World Health Organization

# Web Annex 1. Standard operating procedures (SOPs) for enhanced reporting of cases of acute hepatitis

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

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# STANDARD OPERATING PROCEDURES (SOPS)

# FOR ENHANCED REPORTING OF CASES OF ACUTE HEPATITIS

## CONTENTS

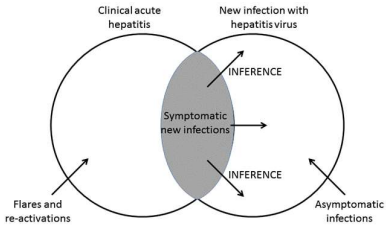
# BACKGROUND

## Information on acute viral hepatitis provides information on incidence

WHO recommends an approach to viral hepatitis surveillance that examines: (1) acute hepatitis, which provides information on new infections, (2) prevalence of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, and (3) mortality from the sequelae, including cirrhosis and hepatocellular carcinoma *(1)*. Reduction in the incidence of HBV and HCV infections is one of the two criteria that the Global Health Sector Strategy (GHSS) on viral hepatitis, 2016–2021 uses to define elimination of hepatitis as a public health threat *(2)*. Hence, countries require methods to measure the incidence of HBV and HCV infection and to identify the risk factors that may be associated with new infections. Surveillance for acute hepatitis is traditionally implemented in the context of communicable disease surveillance systems.

The majority of new infections with HBV or HCV are asymptomatic (50–70% and >80%, respectively) *(1)*. Among symptomatic infections, many remain undiagnosed. The symptoms are not specific, patients do not seek health care and laboratory investigations are not done *(3)*. However, capturing the fraction of new infections that are symptomatic and diagnosed through surveillance for acute hepatitis can be informative. These reported cases of acute hepatitis provide information on new infections. When the proportion of reported cases of acute hepatitis is constant over time, these reported rates can inform trends in new infections (Fig. 1). Even if most new infections are asymptomatic, capturing those cases that are symptomatic is the only way to understand new infections in the community.

**Fig. 1. Relationship between acute hepatitis and new infections***




Clinical acute hepatitis can also be a manifestation of flares or reactivation of chronic HBV infection (Fig. 1). Flares and reactivation are associated with chronic infections and they do not reflect new infections. Surveillance for acute hepatitis that does not exclude chronic infections lacks specificity. Surveillance for acute hepatitis differs from the reporting of newly diagnosed cases of chronic infections, which should be handled through patients' registries, separately from systems that report acute hepatitis. Reporting of cases of acute hepatitis is done for a different objective, which is to contribute to the estimation of incidence and identify risk factors for new infections. Confirmed acute hepatitis case definitions that combine clinical signs and symptoms of acute hepatitis and biomarker criteria increase specificity and ensure that chronic infections are excluded.

WHO has formulated standardized case definitions for surveillance of acute hepatitis *(1)*. In the field of surveillance for acute hepatitis, two different activities need to be distinguished: syndromic surveillance and enhanced case reporting. Syndromic surveillance and enhanced case reporting are complementary and address different objectives *(4,5)*.

## Syndromic surveillance for acute hepatitis documents outbreaks

Syndromic surveillance for undifferentiated acute viral hepatitis involves reporting by all health-care facilities of clinical cases of acute hepatitis in the absence of in-vitro diagnosis. This type of surveillance cannot

* Clinical acute hepatitis can be secondary to new infections or flares of chronic HBV infection. Ideally, surveillance for acute hepatitis would attempt to capture acute, new infections that provide information on all new infections.

distinguish between the various types of hepatitis viruses causing the infection (A, B, C, D or E) and may also capture flares and reactivations. Syndromic surveillance detects outbreaks, which in most circumstances are likely to be due to hepatitis A virus (HAV) or hepatitis E virus (HEV). Acute infections with the hepatitis B, D and C viruses are largely asymptomatic (especially HCV) and less commonly result in outbreaks. Because it mostly captures outbreaks of hepatitis A and acute hepatitis E, syndromic surveillance for undifferentiated acute viral hepatitis is not essential for the elimination of viral hepatitis as a public health threat (most of the burden from viral hepatitis is associated with chronic HBV and HCV infection) *(2)*.

### Enhanced case reporting documents trends and identifies risk factors for infection

Enhanced case reporting involves reporting by health-care facilities of cases of acute hepatitis by type (i.e. A, B, C, D or E), with in-vitro diagnosis (i.e. immunoglobulin [Ig]M tests) and collection of information of possible exposure. Cases of acute hepatitis are uniquely informative as they denote recent infection. Collection of information on possible exposure during the referent exposure period (or the incubation period) informs on the possible routes of transmission. Enhanced case reporting allows a description of trends in type-specific acute hepatitis and contributes to the generation of hypotheses regarding common risk factors in a given setting.

Enhanced case reporting may be difficult to implement countrywide when resources are limited. It is labour intensive to interview patients who meet case definitions. It requires adequate public health infrastructure. Countrywide enhanced case reporting is mostly limited to high-income countries. For example, in the United States of America, the Viral Hepatitis Surveillance Program has been collecting information on serologically confirmed cases of acute viral hepatitis nationwide (A, B and C), including a one-page questionnaire on potential risk factors (similar to the one provided in Table 1). In addition, in the United States of America, enhanced case reporting in sentinel counties provided additional information with a longer questionnaire *(6,7,8,9,10,11)*. A number of countries of the European Union also implement enhanced case reporting on a large scale for HBV and HCV *(12,13)*. If enhanced case reporting is in place countrywide, it is often implemented in the context of the communicable disease surveillance system rather than in clinical centres of excellence.

In resource-limited settings, enhanced case reporting can be done only in sentinel sites where there is access to good in-vitro diagnostics (e.g. emergency departments) and human resources to conduct case investigations. Over the years, Egypt has acquired considerable experience in sentinel enhanced case reporting of acute hepatitis *(14,15,16,17)*. In low- and middle-income countries, national health officials can choose sentinel sites for enhanced case reporting of acute hepatitis, as in Mongolia, for hepatitis A, B, C and D *(18)*. In India, enhanced case reporting has been used successfully to describe the epidemiology of acute hepatitis B and C *(19)*.The draft standard operating procedures (SOPs) in this document outline the key elements by which these sentinel sites can function. A sentinel surveillance system should be centred at sites (health care facilities) where most persons from the community presenting with acute hepatitis would seek care. Sites where patients are routinely tested for chronic infection are not a good choice as the probability of capturing acute hepatitis would be low. Enhanced case reporting at sentinel sites also differs from monitoring specific populations for asymptomatic seroconversion through regular testing (e.g. haemodialysis patients), as it aims to recruit cases of acute hepatitis in the community.

## OVERALL GOAL

- Guide ministries of health on technical approaches to acute hepatitis surveillance.

## OBJECTIVES

The objectives of these SOPs are:

- to describe enhanced case reporting of acute viral hepatitis for sites that are considered for implementation of sentinel surveillance by the Ministry of Health;
- to provide technical guidance to differentiate between acute and chronic hepatitis for enhanced case reporting.

## CRITERIA FOR SELECTING A SITE

Three criteria need to be fulfilled for a site to be selected for enhanced case reporting:

1. the capacity to perform in-vitro diagnosis (IgM biomarker testing) for acute viral hepatitis with quality assurance;
2. access to persons presenting with acute hepatitis;
3. access to human resources who can conduct interviews.

Because each country varies in terms of health-care-seeking behaviour, access to in-vitro diagnosis and staffing, the sentinel sites chosen will vary from country to country (e.g. outpatient clinic, emergency department, hospital inpatient departments and primary care facilities). Persons with signs and symptoms of acute hepatitis should be captured wherever they present themselves and wherever the diagnostic capacity is available. Health-care facilities that receive many patients with acute hepatitis should be prioritized. Countries are best placed to make decisions on where this would happen on the basis of their context.

## PROCEDURES

### Population under surveillance

The population under surveillance constitutes persons presenting with signs and symptoms of acute hepatitis at sentinel sites. Sentinel sites are a subset of health-care facilities that meet the criteria defined above.

### Operational definitions

Acute hepatitis is defined using WHO case definitions (Table 2) *(1)*.

#### *Presumptive case definition*

The presumptive case definition of acute hepatitis is based mostly on clinical criteria. The presumptive case definition may or may not include the criteria of raised alanine aminotransferase (ALT). However, in the context of enhanced case reporting, the requirement of raised ALT for the case definition will improve specificity. Ten times the upper limit of normal (400 IU/L) is the threshold used by the United States' State and Territorial Epidemiologists (CSTE) for the case definition of acute hepatitis. It is aimed at higher specificity and excluding chronic hepatitis. However, countries may also select lower (more sensitive) or higher (more specific) thresholds.

#### *Confirmed case definition*

The confirmed case definition of acute hepatitis by type is based on the combination of the presumptive case definition and biomarker criteria.

### Sampling procedure

Cases of acute hepatitis (as per the WHO definition) presenting at participating health-care facilities will be consecutively invited to participate in the surveillance activity on an ongoing basis, without restriction.

### Sample size considerations

These SOPs are for ongoing surveillance and not for ad-hoc research studies. However, sample size considerations are useful for estimating the minimum number of persons to be included in an analysis in

order to have sufficient statistical power. An estimated frequency of exposure of about 10% with 5% absolute precision among acute hepatitis case-patients would require 139 patients for each type of hepatitis considered (e.g. hepatitis A, acute hepatitis E) over one year for a 95% confidence interval (no design effect). As a first approximation, one centre should aim for at least 500 cases of acute hepatitis to run an analysis. However, this sample size reference is only an inspirational target. Each sentinel site would analyse whatever data they get and interpret the results in the context of appropriate power calculations. Ideally, sentinel surveillance should be institutionalized and implemented in the long term. Sample size considerations are most relevant for interpreting negative results in the analysis. In addition, in a given country, data from multiple sentinel sites could be aggregated to increase the sample size.

## Data collection

Each patient meeting the presumptive case definition of acute hepatitis will undergo in-vitro diagnosis (biomarker testing and ALT estimation). Information on risk factors will also be collected using the one-page questionnaire (Table 1, adapted from the WHO Technical considerations document) *(1)*.

## In-vitro diagnosis

### *Testing strategies*

For each case of presumptive acute hepatitis, a blood specimen will be collected and tested for hepatitis biomarkers, using a national standard diagnosis strategy. Two options could be considered for this testing strategy:

- **Simultaneous testing** of all case-patients of acute hepatitis for all biomarkers of recent infection at once. If this approach is chosen, all case-patients will be tested for IgM antibodies to HAV (IgM anti-HAV) and hepatitis B core antigen (IgM anti-HBc), antibodies to HCV (anti-HCV) and IgM antibodies to HEV (IgM anti-HEV).
- **Sequential testing** of all case-patients of acute hepatitis, starting with markers of the common causes of acute hepatitis (e.g. IgM anti-HAV in a country with intermediate HAV endemicity where acute hepatitis A may be the most common cause of acute hepatitis *(20)*) to finish with the markers of less common causes of acute hepatitis (e.g. IgM anti-HBc).

Simultaneous testing would be ideal because the opportunity to detect other types of viral hepatitis or coinfection would not be missed. However, sequential testing tends to be cheaper. The test should be performed free of charge for the patient. If biomarker testing is not provided free of charge to the patient as part of the health-care system in the country, investigators at the sentinel site will need to allocate funds for biomarker testing. For each test included in the testing strategy, national SOPs will recommend a specific algorithm, listing a limited set of test kits that are approved for use in the country of implementation on the basis of sufficient sensitivity and specificity. The working case definition of acute HCV infection as a non-A, non-B, non-E acute hepatitis that is positive for biomarkers of HCV infection, albeit imperfect, documents trends in new HCV infections. In the United States, for example, the use of this case definition was instrumental in detecting the recent outbreak of HCV infection associated with injection drug use after years of decrease in the reported rates *(10)*.

### *Biomarkers used in selected countries*

In some countries, additional biomarkers that are not included in the reference WHO case definition may be in routine use. This can include, for instance, fecal specimens for the diagnosis of HAV or HEV infection, IgG HEV, IgA HEV and HEV RNA. In the absence of serological tests approved by the US Food and Drug Administration (FDA) for the diagnosis of HEV infection, the methods used to diagnose acute HEV infection differ from country to country. While each country can use their own diagnostic test as per the national case definition and/or the national guidelines, the use of standard diagnostic algorithms as per the WHO reference case definition will

facilitate international comparisons. Each country can adapt or modify these present SOPs and use two definitions along with conducting two analyses to reflect the national and WHO standards. Testing a patient with acute hepatitis for hepatitis D virus (HDV) infection may not be relevant in non-endemic countries. However, in countries highly endemic for HDV infection, testing for HDV infection should be considered.

## Analysis plan

### *Inclusion and exclusion of cases*

At each sentinel site, investigators will include only cases confirmed with biomarker testing. Enhanced case reporting requires the highest level of specificity to exclude chronic infections that are more prevalent in the community. Undifferentiated cases of acute hepatitis (e.g. case-patients that meet the case definition of presumptive acute hepatitis and test negative for biomarkers) will be excluded from the analysis.

### *Data management*

Patients will be deduplicated so that they are counted only once. This will be done through the use of confidential identifiers or codes on the data collection forms. Using a hospital ID or the national ID can help the deduplication process and protect confidentiality. Using a label with the ID is better to avoid mistakes in entering the ID number manually and should be used also on the patient specimen. The initial interview will screen for prior participation to avoid duplication. The only instance where patients could be included twice in the database would be instances of patients who have had two episodes of acute hepatitis caused by two separate exposures (e.g. HAV infection followed by acute HBV infection, or reinfection with HCV in persons at risk of this). The database will stay at the sentinel site, where it will be maintained and not shared with anyone. Only aggregated results will be shared as per the regular data transmission protocol.

### *Data analysis*

The regular analysis will consider:

- the trends in the number of cases by age, sex and place of residence over time (the rate will be calculated if the sentinel site can be linked to a clear, finite reference population);
- the proportion of patients who are exposed to potential risk factors for acute hepatitis A, B, C and E (Table 3).

Collection of data on all risk factors from all patients meeting the case definitions will allow generation of hypotheses regarding modes of transmission. This will be done, for instance, by comparing cases of confirmed acute hepatitis B or C with confirmed cases of hepatitis A in terms of frequency of various exposures of interest, such as nosocomial exposure. This will, however, not constitute a formal control group for a case–control study. Such case–control studies would provide scope for research rather than surveillance.

## Data transmission

### *National level*

Data as analysed will be transmitted on an annual basis to the national hepatitis control programme of the Ministry of Health for interpretation and action.

### International level

WHO will organize the transmission of data from the Ministry of Health to WHO so that trends in new cases of acute hepatitis can be analysed at the international level.

## PROTECTION OF HUMAN SUBJECTS

This project is about setting up a new surveillance system *(21)*. Surveillance for acute hepatitis is one of the three pillars of a national surveillance system for hepatitis, as proposed by WHO *(1)*. It does not consist of research as defined, in the sense that it will not generate generalizable results. For example, results from one country would not apply to another. The protocol would not involve additional data gathering for public health monitoring (e.g. serum specimens would not be kept after testing). However, investigators will take care to protect human subjects, as explained below.

### Maximizing benefit

Patients will benefit from this project by receiving an accurate diagnosis for their disease, along with necessary counselling, as part of routine health care. If the country has chosen to implement sentinel rather than nationwide surveillance, all health-care facilities in the country may not be able to have access to this type of diagnosis.

#### *Assessment for acute liver failure*

As part of the SOPs, patients will be assessed for the potential to develop acute liver failure (Appendix 2). Diagnosing a patient with acute hepatitis provides an opportunity to advise the patient on how to avoid increasing the risk of acute liver failure, such as taking some medications that could be harmful for the liver and when to seek referral for hospitalization.

#### *Diagnosis of the virus involved*

Identification of the virus involved or of the risk factors for infection may benefit patients and their contacts through the implementation of control measures to prevent secondary spread, as per the standards of care in the country of implementation (e.g. administration of hepatitis A or hepatitis B vaccine to the household contacts of a person with hepatitis A or hepatitis B). After data analysis, identification of risk factors for infection will direct better prevention interventions that would benefit society as a whole. All subjects approached for participation will be able to benefit from biomarker testing, whether or not they agree to participate and share the data.

#### *Follow up of patients*

Patients with acute hepatitis B or C will be advised follow up to determine if they progress to chronic infection. Acute hepatitis C patients who do not clear the virus at 6 months would be eligible for treatment. Hepatitis A does not become chronic, while hepatitis E becomes chronic only in patients with immune deficiency.

### Minimizing harm

#### *Standards of care*

The collection of data (i.e. for possible risks factors) and specimens (i.e. for biomarkers of recent infection) in centres where enhanced case reporting will be implemented would be limited to interventions that constitute standard medical and public health practice (even though some patients may find it difficult to access this diagnosis outside of the sentinel site because of the cost involved). No additional procedures or investigations will be done. The systematic collection of data on possible risk factors and recording of information on a questionnaire is an additional feature of the surveillance system. In routine medical care, the clinician may ask only about a few risk factors in a non-systematic fashion.

#### *Confidentiality*

The name of the patient and the identifier will be written on the form and kept in the medical records. Keeping the information in paper form with the identifiers will be necessary for follow up on the contacts of the patient.

However, no personal identifiers will be entered in any computer. A unique identifier code will be used instead, and the link between personal identifiers and identifier code will be kept securely. The local investigators will keep the list of identifier codes in a secure manner (e.g. under lock and key or on a high-security computer). This list would be filed in a restricted location on a password-protected computer.

### Informed consent

#### *Information sheet*

The procedure for collecting information and blood specimens will be part of routine medical care and public health intervention for patients with acute hepatitis. Information and specimen collection will be limited to what is required for enhanced case reporting. All patients included in enhanced case reporting will be informed through an information sheet that the centre is participating in the surveillance activity. This information sheet will explain that this surveillance is based on (a) routine clinical care, and (b) standard public health practice to prevent secondary spread. The information sheet will also explain that the objectives of enhanced case reporting are to find out the viruses involved in causing acute hepatitis and to identify the modes of transmission. It will specify that on the basis of these results, health officials will be able to conduct interventions to stop transmission and that the Ministry of Health could improve plans to respond to hepatitis. It will mention that the information will be used anonymously for surveillance after removal of all identifiers (Appendix 1). The information sheet will fulfil the following conditions:

1) Patients need to be aware of its existence.
2) Sufficient information needs to be provided.
3) Patients need to be informed that they can withdraw their data.
4) Patients must be offered a genuine possibility to refuse to participate.

The clinicians involved in patient care will have no role in introducing the project to patients at the local sites. This will be done by dedicated investigators.

#### *Opt-out process*

An opt-out process will be explained in the information sheet. If a subject does not agree to be included in this project, they can benefit from the opt-out process and be excluded from enhanced case reporting. Subjects who prefer not to participate will still benefit from biomarker testing free of charge.

#### *Ethics clearance*

The project consists of surveillance activities using data collected as part of routine clinical care and routine public health operations. Hence, it may or may not be eligible for ethics committee clearance. However, it will be submitted to the national and WHO ethics committees to determine if a full review, an expedited review or an exception applies. As these SOPs are eligible for WHO ethics committee review, future projects to implement these SOPs with financial or technical support from WHO will require a subsequent review of the national protocol by the national ethics committee and the WHO ethics committee.

## EXPECTED OUTPUT

- Trends in acute hepatitis by type, by centre, and by age and sex
- Comparison of the various types of acute hepatitis in terms of the proportion of the patients who are exposed to the possible risk factors during the incubation period.

## EXPECTED OUTCOMES

- Information can be used locally to better guide prevention and control measures.
- Capacity will be built for surveillance of acute hepatitis (local capacity-building at site improved).

- Lessons will be learnt on how to extend the project (expand the project to more sites).
- A community of practice/partnership would be created with clinicians and laboratory specialists, which could be used for testing, treatment and in-vitro diagnosis support for biomarker surveys.

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## Table 1. Template case report form for acute viral hepatitis*

### Identification [not to be entered in the computer]

Full name:
Present address:
Village / Town / City: State / Province / District:
Date of birth: / / Phone:

### General characteristics

Date of reporting: / / **UNIQUE ID**:
Age (years) Gender: Male Female Other

### Clinical characteristics, testing circumstances and biomarkers

| Clinical characteristics and testing circumstances in the current episode | | Biomarkers | | | |
|---|---|---|---|---|---|
| Onset date of acute hepatitis | / / | Alanine aminotransferase (ALT): | | IU/ litre | Unknown |
| Hospitalization for hepatitis | Yes No | Anti-HAV IgM | Pos | Neg | Unknown |
| Jaundice | Yes No | Anti-HBc IgM | Pos | Neg | Unknown |
| Encephalopathy† | No Grade I Grade II Grade III Grade IV | HBsAg | Pos | Neg | Unknown |
| Discharge date | / / | Anti-HCV | Pos | Neg | Unknown |
| | | HCV RNA | Pos | Neg | Unknown |
| | | HDV testing** | Pos | Neg | Unknown |
| | | 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 |
| Previously history of the other chronic liver disease | Yes | No | Unknown |

### Hepatitis vaccination history

| | | | |
|---|---|---|---|
| Has the person ever received at least one dose of hepatitis A vaccine? | Yes ( doses) | No | Unknown |
| Has the person ever received at least one dose of hepatitis B vaccine? | Yes ( doses) | No | Unknown |
| Has the person ever received at least one dose of combined hepatitis A and B vaccine? | Yes ( doses) | No | Unknown |
| Has the person ever received at least one dose of hepatitis E vaccine? | Yes ( doses) | No | Unknown |

### General characteristics of the patient

| | | | |
|---|---|---|---|
| Is the patient a health-care worker exposed to blood through patient care? | Yes | No | Unknown |
| Is the patient a man who has sex with other men? | Yes | No | Unknown |
| Does the patient undergo haemodialysis? | Yes | No | Unknown |
| Is the patient injecting drugs? | Yes | No | Unknown |

### Possible exposures in the 2–6 weeks before onset

| | | | |
|---|---|---|---|
| Is the patient involved in a reported, identified outbreak? | Yes | No | Unknown |
| Was there contact with patient(s) with the same symptoms? | Yes | No | Unknown |
| Did the patient eat raw, uncooked shellfish (e.g. oysters)? | Yes | No | Unknown |
| Did the patient eat raw, uncooked pork meat, boar meat or venison? | Yes | No | Unknown |
| Did the patient drink water from a well or other unsafe water source? | Yes | No | Unknown |
| Is the patient a child or a staff member in a day-care centre? | Yes | No | Unknown |
| Did the patient travel to an area highly endemic for hepatitis A/hepatitis E? | Yes | No | Unknown |

### Possible exposures in the 1–6 months before onset

| | | | |
|---|---|---|---|
| Did the patient receive injections given for therapeutic purposes? | Yes | No | Unknown |
| Was the patient admitted to hospital? | Yes | No | Unknown |
| Did the patient undergo a surgical procedure? | Yes | No | Unknown |
| Did the patient receive a blood transfusion? | Yes | No | Unknown |
| Did the patient receive dental care? | Yes | No | Unknown |
| Did the patient undergo endoscopy? | Yes | No | Unknown |
| Did the patient undergo tattooing or body piercing? | Yes | No | Unknown |
| Did the patient undergo shaving by a barber? | Yes | No | Unknown |
| Did the patient have unprotected sex with an occasional partner? | Yes | No | Unknown |
| Was there household contact with someone with hepatitis B/C? | Yes | No | Unknown |

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

* 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. This form should be filled by health-care workers, after interviewing the patients and reviewing the medical records.
** HDV testing can be added in highly endemic areas or deleted in non-endemic areas.
† Refer to Appendix 2.

# APPENDIX 1. INFORMATION SHEET ON SURVEILLANCE FOR ACUTE HEPATITIS

**Title:** Surveillance for acute hepatitis

**Person in charge of the surveillance activity in the centre:** [Insert name, title and contact information]

**Survey sponsor:** [Insert name of the institution]

## Description of the surveillance project

The health centre where you are getting care is taking part in a surveillance project that keeps track of acute hepatitis in [name of country]. This surveillance is based on (a) routine health care and (b) standard public health practice. It tries to find out the viruses involved in causing acute hepatitis and to identify the source of the disease. These results should help us prevent hepatitis and the Ministry of Health could better plan prevention work.

## Procedures

A person will ask you some questions to understand how you got acute hepatitis and fill up a form with your answers. The form is one page long and may take about 5 minutes to fill up. We also propose to do a blood test that will find out the type of hepatitis you have (A, B, C or E). This information will be written in your medical record and kept securely as part of your confidential medical information. But if you agree, we would also use the data that we will collect in the surveillance system after we have removed all the information that identifies you. The information would then be used with a code, and without your name or date of birth.

## Risks and discomforts

The risks are very small; however, taking blood may cause some discomfort, bleeding, bruising and/or swelling at the blood draw site. In rare cases, there is also a risk of fainting or an infection. It is also possible that talking about your personal situation in response to our questions may make you feel uncomfortable.

## Getting the results of my tests

At [specify the time], you will be able to receive the results of your test. To obtain the results of your test, you will need to come back to the clinic and ask for your results. We will then give you all the information that you need on what to do next. These tests will also help us determine if we need to take active steps to protect someone else who has been exposed to you and who could get hepatitis from you. This could be done through vaccination, for instance.

## What benefits are there for me in this?

The blood test results will tell us the type of acute hepatitis that you have. If you are found to be positive, we will help you protect others from the disease. The information from the questions will help us understand how you got it and how you can protect yourself better in the future. Acute hepatitis does not require treatment. You just need to abstain from taking medicines that are not strictly necessary.

## Can I refuse the use of my data for surveillance?

You have the right to refuse the use of your data. If you refuse, all your data will stay in your confidential medical record and it will not be used for the project. This will not affect your care at the centre and you can still benefit from the results of the test.

## Contact information

Feel free to contact [Tittle /Name / institution] if you have questions or concerns about this surveillance project.

Feel free to contact [Tittle /Name / institution] if you have questions or concerns about the ethical aspects of the surveillance project.

**Table 2. WHO surveillance case definitions for viral hepatitis***

| **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 raised alanine aminotransferase (ALT) levels more than ten times the upper limit of normal of the laboratory)† | | | |
| **Confirmed case: clinical criteria AND biomarker or epidemiological criteria** | **Hepatitis A** | **Acute hepatitis E** | **Acute hepatitis B** | **Acute hepatitis C** |
| | IgM anti-HAV +ve<br>**OR**<br>Epidemiological link with a confirmed case | IgM anti-HEV +ve‡<br>**OR**<br>Epidemiological link with a confirmed case | IgM anti-HBc +ve§ | HCV RNA +ve and anti-HCV –ve<br>**OR**<br>Seroconversion to anti-HCV **<br>**OR**<br>Anti-HCV +ve<br>**AND**<br>IgM anti-HBc –ve<br>**AND**<br>Anti-HAV IgM –ve<br>**AND**<br>Anti-HEV IgM -ve |

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

* Case definitions are for the purpose of reporting and surveillance and may differ from criteria to be used for the management of patients. All these symptoms must be present in order to diagnose acute hepatitis.

† Ten times the upper limit of normal (400 IU/L) is the threshold used by the United States' State and Territorial Epidemiologists (CSTE). It is aimed at higher specificity and excluding chronic hepatitis. However, countries may also select lower (more sensitive) or higher (more specific) thresholds. In addition, raised ALT is not necessary for the case definition of presumptive acute hepatitis. However, in the context of enhanced case reporting, the requirement of raised ALT will improve specificity.

‡ Adding a second test (e.g. IgA anti-HEV, IgG anti-HEV or HEV RNA) increases specificity to IgM anti-HEV.

§ Hepatitis test panels usually include HBsAg with anti-HBc IgM test (positive predictive value of anti-HBc IgM higher if HBsAg +ve). Specific test/threshold needed to exclude transient rise in IgM during flares of chronic HBV infection.

** Among patients tested regularly at short time intervals, seroconversion to anti-HCV suggests a recent HCV infection. Seroconversion to anti-HCV should be followed by reflex RNA test (when available).

**Table 3. 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, 20XXa**

| 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 exposure | 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% |
| | Haemodialysis | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% |
| | Injecting drug user | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% |
| 2–6 weeks prior to onset | Involved in a reported, identified outbreak | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% |
| | Contact with another patient with same symptoms | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% |
| | Consumption of raw shellfish (e.g. oysters) | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% |
| | Consumption of raw pork, boar meat or venison | 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 | Injection/IV infusion | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% |
| | Hospitalization | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% |
| | Surgical procedure | 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% |
| | Endoscopy | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% |
| | Tattoo | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% | XXX/XXX | XX% |
| | Barber shaving | 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% |
| | Household contact with someone with hepatitis B/C | 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 the 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).

## APPENDIX 2. WEST HAVEN CRITERIA ON HEPATIC ENCEPHALOPATHY

| WHC including MHE | ISHEN | Description | Suggested operative criteria | Comment |
|---|---|---|---|---|
| Unimpaired | | No encephalopathy at all, no history of HE | Tested and proved to be normal | |
| Minimal | Covert | Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change | Abnormal results of established psychometric or neuropsychological tests without clinical manifestations | No universal criteria for diagnosis Local standards and expertise required |
| Grade I | | ・Trivial lack of awareness<br>・Euphoria or anxiety<br>・Shortened attention span<br>・Impairment of addition or subtraction<br>・Altered sleep rhythm | Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioral decay with respect to his or her standard on clinical examination or to the caregivers | Clinical findings usually not reproducible |
| Grade II | Overt | ・Lethargy or apathy<br>・Disorientation for time<br>・Obvious personality change<br>・Inappropriate behavior<br>・Dyspraxia<br>・Asterixis | Disoriented for time (at least three of the following are wrong: day of the month, day of the week, month, season, or year) ± the other mentioned symptoms | Clinical findings variable, but reproducible to some extent |
| Grade III | | ・Somnolence to semistupor<br>・Responsive to stimuli<br>・Confused<br>・Gross disorientation<br>・Bizarre behaviour | Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city, or place) ± the other mentioned symptoms | Clinical findings reproducible to some extent |
| Grade IV | | Coma | Does not respond even to painful stimuli | Comatose state usually reproducible |

All conditions are required to be related to liver insufficiency and/or portosystemic shunting.
HE: hepatic encephalopathy; ISHEN: International Society for Hepatic Encephalopathy and Nitrogen Metabolism; MHE: minimal hepatic encephalopathy

*Source:* Vistrup H, AModio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60(2):715–35.