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

2019 Guidelines

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Public Health England
Wellington House
133-155 Waterloo Road
London SE1 8UG
Tel: 020 7654 8000
www.gov.uk/phe
Twitter: @PHE_uk
Facebook: www.facebook.com/PublicHealthEngland

Prepared by: Samreen Ijaz, Bengü Said, Aisling Vaughan, Clarissa Oeser, Koye Balogun and Richard Tedder.
For queries relating to this document, please contact: zoonoses@phe.gov.uk

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Contents

Document history

Date	Reason for Change	Issue No.
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18 December 2011	Clarification regarding low public health risk, surveillance and follow up Flow-chart updated to clarify recommendations for follow up Appendix added – letter and questionnaire to patient	1.1
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3 December 2014	PHE revised document and enhanced surveillance questionnaire	2.0
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Contact information	
Email	zoonoses@phe.gov.uk

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 UK Standards for Microbiology Investigation V 53: Screening and monitoring for hepatitis E infection: https://www.gov.uk/government/publications/smi-v-53-screening-for-hepatitis-e-infection
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 4 closely related viruses that affect humans referred to as genotypes 1 to 4 (G1-4) each of which has distinct host preferences and patterns of illness[1]. HEV infection and the disease it causes, hepatitis E, are found worldwide.

HEV is hyper-endemic in developing countries where sanitation and food hygiene may be poor. Infections in these countries are usually linked to G1 (South Asia, Middle East and Africa) and G2 viruses (Mexico). Infections with 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 amongst young adults[2].

In contrast, cases in industrialised countries are mainly sporadic and are linked to G3 (Europe, North America and Japan) and G4 viruses (South East Asia). HEV G3 and G4 viruses are enzootic and found widespread in a number of animal species including domesticated pigs, wild boar and deer[3].

Although in Europe and North America, the majority of HEV cases are HEV G3 and acquired indigenously through the dietary route, there are also cases of HEV G1 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 indigenously[4]. One-thousand-two-hundred-and-forty-three (1,243) cases were reported in 2016, including 993 (80%) 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), and bloodborne, meaning transfusion of blood/ blood products (G3).

Incubation period: range 15 to 60 days (average 40 days).

Immunity: uncertain whether infection confers lifelong immunity.

Coincidental infections within households do occur, however person-to-person transmissions are rare.

Source of Infection

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

In industrialised countries 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 meat[5-7]. Case-control studies from England[8] 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 viraemia[9]. In addition, a study performed on a single batch of a small sample of pork sausage from UK retailers at point of sale showed that 10% were HEV RNA positive[10].

Reports of transfusion transmitted hepatitis E demonstrate that the virus can be acquired parenterally[11-17]. A study undertaken in 2014 showed 1:3000 donations to be HEV RNA positive and that asymptomatic infection amongst blood donors is widespread in England[14]. A 42% transmission rate from HEV containing blood components was demonstrated. Following a recommendation by SaBTO, NHS Blood and Transplant (NHSBT) introduced selected hepatitis E screening of blood components from 1 March 2016. This was extended to universal blood donation screening on 10 April 2017.

Clinical features

Clinical illness

There are differences in pathogenicity between the HEV genotypes.

The majority of HEV G3 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 nausea.

Chronic HEV G3 infection is increasingly recognised in immunocompromised individuals including solid organ transplant recipients, patients with haematological disorders and HIV-infected persons[18-23]. These cases are mainly 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.

Acute HEV G3 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 disease. Alcohol consumption is thought to be an important risk factor for a more severe illness following HEV infection. The clinical features following chronic infection are similar to acute hepatitis but are then complicated by decompensation of chronic liver disease, appearance of ascites and hepatic encephalopathy[24-28].

In addition to hepatitis, HEV infection may also lead to a range of neurological syndromes, the symptoms of which may dominate the clinical presentation. In such circumstances hepatitis may be mild or absent[1]. Cases have been associated with both G1 and G3 infections. The commonest neurological manifestations reported are Guillain-Barré syndrome (GBS), neuralgic amyotrophy and encephalitis/myelitis[33]. A distinctive bilateral form of neuralgic amyotrophy is suggested to be a specific clinical phenotype associated with HEV infection[34].

In hyper-endemic areas where G1 viruses circulate, infections during pregnancy, in particular in the third trimester, are associated with a 30% mortality rate in mothers and poor neonatal outcome[29]. G1 infected pregnant women should be referred for clinical management. However, this clinical picture does not appear to be a feature of G3 infections.

Treatment

In the majority of hepatitis E cases no treatment will be required as these infections will clear uneventfully. However, individuals with chronic HEV infection may require intervention. Data from the transplant setting have shown that a reduction in the levels of immuno-suppression led to viral clearance in 30% of cases[26]. Viral 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 ineffective[27].

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 cases:

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 examples[25]) 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:

1. when a sample is found to be HEV IgM reactive but IgG non-reactive

   OR

2. 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. Genotyping is recommended and is performed at the PHE reference laboratory in the Virus Reference Department (VRD), Colindale: https://www.gov.uk/guidance/blood-borne-viruses-unit-bbvu-services

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 treatment[26].

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

Interpretation of testing in the immunocompetent and immunocompromised individual are outlined in Appendices 4 and 5.

Case definition / working diagnosis

A diagnosis of a HEV infection may be confirmed by serology alone, by molecular testing alone or a combination of both. The following case definitions apply to sporadic acute hepatitis E or chronic hepatitis E cases. These definitions may be amended in an outbreak situation.

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

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

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

Criteria for defining a chronic hepatitis E case

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 notifcation 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 a summary of health protection responses.

Since the recognition of bloodborne hepattits E and the introduction of universal screening in donors in April 2016, NHSBT have requested all case-donors to complete a surveillance questionnaire by Selectsurvey. The donor questionnaires are always requested through NHSBT and HPT's do not need to take further action.

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). If confirmed, encourage the local laboratory to send a sample for genotyping to PHE Colindale (laboratories can get further advice from the Blood borne virus unit).
2. For laboratory confirmed cases (as defined in the case definition), the HPT may consider arranging assessment of the following details – this information could be obtained from the clinician at the time of notification or by providing the patient with the Enhanced surveillance questionnaire:

    - date of onset of symptoms if present (symptoms include: loss of appetite, nausea, vomiting, diarrhoea, abdominal pain, fever, headaches, weakness, numbness or tingling of limbs, dizziness, light headedness, joint pain, muscle pain, itching, fatigue, tiredness, lethargy or exhaustion, jaundice, dark coloured urine
    - hospital admission for HEV
    - duration of illness
    - whether the patient has any medical conditions or is pregnant
    - whether infection is related to travel outside the UK (collect information on dates of departure and return to the UK and on countries visited in the 9 weeks prior to diagnosis) – travel history is particularly important in pregnancy as an indicator of potential G1 infection
    - whether the patient has eaten certain food items in the 9 weeks prior to diagnosis (for example, pork meat sausages, pate, shellfish)
    - whether the patient is happy to be contacted again

- the risk of spread of infection is very low in this country – however, advice on good personal hygiene is recommended[31]

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

Immunocompromised individuals (for example, solid organ transplant recipients, patients with haematological disorders and HIV-infected persons with low CD4 levels): at greater risk for the development of chronic HEV G3 infection and prolonged shedding of virus[32]. Recommendation for clinicians is to ensure a sample has been sent to a reference laboratory for genotyping (see 'Testing for Hepatitis E') and to repeat HEV RNA testing until clearance is achieved.

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, therefore it is recommended to ensure a sample has been sent to the reference laboratories for genotyping. In pregnant women with HEV G1, clinicians should monitor signs of illness closely.

Individuals with a history of liver disease, liver injury or heavy alcohol consumption are at increased risk of serious or prolonged illness.

Person-to-person transmission and occupation risk

Person-to-person transmission of HEV is rare in the UK but may be higher in specific risk groups such as MSMs. No formal exclusion is required for HEV infection, but good personal hygiene is recommended. Food handlers, in particular, should comply with routine good food practice and standard infection control advice [31]. Occupational HEV transmission from health care workers has not been demonstrated. As a precautionary measure personnel such as health care workers may be need to be considered on a case-to-case basis in relation to their HEV viral load and conduct of exposure prone procedures (EPPs). In these cases advice should be sought from PHE's Blood Borne Virus Unit in Colindale.

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

PHE Microbiology Services Public Health Laboratories provide:
- advice on laboratory diagnosis
- local testing

Role of other agencies

Clinicians provide:
- diagnosis, reporting and clinical management

NHS laboratories provide:
- referral of samples

Local authorities provide:
- involved in investigation if appropriate

Surveillance and follow up

If required, ensure the enhanced surveillance questionnaire is provided to laboratory confirmed cases of hepatitis E (https://www.gov.uk/government/publications/hepatitis-e-surveillance-form; questionnaires should be returned to zoonoses@phe.gov.uk)

This questionnaire collects key surveillance information including exposures such as travel and food items as well clinical symptoms.

Subsequent / long-term 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 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

After all necessary actions are completed.

Notes relating to specific settings

Not applicable.

National guidance / reference material / information

Some of the resources available include:

- hepatitis E leaflet (see Appendix 2)
- hepatitis E guidance https://www.gov.uk/government/publications/hepatitis-e-symptoms-transmission-prevention-treatment/hepatitis-e-symptoms-transmission-treatment-and-prevention
- enhanced surveillance questionnaire https://www.gov.uk/government/publications/hepatitis-e-surveillance-form
- British Liver Trust Hepatitis E Q&As www.britishlivertrust.org.uk/liver-information/liver-conditions/hepatitis-e/
- British Transplantation Society (BTS) transplant guidance webpage https://bts.org.uk/guidelines-standards/

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Acknowledgements

Hepatitis E Guidelines Working Group

Mike Ankcorn: Clinical research fellow

Koye Balogun: Clinical scientist (Chair of hepatitis E guidelines working group)

Richard Elson: Head of risk assessment and response

Roger Gajraj: Consultant in communicable disease control

Samreen Ijaz: Clinical scientist

Charles Irish: Consultant in communicable disease control and virologist

Miranda Mindlin: Consultant in communicable disease control

Grainne Nixon: Consultant nurse

Clarissa Oeser: Public Health registrar

Bengü Said: Epidemiologist

Richard Tedder: Consultant virologist

Aisling Vaughan: Epidemiologist

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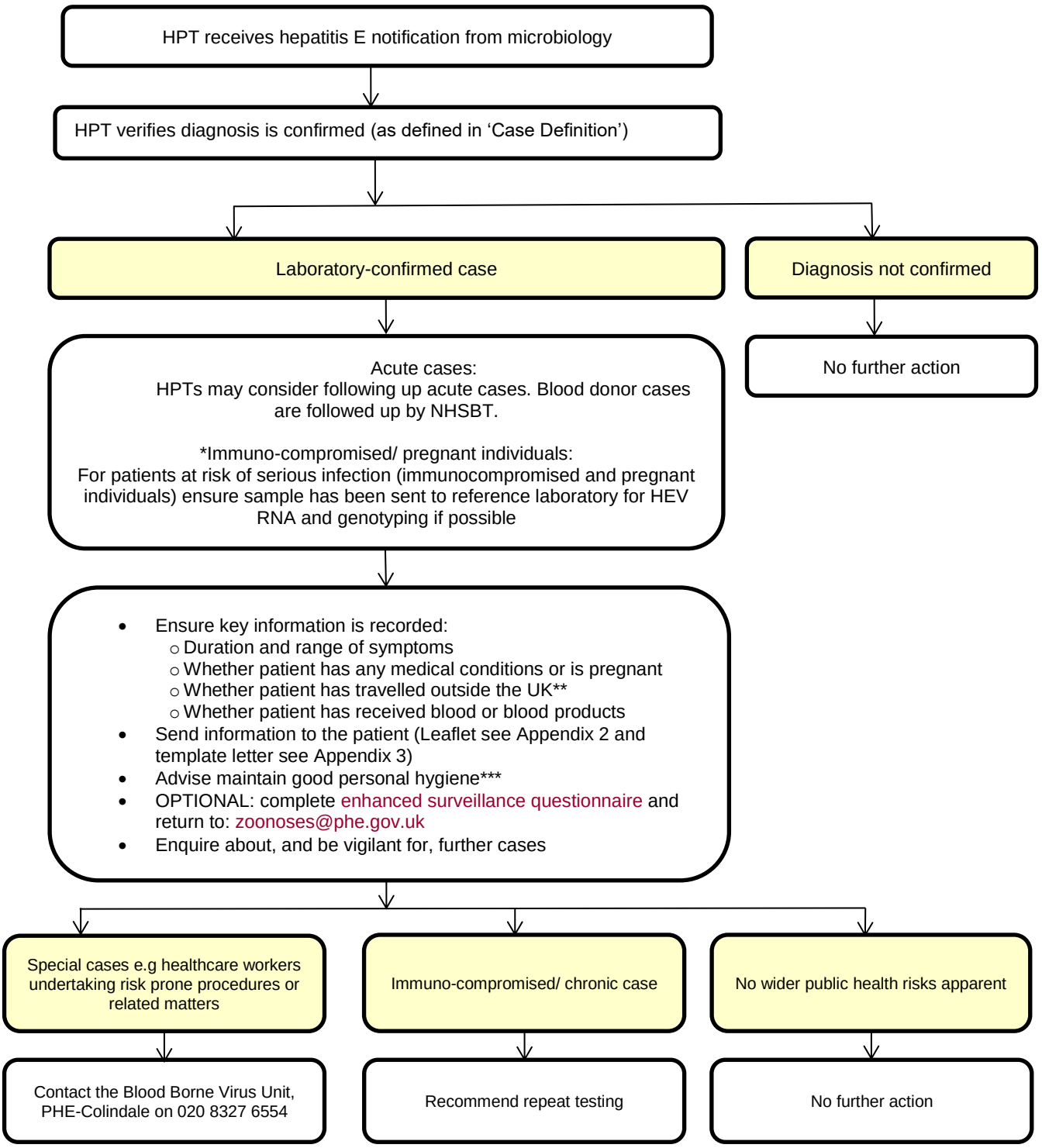
Appendix 1: summary of health protection response to notification of hepatitis E infection



*Immunocompromised individuals may develop chronic infection with HEV G3 (implies that travel associated cases don't). There is an increased risk of serious illness in pregnant individuals with HEV G1.Refer for clinical management.
**Travel history is particularly important for pregnant cases as travel may be the only indication of a potential G1 infection
***Although person-to-person spread is believed to be very rare with hepatitis E, good personal hygiene is advisable as with any organism that can be spread via the faecal-oral route[31]

Appendix 2: information leaflet

Public Health England

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. There are 4 genetic types (G1-G4) of HEV. HEV infection usually causes no symptoms but if it does, it produces only a mild disease, hepatitis E. In rare cases of G1, G2 and G4 infections, however, it can prove fatal, particularly in pregnant women. The common virus in this country and Europe, G3, appears to follow a different pattern and does not affect pregnancy. Normally the G3 virus infection will clear by itself. However, it has been shown that in individuals whose immune system is suppressed following transplantation the virus can result in an asymptomatic persistent infection which may lead to chronic inflammation of the liver.

How can I tell if I have been infected by HEV?

Most people who get infected with HEV will never know this and only a few, no more than 1%, will get any illness at the time. 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. These symptoms usually resolve within 4 weeks. However, in individuals who are immunosuppressed, symptoms may be less obvious or non-existent. A blood test can be undertaken to confirm HEV infection.

How common is hepatitis E?

Hepatitis E due to G1, G2 and G4 occurs in regions of the world where sanitation may be poor including parts of Asia, Africa and Central America. However HEV infection caught in this country is caused by G3. This was first recognised in 2003 and the numbers of confirmed G3 hepatitis E cases and infections have increased significantly over the past few years. It is now likely that as many as 100,000 people may suffer acute infections each year.

How is hepatitis E virus transmitted?

Throughout 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. Person to person transmission of the G3 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 is chronic hepatitis E treated?

Patients with persistent and long term (chronic) infection may find that it either clears by itself or through minor changes in their immunosuppressive regimens. Where this is not the case 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 in the UK. It is important to make sure that food containing pig meat (especially sausages) is thoroughly cooked until steaming hot throughout, the meat is no longer pink and the juices run clear. 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:

- your own GP
- 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/)

Appendix 3: template letter for case

Recipient's name
Street name
Town
County/Country
Postcode

00 Month 20XX

Dear Recipient,

We are contacting you as you have recently been diagnosed with hepatitis E virus infection.

In recent years we have seen a significant increase in the number of cases in the UK. Hepatitis E infection is usually a mild disease which will clear by itself, however it can persist and be potentially life threatening in individuals with a weakened immune system. It is not entirely clear yet why cases of infections with hepatitis E are rising in the UK, but it is suspected that consumption of certain food items may be the cause.

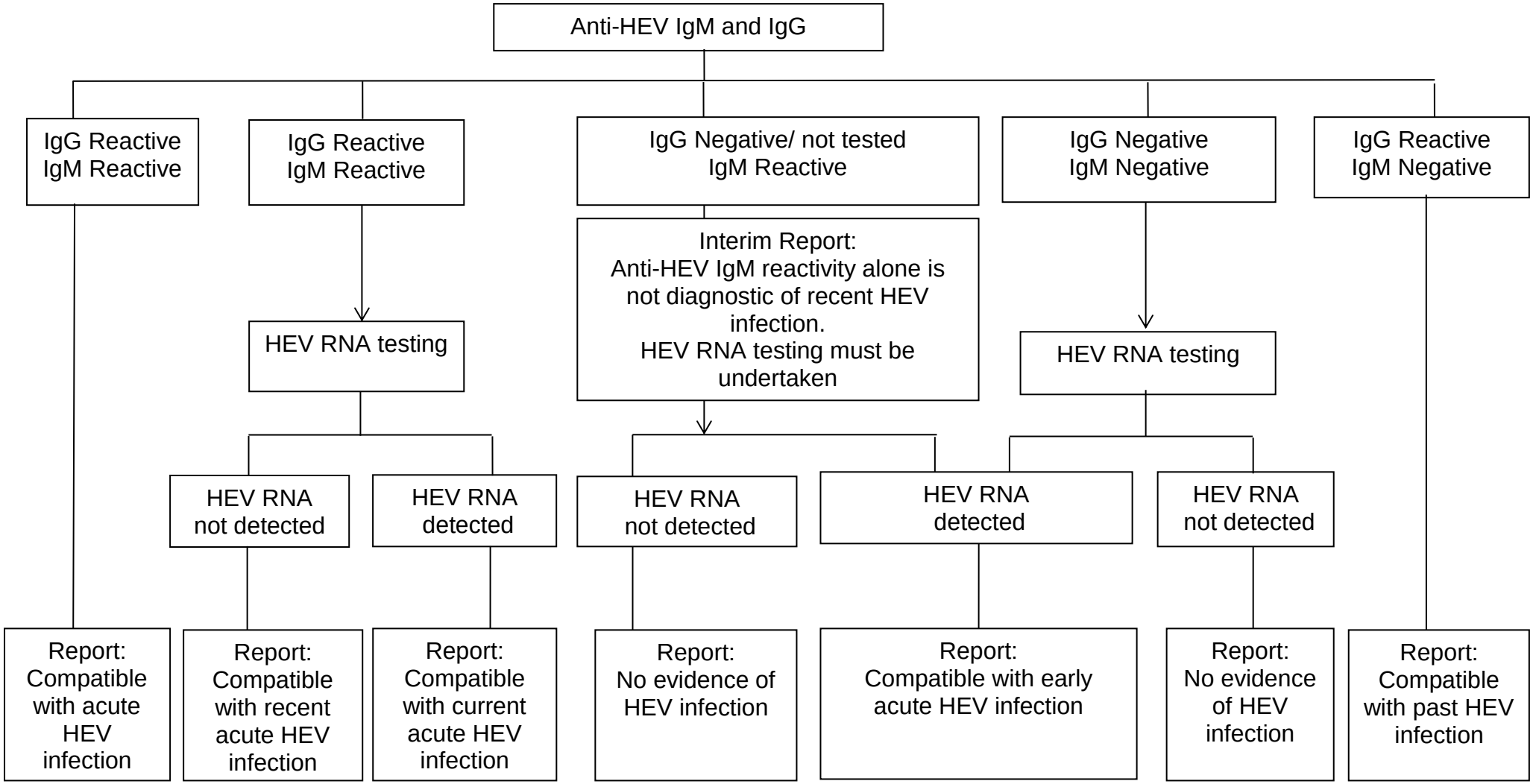
Therefore your participation in this survey is extremely important as it will help establish the source of this public health threat which has become of increasing concern.

An information leaflet and questionnaire are attached for your completion.The questionnaire should be returned to the local Health Protection Team

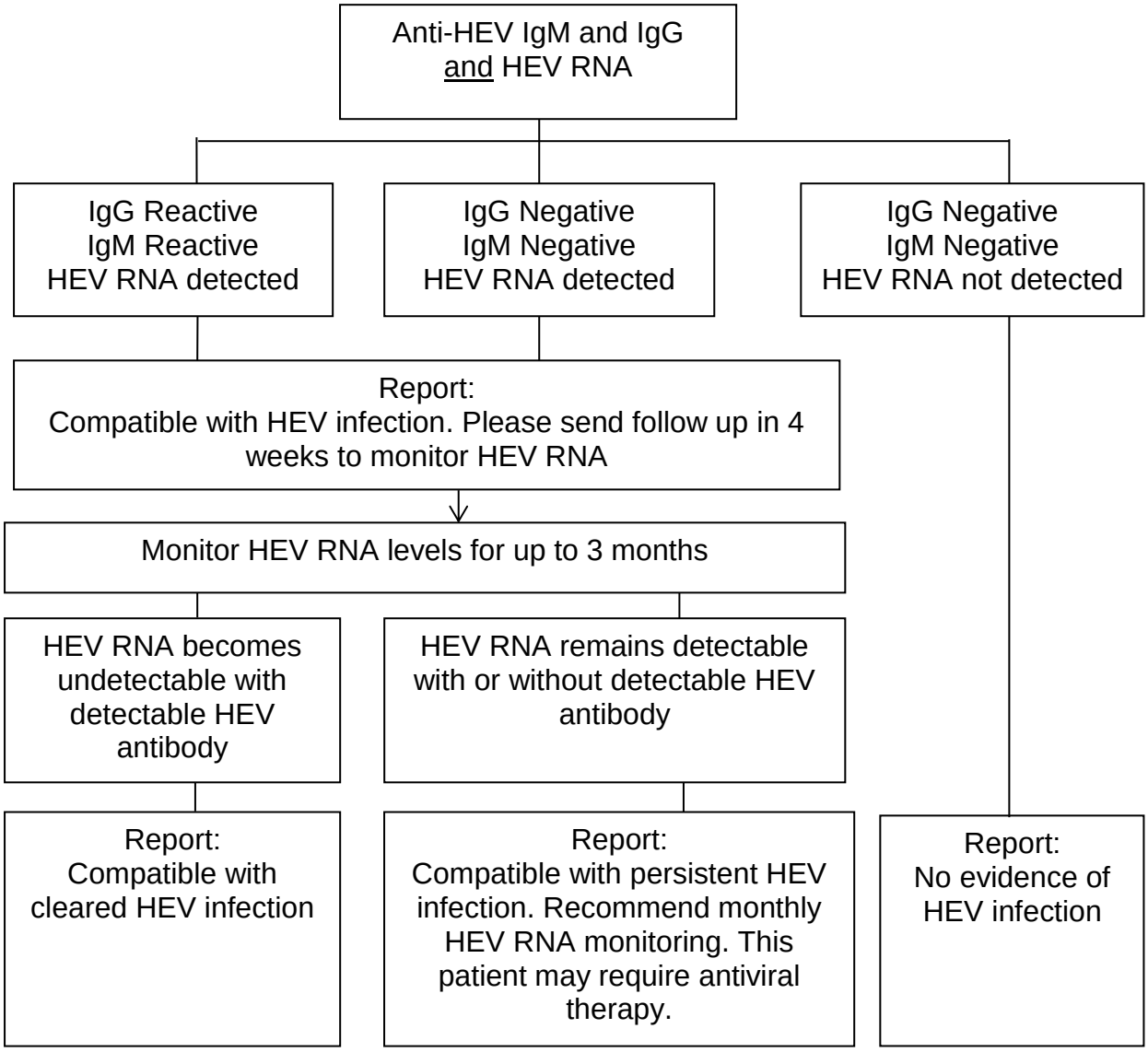
Many thanks in advance.

Yours sincerely,

Appendix 4: interpretation of testing for HEV infection in the immunocompetent presenting with recent or current acute hepatitis



Appendix 5: interpretation of testing for HEV infection in the immunocompromised host



NB: Monthly HEV RNA testing should be undertaken in those patients undergoing treatment for persistent HEV infection. Please note that viral clearance from both stool and plasma should be confirmed prior to any cessation of anti-viral treatment.