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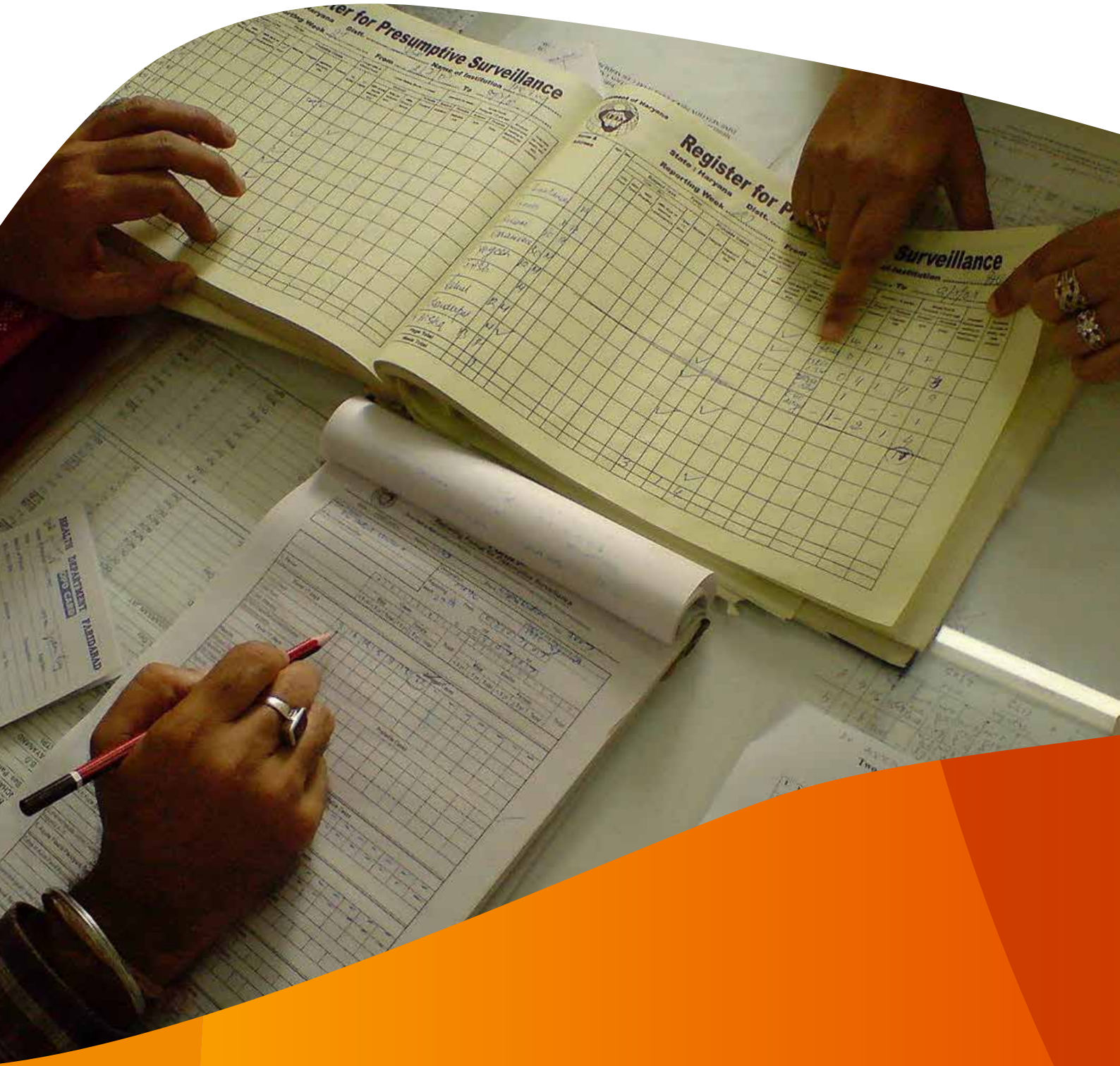

TECHNICAL CONSIDERATIONS AND CASE DEFINITIONS TO IMPROVE SURVEILLANCE FOR VIRAL HEPATITIS

POLICY BRIEF

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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

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

1. **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.

2. **Similar clinical presentation:** the symptoms and signs of acute and chronic viral hepatitides 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.

3. **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.

4. **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 9)

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. 10). 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 anepidemiological 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