British Infection Association Guidelines for the Diagnosis and Management of Enteric Fever in England

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Lay Summary

Enteric fever (EF) is an infection caused by the bacteria called *Salmonella* Typhi or Paratyphi. Infection is acquired through swallowing contaminated food or water. Most EF in England occurs in people returning from South Asia and other places where EF is common; catching EF in England is rare. The main symptom is fever, but stomach pain, diarrhoea, muscle aches, rash and other symptoms may occur. EF is diagnosed by culturing the bacteria from blood and/or stool in a microbiology laboratory.

EF usually responds well to antibiotic treatment. Depending on how unwell the individual is, antibiotics may be administered by mouth or by injection. Since 2016, there has been an ongoing outbreak of drug-resistant EF in Pakistan. This infection is called extensively drug-resistant, or XDR, enteric fever and only responds to a limited range of antibiotics. Occasionally individuals develop complications of EF including confusion, bleeding, a hole in the gut or an infection of the bones or elsewhere. Some people may continue to carry the bacteria in their stool for a long time following treatment for the initial illness. These people may need treatment with a longer course of antibiotics to eradicate infection.

Travellers can reduce their risk of acquiring enteric fever by following safe food and water practices and by receiving the vaccine at least a few weeks before travel.

These guidelines aim to help doctors do the correct tests and treat patients for enteric fever in England but may also be useful to doctors and public health professionals in other similar countries.

Introduction

These are the first published guidelines on the clinical management of enteric fever (EF) in England. They were commissioned by the British Infection Association (BIA) in response to rising antimicrobial resistance in imported cases and requests for treatment advice to the Reference Laboratory, United Kingdom Health Security Agency (UKHSA) (previously known as Public Health England, PHE). They have been written in conjunction with , the Hospital for Tropical Diseases, London (HTD), the Centre for Tropical Medicine and Global Health, University of Oxford, Liverpool School of Tropical Medicine and the National Travel Health Network and Centre (NaTHNaC) by a working group of experts in EF including specialists in infectious disease, microbiology, epidemiology, public health, paediatric and travel medicine.

Aims and Scope of the guidelines

These guidelines aim to describe the epidemiology and clinical presentation of cases of EF presenting in England, and to give pragmatic evidence-based recommendations for the diagnosis and management of suspected and confirmed EF and chronic carriage. The term enteric fever (EF) is used to encompass infection with *Salmonella enterica* subspecies *enterica* serovars Typhi and Paratyphi A, B, and C. These guidelines are applicable to adults and children. The management of invasive disease with non-typhoidal *Salmonella* spp. is beyond the scope of these guidelines.

These guidelines are intended to complement PHE's Public Health Operational Guidelines for Typhoid and Paratyphoid (EF) which directs the public health investigation and management of infection 1). They also complement the Green Book guidance on vaccination (2) and NaTHNaC's guidance on preventing the acquisition of EF whilst abroad (3).

These guidelines are aimed at hospital clinicians, microbiologists, paediatricians and general practitioners treating patients with suspected or confirmed EF in England. They may also be useful to clinicians managing patients with EF in other non-endemic countries.

Methods

Based on their experience of providing advice at the local and national level, the working group agreed a list of key questions which would help clinicians understand the epidemiology, clinical

presentation, diagnosis and management of acute EF and chronic carriage in England. These are outlined in box 1. Definitions are found in table 1.

A literature search was performed using Embase, MEDLINE and Global Health, between 1st January 1946 – 31st December 2019, to identify all English language publications using the key words ('Salmonella Typhi' or 'Salmonella Paratyphi A' or 'Salmonella Paratyphi B' or 'Salmonella Paratyphi C' or 'paratyphoid fever' or 'typhoid fever' or 'enteric fever' AND 'diagnosis'; 'blood culture'; 'serology'; 'faeces'; 'molecular pathology'; 'quinolones'; 'azithromycin'; 'carbapenems'; 'cephalosporins'; 'chloramphenicol'; 'fosfomycin'; 'co-trimoxazole.mp'; 'Trimethoprim, Sulfamethoxazole Drug Combination'; 'penicillin'; 'antibacterial agents'; 'drug resistance bacterial'; 'glucocorticoids'; 'Hydroxycorticosteroids' 'hydroxycorticoids.mp'; 'cholecystectomy'; 'management'; 'carrier state'; 'disease transmission, infectious'; 'disease carrier.mp.'; 'disease carrier'; 'carriage.mp.'; 'Chronic Disease'; 'complication.mp.'; 'Mortality'; 'perforation'; 'perforation.mp.'; 'Shock'; 'Neurology'; 'Treatment Outcome'; 'treatment failure')

The initial search yielded 3338 papers, 709 of which were duplicates. A total of 2629 papers were screened by title and abstract for relevance to key questions by LN (box 1), from which 262 papers were deemed relevant. These were grouped into subject areas of epidemiology, clinical presentation, laboratory diagnosis, treatment and chronic carriage and distributed to the working group. Two members of the working group were allocated as authors for each section. They reviewed the literature search for their section and were permitted to add further references including key papers published in 2020 and 2021 to the core list if they deemed necessary.

The description of the epidemiology of EF in England is based on enhanced surveillance data collected by UKHSA from all reported, confirmed cases as described at https://www.gov.uk/government/collections/typhoid-and-paratyphoid-guidance-data-and-analysis, focusing on the period from 2017 to 2019 (4). Where appropriate, these findings are corroborated with reference to earlier surveillance data from public health agencies in the UK and the peer-reviewed literature. Identification of strains, typing and antimicrobial susceptibility data of *Salmonella* strains causing EF were collected from UKHSA 's Gastrointestinal Bacteria Reference Unit (GBRU), Colindale, London.

Each section of the guideline was reviewed by the whole working group and combined into a single document as per AGREE 2 guidance. The final draft was approved by all members of the working group, and shared with BIA for a wider peer review.

The GRADE system was used to rate the strength of recommendation (1-2) based on the quality of the evidence(A-D), outlined in Box 2(5). Where a recommendation was agreed by the Working Group but there was insufficient published evidence for grading, the term author recommendation (AR) was used. For questions where recommendations were not appropriate, key points (KP) are used to highlight important issues.

1. EPIDEMIOLOGY

1.1 Where do adults and children presenting in England with EF acquire infection?

- **Most cases of EF in England arise in travellers returning from endemic countries (KP)**
- **Cases of *S.* Typhi and *S.* Paratyphi A are most often associated with travel to Pakistan, India and Bangladesh (KP)**
- **Cases of *S.* Paratyphi B are less common, and most often associated with travel to South America and the Middle East (KP)**
- **Children account for 31% of travel-related cases of EF. They have similar patterns of travel to adults, and most frequently acquire infection in Pakistan (KP)**

Since 2010, UKHSA has classified EF cases as travel-related where symptom onset is within 28 days of return from an endemic area. Discretion is allowed in the classification of cases presenting within 60 days of return from travel to an endemic area (1, 6). Among 1,138 cases of EF in England between 2017-2019 for whom information regarding travel was available, 1,101 (97%) were travel-related by this definition: 1,020 had travelled from England to visit an endemic area, 50 were temporary visitors to England, and 31 were new entrants. Of the 37 cases reporting no recent travel, 35 were symptomatic (mostly arising through secondary transmission) and 2 were asymptomatic. Associations with travel were consistent across serovars Typhi, Paratyphi A, and Paratyphi B.

For *S.* Typhi and *S.* Paratyphi A, 92% of travel-related cases diagnosed in England were in people who had travelled to Pakistan, India, and Bangladesh. By contrast, most cases of *S.* Paratyphi B were in people who had travelled to the Americas (48%, principally South America) or the Middle East (41%), with a smaller proportion to South Asia (**Table 2**)(7). These findings are consistent with earlier case series from centres in England(8-13).

1.2 What type of traveller is most at risk of acquiring infection in endemic countries?

- **The largest proportion of travellers acquiring EF had travelled to visit friends and relatives in EF endemic countries (KP)**
- **While any age group may be affected, travellers acquiring EF are mostly younger adults or children (KP)**

From enhanced UKHSA surveillance, 78% of travel-related cases of EF had travelled to visit friends and relatives (VFR), 12% travelled for leisure, 5% were new entrants to England, 2% travelled for business, 2% were foreign visitors to England, and 1% travelled for other reasons (7, 14, 15).

The median age among travel-related cases was 26 (interquartile range 14-38). Children under 18 years old accounted for 31% of travel-related cases; children 0-5 years old accounted for 10% of travel-related cases. The age distribution among non-travel-related cases was similar, with a median age of 22 (interquartile range 6-43), 46% under 18 years old, and 24% 0-5 years old. 52% of travel-related cases and 46% of non-travel-related cases were male. Published case series consistently demonstrate a high proportion of VFR travellers amongst people in the UK with EF, especially among cases returning from South Asia (8, 16).

Some people are at increased risk of transmitting gastrointestinal pathogens. These are classified in UKHSA guidance (table 4) (17). Among 1,058 cases for whom membership of defined risk categories for onward transmission of infection could be ascertained, 73 (7%) were children attending pre-school groups or nursery, 57 (5%) were health, and social care, or nursery staff who have direct contact with highly susceptible patients, 45 (4%) work in the preparation or serving of unwrapped foods, and 17 (2%) had other concerns over access to personal hygiene; 866 (82%) were not in a defined risk group.

1.3 What is the geographical distribution of EF cases within England?

- **Cases arise in all regions of England, with the highest case numbers in London, the South East, the West Midlands, and the North West (KP)**

The largest proportion of cases reported to UKHSA 2014-2019 were identified in London (35%), followed by the South East (13%), West Midlands (13%), and North West (12%). Travel-related cases of *S.* Typhi and *S.* Paratyphi A within England occur disproportionately in residents of more deprived areas [3, 13].

1.4 What proportion of EF cases in England are associated with hospital admission?

- **84% cases reported admission to hospital (KP)**

Among UKHSA enhanced surveillance cases for whom a treatment history could be ascertained, 84% were admitted to hospital in England. Cases frequently require admission for timely exclusion of other causes of acute febrile illness and administration of intravenous (IV) antibiotics (18). Similar rates of admission were seen for children and adults.

1.5 Can azithromycin susceptibility be anticipated for travel-related cases of EF?

- **Isolates of *S.* Typhi and *S.* Paratyphi A, B and C from travellers returning to England have consistently shown azithromycin susceptibility (KP)**

At the time of writing, no azithromycin-resistant isolates of S. Typhi or S. Paratyphi A, B and C have been identified by GBRU(7, 19). Emerging azithromycin resistance has been described in Pakistan, India, Bangladesh and Nepal, and may become more widespread in the future, particularly given high use of macrolide antibiotics for the treatment of EF in endemic regions(20-23).

1.6 Can fluoroquinolone susceptibility be anticipated for any travel-related cases of EF?

- ***S.* Typhi and *S.* Paratyphi A show increasing resistance to fluoroquinolones (FQ) in all geographical regions, with extremely high prevalence of resistance in isolates associated with travel to South Asia (KP)**
- **While the highest prevalence of FQ resistance is found in cases imported from Pakistan, India, and Bangladesh, prevalence among cases imported from elsewhere in Asia and Africa are now sufficiently high to make empirical use of FQ inadvisable (KP)**

Travel-related cases of *S.* Typhi from all regions of the world showed high prevalence of FQ resistance in UKHSA surveillance data 2014-2019, accounting for 98% of cases associated with travel from Pakistan (412/421 isolates with available information), 96% from India (384/399), 88% from Bangladesh (64/73), 70% from elsewhere in Asia (45/64), and 60% from Africa (31/52). In a multivariable logistic regression model (taking account of multiple travel destinations and changes over time), *S.* Typhi resistance to FQ was most strongly associated with travel to Pakistan (adjusted OR 32.0, 95%CI 15.4-66.4, P<0.001), and was also associated with travel to India (OR 21.8, 95%CI 11.6-41.2, P<0.001) and Bangladesh (aOR 6.2, 95%CI 2.8-13.6, P<0.001)(7).

S. Paratyphi A resistance to FQ was present in 97% of cases over this period. Again, FQ resistance was more likely to be encountered in isolates from Pakistan, India, or Bangladesh (aOR 33.4, 95%CI 10.0-112.0, P<0.001) . These findings are consistent with observations in endemic settings: FQ resistance in *S*. Typhi and *S*. Paratyphi A has risen globally from 1990 to 2018 [15]. The extent of this threat has been more evident since the widespread adoption of new thresholds for defining resistance around 2012, prompted by reports of increasing treatment failure [16].

1.7 In which countries are travellers at risk of acquiring multidrug-resistant plus FQ-resistant infection?

- **In isolates from returning travellers, resistance to amoxicillin, chloramphenicol and co-trimoxazole (multidrug-resistant, MDR) often co-exists with FQ resistance (MDR+FQ). This phenotype is increasingly prevalent in *S*. Typhi isolates (KP)**
- **MDR+FQ resistance of S. Typhi is most often associated with travel to Pakistan, and least associated with travel to India (where FQ resistance is common but MDR resistance is not) (KP)**

In multivariable analysis of UKHSA surveillance data 2014-2019, cases were most likely to exhibit *S.* Typhi MDR+FQ resistance in association with travel to Pakistan (OR 2.5, 95%CI 2.4-5.2, P<0.001). This profile was less likely to be associated with travel to India (OR 0.07, 95%CI 0.04-0.15, P<0.001) where most *S.* Typhi isolates are resistant to FQ but susceptible to amoxicillin (97%), chloramphenicol (97%), and co-trimoxazole (95%). There were no MDR *S.* Paratyphi A or *S.* Paratyphi B isolates. Meta-analysis from endemic settings corroborates these findings, as do previous observations of travel-related cases in the UK (24-27).

1.8 In what countries are travellers at risk of acquiring extensively drug-resistant (XDR) infection and other infections resistant to third generation cephalosporins (ESBL) ?

- **As of September 2021, extensively drug-resistant (XDR) *S*. Typhi has only been identified in England among travellers returning from Pakistan (KP)**
- **Extended spectrum beta lactamase (ESBL) producing *S*. Typhi and *S*. Paratyphi A resistant to third generation cephalosporins but susceptible to at least one first-line agent have also**

been identified on rare occasions among travellers returning from Iraq, India, and Bangladesh (KP)

The XDR phenotype, encompassing resistance to amoxicillin, chloramphenicol, co-trimoxazole, FQ, and third generation cephalosporins, has been identified in the UKHSA surveillance dataset in one *S*. Typhi case in 2017, 6 in 2018, and 32 in 2019. All XDR cases over this period have been associated with travel to Pakistan, with the highest risk associated with travel to the province of Sindh (28). In addition to Pakistan, cases of ESBL *S*. Typhi and *S*. Paratyphi A have been observed in England in association with travel to Iraq, India, and Bangladesh.

Currently, the greatest risk of acquiring XDR *S.* Typhi is associated with travel to all districts of Pakistan (28, 29). ESBL *S.* Typhi has also been reported in travellers returning to non-endemic countries from Iraq, the Philippines and Guatemala(30-35) and in individuals in Sri Lanka, Democratic Republic of Congo and Nigeria(35, 36). Further countries are likely to report ESBL *S.* Typhi in the future.

2. CLINICAL PRESENTATION

2.1 Which individuals should be investigated for EF in England?

- **We recommend investigating individuals for EF if they present with fever and have**
  - **Travelled to an area endemic for EF in the 28 days prior to onset of symptoms (1C)**
    OR
  - **Had household contact with a confirmed case of EF (1C)**

The mean incubation period of EF is reported as between 7 and 21 days. In a recent meta-analysis the vast majority of cases developed symptoms within 28 days of exposure and the longest reported incubation period was 41 days (37). Individuals who have travelled to an endemic area between 28 and 60 days prior to symptom onset should be investigated if there is a high degree of clinical suspicion. All cases of clinically suspected EF should be notified to the local Health Protection Unit. The public health management of cases and their contacts is addressed in PHE's Public Health Operational Guidelines(1).

2.2 What are the main presenting symptoms and signs of EF in England and other non-endemic countries?

- **Fever is the cardinal symptom of EF. Gastrointestinal symptoms are common. There are a range of additional signs and symptoms that may also be seen (KP)**

The clinical presentation of infection with *S.* Typhi and *S.* Paratyphi A, B and C are similar in non-endemic countries. Overall, the most common presenting symptom of EF is a reported fever, which is near universal in both adults and children (7, 8, 28, 38-46). This is often gradual in onset over several days. Documented pyrexia is also present in most cases (8, 41-43). Rigors may be seen, more frequently in adults(40, 41).

Gastrointestinal (GI) symptoms are common with at least one GI symptom occurring in 79% individuals(7). Abdominal pain is observed in 32-60% of adult and over 50% of children (8, 16, 38, 40, 41, 43, 45-50). Diarrhoea occurs in 35-84% of adults and 64-74% of children(8, 16, 38-41, 43-49).

Constipation is well described in older children and adults (4-16%) although this may occur less frequently than is commonly thought (16, 39, 44, 51).

Other common symptoms include cough (13-44%), headache (20-80%), myalgia and arthralgia (16, 38-44, 46, 47, 51).

Delirium and drowsiness ("Typhoid encephalopathy") are features of severe disease with rates of 12% described in some endemic settings(38). They are rarely seen or described among the literature in non-endemic regions.

Many patients presenting with EF have few or no physical signs beyond pyrexia. Rose spots - blanching erythematous macules approximately 2-4 mm in diameter and classically found on the trunk- are well described but uncommon. They present in the second week of illness in up to 19% patients and can be difficult to see in darker skin (38-44, 46, 51). Relative bradycardia (classically described in the first week of illness) has been variably observed in more recent studies (39, 41, 43, 52). In non-endemic settings, hepatomegaly has been observed in 3-37% of adults and in 18-32% of children, typically in the third week of illness, whilst splenomegaly is described in 12-37% of adults and children (8, 38, 40, 42, 44-47). This contrasts to endemic settings, where children have been described as having rates of splenomegaly of up to 85%, and hepatomegaly of up to 90% (53).

2.3 What blood test abnormalities commonly occur in patients with EF?

- **Patients with EF may have blood abnormalities including anaemia, a high C-reactive protein and elevated liver transaminases. White cell count is often within the normal range (KP)**

The most common abnormality in the full blood count in patients with EF is anaemia, although this is based largely on reports from endemic countries rather than returning travellers. This occurs in 66-74% children and 16-44% adults(8, 16, 38-41, 43, 44, 49) and may be more common in patients with *S.* Typhi than *S.* Paratyphi infection (8, 40, 49). Total white cell count is not normally elevated in adults(8, 16, 38, 39, 42) and lymphopenia occurs in 20-40% (8, 42, 45). An absolute eosinophil count of zero has been observed in some case series, and may be a particular feature of enteric fever(54, 55). Thrombocytopenia occurs in 16-32% cases (8, 16, 39-41, 43, 45, 46, 49).

C-reactive protein is elevated in 80-100% of cases (16, 39, 40, 42, 43, 49). Liver transaminases are often moderately elevated in both children (39-87%) and adults (47-82%) (16, 39, 41-43, 45, 49) with 62% reaching three times the upper limit of normal for ALT in one case series(42).

2.4 What are the complications of EF in England and other non-endemic countries?

- **The commonest complications of EF are gastrointestinal bleeding, intestinal perforation, typhoid encephalopathy and haemodynamic shock (KP)**

Many complications are well-described in endemic regions but are rarely seen in non-endemic high-income countries. The most important gastrointestinal complications are gastrointestinal bleeding, intestinal perforation, and cholecystitis. Other complications include haemodynamic shock, typhoid encephalopathy (as described above), metastatic infections (such as bone and joint infection), and myocarditis(56-58).

2.5 What is the mortality of EF in England and other non-endemic countries?

- **The mortality of EF in England is less than 1% (KP)**

The mortality of EF in England and other non-endemic high income settings is low, with case fatality rates of <1% (8, 16, 38-47, 49). This compares to an estimated global case fatality rate of around 2 - 2.5%(38, 56, 59).

2.6 Who is at risk of developing complications of EF in England and other non-endemic countries?

- **Complications are more common after ten or more days of illness (KP)**
- **There are no systematic scoring systems to assess the severity of EF or the risk of developing complications (KP)**
- **Clinicians need to be vigilant to identify complications early (AR)**

There is evidence that delayed presentation to hospital is associated with severe disease and complications. In one meta-analysis, the odds of developing complications in children were three times higher at day 10 or more of symptoms (57).

Infants may have higher complication rates than older children and adults in endemic settings, although this was not found to be significant in a 2019 meta-analysis (55). There is no evidence that the severity of EF is worse in people with HIV infection in contrast to the well-described association with HIV infection and invasive non-typhoidal salmonella disease(60). There is insufficient data to assess whether non-HIV immunocompromised states increase the risk of developing EF complications. There is no proven association of pregnancy with increased rates of EF complications(61).

Where complications do occur, they tend to present from the second week of illness(57). Cardiac complications such as endocarditis and myocarditis are rare, but more common in those with underlying valvular or congenital heart disease (58). Gastrointestinal and central nervous system complications typically do not have any predisposing risk factors (58).

3. DIAGNOSIS

3.1 Which microbiological tests should clinicians perform when seeking to diagnose a patient with suspected EF?

- **We recommend that the laboratory investigation of choice for the diagnosis of EF is blood cultures (1B)**
- **We suggest the opportunistic sampling of less invasive specimens (faeces or rectal swabs, pus, urine) as investigations that may improve yield (1B)**
- **We suggest that bone marrow aspiration could be considered, especially in cases of treatment failure, recent antimicrobial exposure or presentation after the first week of illness (2C)**
- **We recommend that serological investigations should NOT be used in the diagnosis of EF in returning travellers (1B)**
- **We recommend that nucleic acid amplification tests should NOT be used without culture-based assays (1B)**

As the clinical presentation of EF is predominantly a non-specific febrile illness without localising signs, laboratory investigations should also include other diagnostic tests for diagnosis of fever in a returning traveller as appropriate (e.g. malaria, amoebiasis, rickettsia, brucellosis, leptospirosis, tuberculosis, syphilis, dengue and other arboviral infections)(62-64)

Definitive Diagnostic tests:

Culture-based investigations:

Diagnosis of EF continues to rest on the culture of a recognised causative serovar from sterile sites such as blood, bone marrow, and urine, as well as from duodenal aspirates or faeces. In addition to providing a definitive diagnosis, microbiological isolation permits increasingly important antimicrobial susceptibility testing to be performed, and the opportunity for microbiological strain typing and epidemiological surveillance.

1. Blood Cultures

Blood cultures are the investigation of choice for diagnosis of EF. Reported positive blood culture sensitivity rates, as compared with marrow aspiration, vary across studies and populations but are

mostly in the range 40-80% (65-69). In one study 15 mL of blood culture showed the same sensitivity as 1 mL of bone marrow(70). Positive peripheral bacteraemia rates decline rapidly after the first week of illness and following antimicrobial administration(65, 71, 72). Adequate blood volume should be sampled. (See 3.2).

2. Bone marrow aspirate

Bone marrow aspiration remains the gold standard investigation for the diagnosis of EF, with bacterial loads in marrow being an order of magnitude higher than those in peripheral blood(73). The viable bacterial load from marrow aspiration appears to be unaffected by the duration of symptoms at presentation, and culture recovery following antimicrobial treatment remains stable for the first week, which may reflect the intracellular location of bacteria in the reticuloendothelial system(74).

3. Bile or duodenal aspirate

Although rarely performed for diagnosis of EF, sampling of duodenal secretions has a reported sensitivity of 40-70% (67, 75). However the test may not be well tolerated, especially in children and is not a routine investigation when other testing modalities are more readily available . It may be best reserved for cases of fever of unknown origin where definitive diagnosis is deemed essential or to establish that empirical treatment has failed.

4. Faeces

The sensitivity of stool culture in EF is approximately 30-40% but the potential additive use of this test is often overlooked when patients are constipated (75). In these circumstances bacteriological culture from rectal swabs should be attempted, although sensitivity is compromised when culturing small faecal volumes (70). The use of selective culture media to improve detection is discussed later. (See 3.4).

5. Urine

Culture of urine specimens for EF *Salmonella* serovars may be attempted, especially during the first week of illness, although the test sensitivity rate is usually low.

Non-culture based investigations:

Serological tests:

The Widal agglutination test detects antibodies to the lipopolysaccharide O and flagellar protein H antigens of *S.* Typhi. In use for well over a century, its shortcomings are both its poor specificity, with significant cross-reactivity to other non-typhoidal *Salmonella* serovars and other Enterobacterales, and a disappointing sensitivity that may relate to the duration of illness at the time of sampling. It is widely available in many endemic countries. Meaningful interpretation of the test's predictive value

is only possible with a detailed understanding of the immunisation and background *Salmonella* exposure history of the individual or population tested(76). The Widal test therefore cannot be recommended for use in returning travellers. (See 3.3).

Rapid Diagnostic Tests (RDTs): Currently, there are a number of other commercially available rapid diagnostic tests (Typhidot, Test-it Typhoid (KIT), TUBEX). These have been designed to detect IgG and/or IgM antibodies to different *S. Typhi* antigens using a variety of platforms. A recent meta-analysis of these tests found the diagnostic accuracy to be only moderate, with sensitivity ranging between 69-85% and specificity 79-90% in endemic countries (77, 78). A major shortcoming of most of the studies examined was that none of the tests assessed were designed to detect antibodies to *S.* Paratyphi antigen. Given the significant limitations of serology, and the availability of excellent laboratory culture systems throughout England, the use of rapid diagnostic tests for EF are not recommended at present.

Therefore serological tests and RDTs should be interpreted with caution and not used exclusively to base clinical decisions for management of EF.

Nucleic Acid Amplification Tests:

Several studies have reported successful detection of EF serovar DNA in peripheral blood and other biological specimens in endemic settings, although assay sensitivities vary (78). The principle of boosting DNA copy number by short culture incubation may improve sensitivity (79). Although a combination of molecular testing and blood culture may improve confirmatory diagnosis in the future, at present, molecular diagnostic tests for typhoidal salmonella are not routinely available in England(80).

By contrast, there are a number of multiplex commercial kits for the detection of *Salmonella* spp in stool. Whilst these assays provide an important step forward allowing the potential identification of multiple pathogens, as may happen when food and water hygiene practices or sanitation systems fail, the tests have been designed to detect both typhi and non-typhi Salmonella serovars, and so cannot diagnose EF specifically. Furthermore, concerns remain over the sub-optimal sensitivity of such assays when bacterial loads are low, leading to recommendations for enrichment stool cultures to diagnose EF (see 3.4)(81, 82).

3.2 How many blood cultures and what volume of blood should be taken to diagnose EF?

- **In adults, we recommend that a minimum of two sets of paired blood culture bottles (20 mL / pair) should be taken as first line investigation (1B)**
- **In children, we recommend that blood cultures should be collected in a single paediatric bottle (1B)**

As discussed above, the reported sensitivity of peripheral venous blood cultures for the diagnosis of EF is variable and estimated to be approximately 60%. This is at least in part due to the fact that bloodstream bacterial counts have been shown to have very low median number of colony forming units/mL of blood (65). It has been estimated that increasing the volume of venous blood taken for culture from 2 mL to 10 mL leads to a concomitant rise in detection sensitivity from 51% to 65%, and volumes over 10 mL may allow sensitivity to approach that of bone marrow aspirates (70, 83). In adults and adolescents, it is therefore strongly recommended that at least two sets of paired blood culture bottles (10 mL each) are taken to increase sensitivity of detection. Cultures should not be refrigerated but be incubated at 37^{o}C and then transported to the laboratory for culture as soon as possible.

Although there is evidence that circulating EF bacteraemias may be higher in children than adults, this effect is outweighed by the smaller blood volumes usually drawn. Recommendations for paediatric blood volume sampling have been developed using both age- and weight-based criteria, according to the body's ability to replace up to 4% of total blood volume safely(84). However, loss of such blood volumes in infants and younger children especially, may need to be modified when malnutrition is present or in those where intensive repeat sampling is predicted (84-87). Reasonable safe volumes for blood culture are 1-3mL from infants < 1 year, 3-5 mL from children < 5 years, 5-10 mL from those aged 5-12 years, and 20 mL for >12 years.

3.3 How should a patient with a serological diagnosis of EF made in another country be managed?

- **We suggest that asymptomatic cases with a serological diagnosis of EF made in another country are not investigated further (AR)**
- **We suggest that symptomatic cases with a serological diagnosis of EF made in another country should be investigated for EF and other pathogens (AR)**

As previously discussed in 3.1, the predictive value of serological tests for EF is dependent upon immunisation history, epidemiological exposure and history of previous EF. Given the suboptimal sensitivities of such tests, and issues regarding specificity with non-enteric *Salmonella* serovars and cross-reactivity with other bacteria, insufficient confidence can be placed on such results to establish the diagnosis. Asymptomatic cases do not need any further follow up. In symptomatic cases, it is recommended that appropriate investigations be conducted for other infections as well as those described above for EF. In particular, if the illness has been prolonged it is advisable to consider performing blood cultures and /or bone marrow sampling if febrile. Repeated stool or rectal swab cultures should be considered as these tests are more likely to be positive in later stages of EF infection.

3.4 What tests should a laboratory perform to identify EF pathogens?

- **We recommend that routine diagnostic laboratories adopt UK Standards of Microbiological Investigation (UK SMI) operating procedures to isolate and identify EF pathogens (1A)**

Work on clinical samples known or suspected to be *S.* Typhi or *S*. Paratyphi A, B or C must be handled at containment level 3 (CL3). Full detailed guidance as to the investigations for *Salmonella* serovars is provided in the relevant UK Standards for Microbiology Investigations (SMI B15, B30, B37 B38, B41, ID24, TP3)(88).

Identification of *Salmonella* spp

- For investigation of *Salmonella* in faecal material, routine diagnostic laboratories may use validated PCR tests that have been shown to be accurate for *Salmonella* species detection.
- Investigation for *S*. Typhi and *S*. Paratyphi A, B and C serovars should include a subculture of mannitol selenite enrichment broth onto MacConkey's and xylose-lysine-desoxycholate (XLD) agar to improve detection sensitivity (89).
- Culture screening of urine samples during the first week of illness may be performed by adding an equal volume of urine with mannitol selenite or selenite F enrichment broth and subculturing for 24 hours before plating on XLD agar.

- It is recommended that routine diagnostic laboratories identify *Salmonella* to genus level as described in the relevant SMIs and to use antisera in validated agglutination tests according to the manufacturer's instructions to identify EF serovars. API kits reliably identify species but cannot differentiate serovars. Although other methods, including molecular detection kits and matrix-associated laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS), show promise for differentiation of serovars they cannot do so reliably at present(81, 90). Readily available commercial antisera recommended for presumptive identification of EF includes 9,d,vi for *S*. Typhi, 2,a for *S*. Paratyphi A, 4,b for *S*. Paratyphi B and 6,7, c for *S*. Paratyphi C.

- All *S.* Typhi and *S*. Paratyphi A, B and C isolates from England, should be sent to the GBRU for formal identification, and those from suspected cases of EF should be sent urgently.

3.5 Which antimicrobial susceptibilities should be performed on EF pathogen isolates?

- **We recommend that routine diagnostic laboratories send isolates from suspected EF cases to the GBRU for formal identification but should first undertake routine antimicrobial susceptibility testing (AR)**
- **We recommend that EF isolates are routinely tested against ceftriaxone, azithromycin, ciprofloxacin and meropenem (AR)**
- **We recommend against reporting cefuroxime, aminoglycoside or cefixime susceptibility (AR)**
- **We recommend that all isolates which appear azithromycin resistant in diagnostic laboratories are sent to the GBRU for confirmatory testing (AR)**

Amoxicillin, chloramphenicol, trimethoprim-sulfamethoxazole, ciprofloxacin, ceftriaxone, azithromycin, and meropenem are all effective antimicrobials for treating EF when the pathogen is known to be susceptible. Resistance to ciprofloxacin should be assessed by MIC estimation using Etest, or a 5µg pefloxacin disc as per EUCAST recommendations. Extremely high rates of FQ resistance are now found in *S.* Typhi and *S.* Paratyphi A, but this agent is still highly effective if full susceptibility is proven (MIC ≤ 0.06mg/L). Cefuroxime and aminoglycoside susceptibility should not be reported as in vitro susceptibility does not translate to in vivo efficacy, as these antimicrobials penetrate poorly into intracellular locations (91). Cefixime susceptibility should not be reported as

this oral third generation cephalosporin has been associated with higher rates of treatment failure and relapse(92, 93).

The EUCAST-approved breakpoint for azithromycin (≤ 16 mg/ L) is an epidemiological cut-off that has only been established for *S.* Typhi and not for the *S.* Paratyphi serovars (94). Currently, there is no evidence that isolates with azithromycin MICs above this breakpoint are associated with clinical treatment failure, but formally validated clinical breakpoints have yet to be established. Routine diagnostic laboratories that do not perform azithromycin MIC estimation regularly should be aware that there may be difficulties with visual interpretation of the MIC (reading the trailing edge of 80% colonial growth), as different manufacturers' strips produce different clarity of breakpoint. A double reader system is advisable to reduce interpretation errors (95). At the time of writing, no azithromycin resistant S. Typhi or Paratyphi isolates have yet been confirmed in England. Therefore presumptive azithromycin resistance reported by diagnostic laboratory (MIC> 16 mg/L) should not preclude clinicians from using it for treatment. All isolates with azithromycin MIC> 16 mg/L should be referred to the reference laboratory for confirmation, assessment of azithromycin genetic determinants and management discussed with clinicians at GBRU.

(Figure 1).

3.6 What diagnostic tests can the reference laboratory perform?

- **We recommend that isolates of presumptive EF serovars are sent to the GBRU for confirmation and typing (AR)**
- **We recommend that all cases of suspected or confirmed EF should be notified to the local Public Health Unit (AR)**

The GBRU provides a national service that offers reference laboratory investigations to aid both routine diagnostic laboratory testing and the public health response. For suspected EF isolates this work currently includes:

1) Whole genome sequencing (WGS) to infer serovar
2) Phenotypic confirmation of unusual antimicrobial resistance patterns, with WGS analysis to understand the genetic basis for resistance profiles (96)
3) WGS analysis to look for strain relatedness, detect emerging threats and support outbreak investigations.

4. TREATMENT

4.1 Which antimicrobial(s) should be used to treat suspected EF in England (excluding patients returning from an XDR EF endemic area)?

At the time of writing, the only XDR EF endemic area is Pakistan. Please consult https://www.gov.uk/government/collections/typhoid-and-paratyphoid-guidance-data-and-analysis when prescribing to ensure no other regions have been added to this list.

- **We recommend treating patients (adults and children) with suspected EF with oral azithromycin (1A)**
- **In patients who have symptoms or signs of complicated infection or who require IV therapy, we recommend IV ceftriaxone (1A)**
- **In patients who require IV therapy and have severe beta-lactam allergy which precludes the use of ceftriaxone, we suggest oral or IV azithromycin in combination with additional broad-spectrum agent(s) to treat other pathogens. Specialist advice should be sought (AR)**
- **We recommend against treating EF with empirical ciprofloxacin before isolate susceptibilities are known, as most isolates from returning travellers will be resistant to ciprofloxacin (1A)**
- **We recommend that other diagnoses are considered in individuals with undifferentiated fever returning from EF endemic regions. In severely unwell people consider also adding doxycycline (or azithromycin in children < 12) as empiric treatment for rickettsial infection and discuss with a specialist infectious disease centre(2C)**

Data from GBRU, collected between 2016 and 2019, show that 99.5% EF isolates were susceptible to ceftriaxone and 100% were susceptible to azithromycin(19). Empiric treatment with either of these agents is very likely to cover EF pathogens imported to England. These data excludes isolates from Pakistan where there is a current outbreak of XDR *S.* Typhi.

By comparison, among returning travellers to England, ciprofloxacin resistance is greater than 90% in *S.* Typhi and Paratyphi A isolates from South Asia, and greater than 60% in S. Typhi isolates from sub-

Saharan Africa. Due to high resistance rates, ciprofloxacin is not recommended for empirical treatment of EF.

Azithromycin is an effective drug for treating uncomplicated EF pathogens with clinical cure rates of between 82 and 100% (97, 98). A Cochrane systematic review evaluated its role in 2008 and found it to be equivalent to comparator drugs including chloramphenicol, ceftriaxone and FQ (99). Four randomised control trials (RCTs) with 564 participants have compared azithromycin with a FQ including ciprofloxacin, ofloxacin, and gatifloxacin (97, 100-102). The meta-analysis favoured azithromycin for clinical failures (OR 0.48 (0.26, 0.89)) but there was no statistical difference for microbiological failure, relapse and duration of fever. The results of two of the studies were influenced by the inclusion of patients infected with *S*. Typhi isolates with low level-resistance to FQ (nalidixic acid resistant isolates).

The role of azithromycin in complicated infection has not been formally evaluated and all published RCTs have excluded patients with complicated infection. Whilst some studies have shown prolonged fever and bacteraemia clearance times when compared with ciprofloxacin(103, 104), relapse rates are universally low (99, 103, 105, 106).

Azithromycin achieves intracellular concentrations in phagocytes of up to 200 times that in serum and has a serum half-life of 68 hours. This makes it highly effective at killing intracellular *S*. Typhi and *S.* Paratyphi and preventing relapse (104). By contrast, extracellular concentrations of azithromycin may not exceed the minimum inhibitory concentration (MIC) which may be the cause of prolonged bacteraemia(103). Optimal length of treatment has not been defined but most RCTs have used 5- or 7-day courses.

Azithromycin can be given orally once a day with an initial loading dose which increases intracellular concentrations to greater than the MIC within the first 24 hours. It is licensed in children from six months of age and is usually well tolerated.

Ceftriaxone is an effective antimicrobial to treat uncomplicated EF with clinical cure rates of 73 – 100% in multiple RCTs (99, 102, 105, 107-118). A meta-analysis of eight RCTs with 442 participants compared ceftriaxone with chloramphenicol (107-114). No significant difference was seen in the risk ratio (95% confidence interval) for clinical failure (RR 1.39 (0.65, 2.97) or relapse (RR 0.44 (0.18, 1.05) and no microbiological failures occurred in either treatment arm.

Studies in the 1990s, before FQ resistance became prevalent, compared ceftriaxone with ciprofloxacin, ofloxacin and fleroxacin (115, 119-121). In four RCTs with 119 participants the analysis favoured FQ for clinical failure (RR 12.34 (2.23-68.30) but there were no significant differences in microbiological failures or relapse. An RCT compared ceftriaxone with gatifloxacin in patients with *S.* Typhi in 2014 in a period that saw the emergence of high-level FQ resistance. The RCT was stopped early due to treatment failure in patients with blood culture confirmed *S*. Typhi in the gatifloxacin arm (102).

Ceftriaxone has been compared head to head with azithromycin for uncomplicated EF in three RCTs involving 196 children(105, 116, 117). There were no significant differences detected in the relative risk of clinical failure (RR 0.40 (0.10-1.59)) or microbiological failure (RR 1.98 (0.35-11.22) between the two groups. Azithromycin was associated with a slightly prolonged time to defervescence (mean difference -0.52 days (-0.91, -0.12) and individuals were more likely to have a persistent bacteraemia during treatment. Relapse at 30 days was found to be significantly more likely in the ceftriaxone arm (RR 11.9 (2.17, 65.06)(99, 105, 116, 117)(14-17).

The role of ceftriaxone in complicated EF has not been fully assessed. With the exception of one small study in the 1990s(119), all RCTs have systematically excluded complicated EF . However, ceftriaxone has been widely used with good response as salvage therapy in clinical trials where patients have failed first line therapy (97, 101, 106). It is also recommended for treatment of complicated disease by the WHO, and in national guidelines including Zimbabwe, Fiji, Pakistan and India (100, 122-125).

Ceftriaxone is given IV as a once daily dose and is usually well tolerated. Various lengths of treatment have been investigated ranging from 3 to 14 days. It has been suggested that shorter durations of ceftriaxone are more likely to lead to relapse with studies using 3 or 7 days of IV ceftriaxone showing variable rates of relapse between 5 and 15%(105, 118, 119). Only one RCT with 57 participants has compared different durations of ceftriaxone for treating EF. In this study which compared 7 and 14 days of ceftriaxone in children, there was no significant difference in clinical failures (RR 2.00 (0.17, 23.39) or relapse (RR 10.06 (0.52, 196.10)(118). Whilst most patients treated with ceftriaxone for EF in England will complete therapy with azithromycin, a 7-10 days course of IV ceftriaxone is likely to be effective. Patients should be told to re-present if fevers or other symptoms return. In patients presenting with symptoms compatible with EF, the differential diagnosis is wide

and includes bacterial, viral and parasitic infections. Rickettsial infections, particularly scrub and murine typhus are common in South Asia and can cause severe disease with high mortality rates if untreated (126-128). Consider adding doxycycline to ceftriaxone in severely unwell patients with EF until cultures confirm infection. Azithromycin is effective against scrub typhus and has some efficacy against murine typhus and spotted fever thus doxycycline does not need to be added if the patient is already on azithromycin (129, 130). Azithromycin may also be considered as an alternative to doxycycline to treat rickettsial infections in children.

4.2 Which antimicrobial(s) should be used to treat confirmed EF in England, once culture results and drug susceptibilities are known?

- **We recommend that patients with uncomplicated EF whose isolate is susceptible to azithromycin and who are already clinically improving on azithromycin, should complete a seven-day course of azithromycin (1A)**
- **In patients treated with ceftriaxone (or other IV therapies), we recommend oral step down once the patient is clinically improving to either**

    1) **oral azithromycin, to complete a seven-day course (1A) OR**

    2) **oral ciprofloxacin, if the isolate is susceptible, to complete a seven-day course (1A)**

Once a patient with confirmed EF is clinically improving and will tolerate and absorb oral medication, they should be stepped down to oral therapy to complete a seven-day course. Whilst a 7 – 10 day course of IV ceftriaxone is effective at treating EF, switching from IV to oral antimicrobials is a central principle of antimicrobial stewardship. It improves patient safety and quality of care and reduces line associated complications, hospital stay and cost (131, 132).

Current UKHSA data shows that most patients will have isolates that are susceptible to azithromycin. This is an effective drug for treating EF pathogens with high clinical and microbiological cure rates and low rates of relapse(99). Following an incomplete course of IV ceftriaxone, a seven-day course of azithromycin should be given to prevent the higher rate of relapse seen with short courses of ceftriaxone(105, 118, 119).

As per current UKHSA data, most EF isolates encountered in England will be ciprofloxacin resistant(19). However, in patients with ciprofloxacin susceptible isolates (usually *S.* Paratyphi B and C), a seven-day course can be considered as oral stepdown therapy. Data from adult human

challenge studies with uncomplicated fully susceptible *S.* Typhi suggests ciprofloxacin is a more effective drug with significantly shorter time to resolution of symptoms, fever clearance, treatment response and length of bacteraemia (103). This is supported by early FQ RCTs which suggest rapid fever clearance and high rates of clinical and microbiological response with FQ including ciprofloxacin in the absence of drug resistance.

4.3 What is the role of ciprofloxacin in the treatment of EF?

- **We recommend against the empiric use of ciprofloxacin for treatment of suspected or confirmed EF before isolate susceptibilities are known (1A)**
- **We recommend that, if an isolate is known to be ciprofloxacin susceptible, a seven-day course of oral ciprofloxacin can be used following initial IV ceftriaxone or failure of oral azithromycin (1A)**

4.4 Which antimicrobial(s) should be used to treat suspected EF in people returning from areas where XDR EF is endemic?

At the time of writing, the only XDR EF endemic area is Pakistan(28). Please consult https://www.gov.uk/government/collections/typhoid-and-paratyphoid-guidance-data-and-analysis when prescribing to ensure no other regions have been added to this list.

- **We suggest treating patients returning from areas endemic for XDR EF with oral azithromycin (1C)**
- **In patients who have symptoms or signs of complicated infection or who require IV therapy, we suggest combining oral azithromycin with IV meropenem (1C)**

There is no high-quality data to evidence the treatment of XDR *S*. Typhi. The most common approach in the literature is to treat with meropenem or azithromycin or a combination of these two antimicrobials. This is supported by the Medical Microbiology and Infectious Diseases Society of Pakistan(125) and has also been adopted by UKHSA and the US Centers for Diseases Control and Prevention.

There are no RCTs which evaluate the use of meropenem in either drug susceptible or resistant EF. As previously discussed there is good data to support the use of azithromycin in uncomplicated EF (99).

A retrospective case review of 81 patients with blood culture confirmed XDR S. Typhi from Pakistan compared 22 patients treated with oral azithromycin to 20 patients treated with IV meropenem and 39 patients treated with combination therapy. Fever clearance time (FCT) was around 7 days in each group with one treatment failure in the azithromycin arm and three in the combination therapy arm. Mean durations of treatment were short; 6.6d (+/-2.7) for azithromycin, 8.1d (+/- 2.5) for meropenem and 7.5/8.5 days (+/-3.8 – 4.3) for azithromycin – meropenem combination therapy. There were no reported relapses (133). Other published case series do not include enough follow up data to ascertain treatment outcomes (134, 135).

There are several case reports which document the treatment of imported XDR *S*. Typhi from Pakistan to non-endemic regions. Two case reports describe patients successfully treated with meropenem alone (136, 137) whilst seven case reports describe patients who had a second agent added to meropenem due to prolonged FCT or persistent bacteraemia (29, 138-143). This was most commonly azithromycin, but one patient received additional fosfomycin (143). Ertapenem was successful in one patient(144). All patients received at least 10 days of one or more antimicrobials to which the isolate was susceptible.

4.5 *What antimicrobial(s) should be used to treat confirmed XDR or ESBL EF, once drug susceptibilities are known?*

- **We suggest a minimum of seven days oral azithromycin is used to treat patients with confirmed XDR or ESBL EF susceptible to azithromycin (1C)**
- **In isolates resistant to azithromycin, we suggest treating with meropenem or another agent to which the isolate is susceptible and discussion with the reference laboratory (AR)**

There are no high-quality data to guide optimisation of XDR or ESBL EF treatment once susceptibilities are known. A seven-day course of oral azithromycin is effective at treating

uncomplicated azithromycin susceptible EF and thus is likely to be effective for azithromycin susceptible XDR infection (99). Meropenem has not been subjected to RCTs for the treatment of EF and so length of treatment is unknown. Extrapolating from ceftriaxone, also a beta-lactam, we suggest treating for at least 10 days to reduce the risk of relapse. We suggest continuing therapy until a minimum of 48 hours after the patient has defervesced and shown clinical improvement.

4.6 When should dual antimicrobial therapy be used in EF?

- **We suggest dual antimicrobial therapy should be considered in the following situations**
    a. **For added empirical treatment of other pathogens such as rickettsia or suspected bacterial sepsis (2c)**
    b. **For broader antimicrobial cover, including anaerobic organisms, in cases of EF intestinal perforation (1A)**
    c. **In patients with suspected or confirmed XDR EF who have symptoms or signs of complicated infection or require IV therapy, we suggest combining azithromycin with meropenem (1C)**

Whilst there may be theoretical benefits to combination antimicrobial therapy in improving clinical and microbiological outcome and reducing resistance pressure, this needs further evaluation by RCT. A small open label study compared monotherapy (ceftriaxone or azithromycin) with dual therapy (ceftriaxone/azithromycin or azithromycin/cefixime) in blood culture confirmed EF in Nepal. In this study, FCT were significantly shorter in the combination arm and fewer patients were bacteraemic at day three of treatment (145). Conversely, an RCT comparing azithromycin, ofloxacin and azithromycin-ofloxacin combination therapy found no difference between the three arms in a population with high level nalidixic acid resistance(97).

In XDR *S*. Typhi, an observational study comparing azithromycin, meropenem and azithromycin-meropenem combination therapy failed to identify a difference between the three treatment arms (146). Although meropenem has now been widely used in XDR EF, it has not been assessed by RCT. Some case reports of imported infection document failure to improve on meropenem until a second agent is added but it is unclear whether subsequent improvement could be attributed to the

additional therapy (29, 135, 138-141, 143). For this reason, we suggest combination therapy in individuals with complicated infection or requiring IV antimicrobials for suspected or confirmed XDR EF.

In individuals with suspected EF it may be appropriate to use additional antimicrobial therapy to treat other differential pathogens such as rickettsia. These should be rationalized once a diagnosis is confirmed.

4.7 Can suspected or confirmed EF be managed as an outpatient in England?

- **We recommend that adults and children with suspected or confirmed uncomplicated EF with mild symptoms who are tolerating oral medication without vomiting may be considered for outpatient management. Clinical judgement should be used to risk assess individual patients (1C)**

Between 2017 and 2019, 15% of culture confirmed EF cases diagnosed in England were managed without hospital admission (see 1.4). A recent case series from the Hospital for Tropical Diseases, London, reports that 52% (48) patients with symptomatic culture confirmed EF presenting between 2009 and 2020 were managed entirely as outpatients (unpublished data). There were no relapses or complications in these patients. This figure is higher still in endemic countries where more than 70% patients may be managed out of hospital (147).

Outpatient management with oral therapy can be safe and cost effective but patients should be individually risk assessed and clinical judgement used when considering this. Patients should have uncomplicated disease with only mild symptoms and be able to tolerate oral therapy without vomiting. Other factors to consider include likely compliance with therapy, ability to selfcare, framework for regular review and agreement to return to hospital if symptoms worsen or complications develop. Of note, a lower threshold for admission should be considered in children and in the second or third week of illness as there is increased risk of complications at this time (see 2.6)(57).

4.8 What is the role of Outpatient Parenteral Antibiotic Therapy (OPAT) in the management of EF in England?

- **OPAT is rarely required in the management of patients with EF (AR)**
- **We suggest that OPAT may be considered in exceptional circumstances in**
    a. **patients who are allergic or intolerant of recommended oral antimicrobials**
    b. **patients who are unable to tolerate or absorb oral medications (AR)**
    c. **patients whose isolate is resistant to oral alternatives (AR)**

Patients with features of severe EF should be managed in hospital. OPAT has been used to complete a 14 day course of IV ceftriaxone in patients with EF who are fit for discharge from hospital (148). Whilst it is safe and efficacious, a seven-day course of oral azithromycin on discharge is equally efficacious and may reduce the risk of relapse and line related complications.

4.9 When should clinicians suspect treatment failure?

- **We recommend that treatment failure is considered in**
    a. **patients with persistent fever AND other symptoms after seven days of effective antimicrobial therapy (1B)**
    b. **Patients with persistent bacteremia at 7 days (1B)**
    c. **Patients who develop complications or clinically deteriorate after five days of treatment with an antimicrobial to which the isolate is sensitive (1B)**
- **We recommend against routinely repeating blood cultures before 7 days of effective therapy, unless the patient is clinically deteriorating (AR)**

It is common for patients with EF to remain febrile for five days or more. Median reported FCT (measured from starting treatment until temperature remains <37.5 c for 48 hours) vary from 79 to 196 hours but typically patients clinically improve before their fever settles (10, 27). If the patient is feeling better and symptoms are improving, even if they have low grade temperatures (<38C) continuing at seven days, this is within the normal range of treatment response.

Bacteremia clearance is usually rapid with ceftriaxone and FQ, both of which achieve high extracellular concentrations (103, 116). By comparison, up to 38% of patients treated with azithromycin remain bacteraemic at 72 hours, despite similar cure rates to ceftriaxone and a significantly lower risk of recurrence (116). For this reason, we recommend against routinely repeating blood cultures before seven days of appropriate treatment, unless the patient has clinically deteriorated. Persistent bacteremia at 7 days may suggest treatment failure and should prompt investigation for deep seated infection.

4.10 *Should high dose dexamethasone be used as adjunctive therapy in complicated disease?*

- **The role of steroids in EF is unsubstantiated and we do not recommend their use in complicated disease (AR)**

The single RCT addressing the use of dexamethasone in severe EF was conducted in 1984 by Hoffman et al in Indonesia, a highly endemic setting, in patients treated with chloramphenicol (149). Patients with suspected EF and shock or abnormal consciousness were randomised to high dose dexamethasone (3mg/kg then 1mg/kg 6 hourly for 48 hours) or placebo. In 263 patients with EF subsequently confirmed by blood culture, 42 met the criteria for severe EF and were included in the study. Of these, 37 had abnormal consciousness and 11 had shock or borderline shock. Four were subsequently excluded (three because they died within 6 hours of study entry and one as they were only culture positive on a rectal swab). The case fatality rates were two (10%) of 20 patients in the dexamethasone arm versus 10 (56%) of 18 patients in the placebo arm(149).

Whilst this study is often cited to justify the use of dexamethasone in complicated EF, it has a number of limitations including its size, the small number of patients with septic shock and the high complication rate, particularly nosocomial bacteremia. A very high dexamethasone dose was used based on regimens used in sepsis studies at the time which have not stood up to further scrutiny. This dose is far higher than is currently recommended in bacterial or tuberculous meningitis or in septic shock resistant to fluid resuscitation. The study has not been replicated under randomised conditions although a small observational study in children at the same hospital (and including data from some patients included in the RCT) also found a mortality benefit in those receiving high dose dexamethasone (150).

Following this, a non-randomised study using the same inclusion criteria as Hoffman et al, compared 100mg and 400mg of hydrocortisone (equivalent to 4 or 15mg dexamethasone) four times daily for

three days with a historical control who did not receive steroids. There was no difference in mortality between the three groups (151).

Whilst further studies would be useful in this area, the current data does not support the use of high dose dexamethasone in patients with complicated EF.

4.11 How should the complications of EF be managed?

- **All patients with complicated EF should be managed in conjunction with a specialist infectious disease centre (AR)**

- **Patients should receive appropriate antimicrobial therapy but may require further management specific to individual complications**

5. CHRONIC CARRIAGE

5.1 *What is the definition of EF chronic carriage?*

- **A temporary or convalescent carrier is defined as a person who is excreting *S.* Typhi or Paratyphi A, B or C after two or more courses of antimicrobial therapy but has been excreting for less than 12 months (KP)**

- **A chronic carrier is defined as a person who is excreting *S.* Typhi or Paratyphi A, B or C after 12 months (KP)**

Following acute EF and clinical resolution of symptoms a small proportion of patients continue to excrete *S*. Typhi or *S.* Paratyphi A, B or C in their stool (and rarely urine). These patients are asymptomatic but pose a risk of onward transmission to others. This state is known as 'carriage' and is distinct from symptomatic relapse or reinfection.

Stages of carriage are usually classified into convalescent (temporary) carriage and chronic (long-term) carriage. Different studies have used different definitions of these periods(152-154). Most studies use excretion for at least 12 months after acute illness to define chronic carriage(100). UKHSA operational guidance defines a convalescent carrier as 'a person who is still excreting after two or more courses of antimicrobial therapy but has been excreting for less than 12 months'(1).

5.2 What is the incidence of carriage?

- **The rate of chronic carriage is approximately 1-5% following acute EF (KP)**

- **Chronic carriage is more common in those with underlying gallstones (KP)**

- **A minority of people with chronic carriage do not have a prior history of acute EF (KP)**

Several studies globally have investigated the rates of convalescent and chronic carriage following infection with *S*. Typhi or Paratyphi A, B or C. The rate of convalescent carriage is up to 10% (152) with chronic carriage occurring in 1-5% of patients following the acute illness (155, 156). Chronic carriage is more common in females, the elderly and those with gallstones (157, 158). The

gallbladder is considered the primary site of pathogen persistence (155, 159).

Prevalence studies and clinical review following incidental laboratory isolates have demonstrated that not all patients with chronic carriage have a history of symptomatic EF infection (63, 160). These patients should be managed in collaboration with local public health or health protection teams.

5.3 What are the consequences of chronic carriage?

- **Chronic carriage poses a risk of secondary transmission of EF to others (KP)**

- **Chronic carriage is associated with an increased risk of gallbladder malignancy (KP)**

S. Typhi and *S*. Paratyphi A, B and C are human-restricted pathogens and therefore carriage plays an important role in maintaining the reservoir of infection in humans. Secondary transmission cases represent 1-4% of all EF cases diagnosed in England every year, despite public health screening of high-risk cases and contacts(160). These cases are presumed to have acquired EF in England either directly from an index case or carrier or via infected food(161).

Secondly, there is evidence that EF chronic carriage is an independent risk factor for gallbladder cancer, which in itself is commoner in those with gallstones(162, 163). A recent meta-analysis reported an overall odds ratio of gallbladder cancer in *S.* Typhi carriers of 4.28 (164).

5.4 Who should be investigated for chronic carriage in England following treatment of acute EF?

- **Patients that fall into high-risk groups for transmission of gastrointestinal pathogens should be investigated for carriage by UKHSA (1C)**

- **Patients that do not fall into the high-risk groups for transmission do not require further investigation for chronic carriage (2C)**

UKHSA has clear guidance on which patients following treatment for EF require ongoing investigation of carriage from a public health perspective (1). To limit secondary transmission public

health guidance focuses on only screening those in high-risk categories and cases falling into any of these groups will be followed up by UKHSA (table 4).

In those that do not fall into the high-risk groups for transmission there are two potential benefits of identifying chronic carriers; to reduce risk of local transmission to household contacts and to reduce the individual's risk of gallbladder cancer.

Analysis by UKHSA has shown that screening all patients for carriage following acute EF has minimal impact on reducing secondary transmission in non-high-risk groups (160). Therefore, routine screening for chronic carriage to reduce secondary or household transmission in non-high-risk groups is not recommended.

Gallbladder cancer is a rare malignancy in the UK with an incidence of 1.6 per 100,000 of population and a lifetime risk of < 0.2%. It is strongly associated with older age with a peak incidence in those aged 75-80 years old (165). Therefore, even those with confirmed chronic carriage have a low lifetime risk of developing gallbladder cancer (<1%). There is no evidence that antimicrobial treatment for chronic carriage reduces this risk.

Given that both chronic carriage and gallbladder cancer are associated with gallstones, the use of ultrasound assessment to look for gallstones could be considered to identify those at higher risk of developing chronic carriage and associated gallbladder cancer. However, there is currently insufficient evidence to make recommend routine use of ultrasound to identify those at risk of gallbladder cancer following acute EF.

5.5 How should people be investigated for chronic carriage in England?

- **In patients at high risk of transmission, UKHSA advises culture of three stool samples taken 48 hours apart one week after completion of antimicrobial therapy. Further sampling will be carried out by UKHSA if any of these samples are positive (1C)**

There is intermittent excretion of *S.* Typhi or *S.* Paratyphi in the stool and therefore a single sample is not sufficient to exclude carriage (166). Culture of three consecutive stool samples has a high negative predictive value in excluding chronic carriage (98%)(167). For those at high risk of

transmission to others, UKHSA advises investigation of carriage by testing three stool culture samples a minimum of 48 hours apart one week after completing antimicrobial therapy for EF (table 4). UKHSA will then investigate and follow-up patients with any positive stool samples. It is recommended any subsequent positive isolations are referred to GBRU for confirmation and typing where genomic analysis can be used to assess if the patient is shedding the same strain, different or multiple strains and detect any unusual antibiotic resistance.

5.6 Who should be treated for chronic carriage in England?

- **We suggest that treatment is offered to anyone confirmed as a chronic carrier (2C)**

Chronic carriers may be identified through public health screening (either following acute infection or close contact with an infected person), or by incidental isolation of *S.* Typhi or *S.* Paratyphi A, B or C in a stool sample. This second group requires further investigation to establish where they acquired infection and to confirm that they are a chronic carrier prior to treatment. This is outlined in UKHSA(previously PHE) Operational Guidelines (1).

There is no evidence that treatment of chronic carriage improves long-term outcomes in EF chronic carriers. However, given the increased risk of gallbladder cancer and of transmitting the pathogen to others, treatment should be considered in all carriers to benefit both the individual (in terms of removing occupational restrictions and possibly reducing cancer risk) and as a public health measure. A risk-benefit discussion should take place between the patient and treating clinician when considering treatment(161).

5.7 How should chronic carriage be treated?

- **We suggest all chronic carriers considered for treatment are discussed with the clinical team at the reference laboratory GBRU (AR)**
- **We suggest antimicrobial treatment options for chronic carriage of oral ciprofloxacin, azithromycin or amoxicillin (2B)**
- **We suggest cholecystectomy could be considered where antimicrobial treatment fails. Ultrasonography should be considered to guide decision-making (2C)**

There is a lack of definitive evidence on effective strategies for treatment of chronic carriage in the current era of antimicrobial resistance, treatment toxicities and patient autonomy. We therefore suggest that all confirmed chronic carriers considered for treatment are discussed with the clinical team at GBRU to discuss possible treatment options. There is evidence that FQ are effective in eradicating chronic carriage with approximately a 90% cure rate after a 28-day course (168, 169). The only double-blinded RCT performed showed an eradication rate of 92% in those given a 28-day course of norfloxacin compared to 11% in those given placebo. Patients with and without gallstones were included in this study and eradication rates were high in both groups (87% vs 100%)(168).

However, these studies were carried out prior to the emergence of widespread FQ resistance and all patients included in these studies had FQ-susceptible isolates. Most patients presenting in England currently have isolates with reduced susceptibility to ciprofloxacin; the median ciprofloxacin MIC for *S*. Typhi in isolates in England from 2017-2019 was 0.5, with 5.5% isolates with an MIC $\geq$1(19). Although ciprofloxacin has excellent penetration into bile reaching 2800-4500% of plasma concentrations (170), there is no clinical outcome data to establish whether it is effective in eradicating chronic carriage in isolates with reduced ciprofloxacin susceptibility (MIC >0.06 mg/L).

It should be noted that recent studies have highlighted potential serious side effects of ciprofloxacin use, particularly tendonitis(171, 172) and heart valve regurgitation(173, 174). They should be avoided in those at increased risk of side effects (those taking systemic steroids, over 60 years, with renal impairment, prior solid organ transplantation or a history of tendonitis)(172, 175).

There is good evidence for the use of amoxicillin in treating chronic carriage, but studies have shown higher failure rates than with FQ. The approximate cure rate is 70% following a 4-6 week course (176-180). Higher doses or IV amoxicillin may be more effective(178, 181).

Azithromycin may be used to treat chronic carriage given that almost all isolates remain susceptible and it has good bile penetration. However, there is currently no published evidence to support this. A single case report showed successful eradication of convalescent carriage in a patient with non-typhoidal salmonella(182).

Cholecystectomy has been employed as a treatment strategy for eradication of EF chronic carriage and may be required in patients that fail antimicrobial therapy. Cholecystectomy has a 70-90% eradication rate and has to be weighed up against the risk of surgical complications(179, 183).

It is often stated that gallstones are a risk factor for antimicrobial treatment failure in chronic carriage and such patients may require cholecystectomy(100, 184). Evidence from mouse models suggests that *S.* Typhi may form a biofilm around gallstones which may lead to increased failure rates with antimicrobials(159, 185, 186). However, the clinical data to support this is unclear and outcomes are likely dependent on the biliary penetration and biofilm activity of the antimicrobial used (168, 177, 179, 187-190). We therefore suggest that ultrasonography assessment could be considered in patients with confirmed chronic carriage to investigate for gallstones, particularly in those who fail first line treatment.

5.8 How should people treated for chronic carriage be followed-up?

- **UKHSA guidance recommends that monthly stool samples should be taken following treatment to confirm clearance, starting one month after treatment completion (2C)**
- **We suggest that all subsequent isolates should be sent to GBRU for confirmation and typing (2D)**

PHE guidance recommends monthly stool samples for carriers at risk of secondary transmission (1). A negative stool sample should be followed by two further samples taken at least 48 hours apart to confirm successful clearance. If all three samples are negative the patients can be presumed to have cleared the infection. However, there is still a small risk of relapse, particularly within the first three months following treatment(168, 188, 191). Therefore, repeated monthly stool samples could be considered depending on the clinical circumstances. If any follow-up samples are positive the patient should be deemed to have relapsed and a second treatment course could be considered if clinically appropriate.

6. PRETRAVEL GUIDANCE

6.1 What are the implications of these guidelines on pretravel advice?

These guidelines complement Green Book guidance on vaccination (2) and NaTHNaC's guidance on preventing the acquisition of EF whilst abroad(3). They reassert the need to emphasise preventive measures to VFR travellers of all ages to South Asia, South America and the Middle East, but particularly children as they account for 31% of travel related cases.

Due to the prevalence of XDR S typhi in UK travellers returning from Pakistan, pre-travel typhoid vaccination is particularly important for this group. Furthermore, despite a sub-optimal response to polysaccharide antigen vaccines in children between the ages of 12 months and two years, it is suggested that pre-travel typhoid vaccination 'off license' is recommended for children in this age group travelling to Pakistan(192).

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Box 1: Key Questions

1 Epidemiology

1.1 Where do adults and children presenting in England with EF acquire infection?
1.2 What type of traveller is most at risk of acquiring infection in endemic countries?
1.3 What is the geographical distribution of EF cases within the England?
1.4 What proportion of EF cases in England are associated with hospital admission?
1.5 Can azithromycin susceptibility be anticipated for travel-related cases of EF?
1.6 Can fluoroquinolone susceptibility be anticipated for any travel-related cases of EF?
1.7 In what countries are UK travellers at risk of acquiring multidrug-resistant plus fluoroquinolone-resistant (MDR+FQ) infection?
1.8 In what countries are UK travellers at risk of acquiring extensively drug-resistant (XDR) infection and other infections resistant to third generation cephalosporins?

2 Clinical Presentation

2.1 Which individuals should be investigated for EF in England?
2.2 What are the main presenting symptoms and signs of EF in England and other non-endemic countries?
2.3 What blood test abnormalities commonly occur in patients with EF?
2.4 What are the complications of EF in England and other non-endemic countries?
2.5 What is the mortality of EF in England and other non-endemic countries?
2.6 Who is at risk of developing complications of EF in England and other non-endemic countries?

3 Diagnosis

3.1 Which microbiological tests should clinicians perform when seeking to diagnose a patient with suspected EF?
3.2 How many blood cultures and what volume of blood should be taken to diagnose EF?
3.3 How should a patient with a serological diagnosis of EF made in another country be managed?
3.4 What tests should a laboratory perform to identify EF pathogens?
3.5 Which antimicrobial susceptibilities should be performed on EF pathogen isolates?
3.6 What diagnostic tests can the reference laboratory perform?

4 Treatment

4.1 Which antimicrobial(s) should be used to treat suspected EF in the UK (excluding patients returning from an XDR EF endemic area)?
4.2 Which antimicrobial(s) should be used to treat confirmed EF in the UK, once drug susceptibilities are known?
4.3 What is the role of ciprofloxacin in the treatment of EF?
4.4 Which antimicrobial(s) should be used to treat suspected EF in people returning from areas where XDR EF is endemic?
4.5 What antimicrobial(s) should be used to treat confirmed XDR or ESBL EF, once drug susceptibilities are known?
4.6 When should dual antimicrobial therapy be used in EF?
4.7 Can suspected or confirmed EF be managed as an outpatient in England?
4.8 What is the role of OPAT in the management of EF in the England?
4.9 When should clinicians suspect treatment failure?
4.10 Should high dose dexamethasone be used as adjunctive therapy in complicated disease?
4.11 How should the complications of EF be managed?

5 Chronic Carriage

5.1 What is the definition of EF chronic carriage?
5.2 What is the incidence of carriage?
5.3 What are the consequences of chronic carriage?
5.4 Who should be investigated for chronic carriage in the England following treatment of acute EF?
5.5 How should people be investigated for chronic carriage in England?
5.6 Who should be treated for chronic carriage in England?
5.7 How should chronic carriage be treated?
5.8 How should people who have been treated for chronic carriage be followed-up in England?

6 Pretravel guidance

6.1 What are the implications of these guidelines on pretravel advice?

Table 1. Definitions used in these guidelines.

Term	Definition
Enteric fever (EF)	Symptomatic infection with *Salmonella enterica* subspecies *enterica* serovars Typhi or Paratyphi A, B or C
Multidrug-resistant EF (MDR EF)	EF caused by *S.* Typhi or Paratyphi A, B or C, resistant to ampicillin, chloramphenicol and co-trimoxazole
Fluroquinolone-resistant EF (FQR EF)	EF caused by *S.* Typhi or Paratyphi A, B or C, resistant to fluoroquinolones
Extensively drug resistant EF (XDR EF)	EF caused by multidrug resistant *S.* Typhi or Paratyphi A, B or C with additional resistance to ciprofloxacin and third-generation cephalosporins.
Extended-spectrum beta-lactamase (ESBL) EF	EF caused by *S*. Typhi or Paratyphi A, B or C resistant to third-generation cephalosporins but susceptible to at least one of chloramphenicol, co-trimoxazole or ciprofloxacin
Complicated EF	Suspected or confirmed EF associated with complications including severe sepsis or shock, gastrointestinal bleeding, intestinal perforation, encephalopathy or metastatic infection
Convalescent carrier	A person who is still excreting *S*. Typhi or Paratyphi A, B or C after two or more courses of antimicrobial therapy but has been excreting for less than 12 months(1).
Chronic carrier	A person who is excreting *S.* Typhi or *S*. Paratyphi A, B or C after 12 months(1).

Box 2: Summary of Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to grading quality of evidence and strength of recommendations(2, 3)

Strength of recommendation 1. Strongly recommend 2. Weakly recommend	**Quality of evidence** A High quality- Randomised controlled trial (RCT) B Moderate quality- downgraded RCT or upgraded observational study C Low quality- Observational study D Very low quality- downgraded observational study
Factors that determine strength of recommendation Balance between desirable and undesirable effects Quality of evidence Values and preferences Cost of intervention	**Factors that may influence grading quality of evidence** **Factors that might decrease the quality of evidence** Study limitations Inconsistency of results Imprecision Publication bias **Factors that might increase the quality of evidence** Large magnitude of effect Plausible confounding, which would reduce a demonstrated effect Dose-response gradient

Table 2. Imported *Salmonella* Typhi, Paratyphi A, and Paratyphi B cases among travellers, by suspected country of acquisition: confirmed cases identified in England, 2017-2019.

	***S.* Typhi**		***S.* Paratyphi A**		***S.* Paratyphi B**		**Total**	
Suspected country of acquisition	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
	650		**381**		**44**		**1075**	
Pakistan	282	(43%)	134	(35%)	3	(7%)	419	(39%)
India	236	(36%)	166	(44%)			402	(37%)
Bangladesh	43	(7%)	38	(10%)			81	(8%)
Other Asia/Pacific	19	(3%)	17	(4%)	18	(41%)	54	(5%)
Africa	27	(4%)					27	(3%)
Americas	9	(1%)	1	(0.3%)	21	(48%)	31	(3%)
Europe	3	(0.5%)					3	(0.3%)
Multiple possible	30	(5%)	23	(6%)	2	(5%)	55	(5%)
Not stated	1	(0.2%)	2	(0.5%)			3	(0.3%)

Figure 1: Geographical distribution of Enteric Fever.

Endemic countries are defined by incidence > 1 per 100,000 population(4).

Isolated cases reported in England with travel in preceding 28 days to Spain, Portugal, Japan and Canada (2017-2019)

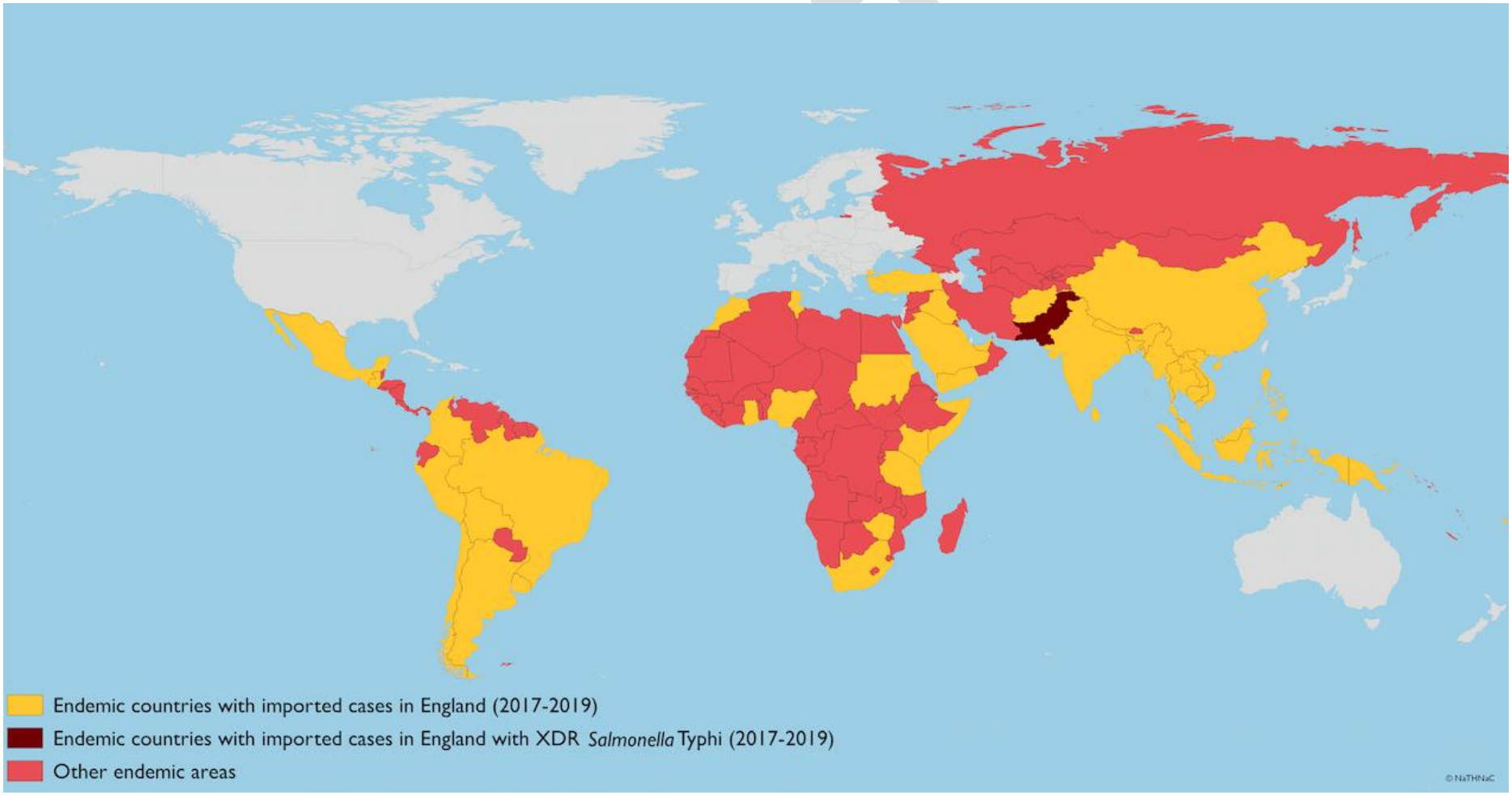
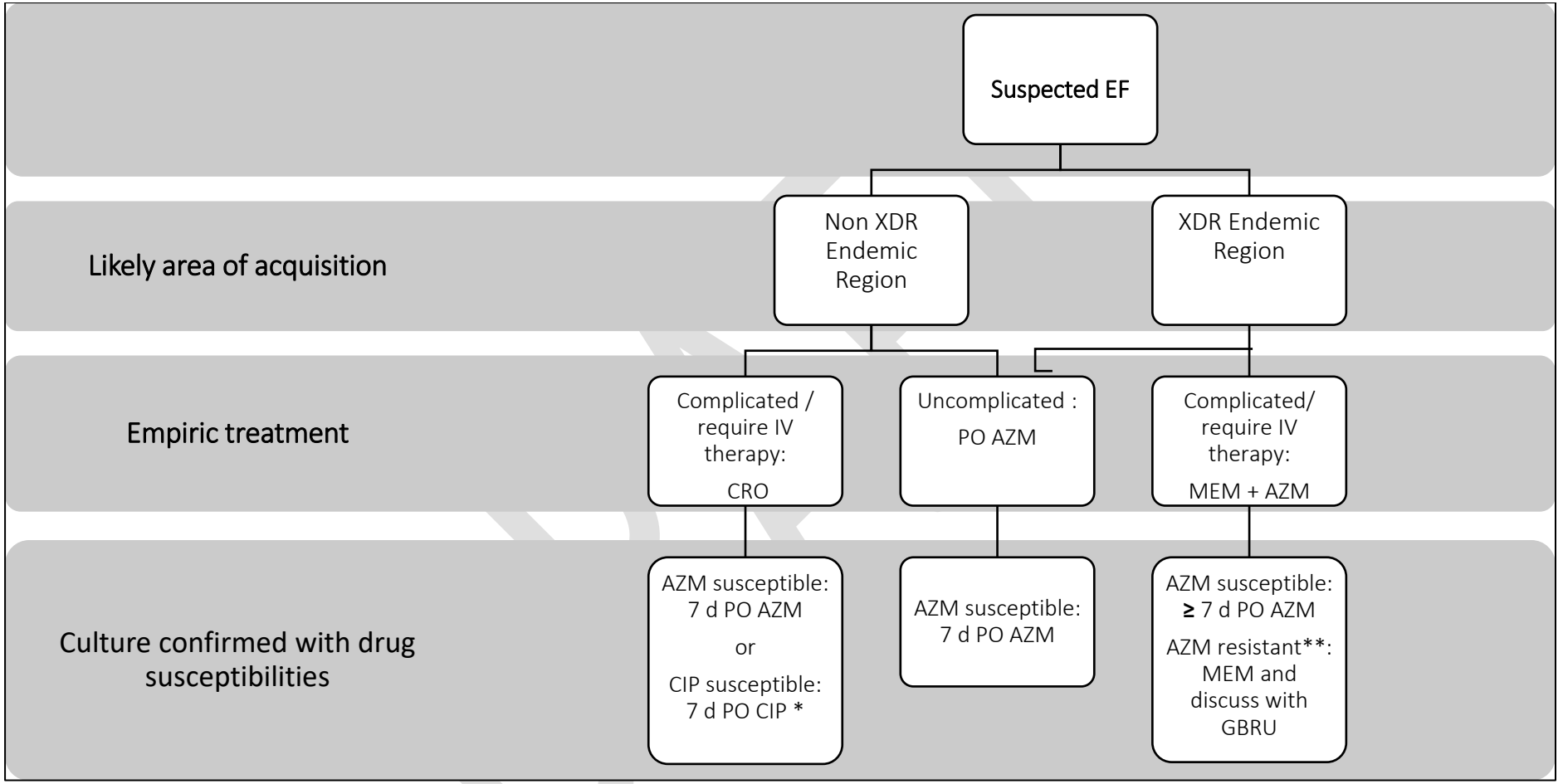


Figure 1: Enteric Fever Treatment Algorithm for adults and children, including pregnant women



CRO- ceftriaxone, AZM- azithromycin, MEM – meropenem, CIP – ciprofloxacin, PO – oral, IV- intravenous, XDR- extensively drug-resistant, d- days

***Ciprofloxacin should be avoided in pregnancy.**

****Azithromycin MICs may be difficult to interpret in routine diagnostic laboratories. All isolates that appear resistant should be referred to and discussed with Salmonella Reference Laboratory (GBRU),UKHSA.**

Table 3: Drug doses

Drug	Adult dose	Paediatric dose	Contraindications	Important safety information
Treatment of acute infection				
Ceftriaxone	2g IV OD x 7-10d	80mg/kg (max 2g) IV OD x 7-10d	Severe allergy to beta-lactam agents History of kidney stones. Hypercalciuria	Pregnancy category B. Manufacturer advises use only if benefit outweighs risk. Concomitant treatment with intravenous calcium – risk of precipitation.
Azithromycin	1g PO loading dose then 500mg OD x 7d (IV dose is the same as oral dose)	15-20 mg/kg (max 500mg) PO OD x 7d	Allergy	QTc prolongation Electrolyte disturbance Pregnancy category B. Manufacturer advises use if alternatives not available.
Ciprofloxacin	750mg PO BD x 7d	20mg/kg (max 750mg) PO BD x 7d	Allergy or previous severe adverse reactions History of tendon disorders relation to quinolone usage. Concomitant steroid use increases risk of tendon damage Caution in Age > 60 years, renal impairment, solid organ transplant, heart valve disease, connective tissue disorders and risk factors for heart valve regurgitation (benefit-risk assessment) (5, 6)	Very rare reports of potentially long-lasting side effects to musculoskeletal and nervous systems including tendon rupture, peripheral neuropathy, seizures, aortic aneurysm and heart valve regurgitation(5, 6). Risk of QT prolongation and electrolyte disturbances. Where indicated in EF, benefit outweighs risk

				Pregnancy category C- avoid in pregnancy
Meropenem	1g IV TDS	10 mg/kg IV TDS	Severe allergy to beta-lactam agents	Risk of hepatotoxicity, monitor liver function tests. Pregnancy category B. Manufacturer advises use only if benefit outweighs risk.
Possible options of treatment of chronic carriage*				
Ciprofloxacin	750mg PO BD x 28 d	20mg/kg (max 750mg) PO BD for 28d	As above	As above Monitor for *C.difficile* , potential fluoroquinolone induced tendinitis/tendon rupture and cardiac side effects with prolonged usage.
Amoxicillin	1g PO TDS x 28d	30mg/kg PO TDS (max 1g) for 28d	Allergy to beta-lactam antibacterials	
Azithromycin	500mg OD x 28d	10mg/kg OD (max 500mg) for 28d	As above	As above

IV- intravenous, PO- oral, d- days, OD- once daily, BD- twice daily, TDS- three times daily

*unlicensed used, to be discussed with the Reference laboratory (GBRU) UKHSA prior to use

Table 4. Groups at higher risk of transmitting gastrointestinal pathogens. Adapted from UKHSA (previously PHE) operational guidelines, 2017(1)

Group	Description
Group A	Any person of doubtful personal hygiene or with unsatisfactory toilet, hand washing or hand drying facilities at home, work or school.
Group B	All children aged five years old or under who attend school, pre-school, nursery or similar childcare or minding groups.
Group C	People whose work involves preparing or serving unwrapped food to be served raw or not subjected to further heating.
Group D	Health care worker, social care or nursery staff who work with young children, the elderly, or other particularly vulnerable people, and whose activities increase the risk of transferring infection via the faeco-oral route. Such activities include helping with feeding or handling objects that could be transferred to the mouth.

Box 3: Quick Guide to Microbiological Investigations of EF

	Suitable sample	**Optional samples/ additional information**
Timing of presentation to healthcare		
Within 1 week of onset	Blood cultures	
After 1 week	Blood cultures and stool / rectal swab culture	Urine, bile, duodenal aspirate, bone marrow
Suspected carrier	Stool culture, at least 3 specimens 48 hours apart	
Clinical samples frequency and volume		
Blood cultures frequency	2 sets of blood cultures taken at least half an hour apart.	
Blood culture volume	Adults and children > 12 years: paired blood culture bottles, 20mL per pair Children: < 1 year - 1-3 mL, 1- 5 years - 3-5mL 5-12 years - 5-10mL	Not to be refrigerated, transported to lab immediately with label of suspected 'Hazard group category 3 pathogen or enteric fever'
Identification of presumptive isolates of enteric fever	Isolate from blood, stool or other clinical specimen	Gram negative rods Non-lactose fermenting Oxidase negative *Salmonella* spp on MALDI-TOF or API Serology O, H, Vi antigens
Antibiotic susceptibility (EUCAST criteria)		
Cases	Azithromycin (Etest or 15 µg disc) Ceftriaxone Meropenem Ciprofloxacin (Etest or pefloxacin disc)	Amoxicillin Chloramphenicol Co-trimoxazole
Carriers	Azithromycin (Etest or 15 ug disc) Ceftriaxone Ciprofloxacin Etest (or pefloxacin disc), Amoxicillin	Chloramphenicol Co-trimoxazole
Tests performed by GBRU		
Confirmation of unusual and emerging resistance	Referral of all azithromycin -resistant isolates for confirmation	
Typing	Referral of at least one isolate per patient	Blood isolate preferred

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