

TECHNICAL CONSIDERATIONS AND CASE DEFINITIONS TO IMPROVE SURVEILLANCE FOR VIRAL HEPATITIS

TECHNICAL REPORT

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ABBREVIATIONS AND ACRONYMS

AIS	AIDS Indicator Survey
ALT	alanine aminotransferase
ANC	antenatal care
anti-HAV	antibody against hepatitis A virus
anti-HBc	antibody against hepatitis B core antigen
anti-HDV	antibody against hepatitis D virus
anti-HEV	antibody against hepatitis E virus
ARV	antiretroviral
CI	confidence interval
DBS	dried blood spot
DHS	Demographic and Health Survey
EIA	enzyme immunoassay
EPI	Expanded Programme of Immunization
EQAS	external quality assessment scheme
HAV	hepatitis A virus
HBeAg	hepatitis B E antigen
HBIG	hepatitis B immune globulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
IARC	International Agency for Research on Cancer
IBBS	integrated HIV biobehavioural surveillance
ICD	International Statistical Classification of Diseases and Related Health Problems
IDSR	Integrated Disease Surveillance and Response
IgM	immunoglobulin M
IHR	International Health Regulations
MICS	Multiple Indicators Cluster Survey
MIS	Malaria Indicator Survey
MSM	men who have sex with men
NAT	nucleic acid testing
NGO	nongovernmental organization
PHIA	population-based HIV impact assessment
PWID	people who inject drugs
QA	quality assurance
RDS	respondent-driven sampling
RDT	rapid diagnostic test
SAGE	Strategic Advisory Group of Experts (of WHO)
SOP	standard operating procedure
STI	sexually transmitted infection
WHO	World Health Organization

TERMINOLOGY

Viral hepatitis

Viral hepatitis: inflammation of the liver that results from infection with a hepatitis virus

Acute viral hepatitis: discrete-onset clinical manifestations of a recent infection with a hepatitis virus

Chronic viral hepatitis: inflammation of the liver that results from a chronic infection with a hepatitis virus

Infection

Recent infection: a newly acquired infection, regardless of whether it is symptomatic or asymptomatic. A recent infection may be suggested by the clinical presentation and/or the epidemiological context and/or the detection of biomarkers.

Chronic infection: persistence of replication of a hepatitis virus in the body six months after the initial infection

Populations at higher risk

The term “populations at higher risk” in these technical considerations refers to the following populations at higher risk for acquiring and transmitting viral hepatitis; the hepatitis viruses they are most likely to acquire and transmit are given in parentheses: persons who inject drugs (hepatitis A, B and C viruses [HAV, HBV and HCV]), sex workers (HBV and HCV), men who have sex with men (HAV, HBV and HCV), health-care workers (HBV, HCV), persons in long-term care facilities (HBV), persons on chronic dialysis treatment (HBV, HCV), prisoners and other persons in closed settings (HBV, HCV), persons who frequently receive blood or blood products (HAV, HBV and HCV) and children born to mothers infected with HBV, hepatitis E virus (HEV) and to some extent HCV.

EXECUTIVE SUMMARY

Viral hepatitis is a global public health problem of epidemic proportions that causes 1.46 million deaths each year. New infections caused by the five known hepatitis viruses – A, B, C, D and E (HAV, HBV, HCV, HDV and HEV) – can be prevented. In addition, testing and treatment can improve the health of persons with chronic infections. Unfortunately, many countries do not have the epidemiological information needed to plan, implement, monitor, evaluate and update national strategies for the prevention and control of viral hepatitis. The technical aspects associated with viral hepatitis surveillance are perceived as complex, and little guidance is available. In the absence of a sound evidence base, viral hepatitis remains a silent epidemic. Tools are available, however, to optimize surveillance and generate information that can effectively direct prevention, control and treatment policies.

In 2010 and 2014, World Health Assembly resolutions called for stronger surveillance of viral hepatitis. In response, the World Health Organization (WHO) has developed these technical considerations to assist and guide Member States in implementing and/or optimizing viral hepatitis surveillance.

Key elements of the epidemiology of viral hepatitis

a. Multiple disease outcomes: infection with the hepatitis viruses may be asymptomatic or cause acute and chronic hepatitis. Although death can occur from fulminant acute hepatitis, it is most often secondary to chronic hepatitis. After a number of years, chronic hepatitis B or C can lead to cirrhosis, liver failure and/or hepatocellular carcinoma (HCC). Decompensated cirrhosis (e.g. chronic liver failure) and the consequences of HCC commonly result in death. Thus, surveillance will need to address acute hepatitis, chronic infections and their sequelae.

b. Similar clinical presentation: the symptoms and signs of acute and chronic viral hepatitis are similar for all the hepatitis viruses. In addition, new infections are difficult to differentiate clinically from chronic infections. Thus, in vitro diagnosis, including laboratory and point-of-care tests, is key to diagnosing the type of hepatitis (HAV, HBV, HCV, HDV or HEV infection) and differentiating recent from chronic infection.

c. Asymptomatic nature of most infections: many new or chronic infections are asymptomatic, because of which affected persons do not seek medical care. They are neither reported nor counted. Thus, estimating the burden of chronic infection requires biomarker surveys to identify those with chronic infection and the type of virus causing it.

d. Multiplicity of modes of transmission and population at risk: while HAV and HEV are transmitted through the fecal–oral route, HCV and HBV are transmitted through exposure to blood and body fluids. Thus, surveillance approaches need to be tailored to each country so that the relevant populations are included. This will help identify the modes of transmission that account for the majority of new infections and direct prevention activities.

Purposes of surveillance for viral hepatitis (see Table 1, page 13)

1) Detect outbreaks, monitor trends in incidence and identify risk factors for new, incident infections

This is achieved through surveillance for acute hepatitis. Surveillance for acute hepatitis may be done in two ways.

- A basic approach is to do **surveillance for unspecified acute hepatitis** (referred to as “syndromic surveillance”) defined on the basis of clinical signs and symptoms. Surveillance for unspecified acute hepatitis in all health-care facilities allows for the detection and investigation of outbreaks.
- If resources allow, **surveillance with quality in vitro diagnosis** will help to detect clusters and describe trends. If combined with collection of epidemiological information, this type of surveillance can also identify risk factors for new infections. Surveillance that combines in vitro diagnosis and collection of epidemiological information is resource intensive. Hence, implementation in selected geographical areas and/or health-care facilities (referred to as “sentinel sites”) is often a preferred option, particularly in resource-limited settings.

Surveillance for acute hepatitis is conducted to some extent in many countries but may require technical improvement and clarification of objectives. Use of standardized case definitions based on the clinical presentation and on the presence of biomarkers allows cases of acute hepatitis to be separated from cases of chronic infection.

2) Estimate the prevalence of chronic infections and monitor trends in sentinel groups

This is done through biomarker surveys that estimate the proportion of the population that is chronically infected in order to plan for testing, management and care. These surveys are ideally integrated with surveys conducted for other purposes (e.g. HIV surveys) and may be repeated over time. Reporting of chronic HBV and HCV infections in health-care facilities can also be used to estimate the number of cases identified and managed in health-care services. This does not constitute a reliable method of estimating burden, as many chronically infected persons never seek care. Repeated visits to health-care facilities may lead to duplicate reporting that needs to be eliminated.

3) Estimate the burden of sequelae of chronic hepatitis, including cirrhosis, liver failure and hepatocellular carcinoma

This is achieved through the use of cancer registries, death certification, and estimates of the prevalence of HBV and HCV infection among cases of cirrhosis and HCC. This may be implemented in selected sentinel tertiary reference centres. Multiplying the estimated number of deaths from cirrhosis, HCC and liver failure by the fractions of sequelae attributable to HBV and HCV can estimate this burden.

Virus-specific surveillance

Surveillance principles are identical across hepatitis viruses. However, WHO proposes standardized case definitions for viral hepatitis A, B, C and E (see Table 2: WHO surveillance case definitions for viral hepatitis, p. 14). These technical considerations do not provide specific guidance or definitions for the surveillance of hepatitis D. However, the generic principles described in these technical considerations would apply to the surveillance of HDV infection.

- **Unspecified acute hepatitis** is defined clinically by the discrete onset of an acute illness with signs/symptoms of an infectious illness (e.g. fever, malaise, fatigue) and liver damage (e.g. anorexia, nausea, jaundice, dark urine, right upper quadrant tenderness, or levels of alanine aminotransferase [ALT] raised more than ten times the upper limit of normal of the laboratory). In the absence of a type-specific diagnosis, the usefulness of this syndromic surveillance is limited to early detection of outbreaks.
- **Confirmed type-specific acute hepatitis** is defined on the basis of the clinical case definition of acute hepatitis (as defined above) along with the following biomarker criteria:
 - **Hepatitis A** requires the demonstration of antibodies to hepatitis A virus (anti-HAV) immunoglobulin (Ig)M (or an epidemiological link with [a] confirmed case[s]).

- **Acute hepatitis B** requires the demonstration of antibodies to hepatitis B virus core antigen (anti-HBc) IgM.^a
- **Acute hepatitis E** requires the demonstration of antibodies to hepatitis E virus (anti-HEV) IgM (or an epidemiological link with [a] confirmed case[s])
- **Acute hepatitis C** requires either:
 - seroconversion to hepatitis C virus antibodies (anti-HCV);
 - presence of HCV RNA in the absence of anti-HCV;
 - positivity for anti-HCV and negativity for anti-HAV IgM, anti-HBc IgM and anti-HEV IgM;
- **Chronic HBV infection** is defined by the absence of acute hepatitis and the presence of HBsAg.^a
- **Serological evidence of past or present HCV infection** is defined by the absence of acute hepatitis and the presence of anti-HCV.^b The prevalence of serological evidence of past or present HCV infection is of interest to understand the annual risk of infection in a population. However, in practice, it has less implication in terms of treatment than the prevalence of chronic infection, which estimates the proportion of the population that needs to be assessed for treatment (*see below*).
- **Chronic HCV infection** is defined by the absence of acute hepatitis and the presence of HCV RNA or HCV core antigen.

Use of viral hepatitis surveillance for programme evaluation

- Surveillance of type-specific acute hepatitis may be used to evaluate the impact of programmes that prevent new infections, including hepatitis A immunization, water and food safety, condom use, injection safety, blood safety, infection control and harm reduction.
- Surveillance of chronic HBV and HCV infection may be used to evaluate the outcome of (a) universal hepatitis B immunization, (b) programmes preventing HBV and HCV infection through injection safety, blood safety, infection control and harm reduction, and (c) programmes for testing and treatment of HBV and HCV infection.
- Surveillance for sequelae may be used to evaluate the impact of prevention and treatment programmes on long-term sequelae (i.e. cirrhosis and HCC) and specific mortality.

In vitro diagnostic support

Viral hepatitis surveillance requires testing strategies for acute hepatitis and chronic infections in the context of quality assurance measures, including through the use of assays that meet safety, quality and performance standards.

Ethical aspects

An ethical approach to viral hepatitis surveillance requires a trade-off between protecting individuals and generating information that will improve the health status of the community. Key principles to protect human subjects include (a) informed consent and autonomy, (b) maximizing the individual and community benefit (without compromising the right to privacy), and (c) reducing risks to individuals. Persons who are tested for viral hepatitis in the context of surveillance need to have provided informed consent. Testing must be linked to care and treatment, and confidentiality must be protected.

^a Most testing strategies would also test for total anti-HBc. The combination of total anti-HBc and HBsAg is more specific of HBV infection than HBsAg alone.

^b Wherever possible, the presence of anti-HCV needs to automatically lead to HCV RNA testing, as chronic infection is what matters from a clinical, epidemiological and public health point of view.

TABLE 1. Viral hepatitis surveillance: technical approaches that may be used to reach specific objectives for acute hepatitis, chronic infections and sequelae

Technical approaches:	If the objective of hepatitis surveillance is to:				
	Detect outbreaks	Describe trends in type-specific acute hepatitis and identify risk factors	Estimate the proportion of chronically infected persons who have been identified	Estimate the burden of chronic infections Model incidence trends	Estimate the incidence of HCC and cirrhosis
Preferred surveillance methods:	Syndromic surveillance in the general population Event-based surveillance ^a	Enhanced case reporting (with in vitro diagnosis and collection of information on risk factors), countrywide or in sentinel sites ^b	Case reporting from laboratories or health-care facilities	Regular surveys	Combination of data from: 1. Cancer registries 2. Death certificates 3. Testing of cirrhosis and HCC patients for HBV and HCV infection
Population under surveillance:	Persons presenting with acute hepatitis in health-care facilities (discrete onset of symptoms)		Persons without acute symptoms tested in health-care facilities/laboratories	Persons without acute symptoms tested during population surveys	Persons diagnosed with cirrhosis and HCC
Condition to look for:	Unspecified acute hepatitis	Type-specific acute hepatitis	Biomarker evidence of past or present infection Chronic infection, irrespective of symptoms		Cases of HCC or cirrhosis with chronic HBV or HCV infection
Analysis and reporting will characterize:	Acute hepatitis that reflects new infections		Burden of chronic, prevalent infections		Burden of sequelae

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

^a In vitro diagnosis needs to be organized on a sample of cases when an outbreak is reported.

^b 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.

TABLE 2. WHO surveillance case definitions for viral hepatitis ^a

Level of case definition	Acute hepatitis			
Presumptive case: clinical criteria	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, AND/OR raised alanine aminotransferase (ALT) levels more than ten times the upper limit of normal) ^b			
Confirmed case: clinical criteria AND biomarker or epidemiological criteria	Hepatitis A	Acute hepatitis E	Acute hepatitis B	Acute hepatitis C
	IgM anti-HAV +ve OR Epidemiological link with a confirmed case ^c	IgM anti-HEV +ve OR Epidemiological link with a confirmed case ^d	IgM anti-HBc +ve ^{e,f}	HCV RNA +ve and anti-HCV –ve OR Seroconversion to anti-HCV ^g OR Anti-HCV +ve AND IgM anti-HBc –ve AND Anti-HAV IgM –ve AND Anti-HEV IgM -ve

Ag: antigen, anti-HAV: antibody against hepatitis A virus, anti-HBc: antibody against hepatitis B core antigen, anti-HCV: antibody against hepatitis C virus, anti-HEV: antibody against hepatitis E virus, Ig: immunoglobulin, RNA: ribonucleic acid

^a These case definitions are for the purpose of reporting and surveillance and may differ from criteria to be used for the management of patients.

^b Ten times the upper limit of normal (400 IU/L) is the threshold used by the State and Territorial Epidemiologists (CSTE). Countries may also select lower thresholds that could be more sensitive or higher thresholds that could be more specific.

^c Contact with a confirmed case-patient during the referent exposure period or context of an etiologically confirmed outbreak

^d Context of an etiologically confirmed outbreak

^e Hepatitis test panels usually include HBsAg with anti-HBc IgM test. The positive predictive value of anti-HBc IgM is higher if HBsAg is positive.

^f A specific test and/or threshold is needed to exclude transient presence of IgM during flares among patients with chronic HBV infection.

^g Among patients tested regularly at short time intervals, seroconversion to anti-HCV suggests a recent HCV infection, which may take place in the absence of clinical, acute hepatitis. Seroconversion to anti-HCV should be followed by a reflex RNA test (when available).

		Chronic HBV infection	Hepatitis C	
Only confirmed cases that all require clinical and biomarker criteria	Clinical criteria	Person not meeting the case definition for acute hepatitis (e.g. person tested in the context of the evaluation of a chronic liver disease, a check-up or a survey)		
	Biomarker criteria	HBsAg +ve ^a	Serological evidence of past or present infection Anti-HCV +ve	Chronic HCV infection HCV RNA +ve OR HCV Ag +ve

Ag: antigen, anti-HCV: antibody against hepatitis C virus, HBsAg: hepatitis B surface antigen, HBV: hepatitis B virus, HCV: hepatitis C virus, RNA: ribonucleic acid

^a Most testing strategies would also test for total anti-HBc. The combination of total anti-HBc and HBsAg is more specific of chronic HBV infection than HBsAg alone.

1. BACKGROUND

1.1. Viral hepatitis is a global public health problem

The Global Burden of Disease study estimates that approximately 1.46 million persons die each year from viral hepatitis (1), most of these from hepatocellular carcinoma (HCC) and cirrhosis secondary to chronic hepatitis B and C (1,2). Systematic reviews of biomarker surveys suggest that approximately 240 million persons live with chronic hepatitis B, and between 130 and 150 million live with chronic hepatitis C (3,4). Hepatitis A and E also contribute to mortality through fulminant disease (14 900 and 52 100 annual deaths, respectively) (1).

1.2. Viral hepatitis is preventable

Death and disability from viral hepatitis is preventable. First, interventions can prevent new infections (e.g. vaccination, food and water safety, harm reduction among people who inject drugs [PWID], safer sex, infection control, including injection safety and blood safety). Second, testing and treatment can improve the health of persons with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. In the past decades, major advances have been made in the prevention and treatment of infections due to the hepatitis viruses. Effective vaccines exist to prevent hepatitis A, B and E infections (5,6).^a Treatments for hepatitis B and C are improving in terms of efficacy and cost. Most persons with hepatitis C infection can be cured with the newer direct-acting antiviral agents (7). Despite the high burden and the availability of effective interventions to mitigate its impact, global and national responses to viral hepatitis are not commensurate with the magnitude of the problem.

1.3. Viral hepatitis is a silent epidemic

Insufficient epidemiological information is available to support advocacy, leverage investment, guide hepatitis control, and evaluate progress in prevention and control. This lack of data limits the planning and monitoring of prevention and treatment programmes tailored to the epidemic in countries. With respect to new infections, most persons who become infected with the hepatitis viruses do not develop acute symptoms and thus do not come to the attention of the health-care system. Hence, even a system that captures all persons diagnosed with acute viral hepatitis who present in clinical settings will underestimate the true number of new infections. With respect to chronic infections, persons with chronic HBV or HCV infection can be infected for decades without symptoms. Thus, active efforts such as biomarker surveys are needed to estimate prevalence in a population (3,4). With respect to sequelae, specific research studies have estimated the global burden of disease from HBV and HCV infection (1,2). However, few surveillance systems routinely document the fraction of cirrhosis and/or HCC that is attributable to HBV and/or HCV (8,9).

^a Hepatitis B immunization also protects from HDV infection, as HDV is an incomplete virus that can only infect persons also infected with HBV.

1.4. Surveillance can effectively guide prevention, control and treatment

All viral hepatitis meet the public health criteria that define diseases to be placed under routine surveillance. They can be diagnosed through sensitive and specific in vitro diagnostics. They can be addressed through appropriate prevention and control mechanisms. They can be monitored using available epidemiological tools (10,11). Surveillance guides response through generation of information in three areas. First, surveillance can detect outbreaks, monitor trends in incidence and identify risk factors for new, incident infections. Implementing surveillance systems for acute viral hepatitis complies with the International Health Regulations (IHR) to strengthen disease detection (12,13). Second, surveillance can estimate the prevalence of chronic infections and monitor trends in the general population or in highly affected groups (14–17). Third, surveillance can estimate the burden of sequelae due to chronic hepatitis, including cirrhosis and HCC (2,9). Surveillance information from these three areas can be used to monitor and evaluate interventions to prevent, control and treat viral hepatitis. Thus, viral hepatitis surveillance can improve a country's overall performance in numerous other synergistic areas, including water and sanitation, blood safety and injection safety.

1.5. Need for stronger viral hepatitis surveillance

In 2012, the World Health Organization (WHO) collaborated with the World Hepatitis Alliance to conduct a baseline survey of all Member States and describe the state of surveillance, prevention and control of viral hepatitis globally (18). Survey results indicated that the scope of viral hepatitis surveillance activities varied widely, particularly in low- and middle-income countries. Of the 126 Member States that participated in the survey, 104 reported having a national surveillance programme that captured cases of acute hepatitis. However, only about half conducted surveillance for chronic HBV and HCV infections, which are responsible for most hepatitis-related deaths. In 2010 (19) and 2014 (20), in recognition of the serious burden of viral hepatitis on global health, the World Health Assembly adopted resolutions calling for a comprehensive approach to the prevention and control of viral hepatitis. These resolutions mandated WHO to work closely with Member States to develop the necessary guidelines, strategies, time-bound goals and tools for the surveillance, prevention and control of viral hepatitis.

2. AIM OF THESE TECHNICAL CONSIDERATIONS

2.1. Audience

These technical considerations are primarily intended for staff from Ministries of Health (or national technical agencies such as national public health institutes) responsible for the design, implementation, management and evaluation of national-level surveillance for infectious diseases. They have been prepared to be most relevant for low- and middle-income countries with little or no experience in viral hepatitis surveillance. However, these technical considerations outline key principles that are relevant in all countries.

2.2. Scope

These technical considerations refer to systems for the surveillance of acute hepatitis that have been in place for a number of years in some countries. They guide the implementation of surveillance for chronic infections, and briefly touch upon the key elements of surveillance for the sequelae of chronic hepatitis. WHO will regularly update these technical considerations as new techniques and innovations develop, and experience is gained from the use of this document in Member States.

2.3. Purpose

The purpose of these technical considerations is to help develop or strengthen the collection, analysis and reporting of data related to viral hepatitis. They provide guidance on how to deal with differences in epidemiology, select locally appropriate surveillance strategies and ensure linkage with other surveillance systems relevant to viral hepatitis. To achieve this, these technical considerations outline the key steps that surveillance officials should consider when developing or improving viral hepatitis surveillance.

2.4. Use of this document

WHO encourages countries to adapt the content of these technical considerations as needed, such as to the local epidemiology, social and cultural norms, and economic factors. Implementation by a national alliance composed of government, civil society, nongovernmental organizations (NGOs), and donors will ensure that these technical considerations achieve their desired impact. These partners may assist in assessing existing surveillance efforts to adapt and implement these technical considerations.

3. HOW THIS DOCUMENT WAS PREPARED

WHO convened a panel of public health professionals involved in viral hepatitis surveillance to review the experience on which these technical considerations are based. Panel members represented all WHO regions. In March 2013, WHO held a technical consultation that framed the scope and outline of these technical considerations. Presentations from country participants helped to provide a contextual background. A consultant reviewed the literature to collect existing hepatitis surveillance guidelines, brought together the notes from the meeting, drafted the document and sent it twice to the panel for review and revisions. In accordance with WHO guidance, all panel members submitted declarations of interest forms that were reviewed by a WHO staff panel. Five panel members reported conflicts of interest. The WHO Secretariat assessed that these declared conflicts of interest did not preclude these five participants from participating in the development of these technical considerations.

4. EPIDEMIOLOGY OF VIRAL HEPATITIS

Five hepatitis viruses (HAV, HBV, HCV, HDV and HEV) can infect humans and cause hepatitis. Several clinical and epidemiological characteristics that are specific to the five hepatitis viruses influence how surveillance is conducted. Taking these elements into account will help in designing or improving surveillance systems.

4.1. Specific aspects of viral hepatitis epidemiology

4.1.1. Multiple disease outcomes

Infection with one of the hepatitis viruses may either be asymptomatic or cause signs and symptoms of (i) acute viral illness and (ii) hepatic injury. New infections may resolve spontaneously with clearance of the virus, or progress to potentially lethal fulminant hepatitis, or lead to chronic infection, whereby the virus continues to replicate in the liver. After a number of years, chronic hepatitis can cause cirrhosis, liver failure or HCC, which are potentially lethal conditions. HAV and HEV cause only acute hepatitis.^a HBV, HCV and HDV cause the majority of their disease burden through chronic hepatitis.

4.1.2. Similar clinical presentation

The natural history, frequency of occurrence of symptoms, the severity and capacity to cause chronic disease may vary across viruses. However, the clinical manifestations of the disease caused by the various hepatitis viruses are indistinguishable. Further, distinguishing between acute and chronic hepatitis may be difficult on the basis of clinical signs and symptoms. Hence, virus-specific diagnosis requires testing for specific serological or virological markers, which includes testing for biomarkers of recent infection in the case of surveillance for acute viral hepatitis.

4.1.3. Asymptomatic nature of most infections

Most infections with the hepatitis viruses are asymptomatic. Persons with asymptomatic infections do not present themselves to the health system. Thus, surveillance for acute hepatitis in health-care facilities captures only a fraction of all new infections. The occurrence of asymptomatic chronic infections means that surveillance of chronic hepatitis requires biomarker surveys.

4.1.4. Multiplicity of modes of transmission and populations at risk

Hepatitis viruses also differ in their modes of transmission and infectiousness. HAV and HEV are typically transmitted through the fecal–oral route, including ingestion of contaminated food or water. HBV, HCV and HDV are transmitted through activities that involve percutaneous (i.e. puncture through the skin) or mucosal contact with infectious blood or body fluids (e.g. semen).

^a Chronic HEV infections have been reported among immune-suppressed patients.

The relative importance of these modes of transmission varies from country to country. Hence, epidemiological information is needed to identify populations at higher risk.

4.1.5. Need for in vitro diagnosis

In vitro diagnosis is essential for viral hepatitis surveillance (i) to identify the virus that may be causing acute or a chronic hepatitis, and (ii) to differentiate between recent infection, past exposure that resulted in resolved infection and chronic infection. In addition, among persons with serological evidence of past or present HBV or HCV infection, in vitro diagnosis can identify persons who have active infection that may require treatment.

TABLE 3. Key characteristics of HAV, HBV, HCV, HDV, HEV and the infections that they cause

Characteristics	HAV	HBV	HCV	HDV	HEV
Incubation period	2–6 weeks	2–6 months	2–6 months	3–7 weeks	2–10 weeks
New infections / year (in millions)	No estimate available	No estimate available	No estimate available	No estimate available	20.1
Estimated number of persons with chronic infection (in millions)	0	240	130–150	10	No estimate available ^a
Estimated incidence of clinical acute hepatitis among new infections	In children less than 6 years: <10%, increases with age	Children aged <5 years are asymptomatic; 30–50% among persons aged >5 years	<20%	N/A	10% of children younger than 10 years, up to 50% in adults
Estimated number of annual deaths (1)	14 900	686 000	703 800	N/A	52 100
Characteristics of acute hepatitis	Case fatality increases with age	Acute hepatitis more common in adults	Acute hepatitis uncommon, almost never fulminant (21)	Superinfection with HDV in chronic hepatitis B may lead to fulminant disease	Higher case fatality in pregnant women
Chronic infection	None	Chronic infection leading to sequelae	Chronic infection leading to sequelae	Chronic hepatitis that complicates chronic hepatitis B	Very rare ^a
Cirrhosis, chronic liver failure and hepatocellular carcinoma	No	Yes	Yes	Yes	No
Biomarker of recent infection	IgM anti-HAV	IgM anti-HBc	None ^b	IgM anti-HDV	IgM anti-HEV (22)
Routes of transmission	Person-to-person Foodborne Waterborne	Perinatal Bloodborne (e.g. health-care setting, PWID) Sexual	Bloodborne (e.g. health-care setting, PWID) Perinatal (uncommon) ^c Sexual (uncommon) ^c	Bloodborne	Waterborne Foodborne Person-to-person ^d
Treatment options	None	Treatment available	Treatment available	Modified treatment of hepatitis B	None
Vaccine	Yes	Yes	No vaccine	No vaccine ^e	Yes ^f
Prevention of new infections	Water, sanitation and hygiene Vaccination	Vaccination Safe injection practices Infection control Blood safety Safe sex Harm reduction for PWID	Safe injection practices Infection control Blood safety Safe sex Harm reduction for PWID	Prevention of HBV infection	Water, sanitation and food hygiene Vaccination

anti-HAV: antibody against hepatitis A virus, anti-HBc: antibody against hepatitis B core antigen, anti-HDV: antibody against hepatitis D virus, anti-HEV: antibody against hepatitis E virus, IgM: immunoglobulin M, PWID: people who inject drugs

^a Chronicity was reported among persons with immunodeficiency (solid organ transplant recipients, HIV, haematological malignancy).

^b RNA or core antigen positive in the absence of anti-HCV suggests recent HCV infection.

^c Risk of mother-to-child transmission higher among HIV-infected pregnant women and risk of sexual transmission higher among HIV-infected men who have sex with men (MSM)

^d Less common than for hepatitis A, but reported during outbreaks

^e Hepatitis B vaccine protects against HDV infection as HDV cannot replicate in the absence of HBV.

^f Vaccine licensed in China, not widely available

4.2. The five hepatitis viruses

4.2.1. Hepatitis A

The Global Burden of Disease study estimates that in 2013, HAV caused 14 900 deaths (1). The risk of developing symptoms increases with age. Most cases of acute hepatitis are self-limited, but death through fulminant hepatitis may occur, with a case fatality that increases with age. Acute hepatitis may relapse after initial resolution of symptoms but the infection does not become chronic. A serological assay (IgM anti-HAV) is available to diagnose recent infection. HAV is transmitted through the fecal–oral route, including through personal contact, water and food. In 1992, a safe and effective vaccine was licensed for use against hepatitis A. WHO recommends universal immunization in intermediate-endemicity settings where the rates of infection are high among adults (23,24). In low-endemicity settings, the disease is uncommon and in high-endemicity settings, most persons acquire the infection at an age when infections are largely asymptomatic. Additional information on hepatitis A is available from the WHO Internet site at <http://www.who.int/csr/disease/hepatitis/whocdscsredc2007/en/index4.html>.

4.2.2. Hepatitis B

In 2013, HBV caused 686 000 deaths, including 68 600 deaths from fulminant hepatitis, 300 000 deaths from HCC and 317 400 deaths from cirrhosis (1). A systematic review suggests that in 2005, 240 million persons were chronically infected in the world (prevalence: 3.7%) (3). The risk of developing chronic hepatitis is highest during the first years of life, and then decreases with age (25,26). The risk of acute hepatitis increases with age, but acute hepatitis B is usually self-limiting, most often leading to clearance of the virus. Death through fulminant hepatitis may also occur but accounts for a small proportion of the burden of disease associated with HBV infection. A serological assay (IgM anti-HBc) is available to diagnose recent infection. HBV is transmitted through exposure to blood and body fluids, including perinatal, percutaneous and sexual. In many low- and middle-income settings, most hepatitis B infections occur through perinatal (from the mother to the child) or early childhood transmission (between small children, often through household contacts). In high-income countries, most new infections occur through sexual transmission and injection drug use, whereas chronic HBV infection is often most prevalent among immigrants born in countries with high endemicity. Hepatitis B infection can be treated with antiviral medications, even though lifelong treatment may be needed (27). Hepatitis B vaccine is the mainstay of HBV prevention, representing the first vaccine against a major human cancer (i.e. HCC) (28–30). Hepatitis B vaccination is recommended for all newborns, with the first dose as soon as possible after birth, ideally within the first 24 hours (31–33). Additional information on hepatitis B is available from the WHO website at: <http://www.who.int/hiv/pub/guidelines/hepatitis/en/index.html>, including treatment guidelines (27).

4.2.3. Hepatitis C

It is estimated that in 2013, HCV caused 703 800 deaths, including 3500 deaths from acute hepatitis, 342 500 deaths from HCC and 357 800 deaths from cirrhosis (1). A systematic review suggests that between 130 and 150 million persons are chronically infected in the world (4). New HCV infections uncommonly cause acute hepatitis. Serological assays for HCV (total anti-HCV) does not distinguish between new, chronic and resolved HCV infection (34,35). Distinguishing resolved infection from chronic infection requires either HCV core antigen testing or nucleic acid testing (NAT) to detect HCV RNA. HCV is mostly transmitted through exposure to infected blood. Injection drug use and unsafe injections in health-care settings are major sources of new infections, along with other percutaneous procedures in health care and other settings. In low- and middle-income countries, the general population is at risk for acquiring hepatitis C

through unsafe health-care procedures. In high-income countries, hepatitis C infections occur primarily among PWID (36–38). Key preventive measures include harm reduction among PWID and infection control, including safe and appropriate use of injections in health-care settings. No vaccine is available yet. Currently available direct-acting antiviral therapy can cure more than 90% of persons treated (39). Additional information on hepatitis C, including on the prevention of HCV infection among PWID, is available from the WHO Internet site <http://www.who.int/hiv/pub/guidelines/hepatitis/en/index.html>, as well as treatment guidelines (7).

4.2.4. Hepatitis D

HDV is a bloodborne, incomplete virus that needs HBV to replicate. Thus, it only infects persons already infected with HBV. HDV infection can be prevented through hepatitis B vaccination, as persons fully immunized against HBV are no longer at risk of acquiring HDV. Treatment of persons with HDV/HBV coinfection differs from treatment in those with HBV mono-infection. Pegylated interferon is the only effective drug against HDV and the rate of sustained virological response is low. These technical considerations do not provide specific guidance for the surveillance of hepatitis D. However, the generic principles described in this document would apply to the surveillance of HDV infection.

4.2.5. Hepatitis E

HEV may cause as many as 20.1 million infections annually worldwide (40). The Global Burden of Disease study estimated that these infections caused 52 100 deaths in 2013 (1). Most cases of acute hepatitis E are self-limited, but death through fulminant hepatitis may occur, with higher case fatality among pregnant women. Chronic hepatitis E has exceptionally been reported in immunosuppressed individuals (41). A serological test (IgM anti-HEV) is available to diagnose recent infection. HEV is transmitted through the fecal–oral route, mostly through fecally contaminated water. Hepatitis E often occurs as large waterborne outbreaks. Person-to-person transmission is uncommon. In 2012, a new vaccine (42) was licensed in China. However, this vaccine is not available in other countries. In 2014, WHO’s Strategic Advisory Group of Experts (SAGE) on immunization did not recommend it for widespread use (43). Additional information on hepatitis E is available from the WHO Internet site at <http://www.who.int/mediacentre/factsheets/fs280/en/>.

5. PURPOSE AND METHODS OF VIRAL HEPATITIS SURVEILLANCE

Viral hepatitis surveillance has three main purposes (see Table 1, page 13):

- (1) Detect outbreaks, monitor trends in incidence and identify risk factors for new infections;
- (2) Estimate the prevalence of chronic infections and monitor trends in the general population and in sentinel groups;
- (3) Estimate the burden of sequelae of chronic hepatitis, including cirrhosis and HCC.

No single method will provide a complete description of the country's epidemiological profile. The epidemiological situation may vary between population groups. In addition, in large countries, the epidemiological situation may vary between geographical areas. Hence, national officials will benefit from combining data from multiple sources (44). Surveillance information addressing these three questions may also be used to evaluate hepatitis prevention and control programmes (see section 7 on "Use of surveillance information to evaluate programmes", page 44).

5.1. Detect outbreaks, monitor trends in incidence and identify risk factors for new, incident infections

New, incident infections with the hepatitis viruses are often asymptomatic. However, when a person develops acute hepatitis, the occurrence of a symptomatic disease provides an opportunity to generate information on new infections. Symptomatic patients present to health-care facilities, and health-care workers who attend to these patients report the case to the public health authorities (a practice referred to as "case reporting"). Many countries have laws, statutes or other regulations that mandate the reporting of cases of acute viral hepatitis among reportable conditions that have the potential to cause outbreaks. Case reporting can be syndromic (e.g. acute viral hepatitis, where no testing is done and cases are reported on the basis of symptoms) or type-specific, based on testing for selected markers (e.g. anti-HBc IgM for acute hepatitis B). Where testing for biomarkers is available, surveillance for type-specific acute hepatitis along with the collection of epidemiological information on risk factors helps in describing type-specific trends and identifying risk factors for infection.

5.1.1. Syndromic surveillance for acute hepatitis

In settings where testing for markers is not available, syndromic surveillance for unspecified acute hepatitis allows early detection of outbreaks that can lead to prompt investigation and control. Table 2 (page 14) summarizes case definitions for viral hepatitis surveillance. By detecting an increase in the number of cases of acute hepatitis

Case definition of acute hepatitis

Clinical criteria: discrete onset of an acute illness with signs/symptoms of (i) acute viral illness (e.g. fever, malaise, fatigue) and (ii) liver damage, which can be clinical (e.g. anorexia, nausea, jaundice, dark urine, right upper quadrant tenderness), and/or biochemical (alanine aminotransferase [ALT] levels more than 10 times the upper limit of normal.^a

^a Ten times the upper limit of normal (400 IU/L) is the threshold used by the State and Territorial Epidemiologists (CSTE). Countries may also select lower thresholds that could be more sensitive or higher thresholds that could be more specific

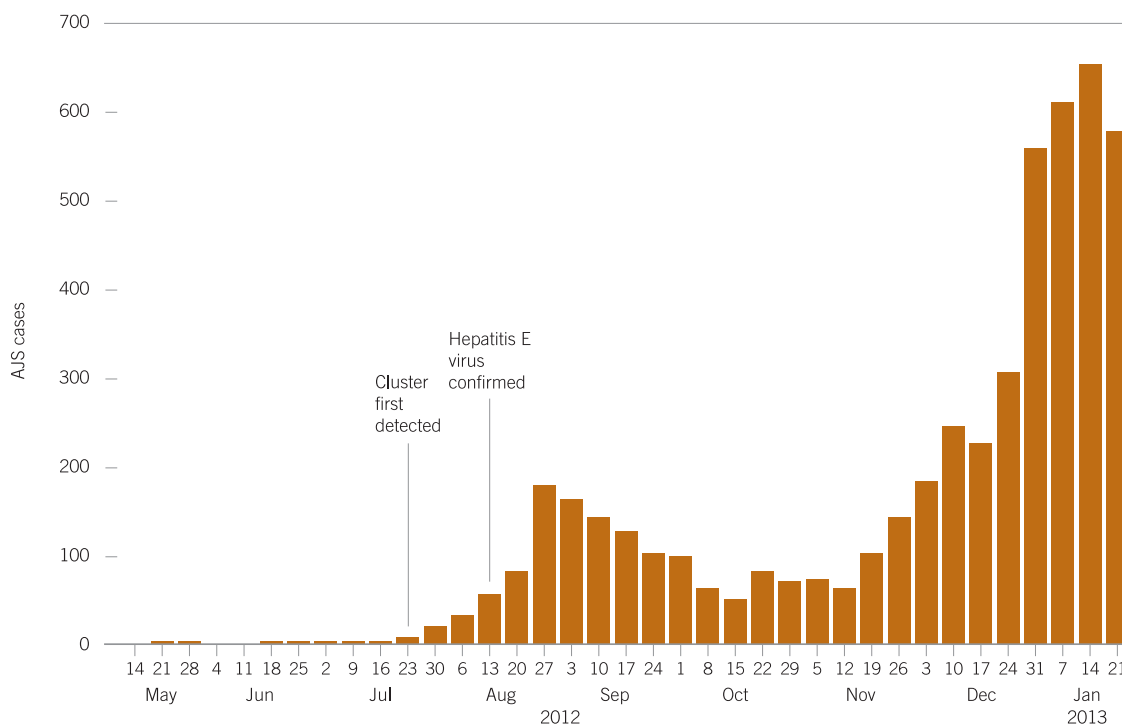
syndrome, syndromic surveillance is useful for triggering outbreak investigations. In the 1990s, the WHO Regional Office for Africa and its Member States, along with their technical partners, adopted a strategy for developing and implementing comprehensive public health surveillance and response systems in African countries. The strategy was called Integrated Disease Surveillance and Response (IDSR) to highlight the essential link between surveillance and response. IDSR is an example of a syndromic surveillance system effectively used in low- and middle-income countries to identify and control outbreak-prone conditions (Box 1) (45,46). As the main objective of syndromic surveillance is to detect outbreaks and investigate them, timeliness is key. Reporting delays must be minimized and the data must be analysed on a regular basis. Event-based surveillance (47),^a the surveillance for outbreaks and follow up of rumours of events rather than for individual cases, may also improve timeliness. When outbreaks are detected, *in vitro* testing is needed to identify the causative virus as the first step in the investigations. Syndromic surveillance, however, does not provide an accurate estimate of the incidence of type-specific viral hepatitis because of the lack of testing for biomarkers, underreporting, and the asymptomatic nature of many new infections. Finally, trends in acute hepatitis defined through syndromic surveillance are difficult to interpret. Different hepatitis viruses and other causes of acute sickness with jaundice may be combined in the notification rates of acute hepatitis.

BOX 1. Detecting outbreaks earlier for action with Integrated Disease Surveillance and Response (IDSR)

During the 1990s, the WHO African Region developed the Integrated Disease Surveillance and Response (IDSR) system following a series of severe outbreaks of preventable disease. IDSR aims at improving disease surveillance and health-care system response through enhanced local capacity, partnership and coordination. Acute hepatitis was one of the priority diseases within IDSR due to its potential for major outbreaks. In 2010, South Sudan implemented IDSR (48). In July 2012, a Médecins Sans Frontières (MSF) hospital reported cases of acute jaundice syndrome. Following the initial cluster of cases, health-care workers searched for cases in each camp; these cases were documented using standardized forms. Since *in vitro* diagnosis was not available locally, specimens were sent to a laboratory in Kenya, which confirmed that the cause of acute hepatitis was HEV infection. As of 27 January 2013, 5080 cases were reported from four refugee camps (Fig. 1) (49). However, because of the improved capacity to detect, verify, report and respond, this outbreak was deemed less severe than the ones in 2006–2007.

^a Event-based surveillance is defined as the organized collection, monitoring, assessment and interpretation of mainly unstructured, ad-hoc information regarding health events, which may represent an acute risk to human health.

FIGURE 1 Acute jaundice syndrome (AJS) cases, by surveillance week, Jamam, Gendrassa and Yusuf Batil refugee camps, South Sudan, 2012–2013 (49)



5.1.2. Surveillance for type-specific acute hepatitis

Where testing for biomarkers is available, surveillance for type-specific acute hepatitis is possible. This may be the case in the whole country. However, in countries where testing for markers may be difficult to access on a large scale, a focus on sentinel sites (sentinel geographical areas or sentinel health-care facilities) may be preferable.

Surveillance for type-specific acute hepatitis in an entire country

If testing for markers is available in the whole country, surveillance for type-specific acute hepatitis may be implemented countrywide, where all health-care facilities are expected to report cases of type-specific acute hepatitis. Many countries of the European Union, for example, report type-specific acute hepatitis (50). In addition to case reporting from health-care facilities, clinical laboratories may also report cases of hepatitis directly to public health authorities, a practice termed as laboratory case reporting. A person who develops acute hepatitis was infected during a known incubation period (see Table 3, page 21). Collection of information on potential risk factors during this incubation period allows the sources of infection to be identified. Thus, surveillance for type-specific acute hepatitis that also collects epidemiological information can direct prevention activities. However, this requires close collaboration between those testing for biomarkers and those collecting epidemiological information. This may be difficult in the case of laboratory case reporting, as the team that reports cases does not include epidemiologists. Such close collaboration may be possible only in sentinel sites (i.e. sentinel geographical areas or sentinel health-care facilities, see *below*).

Enhanced surveillance for type-specific hepatitis in sentinel sites

This consists of surveillance for type-specific acute hepatitis (with biomarker testing) combined with collection of epidemiological information in a subset of geographical areas or in a subset of health-care facilities (Box 2). If testing for biomarkers is not widely available, or if collaboration between those testing for biomarkers and those collecting epidemiological information cannot be organized in the whole country, focusing surveillance efforts at sentinel sites is a rational choice. Sentinel sites for enhanced surveillance may be selected on the basis of their geographical location, population served, patient recruitment, access to accurate and timely diagnosis, and interest and willingness to participate. Surveillance in a few sentinel sites with high-quality in vitro diagnosis and epidemiological information can help to describe trends of type-specific acute hepatitis and risk factors for infection. Fewer sites with high-quality information (e.g. in tertiary centres) may be a better choice than many sites with poor-quality information. In addition, focus on sentinel sites optimizes the use of resources by generating quality information at an affordable cost. In low- and middle-income settings, this cost-efficient sentinel approach is particularly relevant. Sentinel surveillance may not be representative of the general population in the statistical sense of the term. However, it allows the monitoring of trends in incidence by virus type and risk factors. From 1984 to 2006, the United States of America implemented such enhanced surveillance in six sentinel counties. As part of this project, health departments in these counties collected detailed information by contacting cases by telephone or in person (36,51,52). Health department staff regularly interacted with local health providers to maintain a high level of reporting. A template case report for hepatitis is proposed in Annex 1. Pakistan has also used sentinel surveillance to characterize cases of acute hepatitis (Box 2).

BOX 2. Sentinel surveillance points to a higher frequency of health-care exposure among patients with acute hepatitis B and newly reported hepatitis C, Pakistan, 2009–11 (53)

In Pakistan, the prevalence of chronic HCV infection is high and past studies have indicated that new HBV and HCV infections were associated with injections given in health-care facilities. Prior to 2009, surveillance of viral hepatitis was based on syndromic reporting and reported cases were not confirmed with testing for biomarkers. The different viruses were not identified and information on risk factors was not collected. To better understand the epidemiology of viral hepatitis in Pakistan, a hepatitis sentinel surveillance system was established in five large public hospitals. At each selected site, staff members were trained to identify cases of acute viral hepatitis. Additional data regarding exposure during the 6 months prior to onset were collected using a standard investigation form, and test kits were used to diagnose type-specific hepatitis. As anti-HBc IgM was not tested for, the surveillance system considered “newly reported” hepatitis B and hepatitis C cases rather than acute hepatitis B and acute hepatitis C. The results of the analysis indicated that newly reported hepatitis C accounted for the largest proportion of hepatitis and that exposures in health-care settings tended to be more common among newly reported hepatitis B and C cases than among hepatitis A and E cases, pointing to the need for improved infection control practices. Feedback bulletins are published locally to direct hepatitis prevention efforts in Pakistan. Work continues on improving access to in vitro diagnosis, specificity of case definitions, and quality of surveillance information for hepatitis B and C.

TABLE 4. Health-care exposures reported among patients with hepatitis A, B, C and E, sentinel surveillance sites, Pakistan, 2009–2011 (53)

Exposure	Hepatitis A (N=141)	Newly reported hepatitis B (N=77)	Newly reported hepatitis C (N=379)	Hepatitis E (N=87)	P-value (Overall Chi-square)
Surgery	2.1%	14.3%	7.7%	6.9%	0.01
Dentistry	9.2%	24.7%	18.6%	13.8%	0.01
Therapeutic injections	46.8%	62.3%	44.1%	57.5%	0.03
Intravenous infusions	24.1%	40.3%	26.9%	39.1%	0.02

Enhanced surveillance in sentinel sites offers the basis for research studies such as case–control studies that may investigate sources of new infections. Understanding the sources of new infections guides prevention activities. In Egypt, such case–control studies investigated the risk factors for acute hepatitis C (Box 3).

BOX 3. Sentinel surveillance for acute hepatitis allows case–control studies on exploring risk factors for new infections, Egypt, 2007–08

The prevalence of chronic HCV infection is high in Egypt. Frequent use of injections in health-care settings combined with reuse of syringes and needles in the absence of sterilization transmitted HCV on a large scale, including during anti-schistosomal treatment campaigns that made use of injectable drugs in the 1960s–70s. Between 2002 and 2012, sentinel surveillance was conducted in two hospitals of Cairo, one in Alexandria and one in Assiut, with recruitment of more than 500 patients with acute hepatitis C over the study period. Several case–control studies were performed, using family contacts and patients diagnosed with acute hepatitis A as controls. Compared with controls, cases were more likely to report health-care-associated exposure and injecting drug use in the 1–6 months prior to onset of symptoms. On the basis of these results, authors concluded that to minimize transmission, safe injections and safe health-care practices should be the focus of public health interventions (54,55).

5.2. Estimate the burden of chronic infection

Most of the morbidity and mortality attributable to viral hepatitis occur in persons with chronic hepatitis B and C. Estimating the number of persons with chronic HBV and HCV infection is thus necessary for planning care and treatment services. In addition, use of prevalence estimates in models helps to estimate the burden on the health-care system, future treatment needs (including liver transplant needs), and mortality associated with cirrhosis and HCC. Information on the prevalence of chronic infection is obtained from three types of data sources. First, health-care facilities or laboratories may report persons with chronic infection to public health officials. Second, regular biomarker surveys generate population-based estimates of disease burden. They may also estimate the proportion of infected persons who have been identified and who are receiving care. This is particularly useful among populations at higher risk. Third, biological

specimens such as serum, plasma, dried blood spots collected for various purposes (e.g. for antenatal testing) and tested for viral hepatitis may be used to generate some estimation of prevalence. Data from these three sources may be analysed together to generate information on the cascade of care for chronic viral hepatitis infection (i.e. testing followed by prevention, care and treatment) and elucidate patient outcomes after treatment.

5.2.1. Reporting of chronically infected patients

Reporting of chronically infected patients from health-care facilities

Health-care facilities that identify persons chronically infected with HBV and HCV can report them. Such persons would have been tested while undergoing evaluation for a chronic liver disease, a check-up or testing for biomarkers of hepatitis virus infection. However, reporting of cases of chronic infection identified through health-care facilities suffers from two limitations. First, this source of data is prone to duplicate reporting because of repeated clinic visits by persons with chronic HBV or HCV infection or evaluation by different providers. Second, reporting is limited by the availability of testing services, selection bias and underreporting.

Chronically infected patients reported from health-care facilities may be used to estimate the number of infected patients who have been diagnosed, after efforts have been made to identify and remove duplicate reports, which may be resource intensive. This number can be used along with estimates of prevalence in the general population to estimate the proportion of infected patients who have been identified by the health-care services. In fact, reporting of chronically infected patients from health-care facilities reflects test-requesting practices. As such, it can be useful for identifying gaps in testing services. Investigations to determine how these cases of chronic infection were identified and how they were referred to preventive services (e.g. medical evaluation, vaccination of contacts) provides information that can guide programme planning and evaluation. A template case report for hepatitis is proposed in Annex 1, page 67.

Reporting of patients with chronic infection from laboratories

Along with health-care facilities, laboratories conducting hepatitis B and C testing may also report testing results (i.e. laboratory-based reporting). The availability of records of positive test results in the laboratory may facilitate reporting and reduce underreporting. This type of reporting is comparable to the reporting of patients with chronic infection in health-care facilities. Following identification and removal of duplicate reports, the data thus obtained mostly reflect test-requesting practices: they reflect those diagnosed rather than those infected. Datasets originating from laboratories contain a limited number of variables (e.g. age, sex, reason for testing, testing location). Hence, laboratories need to collaborate with public health officials if additional epidemiological information is to be collected following laboratory-based reporting.

5.2.2. Biomarker surveys

Viral hepatitis biomarker surveys in the general population

Biomarker surveys are the most reliable method of estimating the prevalence of chronic infections with HBV and HCV in the population. During such surveys, investigators sample the population to collect epidemiological information (e.g. age, sex, residence, country of birth, history of behaviours that could increase the risk of infection with HBV or HCV, previous knowledge of hepatitis B and C serological status, previous treatment history) and biological specimens (e.g. serum, plasma). Repetition of such surveys using standardized methods as part of routine surveillance provides information that can be compared. Surveys can estimate the prevalence of serological evidence of past or present HCV infection (i.e. proportion of those surveyed who are positive for anti-HCV), infection (i.e. proportion of those surveyed positive for HCV RNA) and fibrosis (i.e. proportion of

those surveyed positive for non-invasive markers of fibrosis). They can estimate the proportion of infected persons who know their status, are eligible for treatment and are receiving antiviral treatment. Finally, biomarker surveys can be designed to collect information regarding history of previous contact with health-care practitioners or other settings in which vaccination could have been given (e.g. sexually transmitted infection [STI] clinics, correctional facilities, drug treatment centres), thereby assessing missed opportunities for prevention.

Population-based HIV Impact Assessment (PHIA) surveys and other surveys

Specific health programmes or investigators may implement regular surveys on a representative national sample of households. Examples include the Demographic and Health Surveys (DHS), the Multiple Indicators Cluster Surveys (MICS) or the Malaria Indicator Surveys (MIS). In the field of HIV/AIDS, there are AIDS Indicator Surveys (AIS) and Population-based HIV Impact Assessment (PHIA) surveys (56). In the field of immunization, there are surveys to evaluate the impact of universal infant immunization against hepatitis B (57). All these surveys may be used to obtain biological specimens to be tested for viral hepatitis (10,58,59). DHS surveys, for example, were used to estimate the prevalence of chronic infection in the general population in Egypt (Box 4).

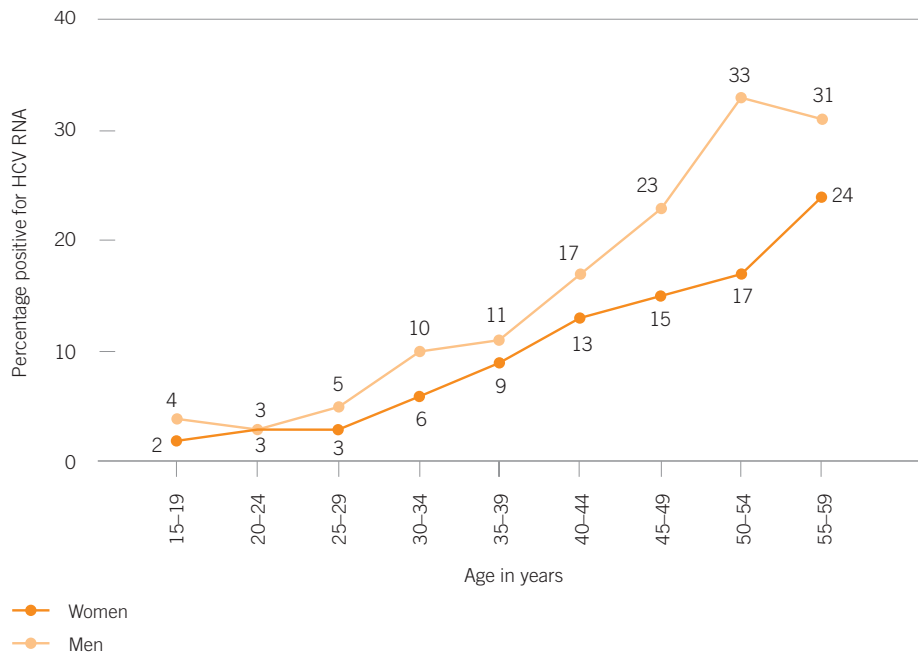
Practical guidance on the implementation aspects of biomarker surveys is available elsewhere. Useful resources include guidance for PHIA surveys (56) or for the evaluation of hepatitis B immunization programmes (57). Key quality elements include the following:

- in vitro diagnostic testing with adequate quality assurance (QA)
- validated testing strategy
- use of validated tests of known sensitivity and specificity
- compliance with ethical principles (protection from harm, maximization of benefits, informed consent, confidentiality and possibility to obtain the results of the tests conducted along with referral to care).

BOX 4. Using the DHS survey to characterize the hepatitis C epidemic in Egypt, 2008 (60)

In 2008, the DHS was undertaken on a nationally representative sample in Egypt to provide estimates for key population indicators such as fertility, contraceptive use, infant and child mortality, immunization levels, maternal and child health, and nutrition. The survey included a number of questionnaire items about hepatitis C and collected biological specimens from more than 11 000 individuals in urban and rural areas to test for biomarkers of HCV infection. Results indicated that 80% of women and 85% of men were aware of hepatitis C. Fifteen per cent of the respondents aged 15–59 years had antibodies to HCV, indicating that they had been exposed to the virus at some point. Ten per cent had HCV RNA, indicating that they had chronic infection. Men were more likely to be infected than women and the prevalence of infection increased with age among both women and men (Fig. 2). Two per cent of women and 6% of men had ever been tested for HCV infection. One per cent of women and 2% of men self-reported that they had been diagnosed with hepatitis C, and half of them said that they had received treatment. In 2015, the survey was repeated. Preliminary analysis of the data suggests that the prevalence of HCV infection has decreased since 2008. Additional analyses will assist in understanding the determinants of this decrease in prevalence. The results of the survey informed the development of a national hepatitis action plan in Egypt.

FIGURE 2 Prevalence of HCV RNA by age group among men and women, by age, Egypt, 2008



Source: El-Zanaty F, Way A. Egypt Demographic and Health Survey 2008. Cairo, Egypt: Ministry of Health, El-Zanaty and Associates, and Macro International; 2009.

Surveys in specific population subgroups

The relative importance of the modes of transmission of hepatitis viruses varies from country to country. To understand transmission in populations at higher risk, information may be needed on the prevalence in populations that may not be well represented in general population surveys, including PWID, men who have sex with men (MSM), prisoners, migrants born in countries with high endemicity and sex workers. Such specific populations may be hard to reach because of stigma or criminalization of practices. Special methods have been proposed to reach these groups in the context of integrated HIV biobehavioural surveillance (IBBS). Respondent-driven sampling (RDS) is a method based on “snowball sampling” (i.e. getting individuals to refer other persons at similar high risk whom they know; these individuals in turn refer other persons that they know, and so on). A mathematical model then weights the sample to compensate for the non-random sampling method (61). Surveying populations at higher risk at the venues where they tend to gather, a strategy referred to as “venue-based” surveys, is an alternate option (62). Hepatitis surveys have been conducted using RDS in special populations in Zanzibar (Box 5).

BOX 5. Viral hepatitis and HIV infection among people who inject drugs (PWID) in Zanzibar, Tanzania, 2012 (63)

In 2012, investigators conducted a survey among 408 PWID ≥ 15 years of age in Zanzibar using RDS. The median age was 32 years, 98% were male and the median duration of injecting drugs was 5 years. Weighted HIV, hepatitis B surface antigen (HBsAg) and anti-HCV prevalence were 11.3% (95% confidence interval [CI]: 7.7, 15.2), 5.9% (95% CI: 3.5, 8.8) and 25.4% (95% CI: 19.1, 32.0), respectively. Among HIV-infected PWID, 9.0% (95% CI: 2.3, 19.3) were coinfecting with HBV, 66.6% (95% CI: 52.3, 83.0) were coinfecting with HCV and 8.5% (95% CI: 1.8, 18.6) were coinfecting with both. Coinfection with HBV and/or HCV was high among HIV-infected PWID in Zanzibar, underlining the importance of testing HIV-infected PWID for HBV and HCV, and of integrating prevention and linkage to care. Other important measures include providing HBV vaccination as indicated, initiating antiretrovirals (ARVs) as early as possible to treat both HIV/HBV using a tenofovir-based regimen, and introducing interventions that have a high impact on reducing needle-sharing as early as possible to reduce the risk of HCV acquisition.

5.2.3. Making use of specimens collected for other purposes (See informed consent, page 55)

Serological testing for infection with the hepatitis viruses may be added to other testing undertaken in different settings for various purposes (e.g. blood donations, women attending antenatal clinics, prisoners, patients at STI clinics, PWID attending needle and syringe programmes, pre-employment or premarital testing, Box 6). Estimation of prevalence from each of these groups may suffer from biases that limit the generalizability of the results. However, they can provide valuable insights on the prevalence and trends of chronic HBV or HCV infection, in the absence of or complementary to information from general population surveys or from specific populations.

Blood donations

Most countries have policies that mandate the testing of all blood donations for transfusion-transmitted infections, including HBV and HCV (64). Obtaining data on the prevalence of HBV and HCV infections from blood transfusion services is a simple, inexpensive source of data. However, estimates of the prevalence of HBV and HCV infection among blood donors suffer from limitations.

First, blood donors are not representative of the general population. In countries where blood donors are voluntary and non-remunerated, they tend to be healthier than the general population. Furthermore, potential donors with known risk factors (e.g. PWID) are excluded from donation. Hence, blood donors may have a lower prevalence of hepatitis virus infections. In countries that use family replacement or paid donors, the prevalence of hepatitis may be higher than in the general population. First-time blood donors more closely reflect the general population than do repeat donors who have been selected on the basis of the absence of transfusion-transmitted infections.

Second, testing itself may have limitations. Some countries may not test all of their blood donations for transfusion-transmitted infections. Some donations in low-income countries are tested without functional QA (65). Local differences in blood-screening regulations, availability of test kits, or special campaigns, for example, may also affect the quality of data.

Further information on international regulations on blood safety can be found on the WHO website at: http://www.who.int/topics/blood_safety/en/.

BOX 6. Data mining to identify sources of information on the epidemiology of HBV and HCV infections in the Americas

While published studies may not be available, and there may be no common and organized source of data on HBV or HCV infection, most countries have unpublished information that can help characterize the epidemiology of HBV and HCV infection. From 2014, the WHO Region of the Americas initiated “data mining”. Data mining is an activity during which stakeholders explore all possible sources of information that can help define the epidemiology of HBV and HCV infection and the national response (e.g. data from blood donations, unpublished surveys). As a result of these data mining activities, countries have been able to gain a better understanding of national and local HBV and HCV epidemics and their impact, as well as data gaps. Using these data, countries have started working on mathematical models to direct national policy and plans for the prevention and control of viral hepatitis in the Region.

Pregnant women attending antenatal care services

Many pregnant women receive antenatal care (ANC) services during their pregnancies. In this context, venous whole blood is usually drawn for syphilis and/or HIV testing as part of programmes to prevent mother-to-child transmission of syphilis and/or HIV. Pregnant women seen in ANC are used as a proxy for the general population of women of reproductive age (15–49 years). Prior to population-based biomarker HIV surveys, ANC surveys were the principal source of HIV prevalence data in low-income countries. Part of these specimens (e.g. serum/plasma) may be used for viral hepatitis testing. Analysis of the data routinely collected during these testing activities may also be used to estimate prevalence. However, this method suffers from limitations. First, it provides information only for women of childbearing age. Women of childbearing age represent a narrow age group. Information from such a narrow age group may not reflect the differences across age groups; in some countries, older age groups suffer from the largest burden. Second, it may overrepresent certain groups (e.g. migrants to the European Union from higher-prevalence countries with higher total fertility rates) (38). Third, the prevalence of chronic hepatitis due to the various hepatitis viruses usually differs by sex (e.g. HBV infection is more prevalent among men) and antenatal data do not provide any information on men. Thus, ANC data have not been widely used for estimating the prevalence of viral hepatitis.

Testing of other specific groups

Some particular population groups may be tested for specific infectious diseases, including HIV and viral hepatitis. These include recruits to the armed forces, prisoners or those applying for work permits or visas to certain countries. While not representative of the general population, prevalence may be monitored in such groups over time. If military recruits are selected by draft or lottery or if military service is compulsory for all, information provided on a yearly basis may provide trends in prevalence that may be more representative. Obtaining this information from these sources, for example, the military services, can be difficult because of administrative barriers or reluctance to share the information.

5.3. Estimate the burden of sequelae

Monitoring the occurrence of cirrhosis and HCC contributes to the measurement of the disease burden of chronic hepatitis B and C, and assesses the impact that these have on the health-care system. Disease outcome data are collected through a variety of means, including cancer

registries, death registries, administrative health data and hospital surveys. A disease registry is a database that tracks the incidence, treatment and response to treatment for a specific condition. Registries are sometimes maintained by large entities (e.g. hospitals, government agencies and pharmaceutical companies) or by private physicians. Disease registries are not a widely available source of data on disease outcomes, as they require considerable resources to establish and maintain. Furthermore, cirrhosis is a condition of gradual onset, which is defined on the basis of pathological criteria. However, it does not have a case definition for the purpose of public health surveillance.

5.3.1. Cancer registries

A cancer registry is a file or register of all cancer cases occurring in a defined population. It includes demographic information on patients as well as clinical and pathological characteristics of the cancer (e.g. identifier, age, sex, birth location, residence, diagnosis, stage of cancer, International Statistical Classification of Diseases and Related Health Problems [ICD]-ninth/tenth revision (9/10) diagnosis code) (66,67). Date and cause of death may be included if applicable. Information from individual doctors and hospitals is typically reported to a regional or national agency that compiles data. A cancer registry helps to identify temporal trends and regional variations in incidence. WHO's International Agency for Research on Cancer (IARC) collates data from 290 cancer registries in 68 countries (68). HCC estimates may be derived from liver cancer data (68). This requires a specific methodological approach, as HCC (primary cancer of the liver that may be secondary to infection with hepatitis viruses) is less common than metastatic liver tumours (68). Cancer registries on HCC usually do not collect information on the history of hepatitis B or C infections. However, local hospital-based data on the prevalence of HBV and HCV infection among patients with HCC may be applied to local registry data to infer the fraction of HCC cases that are attributable to viral hepatitis (2).

5.3.2. Death certificates

Cirrhosis and HCC, the main sequelae of chronic HBV and HCV infection, often lead to death. Mortality data with cause-of-death information can be regularly obtained from death registries using ICD-9 or ICD-10 coding, and may be used to estimate the impact of viral hepatitis in a population. Unfortunately, in many countries, death registries do not accurately collect cause-of-death data and registration does not occur throughout the country. Estimates from modelling are necessary in WHO Member States that lack high-quality death registration systems. As for cancer registry data, death certificates rarely list chronic HCV or HBV infection as a contributing cause of death. However, as for cancer registry data, hospital-based data on the prevalence of HBV and HCV infection among patients with HCC and cirrhosis may be applied to infer the fraction of deaths attributable to viral hepatitis (2).

5.3.3. Clinic/hospital-based data

Hospitals with specialized services (tertiary hospitals) in the area of liver disease are a useful source of information on the proportion of patients with HCC or cirrhosis who have a history of chronic HBV or HCV infection (2). Such information, although not representative of the general population, may be used to estimate the proportion of the HCC- or cirrhosis-specific mortality that is attributable to HBV and HCV. Taking into account the level of alcohol consumption may improve the accuracy of the estimates as some end-stage liver disease may be caused by a combination of alcohol and viral hepatitis. Data on HCC or cirrhosis from clinics or hospitals can also provide insight into the characteristics of persons most affected (demographics, geographical area), treatment used, disease outcome and costs.

6. VIRUS-SPECIFIC SURVEILLANCE

Although the purpose of, method for and approaches to viral hepatitis surveillance are similar for all types of viral hepatitis, viral characteristics, epidemiology and risk populations vary with each type (69). These differences necessitate disease-specific approaches to surveillance. Case definitions are an important element of disease surveillance, as they determine the criteria to be used for cases to be reported, independently of the way they will be managed clinically. For viral hepatitis surveillance, case definitions include a combination of clinical and biomarker criteria. These criteria are used to classify cases as either suspected or confirmed (10). Because the clinical symptoms for all types of viral hepatitis are similar, the clinical criteria for acute viral hepatitis (types A–E) are similar. For chronic hepatitis, the criteria includes the absence of acute hepatitis and the biomarker(s) of chronic infection of the virus involved. Table 2 on page 14 summarizes all case definitions for viral hepatitis surveillance.

6.1. Hepatitis A

HAV infection is highly endemic in most low-income countries. In a highly endemic setting, 90% of children would have acquired infection by the age of 10 years (70). Hence, the potential for disease and of occurrence of outbreaks in such settings is low, because most adults have immunity. However, living standards, including access to safe water, are improving in many countries. In areas with intermediate endemicity, many children escape HAV infection during childhood and persons remain at risk of acquiring HAV infection at older ages when infection is much more likely to lead to clinical hepatitis A. Such countries need surveillance systems in place to assess the burden, detect outbreaks and monitor epidemiological trends to determine whether immunization is needed (71). If vaccination for hepatitis A is integrated in the Expanded Programme on Immunization, surveillance for type-specific acute hepatitis may also be used to evaluate the impact of immunization on rates of reported hepatitis A. Table 5 summarizes the purposes, methods and uses of hepatitis A surveillance.

In vitro diagnosis of hepatitis A is based on a positive IgM anti-HAV result. A confirmed case of hepatitis A must meet the clinical and biomarker criteria or have

Case definition of hepatitis A

Clinical criteria: person meeting the criteria for acute hepatitis (see definition of acute hepatitis on page 24)

Biomarker criterion: positive for IgM anti-HAV

Epidemiological criteria: epidemiological link to a case confirmed with biomarker (i.e. contact^a with a person with hepatitis A confirmed with biomarker testing 2–6 weeks before onset, or occurrence in the context of an outbreak confirmed by biomarker testing)

Case classification:

Confirmed:

- a case of acute hepatitis with biomarker positivity
- OR
- a case of acute hepatitis with epidemiological link to a case confirmed with biomarker positivity

^a e.g. household, sexual or drug-sharing contact

an epidemiological link (e.g. a history of contact) to a case with confirmed biomarkers (10). Molecular techniques (i.e. viral sequence analysis) can be used to investigate outbreaks and determine whether reported cases share a common source of infection. However, molecular testing is not widely available in many countries and is not part of routine surveillance in most countries. If this type of testing is needed, specimens must be transferred to laboratories with sufficient capacity to perform molecular testing.

6.1.1. Detect outbreaks, monitor trends and describe risk factors

Regular analysis of data on reported cases of hepatitis A examines crude rates to detect outbreaks. In addition, hepatitis A surveillance data are analysed periodically by time (i.e. seasonality, yearly trends) and person (i.e. age, sex and risk groups). Estimating the proportion of hepatitis A cases with specific reported risk factors monitors transmission patterns. In low-endemicity countries, surveillance can identify populations at higher risk of infection, which can inform vaccination policy (e.g. MSM, PWID). If surveillance is done in the general population, reported cases can be linked with population denominators and incidence rates may be calculated, including rates by geographical areas, which can be used to prepare maps. However, this may not be possible if the sentinel site is in a tertiary reference centre that cannot be linked with a clear population base. Rates of reported hepatitis A are an indirect reflection of the incidence of HAV infection, as the probability of symptoms in the case of infection varies with age. Most children with HAV infection are asymptomatic. Hence, reported cases represent only a small proportion of the overall burden of HAV infection in this age group. Symptoms are more common in adults, and rates of reported hepatitis A among them are better reflections of the incidence. Increases in the rates of reported hepatitis A can signal a communitywide outbreak that requires investigation.

6.1.2. Estimate burden of disease

In the absence of chronic infections, there is no place for biomarker surveys to assess burden of disease during routine surveillance. However, biomarker surveys have been used as research studies to characterize the age-specific prevalence of total anti-HAV antibodies in populations. Such surveys interpreted in the context of information from hepatitis A surveillance can facilitate the assessment of epidemiological transition of areas/countries from high endemicity to intermediate endemicity. The findings can guide decisions about the introduction of universal vaccination against hepatitis A in intermediate-endemicity settings. Argentina, for example, decided to introduce hepatitis A vaccine in routine immunization of infants on the basis of sero-epidemiological and surveillance information that indicated an intermediate-endemicity profile, which was associated with a substantial burden of disease (72).

6.1.3. Estimate the burden of fulminant hepatitis

Some countries have reported frequent occurrences of fulminant hepatic failure secondary (73) to hepatitis A. If this is a source of concern, countries can place this condition under sentinel surveillance using health-care facilities that are likely to care for such patients (74).

TABLE 5. Hepatitis A surveillance: purpose, methods and use of the information

Purpose	Countries	Surveillance methods	Use of information
Detect outbreaks, monitor trends and describe risk factors.	High endemicity ^a	Reporting of cases of confirmed hepatitis A	Monitor average age at infection to detect possible transition towards intermediate endemicity.
	Transitional epidemiology ^b	Syndromic surveillance	Outbreak detection
		Reporting of cases of confirmed hepatitis A	Identify populations at higher risk. Inform vaccination policy to determine the need for universal childhood immunization. Evaluate vaccination policy after introduction of universal childhood immunization.
Low or very low endemicity ^c	Reporting of cases of confirmed hepatitis A	Outbreak detection Identify populations at higher risk to inform targeted vaccination policy.	
Characterize the sero-epidemiology.	All	Occasional biomarker surveys	Identify intermediate-endemicity settings where universal immunization may be indicated. ^d
Estimate the burden of fulminant hepatitis.	Countries where fulminant hepatitis has been a source of concern	Sentinel surveillance for fulminant hepatitis	Inform vaccination decisions. Identify factors associated with fulminant disease (75).

^a Countries where most children (90%) have been infected with HAV before the age of 10 years.

^b Countries with transitional economies and regions where sanitary conditions are variable, children often escape infection in early childhood.

^c In countries with good sanitary and hygienic conditions, HAV infection rates are low.

^d Serological testing does not differentiate vaccine-induced from natural immunity. This may complicate interpretation where the vaccine has been used extensively.

6.2. Hepatitis B

Hepatitis B remains prevalent in most countries, particularly in low- and middle-income countries. Implementation of universal hepatitis B immunization of infants is reducing the prevalence of chronic infections in children, but 240 million chronically infected persons remain among unvaccinated adults worldwide (3). Table 6 summarizes the purposes, methods and uses of hepatitis B surveillance.

6.2.1. Detect outbreaks, monitor trends and describe risk factors

Biomarker diagnosis of recent HBV infection is based on a positive IgM antibody to hepatitis B core antigen (anti-HBc IgM) (76). However, hepatitis B testing is usually requested as a panel of markers of HBV infection that usually also include HBsAg. The case definition needs to be specific in order for surveillance data to be useful. If not, chronic HBV infection will be reported as acute hepatitis, thereby reducing the value of the information. For example, in settings where IgM anti-HBc assays are not available, surveillance for acute hepatitis B using HBsAg only is unlikely to yield useful information, as most persons identified with HBsAg will have chronic rather than acute infection. Similarly, acute hepatitis due to other causes (e.g. hepatitis A) among patients with chronic HBV infection (who are thus HBsAg positive) will be reported as acute hepatitis B cases.

Outbreaks of hepatitis B are uncommon, but may occur in health-care settings, and among PWID or MSM. Such outbreaks are unlikely to be detected with syndromic surveillance because the number of cases is fewer than in most hepatitis A or hepatitis E outbreaks, and may go unrecognized among other causes of acute hepatitis. Detection of acute hepatitis B outbreaks would require regular (e.g. weekly) analysis of type-specific acute hepatitis data. In addition to outbreak detection, an annual analysis of acute hepatitis B surveillance data may be useful to describe trends and risk factors. In age groups where there is high coverage of universal hepatitis B immunization, acute hepatitis B is expected to be uncommon. Cases of acute hepatitis B occurring among persons belonging to vaccinated age cohorts should prompt an evaluation for possible vaccine failure. Additional investigation can identify the causes for these potential breakthrough infections (e.g. waning of vaccine-induced immunity and infection with viral variants).

Case definition of acute hepatitis B

Clinical criteria: person meeting the criteria for acute hepatitis (*see* definition of acute hepatitis on page 24)

Biomarker criterion: positive for IgM-specific antibodies to hepatitis B core antigen (anti-HBc IgM)^{a,b}

Case classification:

Confirmed:

- a case of acute hepatitis with biomarker positivity

Almost half of new infections in adults are asymptomatic. Therefore, surveillance for acute hepatitis B underestimates incidence. The proportion of cases with specific risk factors can help to monitor disease transmission patterns and identify risk groups to be targeted for vaccination and other prevention programmes. Investigation of persons with acute hepatitis B may include virological investigations (e.g. HBV genotype) that are beyond the scope of routine surveillance (77). If that kind of laboratory infrastructure is available, referral of specimens for molecular testing can be helpful for a comprehensive assessment of reported cases.

6.2.2. Estimate burden of chronic infection

The diagnosis of chronic HBV infection is based on a positive HBsAg test. HBsAg can be detected in virtually all persons with chronic HBV infection. From a surveillance point of view, a single HBsAg-positive test in a person without acute hepatitis tested in the context of evaluation for a chronic liver disease, a check-up or a survey is considered as a case of chronic HBV infection (the probability of picking a case of recent infection about to be cleared in such a context is low).

From a clinical management point of view, two HBsAg tests on two occasions at least six months apart may be required to confirm the diagnosis of chronic infection. Understanding the viral characteristics of reported cases (e.g. HBV viral load, HBV genotype and hepatitis B e antigen [HBeAg] status) can provide insights into HBV-associated infectiousness, severity of disease, rate of progression and eligibility for treatment.

The best estimates of the burden of chronic HBV infection are obtained from biomarker surveys in the general population or in specific populations. Data analysis focuses on estimating the prevalence, disaggregated by age and key populations (3). Biomarker surveys can also provide information for evaluating access to testing, prevention and treatment

Case definition of chronic hepatitis B virus infection

Clinical criteria: person not meeting the case definition for acute hepatitis (this commonly occurs when individuals are tested in the context of evaluation for a chronic liver disease, a check-up or a survey)

Biomarker criterion: detection of HBsAg

Case classification:

Confirmed:

- a case that meets the clinical and biomarker criteria

^a Hepatitis test panels usually include HBsAg with anti-HBc IgM test.

^b A specific test and/or threshold is needed to exclude transient presence of IgM during flares among patients with chronic HBV infection

for chronic HBV infection. Changes in the age-specific prevalence of chronic HBV infection over time document the control of HBV infection over time through immunization (see example of China in Box 7, page 45 and Fig. 3, page 45).

TABLE 6. Hepatitis B surveillance: purpose, methods and use of the information

Purpose	Surveillance methods	Use of information
Detect outbreak, monitor trends and describe risk factors.	Reporting of cases of confirmed acute hepatitis B	Identify risk factors. Prevent HBV infection in populations at higher risk. Describe trends. Identify breakthrough infections among vaccine recipients.
Estimate the burden of chronic infections.	Biomarker surveys	Estimate prevalence. Identify groups with higher prevalence. Strategize prevention and control efforts. Evaluate progress towards hepatitis B control goals following immunization.
	Reporting of chronic infections in laboratories or health-care facilities	Characterize persons with chronic infections who have been tested and identified.
Estimate the burden of sequelae.	Prevalence of HBV infection in cirrhosis and hepatocellular carcinoma (HCC) patients Cancer registries Death certificates	Estimate the proportion of cirrhosis and HCC attributable to HBV infection.

Chronic HBV infections reported in health-care facilities or in laboratories depend on test requesting practices. These chronic infections are often acquired earlier through vertical or early childhood transmission. As the exact date of infection is unknown in a patient with chronic infection, a reference period of exposure cannot be identified. Analysing risk factors with the objective of identifying sources of infection among such prevalent cases is misleading and not useful, as infection may have occurred well before the reported risk behaviour. If health-care facilities or laboratories report cases of chronic HBV infection, they must separate them from cases of acute hepatitis B. Failure to do so may make acute hepatitis B surveillance data uninterpretable (78).

6.2.3. Estimate the burden of sequelae

Estimation of the prevalence of HBV infection among patients with cirrhosis and HCC along with data from cancer registries and death certificates can be used to estimate the proportion of cirrhosis and HCC attributable to HBV infection (see section 5.3 “Estimate the burden of sequelae”, page 33).

6.3. Hepatitis C

While new HCV infections still occur from unsafe health-care practices and injection drug use, the majority of the burden of disease occurs among persons who acquired infection in the past and have chronic HCV infection. This burden must be measured to plan for testing and treatment services. Table 7 summarizes the purposes, methods and uses of hepatitis C surveillance.

6.3.1. Detect outbreaks, monitor trends and describe risk factors

Surveillance for acute hepatitis C is most challenging. First, 50–70% of new infections in adults are asymptomatic, who thus do not seek medical care. Second, many of the persons with symptomatic infection have non-specific manifestations; few actually meet the clinical case definition of acute hepatitis. Third, PWID who may account for a large proportion of new infections in some countries may not seek care for acute hepatitis because of the difficulties they face in accessing health care. Fourth, no simple biomarker can reliably distinguish recent from chronic infection.

Diagnosis of acute hepatitis C requires (a) signs and symptoms of acute hepatitis, and (b) positivity of the relevant biomarkers. A number of biomarker profiles suggest acute hepatitis. First, the presence of HCV RNA without anti-HCV is characteristic of recent infection. Second, the detection of anti-HCV among persons previously negative for this marker defines recent seroconversion. However, seroconversion can be timed precisely only among persons who are regularly tested. Such persons in whom seroconversion could thus be detected include patients with clotting factor disorders, those undergoing chronic haemodialysis, plasma donors or HIV-infected MSM. Availability of information on the date of the last negative anti-HCV test helps in estimating the date of infection. Third, the occurrence of clinical acute hepatitis with a positive anti-HCV test after exclusion of acute hepatitis A, B and E suggests acute hepatitis C. As for acute hepatitis B, the case definition for acute hepatitis C needs to be specific in order for surveillance data to be useful. Failure to use a specific case definition leads to inclusion of cases with chronic HCV infection among cases of acute hepatitis C, which causes confusion.

Acute hepatitis C may be found in specific populations (e.g. PWID) or in the general population of high-endemicity countries. Outbreaks are uncommonly identified and reported, but have been described among PWID, in health-care settings (in relation to the reuse of equipment or multidose vials of medicines), and among MSM with HIV infection.

Rates of reported acute hepatitis C underestimate the incidence of HCV infection because of the large proportion of asymptomatic forms, difficulties in diagnosis and underreporting. However, if a country has implemented sentinel surveillance for acute hepatitis C, an annual analysis can examine trends over time and risk factors for new infections. Further investigations are warranted for acute hepatitis C among persons who have a history of receipt of blood or blood products, haemodialysis, hospitalization, surgery, needle-stick injury or other percutaneous procedures in health-care or other settings.

Case definition of acute hepatitis C

Clinical criteria: person meeting the case definition for acute hepatitis (*see* definition of acute hepatitis on page 24)

Biomarker criterion:

- detectable HCV RNA and negative for anti-HCV antibodies
- OR
- seroconversion to anti-HCV antibodies^a
- OR
- positive for anti-HCV AND negative for IgM anti-HBc, IgM, anti-HAV and IgM anti-HEV

Case classification:

Confirmed:

- a case of acute hepatitis with positivity of one of the three biomarker criteria

^a Among patients tested regularly at short time intervals, seroconversion to anti-HCV suggests a recent HCV infection, which may take place in the absence of clinical, acute hepatitis. Seroconversion to anti-HCV should be followed automatically by RNA testing (also known as “reflex testing”), when available.

Case definition of (1) chronic hepatitis C virus infection and (2) serological evidence of past or present infection

Clinical criteria: person not meeting the case definition for acute hepatitis (this commonly occurs when individuals are tested in the context of evaluation for a chronic liver disease, a check-up or a survey)

Biomarker criteria:

- serological evidence of past or present infection: anti-HCV positive
- chronic HCV infection: detectable HCV RNA or HCV core antigen positive^a

Case classification:

Confirmed serological evidence of past or present infection: a case that meets the clinical criteria and the biomarker criteria for past or present infection

Confirmed chronic HCV infection: a case that meets the clinical criteria and the biomarker criteria for chronic infection

6.3.2. Estimate burden of chronic infections

The surveillance case definition for chronic HCV infection is based on the absence of acute hepatitis (e.g. test in the context of evaluation for a chronic liver disease, a check-up or a survey) and biomarker criterion. Biomarkers can differentiate serological evidence of past or present HCV infection (anti-HCV) from chronic HCV infection (HCV RNA and/or HCV core antigen).

As for hepatitis B, analysing risk factors for reported cases of chronic HCV infection is misleading and not useful (as the date of infection is unknown). Surveillance for chronic HCV infection can make use of biomarker surveys

(that reflect the epidemiology of the disease) or cases reported in health-care facilities or in laboratories (that reflect test requesting practices). If health-care facilities or laboratories report cases of chronic HCV infection, they must separate them from cases of acute hepatitis C. Failure to do so make acute hepatitis C surveillance data uninterpretable. Biomarker surveys of the general population or of specific populations (e.g. PWID) provide the most accurate estimates of the burden of chronic HCV infection (4,79). By documenting changes in prevalence, repeated biomarker surveys can be used to measure the impact of efforts to prevent HCV infection and provide hepatitis C treatment. Mathematical modelling can integrate the results of these repeated surveys in the context of other sources of information (e.g. treatment coverage, mortality) to estimate programme impact and changes in incidence. Surveys using non-invasive markers of fibrosis (serum markers or transient elastography) to estimate the proportion of patients with chronic hepatitis suffering from advanced disease (F3–F4 fibrosis) can further describe the treatment needs in the population. However, it may be logistically difficult to implement fibrosis assessment as part of surveillance.

6.3.3. Estimate the burden of sequelae

Estimation of the prevalence of chronic HCV infection among patients with cirrhosis and HCC along with data from cancer registries and death certificates can be used to estimate the proportion of cases of cirrhosis and HCC attributable to HCV infection (see section 5.3 “Estimate the burden of sequelae”, page 33).

^a For surveillance purposes, if HCV RNA or HCV core antigen testing are not available, about two third of anti-HCV positive individuals will have chronic infection.

TABLE 7. Hepatitis C surveillance: purpose, methods and use of the information

Purpose	Settings	Surveillance methods	Use of the information
Detect outbreak, monitor trends and describe risk factors.	All countries	Reporting of confirmed cases of acute hepatitis C ^a	Identify risk factors. Direct prevention of HCV infection in populations at higher risk. Describe trends.
Estimate burden of chronic infection.	All prevalence settings	Biomarkers surveys	Estimate prevalence. Identify groups with higher prevalence. Allocate resources. Inform prevention and control efforts.
		Reporting of chronic infections from laboratories or health-care facilities	Characterize persons with chronic infection who have been tested and identified.
Estimate the burden of sequelae.	High prevalence in specific population groups (e.g. PWID)	Biomarker surveys in specific population (e.g. PWID)	Estimate burden.
	All	Prevalence of HCV infection in patients with cirrhosis and HCC Cancer registries Death certificates	Estimate the proportion of deaths from cirrhosis and HCC attributable to HCV infection.

HCC: hepatocellular carcinoma, HCV: hepatitis C virus, PWID: people who inject drugs

^a Identification of outbreaks may require genotyping or sequencing data.

6.4. Hepatitis E

Diagnosis of recent HEV infection is based on a positive result for IgM anti-HEV. A confirmed case of hepatitis E is a case of acute hepatitis that either meets the biomarker criteria or has an epidemiological link to a confirmed case (80). Molecular epidemiological techniques (e.g. viral sequence analysis) are used to determine whether cases have a common source of infection during outbreaks. However, as molecular assays are not commonly available, specimens may need to be sent to referral laboratories. Hepatitis E is highly endemic in many low- and middle-income countries, with large outbreaks and sustained sporadic transmission. In such countries, a well-functioning surveillance system can detect outbreaks and describe trends.

6.4.1. Detect outbreaks, monitor trends and describe risk factors

Surveillance must detect outbreaks through syndromic surveillance, event-based surveillance or surveillance for type-specific hepatitis. Syndromic surveillance detected several hepatitis E outbreaks in sub-Saharan Africa and South Asia (81). In outbreak settings, control efforts must include monitoring of water quality and sanitation (82). Analysis of hepatitis E surveillance data can provide information on trends over time, and rates by age and sex. Risk factor information is less informative as most cases are waterborne. If surveillance is conducted in the general population and the data can be linked with population denominators, rates by geographical area may allow mapping of hot spots. However, this may not be possible in the case of sentinel surveillance based in tertiary reference centres that have a complex catchment area. Reported cases of acute hepatitis E reflect ongoing transmission.

Case definition of hepatitis E^a

Clinical criteria: person meeting the case definition for acute hepatitis (*see* definition of acute hepatitis on page 24)

Biomarker criterion: positive for IgM anti-HEV

Epidemiological criterion: occurrence in the context of a biomarker-confirmed outbreak

Case classification:

Confirmed:

- a case of acute hepatitis that tests positive for the biomarker criterion mentioned above

OR

- a case of acute hepatitis with an epidemiological link to a confirmed case

6.4.2. Estimate the burden of chronic infection

Chronic hepatitis E has been reported in patients with immunosuppression, including organ transplant recipients (41). While this requires clinical management in a specialized setting, chronic hepatitis E does not require to be placed under public health surveillance as it affects only a small proportion of the population.

6.4.3. Estimate the burden of fulminant hepatitis

In countries where HEV infection is highly endemic, fulminant hepatic failure (73) secondary

to hepatitis E may be a source of concern. Such countries can establish sentinel surveillance for fulminant hepatic failure secondary to hepatitis E in health-care facilities that are likely to care for such patients. As hepatitis E is associated with high rates of maternal mortality, surveillance of jaundice-associated maternal mortality and collection of information regarding pregnancy among cases of acute hepatitis E may generate information that could help in identifying the possible role of hepatitis E vaccine in the future.

^a In the context of the investigation of an outbreak, WHO proposes additional suggestions for operational case definitions of hepatitis E (82).

7. USE OF SURVEILLANCE INFORMATION TO EVALUATE PROGRAMMES

Monitoring and evaluating the impact of viral hepatitis prevention, control and treatment programmes identify achievements, best practices, weaknesses and missed opportunities. Surveillance information on new infections, prevalent infections and sequelae all contribute to programme evaluation.

7.1. Prevention of new infections

Enhanced surveillance for type-specific acute hepatitis provides information on trends over time and risk factors for infection. This allows evaluation of programmes that aim to prevent new infections, including water safety, food safety, blood safety, condom distribution and use, harm reduction (83,84), injection safety (85) and infection control. Surveillance information on acute hepatitis has also been used to evaluate the impact of universal hepatitis A immunization (e.g. in Argentina (72)). However, as the use of hepatitis B vaccine is primarily directed at preventing chronic infection, which is asymptomatic, surveys using biomarkers to estimate the prevalence of chronic infection are mostly used for evaluation purposes (*see below*).

7.2. Use of estimates of the burden of chronic prevalent infection

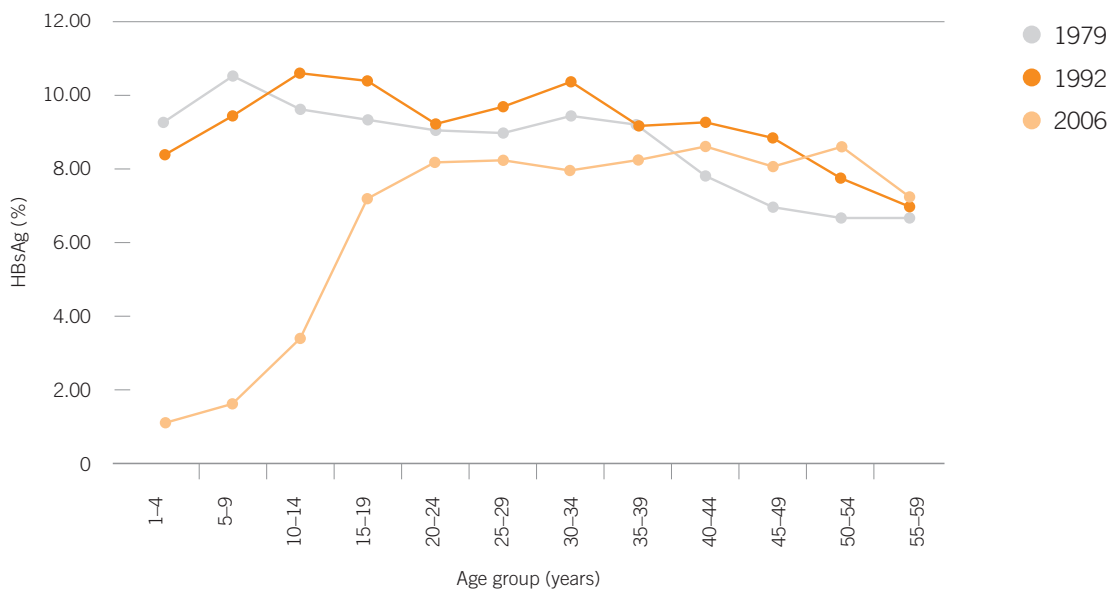
7.2.1. Experience in immunization

Almost all countries have introduced universal routine immunization of infants against hepatitis B (31,32). In addition, some WHO regions (Africa, the Western Pacific and Eastern Mediterranean) have a control goal that is based on the prevalence of HBsAg among children who benefited from universal immunization. Evaluation of universal immunization of infants against hepatitis B is based on surveys estimating the prevalence of chronic infection. Prevalence of HBsAg among children at least five years of age is used to monitor the impact of universal immunization (younger children have not gone through the time period during which they are at high risk of early childhood transmission that can lead to chronic liver disease in adulthood). The WHO Regional Office for the Western Pacific established a verification procedure to document national achievements in hepatitis B control, which requires implementation of at least one representative survey measuring HBsAg prevalence in cohorts born after the introduction of a national hepatitis B vaccination programme (86,87).

BOX 7. Repeated biomarker surveys in China document the baseline burden of hepatitis B, impact of universal immunization and residual burden of chronic HBV infection among adults (88)

China was highly endemic for HBV infection. In 1979, the prevalence of HBsAg in the general population was 9.8% among the population aged 1–59 years. In 1992, China introduced hepatitis B vaccination in the Expanded Programme on Immunization (EPI) with a first dose within 24 hours of birth. Transmission of HBV fell among cohorts that received the vaccine. In 2006, a new national biomarker survey documented that among persons under 15 years of age, the prevalence of HBsAg among vaccinated persons was 1.1%, compared with 5.4% among those who were unvaccinated (Fig. 3). In 2012, the WHO Regional Office for the Western Pacific officially reported that China had achieved the control goal of hepatitis B through universal immunization (prevalence below 1%). However, the 2006 survey that also included older age groups indicated that the prevalence of HBsAg remained high in age cohorts that had not been protected by infant immunization, underlining the need to address these prevalent chronic infections through testing and treatment.

FIGURE 3 Prevalence of HBsAg in China by age group in biomarker surveys conducted in 1979 and 2006



7.2.2. Emerging needs in the field of care and treatment

Several antiviral agents are available to treat chronic hepatitis B and C. Although treatment for hepatitis B is not curative, treatment for chronic hepatitis C results in cure in a large proportion of persons treated (89). The cost of treatment is rapidly decreasing in many low- and middle-income countries, and further progress is expected in the future. Thus, countries are increasingly considering approaches to testing and treatment. Data regarding access to hepatitis care and treatment can be obtained from other clinical and administrative databases. For instance, pharmacy prescription data can quantify the number of persons receiving antiviral therapy for hepatitis B and C (90). Data obtained from national biomarker

surveys on the estimated number of persons with chronic HBV or HCV infection can guide initial assessment of the number of persons needing treatment. The number of hepatitis tests conducted can be analysed over time to determine the number of persons tested for hepatitis and to determine trends in testing. As access to treatment is increasing, regular surveillance with biomarker surveys will document a reduction in the prevalence of chronic infection as a key outcome indicator.

7.3. Use of estimates of the burden of sequelae

Asian countries that introduced universal hepatitis B immunization more than twenty years ago have already used cancer registries to report that the rates of HCC have decreased in cohorts of children that were immunized (30). Similarly, with progress in care and treatment, surveillance for the proportion of cirrhosis and HCC attributable to chronic HBV and HCV coupled with cancer registries and mortality data will ultimately document an impact on specific mortality reduction.

8. ORGANIZING VIRAL HEPATITIS SURVEILLANCE

Viral hepatitis surveillance requires some understanding of the epidemiology of hepatitis (particularly to separate incidence of acute hepatitis from chronic infections that are prevalent) and support for in vitro diagnosis. Depending on the need for information, availability of technical and testing resources, and political commitment, hepatitis surveillance could be organized in a series of steps, starting with the highest-priority data needs.

The first priority is to make an inventory of the existing sources of data on viral hepatitis (e.g. blood donations, existing surveillance for acute hepatitis; see Data mining, Box 6, page 33). All countries usually have some system in place for surveillance of viral hepatitis. Building on what is already working well might be easier and less expensive than starting a new system.

The second priority is to make sure that there is an initial estimate of the prevalence of chronic HBV and HCV infection in the general population and/or in special populations, depending on the local epidemiology. If a reliable source of information has not been identified at step one, a survey may need to be planned. Coordination with other population-based surveys (DHS-plus, HIV) may optimize the costs of collecting key data at an affordable incremental cost.

The third priority is to examine what is in place in terms of surveillance for acute hepatitis to determine how it can be optimized (e.g. options in terms of implementation of surveillance for unspecified acute hepatitis, deciding to focus on sentinel sites for biomarker testing and collection of epidemiological information).

The fourth priority as more data become available is to implement surveillance for sequelae (i.e. chronic liver disease).

Surveillance for viral hepatitis must cover the different viruses and help inform a variety of questions. As such, those coordinating surveillance may draw on various data elements from existing surveillance systems and plan dedicated activities to collect data for hepatitis surveillance (e.g. hepatitis biomarker surveys). The amount of effort expended needs to match the priority questions in a country. WHO has published a manual for the development and assessment of national viral hepatitis plans (91). The initial assessment of this planning process identifies public health priorities and areas where more information is needed. Information needs may be addressed through studies or through surveillance. Once a country identifies the questions to be answered by surveillance, consideration must be given to the utility and feasibility of specific approaches, and the surveillance methods capable of answering these questions. The surveillance system that will serve the national hepatitis programme needs to be developed or improved in the context of the national plan.

8.1. Engaging stakeholders, including key populations

Stakeholders need to be identified and brought together before proposing developments or improvements in the field of surveillance. A stakeholder can be any person or organization that uses data for the promotion of healthy lifestyles and the prevention and control of disease. Agencies, organizations, foundations, public health practitioners, data providers and users, monitoring and evaluation officers, those who conduct population-based and other key surveys, government organizations at the national, subnational and district levels, and members of the affected communities may be considered as potential stakeholders. Among these stakeholders, public health officials need to identify the ones that will be key for surveillance activities so as to keep the working group at a manageable size (see Table 8).

Surveillance must generate information from key populations. This allows early detection of emerging epidemics in specific populations. Failure to do so may lead to high levels of transmission among key populations (e.g. PWID), which are difficult to control. Engaging key populations in the pre-surveillance process may help in generating this information and preventing discrimination or legal issues. (Activities that expose people to viral hepatitis may be stigmatized or illegal in some countries.)

TABLE 8. Stakeholders who should be involved in viral hepatitis surveillance^a

Types of stakeholders	Definition	Examples
Implementers	Those directly involved in the operations of hepatitis surveillance	<ul style="list-style-type: none"> • Chief of communicable diseases • Focal point for hepatitis • Surveillance officers • Persons involved in testing services (including laboratories)
Decision-makers	Those in a position to do or decide something about the viral hepatitis programme	<ul style="list-style-type: none"> • Chief of communicable diseases • Expanded Programme on Immunization (EPI) manager • HIV programme manager • Essential medicines manager • In vitro diagnostics programme manager (including representatives of the regulatory authorities for medicines and diagnostics) • Health-care service officials
Participants	Those being served or affected by the viral hepatitis surveillance and hepatitis programmes	<ul style="list-style-type: none"> • Representatives of populations at increased risk or burden • People living with viral hepatitis, including patient groups • Peers • Health-care workers (e.g. caregivers, clinicians) • Counsellors, social support persons • Nongovernmental organizations • Health educators • Ministry of Health officials • Donors and partners

^a Adapted from Salabarría-Peña Y, Apt BS, Walsh CM. Practical use of program evaluation among sexually transmitted disease (STD) programs. Atlanta (GA): Centers for Disease Control and Prevention; 2007 (<http://www.cdc.gov/std/program/pupestd/Step-1-SPREADS.pdf>, accessed 30 November 2015).

8.2. Assessing the situation

An assessment can examine barriers (e.g. policy-, legal-, systems-related) that could potentially impede surveillance. Although the assessment is to be conducted as part of the development of national viral hepatitis plans, the following questions may help in improving hepatitis surveillance:

- What are the key objectives of the viral hepatitis programme?
- What prevention and control activities will be most important to reach these objectives?
- What information will be needed to direct these prevention and control activities?
- Among those, what are the information elements that are currently not generated?
- What are the local and national resources for in vitro diagnosis?
- Is there a dedicated budget for surveillance?
- How will it be possible to improve surveillance through building on and integrating already existing activities (e.g. existing hepatitis surveillance, regular surveys already being conducted)?

If needed, a technical assessment of the existing surveillance system may help in this overall assessment (see section 12 “Evaluation of viral hepatitis surveillance”, page 59).

8.3. Integrating with other data sources, programmes and systems

Upon completion of the assessment, a plan to improve surveillance may be prepared, which builds upon existing surveillance activities and programmes. The following programmes and systems may be approached as partners (Table 9).

TABLE 9. Collaborations that may optimize viral hepatitis surveillance

Group to approach	Examples
National immunization programme (hepatitis A, hepatitis B)	<ul style="list-style-type: none"> • Acute hepatitis surveillance • Plans for surveys to evaluate the need for hepatitis A immunization or to evaluate universal hepatitis B immunization
HIV surveillance and programmes	<ul style="list-style-type: none"> • Engagement of key populations • Plans to include viral hepatitis biomarkers in HIV surveys • Coordination between HIV and viral hepatitis testing services
Blood transfusion safety	<ul style="list-style-type: none"> • Information on prevalence of chronic HBV /HCV infections among blood donors • In vitro diagnosis quality assurance
Injection safety	<ul style="list-style-type: none"> • Information on facility-level injection safety • Information on injection frequency in the population • Hepatitis B vaccine coverage among health-care workers
Harm reduction, and other services for drug use disorders, for PWID	<ul style="list-style-type: none"> • Data available on viral hepatitis among PWID • Harm reduction activities
Antenatal, maternal and child health, and maternal mortality initiatives	<ul style="list-style-type: none"> • Information on prevalence of chronic HBV infection among pregnant women • Information on HBsAg positivity among children born to HBsAg-positive mothers
Tertiary centres caring for acute hepatitis and end-stage liver disease (e.g. referral, testing, diagnosis and treatment)	<ul style="list-style-type: none"> • Disease outcome surveillance (cirrhosis, cancer registries)

HBsAg: hepatitis B surface antigen, HBV: hepatitis B virus, HCV: hepatitis C virus, PWID: people who inject drugs

9. CONSIDERATIONS FOR IN VITRO DIAGNOSIS

Patients' symptoms and signs cannot be used to distinguish acute from chronic hepatitis and/or the type of virus involved. Furthermore, chronic hepatitis is asymptomatic in most persons. Therefore, in vitro diagnostics are needed for the accurate diagnosis of type-specific hepatitis and to differentiate between acute hepatitis and chronic infection.^a Diagnosis of acute hepatitis requires testing for IgM antibodies and diagnosis of chronic HCV infection requires NAT. Some of these assays are not widely available.

9.1. Testing strategy

A testing strategy is a sequence of tests used in combination for in vitro diagnosis, with certain tests performed only if others are positive. Use of a testing strategy improves accuracy and reduces cost. NAT is usually done on a subset of specimens that are serologically reactive (antibody positive). This sequenced approach improves accuracy because the positive predictive value of NAT will be higher when the specimens are already serologically reactive (the prevalence will be higher in the subset of specimens). This sequenced approach also reduces the cost by reducing the number of specimens requiring the more expensive virological assays (92). For example, HBV NAT is best performed on specimens that are HBsAg positive. HCV NAT yields useful information when conducted in anti-HCV positive persons.

9.2. Quality assurance

9.2.1. In vitro diagnosis networks

Hepatitis testing using standard serological assays (such as enzyme immunoassay [EIA]) and virological assays requires a high level of technical competence. Planning in vitro diagnostic support for viral hepatitis surveillance requires an inventory of the capacity for in vitro diagnosis, from the national reference laboratory to the public health laboratories, clinical laboratories and other facilities that use rapid tests. In countries and settings with limited capacity for viral hepatitis testing, biomarker surveys may require support from a centralized laboratory location. In countries where adequate in vitro diagnostic support is widespread, surveillance data can be collected from more clinical laboratories, public health laboratories or facilities using rapid tests. Some clinical facilities may have the capacity to use sophisticated assays that are important for treatment decisions. Surveillance can take advantage of this laboratory capacity and work closely with such institutions.

^a For WHO recommendations on laboratory and diagnostic technology, see: http://www.who.int/diagnostics_laboratory/en/.

9.2.2. Assays

Numerous serological assays for the diagnosis of acute hepatitis A, B and E are available. However, the sensitivity and specificity of these tests vary (23,76,93). In high-income countries, approval by regulatory authorities, including founding members of the Global Harmonization Task Force (U.S. Food and Drug Administration, Health Canada, Therapeutic Goods Administration Australia, Ministry of Health, Labour and Welfare Japan, and the European Community) helps assure that assays meet quality and performance standards. However, substandard assays are sometimes marketed in countries where pre-market assessment is not available or not functional. WHO has a system for prequalification of in vitro diagnostics that provides a level of assurance for the safety, quality and performance of assays for viral hepatitis. However, the number of companies applying for WHO prequalification is limited because of a perceived lack of market. Hence, few hepatitis tests are WHO prequalified. As a result, assays primarily used in low- and middle-income countries (particularly rapid diagnostic tests [RDTs]) are often of unknown sensitivity and specificity. This poses a challenge to clinical diagnosis and surveillance. Registration and regulatory controls (both pre- and post-market) is a preliminary step to assessing a country's ability to accurately test for viral hepatitis.

9.2.3. Quality assurance

Laboratory QA encompasses a range of activities that enable laboratories to achieve and maintain high levels of accuracy and proficiency, despite changes in test methods and volume of specimens tested. Important elements of a quality management system include documentation, standard operating procedures (SOPs), quality control samples and external quality assessment schemes (EQAS) (94). Information on QA for in vitro diagnostics and laboratory technology is available from the WHO Internet site (95).

9.3. Testing considerations for case reporting

In routine case reporting, clinicians or laboratories report cases of hepatitis. Ideally, patients with signs and symptoms suggestive of acute viral hepatitis are offered a standard panel of hepatitis serological assays, which includes tests for hepatitis A, B and C. In some cases, hepatitis E testing is done automatically when the test results for hepatitis viruses A, B and C are negative (this is referred to as reflex testing). However, because standard panels of hepatitis serological assays are costly, this approach may not be feasible in some low-and middle-income countries. In these settings, providers usually take what is known as the “sequential approach” to testing, whereby serological testing is performed first for the most common type of hepatitis. If this test is negative, a test is done for the next most common type and so on. Although this approach is less costly, it can pose a problem to properly categorize surveillance cases as some case definitions require exclusion of other hepatitis diagnosis (e.g. biomarker criteria for acute hepatitis C) and dual infections occur (i.e. infections with more than one virus).

In countries where most persons with signs and symptoms of acute hepatitis seeking care receive diagnostic testing, surveillance for type-specific acute hepatitis can be widespread. In settings where testing is not frequently done or where reporting is unreliable, it is preferable to limit surveillance for type-specific acute viral hepatitis to sentinel sites that have good diagnostic support and to use syndromic surveillance elsewhere.

9.4. Testing considerations for biomarker surveys

Unlike viral hepatitis testing that is initiated by the provider on the basis of a patient's clinical presentation, hepatitis testing as part of biomarker surveys is done in a predefined population and follows a defined protocol to address specific questions. The testing strategy (i.e. sequence and type of test) and the testing algorithm (i.e. which specific assays to be used) are generally defined in the survey protocol and the testing algorithm. The selection of a testing strategy and the required resources are determined by the type of population to be surveyed, the maximal length of time required for the specimens to reach a laboratory (if applicable), the type (e.g. serum/plasma versus dried blood spot [DBS]) and volume of biological specimen to be collected, available laboratory capacity and resources, and the need to return results to survey participants.

9.5. Rapid diagnostic tests

RDTs provide same-day results and do not require complex equipment or advanced training. They can be performed outside of a traditional laboratory setting by persons without a laboratory background who have been trained to conduct the testing process using an RDT. The sensitivity and specificity of some of the latest generation of RDTs can be comparable to those of EIAs. However, the quality of assays is variable. A variety of RDTs are under evaluation and/or are currently in use in low- and middle-income countries for screening, diagnostic and surveillance purposes.

RDTs can be used in the setting of biomarker surveys, but their use is limited by multiple factors. Most RDTs provide information only on the virus type (e.g. HBsAg) that is included in the assay and thus do not allow for testing of other antigens/antibodies (even though RDTs with more than one analyte are being introduced). The results cannot be validated and additional testing (e.g. HBeAg or viral load testing after an HBsAg-positive result) cannot be done because no leftover specimen is available. However, RDTs require less technical competency and provide results within minutes. This facilitates the return of results during a single visit, which can be especially useful when conducting surveys among hard-to-reach populations (e.g. PWID).

9.6. Dried blood spot specimens

Collecting venous or capillary blood onto filter paper for dried blood spot (DBS) specimens provides another option for specimen collection and laboratory testing. This approach is technically easy and DBS can be stored for some time. DBS can be used to collect specimens in biomarker surveys. They are useful for confirming the diagnosis of acute hepatitis outbreaks in remote areas where in vitro diagnostics for hepatitis are not available (96). However, manufacturers of hepatitis B and C assays have not validated their assays for testing with DBS. Thus, test results cannot be returned to the study participant. Individuals wanting to know their hepatitis infection status would need to be referred for additional testing. While DBS specimens are widely used for the detection of HIV antibodies and RNA, these have not been validated either. Furthermore, use of DBS as a specimen has not been as fully developed for hepatitis testing due to rapid degradation of antigen (HBsAg), which results in false negativity. This lack of validated hepatitis testing on DBS was a barrier to integrating viral hepatitis testing into other surveys that employ this method of testing (e.g. DHS, AIS).

9.7. Testing stored specimens

Performing laboratory testing on stored specimens can be an efficient approach to gaining information about the prevalence of specific hepatitis biomarkers in a population. Before initiating this type of analysis, a number of issues must be addressed. First, the informed consent that was obtained initially needs to be reviewed to determine if it included the consent for additional testing (see section 10 “Ethical considerations”). Second, the protocol for specimen collection, storage and transport must be understood to make sure that the quality of specimens is adequate. Third, stored specimens are usually not linked with the epidemiological data of the survey. Addressing these issues will require coordination between the surveillance coordinator and the managers of the specimen repository (see section 10.5 “Linked and unlinked anonymous data”).

9.8. Molecular studies

Molecular studies can provide information on important characteristics, such as the stage of infection and the virus strains in a population, including viral load, genotype and presence of drug-resistance mutations. Molecular testing requires that specimens be collected in an appropriate manner and transported at a specified temperature. This requirement poses a challenge when these factors are not taken into consideration at the pre-implementation stage.

10. ETHICAL CONSIDERATIONS

Ethical considerations in surveillance need to find the right balance between the rights of an individual and the commitment to public well-being (97). Ethical principles guiding surveillance emanate from those of research involving human subjects where the primary concern is protecting the autonomy of the individual. Yet, governments also have an obligation to protect public health, and this requires the collection of information related to individuals' health. For example, a national law may authorize mandatory reporting of cases without the consent of the individual. These ethical issues must be addressed for the surveillance system to generate useful information while addressing human rights and ethical principles. Some routine surveillance activities such as case reporting operate in the context of the core functions of the health-care system and usually do not require ethical review as per national regulations. Thus, there is an additional obligation on those responsible for surveillance to take into considerations ethical principles. However, when regular biomarker surveys are used for surveillance, ethical review is likely to be required by national regulations and/or funding agencies. These relate primarily to (i) informed consent and autonomy, (ii) maximizing benefits, and (iii) reducing risks.

10.1. Key ethical principles for surveillance (97)

10.1.1. Informed consent and autonomy

- Obtain informed consent when collecting data in the context of activities that are not part of routine patient management or evaluation, such as during biomarker surveys.
- Protect confidentiality of data collected from subjects regarding their identifying information and the results of the testing.

10.1.2. Maximizing individual and community benefits

- Provide individuals with the results of their viral hepatitis tests in a context that will benefit their health and facilitate access to care and treatment when indicated.
- Provide known contacts with prevention services where feasible.
- Use the results of surveillance to support viral hepatitis prevention programmes and policies.

10.1.3. Reducing risks

- Ensure that confidentiality and ethical standards are upheld when surveillance data on viral hepatitis are linked to HIV management information systems. This is particularly important for persons who engage in behaviours that are stigmatized or illegal in the country (e.g. PWID, MSM, sex workers, transgender persons).
- Avoid reporting results of surveillance from small geographical units or small populations as it may be possible for the identity of the affected individuals to be known.

- Address additional safeguards that may apply to vulnerable populations (e.g. children, pregnant women, prisoners).

10.2. Security and confidentiality

The surveillance system must maximize the confidentiality of patient data. Surveillance staff who ensure confidentiality during data entry and processing will benefit from training in ethical and regulatory issues applied to surveillance. If identifying information (e.g. name, identification number and address) is necessary, it must be kept in a secure location. A unique identifier needs to be assigned to each case and used to replace personal identifying information in electronic data files. The code that connects unique identifiers to personal data needs to be kept in a secure place, separate from the data collection forms that include identifying information. It may be preferable to keep identifying information at the local level to follow up cases for referral to care and treatment. It is rarely necessary to keep identifying information at the national level. If identifying information is not used for linking to prevention or care, it should be destroyed. Data files containing personal information must not be stored on computer networks. If personal information is stored on a computer, the file must be password protected or encrypted. When linking epidemiological and behavioural data with biomarker data, special arrangements must be made to ensure that linked data are not inadvertently disclosed.

10.3. Informed consent

When data and specimens are collected in the context of medical care for diagnosis and treatment, surveillance systems do not require additional, specific consent procedures. However, informed consent is required when obtaining information or specimens that would not be routinely collected for diagnosis or treatment of patients (e.g. biomarker surveys). If additional specimens or information is collected for surveillance, the consent of the participant must be documented on a signed informed consent form. This form is used to provide the patient with a description of the information/specimen to be collected, explain intended use of the information/specimen, state the benefits and risks, and communicate that medical care will not be affected by participation or refusal to participate.

10.4. Returning test results to individuals

In general, persons who provide biological specimens should be given the opportunity to learn their test results and be referred for medical consultation where guidance would be provided regarding prevention (e.g. vaccination for hepatitis A and B when indicated), HIV testing (if indicated) and management, including counselling on treatment options. Participants in surveillance systems (including those in biomarker surveys) must be provided with the results of diagnostic tests. If positive for HBV or HCV infection, they should be referred for treatment and care, which includes HIV testing unless there is recent documentation of serological status (98).

Viral hepatitis biomarker surveys among populations at high risk for infection (e.g. MSM, PWID, dialysis patients and sex workers) are now being conducted in conjunction with HIV biomarker surveys. With this approach, persons will be offered testing for viral hepatitis along with HIV and they will receive their results. Viral hepatitis test results must be provided in the same manner as those for HIV. The core human rights ethics apply: Consent, Confidentiality, Counselling, Correct test results, and Connecting to care, treatment and prevention (98).

Coordinators of biomarker surveys need to identify the approach to making sure that the test results can be returned to individuals. They must consider the intrinsic characteristics of the test used and the expected prevalence to judge if the positive predictive value will be sufficient to allow return of results. If not, supplemental testing may be required. Results of assays conducted on DBS cannot be returned to the individual, as most serological and molecular assays are not validated with these kinds of specimens. The time span between specimen collection and availability of results needs to be anticipated, particularly for remote areas where communication is poor, and for mobile populations. If returning the results is challenging, participants must be offered alternative methods to access testing. RDTs may facilitate the return of results at the time the survey is conducted, as results are available within one hour of testing (98).

10.5. Linked and unlinked anonymous data

Because surveillance case definitions for viral hepatitis generally require both clinical and testing information, it is often necessary to link these data. Understanding morbidity and mortality patterns may also require obtaining information about comorbidities, resulting in linkage between the viral hepatitis surveillance system and other surveillance systems or sources of data. Linkages between databases are usually performed using personal identifying information. Personal identifying information needs to be replaced by a unique identifier after the data have been linked.

Unlinked (i.e. removal of identifying information) biological specimens may be used to estimate the prevalence of hepatitis in a given population if the individuals had given their consent at the time of the initial blood draw to have their specimens stored and analysed at a later date. For example, in the United Kingdom, the Unlinked Anonymous Prevalence Monitoring Programme estimated the prevalence of chronic HCV infection among PWID (62). However, in general, every effort must be made to return results to individuals.

11. MANAGING, ANALYSING AND COMMUNICATING VIRAL HEPATITIS SURVEILLANCE DATA

11.1. Managing data to ensure quality

The purpose of data management is to preserve data integrity between data collection and analysis and reporting. Public health decision-makers, clinical case reporters, and other health professionals require periodic summaries of analysed surveillance data accompanied by a concise interpretation.

Regular monitoring of surveillance data for quality, completeness and timeliness can identify specific aspects of surveillance and case investigation that need improvement.

- Completeness of surveillance data is assessed by estimating the frequency with which individual data elements are reported with non-missing data.
- The quality or validity of the data is measured by the proportion of each data element that is reported with a correct or valid value.
- Timeliness can be measured by estimating the average length of time required for each of the steps in the surveillance process.

The use of standardized indicators for completeness, quality or timeliness will facilitate interpretation and comparisons. The development of data quality indicators to measure the completeness of case investigation and follow-up activities (e.g. proportion of at-risk contacts immunized) might also be useful to track how surveillance data lead to prevention.

11.2. Analysing data

Data analysis consists of the transformation of raw data (e.g. dataset) into usable information (e.g. tables, graphs, maps). The type of data analysis will depend on the methodology used for data collection (e.g. national population-based survey, sentinel surveillance, etc.) and on the original objectives, aims and priorities of surveillance. For example, if Country A needs a baseline on the prevalence of chronic HBV and HCV infection among adults in the general population and a DHS is used as the survey method, then the appropriate analytical methods for population estimates will be used. Dummy tables prepared before data collection will help the data analysis process (see Table 10, page 68 and Table 11, page 68). Given the importance of in vitro diagnostics in viral hepatitis surveillance, the results of the analysis of surveillance data need to be interpreted in the context of the sensitivity and specificity of the in vitro diagnostic tests or the sequence in which they have been used (use of a sequence of tests may increase specificity).

11.3. Communicating results

Communication of surveillance information must facilitate public health action (e.g. communication of the results of an outbreak investigation to implement prevention measures). Before preparing any report, one needs to identify the target audience and what is expected from the target audience on reading the report. Understanding current issues, trends in the specific indicators, and differences in the data by key sociodemographic indicators will help frame the message. The content can then be communicated and disseminated with supporting facts, figures, tables and graphs.

Health officials may want to consider developing specialized communications for dissemination of annual reports to different audiences, including civil society. These communications might also include reports to data providers identifying providers' specific contribution to surveillance efforts, and newsletters or bulletins that provide concise data interpretation and advice to clinicians and laboratory directors. Press releases/reports can be developed for the general public. In addition to dissemination via the print media, other dissemination mechanisms such as the Internet should be explored. The regular (at least quarterly) provision of summarized surveillance data can be useful to local, subnational and national ministries of health in monitoring the reporting of cases and in providing feedback to health officials and other stakeholders.

11.4. Engaging stakeholders with surveillance information

Stakeholders that have been engaged at the stage of the organization of viral hepatitis surveillance need feedback once the results are available. This may require the use of adapted content and media. Table 8, page 48 provides an example of the types of stakeholders to include in the dissemination of results to ensure that the engagement obtained to implement surveillance is sustained in the long term.

12. EVALUATION OF VIRAL HEPATITIS SURVEILLANCE

12.1. Attributes of surveillance systems (99)

Evaluation of public health surveillance examines certain attributes, including (1) simplicity, (2) flexibility, (3) data quality, (4) acceptability, (5) sensitivity, (6) positive predictive value, (7) representativeness, (8) timeliness, (9) stability and (10) cost. Because public health surveillance systems vary in methods, scope, purpose and objectives, attributes that are important to one system might be less important to another. Efforts to improve certain attributes (e.g. sensitivity, the ability of a public health surveillance system to detect health events) might negatively affect other attributes (e.g. simplicity or timeliness). Surveillance evaluation must therefore prioritize those attributes that are of the highest priority for the system to reach its objectives.

12.2. Key attributes of viral hepatitis surveillance

12.2.1. Timeliness

To ensure that outbreaks of acute hepatitis are investigated in time, syndromic surveillance for acute hepatitis needs to be timely. Event-based surveillance may improve timeliness. Indicators of timeliness may include the time interval between onset and reporting (individual case reporting), and time interval between the beginning of an outbreak and the reporting date (event-based surveillance). Aside from the need for timeliness for outbreak detection, most issues in viral hepatitis surveillance can be addressed through an annual in-depth report and do not require more frequent analyses.

12.2.2. Positive predictive value

In surveillance, the positive predictive value is the proportion of reported cases that actually have the health-related event under surveillance (100). This is critical to viral hepatitis surveillance as (1) case reporting may not distinguish between acute and chronic cases, and (2) case definitions rely heavily on in vitro diagnosis that may be difficult to obtain. The positive predictive value is calculated by dividing the number of reported cases that are confirmed to be real cases (for instance, after a validation study) by the total number of reported cases (101).

12.2.3. Representativeness

To accurately represent risk factors for acute hepatitis and prevalence across different populations, viral hepatitis surveillance requires representativeness. Nevertheless, if the main objective is to monitor incidence or prevalence trends over time, sentinel groups drawn from high- or low-risk populations may be preferred over samples representative of the general population. There is no formal indicator of representativeness. Representativeness may be assessed through comparing information generated using surveillance data with information from validation studies or special surveys.

12.2.4. Sensitivity

The sensitivity of a surveillance system can be considered on two levels. First, at the level of case reporting, sensitivity is the proportion of cases of a disease or health condition detected by the surveillance system. Second, sensitivity may be considered at the level of events as, for example, outbreaks. Underreporting and low sensitivity is often a cause of concern in viral hepatitis surveillance. In the United States, an evaluation of the national case-reporting surveillance for hepatitis C noted that 22% of cases were not reported and that 60% of reported cases lacked information about risk factors (100). In addition, many new infections with the hepatitis viruses are asymptomatic and go unrecognized. However, the ability to identify each and every case is less critical for viral hepatitis than for diseases targeted by eradication (e.g. polio) or those for which control of secondary transmission is key (e.g. tuberculosis). Hence, information that is useful for viral hepatitis surveillance, particularly for monitoring trends in incidence or prevalence over time, may be generated with a fraction of all cases, as long as this fraction is estimated and stable over time. Evaluating sensitivity (the proportion of all cases that are captured by surveillance) may also be complex, and involve special studies. One approach is to divide the number of reported cases by the estimated number of clinical acute hepatitis cases calculated using modelling techniques (102).

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ANNEX 1. Template case report form for acute or chronic viral hepatitis^a

General characteristics – identification						
Date of reporting:	/	/	ID:			
Last name:			District:			
First name:			Address:			
Date of birth:	/	/	Phone:			
Country of birth			Gender:	Male	Female	Transgender
Clinical characteristics, testing circumstances and biomarkers						
Clinical characteristics and testing circumstances			Biomarkers			
Clinical diagnosis	Acute	Chronic	Alanine aminotransferase (ALT):			IU/ litre
Acute onset	Yes	No	Anti-HAV IgM	Pos	Neg	Unknown
If acute hepatitis, onset date:	/	/	Anti-HBc IgM	Pos	Neg	Unknown
Systematic testing	Yes	No	HBsAg	Pos	Neg	Unknown
History of chronic hepatitis	Yes	No	Anti-HCV	Pos	Neg	Unknown
Hospitalization for hepatitis	Yes	No	HCV RNA	Pos	Neg	Unknown
Jaundice	Yes	No	HCV core Ag	Pos	Neg	Unknown
Death	Yes	No	HCV genotype			
Date of death	/	/	Anti-HEV IgM	Pos	Neg	Unknown
Prior diagnosis and treatment history						
Previously identified with chronic HBV infection				Yes	No	Unknown
Previously identified with chronic HCV infection				Yes	No	Unknown
Hepatitis vaccination history						
Has the person ever received at least one dose of hepatitis A vaccine?				Yes (___ doses)	No	
Has the person ever received at least one dose of hepatitis B vaccine?				Yes (___ doses)	No	
Has the person ever received at least one dose of combined hepatitis A and B vaccine?				Yes (___ doses)	No	
General exposures						
Is the person a health-care worker exposed to blood through patient care?				Yes	No	Unknown
Is the person a man who has sex with other men?				Yes	No	Unknown
Does the person undergo chronic haemodialysis?				Yes	No	Unknown
Does the person inject recreational drugs?				Yes	No	Unknown
Is the person involved in a reported, identified outbreak?				Yes	No	Unknown
Possible exposures in the 2–6 weeks before onset (acute hepatitis only)						
Was there contact with patient(s) with the same symptoms?				Yes	No	Unknown
Did the person eat raw, uncooked shellfish?				Yes	No	Unknown
Did the person drink water from a well or other unsafe water source?				Yes	No	Unknown
Is the person a child or a staff member in a day-care centre?				Yes	No	Unknown
Did the person travel to an area highly endemic for hepatitis A?				Yes	No	Unknown
Possible exposures in the 1–6 months before onset (acute hepatitis only)						
Did the person receive injections in a health-care setting?				Yes	No	Unknown
Was the person hospitalized?				Yes	No	Unknown
Did the person undergo surgery?				Yes	No	Unknown
Did the person receive a blood transfusion?				Yes	No	Unknown
Did the person go to the dentist?				Yes	No	Unknown
Was there sexual contact with someone with hepatitis B?				Yes	No	Unknown
Was there household contact with someone with hepatitis B?				Yes	No	Unknown
Was there unprotected sex with non-regular partner(s)?				Yes	No	Unknown

Ag: antigen, anti-HAV: antibody against hepatitis A virus, anti-HBc: antibody against hepatitis B core antigen, anti-HCV: antibody against hepatitis C virus, anti-HEV: antibody against hepatitis E virus, HBsAg: hepatitis B surface antigen, Ig: immunoglobulin, RNA: ribonucleic acid

^a Information must be collected on risk factors for all cases of acute hepatitis for the 2–6 weeks and 1–6 months referent exposure period. Acute hepatitis A/E cases can then be used as controls for acute hepatitis B/C and vice versa.

ANNEX 2. Dummy tables

TABLE 10. Dummy table shell for the analysis of enhanced surveillance for acute viral hepatitis: characteristics of acute cases of hepatitis A, E, B and C among persons XX–XX years of age, location, 20XX^a

Reported characteristics		Hepatitis A (N=XXX)		Acute hepatitis E (N=XXX)		Acute hepatitis B (N=XXX)		Acute hepatitis C (N=XXX)	
		#/Total	%	#/Total	%	#/Total	%	#/Total	%
General exposures	Health-care worker	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Man who has sex with other men	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Chronic haemodialysis	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Injection of recreational drugs	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
2–6 weeks prior to onset	Contact with another patient with same symptoms	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Raw shellfish consumption	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Consumption of water from unsafe sources	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Attendance at a day-care centre	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Travel to high-endemicity areas	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
1–6 months prior to onset	Received an injection/IV infusion	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Hospitalized	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Surgery	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Blood transfusion	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Dental care	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Sexual contact with someone with hepatitis B	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Household contact with someone with hepatitis B	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Unprotected sex with occasional partner	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%

^a Reported risk factors for HAV, HBV, HCV and HEV infection in bold. However, collection of data on all risk factors from all case-patients allows generation of hypotheses through use of reference groups (e.g. acute hepatitis A cases function as a reference group for acute hepatitis C cases to explore the association between dental care and HCV infection).

TABLE 11. Dummy table shell for the analysis of a viral hepatitis biomarker survey, location, 20XX^a

Characteristics		Hepatitis B				Hepatitis C			
		Serological evidence of past or present HBV infection (anti-HBc +) (N=XXX)		Chronic HBV infection (HBsAg +) (N=XXX)		Serological evidence of past or present HCV infection (anti-HCV+) (N=XXX)		Chronic HCV infection (HCV RNA +) (N=XXX)	
		#/Total	%	#/Total	%	#/Total	%	#/Total	%
Age (years)	0–14	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	15–29	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	30–59	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	60+	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
Sex	Male	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Female	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
Regions	North	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	East	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	South	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	West	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Centre	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
Specific populations	PWID	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	MSM	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%
	Prisoners	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%	XXX/XXX	XX%

anti-HBc: antibody against hepatitis B core antigen, anti-HCV: antibody against hepatitis C virus, HBV: hepatitis B virus, HCV: hepatitis C virus, MSM: men who have sex with men, PWID: people who inject drugs, RNA: ribonucleic acid

^a Age groups, geographical area and/or specific population would need to be defined on the basis of the local epidemic.

Viral hepatitis is a global public health problem of epidemic proportions. Unfortunately, many countries do not have the epidemiological information needed to plan, implement, monitor, evaluate and update national strategies for prevention and control. These technical considerations aim at optimizing viral hepatitis surveillance to generate information that can effectively direct policies. They explain that viral hepatitis surveillance can have three main purposes:

1. Detect outbreaks, monitor trends in incidence and identify risk factors for new, incident infections;
2. Estimate the prevalence of chronic infections and monitor trends in sentinel groups;
3. Estimate the burden of sequelae of chronic hepatitis, including cirrhosis, liver failure and hepatocellular carcinoma.

This document also provides case definitions for viral hepatitis surveillance, including case definitions for:

- Unspecified acute hepatitis defined on the basis of clinical signs and symptoms;
- Confirmed, type-specific viral hepatitis defined on the basis of clinical and biomarker criteria, including case definitions for hepatitis A, acute hepatitis B, chronic hepatitis B virus infection, acute hepatitis C, serological evidence of past or present hepatitis C virus (HCV) infection, chronic HCV infection and acute hepatitis E

Feedback and suggestions for improvement may be sent to: hepatitis@who.int.

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