

Hepatitis D

PROTOCOL CHECKLIST

- Enter available information into Merlin upon receipt of initial report
- Review background on disease, case definition, and laboratory testing
- Contact provider
 - Confirm patient's diagnosis and infection with the Hepatitis B virus
- Interview patient
 - Review disease facts
 - Modes of transmission
 - Incubation period
 - Symptoms
 - Ask about exposure to relevant risk factors
 - Blood to blood contact with someone with Hepatitis D
 - Occupational exposure
 - Drug use
 - Tattoos/body piercings
 - Sexual contact
 - Identify contacts
 - Refer symptomatic contacts to a health care provider
 - Counsel Hepatitis B positive contacts to take precaution to avoid co-infection with Hepatitis D
 - Counsel any contacts who have not been vaccinated against Hepatitis B to begin the immunization sequence
 - Determine if patient can be epi-linked to an existing case and if patient is part of an outbreak
 - Provide information on how to prevent further transmission
 - Address patient's questions or concerns
- Follow-up on special situations, including outbreaks or cases in sensitive situations
- Enter additional data obtained from interview into Merlin

Hepatitis D

1. DISEASE REPORTING

A. Purpose of reporting and surveillance

1. To identify those persons who are carriers and may still be infectious to educate and prevent further transmission.
2. To identify outbreaks and other undiagnosed cases.
3. To determine if there is a source of infection of public health concern and to stop transmission from such a source.
4. To identify carriers so that they may seek treatment to prevent long term complications due to Hepatitis D infection.

B. Legal reporting requirements

Laboratories and physicians are required to report Hepatitis D to the county health department (CHD) within one working day of identification/diagnosis.

C. County health department investigation responsibilities

1. Begin investigation within one business day of receiving report from a provider or laboratory.
2. Contact patient and/or provider to complete case interview.
3. Report all confirmed and probable cases in Merlin.
4. Report liver enzyme results for all patients where these are available.

2. THE DISEASE AND ITS EPIDEMIOLOGY

A. Etiologic agent

The Hepatitis D virus (HDV) causes infection only in people with acute or chronic Hepatitis B virus (HBV) infection. HDV requires HBV as a helper virus and cannot produce infection in the absence of HBV. The Hepatitis D virus is a small circular virus consisting of an RNA genome and a delta antigen protein, both of which are coated with Hepatitis B surface antigen (HBsAg). Eight genotypes of HDV have been described, each with a typical geographic distribution. HDV is prevalent in southern Italy, parts of Eastern Europe, South America, Africa, and the Middle East. It is uncommon in the United States.

B. Description of illness

HDV can cause an infection at the same time as the initial HBV infection (co-infection) or it can infect a person already chronically infected with HBV (known as superinfection).

Superinfection with HDV can convert an asymptomatic or mild chronic HBV infection into fulminant, more severe, or rapidly progressive hepatitis. Acute co-infection usually causes an acute illness indistinguishable from acute HBV infection alone, although with a higher likelihood of fulminant hepatitis.

Signs and symptoms of Hepatitis D co-infection or superinfection are indistinguishable from those of Hepatitis A or Hepatitis B infection.

When present, signs and symptoms can include:

- Fever
- Fatigue
- Loss of appetite
- Nausea
- Vomiting
- Abdominal pain
- Dark urine
- Clay-colored bowel movements
- Joint pain
- Jaundice
- Cirrhosis
- Liver failure
- Hepatocellular cancer

C. Reservoirs

Hepatitis D does not have any other known reservoirs besides humans.

D. Modes of transmission

Hepatitis D virus is transmitted primarily by parenteral exposure to blood of HDV-infected people. However, infection can only occur in those already infected with Hepatitis B. The virus can be spread by:

- Contact with infected blood or blood products.
- Contact with contaminated needles, especially injection drug equipment.
- Sexual contact with an infected partner.

HDV transmission from mother to newborn is uncommon. Spread among family members can occur among people with chronic HBV infection.

E. Incubation period

The incubation period for Hepatitis D superinfection is approximately two to eight weeks. When HBV and HDV viruses infect simultaneously, the incubation period is similar to that of HBV, 45-160 days with an average of 90 days.

F. Period of communicability

All persons with detectable HDV RNA in their blood are potentially infectious to others.

G. Treatment

HDV has proven difficult to treat. Data suggest pegylated interferon-alpha may result in up to 40% of patients having a sustained response to treatment. Clinical trials show that at least a year of therapy is needed for the best sustained responses, and longer courses may be warranted if the patient is able to tolerate the adverse events associated with therapy.

H. Prophylaxis

There is no hyperimmune D globulin available for pre- or postexposure prophylaxis.

I. Vaccination

HDV cannot be transmitted without the presence of Hepatitis B infection. Therefore, HBV immunization protects against HDV infection. Those with chronic HBV infection should take extreme care to avoid exposure to HDV.

J. Hepatitis D in Florida

Hepatitis D is rare in the United States. Florida's most recent case of HDV was in 2009. There was one case reported in each of the previous three years (2008, 2007, 2006).

3. CASE DEFINITION

A. Clinical description

An acute viral illness with:

- a. Discrete onset of symptoms,
AND
- b. Jaundice **or** elevated liver enzymes.

Symptoms most commonly include fatigue, abdominal pain, loss of appetite/anorexia, nausea, vomiting, or dark urine (tea colored).

B. Laboratory criteria for diagnosis

Evidence of Hepatitis B infection:

- Positive IgM anti-HBc,
OR
- HBsAg positive,
AND one of the following:
 - IgM anti-HDV positive,
OR
 - Positive HDV RNA (PCR),
OR
 - Positive total anti-HDV.

C. Case classification

Confirmed: A case that meets the clinical case definition and is laboratory confirmed.

Probable: A case that has a discrete onset of symptoms, lacks jaundice or elevated liver enzymes, but is laboratory confirmed.

4. LABORATORY TESTING

A. Criteria for diagnosis

Hepatitis D serology is the only way to determine the state of infection. Only individuals with acute or chronic Hepatitis B infection should be tested for Hepatitis D.

B. Services available at the BPHL

The Bureau of Public Health Laboratories (BPHL) does not currently offer serology testing for Hepatitis D. Suspected cases of Hepatitis D must be brought to the attention of Bureau of Epidemiology staff. The Division of Disease Control Bureau of Epidemiology (DCBE) staff will coordinate shipping of samples to the CDC for serology and HDV RNA testing.

C. Testing requests

1. Contact the regional laboratory liaison to facilitate testing the sample at the CDC.
http://dohiws/Divisions/Disease_Control/epi/InvestigationUnitMap_color.pdf
2. Specimen collection:
 - a. Three ml of serum or 6-8 ml of whole blood that is properly labeled (name, date of birth, date collected) should be submitted for testing.
3. Packaging and shipping
 - a. Specimens should be stored in plastic vials and sealed tightly to prevent desiccation of the sample.
 - b. Serum is best stored frozen, and freeze/thaw cycles should be kept to a minimum. Store samples at 4-8° C for no more than five days.
 - c. For storage more than five days, samples should be held at -20° C.
 - d. http://www.doh.state.fl.us/lab/PDF_Files/Packaging_Flowchart_0422051.pdf
 - e. http://www.doh.state.fl.us/lab/PDF_Files/Packaging_Flowchart_notes_0422051.pdf

D. Interpretation of results:

Only those infected with Hepatitis B (acute or chronic) should be tested for HDV. Hepatitis D antibodies (anti-HDV) may not be present until several weeks after onset of illness and acute and convalescent sera may be required to confirm the diagnosis. Those with both positive anti-HDV and positive IgM anti-HBc have co-infection with Hepatitis D and Hepatitis B. Those testing positive for HDV but lacking IgM anti-HBc have chronic Hepatitis B infection and superinfection with Hepatitis D. The presence of anti-HDV IgG antibodies does not prove active infection. HDV RNA testing should be performed for diagnostic and therapeutic considerations. Patients with circulating HDV RNA should be evaluated for severity of liver disease and hepatocellular carcinoma. The presence of anti-HDV IgM is of lesser utility, because it is present in both acute and chronic HDV infections.

HDV antibodies (anti-HDV): may indicate acute or chronic infection with HDV

anti-HDV immunoglobulin G (anti-HDV IgG): indicate past or current HDV infections

anti-HDV immunoglobulin M (anti-HDV IgM): detectable in the first months of an acute infection

HDV RNA: detects the presence of absence of HDV RNA, the method of choice for diagnosis with HDV infection

Hepatitis B surface antigen (HBsAg): A protein on the surface of HBV and HDV; it can be detected in high levels in serum during acute or chronic HBV infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is also the antigen used to make Hepatitis B vaccine.

IgM antibody to Hepatitis B core antigen (IgM anti-HBc): Positivity indicates recent infection with HBV (≤ 6 months). Its presence indicates acute HBV infection.

Hepatitis B envelope antigen (HBeAg): A secreted product of the nucleocapsid gene of HBV that is found in serum during acute and chronic Hepatitis B. Its presence indicates that the virus is replicating and the infected person has high levels of HBV.

Acute HBV-HDV co-infection	HBV-HDV superinfection
HBsAg+, HBeAg+, HBV DNA during incubation period	HDV RNA and high titers of both Ig M anti-HDV and Ig G anti-HDV
Ig M anti-HDV and HDV RNA in serum	Declining titer of HBsAg and increasing titer of anti-HDV

5. CASE INVESTIGATION

A. Contact the physician or hospital

1. Confirm acute or chronic Hepatitis B infection has been diagnosed in the reported patient.
2. Obtain as much information as possible about the patient, such as:
 - a. Contact information
 - b. Demographic information (e.g., DOB, gender, race, ethnicity)
 - c. Date of onset
 - d. Symptoms
 - e. Laboratory tests performed
 - f. Hepatitis A and B vaccine history
 - g. Underlying conditions
 - h. Recent travel
3. Ask what information has been given to the patient, including whether the patient knows about the diagnosis.

4. Notify the physician that you will be contacting the patient as DOH follows up on all cases of Hepatitis D to assess risk factors, to better characterize the occurrence of Hepatitis D in Florida and to take necessary steps to prevent additional cases. Also review infection control recommendation and address any concerns regarding the CHD contacting the patient.

B. Interview the case

1. Complete an interview as soon as possible after the case is reported to optimize recall.
 - a. Make at least three phone call attempts to reach the patient; calls should be made at different times of the day with at least one call being made in the evening.
 - b. If phone calls are unsuccessful, mail a letter to the patient requesting that he/she contact the CHD and/or conduct a home visit or leave a letter for the patient.
 - c. If the patient is unable to provide information, interview a proxy (e.g., a spouse, parent) to gather further information. However, do not reveal patient's disease status without his or her consent.
2. Once contact is made, education about Hepatitis D infection should be provided and an interview should be conducted to obtain any further information not already gathered from the provider or hospital. A viral Hepatitis Case Report Form is available to guide the investigation and assist in follow-up:
http://www.doh.state.fl.us/Disease_ctrl/epi/surv/Hepatitis_Viral_CRF.pdf.
3. Pertinent items to cover during the interview include:
 - a. Education
 - i. Any contacts known to be infected with Hepatitis B, acute or chronic, should take precautions to avoid co-infection or superinfection with Hepatitis D
 - b. Demographic information
 - c. Identification of possible exposures and risks during exposure period (six weeks to six months prior to onset of symptoms)
 - i. Close contact (e.g., household member, sexual partner) with any person who had an illness compatible with Hepatitis B or D or any person with a known acute or chronic Hepatitis B infection
 - ii. Injection and non-injection drug use
 - iii. Tattoos and/or body piercings
 - iv. Surgery, dental work, other invasive procedures
 - d. Information on where to obtain the Hepatitis A vaccine

C. Merlin data entry

Create a case in Merlin under disease code **HEPATITIS D-07052**. Enter available data, being sure to include all required fields on the Basic Data screen, complete the Case Symptoms screen, and attach all relevant laboratory results. Please note that liver function test results should be entered as a laboratory result. The extended data screen should also be completed in Merlin. Travel history, if relevant, should be entered as well.

6. CONTROLLING FURTHER SPREAD

A. Patient/Household education on prevention recommendations

1. Disinfect all items that may come in contact with blood and body fluid.
2. Do not share personal items that may have blood on them: razorblades, toothbrushes.
3. Cuts and sores on the skin should be covered to prevent the spread of infected blood or body fluid.
4. Patients should be informed of the risk of sexual transmission. Hepatitis B virus-positive individuals engaged in high risk sexual activities* should be counseled to use latex barriers correctly every time they have sex.
5. Do not share needles or syringes. Disposable needles should be used only once then discarded. As a last resort, undiluted household bleach** can be used to clean syringes and needles.
6. Active injection drug users should be directed to needle exchange programs and drug rehabilitation services.
7. Blood spills, including dried blood, still carry a risk of infection. All blood spills should be cleaned using 1:10 dilution of one part bleach to 10 parts water.

* High-risk sexual activities are any type of penetrative sexual contact without using barrier protection, especially if the person has multiple sexual partners (even if one is a steady) regardless of vaccination status.

**For details on using undiluted bleach for disinfection of syringes, see <http://www.cdc.gov/idu/facts/disinfection.pdf>.

B. Isolation of cases

Standard precautions should be observed to prevent exposures to blood and body fluids in healthcare settings.

C. Management of contacts

To identify who may be a contact (see Modes of Transmission). Case contacts should be Epi-linked in Merlin.

Hepatitis B infected contacts: People with acute or chronic Hepatitis B infection should take extreme care to avoid exposure to HDV.

Contacts not infected with Hepatitis B: Because HDV cannot be transmitted in the absence of HBV infection, HBV immunization protects against HDV infection. Any contacts that have not yet been immunized against HBV should be advised to begin the Hepatitis B vaccination sequence.

Use universal precautions for individuals in contact with body fluids in healthcare settings. High-risk groups for infection include:

- Hepatitis B infected individuals

- drug abusers who share needles
- healthcare workers who have contact with infected blood
- men who have sex with men
- people who have multiple sexual partners
- household contacts of infected persons
- infants born to mothers who are Hepatitis D carriers

7. MANAGING SENSITIVE SITUATIONS

A. Identifying a sensitive situation

As defined by *Florida Administrative Code* 64D-3.208, a sensitive situation is a setting in which the presence of a case would increase significantly the probability of spread of the diagnosed or suspected disease or condition and would, therefore, constitute a public health hazard. Examples of such settings are schools, childcare facilities, hospitals and other patient-care facilities.

B. Work or child-care restrictions

No occupational, school, or child-care restrictions are necessary for Hepatitis D infected individuals.

C. Needle stick and similar exposure

Accidental needle sticks carry a risk for transmission of Hepatitis D.

D. Case is a recent blood donor or recipient

Notify the blood bank immediately so that any unused product can be recalled.

8. IMPORTANT LINKS

A. Viral Hepatitis Case Report Form:

http://www.doh.state.fl.us/Disease_ctrl/epi/surv/Hepatitis_Viral_CRF.pdf

B. CDC Hepatitis D Page

<http://www.cdc.gov/hepatitis/ChooseD.htm>

C. WHO Hepatitis D Page

<http://www.who.int/csr/disease/hepatitis/whocdscsrncs20011/en/index.html>

D. Florida Department of Health Bureau of HIV/AIDS and Hepatitis

http://www.doh.state.fl.us/disease_ctrl/aids/index.html

9. REFERENCES

- A. American Academy of Pediatrics. (2012). *Red Book: 2012 Report of the Committee on Infectious Diseases* (29th ed.). Grove Village, IL: American Academy of Pediatrics.

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- C. CDC. (2001). *MMWR: Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis*. June 29, 2001/ 50(RR11);1-42.**
- D. World Health Organization (WHO) Department of Communicable Disease Surveillance and Response (2001). *Hepatitis Delta*.**