

HEPATITIS E VIRUS (HEV) INFECTION

I. DESCRIPTION AND EPIDEMIOLOGY

A. Overview

Hepatitis E virus (HEV) is an important cause of acute hepatitis worldwide. The World Health Organization estimates that HEV causes 3 million cases of acute hepatitis and over 55,000 deaths annually; the vast majority of these infections occur in developing countries.

HEV is a non-enveloped ribonucleic acid (RNA) virus with four clinically relevant genotypes (G1-4); with varying prevalence geographically and different modes of transmission. Genotypes 1 and 2 are most commonly detected in humans and endemic in developing countries in areas with poor sanitation and hygiene. Genotypes 3 and 4 are considered zoonotic, with humans as accidental hosts, and have caused sporadic illness in North America, Asia, and Europe. (See Section V. C. Table. Characteristics of HEV genotypes).

B. Hepatitis E Virus Infection in the U.S. and California

Acute HEV infection is reportable by providers and laboratories in California under the California Code of Regulations, Title 17, but is not reportable nationally. In California, 29 cases of HEV infection were reported in 2018, with a median of 35 cases reported annually since 2014 (range, 29-48). However, surveillance has been limited by the lack of a standardized case definition.

C. Symptoms and Clinical Course

Most HEV infections are asymptomatic. When symptoms do occur, they are like other types of viral hepatitis and include fever, fatigue, nausea, vomiting, and abdominal pain followed by jaundice, dark urine, and pale stools. Most patients recover without treatment within a few weeks, and there is no antiviral treatment available specifically for HEV infection. Progression to fulminant liver failure is rare, but is more likely to occur in patients with pre-existing liver disease such as cirrhosis or other viral hepatitis infections, or pregnancy. Pregnant women are at notable risk of serious illness with high risk of miscarriage, stillbirth, fulminant hepatitis, and maternal death. Maternal mortality after HEV genotype 1 infection during the third trimester of pregnancy has been reported to be 10-30%. HEV infection in pregnancy is also associated with poor fetal outcomes, including miscarriage, premature delivery, and stillbirth. In addition to liver injury, patients occasionally have extrahepatic findings, including glomerulonephritis, hematological disorders, and neurological conditions including Guillain-Barré syndrome.

Chronic HEV infection is typically associated with HEV genotype 3 infection, and occurs almost exclusively in immunosuppressed patients (e.g., post-transplant or receiving immunosuppressive therapy). Symptoms are nonspecific; patients typically have persistently elevated aminotransferase levels, detectable serum HEV RNA for six months or longer, and liver histological findings compatible with chronic viral hepatitis.

D. Transmission

HEV transmission occurs most commonly through contaminated food or water; routes of transmission differ by genotype. Infection with HEV genotypes 1 and 2 occurs in humans and spreads by the fecal-oral route, with epidemics occurring due to contaminated water in developing countries. Zoonotic and foodborne transmission, mostly through the consumption of contaminated

meat, is described to be the likely cause of most HEV genotype 3 and 4 infections. Specifically, consumption of raw or undercooked pig, boar, or deer meat; organ meats; and processed pork products have been reported to cause HEV infections acquired in western European countries. HEV infection due to the consumption of filter feeder shellfish and camel milk have also been described. A variety of animal species, including rodents in California, have been suspected to be animal reservoirs of HEV genotypes 3 and 4. Moreover, high anti-HEV seroprevalence have been recorded among individuals with occupational exposure to animals, further supporting zoonotic transmission. Direct human-to-human transmission is rare, but patients are infectious during the fecal shedding period. Further, HEV transmission has been reported through blood transfusion and perinatal transmission.

The infectious period for HEV is from approximately 1 week prior to illness onset until approximately four weeks after onset of jaundice, although the highest risk of transmission occurs during the first two weeks after onset of jaundice. (See Section V. C. Figure. HEV shedding and serological response). However, prolonged shedding has been reported in some patients during convalescence and those with chronic infection.

E. Incubation Period

The incubation period for HEV infection is 15-60 days with a mean of 40 days.

F. Clinical Management

Clinical management decisions should be made by the patient's primary care physician or infectious diseases or liver specialist. Most patients recover without treatment after a period of weeks. Healthcare providers may recommend rest, drinking lots of fluids, and avoiding alcohol or other potentially hepatotoxic agents, such as acetaminophen. Patients at highest risk for fulminant or chronic disease, such as pregnant women, persons with existing liver disease or other immunocompromising conditions should be monitored carefully.

G. Prevention

In areas where HEV is endemic, most infections are waterborne. Travelers to these countries should follow the general precautions used for the prevention of traveler's diarrhea. This includes only drinking water that has been boiled or chlorinated, and avoiding food from street vendors, raw or undercooked seafood, meat or pork products, and raw vegetables. A map of countries where HEV is endemic can be found on the [CDC Hepatitis E Questions and Answers for Health Professionals webpage](http://www.cdc.gov/hepatitis/hev/hevfaq.htm) (<http://www.cdc.gov/hepatitis/hev/hevfaq.htm>).

In areas where zoonotic transmission predominates, risk of infection can be reduced by proper preparation of high-risk foods, such as pork and game meat. Those at highest risk of complications should take particular precautions and ensure thorough cooking or avoidance of uncooked/undercooked foods.

Infected patients should be advised to wash hands after using the bathroom and before eating or preparing food. No U.S. Food and Drug Administration-approved vaccine for HEV is currently available in the United States; however, a recombinant vaccine was approved for use in China in 2011 and is effective against HEV. Please refer to Section IV: Case Management and Public Health Control Measures for additional information.

II. CALIFORNIA SURVEILLANCE CASE DEFINITION (CDPH 2019)

There is no standardized Council of State and Territorial Epidemiologists (CSTE) case definition for HEV infection. However, it is necessary for CDPH to evaluate epidemiologic trends in acute HEV infection in California and support local health jurisdictions in their ability to detect and prevent instances of local transmission for public health purposes. Thus, CDPH proposes the following surveillance case definition for acute HEV infection:

Clinical Criteria

An acute illness with discrete onset of any sign or symptom associated with acute viral hepatitis (e.g., fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, abdominal pain, or dark urine),

AND

- Jaundice or elevated total bilirubin levels >3.0 mg/dL, **OR**
- Elevated serum alanine aminotransferase (ALT) levels >200 IU/L.

Laboratory Criteria

Confirmatory laboratory evidence

- Detection of HEV RNA by nucleic acid amplification testing (NAAT; such as polymerase chain reaction [PCR] or genotyping) in any clinical specimen, **OR**
- Detection (in blood) of
 - Anti-HEV immunoglobulin M (IgM), **and**
 - Anti-HEV immunoglobulin G (IgG), **and**
 - Negative tests for other causes of acute viral hepatitis including negative hepatitis A virus IgM antibody, hepatitis B virus surface antigen, hepatitis C virus RNA, and hepatitis D virus IgM antibody and other causes of liver injury, such as drug-induced liver injury and hepatotropic viruses such as Epstein-Barr Virus (EBV) and cytomegalovirus (CMV), **OR**
- Detection of a four-fold increase in quantitative anti-HEV IgG in acute and convalescent serum specimens.

Probable laboratory evidence

- Detection of anti-HEV IgM **and** negative tests for other causes of acute viral hepatitis including negative hepatitis A virus IgM antibody, hepatitis B virus surface antigen, hepatitis C virus RNA, and hepatitis D virus IgM antibody and other causes of liver injury, such as drug-induced liver injury and hepatotropic viruses such as EBV and CMV.

Epidemiologic Linkage

- A clinically compatible illness in a person who is an epidemiologic contact (e.g., household, meal sharer, travel partner, or sexual partner) to a confirmed or probable HEV case, 15-60 days prior to symptom onset.

Case Classification

Confirmed (Acute)

- A person meeting clinical criteria AND confirmatory laboratory criteria.

Probable (Acute)

- A person meeting clinical criteria AND probable laboratory criteria.
- A person meeting clinical criteria who is epidemiologically linked to a confirmed case of HEV.

Chronic

- A person from whom HEV RNA is detected in a clinical specimen for longer than six months.

III. HEV CASE INVESTIGATION AND REPORTING

A. Purpose of Reporting and Surveillance

- To better understand the epidemiology of HEV infection in California and develop informed interventions to decrease illness.
- To detect HEV outbreaks and identify potential sources of ongoing transmission.
- To help educate people on how to reduce their risk of HEV infection.

B. Local Health Department (LHD) General Case Investigation Guidelines

- HEV reporting does not require filling out a case report form (CRF). However, a CDPH CRF for HEV investigation has been developed for voluntary use. Using the HEV CRF will allow for identification of local clusters or outbreaks, consistent collection of information for analysis of local risk factors, and comparison of risk factors across jurisdictions.

For all HEV cases:

- Verify the laboratory results to determine if the appropriate laboratory testing has been completed; only cases that meet confirmed or probable case definitions need to be reported. Of note:
 - A single HEV IgG test is not enough to meet laboratory case criteria.
 - Asymptomatic cases or cases that otherwise do not meet the clinical criteria for HEV infection do not need to be reported unless the patient is suspected to have chronic hepatitis E infection.
- Determine the following for confirmed or probable HEV cases (either by completing the HEV CRF or using the CRF as a guide):
 - The date of onset of jaundice or other symptom of acute hepatitis;
 - Whether the infection was related to international travel or domestically-acquired;
 - Whether the patient is pregnant, immunocompromised, or has a history of chronic liver disease and is at higher risk of severe illness;
 - Whether the patient is in a sensitive occupation or situation (i.e., where there is increased risk of transmission from the patient to the public).

- We encourage completion of the CRF or case follow-up by patient interview and/or review of medical records as soon as feasible after receipt of the initial report for all reported HEV cases who have not travelled outside the U.S.
- Please alert the CDPH Disease Investigations Section (DIS) of any outbreak or cluster of HEV at 510-620-3434. We will be happy to provide assistance with your investigation as needed.

C. LHD Reporting

HEV infection is reportable in California by clinicians and laboratories.

California residents who meet either the confirmed or probable California case definition for HEV infection should be reported to their LHD and then to CDPH. If a patient with suspected chronic HEV infection is identified, please consult the HEV SME in the CDPH Infectious Diseases Branch at 510-620-3434.

Instructions for entering an HEV incident into CalREDIE:

- Enter the patient information into CalREDIE upon notification of the case by the clinical laboratory or health care provider. Select “Hepatitis E” as “Disease Being Reported”.
- The CalREDIE HEV case report is under development as of January 2020. If possible, please complete the HEV CRF that is available through the CalREDIE Document Repository under the CDPH tab of the ribbon in the CalREDIE application. Completion of the HEV CRF is not required. Therefore, completion of the Clinical, Laboratory, and Epidemiological Information Sections is not required but is encouraged, as this would allow for the consistent collection of risk exposures and rapid comparison if needed.

Instructions for LHDs not reporting HEV through CalREDIE:

- Report cases using the standard Confidential Morbidity Report form (CDPH 110a):
- HEV infection is not a CRF-required condition. However, the use of the CDPH HEV CRF (CDPH 8701) is encouraged, as this would allow for the consistent collection of risk exposures and rapid comparison if needed.
- If a hard-copy version of the HEV CRF is needed, please contact the CDPH Disease Investigations Section (DIS) at 510-620-3434 and ask to speak with the HEV subject matter expert.

Reporting Outbreaks and Clusters

Suspected HEV clusters and outbreaks, including point-source outbreaks within your jurisdiction, should be reported within 24 hours to CDPH. Please alert DIS of any outbreak of HEV at 510-620-3434.

D. Laboratory Resources

The CDPH Viral and Rickettsial Disease Laboratory (VRDL) currently does not have the capacity to test for HEV. However, VRDL will assist the LHD or their public health laboratory in forwarding specimens to the U.S. Centers for Disease Control and Prevention (CDC) for HEV RNA testing. For assistance, contact the VRDL at 510-307-8585.

CDC will consider testing clinical specimens for HEV RNA and will perform genotyping if the following conditions are met:

- Clinically compatible illness;
- HEV IgM positive;
- Other causes of acute hepatitis are excluded (including infectious, metabolic and drug induced liver injury);
- Not acquired by traveling to endemic countries;
- Or in the setting of a suspected outbreak.

Specimen handling instructions are found on the [CDC Viral Hepatitis Laboratory Testing Requests webpage](https://www.cdc.gov/hepatitis/HEV/LabTestingRequests.htm) (<https://www.cdc.gov/hepatitis/HEV/LabTestingRequests.htm>).

Of note, the window of hepatitis E viremia is very short (approximately from one week before to two weeks after onset of jaundice). Therefore, a serum specimen from the time of initial evaluation, if available, would be optimal. HEV is shed in the stool for slightly longer (up to 4 weeks); therefore, a stool specimen should also be included.

Please discuss with the CDPH HEV subject matter expert if additional testing is requested.

IV. CASE MANAGEMENT AND PUBLIC HEALTH CONTROL MEASURES

HEV infection is not easily transmitted from person to person, but limited information exists on household transmission during clusters and outbreaks. Infected individuals should be advised to follow proper hand washing and sanitation after using the bathroom or changing diapers and before eating or preparing food. The infectious period is from approximately 1 week before illness onset until approximately 4 weeks after onset of jaundice, although the highest risk of transmission occurs during the first 2 weeks after onset of jaundice. (See Section V. C. Figure. HEV shedding and serological response).

Special Considerations:

Hygiene should be especially meticulous if the patient lives in a household with persons at high risk for severe illness (e.g., patients with chronic liver disease, immunocompromising conditions, or pregnant).

There are no specific guidelines for the management of a situation where a person in a sensitive occupation (including food handler or health care worker) may have worked during the infectious period. There has been no documentation of transmission of HEV from a food handler or healthcare worker; nonetheless, patients in those occupations should be educated on hygiene and restricted from working while acutely ill.

There is no vaccine that is recommended for post-HEV exposure prophylaxis. A safe and effective HEV vaccine is currently only licensed in China, and has not been approved for use in the United States. The efficacy of pre-or post-exposure immune globulin prophylaxis for the prevention of HEV has not been established.

Chronic HEV infection occurs almost exclusively in highly immunocompromised patients and should be managed by a medical specialist.

APPLICABLE STATE STATUTES AND REGULATIONS

A. [California Code of Regulations, Title 17, Public Health, Sections 2500, 2505](#)

(<http://ccr.oal.ca.gov/linkedslice/default.asp?SP=CCR-1000&Action=Welcome>)

2500: Health care providers shall submit reports for HEV to the local health officer for the jurisdiction where the patient resides by mailing a written report, telephoning, or electronically transmitting a report within seven calendar days of the time of identification.

2505: HEV detection shall be reported by laboratories within one working day after the health care provider or other person authorized to receive the report has been notified. Laboratories shall transmit these reports to the local health officer by courier, mail, electronic facsimile or electronic mail.

V. ADDITIONAL RESOURCES

A. General Information/ Patient Education

- [CDC Hepatitis E Questions and Answers for the Public](http://www.cdc.gov/hepatitis/hev/efaq.htm)
(<http://www.cdc.gov/hepatitis/hev/efaq.htm>)
- [CDPH Hepatitis E webpage](https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Hepatitis-E.aspx)
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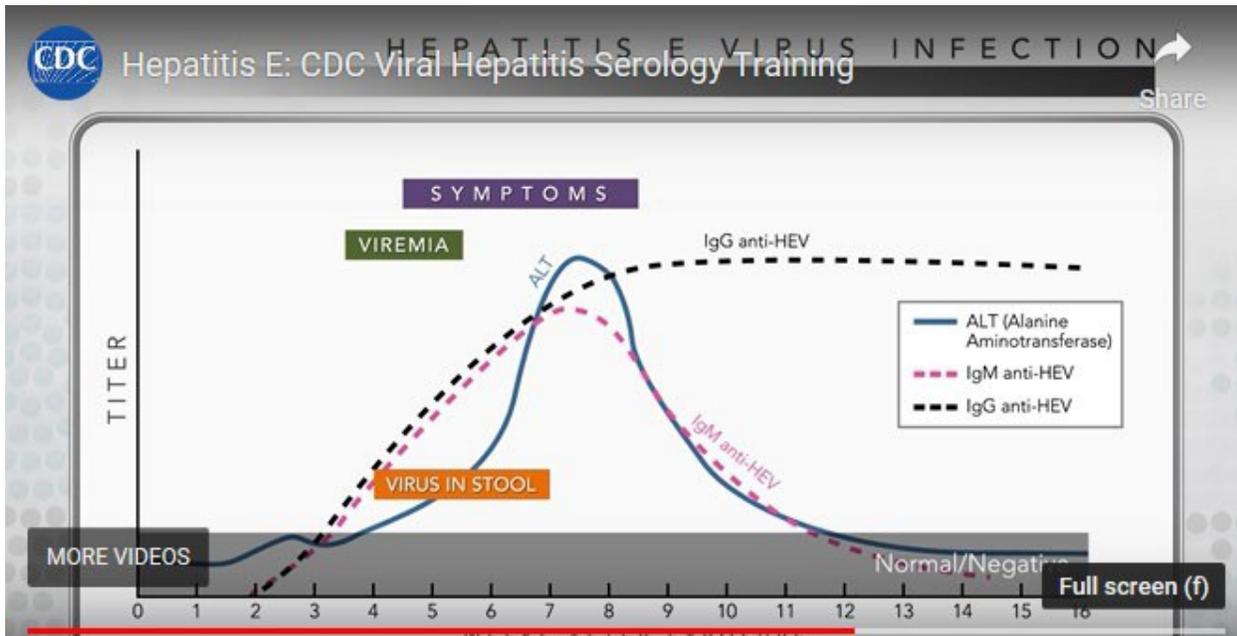
C. Tables and Figures

Table. Characteristics of HEV genotypes

Characteristics	Genotype 1	Genotype 2	Genotype 3	Genotype 4
Geographic Location	Africa and Asia	Mexico, West Africa	Developed Countries	China, Taiwan, Japan
Transmission route	Water-borne Fecal- oral Person to Person	Water-borne Fecal-oral	Food-borne	Food-borne
Groups at high risk for infection	Young Adults	Young Adults	Older Adults (>40 years) and Males Immuno-compromised persons	Young Adults
Zoonotic transmission	No	No	Yes	Yes
Chronic Infection	No	No	Yes	No
Occurrence of Outbreaks	Common	Smaller scale outbreaks	Uncommon	Uncommon

Source: [CDC Hepatitis E Questions and Answers for Health Professionals](https://www.cdc.gov/hepatitis/hev/hevfaq.htm#section1) (https://www.cdc.gov/hepatitis/hev/hevfaq.htm#section1)

Figure. HEV shedding and serological response



Source: [CDC Viral Hepatitis Serology Training](https://www.cdc.gov/hepatitis/resources/professionals/training/serology/training.htm)
(<https://www.cdc.gov/hepatitis/resources/professionals/training/serology/training.htm>)

VI. UPDATES

Original version finalized and completed on December 11, 2019

VII. Summary of Action Steps: HEPATITIS E

Action	Specific Steps
Begin case investigation as soon as possible after a new case of HEV infection is reported from a clinical laboratory or health care provider.	<ul style="list-style-type: none"> • Contact health care provider for medical records and/or contact patient for interview. Use CDPH HEV CRF (CDPH 8701) to guide interview.
Verify that patient meets the confirmed or probable case definition for HEV	<ul style="list-style-type: none"> • Does the patient meet clinical criteria? • Does the patient have any of the following laboratory criteria: <ul style="list-style-type: none"> ○ Detection of HEV RNA from a clinical specimen. ○ Detection of HEV IgM and HEV IgG in serum ○ Demonstration of a four-fold rise in HEV IgG in acute/convalescent serum specimens. ○ Negative tests for other causes of acute viral hepatitis. • Does the patient meet clinical criteria and epidemiologically linked to a confirmed case of HEV?
Proceed with investigation for patients meeting the confirmed or probable case definition	<p>Use CRF, or at a minimum, collect:</p> <ul style="list-style-type: none"> • Date of onset; • Whether internationally or domestically acquired; • Whether patient is pregnant, immunocompromised, has underlying liver disease- these patients should be monitored by provider for complications; • Assess need for confirmatory laboratory testing by CDC.
Be aware of patients in sensitive occupations or situations	<ul style="list-style-type: none"> • Risk of person-to-person spread is very low. • Patients should be educated on good personal hygiene.
Report Confirmed and Probable cases	<ul style="list-style-type: none"> • Completion of the Clinical, Laboratory, and Epidemiological Information Tabs in CalREDIE, is not required but encouraged to standardize assessment of risk factors. • Jurisdictions participating in CalREDIE may fill out CDPH 8701
If the patient appears to be part of a point-source outbreak, follow your protocol for outbreak investigations.	<ul style="list-style-type: none"> • Suspected outbreaks should be reported within 24 hours to CDPH.

If you require assistance with your investigation of hepatitis E virus, call DIS at 510-620-3434.