

## CLINICAL REVIEW

## Management of adolescents and adults with febrile illness in resource limited areas

John A Crump *associate professor of medicine and pathology*<sup>1 2 3 4</sup>, Sandy Gove *team leader*<sup>5</sup>, Christopher M Parry *senior clinical consultant*<sup>6 7</sup>

<sup>1</sup>Division of Infectious Diseases and International Health, Department of Medicine, and Department of Pathology, Duke University, Durham, NC 27710, USA; <sup>2</sup>Duke Global Health Institute, Duke University, Durham, NC, USA; <sup>3</sup>Kilimanjaro Christian Medical Centre, Moshi, Tanzania; <sup>4</sup>Kilimanjaro Christian Medical College, Tumaini University, Moshi, Tanzania; <sup>5</sup>Integrated Management of Adolescent and Adult Illness (IMAI), World Health Organization, Department of HIV/AIDS, Geneva, Switzerland; <sup>6</sup>Wellcome Trust Major Overseas Programme, Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand; <sup>7</sup>Angkor Hospital for Children, Siem Reap, Cambodia

Fever is common among adolescents and adults seeking healthcare in low income countries; in this setting, case fatality rates are often high and the range of potential infectious and non-infectious causes is broad (table 1).<sup>1 2</sup> These differences, combined with limited resources, mean that management guidelines developed for high income countries cannot readily be adapted to resource limited areas. It is often difficult to establish a diagnosis from the clinical history and physical examination alone because a range of diseases share similar clinical features. The diagnostic problem may be compounded by limited laboratory capacity for diagnostic testing.<sup>3</sup> There may be limited or no laboratory services available; laboratory services may be prohibitively expensive for users; concerns may exist regarding the quality of results; and practical reliable diagnostic tests may not have been developed for some infections of local importance. When clinical and laboratory evaluations do not identify a specific cause for fever, healthcare providers may treat empirically according to the “syndrome” of clinical features that the patient presents with, often guided by management guidelines that recommend approaches to treatment based on syndromes. World Health Organization algorithms for the management of infants and children with a range of clinical syndromes have been developed for primary healthcare providers and district hospital clinicians in low income countries.<sup>4 5</sup> Similar guidelines for adolescents and adults were published in 2004 and updated in 2009 for primary healthcare providers at first level health facilities.<sup>6</sup> A WHO manual to guide district hospital clinicians is in development. Ideally, guidelines should be validated, adapted to local conditions, and improved on the basis of the results of locally or nationally available surveillance or sentinel hospital studies.

We review the approach to the management of adolescents and adults with febrile illness—which we define as having a history of fever in the past 48 hours, feeling hot, or having an axillary temperature of 37.5°C or more—in low income areas. Focusing

on infectious causes, we will draw on international guidelines and evidence from systematic reviews and take into account resources currently available to most clinicians.

### How should febrile adults be managed at the first level health facility?

#### Rapid triage and emergency management

The WHO acute care guideline on integrated management of adolescent and adult illness (IMAI) recommends that the patient be rapidly assessed for the presence of emergency signs.<sup>6</sup> Patients with airway obstruction, central cyanosis, severe respiratory distress, or circulatory failure (weak or fast pulse, or slow capillary refill) require urgent management, and referral to a hospital is recommended. Fever from a life threatening cause is defined as fever that is associated with neck stiffness, extreme weakness or inability to stand, lethargy, unconsciousness, convulsions, severe abdominal pain, or respiratory distress. For those with fever from a life threatening cause, the guideline recommends assessment of temperature and blood pressure and quick establishment of intravenous access, so that fluids and antimicrobial agents can be given if the patient is in shock or if sepsis is suspected. For patients with life threatening febrile illness, such as severe sepsis as a result of bacteraemia and meningitis, the guidelines recommend administering parenteral antibacterials, antimalarials, and glucose; patients should then be urgently referred to hospital.<sup>6</sup> Selection of the parenteral antibacterial agent should ideally be based on knowledge of patterns of antimicrobial susceptibility among relevant organisms in the area. However, because of widespread resistance to traditional first line antimicrobials, such as penicillins, and invasive *Salmonella* making aminoglycoside monotherapy a poor choice in many areas, extended spectrum cephalosporins such as ceftriaxone are commonly used (boxes 1 and 2).

**Summary points**

Overlap in the clinical features of febrile illnesses and limited laboratory services make the management of febrile patients in resource limited settings challenging

WHO guidelines for managing febrile adolescents and adults in resource limited settings are available for first level health facilities and are forthcoming for district hospitals

First level health facility guidelines recommend antimalarials for those with a positive malaria diagnostic test, antibacterials for those with signs of severe illness or specific bacterial infections, and hospital referral of those with severe illness or no apparent diagnosis

Management guidelines should be validated, locally adapted, and improved on the basis of local or national surveillance data and sentinel hospital studies

Malaria, tuberculosis, and HIV diagnostic tests can enhance management by ruling out a specific illness or by directing towards a particular diagnosis

Clinical trials of empirical treatment strategies and advocacy for better clinical laboratory services could help improve management guidelines and patient outcomes

**Sources and selection criteria**

We searched for papers that were published between 1990 and January 2011 using the following MeSH terms: "(developing countries and guideline) and (fever, bacter(a)emia, HIV, hospital laboratories, malaria, tuberculosis)" in the National Library of Medicine's computerised search service PubMed. We sought Cochrane database systematic reviews. We reviewed relevant articles and sought online resources.

**Box 1 Practical examples of the use of the integrated management of adolescent and adult illness algorithm in febrile patients***Severe illness**At first level health facility*

Clinical features: Triage assessment shows patient weak and unable to stand; weak fast pulse, and capillary refill >3 seconds. Oral temperature 39.5°C, pulse 126 beats/min, and blood pressure 85/40 mm Hg. Conscious; no neck stiffness, abdominal pain, or signs of respiratory distress

Epidemiological context: Area of low malaria transmission intensity

Rapid diagnostic tests: Negative for malaria and HIV

Syndromic diagnosis: Very severe febrile disease or suspected sepsis with shock

Management: Pre-referral intramuscular antimicrobial (extended spectrum cephalosporin, or ampicillin plus gentamicin) and glucose given; urgent referral to district hospital

*At district hospital level*

Clinical features: Triage assessment by the nurse confirmed the patient is in shock with systolic blood pressure of 85 mm Hg

Management: Initially in emergency section for septic shock: intravenous fluids; extended spectrum cephalosporin, or ampicillin plus gentamicin; supplemental oxygen titrated to oxygen saturation of 90% by pulse oximetry

Laboratory investigations: Peripheral blood smear preparation and microscopy negative for malaria parasites; haemoglobin concentration 80 g/L; serum glucose concentration normal

Further management: Clinical assessment and investigations to identify the source of infection while continuing resuscitation with close monitoring

*Non-severe illness*

Location: First level health facility

Clinical features: Fever for three days; patient fully ambulatory; pulse normal character and rate, capillary refill <2 seconds. Oral temperature 38.0°C, pulse 90 beats/min, and blood pressure 124/82 mm Hg. Conscious; no neck stiffness, abdominal pain, or signs of respiratory distress

Epidemiological context: Area of high malaria transmission intensity

Rapid diagnostic tests: Positive for malaria; negative for HIV

Syndromic diagnosis: Malaria, non-severe

Management: Oral artemisinin combination treatment; follow-up at three days if still febrile; took blood for culture

Clinical course: Patient remained febrile after seven days; sent sputum for tuberculosis and referred to district hospital

**Assessment, classification, and management of acute illness**

The updated IMAI acute care guidelines, based on current WHO malaria guidelines,<sup>7</sup> recommend that once emergency conditions are identified and managed, assessment of the acute illness

**Box 2 Recommendations for first level health providers**

- Perform a rapid assessment for the presence of emergency signs and manage emergency conditions
- Identify patients with fever from a life threatening cause: fever with stiff neck, extreme weakness or inability to stand, lethargy, unconsciousness, convulsions, severe abdominal pain, or respiratory distress
- Use intravenous fluids for patients with shock and start appropriate parenteral antibacterials, antimalarials, and the administration of glucose; refer urgently to hospital
- Routinely offer HIV testing
- Assess the severity of the acute illness; treat and refer patients who have severe illness or no apparent diagnosis to hospital

should focus on classifying the patient's health problem on the basis of the presenting symptoms. For patients who give a history of fever in the past 48 hours, feel hot, or have an axillary temperature of 37.5°C or more, the history and physical examination focus on trying to identify a source for the fever and on stratifying their malaria risk. Risk of malaria is based on age, malaria transmission in the area of residence, travel history, pregnancy, and HIV infection status. A malaria rapid diagnostic test or malaria smear is indicated if the patient is considered to be at high risk of malaria, or if no obvious source of the fever can be found in a patient at low risk of malaria. Further management depends on the presence or absence of specific signs of illness. Among those without severe disease, especially if the malaria test is negative, other causes of fever should be considered using the full IMAI acute care algorithm.<sup>6</sup> Other causes include upper respiratory tract infections such as sinusitis, pneumonia, gastroenteritis, urinary tract infection, pelvic inflammatory disease, tuberculosis, HIV related illness, antiretroviral drug reactions, and severe soft tissue or muscle infection. Very severe illness in patients not at risk for malaria is managed with parenteral antibacterials and glucose. Artesunate, artemether, or quinine is suggested for treatment of severe malaria. However, when illness persists for at least seven days, it is recommended that the apparent cause be treated, that tuberculosis and other HIV related conditions be considered, and that patients with no apparent cause be referred for assessment at the district hospital. Simple fevers in patients with no malaria risk are managed by treating the apparent cause and evaluating after one week (box 1).

**Quality of evidence**

The IMAI acute care algorithms incorporate elements of other WHO guidelines such as those for lung health, HIV counselling and testing, tuberculosis, sexually transmitted infections, and malaria, and they have been developed from expert group meetings and review of the published literature. The algorithms have been refined by validation studies in low income countries through the country's own experience with adaptation and use.<sup>6</sup> Although interventions for specific infections such as malaria have been evaluated in randomised, controlled trials, trial data are not available from low income countries for some syndrome based interventions, such as those for very severe illness.

**What are the challenges for clinicians at the district hospital level?**

WHO is developing resources to guide the management of adolescent and adult illness at the district hospital level, including the assessment, classification, and management of febrile illness.<sup>8</sup> This manual, which will be available soon, will be analogous to the currently available pocket book of hospital care for children.<sup>5</sup> As at the first referral level, clear processes

for rapid triage and emergency management of patients must be in place at the district hospital.

**Inadequate facilities for diagnosis**

The IMAI guidance for first level health facilities anticipates that the hospital to which the severely ill febrile adult or adolescent is referred will have enhanced facilities for diagnosis and management, but this is not always the case. Table 2 lists tests that are valuable for managing febrile patients and that should be made available at the district hospital level, according to expert consensus and the IMAI second level learning programme.<sup>9</sup> If these capacities are not already in place, it is recommended that they be prioritised for development. However, district clinicians need to be prepared to form a differential diagnosis of fever based on a wider range of main symptoms; to recognise diseases presenting with symptoms in multiple organ systems such as endocarditis, dengue, typhoid, and paratyphoid fever; and to have an approach to the diagnostic challenge presented by fever with no obvious clinical cause that uses both clinical assessment and limited laboratory tests.<sup>10</sup> Table 1 lists the differential diagnoses for fever without an obvious cause according to whether the fever lasts for less than seven days or seven days or more.

**Few point of care tests**

At present, no rapid point of care tests exist for the detection of most of the micro-organisms that cause bloodstream infections. Reliable, inexpensive, simple, and rapid point of care tests are useful in situations where it is not feasible to establish a conventional clinical laboratory. Despite considerable attention and resources having been directed towards developing such tests in recent years, only a few have become widely used in routine practice. Rapid tests that are in widespread use include those for HIV, malaria, and syphilis. Others have been hampered by inadequate test performance characteristics (for example, typhoid rapid antibody tests<sup>11</sup>) or prohibitive cost (for example, tests detecting urine pneumococcal antigen<sup>12</sup>). Use of rapid diagnostic tests with poor performance characteristics has the potential to harm patients by directing clinicians towards incorrect diagnoses. A rapid tuberculosis nucleic acid amplification test suitable for use at the district hospital level has recently been endorsed by WHO, but is not yet in widespread use.<sup>13</sup> Because of the wide range of potential causes of fever, integration of tests on single platforms is an important goal.

**Barriers to changing clinicians' behaviour**

In settings where empirical management supported by few diagnostic tests is the established norm, it can be difficult to change the behaviour of clinicians so that they respond to additional diagnostic information. Clinicians may fail to use available laboratory services because they think that results are

unreliable. When a new diagnostic test is introduced, the results may not necessarily change the way that patients are managed and the degree of adherence to management guidelines may be limited. The introduction of malaria rapid diagnostic tests in some settings, for example, may not reduce the overtreatment of malaria.<sup>14</sup>

## Why is ruling out malaria important?

In some areas most patients treated empirically for malaria do not have malaria when rigorously assessed.<sup>15</sup> Consequently, WHO recommends that the diagnosis of malaria be confirmed by a malaria diagnostic test.<sup>7</sup> In areas with any malaria risk, the ability to rule out malaria by malaria film or by use of a malaria rapid diagnostic test can prevent unnecessary use of antimalarial drugs and direct clinical thinking towards alternative diagnoses (such as bacterial infection) and treatment options. Furthermore, in areas of high malaria transmission intensity, a positive malaria film may be an incidental finding, and other causes for the current febrile illness, such as bacteraemia, may be present. Clinicians need to be reminded that the overdiagnosis of malaria may lead to poor outcomes for febrile patients with non-malaria infections who are subsequently treated inappropriately with antimalarial drugs.<sup>15</sup>

## Is it strictly necessary to diagnose HIV infection?

WHO/Joint United Nations Programme on HIV/AIDS guidance recommends that providers initiate HIV diagnostic testing for all patients, including those with fever. The results of HIV counselling and testing in turn provides a risk assessment for HIV coinfections.<sup>16</sup> A recent observational study of febrile inpatients in Tanzania showed that the population with fever had a much higher prevalence of HIV infection than the general population from which it was drawn, because people infected with HIV have increased risk for a range of febrile illnesses.<sup>17</sup> Furthermore, acute HIV infection may be a cause of febrile illness in its own right but is not reliably detected by antibody testing.<sup>18</sup> The diagnosis of HIV in a febrile inpatient greatly raises the probability of particular coinfections, such as cryptococcal disease; tuberculosis (including disseminated forms of the disease that may not localise to the lung<sup>19</sup>); invasive non-typhoidal *Salmonella* infection; pneumococcal disease<sup>20</sup>; and, in southeast Asia, penicilliosis.<sup>21 22</sup> Furthermore, clinical staging or staging based on immunological status using the CD4 positive T cell count supports risk stratification for specific HIV coinfections.<sup>23</sup>

## Why is it important to know the local causes of fever?

### Limitations of empirical treatment

A diverse range of invasive bacterial and fungal infections may occur in developing countries, often with high case fatality rates. These may not respond to standard empirical antimicrobials.<sup>20</sup> The range of potential causative agents of fever are too numerous to cover comprehensively in this review, but table 1 lists some of the main ones. Aggregate data on invasive infections and anticipated patterns of antimicrobial resistance can provide useful local epidemiological data to inform and validate empirical management recommendations.

Multidrug resistant bacterial infections—such as typhoid, extended spectrum  $\beta$  lactamase producing Gram negative infections, and infections with meticillin resistant

*Staphylococcus aureus*—and difficult to treat infections, such as melioidosis caused by *Burkholderia pseudomallei*, may be common in some areas.<sup>24-26</sup> Leptospirosis, Q fever, and rickettsial infections may be common but under-appreciated in many resource limited settings.<sup>27-29</sup> Arthropod borne infections, including arboviruses, other viral diseases, parasitic infections, such as leishmaniasis and trypanosomiasis, and other conditions of local importance should be considered on the basis of clinical features, risk factors, and local epidemiological data.

### Limited diagnostic testing

Diagnostic tests such as blood culture or other techniques for identifying invasive infections (such as cryptococcal antigen testing, urine antigen testing for pneumococcal disease), along with the results of antimicrobial susceptibility testing, if available, will help in the subsequent rationalisation or discontinuation of initial antimicrobial treatment. However, reliable diagnostic tests for many infections are often not available at the hospital level or even at the national reference laboratory in resource limited settings. Although *Leptospira* spp are susceptible to antimicrobial agents usually used in the empirical management of febrile adolescents and adults, *Coxiella burnetii* and *Rickettsia* spp are not. Thus, a tetracycline should be considered for patients in whom Q fever or rickettsial infection is highly likely, and in those patients who do not respond to initial empirical treatment.

## How can local epidemiological data be acquired?

Systematic surveillance or sentinel site studies of the causes of febrile illness may identify a mismatch between treatment strategies and local causative agents associated with poor patient outcomes.<sup>17</sup>

### Local and national surveillance

If a local clinical laboratory is used systematically by clinicians and can provide quality controlled diagnostic tests for patients with febrile illness, data on invasive infections and patterns of antimicrobial resistance can be aggregated to provide useful local epidemiological information and to validate and guide recommendations for empirical management. When available, reliable national surveillance data for specific infections (such as malaria, dengue) can help to establish background rates of endemic infections and to identify disease outbreaks.

### Sentinel hospital studies

In instances where routinely collected data on causes of febrile illness are not available, sentinel hospital studies are a useful means of improving local recommendations on empirical management.<sup>17 20 24 25 27 30</sup> Such studies are typically conducted over a year or more, enrol participants who meet the eligibility criteria for the syndrome of interest, collect data that match symptoms and signs in management guidelines, and provide an expanded range of diagnostic tests for the period of the study. The findings are used to validate and improve local management recommendations.

### Future directions

The development and implementation of hospital level guidelines for the management of adolescents and adults, complementing those already available for children, will provide an important framework for improving the management of

febrile illness in low income countries. Validation, local adaptation, and improvement of these guidelines using studies incorporating both patient outcomes and laboratory end points will be needed. The evidence base for interventions could be strengthened by clinical trials that evaluate empirical treatment strategies for severely ill patients. Support and advocacy for excellent clinical laboratory services in resource poor settings is warranted. High quality laboratory data can inform the selection and rational use of antimicrobial treatment and provide local data on the epidemiology of infectious causes of febrile illness. This effort should be supplemented by evaluation and implementation of reliable, inexpensive, simple, and rapid point of case tests that influence patient management decisions and improve patient outcomes.

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**Questions for future research**

- How can choice, dose, and duration of empirical treatment be improved so that it better matches local causative agents and avoids overuse of antimicrobials?
- Can our understanding of local causes of febrile illness be improved by expanding the use of sentinel hospital studies or enhanced national surveillance?
- Do randomised controlled trials have a role in identifying the best empirical management strategies for febrile illness in resource poor settings?
- How can diagnostic services be improved in clinical laboratories and at the point of care in low income countries?
- Can rapid, practical and reliable point of care diagnostic tests be designed for common causes of fever other than malaria, tuberculosis, and HIV?
- What determines the behaviour of clinicians managing febrile patients?

**Additional educational resources**

*Resources for healthcare professionals*

- Malaria Atlas Project ([www.map.ox.ac.uk/](http://www.map.ox.ac.uk/))—Uses a spatial database of linked information based on medical intelligence and satellite derived climate data to constrain and map the limits of malaria transmission and to provide an archive of community based estimates of prevalence of the malaria parasite
- WHO. Guidelines for the treatment of malaria. 2nd ed. 2010. [www.who.int/malaria/publications/atoz/9789241547925/en/index.html](http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html)
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*Resources for patients and the community*

- WHO ([www.who.int/hiv/topics/capacity/en/index.html](http://www.who.int/hiv/topics/capacity/en/index.html))—Integrated management of adolescent and adult illness (IMAI) resources for patients
- WHO patient self management booklet ([www.who.int/hiv/pub/imai/patient\\_self/en/index.html](http://www.who.int/hiv/pub/imai/patient_self/en/index.html))—Designed to be used by patients, treatment supporters, and caregivers in resource poor settings; focused on HIV/AIDS
- WHO caregiver booklet ([www.who.int/hiv/pub/imai/patient\\_caregiver/en/index.html](http://www.who.int/hiv/pub/imai/patient_caregiver/en/index.html))—Designed to be used by health workers to educate family members and other caregivers and then be used by patients as a reference in the home based care of serious long term illness

**A patient’s story from east Africa**

On the first day of illness, I awoke with headache, fever, chills, nausea, vomiting, somnolence, and fatigue. These symptoms worsened over the course of the day. A malaria smear was performed at a private hospital; it was negative. I was very unwell so I was brought to a large referral hospital. Two more malaria slides were performed; both were negative. Nevertheless, I was started on a quinine drip for treatment of malaria. I was also given an intravenous injection of ceftriaxone. No blood was drawn for culture. The next morning I felt much better. I was discharged and told to continue with a five day course of oral antimalarials. I received ceftriaxone injections for two days. Three days after discharge and one day after stopping ceftriaxone my initial symptoms recurred. Although I was still taking artemisinin combination treatment for presumed malaria, when my symptoms relapsed the doctor insisted on starting a quinine drip. A colleague recommended that ceftriaxone be restarted. The next morning, my symptoms had again resolved and I was discharged. The doctor advised me to continue oral antimalarials and ceftriaxone injections for five days. I took only ceftriaxone and experienced no recurrence. The cause of my fever was never identified.

**Tables**

**Table 1 | Differential diagnosis for fever without obvious cause at the district hospital level**

Syndrome	Differential diagnosis
Fever <7 days without clinically obvious focus or site	Malaria
	Bacteraemic sepsis
	Meningococcal disease

Table 1 (continued)

Syndrome	Differential diagnosis
	Typhoid and paratyphoid fever
	Rickettsial disease
	Dengue fever
	Chikungunya
	Influenza
	Yellow fever
	Primary HIV infection
	Acute strongyloidiasis
	Relapsing fever (tick or louse borne borreliosis)
	Acute schistosomiasis
	Immune reconstitution inflammatory syndrome
	Drug induced fever
	Rheumatic fever
	Mononucleosis caused by Epstein-Barr virus or cytomegalovirus
	Toxoplasmosis
	Q fever
	Leptospirosis
Fever ≥7 days without clinically obvious focus or site	Tuberculosis
	Typhoid and paratyphoid fever
	Malaria
	Osteomyelitis
	Infective endocarditis
	Liver abscess
	Brucellosis
	Yellow fever
	Plague
	Cryptococcosis
	Non-tuberculous mycobacterial infection
	Lymphoma
	Deep fungal infections, such as histoplasmosis, penicilliosis, coccidiomycosis, paracoccidiomycosis
	Cytomegalovirus
	Toxoplasmosis
	Human African trypanosomiasis (sleeping sickness)
	American trypanosomiasis (Chagas disease)
	Visceral leishmaniasis (kala azar)

Table 2| Laboratory tests at the district hospital\*

Category	Test type
General	Full blood count and differential
	Blood collection and crossmatching for transfusion
HIV	Rapid HIV antibody tests: first, second, and third tests
	CD4 absolute count and percentage: on site or sent out
	Early infant diagnosis preparation of dried blood spot: sent out for virological testing
Tuberculosis	Acid fast stain and microscopy
Malaria (endemic areas)	Peripheral blood smear preparation and microscopy
	Rapid test to detect and discriminate between <i>Plasmodium falciparum</i> and mixed <i>Plasmodium</i> species
Other laboratory evaluations	Rapid syphilis test
	Syphilis: rapid plasma reagin
	Urine dipstick for sugar, protein, leucocytes, ketones
	Gram stain
	Microscopy and chemistry for cerebrospinal fluid, urine, thoracentesis, and paracentesis
	Saline wet mount and potassium hydroxide for bacterial vaginosis and <i>Trichomonas vaginalis</i>
	Blood and sputum cultures: sent out
	Cryptococcal antigen or India ink stain (or both)
	Lactic acid
	Stool microscopy for ova and parasites: on site or sent out
	Rapid hepatitis B test
	Hepatitis B enzyme linked immunosorbent assay
	Other investigations
Oxygen saturation by pulse oximetry	
Radiography: chest, plain film abdomen, cervical spine, bone	
Ultrasound examination	
Additional investigations that may be available at regional or central laboratories as send-out tests	Serum and cerebrospinal fluid total protein
	Liver enzymes
	Mycobacterial culture and susceptibility testing
	Nucleic acid amplification tests for <i>Mycobacterium tuberculosis</i>
	Cryptococcal antigen testing of serum and cerebrospinal fluid
	Measurement of HIV-1 RNA
	Fungal stains
	Blood culture
	Urine culture
	Stool culture
	<i>Toxoplasma</i> serology
	Cytology: for example, cerebrospinal fluid, cervical
	Silver stain or direct fluorescent antibody test for <i>Pneumocystis jirovecii</i>
	Fungal cultures, including of blood
	Nucleic acid amplification tests for respiratory viruses including influenza
	Histopathology: for example, cervical, lymph node, skin biopsy
	Serological tests, nucleic acid amplification tests, other investigations or special cultures may be available at a central laboratory to diagnose brucellosis, dengue, fascioliasis, leishmaniasis, cysticercosis, strongyloidiasis, trypanosomiasis, and other infections

\*Prioritisation and availability of tests will vary according to geographical location and epidemiology.