Hepatitis B
Hepatitis B virus (HBV) is transmitted by exposure of mucosal membranes or non-intact skin to infected blood or other body fluids. Transmission can occur perinatally from mother to child and from person to person. The incubation period for acute hepatitis B is 75 days on average, but may vary from about 30 to 180 days. Most new infections are asymptomatic. Acute hepatitis B occurs in approximately 1% of perinatal infections, 10% of early childhood infections and 30% of infections among persons ≥ 5 years of age. Children are frequently asymptomatic when they become infected with HBV, making surveillance challenging in this population. Acute liver failure develops rarely in infants and children but occurs in 0.5%–1.0% of adult cases, with a case-fatality rate of 20%–33%. Chronic hepatitis B occurs in > 80% of perinatal infections, but in < 5% of those infected as healthy adults. Chronic hepatitis B infection has a spectrum of clinical severity, from asymptomatic to liver cirrhosis and hepatocellular carcinoma.

Hepatitis B vaccine is recommended for children as a three- or four-dose regimen, including a birth dose to protect against perinatal transmission (1). The introduction of hepatitis B vaccines in the 1980s has resulted in dramatic decrease in chronic hepatitis B prevalence worldwide among children.

DISEASE AND VACCINE CHARACTERISTICS

Hepatitis B results in multiple disease outcomes, including acute hepatitis, chronic infections and long-term sequelae such as cirrhosis and hepatocellular carcinoma. Surveillance can be done for any or all of these. However, acute infection and chronic infections are frequently asymptomatic in children. Surveillance for chronic hepatitis B cannot inform vaccine program impact in a timely manner due to the long time between infection and chronic sequelae.

The objectives of surveillance for hepatitis B are to:

- detect outbreaks of viral hepatitis (local)
- monitor trends in incidence among high-risk adult populations and identify risk factors for new incident infections (local, national)
- estimate the prevalence of chronic infections and monitor trends in sentinel groups, including the impact of national vaccination programs in these groups (local, national, regional/global)
- estimate the burden of sequelae and mortality of chronic hepatitis, including cirrhosis, liver failure and carcinoma (national, regional/global)
- provide data to inform vaccine introduction in high-risk populations (national).

RATIONALE AND OBJECTIVES OF SURVEILLANCE
Surveillance for hepatitis B can focus on three phases of infection: acute, chronic and sequelae of chronic infection. The below focuses specifically on acute hepatitis surveillance.

**MINIMAL SURVEILLANCE**
Minimal surveillance for acute hepatitis is based on clinical signs and symptoms in all health facilities. Syndromic acute hepatitis surveillance is usually national, passive, aggregate and facility-based. Detection of acute hepatitis outbreaks should lead to laboratory testing to confirm the etiology of the outbreak, as it might be due to a hepatitis virus, non-hepatitis virus or non-viral cause.

**ENHANCED SURVEILLANCE**
Syndromic acute hepatitis surveillance can be supplemented by case-based surveillance that includes laboratory confirmation and collection of more data elements on all suspect cases. This is often referred to as “enhanced case reporting”. This is usually done in two settings: a) in outbreaks of acute hepatitis, and b) in sentinel sites to define viral hepatitis epidemiology. For enhanced surveillance, case reporting with laboratory confirmation could also be implemented nationwide, depending on resources and the objectives of surveillance.

In paediatric cohorts, who are frequently asymptomatic, surveillance for acute infection is not able to detect the impact of childhood vaccination programs. However, data from this type of surveillance can guide vaccination strategies for high-risk adult populations that a country might be considering.

**CASE DEFINITIONS AND FINAL CLASSIFICATION**

**PRESumptive CASE OF ACUTE HEPATITIS**
For viral hepatitis the preferred term for suspected cases is presumptive because of possible stigma related to use of the word suspected. A presumptive case of acute hepatitis B is a person with either or both of the following:

- discrete onset of an acute illness with symptoms of acute infectious illness (fever, malaise, fatigue) AND signs of liver damage (anorexia, nausea, jaundice, dark urine, right upper quadrant tenderness)

  OR

- raised alanine aminotransferase (ALT) levels more than ten times the upper limit of normal (400 IU/L), the threshold used by the U.S. Council of State and Territorial Epidemiologists (CSTE) (2). Countries may also select lower thresholds that could be more sensitive or higher thresholds that could be more specific.

**FINAL CASE CLASSIFICATION WITH ENHANCED REPORTING**

- Laboratory confirmed acute hepatitis B case: A laboratory-confirmed case meets the prospective case definition and is IgM anti-HBc positive.
Surveillance for acute hepatitis as part of hepatitis B surveillance

WHO recommends that syndromic surveillance for acute hepatitis include enhanced case reporting with testing for all viral hepatitis that cause acute infection (hepatitis A, B and E). For hepatitis A and E, syndromic surveillance mostly serves to detect outbreaks. For hepatitis B, outbreaks are less common and most often health care-related. Enhanced case detection with biomarker testing is important in defining high-risk groups, risk factors and incidence of acute hepatitis B.

However, surveillance for acute hepatitis alone will not provide sufficient epidemiologic information to make decisions regarding hepatitis B control programs, where the real burden of illness is due to chronic infection and sequelae. In keeping with other VPDs in these surveillance standards, the main focus of this chapter is on acute manifestations of infection with HBV. More detailed recommendations for surveillance for chronic infection and sequelae (such as cancer registries) are available elsewhere (2). Decisions regarding hepatitis B vaccine policy must triangulate data from surveillance for acute hepatitis with that of chronic infection and long-term sequelae.

CASE INVESTIGATION

With syndromic surveillance for acute hepatitis, individual cases are not investigated. All outbreaks should be investigated immediately and confirmed serologically. In the setting of enhanced surveillance, individual cases of acute hepatitis should have case report forms filled out and appropriate specimens should be collected for confirmatory testing.

SPECIMEN COLLECTION

If biomarker testing is available, a venipuncture blood sample should be collected and sent to the laboratory for testing by ELISA. Blood should be drawn from acutely ill patients; IgM can persist up to six months after onset. Blood collection tubes can be those for serum or plasma. Serum and plasma samples may be stored for up to five days at 2–8°C or four weeks at -20°C.

At this time, dried blood spot specimens have not been validated for hepatitis diagnostics.
LABORATORY TESTING

ELISA testing for the presence of antigen or antibody is the recommended testing methodology if biomarker testing is conducted by the country as part of enhanced case reporting in setting of outbreaks or sentinel-site surveillance. The following results of biomarker testing define acute and chronic hepatitis B infection.

- **Acute:** ELISA testing for immunoglobulin M antibodies to core antigen of hepatitis B virus (anti-HBc IgM).
- **Chronic:** ELISA or rapid diagnostic test for hepatitis B surface antigen (HBsAg).

Test panels usually include HBsAg with anti-HBc IgM test. The positive predictive value of the anti-HBc IgM is higher if HBsAg is positive. For diagnosis of acute hepatitis B, a specific test or threshold is needed to exclude transient presence of IgM during flares among patients with chronic HBV infection. For chronic hepatitis B, most testing strategies would also test for total anti-HBc. The combination of total anti-HBc and HBsAg is more specific for chronic hepatitis B infection than HBsAg alone.

In most settings with enhanced case reporting, patients meeting the presumptive case definition at sentinel sites undergo testing with a standard panel of hepatitis serologic assays for all the hepatitis viruses. In some settings with limited resources, a serial approach to testing might be considered in which initial testing is performed for the most common type of hepatitis. If this first test is negative, a test is done of the next common type, and so on.

ALT level might also be tested for to determine if a patient should be included in the presumptive case definition.

Genotype testing can be undertaken for hepatitis B, though it is of limited utility in routine surveillance.

DATA COLLECTION, REPORTING AND USE

**RECOMMEND DATA ELEMENTS**

- For aggregated data collection
  - Number of total acute hepatitis cases by age group, month and geographical area.
- For case-based data collection
  - Name (if confidentiality is a concern the name can be omitted so long as a unique identifier exists)
  - Unique identifier
  - Date of birth (or age if date of birth not available)
  - Sex
  - Place of residence (city, district and province)
  - Date of onset
  - Signs and symptoms: Fever, malaise, fatigue, anorexia, nausea, jaundice, dark urine, right upper quadrant tenderness
  - **Acute liver failure?**
  - **Contact of a laboratory confirmed case of HBV?**
  - **Number of hepatitis B vaccine doses received**
  - **Dates of all hepatitis B vaccine doses (if card available)**
  - **Laboratory**
    - Specimen collected?
    - Date of specimen collection
    - Date specimen sent to laboratory
    - Date specimen received in laboratory
    - Results of HBV serology tests (IgM-anti HBc, HBsAg, others)
    - Results of testing for other viral hepatitis
    - ALT result
  - **Date of notification to public health**
  - **Date of investigation**
  - **Final case classification (laboratory-confirmed)**
Hepatitis B

REPORTING REQUIREMENTS AND RECOMMENDATIONS

- Healthcare workers should report cases of acute viral hepatitis to the local public health authority. Case reporting can be syndromic (as with acute hepatitis, where no testing is done and cases are reported on the basis of signs and symptoms), or it can be type-specific, based on biomarker testing.
- Routine monthly reporting of aggregated data on presumptive cases should be done, and if available, the number of confirmed cases of each type of hepatitis should be reported from the peripheral level to the intermediate and central levels.
- Designated reporting sites at all levels should report at a specified frequency (such as weekly or monthly) even if there are zero cases (“zero reporting”).
- HBV is not currently reportable under International Health Regulations (2005) nor as part of the Joint Reporting Form.

RECOMMENDED DATA ANALYSES

Data analysis for acute hepatitis surveillance with enhanced case reporting data includes:

- number of acute hepatitis B cases and incidence rate by month, year and geographical area
- age-specific, gender-specific and district-specific acute hepatitis B incidence rates by month/year.

USING DATA FOR DECISION-MAKING

Acute hepatitis surveillance data may be used to:

- identify risk factors
- prevent hepatitis B infections in populations at higher risk by implementing prevention strategies including potentially vaccination
- describe trends
- identify breakthrough infections among vaccine recipients. Additional investigation can identify the causes for these potential breakthrough infections (for example, waning of vaccine-induced immunity and infection with viral variants). Cases of acute hepatitis B in children can be used to estimate vaccine efficacy using the screening method.

Surveillance data should be analysed and used in the context of the key objectives for which the surveillance system was designed. Data should be interpreted within the context of the limitations of the surveillance system, such as type of surveillance system (syndromic versus laboratory-based), the clinical nature of hepatitis (frequently asymptomatic in children), representativeness of the population under surveillance (general population versus risk groups), test sensitivity and specificity, and testing sequence chosen. Syndromic surveillance 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 paediatric infections, making trends in acute hepatitis defined through syndromic surveillance difficult to interpret. Syndromic surveillance for acute hepatitis is of limited use outside outbreak detection.

Given the potential for multiple data sources from different surveillance systems (acute, chronic, long-term sequelae), and special studies (serosurveys, antenatal care testing, blood bank testing), and the fact that no system is perfect, it is important to review data from all sources together to formulate appropriate public health actions.

Several considerations need to be made when interpreting surveillance data for HBV:

- Children are frequently asymptomatic; routine surveillance information is not useful in determining paediatric vaccination introduction or impact.
- Care should be taken when cleaning and analysing surveillance data from chronically infected patients since patients might be serially tested and duplicate reporting could be an issue.
- Risk groups might be under-represented or missed in population-based surveillance or surveys of the general population.
SURVEILLANCE PERFORMANCE INDICATORS

There are no formal performance indicators for acute hepatitis surveillance. However, countries might wish to do regular monitoring of surveillance to identify specific areas of the surveillance and reporting system that need improvement. At the most basic level, syndromic surveillance should be evaluated to determine if it is detecting outbreaks as designed.

CLINICAL CASE MANAGEMENT

Clinical care for hepatitis B should be in line with country guidance.

CONTACT TRACING AND MANAGEMENT

Contact investigations are not usually done in acute hepatitis surveillance. In some settings with enhanced case reporting (such as health care facilities), after known exposure to hepatitis B through percutaneous or mucus-membrane contact, exposed persons should receive post-exposure prophylaxis with the hepatitis B vaccine, hepatitis B immunoglobulin (HBIG) or both, depending on their history of HBV vaccination and the serostatus of the source of exposure. Guidelines on post-exposure prophylaxis for occupational exposure are given elsewhere (3).

SURVEILLANCE, INVESTIGATION AND RESPONSE IN OUTBREAK SETTINGS

DEFINITION OF AN OUTBREAK
An outbreak of acute hepatitis B is an increase of incidence over the reported baseline. Most outbreaks of hepatitis B are healthcare related (for example, haemodialysis centres or unsafe injections).

CHANGES TO SURVEILLANCE DURING AN OUTBREAK
If a country is conducting syndromic surveillance for acute hepatitis, detection of an outbreak should trigger an investigation, which should include laboratory testing of acute hepatitis cases to determine the etiology. Case report forms will likely include new data elements in outbreak settings pertaining to hepatitis B’s mode of transmission through blood and body fluids.

PUBLIC HEALTH RESPONSE
Contacts of cases should be offered testing, post-exposure prophylaxis and prevention services where feasible (4).
Hepatitis B

SPECIAL CONSIDERATIONS FOR HEPATITIS B SURVEILLANCE

- Some behaviours that put a person at increased risk for hepatitis B can be considered sensitive, stigmatized or illegal in the country (for example, injection drug users or men who have sex with men). Confidentiality of all collected data is of the utmost importance.

- Laboratory test results should be returned to the patient. Positive hepatitis B test results are especially important to return, as the infected person should be counselled on appropriate clinical follow up and how to reduce the risk of transmission to contacts.

- To measure impact of routine childhood vaccination, conduct serosurveys of hepatitis B biomarkers. Details on how to conduct this survey are described in two WHO documents about documenting the impact of vaccination (5/6). Surveillance cannot be used to measure the impact of childhood vaccination in a timely manner.

REFERENCES

REFERENCES CITED


