



Public Health
England

Protecting and improving the nation's health

Public health operational guidelines for hepatitis E

Health protection response to reports of hepatitis E infection

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. It does this through world-class science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. PHE is an operationally autonomous executive agency of the Department of Health.

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Document History

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Level of evidence	Expert opinion and previous scientific observation
Disease (name)	Hepatitis E virus (HEV) and its associated illness hepatitis E
Purpose, background, introduction, intended audience	To enable health protection teams (HPT) to respond appropriately to laboratory reports of HEV infection and clinical notifications of HEV infection. This guideline supports health protection professionals and is intended as a supplement to, rather than a replacement of, professional judgement
Risk assessment	The HPT should ensure risk assessment including verification of the diagnosis

Table of Abbreviations

EHO	Environmental health officer
HEV	Hepatitis E virus
HPT	Health Protection Team
IgG	Immunoglobulin G
IgM	Immunoglobulin M
RNA	Ribonucleic acid

Further Reading

UK Standards for Microbiology Investigations for Acute Infective Hepatitis http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317131679525
Hepatitis E https://www.gov.uk/government/publications/hepatitis-e-symptoms-transmission-prevention-treatment/hepatitis-e-symptoms-transmission-treatment-and-prevention
British Liver Trust www.britishlivertrust.org.uk/liver-information/liver-conditions/hepatitis-e/
Also see References

Epidemiology

HEV is a family of at least four closely related viruses referred to as genotypes 1 to 4 (G1-4) each of which has distinct host preferences and patterns of illness¹. HEV infection and the disease it causes, hepatitis E, are found worldwide.

HEV is hyper-endemic through much of the developing world where sanitation and food hygiene may be poor. Infections in the developing world are usually linked to G1 (South Asia, Middle East and Africa) and G2 viruses (Mexico). In these countries the virus results in sporadic cases of hepatitis but also in large water-borne outbreaks associated with faecal contamination of water. Data from both epidemic and sporadic hepatitis E cases in hyper-endemic regions indicates the clinical attack rates are highest among young adults².

In contrast, cases in the developed world are mainly sporadic and are linked to G3 (Europe, North America and Japan) and G4 viruses (South East Asia). Both G3 and 4 viruses are enzootic and found widespread in a number of animal species including domesticated pigs, wild boar and deer³.

In Europe and North America, the majority of HEV cases are acquired indigenously through the dietary route although cases are also observed in travellers returning from areas where HEV is hyper-endemic. Thus hepatitis E cases will reflect infection by both indigenous viruses and by imported viruses. Indigenous virus is thought to transmit in humans as a zoonosis resulting in widespread infections which present, if at all, as sporadic cases of hepatitis E. Human infection with HEV in high income countries rarely if ever leads to secondary transmission.

A programme of enhanced surveillance of hepatitis E has been running in England and Wales since 2003 and shows the majority of cases to be acquired indigenously⁴. Six hundred and ninety-one cases were reported in 2013 including 477 (69%) indigenously acquired infections. The demography of indigenous hepatitis E is striking with the majority occurring in males over the age of 50 years. All but one of the indigenous cases characterised in the last 10 years are G3.

Transmission:

- mode of transmission – faecal-oral (G1 and G2), zoonotic (G3 and G4), parenteral (reports from Asia and Europe)
- incubation period – range 15-60 days (average 40 days)
- immunity – uncertain whether infection confers lifelong immunity
- coincidental infections within households do occur, however secondary/ intra-familial transmissions are rare

Source of infection

In the developing world the virus transmits enterically via the faecal-oral route. Infection is linked to the consumption of human sewage-contaminated food or water.

In the developed world the virus transmits zoonotically. There is good evidence from Japan and France supporting the acquisition of HEV through the consumption of raw/ undercooked deer, boar and pig meat⁵⁻⁷. Case-control studies from England⁸ have indicated that HEV infection is linked to the consumption of processed pork. A study of HEV in pigs entering the food chain at the time of slaughter showed that nearly 95% of animals were seropositive at slaughter and that 1% of animals carried a high viraemia⁹. In addition, a recent study showed that 10% of pork sausages sampled at point of sale from UK retailers to be HEV RNA positive¹⁰.

Reports of transfusion transmitted hepatitis E demonstrate that the virus can be acquired parenterally¹¹⁻¹³. A recent study showed 1:3000 donations to be HEV RNA positive and that asymptomatic infection among blood donors is widespread in England¹⁴. A 42% transmission rate from HEV containing blood components was demonstrated.

Clinical features

Clinical illness

There is good evidence to suggest differences in pathogenicity between the HEV genotypes. The majority of HEV infections are asymptomatic. In symptomatic cases the disease is usually mild. Symptoms typical of acute hepatitis E include jaundice, dark urine, pale stools, fatigue, loss of appetite, abdominal pain, fever and nausea¹.

Infections during pregnancy, in particular in the third trimester, are associated with a 30% mortality rate in mothers and poor neonatal outcome¹⁵. This has been reported in hyper-endemic areas where G1 viruses circulate and does not appear to be a feature of G3 infections in this country.

Chronic HEV infection is increasingly recognised in immunocompromised individuals including solid organ transplant recipients, patients with haematological disorders and HIV-infected persons¹⁶⁻¹⁸. These cases are in the main asymptomatic with only mild liver enzyme derangement although the long-term prognosis for individuals with chronic hepatitis E is poor. Chronic hepatitis E infection can result in rapidly progressive liver fibrosis and cirrhosis with death due to decompensated liver disease. All but one of the cases of chronic hepatitis E has been linked to G3 infections, the remaining case has been linked to a G4 infection.

Acute HEV infection in patients with pre-existing chronic liver disease has been associated with a poor outcome. A 70% mortality rate linked to HEV infections has been reported in patients with chronic liver disease¹⁸⁻¹⁹. Alcohol consumption is thought to be an important risk factor as a more severe illness following HEV infection has been demonstrated in individuals with hepatic steatosis or hepatic fibrosis due to alcohol²⁰. The clinical features following infection are similar to acute hepatitis but are then complicated by decompensation of chronic liver disease, appearance of ascites and hepatic encephalopathy²¹.

Treatment

In the majority of hepatitis E cases no treatment will be required as these infections will clear uneventfully. However, individuals with persistent HEV infection may require intervention. Data from the transplant setting have shown that a reduction in the levels of suppression of an individual's immune system led to viral clearance in 30% of cases²². Clearance in this setting is usually associated with seroconversion and frequently with a transaminitis. Antiviral treatment with pegylated interferon and/ or ribavirin has also been used successfully to treat chronic HEV infections where alteration of the level of immune suppression has either been impossible or ineffective²³⁻²⁴.

Vaccine

There is currently no vaccine licensed for use in the UK. A vaccine termed Hecolin® (HEV 239) is licensed for use in adults in China.

Testing for hepatitis E

Recommendations for testing

Virological testing for HEV infection is recommended in the following:

1. Any individual, regardless of travel history, displaying signs and symptoms of acute hepatitis (including jaundice and raised liver transaminases). It is recommended that HEV testing is included as part of the initial acute viral hepatitis screen, as today it is a far more common cause of acute viral hepatitis than hepatitis A virus.
2. Immunocompromised individuals (see 'Green Book' Chapter 6 for examples²⁵) with persistently deranged liver transaminases (please note that in these individuals liver enzymes may be only mildly deranged). There is value in considering that such individuals should have regular testing for HEV infection in the absence of elevated liver enzymes.

Laboratory testing

HEV IgM and IgG detection plus HEV RNA testing can be undertaken on plasma or serum samples. Methods for HEV RNA detection on stool samples are also available.

The detection of HEV IgM alone is not diagnostic of HEV infection. This may occur in either of the below times:

- when a sample is found to be HEV IgM reactive but IgG non-reactive OR
- when only HEV IgM testing has been undertaken

If testing finds a sample to be HEV IgM reactive alone then additional IgG antibody and HEV RNA testing must be undertaken prior to a hepatitis E diagnosis being given.

HEV RNA testing must be undertaken when screening samples from immunocompromised individuals. Diagnosis through HEV antibody testing alone is not reliable in this setting.

Laboratory monitoring of viral load in plasma can indicate successful therapy. Therapy should be continued until there is clearance of virus from the stool to ensure that relapse does not occur after stopping treatment²⁶.

HEV RNA testing and genotyping are recommended in cases of pregnant women who are found to be infected.

Case definition/ working diagnosis

The following case definitions apply to sporadic acute hepatitis E or chronic hepatitis E cases. These definitions may be amended in an outbreak situation.

A diagnosis of a HEV infection may be confirmed by serology alone, by molecular testing alone or a combination of both. Therefore:

Criteria for defining an acute HEV infection in a patient with acute hepatitis

An acute HEV infection is confirmed by one of the following virology laboratory markers:

- HEV IgM and IgG positive
- HEV RNA positive (with or without detectable HEV antibodies)

Criteria for defining a chronic hepatitis E case with acute hepatitis

A case of chronic HEV infection is confirmed by the following virology laboratory markers:

- HEV RNA persisting for at least 3 months (with or without detectable HEV antibodies)

Notifiable disease

As one of the causes of acute infectious hepatitis, HEV infection is a notifiable disease in accordance with the Health Protection (Notification) Regulations 2010, Statutory Instruments no.659. Registered medical practitioners attending patients are required to notify the proper officer of the local authority, in which they attended the patient, of a case or clinically suspected case of acute infectious hepatitis. Diagnostic laboratories also have a duty under the Regulations to notify the PHE electronically when they identify evidence of hepatitis E infection, through the laboratory reporting system.

Health protection response to notification of hepatitis E

As HEV does not transmit readily from person-to-person, the public health risk is thought to be minimal from this route. See [Appendix 2](#) for summary of health protection response.

Immediate actions

On receipt of a report or notification of a case of acute or chronic hepatitis E infection, the HPT should:

1. Verify the laboratory results to determine whether the case is confirmed (see case definition).
2. For laboratory confirmed cases (as defined in the case definition), the HPT should arrange assessment of the following details to guide health protection management; this information could be obtained from the clinician at the time of notification or by posting the [enhanced surveillance questionnaire](#) to the patient:
 - date of onset of jaundice or other illness (anorexia, nausea, vomiting, fever, abdominal pain, abdominal tenderness, hepatomegaly)
 - whether infection is related to travel outside the UK; collect information on dates of departure and return to the UK and on countries visited
 - whether the patient is pregnant, immunocompromised (see 'Green Book' Chapter 6 for examples²⁴), has a history of liver disease/ liver injury or is in a group for which there is potentially an increased risk of spreading infections via the faecal-oral route

Identify groups for which there is increased risk of spreading infection

The risk of spread of infection is very low in this country. However, good personal hygiene is recommended.

Be aware of groups who are at risk of more serious illness

Immunocompromised individuals (eg solid organ transplant recipients, patients with haematological disorders and HIV-infected persons with low CD4 levels): at greater risk for the development of chronic infection and prolonged shedding of virus.

Pregnancy: increased risk of more serious illness in those with a G1 infection. We have no evidence as yet that G3 infections are associated with a poor outcome.

Individuals who have a history of liver disease, liver injury or heavy alcohol consumption could be prone to more serious or prolonged illness.

Identify exclusions

No evidence of person-to-person transmission. However, good personal hygiene is recommended.

Communications (information for patient)

Send an information leaflet to the patient with advice about preventing spread to others, see [Appendix 2](#). Further information is also available on the British Liver Trust website at: www.britishlivertrust.org.uk/liver-information/liver-conditions/hepatitis-e/

Out of hours/ Identification of contacts/ Urgent contact with HPTs, RD, Comms

No action for sporadic cases.

Role of other parts of PHE

PHE Colindale:

- expert advice on laboratory diagnosis
- reference testing
- expert advice on investigation of clusters/outbreaks/transmissions

PHE Microbiology Services Public Health Laboratories:

- advice on laboratory diagnosis
- local testing

Role of other agencies

- clinicians: diagnosis and reporting
- NHS laboratories: referral of samples
- local authorities involved in investigation if appropriate

Surveillance and follow up

A structured enhanced surveillance questionnaire is available for laboratory confirmed cases of hepatitis E (as defined in the case definition) at:

<https://www.gov.uk/government/publications/hepatitis-e-surveillance-form>

The first section of the enhanced surveillance questionnaire collects key surveillance information including travel. Subsequent sections are designed to collect exposure information for indigenous cases only if collection of detailed information is felt to be useful, eg in an outbreak, cluster or for an unusual case of HEV (eg hepatitis E in an infant).

Copies of the enhanced surveillance questionnaires should be returned to zoonoses@phe.gov.uk

Subsequent actions (with timescales if appropriate)

If HEV infection is diagnosed in an immunocompromised individual then follow-up virological testing is essential for monitoring antibody development, determining viral clearance and for monitoring the viral load in plasma and stool during antiviral therapy (see Clinical Features; Treatment). It is advised that the HPT recommend referral of the individual to a hepatologist through the GP.

Outbreak investigations

If associated cases are identified – outbreak investigation and control in accordance with the HPT's standard practice and in liaison with PHE Colindale.

Identification of case closure criteria

Do this after all necessary actions are completed.

Notes relating to specific settings

Not applicable

Identification of long term follow up actions

If HEV infection is diagnosed in an immunocompromised individual then follow up virological testing is essential for monitoring antibody development, determining viral clearance and for monitoring the viral load during antiviral therapy (see clinical features/ treatment section).

National guidance/reference material/information

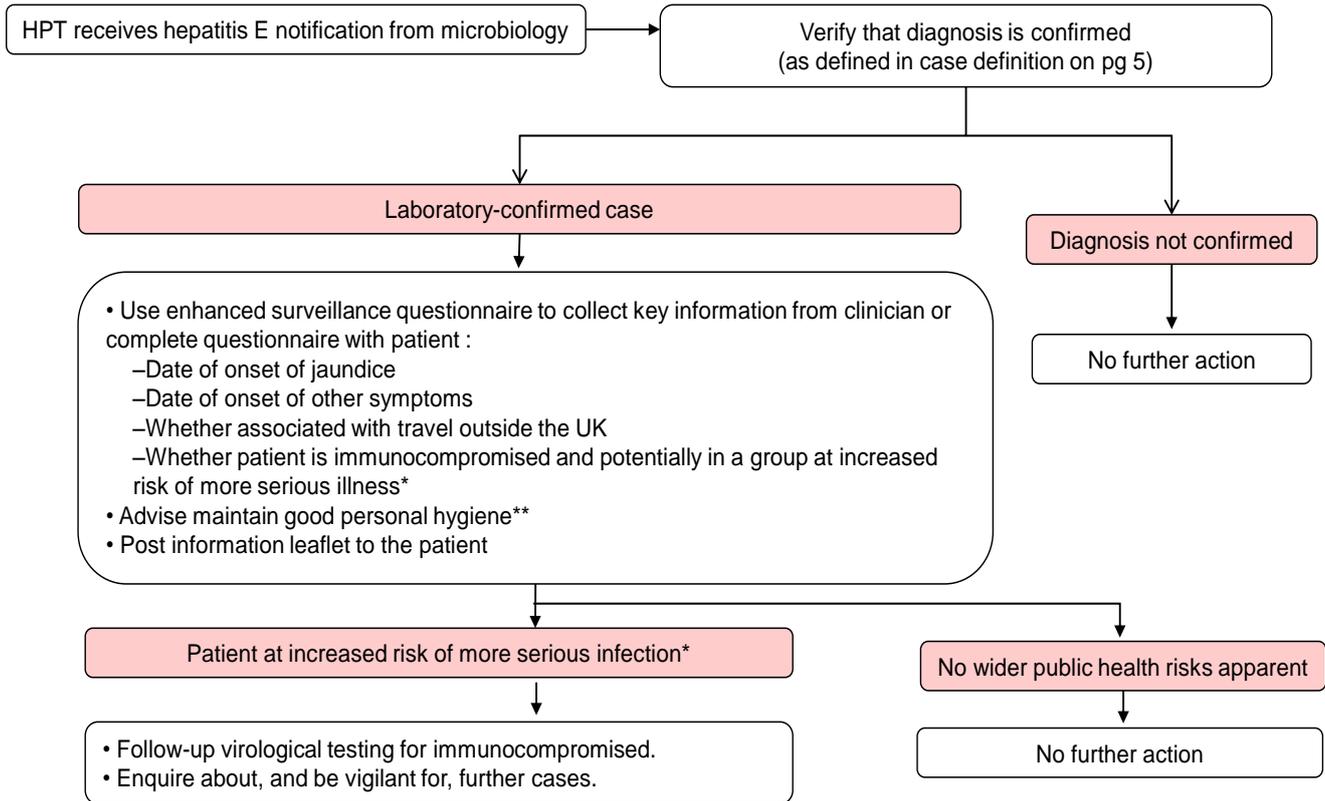
- Hepatitis E leaflet (see [Appendix 2](#))
- Enhanced surveillance questionnaire
<https://www.gov.uk/government/publications/hepatitis-e-surveillance-form>
- British Liver Trust Hepatitis E Q&A's
www.britishlivertrust.org.uk/liver-information/liver-conditions/hepatitis-e/

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Appendix 1: Summary of health protection response to a notification of hepatitis E infection



*Immunocompromised individuals may develop chronic disease and shed virus for longer. For pregnant individuals there is an increased risk of serious illness in those with G1 infection. (Note: Individuals who are pregnant or who have a history of liver disease, liver injury or heavy alcohol consumption could be more prone to HEV infection or have prolonged duration of illness. However, monitoring is not usually required.)

**Person-to-person spread is very rare in hepatitis E. However, good personal hygiene is advisable as with any organism spread via the faecal-oral route. Reference: Preventing person-to-person spread following gastrointestinal infections: guidelines for public health physicians and environmental health officers. *CDPH* 2004; 7(4): 362-384. Available at:

<https://www.gov.uk/government/publications/preventing-person-to-person-gastrointestinal-infections>

Appendix 2: Information leaflet



Public Health
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Hepatitis E virus information leaflet

What is hepatitis E?

Hepatitis E is an illness of the liver caused by the hepatitis E virus (HEV), a virus which can infect both animals and humans. HEV infection usually causes no symptoms but if it does, it produces only a mild disease, hepatitis E. In rare cases, however, it can prove fatal, particularly in pregnant women but seems not to do so in this country. Normally the virus infection will clear by itself. However, it has been shown that in individuals whose immune system is suppressed (eg HIV-infection, chemotherapy or in transplant patients) the virus can result in a persistent infection which may lead to chronic inflammation of the liver.

How can I tell if I have hepatitis E?

Symptoms of hepatitis E include yellowing of the skin and eyes (jaundice), darkening of the urine and pale stools preceded by tiredness, fever, nausea, vomiting, abdominal pain and loss of appetite. The illness usually resolves within one to four weeks. A test for HEV antibodies and RNA can be undertaken to confirm HEV infection on either blood or oral fluid samples.

How common is hepatitis E?

Hepatitis E occurs in regions of the world where sanitation may be poor including Asia, Africa and Central America. However, we now know that HEV infection and hepatitis E can be caught in this country. This was first recognised in 2003 and the numbers of confirmed hepatitis E cases and infections have increased significantly over the past few years.

How is hepatitis E virus transmitted?

Through the developing world, the virus is transmitted by the consumption of human sewage-contaminated food or water. In the developed world the virus is believed to transmit from animals to humans through the consumption of undercooked or raw pig and game meat, processed pork and shellfish. The transmission routes in the UK remain unknown. Person to person transmission of the virus is very rare though the virus has been transmitted through blood transfusion and transplantation. Someone with hepatitis E should always wash their hands after using the toilet.

How long can I have the infection before developing symptoms?

The average incubation period for hepatitis E is 40 days (range 15-60 days).

How is hepatitis E treated?

There is normally no need for any treatment. However in patients with chronic infection antiviral treatment has been used successfully. Pregnant women should seek advice from their antenatal carer.

Can hepatitis E infection be prevented?

Currently, there is no licensed vaccine for hepatitis E. When travelling to countries with poor sanitation, it is advisable to boil all drinking water, including water used for brushing teeth. Avoid the consumption of raw or undercooked meat and shellfish.

Where can I get further help?

Further information and advice is available from:

- PHE (<https://www.gov.uk/government/collections/hepatitis-e>)
- The British Liver Trust (0800 652 7330 or www.britishlivertrust.org.uk/liver-information/liver-conditions/hepatitis-e/)
- Your own GP

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