data abstraction of routine clinical records at fixed sentinel sites in health-care facilities caring for chronic liver diseases or liver cancer or in cancer registries *(16)*. WHO's Global Reporting System for Hepatitis is a mechanism for countries to report the fraction of cirrhosis and HCC that is attributable to HBV and HCV (*see* Monitoring the cascade of testing and treatment on page 11) *(20)*.

MONITORING AND EVALUATION FRAMEWORK

WHO has described a comprehensive monitoring and evaluation framework for viral hepatitis B and C (Table 4) that follows the result chain, from context and needs to inputs, outputs, outcomes and impact *(6)*. It uses surveillance and programmatic information, and lists 10 core indicators numbered C.1 to C.10.

Indicators

The prevalence of HBV and HCV infection in the population reflects context, disease burden and needs (C.1). The ratio of health-care facilities that are able to test for HBV and HCV infections per 100 000 population is the core input indicator (C.2). Core indicators reflecting prevention include hepatitis B vaccine coverage (C.3.b), coverage of hepatitis B vaccine birth-dose or other methods to prevent mother-to-child transmission of HBV infection (C.3.a), sterile syringe and needle sets distributed to persons who inject drugs (C.4) *(21)*, and health-care injection safety (C.5) *(22)*. Other core indicators reflect the cascade of care (for HBV) or cure (for HCV). These include the proportion of people living with viral hepatitis who have been diagnosed (C.6), received treatment (for HBV, C.7.a) or initiated on treatment (for HCV, C.7.b), and treatment outcome, including viral suppression (C.8.a for HBV) or cure (C.8.b for HCV).

Finally, impact measurement is based on incidence and mortality. The cumulative incidence of chronic HBV infection among children at 5 years of age (C.9.a) evaluates progress in "combating hepatitis" as per the SDGs *(23)*. Measurement of cumulative incidence is restricted to this age group because HBV infections among children under 5 years of age contribute most to the burden of chronic infections among adults *(24)*. Prevalence of HBV infection among children under 5 years (defined by the presence of hepatitis B surface antigen [HBsAg]) is used as a surrogate indicator of the cumulative incidence of chronic HBV infection. The incidence of HCV infection is estimated in the whole population (C.9.b). Mortality indicators are disaggregated for HBV (C.10.a) and HCV (C.10.b).

Sources of data

The data systems needed to report against the core indicators of the monitoring and evaluation framework for viral hepatitis (Table 4) ideally include the following:

1. viral hepatitis surveillance, which includes surveillance of acute hepatitis. This reflects new infections (C.9), surveillance of chronic infections ideally through biomarker surveys (C.1), and surveillance of mortality from sequelae (C.10);

2. programme data or health-care facility surveys such as the Service Availability and Readiness Assessment (SARA) *(25)* to estimate the ratio of facilities that can test for HBV and HCV infection per 100 000 population (C.2);

3. routine data from the Expanded Programme on Immunization (EPI) *(26)*, and programmes for prevention of mother-to-child transmission, injection safety and harm reduction for prevention activities (C.3–C.5);

4. data from patients' registers or databases to monitor the cascade of diagnosis and treatment (C.6–C.8, *see below*).

At the initial assessment stage, in the absence of established data systems, rapid data extraction can be conducted using the approach outlined in Table 4.

Monitoring the cascade of testing and treatment

Monitoring the cascade of testing and treatment improves individual patient management and identifies bottlenecks in the continuity of care. At the initial stage of a programme, estimates of the cascade of testing and treatment may be obtained from ad-hoc mechanisms (e.g. surveys, data on sales of medicines). However, the best approach to monitoring and evaluating a national programme for testing and treatment of HBV and HCV infection is to establish a data system that will capture these services as part of the blueprint coordinated and decided by the broader governance framework of the national health management information system. Databases of persons with chronic infection can provide longitudinal data based on individual records. However, data entry and management of databases made of individual records are resource intensive. Where such systems already exist, they are often employed in high-burden settings with electronic platforms (e.g. electronic reporting systems, medical records and health records) and reflect primary clinical tools. Hepatitis programmes may be able to leverage existing individual data systems to monitor the cascade of care from individual patient monitoring at facility level to aggregate reporting to the central level. However, estimates of the core indicators of the

cascade of testing and treatment can also be generated in a simpler way using aggregated data reported from all health-care facilities involved in treatment. Aggregated data management is much less labour intensive and probably best suited for programmes at the early stages of scale up.

Patient databases

Combining case reporting and patient monitoring systems can create a database of patients with chronic HBV and HCV infection, which should be integrated with other databases in use (e.g. for HIV or tuberculosis or other electronic records) *(9)*. The template patient management card (Appendix 1) can be used in paper form or electronically in electronic medical records to document and frame good care practices in health-care facilities. A subset of variables can then be entered in a computer or extracted from the electronic medical records to feed into a case surveillance database (database of patients). When a person is initially diagnosed (i.e. newly identified with chronic infection), his/her record is added to the database. The record is removed when the person is cured or dies. Health-care providers can use such databases to manage data on personal characteristics, diagnosis, treatment, monitoring and viral suppression or cure.

Unique identifiers and compatibility of data systems are necessary to identify and remove duplicate reports (i.e. deduplication) and protect confidentiality. They can also be used to follow individuals as in an epidemiological cohort along the cascade of services over the medium term and as they move between facilities. However, within a single country, different health systems may use different databases. This may lead to interoperability issues. Automated data analysis that aggregates individual data and calculates core indicators on diagnosis, treatment and treatment effectiveness along the reporting requirements (Appendix 2) is a way to compile data from different systems. Aggregated data on the cascade of care or cure can then be reported to the national level and ultimately to WHO through the Global Reporting System on Hepatitis *(20)*.

TABLE 4 Monitoring and evaluation framework: minimum set of 10 core indicators to monitor and evaluate the health sector response to viral hepatitis B and C along the result chain in countries

Level	Domain	Indicators	Data sources			Data management and analysis
			Reference methods (statistical sampling)	Alternative option (other samples)	Rapid assessment technique	
Context and needs	Prevalence of infection	C.1. Prevalence of chronic HBV and HCV infections	Recent biomarker survey	Data mining (e.g. blood donors and pregnant women)	Regional average, modelled estimates*	• Estimates may be modelled from older biomarker surveys.
Input	Capacity to diagnose	C.2. Capacity for testing	Health facility surveys (e.g. SARA) *(25)*	Data from accreditation bodies, or national reference laboratory	Rapid calculations: facilities usually doing the test x number of facilities	• Results expressed as the ratio of facilities that can test per 100 000 population
Outputs and outcomes	Prevention	C.3 Hepatitis B vaccine, including timely birth-dose coverage†	Recent immunization coverage survey	Joint WHO/UNICEF reporting form	EPI routine data	• Coverage expressed in percentage
		C.4. Needles and syringes distributed/ PWID	Data from harm reduction programmes	NA	Regional estimates reported by WHO	• Results are expressed as sets/PWID /year.
		C.5. Proportion of safe health-care injections	Health facility surveys (e.g. SARA) *(25)*	Population survey (e.g. demographic and health surveys)	Regional estimate reported by WHO	• Results are expressed as the proportion of injections given with new, sterile syringes.
Outputs and outcomes	Cascade of care and treatment	C.6. Proportion of HBV/HCV infections diagnosed	Population-based survey	Reports from diagnosis centres/prevalence estimate	Reported cases/ prevalence estimate	• Lifelong HBV treatment. Coverage is the proportion treated, and effectiveness is the proportion virologically suppressed. • Short curative HCV treatment. Coverage is treatment initiation rate, and effectiveness is the proportion of sustained virological responses.
		C.7. Treatment coverage (HBV)/ initiation rate (HCV)	Database of patients	Reports from treatment centres	Expert opinion/medicines sales audit data	
		C.8. Treatment effectiveness rate	Database of patients	Reports from treatment centres	Expert opinion based on clinical experience	

TABLE 4 Monitoring and evaluation framework: minimum set of 10 core indicators to monitor and evaluate the health sector response to viral hepatitis B and C along the result chain in countries (contd)

Level	Domain	Indicators	Data sources			Data management and analysis
			Reference methods (statistical sampling)	Alternative option (other samples)	Rapid assessment technique	
Impact	Incidence	C.9.a Incidence of HBV infections	Recent biomarker survey	Estimates modelled by WHO*	NA	• The prevalence of HBV infection at 5 years of age is a surrogate indicator of the cumulative incidence of chronic HBV infections.
		C.9.b Incidence of HCV infections	Modelled estimates using multiple biomarker surveys	Estimates based on trends of acute hepatitis C	Prevalence of serological evidence of past or present infection in younger age groups	• Hardest indicator to estimate as most new HCV infections are asymptomatic
Impact	Mortality	C.10. Mortality from HBV/HCV infections	Data from vital registration and cancer registries combined with the fraction of sequelae attributable to HBV/HCV from fixed sentinel centres	WHO Global Health Estimates by country available on the WHO Internet site	NA	• Requires collaboration between vital statistics and fixed sentinel centres managing end-stage liver disease

EPI: Expanded Programme on Immunization; HBV: hepatitis B virus; HCV: hepatitis C virus; PWID: person who injects drugs; SARA: Service Availability and Readiness Assessment; UNICEF: United Nations Children's Fund; WHO: World Health Organization

* http://whohbsagdashboard.com/ for HBV infection
† Timely birth dose means administered within 24 hours of birth. Indicator 3b refers to timely birth dose and other interventions to prevent mother-to-child transmission of HBV.

Aggregated data

If it is not possible to develop a database of individual patients with HBV or HCV infection, health-care workers in facilities can report the total number of persons tested, diagnosed, put on treatment and virally supressed or cured (Appendix 2). This core set of aggregated data can be compiled at the subnational and national levels to generate cascades of care *(27)*. Use of aggregated data does not allow follow up of individuals who move between facilities. No deduplication is possible and the cascade is not an epidemiological cohort. This limitation needs to be considered when interpreting the results of the analysis.

Another limitation is that disaggregated analyses are limited to the extent of the disaggregation in the reporting tool. Disaggregated analyses (i.e. geographical and sociodemographic) can be powerful drivers of programme management. They identify differential service coverage and quality. Despite their limitations, the core set of data from programmatic cascades of care can be reported in aggregate format to the national level through computer platforms, using the analysis plan proposed by WHO *(27)*. The Global Hepatitis Programme has prepared a generic application based on the District Health Information System 2 software (DHIS2), which can be provided to countries upon request. Once data have been reported at the national level, they can then be reported to WHO using the same reporting requirement (Appendix 2) through the Global Reporting System on Hepatitis, which also uses a DHIS2 application *(20)*.

STRATEGIC INFORMATION AT THE VARIOUS STAGES OF A PROGRAMME

The stages of a hepatitis programme cycle include (i) initial assessment, (ii) planning, (iii) implementation and (iv) evaluation (Fig. 1).

FIG. 1 Use of strategic information at all stages of a national viral hepatitis programme

Initial assessment

At the stage of initial assessment, obtaining a baseline estimate of the prevalence of HBV and HCV infections is key to setting priorities. Extraction of data already available along the 10 core indicators can provide an overview of the baseline situation (Table 4). In addition, policy uptake indicators (e.g. availability of policies and plans) document the status of commitment at the national level. These were surveyed by WHO in 2017 *(28)* and are now collected every year by WHO in the context of the Global Reporting System on Hepatitis *(20)*. Finally, the assessment phase can include an analysis of the capacity of the national health information system to collect, analyse, disseminate and use data for the elimination of hepatitis (*see* Appendix 3: Data systems needed to generate viral hepatitis strategic information: checklist for viral hepatitis programmes).

Planning

At the planning stage, estimating the size of the population that needs treatment will inform resource allocation. Core interventions for the prevention of viral hepatitis have already been established as being cost effective or cost-saving *(4)*. For testing and treatment, country-specific cost–effectiveness analyses from a health-care perspective along with budget impact analyses can help make the case for inclusion of these interventions into national health benefit packages as part of Universal Health Coverage. WHO has tools to conduct these economic analyses online, including the online HBV calculator (www.hepbcalculator.org) *(29)* and the HCV calculator (www.hepccalculator.org) *(30)*. Input parameters required include the cost of diagnostics, medicines and monitoring; and the annual cost of managing sequelae, including cirrhosis and HCC. The online calculator can estimate the net cost of HBV and HCV treatment (the cost to the health system, minus the future saving through sequelae prevented) in relation to the healthy life years gained through an incremental cost–effectiveness ratio (ICER). The results of the analysis are expressed in cost per healthy life year gained. When the net cost is zero or less, hepatitis treatment is cost-saving from a health-care perspective.

In most low- and middle-income countries that can access low-price, high-quality generic HBV and HCV medicines, treatment can be highly cost effective or cost-saving from a health-care perspective *(31–33)*. Apart from very high-burden countries *(34,35)* where the societal impact can be exceptionally high, WHO recommends these cost–effectiveness analyses from a health-care perspective rather than cost–benefit analyses or investment case. The investment case is preferably done for Universal Health Coverage at the level of the whole health system *(36)*.

Implementation

At the implementation stage, countries need to report and use the data they generate domestically to identify differential service coverage and quality, and to address these programme gaps in a systematic, prioritized fashion. Countries can also report progress internationally. Prevention programmes can report on prevention indicators (C.3–C.5). Viral hepatitis testing and treatment services can report on the cascade indicators (C.6–C.8) nationally *(27)* and internationally to WHO using the Global Reporting System for Hepatitis *(20)*.

Final evaluation

At the final evaluation stage, the framework with the full set of the 10 core indicators can document the result chain, with a special emphasis on the impact in terms of incidence and mortality.

ROLE OF MODELLING

Most programme decisions on viral hepatitis can be made using empirically collected data. However, mathematical models can usefully complement empirically collected data in a number of areas. These include the following:

1. estimation of the prevalence of HBsAg in the general population and in children 5 years of age. WHO used a modelling approach to generate the HBsAg dashboard (http://whohbsagdashboard.com/);

2. estimation of the incidence of HCV infection using biomarker data and/or trends from enhanced case reporting of acute hepatitis C. WHO worked with the Center for Disease Analysis and used this approach to estimate the incidence of HCV infection for the *Global Hepatitis Report (1,37);*

3. estimation of the current mortality from past HBV and HCV infections using data from vital registration and sequelae surveillance. WHO *(1)* and the Global Burden of Disease *(38)* generate mortality estimates using this approach;

4. analysis of cost and impact of combinations of various service coverage options on national viral hepatitis elimination plans. WHO used this approach for the hepatitis B (www.hepbcalculator.org) *(29)* and hepatitis C *(30)* (www.hepccalculator.org) calculators.

CONCLUSIONS

Viral hepatitis should be eliminated through the implementation of core interventions coordinated across different health programmes and services. Similarly, strategic information for elimination of viral hepatitis may be collected, transmitted and analysed through different components but needs to be consolidated within the health information system to provide a comprehensive picture that will guide hepatitis elimination at all stages of the programme. While the strategic information system described here can appear ambitious, countries can start with simple elements and build on these in the context of the national health information system. The WHO Secretariat at the country, regional and headquarters levels will be available to provide technical assistance as needed.

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APPENDICES

APPENDIX 1 WHO template for a chronic hepatitis B and C patient management card

IDENTIFICATION:		
Unique identifier I_I_I_I_I_I_I_I_I_I_I		
District:	Health unit:	District clinician/team:
Name:	First name:	Patient clinic number:
Sex: I_I Female I_I Male I_I Other	Date of birth: ___ / ___ / ___	Nationality:
Address:	District:	Telephone:

INFECTION STATUS ON ENROLMENT:		Enrolment date: ___ / ___ / ___
HBsAg: I_IPositive I_I Negative I_I Not done Date of first diagnosis of HBV infection: ___ / ___ / ___	HBV DNA (IU/mL): I___IValue I_I Negative I_I Not done HDV RNA (IU/mL): I_IPositive I_I Negative I_I Not done	HBeAg: I_IPositive I_I Negative I_I Not done Anti-HDV: I_IPositive I_I Negative I_I Not done
Anti-HCV: I_IPositive I_I Negative I_I Not done Date of first diagnosis of HCV infection: ___ / ___ / ___	HCV RNA (IU/mL): I_IValue I_I Negative I_I Not done HCV genotype: I_I	HCV core Ag: I_IPositive I_I Negative I_I Not done
Anti-HIV: I_IPositive I_I Negative I_I Not done Latest HIV viral load (copies/mL): _____I_I Not done Tuberculosis: I_IActive I_I On treatment I_I No	HIV treatment regimen: CD4 count: _____ x 10^9/L I_I Not done	Date HIV treatment started:
Injection drug use: I_IActive (last 12 months) I_I Past history I_I No	Daily alcohol consumption:	Metabolic syndrome:

STAGING:		Staging date: ___ / ___ / ___
ALT: ___ IU/L AST: ___ IU/L PLT:____ /mL	Clinical diagnosis of cirrhosis: I_IYes I_I No	If yes, Child–Pugh score:
APRI score: ___ I_I Not done FIB4: ____ I_I Not done	Transient elastography (kPa): _____ I_I Not done	Liver biopsy stage (F): _____ I_I Not done
Bilirubin: Total____µmol/L and Direct: _____µmol/L__	Ultrasound scan:	Prothrombin time/INR: _____

HEPATITIS B TREATMENT:		
Past experience with treatment: I_IYes I_I No	Past treatment regimen:	
HBV treatment regimen started (medicine):	Date started: ___ / ___ / ___	Date stopped: ___ / ___ / ___
First annual viral response assessment		
Date tested: ___ / ___ / ___	HBV DNA(IU/mL: I_IPositive I_I Negative I_I Not done	ALT: ____ IU/L

HEPATITIS C TREATMENT:		
Past experience with treatment: I_IYes I_I No	Past treatment:	
HCV treatment regimen started:	Date started: ___ / ___ / ___	Date completed: ___ / ___ / ___
Sustained viral response assessment post treatment (usually at SVR12, i.e. 12 weeks after the completion of treatment)		
Date tested: ___ / ___ / ___	HBV DNA(IU/mL: I_IPositive I_I Negative I_I Not done	

FOLLOW-UP VISITS

Unique identifier |_|_|_|_|_|_|_|_|_|_| Name: _____ First name: _____ Patient clinic number: _____

Date	Clinical assessment	Liver function test and staging					HBV tests			HCV tests	Renal function	Screening for hepatocellular carcinoma		Treatment regimen used	Side-effects/ toxicity	Observations
		ALT (IU/L)	AST (IU/L)	Platelets (#/mL)	APRI	Transient elastography (kPa)	HBsAg (+/–)	HBeAg (+/–)	HBV DNA (IU/mL)	HCV RNA (+/–)	Creatinine (mg/dL)	Ultrasound	AFP (ng/mL)			

AFP: alpha fetoprotein; ALT: alanine aminotransferase; AST aspartate aminotransferase; APRI: AST to platelet ratio index; DNA: deoxyribonucleic acid; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; INR: International Normalized Ratio; IU: international units; PLT: platelet; RNA: ribonucleic acid

APPENDIX 2 Reporting form to monitor the cascade of care for HBV and HCV infection from health-care facilities to the national level

	Data during the quarterly reporting period										
	Testing and diagnosis (C.6)			Treatment initiation and continuation (C.7)				Monitoring of treatment effectiveness (C.8)		Mortality from sequelae* (C.10)	
	Number of infected people already identified before the reporting quarter (treated or not)	Number of people tested with serology (HBsAg or anti-HCV) in the reporting quarter†	Number of infected people newly diagnosed with infection in the reporting quarter (HBsAg positive or HCV RNA or HCV core antigen positive, treated or not)	Number of people continuing treatment started before the reporting quarter‡	Number of people newly starting treatment in the selected quarter§		Number of people completing treatment**	Number of people assessed for treatment effectiveness in the reporting quarter††	Number of people with effective treatment in the reporting quarter‡‡	Proportion (%) of people dying from cirrhosis who were positive for viral hepatitis infection	Proportion (%) of people dying from hepatocellular carcinoma who were positive for viral hepatitis infection
					Total	Among people who inject drugs in the reporting quarter (among the total above)					
HBV	[Cell B1]	[Cell B2]	[Cell B3]	[Cell B4]	[Cell B5]	[Cell B6]	NA	[Cell B8]	[Cell B9]	[Cell B10]	[Cell B11]
HCV	[Cell C1]	[Cell C2]	[Cell C3]	NA	[Cell C5]	[Cell C6]	[Cell C7]	[Cell C8]	[Cell C9]	[Cell C10]	[Cell C11]

ALT: alanine aminotransferase; DNA: deoxyribonucleic acid; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; NA: not applicable; RNA: ribonucleic acid

* Estimates from sentinel sites
† Needs to include testing activities conducted with rapid diagnostic tests
‡ Does not apply to HCV infection
§ Regardless of eligibility (HBV infection)
** Does not apply to HBV infection
†† Tested for viral suppression with ALT or HBV DNA (HBV) or tested for sustained viral response using HCV RNA or HCV core antigen (HCV)
‡‡ Normal ALT or viral suppression (HBV) or sustained viral response (HCV)

APPENDIX 3 Data systems needed to generate viral hepatitis strategic information: checklist for viral hepatitis programmes*

Data systems	Individual activities and field of application		Implementation levels				
	Activity	Application	Lowest – 1	2	3	4	Highest – 5
Surveillance	Surveillance for acute hepatitis	All viruses	No information	Syndromic surveillance for acute hepatitis	Surveillance for type-specific acute hepatitis, but without standard case definitions	Sentinel surveillance for type-specific hepatitis with WHO case definitions	Sentinel surveillance for type-specific hepatitis with WHO case definitions and collection of information on risk factors
	Surveillance for chronic infections	HBV	No information	Information from sources other than population-based surveys (e.g. screening of blood donors)	Information from one population-based survey	Information from population-based survey with estimates by age group	Information from repeated population-based surveys with estimates by age group
		HCV	No information	Information from sources other than population-based surveys (e.g. screening of blood donors)	Information from one population-based survey	Information from population-based survey with estimates by age group	Information from repeated population-based surveys with estimates by age group
		Coverage of cancer registry, including HCC	None (0%)	<20%	20–40%	40–60%	>60%
		Data on proportion of HCC cases with HBV/HCV infection	None	Estimates extrapolated from regional data/ neighbouring countries	Estimations using ad-hoc data sources/ published studies	Estimates from routine data collection at sentinel sites	Estimates from routine data collection at national level
		Data on proportion of cirrhosis cases with HBV/HCV infection	None	Estimates extrapolated from regional data/ neighbouring countries	Estimations using ad-hoc data sources/ published studies	Estimates from routine data collection at sentinel sites	Estimates from routine data collection at national level
Surveillance	Surveillance for sequelae	Coverage of death registration system	None (0%)	<20%	20–40%	40–60%	>60%

APPENDIX 3 Data systems needed to generate viral hepatitis strategic information: checklist for viral hepatitis programmes* (contd)

Data systems	Individual activities and field of application		Implementation levels				
	Activity	Application	Lowest – 1	2	3	4	Highest – 5
Programme indicators	Prevention	Hepatitis B vaccination and prevention of mother-to-child transmission	No information	Estimates extrapolated from regional data/ neighbouring countries	National administrative coverage	National administrative coverage validated by surveys	Validated data at subnational level
		Harm reduction	No information	Estimates extrapolated from regional data/ neighbouring countries	Estimates from one programme/region	National estimates	Validated national estimates
		Injection safety	No information	Estimates extrapolated from regional data/ neighbouring countries	Estimates from national survey but >5 years old	Estimates from national survey <5 years old	Validated data at subnational level
	Testing capacity†	HBV	No information	Estimates extrapolated from regional data/ neighbouring countries	Estimates from national survey but >5 years old	Estimates from national survey <5 years old	Validated data at subnational level
		HCV	No information	Estimates extrapolated from regional data/ neighbouring countries	Estimates from national survey but >5 years old	Estimates from national survey <5 years old	Validated data at subnational level
	Care and treatment	HBV	No information	Estimates extrapolated from regional data/ neighbouring countries	Estimations using ad-hoc data sources/ published studies	Estimates from surveys	Estimates from a patient registry
		HCV	No information	Estimates extrapolated from regional data/ neighbouring countries	Estimations using ad-hoc data sources/ published studies	Estimates from surveys	Estimates from a patient registry

HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus

* This checklist does not propose minimum or gold standards but describes a range of possible options. National stakeholders must decide the level of data quality that is required and affordable in the national context.
† Core indicator C2 on the ratio of facilities that can test for HBV and HCV infection per 100 000 population

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