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Interim Public Health Operational Guidelines for Amoebiasis (*Entamoeba histolytica*)

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Contents

About Public Health England	2
Introduction and summary of key recommendations	5
1. Case and contact definitions for public health action	7
2. Microbiological confirmation of diagnosis	8
3. Public health management of possible or probable cases	8
4. Public health management of confirmed cases	9
5. Public health management of contacts	10
6. Algorithm for public health management of cases and contacts	11
7. Outbreaks	12
8. Supporting documents – Fact sheet and Template letter for GPs	13
9. Appendix A: Membership of the <i>Entamoeba histolytica</i> working group	16
10. Appendix B: Disease Information	17
11. Appendix C: Evidence and rationale for public health action	20
12. References	32

Introduction

Entamoeba histolytica (*E. histolytica*) is notifiable by laboratories to the proper officer of the local authority as a causative agent under the Health Protection Regulations 2010. Amoebic dysentery and amoebiasis are not specifically notifiable by registered medical practitioners.

Amoebiasis is an infection caused by the protozoan parasite *E. histolytica*. Two species of parasite with the same morphological characteristics have been recognised - *E. histolytica* and *Entamoeba dispar* (*E. dispar*). It is now recognised that only *E. histolytica* is able to cause invasive disease and these guidelines refer to the public health management of the disease-causing *E. histolytica* species.

The majority of cases of amoebiasis develop asymptomatic infection (90%), although potentially pose an infectious risk due to excretion of infectious cysts. Clinical features include diarrhoea, dysentery and abdominal pain in intestinal disease. Extra-intestinal disease may also exist, with amoebic liver abscess (ALA) being the commonest manifestation which may be fatal if left untreated.

It is endemic in areas with poor sanitation, with most cases seen in the UK being amongst travellers recently returned from endemic areas. Transmission is mainly through contaminated water consumption but person-to-person spread is also recognised.

There is no consistent approach to the public health management of cases and contacts of *E. histolytica* amongst developed, non-endemic countries. These guidelines are based on reviews of the available evidence for transmission of *E. histolytica* infections amongst household or other outbreak settings from published case reports or case series as well as a review of some of the existing guidelines for the public health management in non-endemic countries other than the UK.

Key updates to amoebic dysentery guidance in 2004 Preventing person to person spread following gastrointestinal infection:

- PCR is the method of choice for diagnosis of *E. histolytica* in symptomatic and asymptomatic cases
- microbiological clearance is not required for cases in any risk group
- cases should submit one stool sample, one week after treatment completion to confirm treatment success
- household, co-traveller and sexual contacts should be tested for asymptomatic infection to facilitate early treatment

Summary of key recommendations for public health management

Cases	<ul style="list-style-type: none"> • Laboratory confirmation of a diagnosis of <i>E. histolytica</i> is required to distinguish between the pathogenic <i>E. histolytica</i> and <i>E. dispar</i> • Identification of a source of infection should be attempted, including a history of foreign travel to an endemic area or epidemiological link to a confirmed <i>E. histolytica</i> case • Universal enteric precautions and exclusion for 48 hours after the resolution of diarrhoeal symptoms should be followed for all cases with diarrhoea • No additional formal exclusion periods or microbiological clearance for public health reasons for confirmed cases of <i>E. histolytica</i> infection are required • Cases should undergo screening one week after treatment completion for clinical reasons to confirm treatment success
Contacts	<ul style="list-style-type: none"> • Household, co-traveller and sexual contacts of a confirmed case should be tested for asymptomatic <i>E. histolytica</i> infection to facilitate early treatment

1. Case definitions for public health action

Table 1: Definitions of cases of *E. histolytica* infection

Possible case
<p>A)</p> <ul style="list-style-type: none"> A person with or without clinical features compatible with <i>E. histolytica</i> infection AND Local laboratory identification of <i>E. histolytica/dispar</i> on faecal microscopy pending PCR results <p>B)</p> <ul style="list-style-type: none"> A person with a clinical diagnosis of amoebic liver abscess (ALA)
Probable case
<ul style="list-style-type: none"> A possible case with an established epidemiological link to a confirmed case (usually identified via testing of contacts of a confirmed case)
Confirmed case
<ul style="list-style-type: none"> A person with <i>E. histolytica</i> infection determined by demonstration of <i>E. histolytica</i> using PCR* on a stool specimen OR A clinically compatible case AND demonstration of trophozoites on stool microscopy OR demonstration of trophozoites of <i>E. histolytica</i> in intestinal/rectal biopsy by histopathology OR A person with a clinical diagnosis of amoebic liver abscess (ALA) AND positive serology for antibodies to <i>E. histolytica</i> <p>*PCR may be accessed via the Department of Clinical Parasitology, Hospital for Tropical Diseases, London</p>

Table 2: Definition of contacts of a case of *E. histolytica* infection

CONTACTS
<p>Co-traveller: someone who has travelled with the case to an <i>E. histolytica</i> endemic country and is likely to have been exposed to the same source of infection as the case</p>
<p>Household: someone who has lived or stayed in the same household as the case whilst the case was symptomatic, on treatment for <i>E. histolytica</i> infection or at any time following the suspected time of initial infection</p>
<p>Sexual contacts: any sexual contact of the case following the suspected time of initial infection</p>

2. Microbiological confirmation of diagnosis

All cases, whether symptomatic or not, require laboratory confirmation of *E. histolytica* infection for appropriate management and treatment.

Several different diagnostic methods exist but in the UK, the use of PCR is the method of choice for definitive diagnosis in both symptomatic and asymptomatic cases (see Appendix C). PCR may be accessed via the Department of Clinical Parasitology, Hospital for Tropical Diseases, London.

3. Public health management of possible or probable cases

Refer to Section 1, Table 1 for case definitions for possible and probable cases of *E. histolytica* infection

Refer to the algorithm for public health management of cases and contacts of *E. histolytica* in Section 6

- Local laboratories should be recommended to send stool specimens positive on microscopy for *E. histolytica/dispar* for confirmatory PCR testing or directly send a stool for *E. histolytica* PCR to the Department of Clinical Parasitology, HTD, London.
- No further action should be taken on these cases until confirmation is received as the majority of cases are likely to be *E. dispar* which is indistinguishable from *E. histolytica* on microscopy examination

4. Public health management of confirmed cases

Refer to Section 1, Table 1 for case definitions for confirmed cases of *E. histolytica* infection

Refer to the algorithm for public health management of cases and contacts of *E. histolytica* in Section 6

- The following information should be obtained for all confirmed cases:
 - Relevant history of symptoms in the case and any close contacts
 - History of foreign travel, especially to endemic countries, even if travel occurred several months prior to diagnosis
 - Details of any close contacts of the case for clinical follow-up and assessment (refer to **Section 1, Table 2 for definitions of contacts of a case of *E. histolytica* infection**)
- Cases should be provided with advice on personal hygiene. The **PHE Amoebiasis (*Entamoeba histolytica*) fact sheet for members of the public** is available in Section 8 and includes hygiene advice and advice for the prevention of spread of infection
- No microbiological clearance for public health reasons for confirmed cases of *E. histolytica* infection is required
- Universal enteric precautions and exclusion for 48 hours after the resolution of diarrhoeal symptoms should be followed for all cases with diarrhoea
- No exclusion is required for asymptomatic cases
- Appropriate treatment, according to current recommendations in the BNF, should be prescribed
- Cases require 1 further stool sample to be sent for confirmation of treatment success, 7 days after treatment completion. This additional sample is for treatment assessment only, not for exclusion purposes

Any case that remains PCR positive following treatment completion should be referred to an Infectious Diseases physician for further assessment

- Contacts should be tested for *E. histolytica* infection for the purpose of early detection
- Consideration should be given to informing local Environmental Health teams of any confirmed case, including the likely source of infection
- A template letter for GPs of a confirmed case of *E. histolytica* infection is available in Section 8 of this document.

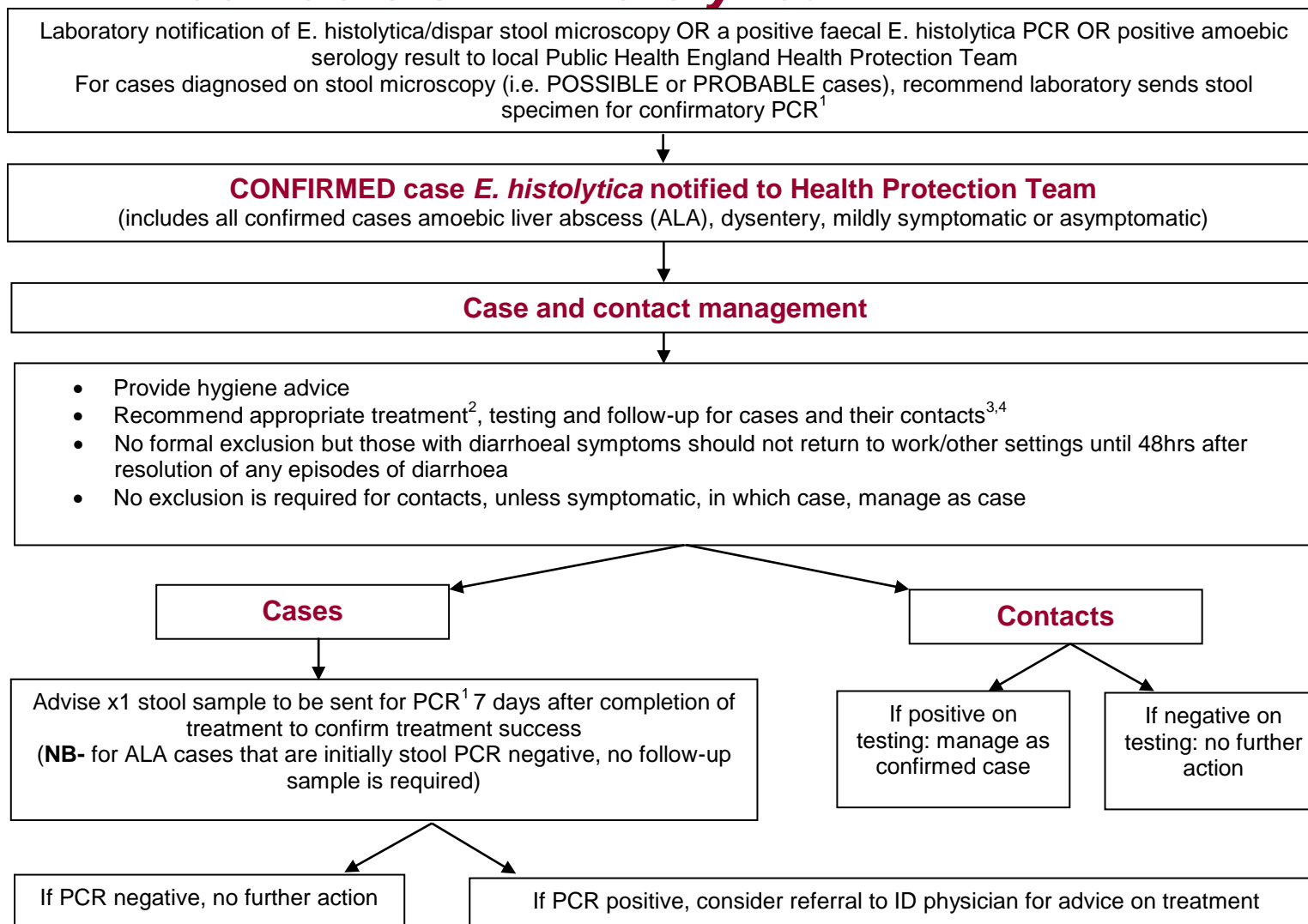
5. Public health management of contacts

Refer to Section 1, Table 2 for definitions of contacts of a case of *E. histolytica* infection

Refer to the algorithm for public health management of cases and contacts of *E. histolytica* in Section 6

- Contacts should be identified and advised to be tested for *E. histolytica* infection using stool microscopy followed by confirmatory PCR or directly by stool PCR for the purpose of early detection
- If a contact is found to be PCR positive, they should be managed as a confirmed case (refer to **Section 1, Table 1 for case definitions for confirmed cases of *E. histolytica* infection**)
- No further action is required for contacts found to be negative on testing
- Contacts with diarrhoeal symptoms should be managed as cases (refer to **Section 1, Table 1 for case definitions for probable and confirmed cases of *E. histolytica* infection**) and excluded until 48 hours after the resolution of diarrhoeal symptoms
- Contacts should be provided with advice on personal hygiene. The **PHE Amoebiasis (*Entamoeba histolytica*) fact sheet for members of the public** is available in Section 8 and includes hygiene advice and advice for the prevention of spread of infection

6. Algorithm for public health management of cases and contacts of *E. histolytica*



NOTES:

¹PCR is available at the Dept. of Clinical Parasitology at HTD, London. See below:

<https://www.gov.uk/government/collections/national-parasitology-referencelaboratory-nprl>

The Department of Clinical Parasitology, The Hospital for Tropical Diseases, 3rd Floor Mortimer Market Centre, Mortimer Market, London WC1E 6JB Dx Number: DX 6640701 Exchange: TOTTENHAM CT RD 91 WC

²Treatment: as advised in the BNF.

³Contacts: identification of undiagnosed cases and asymptomatic carriers enables early treatment to prevent development of invasive disease at a later date.

Household contact: someone who has lived or stayed in the same household as the case whilst the case was symptomatic, on treatment or at any time following the suspected time of initial infection

Co-traveller contact: someone who has travelled with the case to an *E. histolytica* endemic country and is likely to have been exposed to the same source of infection as the case

Sexual contact: anyone who has had sexual contact with the case following the suspected time of initial infection

⁴Contact testing: test using stool microscopy followed by confirmatory PCR or directly by stool PCR at Dept. of Clinical Parasitology at London HTD Mark the form: "Contact of confirmed case of *E. histolytica*"

7. Outbreaks

Outbreaks of *E. histolytica* infection are rare in developed countries such as the UK. Any suspected outbreaks should be managed in accordance with current PHE Outbreak Plans.

8. Supporting documents

Fact sheet for confirmed cases and contacts of *E. histolytica* infection

Amoebiasis (*Entamoeba histolytica*) Fact sheet for members of the public

What is amoebiasis?

Amoebiasis is a condition caused by infection with a parasite called *Entamoeba histolytica*, often called *E. histolytica*. There are at least six species of *Entamoeba* that can infect the human gut, but only *E. histolytica* causes disease.

The symptoms are often quite mild and can include loose stools, stomach pain, and stomach cramping. Amoebic dysentery is a more severe form of amoebiasis associated with stomach pain, bloody stools, and fever. Rarely, *E. histolytica* invades the liver and forms an abscess. Even less commonly, it may spread to other parts of the body, such as the lungs or brain.

Symptoms usually start within 2 to 4 weeks, but can be weeks or months after exposure. Nine out of ten people infected with *E. histolytica* do not develop any symptoms.

How do you get infected with *E. histolytica*?

You usually get infected with *E. histolytica* by drinking water contaminated by infected faeces or eating food prepared or washed using contaminated water. *E. histolytica* is more likely to infect people who live in developing countries where sanitation and hygiene are poor. In the UK, most people with *E. histolytica* infection have caught it whilst travelling or living abroad. Transmission between sexual partners and people in the same household is also possible.

E. histolytica cysts can also survive in the environment for 12 days and up to 30 days in water.

How can you avoid passing *E. histolytica* to others?

Infection can spread from person-to-person; however, the risk is low if the infected person is treated with antibiotics and practices good personal hygiene. This includes:

- Washing your hands with soap and water after using the toilet
- Washing your hands before handling, preparing, eating or cooking food
- Cleaning toilet seats, toilet bowls, flush handles, taps and wash hand basins after use with detergent and hot water, followed by a household disinfectant.
- Staying away from work/school/serving food outside of the home until 48hrs after resolution of any episodes of diarrhoea.
- Men who have sex with men should abstain from sexual contact until 48 hours after symptoms have subsided

How do you treat infection with *E. histolytica*?

Treatment is usually by one or a combination of two antibiotics, depending on the symptoms you are experiencing. It is very important to complete treatment to prevent passing the infection to others and avoid developing further symptoms at a later stage.

After treatment is completed, testing of a follow-up stool sample is advised to ensure that the parasites have been cleared from your gut.

General advice to avoid travel related infections

- Drink bottled water (make sure the seal is intact) or ensure water for drinking is sterilised appropriately
- Do not have ice in your drinks
- Do not eat fresh fruit or vegetables that cannot be peeled before eating
- Avoid eating food or drink bought from street vendors (except drinks in sealed cans or bottles or food which has been thoroughly cooked in front of the traveller and served hot on clean crockery) (See www.nathnac.net for further advice)

If you develop diarrhoea after travelling abroad to places where *E. histolytica* is common, you should see your doctor so that amoebiasis or other infections can be excluded.

If you have concerns about your health contact NHS 111, visit the NHS Choices website on <http://www.nhs.uk/conditions/dysentery/Pages/Introduction.aspx> or see your family doctor. Further information is available on the PHE website: www.gov.uk/phe.

Template letter for GPs of a confirmed case of *E. histolytica* infection

PRIVATE AND CONFIDENTIAL

Reference no:

Dear Doctor

Re:

The Health Protection Team has been notified that your patient has been diagnosed with *Entamoeba histolytica* (*E. histolytica*) infection.

Infection by *E. histolytica* (amoebiasis) is often asymptomatic but may cause intermittent diarrhoea, dysentery-like illness as well as extra-intestinal conditions such as liver abscess. Treatment is recommended in all cases to prevent development of invasive disease at a later date. The infection is usually acquired abroad in developing countries and has an incubation period of 2-4 weeks, but may be months or even years. Your patient will require treatment if this has not previously been arranged. Please consult the BNF, or you may wish to obtain the opinion of an ID physician for guidance on treatment. It is recommended that a stool sample is submitted one week after completing treatment to ensure treatment success (please see attached algorithm for guidance).

There is some evidence that this infection may pass from person to person during close prolonged contact. Therefore, please encourage all close contacts (co-travellers, household and sexual contacts) to be tested for *E. histolytica* infection, whether or not they have symptoms, as early treatment may prevent progression to more serious disease later. This may be arranged by submitting a stool sample to the local laboratory who will arrange for appropriate testing.

Please ensure your patient is made aware of this information and is given the enclosed fact sheet.

Thank you for your help with this matter.
Yours sincerely,

Encl: Algorithm, fact sheet.

9. Appendix A: Membership of the *Entamoeba histolytica* working group

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Katie Fleet, Nurse Consultant, London PHE Centre/Region (NENC London HPT) **(Joint Chair)**

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Gordon Nichols, Consultant Epidemiologist, GEZI PHE Colindale

Peter Sheridan, Consultant in Communicable Disease Control (retired), South Midlands and Hertfordshire PHE Centre

Nandini Shetty, Consultant Microbiologist and PHE Training Lead, PHE

Acknowledgements

With thanks to Shailen Sutaria, Specialty Registrar in Public Health and General Practitioner, London PHE Centre

10. Appendix B: Disease Information

Summary of key features

- *Entamoeba histolytica* (*E. histolytica*) is notifiable by laboratories directly to Public Health England (previously Health Protection Agency) as a causative agent under the Health Protection Regulations 2010 (1). Amoebic dysentery and amoebiasis are not specifically notifiable by registered medical practitioners
- The majority of cases of amoebiasis, caused by the *E. histolytica* parasite develop asymptomatic infection (90%) although potentially pose an infectious risk due to excretion of infectious cysts
- It is endemic in areas with poor sanitation, with most cases seen in the UK being in travellers recently returned from such areas
- The incubation period of *E. histolytica* is usually between 2-4 weeks but may be months or even years
- Transmission is mainly through contaminated water consumption but person-to-person spread is also recognised
- Clinical features include diarrhoea, dysentery and abdominal pain in intestinal disease. Extra-intestinal disease may also exist, with amoebic liver abscess being the commonest manifestation, which left untreated may be fatal
- There is no consistent approach to the public health management of cases and contacts of *E. histolytica* amongst developed, non-endemic countries

Background

Amoebiasis is an infection caused by the protozoan parasite *E. histolytica*. Two species of parasite with the same morphological characteristics have been recognised – *E. histolytica* and *Entamoeba dispar* (*E. dispar*). It is now recognised that only *E. histolytica* is able to cause invasive disease and these guidelines refer to the management of the disease-causing *E. histolytica* species (2).

E. histolytica exists in two forms- the infectious cyst and the invasive trophozoite. Transmission is via the faecal-oral route by ingestion of cysts which are relatively resistant to chlorination of water and may survive in moist environments for months (3). The cyst passes through the stomach and small bowel, with the parasite escaping its cystic form in the lumen of the bowel to form trophozoites. These trophozoites join together to form new cysts, usually leading to asymptomatic infection, although symptomatic infection and

spread outside the intestine may occur (4). The cysts are mostly excreted with solid stools whilst trophozoites, present in diarrhoeal stools of patients with acute disease, are fragile and cannot survive in the environment (5).

Reservoir and mode of transmission

The only known natural hosts are humans (chronic patients excreting cysts or asymptomatic carriers) and perhaps some non-human primates (6, 7).

Transmission may occur via ingestion of food and water contaminated by cysts (usually via contaminated water supplies), person-to-person contact, oral-anal sexual contact or by direct inoculation, such as colonic irrigation (3, 7-9).

Patients with acute diarrhoeal illness do not pose a significant risk to contacts as the stools at that stage primarily contain fragile trophozoites which if ingested, do not survive in the gastric acidic environment (3, 5).

Clinical features

The majority of cases (90%) develop asymptomatic intestinal infection only which usually resolves spontaneously (10). In addition, around 4-10% of asymptomatic cases may develop invasive disease over a one year period, hence treatment of such cases is recommended (11).

The incubation period is usually between 2-4 weeks but may be up to several years (12). Cases may be considered infectious as long they excrete cysts in their stools and this may last several years (12).

Although reinfection has been demonstrated in the literature, this is rare and the majority of recovered cases are considered to no longer be susceptible (3).

Invasive disease

Invasive disease seen in 10% of cases may cause intestinal disease or spread via the blood stream (<1% of the cases) to other viscera causing liver abscess, respiratory tract infections or infections of the central nervous system (10). It is uncertain if protective immunity develops following invasive infection (13).

Intestinal manifestations

Amoebic diarrhoea without dysentery (without mucus and microscopic blood) is the commonest manifestation (4) with a mean duration of diarrhoea of around 3 days (14). In amoebic colitis or dysentery, mucoid diarrhoea is seen with blood (gross or microscopic) (4).

In 70% of cases the onset of both amoebic diarrhoea and dysentery is often over 3-4 weeks following infection and is associated with abdominal pain and tenderness (4). Fever is infrequent (38%) and other constitutional symptoms and signs include anorexia, weight loss, dehydration and anaemia (7, 15).

Some patients may present with chronic intestinal infection with intermittent diarrhoea alternating with constipation, weight loss and abdominal pain (7, 11).

Toxic megacolon, fulminant necrotising colitis and amoeboma (granulation tissue in the caecum- to be differentiated from colon cancer) are some of the rare presentations of infection (4, 7).

Extra-intestinal disease

Amoebic liver abscess (ALA) is the commonest extra-intestinal manifestation following haematogenous dissemination. ALA when recognised and treated promptly carries a favourable prognosis and is 10 times more common in men (4, 11). Symptoms are usually acute and include fever, right upper quadrant pain, tenderness over the liver. Chronic symptoms include weight loss and anorexia. The majority of patients with ALA do not have accompanying bowel symptoms and stool microscopy is usually negative for *E. histolytica* (11). Travel history should be obtained in patients presenting with these symptoms but consideration should be given to the fact ALA symptoms may not present for months or years after travel to or residency in an endemic country (11).

Other less common extra-intestinal presentations include lung and brain abscesses (10). Cutaneous amoebiasis may result from direct extension, such as liver lesions, intestinal lesions (perianal ulcers) or penile ulcers in men who have sex with men (MSM) (3).

Epidemiology

E. histolytica infections occur worldwide and are endemic in areas with inadequate sanitation and overcrowding (3). Worldwide prevalence estimates of *E. histolytica* are challenging due to the high proportion of asymptomatic cases and difficulty distinguishing *E. histolytica* from non-pathogenic strains. Best prevalence estimates suggest between 34-50 million symptomatic cases globally every year (4) with the Bulletin of the World Health Organization (*Entamoeba* taxonomy) quoting an annual worldwide mortality rate of up to 100,000 deaths per year (2).

Cases in the UK are most likely to affect young adults, with the infection being rare in pre-school aged children. The majority are in those who have returned from travel to developing countries (12).

E. histolytica laboratory reports for England and Wales from 1992-2012 report a total of 6,931 cases (16). As at 2014, over the previous 10-year period there were an average of 101 cases reported each year. London has the highest number of reported cases annually, although this may in part reflect that the PHE National Parasitology Reference Laboratory for *E. histolytica* does not report the source laboratory.

11. Appendix C: Evidence and rationale for public health action

Transmission of *E. histolytica*

The main source of evidence for the transmission of *E. histolytica* infections amongst household or other outbreak settings comes from published case reports or case series' (Level 3 evidence).

Household and sexual transmission

The main route of transmission of *E. histolytica* is via the consumption of contaminated food or water, primarily following travel to developing countries where sanitation may be poor. However, person-to-person transmission through the faecal-oral route has also been documented.

Although transmission in developed countries is considered rare, in Canada, a cluster of 7 cases was reported in 2009 (17). The index case had travelled to Europe and presented with a symptomatic liver abscess 5 months later, with *E. histolytica* infection confirmed via serological testing. Two co-travellers were also identified as confirmed cases (1 asymptomatic). Sexual contacts of the confirmed cases were identified and tested with 2 of these contacts having no history of foreign travel and considered to have contracted the infection via sexual contact alone. The authors note that this cluster may represent the first documented evidence of sexual transmission between female homosexual partners, as well as amongst heterosexual partners, highlighting the fact that risk of transmission should not purely be considered in male homosexual activity, which has been well documented in the literature (7).

A family outbreak of *E. histolytica* in the Netherlands has also been documented (18). The index case was a 5-year-old child with symptomatic diarrhoeal infection but no history of foreign travel. Investigations identified the source of infection as being the case's mother who had experienced persistent *E. histolytica* cyst excretion despite treatment for amoebic dysentery following travel to India 13 years earlier. 4 other household contacts were tested for infection and all found to have trophozoites and/or cysts of *E. histolytica*/*E. dispar* in stool specimens, with PCR-SHELA identifying these as being *E. histolytica* in 5 of the 6 cases. The cause of the household transmission observed was not identified as investigations did not reveal any evidence of poor sanitation or personal hygiene and there was no evidence of spread amongst the childcare facilities the children in the family attended. All contacts received treatment, with the 3 children in the family requiring repeat treatment before follow-up stool specimens became negative for cyst excretion.

Less recently, evidence of transmission within a family complex in Italy has also been reported (19). In this instance, the index case was believed to be an asymptomatic housemaid who had been working in the household for a few months but was originally from the Philippines, where the infection was thought to have been acquired. There were 6 symptomatic cases linked to the index case - a family of 2 parents and 2 children as well as 2 family friends. None of these 6 linked cases had a history of foreign travel to tropical

areas. One of the cases identified as a family friend developed severe abdominal symptoms, including diarrhoea, as well as evidence of liver abscesses and died one month following the onset of symptoms. For all cases, a delay in diagnosis and effective treatment commencement was identified. The most likely source of infection was believed to be the housemaid, with probable transmission via food or beverages, although further details are not provided.

Outbreaks of *E. histolytica*

As discussed above, the evidence for outbreaks of *E. histolytica* in developed countries is limited and they are considered to be rare occurrences, with only a few reported in household-type settings as described.

Recent searches of regional HPZone records by the *E. histolytica* working group members did not find any record of outbreaks of *E. histolytica* infections notified to PHE (formerly HPA) local health protection teams. A number of outbreaks in other settings have been described in the literature. A case-control study was conducted in the city of Tbilisi, Republic of Georgia in 1998 (20) following reports of 120 cases of suspected amoebiasis. Seroprevalence studies included in the investigation suggested that the outbreak was much more widespread than the number of suspected cases had initially indicated. The main mode of disease transmission was considered to be via contaminated drinking water in the region, with some evidence of a foodborne component and secondary person-to-person spread.

In Taiwan in 2008, a cluster of 9 residents on the same floor of a rehabilitation institution for patients with mental health disorders was reported (21). The index case was the most recent admission to the unit, although faecal microscopy at the time of admission was negative for amoebiasis. All 9 PCR-confirmed *E. histolytica* cases were asymptomatic and no staff members were found to be positive. Due to shared tap water supply to the institution, no food being prepared on site and no staff members being affected, the most likely source of transmission amongst residents was considered to be faecal-oral transmission amongst residents, possibly due to poor hygiene practices. The authors note that the true source of the outbreak was not identified (p793).

No literature was identified reporting outbreaks in the risk groups for transmitting GI pathogens specifically (as defined in the 2017 Interim- Public Health Operational Guidelines for Typhoid and Paratyphoid (Enteric Fever) (22).

Microbiological investigation of suspected cases and contacts

All cases, whether symptomatic or not, require laboratory confirmation of *E. histolytica* infection for appropriate management and treatment. Several different diagnostic methods exist and the choice will, in part, reflect availability of the techniques.

Microscopy

Microscopy relies on observation of cysts and trophozoites in faeces (wet preparation, concentration and staining), colonic scrapings, aspirates and tissue samples. There are several limitations to microscopy, including the fact that *E. histolytica* and the non-pathogenic *E. dispar* are morphologically indistinguishable on microscopy. Samples should

also be examined within an hour of collection for red blood cells in motile trophozoites which may not be seen in patient without symptoms of acute dysentery (11).

The overall sensitivity is also low and a minimum of 3 specimens taken on separate days is recommended to increase the yield from 50% for a single specimen to 85-90% due to the intermittent excretion of organisms in the stool (3, 11).

Culture methods

Culture methods for the diagnosis of *E. histolytica* have been in use for several decades and can be used for a variety of specimens, although aspirates from ALA patients are usually sterile and require additional techniques (11). Culture is generally not recommended for *E. histolytica* diagnosis as a routine procedure due to it being less sensitive than microscopy, expensive and labour-intensive (11).

Serological tests

The detection of antibodies may be of particular use in ALA patients where there are no organisms identifiable in stool specimens and the sensitivity has been reported to be about 100% (11). Serum IgG antibodies will persist for years after infection but IgM antibodies are present in the acute phase and may be detected by enzyme-linked immunosorbent assay (ELISA) methods, although these are not recommended in countries with endemic *E. histolytica* infection due to the difficulty in distinguishing between current or previous infection.

Antigen detection tests

Antigen-based ELISA tests specific for *E. histolytica* have been well studied and have several advantages, including their technical simplicity, relative low cost and rapid turnaround (23). The TechLab *E. histolytica* II kit is a second-generation test kit found to be highly sensitive and specific when compared with microscopy in areas where *E. histolytica* infection is endemic (11). A study comparing antigen detection kits with PCR in Australia, however, suggested that the sensitivity is much lower in countries where *E. histolytica* is less frequent and recommended local evaluation of the tests, compared to PCR, prior to recommendation of their use (24).

Polymerase chain reaction (PCR)

PCR diagnostic methods are considered to be the “method of choice” (p.520) in developed countries (11). They have the advantages of being able to identify *E. histolytica* in a range of samples, such as faeces, liver abscess aspirates and tissue samples and fulfil the WHO recommendations for specific identification of *E. histolytica* by being able to distinguish *E. histolytica* from non-pathogenic *Entamoeba* strains (11).

Both conventional and real-time PCR methods have been used for identification with real-time PCR offering advantages in terms of faster turnaround times, improved sensitivity, minimal risk of contamination due to elimination of post-PCR analysis and reduced reagent costs (11).

The PCR-solution hybridization enzyme-linked immunoassay (PCR-SHELA) method has been developed by the London School of Hygiene and Tropical Medicine, UK and has been shown to be a highly sensitive assay for identifying the *E. histolytica* species (23). The availability of PCR methods in routine diagnostic laboratories and the fact that the PCR-SHELA assay takes 1.5 days in total to process make these methods most suitable for regional or reference laboratories where samples may be “batched” and processed at intervals (23).

In the UK, the use of PCR methods, such as those available at the Department of Clinical Parasitology at London HTD, is the method of choice for the definitive diagnosis of *E. histolytica* infection in both symptomatic and asymptomatic cases.

The rationale for public health action in response to *E. histolytica* cases and contacts

Although only a small proportion of those infected with *E. histolytica* develop symptomatic disease (around 10%), symptoms and complications of infection can be severe and worldwide mortality has been quoted as being up to 100,000 deaths per year (2). Treatment with amoebicide drug therapy, such as metronidazole and diloxanide furoate, is known to be effective in both acute and asymptomatic cases (25).

Asymptomatic cases represent the majority of the disease burden and pose a greater public health risk due to the more stable nature of infectious cysts excreted in their stools. Evidence from the literature highlights examples of transmission from asymptomatic index cases, leading to both symptomatic and asymptomatic infection in contacts.

Although outbreaks of *E. histolytica* infection are rare in developed countries, there is documented evidence from case reports and case series of transmission amongst household and sexual contacts, sometimes many years after an index case’s travel to an endemic area.

Existing guidelines for the public health management of *E. histolytica* in non-endemic countries other than the UK

There is limited evidence available about the public health management of *E. histolytica* cases and contacts other than that from case reports and case series as discussed and no literature was identified specifically reporting outbreaks in the risk groups for transmitting GI pathogens.

A summary review of some of the existing guidelines for the public health management of *E. histolytica* in non-endemic countries other than the UK, including Canada, USA and Australia is included in Appendix C. In all situations, the need to obtain detailed travel history for cases was stressed, as was the need to provide hygiene advice to cases and contacts.

However, a consistent response to the management, exclusion and screening of cases and contacts was not identified, with variations in the definition of cases, exclusion requirement for symptomatic cases and screening and management of contacts.

In outbreak situations, the majority of regions recommended the investigation and management of outbreaks of *E. histolytica* according to existing outbreak management guidelines, although some emphasised that chemoprophylaxis was not indicated for contacts of confirmed cases and that requirements for clearance samples may be enhanced during outbreak situations.

Given the variation in guidance for the management of cases and contacts of *E. histolytica* infection between non-endemic developed countries, it is important that the UK considers the evidence for transmission of infection, assessment of the risk of outbreaks and risks to the public in making recommendations for public health action.

Detailed recommendations for the public health management of cases and contacts are detailed in Sections 3-5. In particular, the following should be noted:

- Although all cases with diarrhoea should be advised not to attend work, school or childcare until 48 hours following the last episode of diarrhoea, no formal exclusion for GI risk groups or clearance samples following treatment completion are required for infections with *E. histolytica*. This recommendation is based on the limited evidence of outbreaks outside of household-type settings, other than those associated with large-scale contaminated water supplies. Outbreaks are rare in all developed countries, including the UK. Infection is also considered to be rare in pre-school aged children (Hawker, 2012) so outbreaks in childcare settings are unlikely.
- In view of the fact that the majority of *E. histolytica* infections do not lead to clinical symptoms, it is highly likely that cases will have continued to work following their initial infection, making exclusion following laboratory diagnosis of reduced benefit. Cyst excretion may also last several years, making exclusion from work or school settings for the duration of the communicable period inappropriate for such cases.
- The use of PCR (currently available at the Department of Clinical Parasitology, HTD and Public Health Laboratory, London) for the confirmation of *E. histolytica* infection is recommended given the benefits of PCR testing described in this document and is in accordance with the PHE Guidance for the interpretation of PCR assays for gastrointestinal pathogens document dated March 2013 (26).
- Although the recommendations for the screening of contacts varies between those countries whose guidelines have been examined, the evidence for household, sexual and transmission between co-travellers, as discussed in Appendix C of this document, provides the basis for the recommendation for testing all such contacts and treating those that are subsequently confirmed to be *E. histolytica* cases. Treatment is known to be beneficial for symptomatic and asymptomatic cases and although the complications of *E. histolytica* infection are rare, they may be associated with significant morbidity and mortality, which early effective treatment may prevent.

Levels of evidence for intervention studies

Taken from p7-6 of the National Institute for Clinical Excellence (February 2004, updated 2005) *Guideline Development Methods: Information for National Collaborating Centres and Guideline Developers*. London: National Institute for Clinical Excellence. **Available from: www.nice.org**
(27)

Level of evidence	Type of evidence
1 ⁺⁺	High-quality meta-analyses, systematic reviews of PCTs, or RCTs with a very low risk of bias
1 ⁺	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1 ⁻	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*
2 ⁺⁺	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2 ⁺	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2 ⁻	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal*
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus
*Studies with a level of evidence '-' should not be used as a basis for making a recommendation	

Summary of information from *E. histolytica* guidelines from non-endemic countries, other than the UK

AREA	DEFINITION OF CONFIRMED CASE	CLINICAL MANAGEMENT OF CASES	PH MANAGEMENT OF CASES	DEFINITION OF CONTACTS	PH MANAGEMENT OF CONTACTS
Alberta, Canada (28)	<p>One of the following, with OR without clinical illness:</p> <ul style="list-style-type: none"> • Trophozoites or cysts identified on microscopy of stool, aspirates, tissue or scrapings • Positive stool antigen test • Positive serology 	<ul style="list-style-type: none"> • Symptomatic cases should receive appropriate antibiotic treatment 	<ul style="list-style-type: none"> • Exclusion for symptomatic cases until 48 hours after treatment is completed for those who are: <ul style="list-style-type: none"> – Food handlers whose work involves touching utensils or food that is unwrapped to be eaten raw or without further heating – Healthcare, daycare or other staff who have contact through serving food with highly susceptible patients – Involved in the care of patients, young children, elderly or dependent persons – Children attending daycare or similar who are in nappies of unable to implement good personal hygiene – Others who are unable to implement good personal hygiene • Asymptomatic cases in the above risk groups may be excluded after discussion with the local Medical Officer for Health 	<ul style="list-style-type: none"> • Persons living in the household • Children and childcare workers in daycare/ home • Those exposed to the same source if known 	<ul style="list-style-type: none"> • Provision of disease and hygiene information • Assessment of symptomatic contacts by a physician • Exclusion of those who are symptomatic and in a risk group (as for cases) based on individual assessment • No exclusion of asymptomatic contacts
Manitoba, Canada (29)	<p>One of the following:</p> <ul style="list-style-type: none"> • Identification of trophozoites via microscopy of stool or tissue samples • Positive PCR for any 	<ul style="list-style-type: none"> • Appropriate treatment of both confirmed asymptomatic and symptomatic 	<ul style="list-style-type: none"> • Contact precautions (including the use of gloves and gowns) for paediatric patients unable to comply with hygiene and adults with poor hygiene • Exclusion from food handling and direct patient care for symptomatic cases until 	<ul style="list-style-type: none"> • Household members • Those with close ongoing contact e.g. sexual partners 	<ul style="list-style-type: none"> • Provision of disease and hygiene information • Adequate stool examination of contacts (no further details provided) • Treatment of positive contacts

	specimen <ul style="list-style-type: none"> Clinical features of ALA and positive <i>E. histolytica</i> serology 	cases is recommended	treatment completion		<ul style="list-style-type: none"> Assessment of symptomatic contacts by a physician
Ontario, Canada (30)	One of the following, with OR without clinically compatible signs and symptoms <ul style="list-style-type: none"> Demonstration of ingested red blood cells in hypertrophied trophozoites of <i>Entamoeba histolytica</i> (<i>E. histolytica</i>) in preserved stool samples Positive for <i>E. histolytica</i> by stool antigen ELISA on unpreserved stool samples Demonstration of hypertrophied trophozoites in intestinal tissue biopsy or ulcer scrapings Demonstration of hypertrophied trophozoites in extra-intestinal tissues 	<ul style="list-style-type: none"> Appropriate treatment following laboratory confirmation 	<ul style="list-style-type: none"> Exclude symptomatic cases from activities in the food industry, healthcare or daycare for 24 hours after diarrhoea has resolved or for 48 hours after completion of antibiotic treatment 	<ul style="list-style-type: none"> Household members Others not defined 	<ul style="list-style-type: none"> Assess contacts for symptoms and advise medical care if symptomatic Provide information on transmission and prevention Manage symptomatic contacts as for cases
Kansas, USA (31)	<ul style="list-style-type: none"> Clinical intestinal amoebiasis with laboratory confirmation (cysts/ 	<ul style="list-style-type: none"> Appropriate treatment of both confirmed asymptomatic 	<ul style="list-style-type: none"> Exclusion of amoebiasis cases that are food handlers until 3x negative stool samples submitted, >48 hours apart Food handlers with diarrhoea, fever or 	<ul style="list-style-type: none"> Household members Daycare co-attende 	<ul style="list-style-type: none"> Stool microscopy examination for close contacts Contacts with diarrhoea and are food handlers are excluded as for

	<p>trophozoites in stool, trophozoites in tissue biopsy or ulcer scrapings)</p> <ul style="list-style-type: none"> Demonstration of trophozoites in extra-intestinal tissue or clinical extra-intestinal amoebiasis with positive serology via ELISA 	<p>and symptomatic cases is recommended</p>	<p>vomiting be restricted or excluded if serving high risk groups until 24 hours after symptom resolution</p> <ul style="list-style-type: none"> The same restrictions apply to workers in schools, residential programmes, daycare or healthcare who feed, give mouth care or dispense medications Children with amoebiasis should be excluded from daycare/school until diarrhoea has resolved Symptomatic and asymptomatic daycare/school/long-term facility workers with positive stool samples must not prepare food until 3x negative stool samples submitted, >48 hours apart Residents in long-term facilities should be placed on enteric precautions until 3x negative stool samples submitted, >48 hours apart 	<ul style="list-style-type: none"> Daycare workers Sexual contacts Patrons of cases who are food-handlers if food handling practices are in question 	<p>cases</p>
<p>Los Angeles, USA (32)</p>	<ul style="list-style-type: none"> Intestinal amoebiasis: a clinically compatible illness that is laboratory confirmed Extra-intestinal amoebiasis: a parasitologically confirmed infection of extra-intestinal tissue, or among symptomatic persons (with clinical or radiographic findings consistent with extra-intestinal infection), demonstration of 	<ul style="list-style-type: none"> Treatment for all cases (those with <i>E. histolytica/dispar</i> complex as most laboratories are unable to distinguish between them) Treat symptomatic cases with a systemically active compound followed by a 	<ul style="list-style-type: none"> Enteric precautions until clinical recovery Food handlers: <ul style="list-style-type: none"> Symptomatic – restrict/exclude until 3x negative stool samples taken >3 days apart Previously symptomatic in past 48-72 hours – restrict/exclude until 3x negative stool samples taken >3 days apart Other sensitive occupation/setting: <ul style="list-style-type: none"> Symptomatic – restrict/exclude until 48 hours after resolution of signs and symptoms. No clearance required Previously symptomatic in past 48-72 hours – no restriction Child 5 years and under in group setting: 	<ul style="list-style-type: none"> Household members Persons who share a common source 	<ul style="list-style-type: none"> Food handlers: <ul style="list-style-type: none"> Symptomatic – collect 1 stool sample for testing. Restrict/exclude until sample negative Asymptomatic – no exclusion Other sensitive occupation/setting: <ul style="list-style-type: none"> Symptomatic – collect 1 stool sample for testing. Restrict/exclude until sample negative Asymptomatic – no exclusion Child 5 years and under in group setting:

	specific antibody against <i>E. histolytica</i> as measured by indirect haemagglutination or other reliable immunodiagnostic test (e.g. ELISA)	luminal amoebicide <ul style="list-style-type: none"> • Treat asymptomatic carriers with luminal amoebicide to protect from symptomatic amoebiasis 	<ul style="list-style-type: none"> ○ Currently symptomatic – restrict/exclude until 48 hours after resolution of symptoms. No clearance required ○ Previously symptomatic in past 48-72 hours – may return to group care if asymptomatic for 48 hours • Non-sensitive occupations: <ul style="list-style-type: none"> ○ Exclude until clinically recovered 		<ul style="list-style-type: none"> ○ Symptomatic – collect 1 stool sample for testing. Restrict/exclude until sample negative ○ Asymptomatic – no exclusion • Non-sensitive occupations: <ul style="list-style-type: none"> ○ No action
New York, USA (33-35)	<ul style="list-style-type: none"> • Not described but laboratory reporting guidelines indicate reporting of cases with positive cyst, trophozoite, or antigen noted by any method 	<ul style="list-style-type: none"> • Not described 	<ul style="list-style-type: none"> • Exclude children with diarrhoea until symptoms resolved or stool culture is normal • Childcare staff require approval prior to returning to work • Food handlers excluded unless no longer ill and 2x negative stool specimens >24 hours apart, >48 hours after treatment completion 	<ul style="list-style-type: none"> • Not described 	<ul style="list-style-type: none"> • Not described
Utah, USA (36)	<ul style="list-style-type: none"> • Confirmed intestinal amoebiasis: a case that has a clinically compatible illness and that is laboratory confirmed (demonstration of cysts of trophozoites of <i>E. histolytica</i> in stool OR demonstration of <i>E. histolytica</i> trophozoites in tissue biopsy or ulcer scrapings by culture or histopathology) • Confirmed 	<ul style="list-style-type: none"> • Appropriate antibiotic treatment 	<ul style="list-style-type: none"> • Food handlers: <ul style="list-style-type: none"> ○ Exclude until treatment is completed, regardless of symptoms ○ Stool samples may be required in some situations based on local health department assessment • Children in daycare/schools: <ul style="list-style-type: none"> ○ Exclude until diarrhoea has resolved ○ Asymptomatic cases may remain in setting with special precautions, or may be excluded • Staff in daycare/schools/ long-term facilities excluded from food preparation until diarrhoea has resolved. Stool specimens may be required 	<ul style="list-style-type: none"> • Not described 	<ul style="list-style-type: none"> • Food handling contacts with diarrhoea should be excluded as for cases • No other restrictions

	<p>symptomatic extra-intestinal amoebiasis: a case that presents as either abscess (e.g. hepatic, brain, splenic etc.) or radiographic findings consistent with extra-intestinal infection that also has a demonstration of specific antibody against <i>E. histolytica</i> as measured by indirect haemagglutination or other reliable immunodiagnostic test (e.g. ELISA)</p> <ul style="list-style-type: none"> Confirmed asymptomatic extra-intestinal amoebiasis: a case that has a demonstration of <i>E. histolytica</i> trophozoites in extra-intestinal tissue 		<ul style="list-style-type: none"> Long-term facility residents placed on enteric precautions until symptoms resolved 		
Victoria, Australia (37-38)	<ul style="list-style-type: none"> Not described 	<ul style="list-style-type: none"> Treatment for symptomatic cases only 	<ul style="list-style-type: none"> All cases with symptoms should be excluded until symptoms have stopped No additional exclusions 	<ul style="list-style-type: none"> Household members Institutional contacts Co-travellers 	<ul style="list-style-type: none"> Faecal screening should be considered for contacts Confirmed carriers should be treated
Western Australia (39-41)	<ul style="list-style-type: none"> Microbiological identification of cysts/ trophozoites in faeces, tissue biopsy 	<ul style="list-style-type: none"> Appropriate treatment recommended 	<ul style="list-style-type: none"> Enteric precautions for hospitalised/ institutional patients Exclude cases for 24 hours after symptoms have resolved and return of normal stools 	<ul style="list-style-type: none"> Household members Co-travellers Others who may 	<ul style="list-style-type: none"> No exclusions or actions required

	<p>or extra-intestinal tissue</p> <ul style="list-style-type: none"> • Positive serology in patients with symptoms/signs of amoebiasis 		<ul style="list-style-type: none"> • Exclude cases in a risk group (workers in healthcare, residential care and child care, food handlers, children in child care and people who are faecally incontinent) for 48 hours after symptoms have resolved 	share a common source of infection	
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