Assessment and initial management of acute undifferentiated fever in tropical and subtropical regions

Anurag Bhargava,[1,2,3] Ravikar Ralph,[4] Biswaroop Chatterjee,[5] Emmanuel Bottieau[6]

[1]Department of Medicine, Yenepoya Medical College, Mangalore, Karnataka, India
[2]Center for Nutrition Studies, Yenepoya (Deemed to be University), Mangalore, Karnataka, India
[3]Department of Medicine, McGill University, Montreal, Canada
[4]Department of Medicine, Christian Medical College, Vellore, Tamil Nadu, India
[5]Department of Microbiology, IQ City Medical College, Durgapur, West Bengal, India
[6]Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

Correspondence to: A Bhargava anurag.bhargava@yenepoya.edu.in

Acute undifferentiated febrile illnesses (AUFI) are characterised by fever of less than two weeks' duration without organ-specific symptoms at the onset.[1] These may begin with headache, chills, and myalgia. Later, specific organs may be involved. AUFIs can range from mild and self limiting disease to progressive, life threatening illness. A mortality rate of 12% has been reported in severely ill hospitalised patients in tropical regions.[2]

AUFIs are classified into malaria and non-malarial illnesses with the help of microscopy or rapid diagnostic tests for malaria.[3] The overlap of epidemiological and clinical features often renders clinical diagnosis difficult. There is greater focus on non-malarial AUFIs with the decline of malaria in many regions of the world.[4] They account for 20-50% of all fevers in children over 5 years of age and adults in Asia and Africa.[5] Laboratory confirmation is difficult—in contrast to malaria and dengue, for which high accuracy rapid diagnostic tests are now available. Current guidelines do not comprehensively address undifferentiated infections, which can fuel indiscriminate use of antimalarials and antibiotics.[6 7]

In this clinical update, we present an approach to the diagnosis and initial management of common AUFIs in children older than 5 years and in adults in tropical regions, taking into consideration availability of limited resources in some settings.

WHAT YOU NEED TO KNOW

- Malaria, arboviral infections (such as dengue), enteric fever, and bacterial zoonotic diseases (such as scrub typhus and leptospirosis) are common causes to consider in patients presenting with acute fever and no localising symptoms in tropical regions
- A step-wise approach—with a careful interpretation of local disease patterns, possible exposures and risk factors, clinical features, and basic laboratory data—can help clinicians recognise specific diseases
- Request testing for malaria and a full blood count in all patients with acute undifferentiated fever
- Early presumptive antibiotic therapy may be started for suspected bacterial zoonoses if diagnostic confirmatory tests are awaited or not available, as these infections may progress rapidly into a life threatening illness with multi-system involvement
- Treatment for enteric fever needs to account for increasing drug resistance, especially in South Asia

Sources and selection criteria

We searched PubMed for studies published in English between January 1990 and August 2018 using the MeSH terms: "(epidemiology, diagnosis, therapy, guideline) and (fever, bacteremia, typhoid fever, scrub typhus, rickettsial infections, spirochetal infections, arbovirus infections, malaria, brucellosis, melioidosis)." We also searched the Cochrane Database for related systematic reviews. Key references identified in review articles and textbooks were hand searched.

What are the causes of non-malarial AUFI?

Studies from Asia and Africa report arboviral infections (17.5% of severe febrile illnesses), bacterial bloodstream infections (mainly enteric fever) (10.5%), and bacterial zoonoses such as leptospirosis and rickettsioses (4.0% each) as major causes of non-malarial AUFI.[6 8-13] Box 1 presents the mnemonic "MA-ESR" as an aid to recall the common AUFIs, and figure 1 gives an overview of how undifferentiated fever is classified. Enteric fever affects an estimated 11.9 million people annually in Asia and Africa.[14] Globally, over one million cases each of leptospirosis and scrub typhus occur annually.[15 16]

Rarer infections include viral haemorrhagic fevers such as Ebola virus disease and Lassa fever seen in Africa, and Crimean-Congo haemorrhagic fever (CCHF) with a wider distribution. Outbreaks of CCHF (also sometimes referred to as Asian Ebola virus) have been documented in Pakistan and India in recent years with high mortality.[17-20] Timely recognition of these illnesses is important as they cause high mortality and spread rapidly.

How is it diagnosed?

Follow a typical stepwise approach to synthesise information from history and epidemiology. A careful history and physical examination can provide vital clues. Clinicians in settings with limited access to testing may have rely solely on these to formulate a probable diagnosis and start treatment (see fig 2).

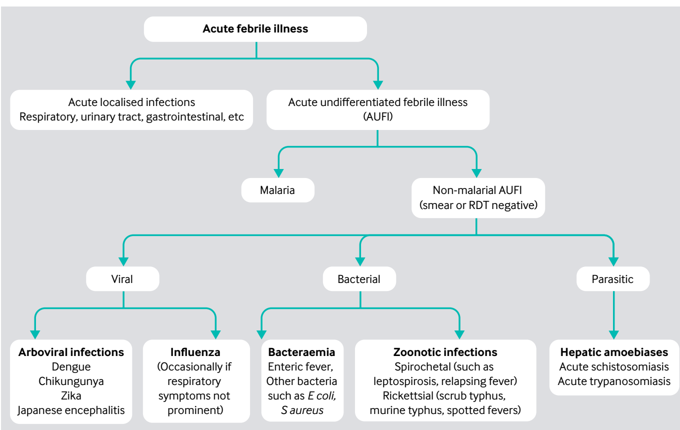
Consider local pathogens, what season it is (some infections are particularly prevalent around rainy season), and activities or specific events that might give clues to the cause. Ask out about the onset, nature and features of the illness

Locally prevalent pathogens

The infographic lists common infections to consider by region (also see appendix 1 on bmj.com).[21] Within regions considered endemic, the epidemiology of AUFIs is continuing to evolve. Scrub typhus and leptospirosis, once considered rural diseases, now affect urban populations too. Urban parks, and flooding in slums have emerged

Box 1 | Mnemonic MA-ESR lists the five main disease groups that cause acute undifferentiated febrile illnesses

- **Malaria**—Including all malaria due to *Plasmodium falciparum*, *P vivax*, *P ovale*, *P malariae*, *P knowlesi*
- **Arboviral infections**—Such as dengue, chikungunya, Japanese encephalitis, Zika, yellow fever
- **Enteric fever**—Due to *Salmonella enterica* serovar Typhi and Paratyphi A, B, C
- **Spirochaete infections**—Such as leptospirosis and tick-borne or louse-borne relapsing fever
- **Rickettsial infections**—Including scrub typhus, murine typhus, spotted fevers



RDT = rapid diagnostic test. E coli = Escherichia coli. S aureus = Staphylococcus aureus.

Fig 1 | Broad classification of acute febrile illness. In patients with high fever and rhinorrhoea, consider ruling out influenza

as risk factors for these respectively.[22,23] Dengue, once considered an urban disease, is increasingly observed in rural and peri-urban areas in India.[24] Melioidosis is an important cause of community-acquired sepsis in northern Thailand and northern Australia, and is now recognised to be endemic in many countries of the Indian subcontinent, East Asia, sub-Saharan Africa.[8,25]

Seasonality
Arboviral infections, scrub typhus, leptospirosis, and melioidosis peak during the rainy season, similar to malaria. In many tropical areas, malaria occurs round the year. Seasonal dynamics of enteric fever are variable, with peaks after rainfall seen in northern latitudes.[26] Information on ongoing outbreaks or a cluster of cases in a family or neighbourhood are useful clues to guide diagnosis.

Potential exposures
Consider asking about:

- Insect or mosquito bites, which are involved in transmission of several infections (malaria, dengue, chikungunya, Zika, CCHF, scrub typhus, murine typhus, spotted fevers, relapsing fever).
- Ingestion of contaminated food and water, implicated in enteric fever.
- Contact with body fluids or products of animals or contaminated water and soil, through skin abrasions or conjunctiva, which is linked to leptospirosis.
- Walking barefoot, working in paddy fields, and flooding in urban areas, which are risk factors for scrub typhus and leptospirosis. In rural areas, the risks of exposure to a contaminated environment, contact with animals, and exposure to multiple vectors can coexist, making it difficult to estimate the risk of any particular disease.

Fig 2 | The diagnostic and management approach for acute undifferentiated febrile illnesses in low resource settings

Onset, duration and pattern of fever and illness
The pattern of fever can be disrupted by fever medications such as paracetamol and ibuprofen but may sometimes be typical of a specific infection.

- Malaria, arboviral infections, scrub typhus, and leptospirosis have an abrupt onset and can rapidly progress to complications in the first week. A peak in temperature every other day is seen in malaria due to *Plasmodium vivax* or *P ovale*.[27]
- Enteric fever has a more insidious onset. Fever >39°C (102.20°F) for more than three days with abdominal pain and diarrhoea or constipation can suggest enteric fever.
- Dengue has a self limiting course with fever for up to 7-12 days.
- Fever in influenza classically lasts three days but may persist for up to eight days.[28]
- Fever may be absent or low grade in Zika infection.
- Tropical borrelioses cause relapsing fever lasting 3-5 days between afebrile periods of 4-10 days.

Patient related factors
Age, comorbidities, immunosuppression, and pregnancy can help narrow the differential diagnosis, and also affect outcomes. For example, patients with diabetes have a higher risk of

melioidosis.[8 25] Bloodstream infection due to non-typhoidal Salmonella, disseminated tuberculosis, and deep mycoses are more commonly observed in adults with HIV infection.[29] Pregnancy related immunosuppression is associated with increased severity of infections, in particular with more severe falciparum malaria.

Examination

Assess severity of illness

Look for signs of severe disease (see box 3) which indicate the need for urgent referral and hospitalisation.

Rule out localised infections

Figure 3 indicates examination features consistent with a possible localised infection. Evaluate patients with fever, especially severe infection, for both localised infections and AUFIs. Influenza may be confused with AUFIs as fever and myalgia can initially overshadow respiratory symptoms, which may be absent in older people.[28] Complicated AUFIs may also evolve and mimic localised infections—such as falciparum malaria (encephalitis), scrub typhus (severe pneumonia), or icteric leptospirosis (hepatobiliary infections).

Look for diagnostic clues of AUFIs

Certain clues on examination, which we term rule-in signs, help narrow the differential diagnoses (see infographic and appendix 2 on bmj.com). Rule-in signs, if present singly or in combination, indicate a moderate to high likelihood of a particular AUFI—that is, they are good predictors of a particular disease. There is limited evidence, however, on the diagnostic value of these signs.

Scrub typhus has a characteristic skin lesion—an eschar (fig 4)—seen in 17-57% of patients as per recent reports from India,[33 34] and in 56-86% of patients in reports from elsewhere in Asia.[33-35] Examine the neck, chest, axilla, abdomen, and groin for such lesions not associated with pain, pruritus, or oedema. A similar lesion in a patient with a milder illness in Africa is suggestive of African tick-bite fever, seen often in travellers returning from game parks. The lack of pain and oedema in eschars of rickettsial origin distinguish them from those of rarer causes such as tularaemia, anthrax, or East African trypanosomiasis.

Conjunctival suffusion (red eyes and oedema without exudate) and haemorrhage, jaundice, and marked muscle tenderness suggest

Box 3 | Red flag signs in patients with acute undifferentiated febrile illnesses indicating need for hospitalisation and urgent treatment

- *Prostration*—Unable to stand, sit, or walk without support[30]
- *Temperature*—Hyperpyrexia (temperature >41.5°C) or hypothermia (temperature <36°C) or rigors
- *Respiration*—Shortness of breath, respiratory rate >22 breaths/minute, cyanosis, arterial oxygen saturation <92% on room air[31]
- *Circulation*—Blood pressure <100 mm Hg systolic,[31] cold clammy extremities, capillary refill >3 seconds
- *Neurological*—Altered mental status (Glasgow coma scale <13), convulsions, positive meningeal signs (such as neck stiffness and Kernig's sign)[31]
- *Abdominal pain*—Severe or persistent vomiting[32]
- *Severe conjunctival or palmar pallor*[30]
- *Jaundice on examination of sclera*[30]
- *Petechial or purpuric rash*
- *Bleeding*—From nose, gums, or venepuncture sites; haematemesis, melaena[30]

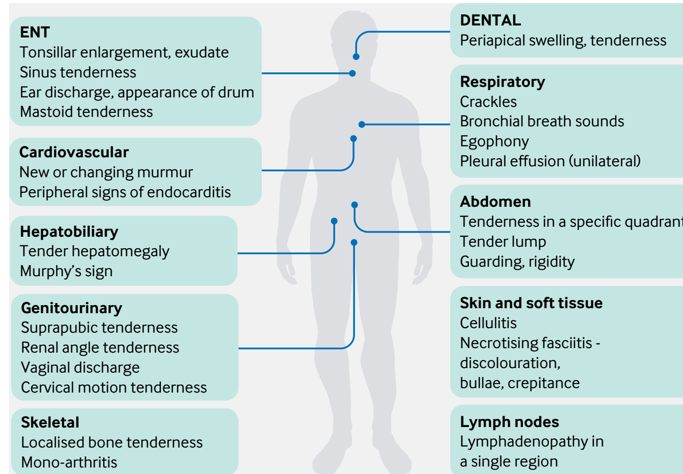


Fig 3 | Potential diagnostic clues to causes of acute localised infections

leptospirosis (fig 5).[36] A non-purulent conjunctivitis is also frequently seen in Zika virus infection, but not in other arboviral infections.

Rash and/or polyarthritis are suggestive of arboviral infections such as dengue, Zika or chikungunya. In Zika virus infection, a maculopapular rash appears typically on the first day with a cephalocaudal distribution and is intensely pruritic (worse in sleep). In contrast, the rash in dengue appears first on the trunk around five days after onset of fever.[37]

Symmetric arthritis of small joints with oedema is typical of chikungunya.[37]

Conversely, rule-out signs exclude a particular disease. For example, the presence of rash or lymphadenopathy renders malaria highly unlikely.[38] Likewise, generalised lymphadenopathy is uncommon in enteric fever.[39 40] Jaundice with high fever makes a diagnosis of viral hepatitis less likely and instead suggests leptospirosis or other AUFIs with hepatic involvement.

What are the first investigations?

In endemic areas, request a complete blood count, urine analysis, and smear microscopy and/or rapid diagnostic test (RDT) for malaria in all patients with fever. Urine examination may reveal urinary tract infection, especially in women and older people as they may not present with localised symptoms. Biochemical tests (such as liver and renal function tests) and imaging (x ray and ultrasound) are useful in patients with

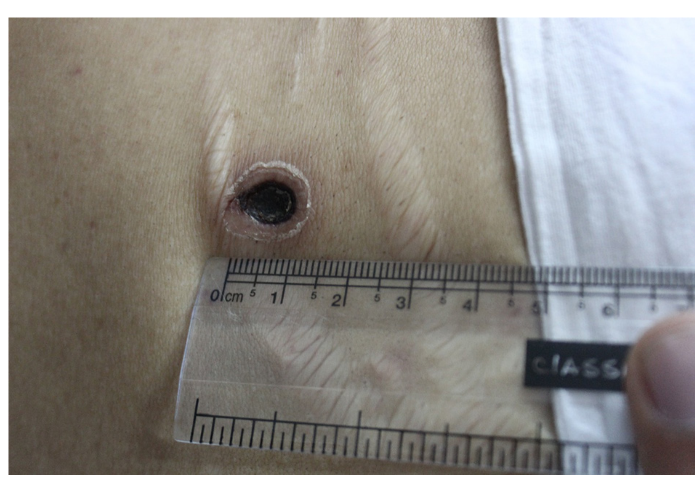


Fig 4 | An eschar on abdomen. Note the characteristic punched-out ulcer with a central black scab (often missing in eschars in moist areas)

Fig 5 | Characteristic eye signs of leptospirosis: conjunctival suffusion, jaundice, and sub-conjunctival haemorrhage

localised symptoms and in patients with severe illness to detect complications. Table 1 describes the diagnostic value of findings on initial investigations.

Based on the suspected diagnosis, confirmatory tests for specific infections are requested (table 2). Spirochetal and rickettsial infections are confirmed by demonstration of either a IgM seroconversion (appearance of IgM in specimens about 10 days apart), or a fourfold elevation of IgG titre in a pair of specimens at least two weeks apart. This precludes their use in the immediate clinical decision making. Further, these tests have limitations in availability and sensitivity. The sensitivity of blood culture and PCR is influenced by duration of illness (highest in the first week), specimen type (highest with eschar in the case of scrub typhus), and by previous antibiotic treatment.

The specificity of serological tests is affected by cross-reactions among pathogens, and by persistence of IgM antibodies after infections. In practice therefore, diagnostic certainty eludes the physician dealing with a non-malarial AUFI, and the demonstration of IgM antibody in a single acute-phase specimen contributes, at best, to a "probable diagnosis" of leptospirosis and scrub typhus.

What are the possible complications?

Malaria, scrub typhus and leptospirosis can progress rapidly to multi-organ dysfunction within the first week. Severe scrub typhus and leptospirosis can present as bilateral pneumonia or pulmonary haemorrhage respectively, and evolve to acute respiratory distress

Table 1 | Findings on investigations in patients with acute undifferentiated febrile illnesses (AUFI)

Basic investigations	Diagnostic value*	Suggests severe illness*
Complete blood count:	Perform in all patients	
• Haematocrit	—	Anaemia in patients with malaria, rising haematocrit in severe dengue.
• Leucocytosis	Seen often in leptospirosis, enteric fever in children, and in scrub typhus. Seen in the majority of patients of hepatic amoebiasis.	Leucocytosis may occur in enteric fever in adults with onset of complications (intestinal perforation); associated with severe forms of leptospirosis, scrub typhus, malaria and dengue fever.
• Leukopenia	Leukopenia occurring early in illness and in association with thrombocytopenia is suggestive of dengue.[41] Seen later in course of typhoid fever.	Falling TLC + thrombocytopenia + rising haematocrit seen with severe dengue
• Lymphocytosis	May be seen in rickettsial and viral infections	—
• Thrombocytopenia	Thrombocytopenia may be seen in all common AUFIs, so poor discriminatory value. Thrombocytopenia + splenomegaly suggestive of malaria, Thrombocytopenia + bleeding is seen in dengue and other VHFs, but is unusual in malaria.	Dengue fever: in association with bleeding
• Eosinophilia	Seen in filariasis, acute schistosomiasis, Loeffler's syndrome	—
Peripheral blood smear examination	Perform in all patients if facilities for microscopy available	
	Malaria, borreliosis, filariasis, Acute trypanosomiasis can be diagnosed on smear	Parasite density correlates with severity in malaria
Urine examination	Perform in severely ill patients. May be performed, especially in women and elderly, since UTIs may not have localising symptoms	
	Proteinuria and haematuria seen in leptospirosis	Haemoglobinuria in patients with severe malaria
Biochemistry	Perform in severely ill patients to assess organ dysfunction. Hepato-renal involvement is common in leptospirosis, scrub typhus, and malaria, while pulmonary-renal syndrome is seen in scrub typhus and leptospirosis	
Liver enzymes	Raised in several AUFIs, so no discriminatory value[42]	WHO has defined ALT or AST >1000 as suggestive of severe dengue
Bilirubin	Raised bilirubin distinguishes malaria from dengue[43] Raised bilirubin + modest rise in transaminases (<200 IU/L) + raised CPK seen in leptospirosis[44]	In severe leptospirosis, hyperbilirubinaemia may be marked (up to 300-400 mg/L)
Renal function	AKI common in malaria, scrub typhus, leptospirosis. Non-oliguric renal failure with potassium wasting seen in leptospirosis[45]	Correlate with prognosis especially when patient has multiorgan dysfunction syndrome
Imaging:	Perform in patients with tachypnoea and/or severe illness	
• Chest x ray	Scrub typhus: pneumonia is most common systemic involvement.[33,46] Bilateral opacities progressing to ARDS may be seen in scrub typhus, leptospirosis, and occasionally in malaria. Pneumonia occurs occasionally in enteric fever. Pleural effusion occasional in dengue fever (sign of capillary leakage). Others: Bilateral nodular opacities or upper lobe cavitating pneumonia in melioidosis	
• Ultrasound scan of abdomen	May be done in severely ill patients, especially those with jaundice, shock, abdominal pain, or persistent fever without obvious cause	
	May be helpful in diagnosing infections such as hepatic amoebiasis, melioidosis (liver and splenic abscesses). Findings such as mesenteric lymphadenopathy may help in diagnosis of enteric fever[47]	Ascites, pleural effusion, and gallbladder wall oedema are associated with severe dengue infection and are signs of plasma leakage. Acute acalculous cholecystitis and acute pancreatitis has been reported in all common causes of AUFI

TLC: total leucocyte count; UTI: urinary tract infections; AUFI: acute undifferentiated febrile illness; VHF: viral haemorrhagic fevers; WHO: World Health Organization; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CPK: creatine phosphokinase; ARDS: acute respiratory distress syndrome; AKI: Acute kidney injury

*Alone or in combination with other abnormalities. If confirmatory tests are not available, then the diagnosis may be "suspected" at best, if the epidemiological and clinical features and results of basic laboratory investigations are compatible. As such, treatment may be started on clinical grounds.

Table 2 | Confirmatory tests for select pathogens causing AUFI

Tests	Findings	Test performance	Advantages	Disadvantages
Malaria[48-51]				
RDT for malarial antigens (ICT format): histidine-rich protein 2 (HRP-2), *Plasmodium* lactate dehydrogenase (pLDH), *Plasmodium* aldolase (pAldolase)	Parasite antigens in blood. HRP-2 antigen is unique to *P falciparum*. pLDH can be common to genus *Plasmodium* or specific to *P falciparum* or *P vivax*	~95% sensitive and specific for *P falciparum*. Acceptable as standalone test for *P falciparum*. HRP-2 kits are the most sensitive	Results in minutes, no need for laboratory, little technical skill needed. pLDH can be used to monitor treatment response.	Low sensitivities for low level parasitaemia (<100 parasites/μL). RDTs of different brands vary greatly in performance. Cannot quantify parasitaemia. Kits deteriorate above 35°C. In areas where HRP-2 deletion *P falciparum* exist, only pLDH based tests are effective.
Confirmatory test: microscopy	Presence of parasites in blood. Presence of only gametocytes suggests that current illness is not malaria	Detects as few as 5-10 parasites per μL of blood. Turnaround time 20-30 minutes	Current gold standard: inexpensive, quantifies parasitaemia, identifies species	Needs skilled staff. Asymptomatic parasitaemia in hyperendemic areas can confound diagnosis
Dengue[52-55]				
RDT NS1 antigen	NS1 antigen in blood collected within 6 days of onset	Pooled sensitivity 66%, pooled specificity 97.9%	Results in minutes, no need for laboratory, little technical skill needed	Reduced sensitivity in dengue serotype 4 infection, and in case of previous infection with any serotype
RDT IgM	Dengue-specific IgM antibody in blood. Many RDT kits test NS1 antigen and dengue IgM in same cassette.	Pooled sensitivity 83%, pooled specificity 86% (if taking either NS1 or IgM as proof of infection)	Results in minutes, no need for laboratory facilities, little technical skill needed	IgM can persist for months and may not appear at all in secondary infections. Prior exposure to WNV, JE, or YF dampens dengue IgM response
Confirmatory test: culture	Isolation of virus from blood or tissue collected within 5 days of onset of fever	Sensitivity ~40%, specificity 100%	—	Turnaround time 1-2 weeks, expensive
Confirmatory test: NAA	Detection of dengue RNA in blood or tissue collected within 5 days of onset.	Sensitivity 60-100%, specificity >95%	Same-day diagnosis with nearly 100% sensitivity and specificity	Expensive
Confirmatory test: serology	≥4-fold rise in titre.* Seroconversion*	Specificity 100% for ≥4-fold increased titre or seroconversion*	Less expensive than culture or NAA	Results are retrospective and of no use in management
Enteric fever[40 56-58]				
RDT for antibody	Detection of antibody against salmonellae in single serum specimens	Sensitivity 69-78%, specificity 77-90%	Turnaround time 2-4 hours	Test performance of kits has varied widely among studies. No RDT for enteric fever is accurate enough to replace reference tests.
Confirmatory test: Culture	Isolation of enteric fever *Salmonella* from blood and bone marrow	Sensitivity 40-87% in blood and 80% in marrow, specificity 100%	Isolation allows drug sensitivity testing	Turnaround time 3-6 days. High level of expertise needed. Decreased sensitivity with prior therapy
Widal test†	≥4-fold rise in titre*	Sensitivity depends on local prevalence, specificity 100%	Affordable	≥4 fold increase may not occur in partially treated patients, ≥4-fold rise can be missed if antibody level peaks before first specimen is collected.
Scrub typhus[59-63]				
RDT for specific IgM (ICT format)	Detection of IgM in single specimens	Pooled sensitivity 66.0%, pooled specificity 92.0%[59]	Rapid	IgM can remain elevated over diagnostic cut-off for 12 months post-infection.[64] IgM may not appear in second or subsequent attacks. Higher specificity means test is more useful for ruling in a diagnosis of scrub typhus than for ruling out.
ELISA for specific IgM using recombinant antigens	≥4-fold rise in titre or seroconversion.* IgM OD reading above a predetermined cut-off in a single specimen	Sensitivity variable (91% seen in a study in northern Thailand), specificity 100% for paired sera, ≥90% for single sera	Simpler, cheaper, and more reproducible than IFA test	Same limitations as for rapid IgM tests
Confirmatory test: IFA or IPA for antibodies	≥4-fold rise in titre, seroconversion*	Specificity 100%	Current gold standard	Expensive, laborious, endpoints can be subjective
Confirmatory test: Weil-Felix test	≥4-fold rise in titre or seroconversion* for heterophile antibodies against *Proteusmirabilis* OX-K strain	Sensitivity variable, specificity high for paired specimens, low for single specimens	Inexpensive, easy to perform, turnaround time1 day	Low sensitivity and specificity
Leptospirosis[65-70]				
RDT for IgM	Specific IgM in serum	Sensitivity 13-22% in 1st week, ~60% in 2nd week, ~80% afterwards; specificity low	Short turnaround time of hours, no special expertise needed	IgM can persist for months. False positive IgM possible in co-infection with HIV, EBV, hepatitis B or A, and *Salmonella* and *Plasmodium* spp
IgM ELISA	Specific IgM in serum	Sensitivity 84% in acute phase and 86% overall, specificity 91% in acute phase and 90% overall	Short turnaround time, specific enough to rule in leptospirosis in presence of compatible clinical picture	IgM can persist for months after infection.

(*Continued*)

Table 2 | (*Cont.*)

Tests	Findings	Test performance	Advantages	Disadvantages
Confirmatory test: Microscopic agglutination test for antibody	≥4-fold rise in titre or seroconversion*	Sensitivity 41% in 1st week, 82% in 2nd-4th week; specificity depends on cut-off titre adopted	Highly sensitive and specific	Expensive, high technical skill needed. Need to include local serotypes in antigen pool to ensure satisfactory sensitivity
Confirmatory test: Nucleic acid amplification	Detection of *Leptospira* DNA in blood, CSF, and urine after amplification	Analytical sensitivity ~10^5 bacilli/mL sample, diagnostic sensitivity no data, specificity >95%	NAA is only test with high sensitivity in 1st week of illness	Expensive, high technical skill needed.
Confirmatory test: Culture	Isolation of *Leptospira* spp from blood, CSF, dialysate in first 10 days, and from urine afterwards	Sensitivity low, specificity 100%	Gold standard. Identifies pathogenic serovars prevalent in the locality	Expensive, very slow

RDT: Rapid diagnostic test; ELISA: Enzyme-linked immunosorbent assay; HRP-2 Histidine-rich protein 2; ICT: Immunochromatographic test; NAA: Nucleic acid amplification; IgG: Immunoglobulin G; IgM: Immunoglobulin M; NS-1: Non-structural antigen 1; IFA: Immunofluorescent assay; IPA Immunoperoxidase assay. WNV: West Nile virus; JE: Japanese encephalitis; YF: Yellow fever.
*Fourfold or higher rise of specific antibody level in the 2nd of two serum specimens collected 10-14 days apart compared to the 1st specimen. Seroconversion is presence of antibody above a fixed level in the second of two serum specimens collected 10-14 days apart when none is detectable in the first specimen.
†Performing Widal test on a single serum specimen has very poor sensitivity and specificity.

syndrome.[33 34 71] Scrub typhus is an important cause of fever in pregnant women in Asia,[72 73] and has been associated with high rates of miscarriage (17%) and poor neonatal outcomes (42%).[74]

Dengue usually resolves within a week. Complications such as shock or bleeding characteristically occur 3-5 days after the onset of fever. Enteric fever typically has a subacute onset with complications such as encephalopathy, intestinal perforation, and bleeding only in the second or third week of illness.

Untreated, case fatality ratios range from 2.49% in enteric fever,[75] 0-39.7% in icteric leptospirosis,[76] and 0-33% in scrub typhus.[77]

How is it managed?

Clinically stable patients

Patients who are clinically stable with no red-flag features can be managed in the community. Treat patients with a confirmed diagnosis of malaria or dengue as per national guidelines or your local formulary.[78 79]

For suspected bacterial AUFIs with characteristic clinical features it is prudent to start early presumptive antibacterial therapy if diagnostic confirmatory testing is awaited or not available. Infections such as rickettsioses and leptospirosis are rapidly progressive, and delay in treatment can increase severity and mortality.[80-82]

Choose an appropriate antibiotic based on local disease and resistance patterns. In regions which are co-endemic for rickettsial infections and leptospirosis, especially in South-East Asia, doxycycline is an appropriate choice.[83] Oral azithromycin is effective for uncomplicated enteric fever, scrub typhus, leptospirosis, and relapsing fever, and is another possible choice in regions co-endemic for these infections.[84] Oral doxycycline is not advised in pregnancy, and azithromycin is an alternative.[85]

Severely ill patients

These patients must be immediately referred to a hospital and managed as inpatients. Empirical therapy with a combination of parenteral third generation cephalosporin (ceftriaxone) along with doxycycline or azithromycin is appropriate while diagnostic confirmation is awaited.[86 87] Ceftriaxone provides coverage for enteric fever, and leptospirosis; while doxycycline provides coverage for rickettsial infections. This combination is also appropriate for AUFIs complicated by pneumonia or acute respiratory distress syndrome, encephalopathy, and liver involvement[87] and does not require dose modification in renal failure[79 88] and multi-organ failure. Finally, this combination may also be administered to patients suspected of, or diagnosed with, severe malaria, in addition to intravenous artesunate. Doxycycline would serve as a companion antimalarial drug to artesunate, and ceftriaxone and would address concomitant bacterial sepsis frequently seen in such patients.[89]

It is important to be aware of local resistance patterns. For example, extensively resistant typhoid fever has been documented in Pakistan since 2016, requiring the use of carbapenems or azithromycin.[84] Additionally, local disease patterns guide choice of treatment. For example, in patients with AUFI followed by a severe pneumonia, if there is an influenza epidemic, it would be prudent to add oseltamivir pending confirmation of influenza by antigen test or RT-PCR, if available.[90] In regions where melioidosis is common ceftazidime or meropenem may be an appropriate initial choice.

Further management

The response of fever to antibiotics can vary: rickettsial infections usually respond within 48 hours, while it may take up to a week in enteric fever, and longer in conditions such as melioidosis. The results of blood culture or serological tests may confirm the diagnosis and guide further therapy. Even if the fever responds to empirical therapy, a repeat specimen may be tested at follow-up a few weeks later to demonstrate IgM seroconversion or a fourfold rise in titre (see table 2) to confirm the probable diagnosis.

Review the diagnosis if fever persists after appropriate antibiotic therapy for other infectious causes of persistent fever.[91] Clinical features of other causes of acute undifferentiated fever are mentioned in appendix 3.

We thank Dr Anand Zachariah for his comments on the manuscript, Dr Prashant Upadhyaya for designing the infographics, and Dr Madhavi Bhargava, Dr Vineeth Nair, and Dr Sajjad Munaf for their help on preparing the manuscript for submission.

Contributors: AB formulated the approach and wrote the initial draft. All authors searched the literature, framed the content of the manuscript, made critical revisions, and approved the final version. RR and BC contributed equally.

Competing interests: We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

Funding: None.

Patient consent: Obtained.

EDUCATION INTO PRACTICE

From your practice records, identify the five most common causes of acute undifferentiated fever you have seen in your practice in the past six months?

How would you investigate a person presenting with acute undifferentiated fever?

What signs would prompt you to refer a patient with fever for hospitalisation?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

No patients were involved in the creation of this article.

1 Phuong HL, de Vries PJ, Nga TT, et al. Dengue as a cause of acute undifferentiated fever in Vietnam. *BMC Infect Dis* 2006;6:123. doi:10.1186/1471-2334-6-123
2 Prasad N, Murdoch DR, Reyburn H, Crump JA. Etiology of Severe Febrile Illness in Low- and Middle-Income Countries: A Systematic Review. *PLoS One* 2015;10:e0127962. doi:10.1371/journal.pone.0127962
3 Naing C, Kassim AI. Scaling-up attention to nonmalaria acute undifferentiated fever. *Trans R Soc Trop Med Hyg* 2012;106:331-2. doi:10.1016/j.trstmh.2012.03.003
4 D'Acremont V, Lengeler C, Genton B. Reduction in the proportion of fevers associated with Plasmodium falciparum parasitaemia in Africa: a systematic review. *Malar J* 2010;9:240. doi:10.1186/1475-2875-9-240
5 World Health Organization. WHO informal consultation on fever management in peripheral health care settings: a global review of evidence and practice. 2013. www.who.int/malaria/publications/atoz/9789241506489/en/.
6 Crump JA, Morrissey AB, Nicholson WL, et al. Etiology of severe non-malaria febrile illness in Northern Tanzania: a prospective cohort study. *PLoS Negl Trop Dis* 2013;7:e2324. doi:10.1371/journal.pntd.0002324
7 Hopkins H, Bruxvoort KJ, Cairns ME, et al. Impact of introduction of rapid diagnostic tests for malaria on antibiotic prescribing: analysis of observational and randomised studies in public and private healthcare settings. *BMJ* 2017;356:j1054. doi:10.1136/bmj.j1054
8 Limmathurotsakul D, Wongratanacheewin S, Teerawattanasook N, et al. Increasing incidence of human melioidosis in Northeast Thailand. *Am J Trop Med Hyg* 2010;82:1113-7. doi:10.4269/ajtmh.2010.10-0038
9 Chrispal A, Boorugu H, Gopinath KG, et al. Acute undifferentiated febrile illness in adult hospitalized patients: the disease spectrum and diagnostic predictors - an experience from a tertiary care hospital in South India. *Trop Doct* 2010;40:230-4. doi:10.1258/td.2010.100132
10 Suttinont C, Losuwanaluk K, Niwatayakul K, et al. Causes of acute, undifferentiated, febrile illness in rural Thailand: results of a prospective observational study. *Ann Trop Med Parasitol* 2006;100:363-70. doi:10.1179/136485906X112158
11 Manock SR, Jacobsen KH, de Bravo NB. Etiology of acute undifferentiated febrile illness in the Amazon basin of Ecuador. *Am J Trop Med Hyg* 2009;81:146-51. doi:10.4269/ajtmh.2009.81.146
12 Susilawati TN, McBride WJ. Acute undifferentiated fever in Asia: a review of the literature. *Southeast Asian J Trop Med Public Health* 2014;45:719-26.
13 Mørch K, Manoharan A, Chandy S, et al. Acute undifferentiated fever in India: a multicentre study of aetiology and diagnostic accuracy. *BMC Infect Dis* 2017;17:665. doi:10.1186/s12879-017-2764-3
14 Mogasale V, Maskery B, Ochiai RL. Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment. *Lancet Glob Health* 2014;2:e570-80. doi:10.1016/S2214-109X(14)70301-8
15 Costa F, Hagan JE, Calcagno J, et al. Global Morbidity and Mortality of Leptospirosis: A Systematic Review. *PLoS Negl Trop Dis* 2015;9:e0003898. doi:10.1371/journal.pntd.0003898
16 Xu G, Walker DH, Jupiter D, Melby PC, Arcari CM. A review of the global epidemiology of scrub typhus. *PLoS Negl Trop Dis* 2017;11:e0006062. doi:10.1371/journal.pntd.0006062
17 Smego RAJr, Sarwari AR, Siddiqui AR. Crimean-Congo hemorrhagic fever: prevention and control limitations in a resource-poor country. *Clin Infect Dis* 2004;38:1731-5. doi:10.1086/421093
18 Jamil B, Hasan RS, Sarwari AR, Burton J, Hewson R, Clegg C. Crimean-Congo hemorrhagic fever: experience at a tertiary care hospital in Karachi, Pakistan. *Trans R Soc Trop Med Hyg* 2005;99:577-84. doi:10.1016/j.trstmh.2005.03.002
19 Yadav PD, Gurav YK, Mistry M, et al. Emergence of Crimean-Congo hemorrhagic fever in Amreli District of Gujarat State, India, June to July 2013. *Int J Infect Dis* 2014;18:97-100. doi:10.1016/j.ijid.2013.09.019
20 Yadav PD, Patil DY, Shete AM, et al. Nosocomial infection of CCHF among health care workers in Rajasthan, India. *BMC Infect Dis* 2016;16:624. doi:10.1186/s12879-016-1971-7
21 Leder K, Torresi J, Libman MD, et al, GeoSentinel Surveillance Network. GeoSentinel surveillance of illness in returned travelers, 2007-2011. *Ann Intern Med* 2013;158:456-68. doi:10.7326/0003-4819-158-6-201303190-00005
22 Wei Y, Luo L, Jing Q, et al. A city park as a potential epidemic site of scrub typhus: a case-control study of an outbreak in Guangzhou, China. *Parasit Vectors* 2014;7:513.
23 McBride AJ, Athanazio DA, Reis MG, Ko AI. Leptospirosis. *Curr Opin Infect Dis* 2005;18:376-86. doi:10.1097/01.qco.0000178824.05715.2c
24 Chakravarti A, Arora R, Luxemburger C. Fifty years of dengue in India. *Trans R Soc Trop Med Hyg* 2012;106:273-82. doi:10.1016/j.trstmh.2011.12.007
25 Limmathurotsakul D, Golding N, Dance DA, Messina JP, Pigott DM, Moyes CL, et al. Predicted global distribution of Burkholderia pseudomallei and burden of melioidosis. *Nature Microbiology* 2016;1:15008. doi:10.1038/nmicrobiol.2015.8.
26 Saad NJ, Lynch VD, Antillón M, Yang C, Crump JA, Pitzer VE. Seasonal dynamics of typhoid and paratyphoid fever. *Sci Rep* 2018;8:6870. doi:10.1038/s41598-018-25234-w
27 Ogoina D. Fever, fever patterns and diseases called 'fever'--a review. *J Infect Public Health* 2011;4:108-24. doi:10.1016/j.jiph.2011.05.002
28 Treanor JJ. Influenza. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases.* 8th ed. Elsevier Saunders, 2015.
29 Crump JA, Gove S, Parry CM. Management of adolescents and adults with febrile illness in resource limited areas. *BMJ* 2011;343:d4847. doi:10.1136/bmj.d4847
30 World Health Organization. *Guidelines for the treatment of malaria.* WHO, 2015.
31 Seymour CW, Liu VX, Iwashyna TJ. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:762-74. doi:10.1001/jama.2016.0288
32 World Health Organization. *Guidelines on Clinical Management of Chikungunya Fever.* 1st ed. WHO-SEARO, 2008.
33 Bhargava A, Kaushik R, Kaushik RM, et al. Scrub typhus in Uttarakhand & adjoining Uttar Pradesh: Seasonality, clinical presentations & predictors of mortality. *Indian J Med Res* 2016;144:901-9. doi:10.4103/ijmr.IJMR_1764_15. doi:10.4103/ijmr.IJMR_1764_15
34 Abhilash KP, Jeevan JA, Mitra S, et al. Acute Undifferentiated Febrile Illness in Patients Presenting to a Tertiary Care Hospital in South India: Clinical Spectrum and Outcome. *J Glob Infect Dis* 2016;8:147-54. doi:10.4103/0974-777X.192966
35 Jung HC, Chon SB, Oh WS, Lee DH, Lee HJ. Etiologies of acute undifferentiated fever and clinical prediction of scrub typhus in a non-tropical endemic area. *Am J Trop Med Hyg* 2015;92:256-61. doi:10.4269/ajtmh.14-0377
36 Watt G. Leptospirosis. In: Magill AJ, Hill DR, Solomon T, Ryan ET, eds. *Hunter's Tropical Medicine and Emerging Infectious Disease.* 9th ed. W.B. Saunders, 2013: 597-601. doi:10.1016/B978-1-4160-4390-4.00074-6 .
37 Pan American Health Organization. *Tool for the diagnosis and care of patients with suspected arboviral diseases.* PAHO, 2017.
38 De Santis O, Kilowoko M, Kyungu E, et al. Predictive value of clinical and laboratory features for the main febrile diseases in children living in Tanzania: A prospective observational study. *PLoS One* 2017;12:e0173314. doi:10.1371/journal.pone.0173314
39 Maskey AP, Day JN, Phung QT, et al. Salmonella enterica serovar Paratyphi A and S. enterica serovar Typhi cause indistinguishable clinical syndromes in Kathmandu, Nepal. *Clin Infect Dis* 2006;42:1247-53. doi:10.1086/503033
40 Crump JA, Sjölund-Karlsson M, Gordon MA, Parry CM. Epidemiology, Clinical Presentation, Laboratory Diagnosis, Antimicrobial Resistance, and Antimicrobial Management of Invasive Salmonella Infections. *Clin Microbiol Rev* 2015;28:901-37. doi:10.1128/CMR.00002-15
41 Low JG, Ong A, Tan LK. The early clinical features of dengue in adults: challenges for early clinical diagnosis. *PLoS Negl Trop Dis* 2011;5:e1191. doi:10.1371/journal.pntd.0001191
42 Herbinger KH, Hanus I, Felbinger TW. Elevated Values of Clinically Relevant Transferases Induced by Imported Infectious Diseases: A Controlled Cross-Sectional Study of 14,559 Diseased German Travelers Returning from the Tropics and Subtropics. *Am J Trop Med Hyg* 2016;95:481-7. doi:10.4269/ajtmh.16-0224
43 Kutsuna S, Hayakawa K, Kato Y, et al. The usefulness of serum C-reactive protein and total bilirubin levels for distinguishing between dengue fever and malaria in returned travelers. *Am J Trop Med Hyg* 2014;90:444-8. doi:10.4269/ajtmh.13-0536
44 Johnson WDJr, Silva IC, Rocha H. Serum creatine phosphokinase in leptospirosis. *JAMA* 1975;233:981-2. doi:10.1001/jama.1975.03260090047022
45 Andrade L, de Francesco Daher E, Seguro AC. Leptospiral nephropathy. *Semin Nephrol* 2008;28:383-94. doi:10.1016/j.semnephrol.2008.04.008
46 Varghese GM, Trowbridge P, Janardhanan J. Clinical profile and improving mortality trend of scrub typhus in South India. *Int J Infect Dis* 2014;23:39-43. doi:10.1016/j.ijid.2014.02.009
47 Nakachi S, Nakamura T, Agha N, et al. Clinical features and early diagnosis of typhoid fever emphasizing usefulness of detecting mesenteric lymphadenopathy with ultrasound as diagnostic method. *Southeast Asian J Trop Med Public Health* 2003;34(Suppl 2):153-7.
48 Abba K, Deeks JJ, Olliaro P. Rapid diagnostic tests for diagnosing uncomplicated P. falciparum malaria in endemic countries. *Cochrane Database Syst Rev* 2011;(7):CD008122.
49 Abba K, Kirkham AJ, Olliaro PL, et al. Rapid diagnostic tests for diagnosing uncomplicated non-falciparum or Plasmodium vivax malaria in endemic countries. *Cochrane Database Syst Rev* 2014;(12):CD011431.
50 Houzé S, Boutron I, Marmorat A. Performance of rapid diagnostic tests for imported malaria in clinical practice: results of a national multicenter study. *PLoS One* 2013;8:e75486. doi:10.1371/journal.pone.0075486
51 World Health Organization. FIND, CDC. *Malaria rapid diagnostic test performance summary. Results of WHO product testing of malaria RDTs: rounds 1-7 (2008-2016).* 2017. https://www.who.int/malaria/publications/atoz/978924151268/en/.
52 Zhang H, Li W, Wang J, et al. NS1-based tests with diagnostic utility for confirming dengue infection: a meta-analysis. *Int J Infect Dis* 2014;26:57-66. doi:10.1016/j.ijid.2014.02.002
53 World Health Organization. *Dengue: guidelines for diagnosis, treatment, prevention and control.* 2009. http://www.who.int/rpc/guidelines/9789241547871/en/.
54 Shan X, Wang X, Yuan Q, et al. Evaluation of the diagnostic accuracy of nonstructural protein 1 Ag-based tests for dengue virus in Asian population: a meta-analysis. *BMC Infect Dis* 2015;15:360. doi:10.1186/s12879-015-1088-4
55 Prince HE, Matud JL. Estimation of dengue virus IgM persistence using regression analysis. *Clin Vaccine Immunol* 2011;18:2183-5. doi:10.1128/CVI.05425-11
56 Storey HL, Huang Y, Crudder C, Golden A, de los Santos T, Hawkins K. A Meta-Analysis of Typhoid Diagnostic Accuracy Studies: A Recommendation to Adopt a Standardized Composite Reference. *PLoS One* 2015;10:e0142364. doi:10.1371/journal.pone.0142364
57 Islam K, Sayeed MA, Hossen E, et al. Comparison of the Performance of the TPTest, Tubex, Typhidot and Widal Immunodiagnostic Assays and Blood Cultures in Detecting

Patients with Typhoid Fever in Bangladesh, Including Using a Bayesian Latent Class Modeling Approach. *PLoS Negl Trop Dis* 2016;10:e0004558. doi:10.1371/journal.pntd.0004558
58 Wijedoru L, Mallett S, Parry CM. Rapid diagnostic tests for typhoid and paratyphoid (enteric) fever. *Cochrane Database Syst Rev* 2017;5:CD008892.
59 Saraswati K, Day NPJ, Mukaka M, Blacksell SD. Scrub typhus point-of-care testing: A systematic review and meta-analysis. *PLoS Negl Trop Dis* 2018;12:e0006330. doi:10.1371/journal.pntd.0006330
60 Paris DH, Dumler JS. State of the art of diagnosis of rickettsial diseases: the use of blood specimens for diagnosis of scrub typhus, spotted fever group rickettsiosis, and murine typhus. *Curr Opin Infect Dis* 2016;29:433-9. doi:10.1097/QCO.0000000000000298
61 Koh GC, Maude RJ, Paris DH, Newton PN, Blacksell SD. Diagnosis of scrub typhus. *Am J Trop Med Hyg* 2010;82:368-70. doi:10.4269/ajtmh.2010.09-0233
62 Watthanaworawit W, Turner P, Turner C, et al. Diagnostic Accuracy Assessment of Immunochromatographic Tests for the Rapid Detection of Antibodies Against Orientia tsutsugamushi Using Paired Acute and Convalescent Specimens. *Am J Trop Med Hyg* 2015;93:1168-71. 10.4269/ajtmh.15-0435
63 Blacksell SD, Paris DH, Chierakul W, et al. Prospective evaluation of commercial antibody-based rapid tests in combination with a loop-mediated isothermal amplification PCR assay for detection of Orientia tsutsugamushi during the acute phase of scrub typhus infection. *Clin Vaccine Immunol* 2012;19:391-5. doi:10.1128/CVI.05478-11
64 Varghese GM, Rajagopal VM, Trowbridge P, Purushothaman D, Martin SJ. Kinetics of IgM and IgG antibodies after scrub typhus infection and the clinical implications. *Int J Infect Dis* 2018;71:53-5. doi:10.1016/j.ijid.2018.03.018
65 World Health Organization. *Human leptospirosis: guidance for diagnosis, surveillance and control.* World Health Organizatioin, 2003.
66 Vijayachari P, Sehgal SC. Recent advances in the laboratory diagnosis of leptospirosis and characterisation of leptospires. *Indian J Med Microbiol* 2006;24:320-2. doi:10.4103/0255-0857.29408
67 Musso D, La Scola B. Laboratory diagnosis of leptospirosis: a challenge. *J Microbiol Immunol Infect* 2013;46:245-52. doi:10.1016/j.jmii.2013.03.001
68 Khaki P. Clinical laboratory diagnosis of human leptospirosis. *Int J Enteric Pathog* 2016;4:1-7. doi:10.17795/ijep31859 .
69 Niloofa R, Fernando N, de Silva NL, et al. Diagnosis of Leptospirosis: Comparison between Microscopic Agglutination Test, IgM-ELISA and IgM Rapid Immunochromatography Test. *PLoS One* 2015;10:e0129236. doi:10.1371/journal.pone.0129236
70 Rosa MI, Reis MFD, Simon C, et al. IgM ELISA for leptospirosis diagnosis: a systematic review and meta-analysis. *Cien Saude Colet* 2017;22:4001-12. doi:10.1590/1413-812320172212.14112016
71 Carvalho CR, Bethlem EP. Pulmonary complications of leptospirosis. *Clin Chest Med* 2002;23:469-78. doi:10.1016/S0272-5231(01)00010-7
72 McGready R, Ashley EA, Wuthiekanun V, et al. Arthropod borne disease: the leading cause of fever in pregnancy on the Thai-Burmese border. *PLoS Negl Trop Dis* 2010;4:e888. doi:10.1371/journal.pntd.0000888
73 Chansamouth V, Thammasack S, Phetsouvanh R, et al. The Aetiologies and Impact of Fever in Pregnant Inpatients in Vientiane, Laos. *PLoS Negl Trop Dis* 2016;10:e0004577. doi:10.1371/journal.pntd.0004577
74 McGready R, Prakash JA, Benjamin SJ, et al. Pregnancy outcome in relation to treatment of murine typhus and scrub typhus infection: a fever cohort and a case series analysis. *PLoS Negl Trop Dis* 2014;8:e3327. doi:10.1371/journal.pntd.0003327
75 Pieters Z, Saad NJ, Antillón M, Pitzer VE, Bilcke J. Case fatality rate of enteric fever in endemic countries: A systematic review and meta-analysis. *Clin Infect Dis* 2018;67:628-38. doi:10.1093/cid/ciy190
76 Taylor AJ, Paris DH, Newton PN. A Systematic Review of the Mortality from Untreated Leptospirosis. *PLoS Negl Trop Dis* 2015;9:e0003866. doi:10.1371/journal.pntd.0003866
77 Bonell A, Lubell Y, Newton PN, Crump JA, Paris DH. Estimating the burden of scrub typhus: A systematic review. *PLoS Negl Trop Dis* 2017;11:e0005838. doi:10.1371/journal.pntd.0005838
78 World Health Organization. *Handbook for clinical management of Dengue.* 1st ed. WHO, 2012.
79 World Health Organization. *Guidelines for the Treatment of Malaria.* 3rd ed. WHO, 2015.
80 Lee N, Ip M, Wong B, et al. Risk factors associated with life-threatening rickettsial infections. *Am J Trop Med Hyg* 2008;78:973-8. doi:10.4269/ajtmh.2008.78.973
81 Tubiana S, Mikulski M, Becam J, et al. Risk factors and predictors of severe leptospirosis in New Caledonia. *PLoS Negl Trop Dis* 2013;7:e1991. doi:10.1371/journal.pntd.0001991
82 Nicholson WL, Paddock CD. Rickettsial (spotted & typhus fevers) & related infections, including anaplasmosis & ehrlichiosis. In: Brunette GW, ed. *CDC Yellow Book 2018: health information for international travel.* Centers for Disease Control and Prevention, 2017: 297-302.
83 Rahi M, Gupte MD, Bhargava A, Varghese GM, Arora R. DHR-ICMR Guidelines for diagnosis & management of Rickettsial diseases in India. *Indian J Med Res* 2015;141:417-22. doi:10.4103/0971-5916.159279
84 Klemm EJ, Shakoor S, Page AJ, et al. Emergence of an Extensively Drug-Resistant *Salmonella enterica* Serovar Typhi Clone Harboring a Promiscuous Plasmid Encoding Resistance to Fluoroquinolones and Third-Generation Cephalosporins. *MBio* 2018;9:e00105-18. doi:10.1128/mBio.00105-18
85 Rajapakse S, Rodrigo C, Fernando SD. Drug treatment of scrub typhus. *Trop Doct* 2011;41:1-4. doi:10.1258/td.2010.100311
86 Thompson CN, Karkey A, Dongol S, et al. Treatment Response in Enteric Fever in an Era of Increasing Antimicrobial Resistance: An Individual Patient Data Analysis of 2092 Participants Enrolled into 4 Randomized, Controlled Trials in Nepal. *Clin Infect Dis* 2017;64:1522-31. doi:10.1093/cid/cix185
87 Singhi S, Chaudhary D, Varghese GMFrom: The Indian Society of Critical Care Medicine Tropical fever Group. Tropical fevers: Management guidelines. *Indian J Crit Care Med* 2014;18:62-9. doi:10.4103/0972-5229.126074
88 Meyers B, Salvatore M. Tetracyclines and chloramphenicol. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases.* 6th ed. Churchill Livingstone, 2005.
89 Mayxay M, Castonguay-Vanier J, Chansamouth V, et al. Causes of non-malarial fever in Laos: a prospective study. *Lancet Glob Health* 2013;1:e46-54. doi:10.1016/S2214-109X(13)70008-1
90 Thwaites GE, Day NP. Approach to Fever in the Returning Traveler. *N Engl J Med* 2017;376:548-60. doi:10.1056/NEJMra1508435
91 Wilson ME, Boggild AK. Fever and systemic symptoms. In: Guerrant RL, Walker DH, Weller PF, eds. *Tropical Infectious Diseases: Principles, Pathogens, and Practice.* 3rd ed. Elsevier Saunders, 2011: 925-37. doi:10.1016/B978-0-7020-3935-5.00130-0

Infographic: Fever identification charts: A quick guide to differentiation and diagnosis in low resource settings
Appendices 1-3: Prevalence of main causes of AUFIs by geographic region; Clinical features of the main causes of AUFIs; Clinical features of other important causes of AUFIs