

**Appendix 1. Prevalence of main aetiologies of acute undifferentiated febrile illnesses in geographic regions with low resource settings<sup>1-4</sup>**

	Protozoal*	Bacterial	Rickettsial	Spirochetal	Viruses		Helminthic
					Arboviruses	Other viruses	
<b>ASIA</b>							
South and South-East Asia	Malaria: PF, PV, & <i>P. knowlesi</i>	Enteric fever, Brucellosis, Melioidosis	Scrub typhus, Murine Typhus	Leptospirosis	Dengue, Chikungunya, Zika	Crimean-Congo Hemorrhagic Fever (CCHF), Kyasanur Forest Disease	Filariasis#, Acute schistosomiasis (SE Asia)
East Asia	Malaria (parts of China)	Enteric fever, Brucellosis, Melioidosis	Scrub typhus, Murine Typhus	---	Dengue	Hantavirus -Hemorrhagic fever with renal syndrome (HFRS),	Filariasis, Acute schistosomiasis
Australia, New Zealand	-	Melioidosis	Australian tick typhus, Q fever	Leptospirosis	Ross River virus, Chikungunya		
Oceania	Malaria in some countries	Melioidosis	-	Leptospirosis	Ross River virus, Dengue, Zika,		Filariasis
<b>AFRICA</b>							
North	Limited risk of malaria	Enteric Fever, Brucellosis, Q fever	Murine typhus, Mediterranean spotted fever	? Leptospirosis	No yellow fever risk, Limited risk of other arboviral		Filariasis, Acute Schistosomiasis
West	Malaria: PF>PV, Acute African Trypanosomiasis	Enteric Fever, Brucellosis, Epidemic meningococcal disease	Murine typhus	Leptospirosis, ATBF	Yellow fever, Dengue, Zika, Chikungunya	Other Viral Hemorrhagic fevers (Ebola, Lassa, CCHF)	Filariasis, Acute Schistosomiasis
East	Malaria: PF >PV, East African trypanosomiasis	Enteric fever, Epidemic meningococcal disease, Brucellosis	Murine typhus, ATBF	Leptospirosis, Tick/louse-borne	Yellow fever, Dengue, Chikungunya	Other Hemorrhagic fevers (Rift valley fever, CCHF)	Filariasis, Acute Schistosomiasis
Central	Malaria: PF > PV, West African trypanosomiasis	Enteric fever, Epidemic meningococcal disease, Brucellosis	Murine typhus, ATBF, Epidemic Typhus	Leptospirosis, Tick-borne relapsing fever	Yellow fever, Dengue, Chikungunya, Zika	Other Viral hemorrhagic fever (Ebola, Marburg, CCHF)	Filariasis, Acute Schistosomiasis, Trichinosis
South	Malaria: PF > PV	Enteric fever, Brucellosis	Murine typhus, ATBF	Leptospirosis	Dengue, Chikungunya		Filariasis, Acute Schistosomiasis, Trichinosis
<b>AMERICAS</b>							
Latin America and Caribbean	Malaria risk (Limited): PV > PF, Acute American trypanosomiasis (T. cruzi)	Enteric Fever, Oroya fever (Bartonellosis), Brucellosis	Rocky Mountain Spotted Fever, Murine typhus, Scrub typhus, African tick bite fever	Leptospirosis, Tick-borne relapsing fever	Dengue, Chikungunya, Zika	HFRS, Hantavirus pulmonary syndrome (HPS), Other viral hemorrhagic fevers: Junin, Machupo, Sabia, Guanarito	Filariasis, Acute Schistosomiasis, Trichinosis

\*Other protozoal causes of acute fever include **Hepatic amebiasis**: This has wide distribution with high incidence in Asia (esp. India and Vietnam), tropical regions of Africa, Mexico, Venezuela and Colombia. # Acute filariasis usually has fever with localising features like tender adenopathy, lymphangitis or funiculitis, orchitis and epididymitis. Abbreviations: PF: *Plasmodium falciparum*; PV: *Plasmodium vivax*; *P. knowlesi*: *Plasmodium knowlesi*; ATBF: African Tick-Bite Fever;

**Appendix 2. Clinical features of the common and important causes of acute undifferentiated febrile illnesses<sup>5</sup>**

Disease		Rash	Eschar	Jaundice	Conjunctival Suffusion	Lymphadenopathy	Muscle tenderness	Spleen	Dyspnoea	Encephalopathy	Acute Renal Failure	Shock	Bleeding	White blood cell count	Thrombocytopenia (< 150,000)	Rule-in features (good predictors)	Rule-out features (good excluders)
Malaria	Uncomplicated	0	0	+	0	0	0	+++	0	0	0	0	0	N	+++ <sup>b</sup>	Fever >40 degrees. <sup>54</sup> Splenomegaly, thrombocytopenia and hyperbilirubinemia <sup>55 56</sup>	Rash and Lymphadenopathy suggest alternative diagnosis. <sup>51</sup>
	Severe	0	0	+++	0	0	0	+++	+ <sup>a</sup>	++	+++ <sup>a</sup>	++	(+)	H	+++ <sup>b</sup>		
Dengue	Uncomplicated	+++	0	0	++	++	+	+	0	0	0	0	+	N/L	+++	Leukopenia and thrombocytopenia. <sup>57</sup> Positive tourniquet test is a good predictor of infection (OR: 4.86) and ascites is a good predictor of severe dengue (OR:13.91). <sup>58</sup>	Fever >12 days, combination of normal tourniquet test & normal leucocyte count. <sup>59</sup>
	Severe	+++		(+)	++	++	++	+	(+)	+	+	++	+++	L	+++ <sup>c</sup>		
Enteric fever (similar features in typhoid & paratyphoid fever) <sup>52</sup>	uncomplicated	(+)	0	0	0	(+)	0	+/ <sup>+</sup> <sup>d</sup>	+	0	(+)	0	0	N/L	0	Fever in endemic areas > 3 days duration & presence of abdominal tenderness (51)	Generalised rash or lymphadenopathy
	complicated	(+)	0	++	0	(+)	0	+++ <sup>d</sup>	+	++	(+)	+	+++ <sup>e</sup>	H	+		
Leptospirosis	Mild (anicteric)	+	0	0	+++	++	++	(+)	++	0	0	0	0	N	+++	Combination of suffusion, icterus and conjunctival hemorrhage is characteristic of Leptospirosis. <sup>49</sup> A THAI-LEPTO score of > 5 useful for suspecting diagnosis, especially severe Leptospirosis. <sup>60</sup>	No reliable information available
	Severe (icteric)	+	0	+++	+++	++	+++	+	++	++	+++	++	++	H	+++ <sup>f</sup>		
Scrub typhus (see appendix 3 for spotted fever, and murine typhus)	Non-severe	++	+++	0	++	++/+++	0	+	0					L/N/	+++ <sup>h</sup>	Eschar is pathognomonic for scrub typhus (OR 46). <sup>61</sup>	No information available
	Severe	++	+++	++	++	++		+/ <sup>+</sup> <sup>+</sup>	+++ <sup>g</sup>	++	++	++	+	H	+++ <sup>i</sup>		

Notes: <sup>a</sup>: ARDS and ARF are commoner in adults than children. <sup>b</sup>: Thrombocytopenia is frequent, but bleeding is uncommon in malaria. <sup>c</sup>: bleeding can occur in skin or in mucous membranes. <sup>d</sup>: splenomegaly may be absent in 1<sup>st</sup> week of illness. <sup>e</sup>: Gastro-intestinal hemorrhages occur in around 10% of patients with severe enteric fever. <sup>f</sup>: Bleeding manifestations include severe pulmonary hemorrhage with ARDS. <sup>g</sup> pneumonia is a common complication of scrub typhus in south Asia, and can progress rapidly to ARDS. <sup>h</sup>: thrombocytopenia frequent but mild in non-severe scrub typhus, <sup>i</sup>: severe scrub patients may have severe thrombocytopenia. Abbreviations: 0: does not occur/usually not associated with the disease; (+): Rare (frequency <5%); + Uncommon (frequency 6-10%); ++: Occasional (10-30%); +++: Common (>30%); cut-offs are arbitrary; N: normal (4.0 -11.0 x 10<sup>9</sup>/L); H: high (> 11.0 x 10<sup>9</sup>/L); L: low (< 4.0 x 10<sup>9</sup>/L); S: severe. TT: Tourniquet test; OR: Odds ratio; LR: ARDS: Acute Respiratory Distress syndrome; ARF: Acute Renal Failure

### Appendix 3. Clinical features of some other important causes of AUFIs

Disease	Epidemiology	Characteristic symptoms	Systemic involvement	Other features and points of discriminatory value
<b>Zika virus</b>	Vector borne ( <i>Aedes aegypti</i> , <i>albopictus</i> in Americas), <i>Other Aedes spp</i> in Micronesia Also parenteral, transplacental and sexual	Low grade Fever with 2 out of the following 3 features: Pruritic maculopapular rash (90%), arthralgia, Non-purulent conjunctivitis	GI and Liver: Transaminases ↑ Lungs: Rare. Neurological Guillain-Barre syndrome strongly associated (OR >34) post Zika fever. Renal: Rare -	Risk of fetal microcephaly, ocular abnormalities. Fever lesser than in dengue, Arthralgia lesser than in Chikungunya Conjunctivitis present. Rash is pruritic and cephalocaudal in distribution.
<b>Ebola virus disease</b>	Zoonoses. Fruit bats possible reservoirs of virus. Person to person transmission by contact with body fluids. Outbreaks seen.	History of being in an endemic area, and exposure to Ebola virus in past 21 days, in association with a febrile illness with myalgia, conjunctival injection	GI and Liver: Abdominal pain, vomiting, watery diarrhea between 3-10 days from onset. GI bleeding late feature. Lungs: rare involvement. CNS: Symptoms suggestive of meningo-encephalitis typically after day 10. Confusion, seizures, hiccups. Acute renal failure due to hypovolemia	Maculo-papular rash occasional. Secondary infections Features similar to other AUFIs. Fever, rash, conjunctival injection uncommon in cholera .
<b>Spotted fever group</b>	Vector borne (ticks) Zoonosis Mediterranean spotted fever (MSF) - <i>Rickettsia conorii</i> ; African tick bite fever(ATBF) - <i>Rickettsia africae</i> ; Indian Tick Typhus(ITT)- <i>Rickettsia conorii indica</i>	Fever with rash and eschars are prominent findings in spotted fevers. ATBF has prominent adenopathy & multiple eschars. Rash commoner in MSF and ITT.	No systemic complications in ATBF GI and Liver: Transaminases ↑ Lungs: Occasional pneumonia in MSF. Neurological: Very occasional encephalitis in MSF/ITT Renal: ARF Reported in MSF/ITT	ATBF mild, non-fatal. In MSF serious complication seen in presence of diabetes, alcoholism heart failure
<b>Typhus group</b>	Vector borne, Rat flea: Murine /Endemic typhus- ( <i>Rickettsia typhi</i> ) Body lice: Epidemic typhus ( <i>Rickettsia prowazekii</i> ) Epidemic Potential	Fever with rash with no eschar or adenopathy. Rash begins on trunk, centrifugal spread to limbs sparing palms and soles, face., commoner in epidemic typhus	GI and Liver: Transaminase elevation Jaundice may be seen Lungs: Pneumonia in both epidemic and endemic typhus, more prominent in murine typhus. Neurological: Confusion, coma may occur. Renal: ARF Reported in both Epidemic and endemic typhus	Illness mild in murine typhus low mortality. Serious CNS complications rare. Epidemic: CNS complications prominent, high mortality. Rash absent in 60% of epidemic typhus in Africa
<b>Relapsing fever (RF)- Tick borne relapsing fever(TBRF) &amp; Louse borne relapsing fever(LBRF)</b>	TBRF –zoonoses caused by various species of <i>Borrelia</i> transmitted by soft ticks LBRF – humans are reservoir. <i>Borrelia recurrentis</i> transmitted by body louse. .	Febrile episodes (3-10) of ~ 3-5 days & afebrile periods of ~7-10 days. Patients become tachycardic, tachypneic in the chill phase and may have hypotension when fever subsides	Jaundice occasional in LBRF Hepatosplenomegaly occasional. Dry cough common Pneumonia unusual Confusion common Meningitis occasional	Louse borne relapsing fever seen usually in overcrowding and refugee populations. Relapsing fever should be considered if patients has symptoms resembling malaria but is persistently smear negative.

<b>Melioidosis</b>	Vehicle borne disease caused by <i>Burkholderia pseudomallei</i> Moist soil, water, fruits, vegetables. Rainy season. DM, COPD, alcohol put at risk. Incubation period variable, and disease may occur years after exposure.	Variable presentations but may present as a community acquired pneumonia or septicemic along with abscesses in skin, parotid and prostate.	GI and Liver: Abscesses in liver, spleen may be seen in acute and chronic forms of melioidosis (Swiss cheese appearance on USG). Commonest cause of splenic abscess in Thailand. Lungs: Pneumonia commonest presentation. Multiple nodules, patchy alveolar opacities which coalesce. Neurological: Meningo-encephalitis, Brain abscesses. Acute renal failure may occur	May mimic pyogenic infection with abscesses, Gram negative sepsis & TB (upper lobe cavities) May mimic pulmonary TB (chronic fever, upper lobe cavities)
<b>Brucellosis</b>	Consumption of unpasteurised milk products Contact with livestock <i>Brucella abortus</i> <i>Brucella melitensis</i> commonest	Acute mono-arthritis of hip or knee in a young child. Vertebral osteomyelitis in an older person	Transaminases ↑. Hepatosplenic abscesses in a small proportion. Pneumonia. May present as bronchopneumonia or even with miliary lesions. Meningoencephalitis (Rare) -	Lumbar vertebra affected; with late discal involvement. Cord compression is unusual, compared with tuberculosis which may affect the lower thoracic vertebrae, with early discal involvement and result in cord compression.
<b>Plague</b>	Vector borne (Rat flea) Zoonosis Outbreak may follow an outbreak and deaths in rodent populations (epizootic)	Bubonic plague: commonest form. Fever with enlarged very painful, tender lymph nodes in any region.	Abscesses in liver, spleen in septicemic plague. Pneumonia- in plague may be bilateral (bubonic) or segmental progressing to bilateral alveolar(pneumonic) Occasional meningitis seen. ARF may occur as part of multi-organ failure	Adenopathy in plague occurs as part of a rapidly progressive illness, with no lymphangitis or cellulitis
<b>Human African Trypanosomiasis (HAT)</b>  <b>Stage I (haemolympathic) may present as an AUFI:</b>	Vector borne disease due to 2 subspecies of <i>Trypanosoma brucei</i> . ( <i>T.b</i> ) Transmitted by bites of tsetse flies <i>T.b. gambiense</i> HAT: predominant form, prevalent in Central and West. <i>T.b. rhodesiense</i> HAT can present as AUFI in east and south Africa	<i>T.b. rhodesiense</i> Intermittent high fevers →afebrile periods. Painful chancre at site of bite in half of <i>T.b. rhodesiense</i> infections. Less often in <i>T.b. gambiense</i> Posterior cervical node enlargement in <i>T.b. gambiense</i> - Winterbottom sign	GI and Liver disease Hepatosplenomegaly occasional CNS: In Stage II disease -Daytime somnolence, ataxia Cardiac: Persistent tachycardia, arrhythmias CHF in <i>T.b. rhodesiense</i>	<i>T.b. rhodesiense</i> infections have an acute onset with fever, rapid progression resembling malaria/sepsis. Chancre frequent. Death can occur in acute stage due to cardiac failure. <i>T.b. gambiense</i> infections are slower in onset and progression, and may present with CNS symptoms.

Abbreviations: GI: Gastrointestinal; Acute renal failure; CNS: Central Nervous system; MSF: Mediterranean spotted fever; ATBF: African Tick Bite fever; ITT: Indian Tick

Typhus; TBRF: Tick-borne relapsing fever; LBRF: Louse-borne relapsing fever; HAT: Human African Trypanosomiasis; T.b.: *Trypanosoma brucei*

1. Brunette GW, ed. *CDC Yellow Book 2018: Health Information for International Travel*. Centers for Disease Control and Prevention, 2017.
2. Leder K, Torresi J, Libman MD, et al. GeoSentinel surveillance of illness in returned travelers, 2007-2011. *Ann Intern Med* 2013;158:456-68.
3. Wilson ME, Weld LH, Boggild A, et al. Fever in returned travellers: results from the GeoSentinel Surveillance Network. *Clinical Infectious Diseases* 2007;44:1560-8.
4. Jensenius M, Han PV, Schlagenhauf P, et al. Acute and potentially life-threatening tropical diseases in western travelers--a GeoSentinel multicenter study, 1996-2011. *Am J Trop Med Hygiene* 2013;88:397-404.
5. Peters CJ, Zaki SF. Overview of viral hemorrhagic fevers. In: Guerrant RL, Walker DH, Weller PF, eds. *Tropical Infectious Diseases: Principles, Pathogens and Practice*. 1. Elsevier, 2006.