



Published in final edited form as:

Clin Microbiol Infect. 2018 August ; 24(8): 808–814. doi:10.1016/j.cmi.2018.02.011.

The epidemiology of febrile illness in sub-Saharan Africa: implications for diagnosis and management

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Abstract

Background—Fever is among the most common symptoms of people living in Africa, and clinicians are challenged by the similar clinical features of a wide spectrum of potential aetiologies.

Aim—To summarise recent studies of fever aetiology in sub-Saharan Africa focusing on causes other than malaria.

Sources—A narrative literature review by searching the MEDLINE database, and recent conference abstracts.

Content—Studies of multiple potential causes of fever are scarce, and for many participants the infecting organism remains unidentified, or multiple coinfecting microorganisms are identified, and establishing causation is challenging. Among ambulatory patients, self-limiting arboviral infections and viral upper respiratory infections are common, occurring in up to 60% of children attending health centres. Among hospitalised patients there is a high prevalence of potentially fatal infections requiring specific treatment. Bacterial bloodstream infection, and bacterial zoonoses are major causes of fever. In recent years, the prevalence of antimicrobial resistance among bacterial

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Conflict of Interest

All authors declare they have no conflict of interest.

isolates has increased, notably with spread of extended spectrum betalactamase-producing *Enterobacteriaceae* and fluoroquinolone resistant *Salmonella enterica*. Among those with HIV infection, *Mycobacterium tuberculosis* bacteraemia has been confirmed in up to 34.8% of patients with sepsis, and fungal infections such as cryptococcosis and histoplasmosis remain important.

Implications—Understanding the local epidemiology of fever aetiology, and use of diagnostics including malaria and HIV rapid-diagnostic tests, guides healthcare workers in the management of patients with fever. Current challenges for clinicians include assessing which ambulatory patients require antibacterial drugs, and identifying hospitalised patients infected with organisms that are not susceptible to empiric antibacterial regimens.

Keywords

fever; bacteraemia; tuberculosis; arbovirus; viruses; zoonoses

Increasing recognition of causes of fever other than malaria

The global burden of febrile illness, and the contribution of many fever-inducing pathogens have been difficult to quantify and characterize. However, in sub-Saharan Africa it is clear that fever is a common symptom (1), and febrile illness a major cause of illness and death (2).

Recently, there have been major advances in our knowledge of the causes of fever, which vary considerably across Africa. They are influenced by age and co-morbidities, and vary between ambulatory and hospitalised patients. Malaria remains a major cause of fever, although its incidence has been steadily declining since 2003 (3, 4). In places where the presence of fever used to be equated with malaria, malaria rapid diagnostic tests (RDTs) have identified the often large proportion of febrile patients who do not have malaria. Diagnosis of individual patients with febrile illness is challenging, due to the non-specific presentation of a broad variety of conditions, and the lack of available diagnostic tests. Therefore understanding the epidemiology of causes of fever has important implications for management of febrile patients. We aim to review recent studies of community-acquired fever aetiology in sub-Saharan Africa focusing on causes other than malaria and describe the implications for diagnosis and management among ambulatory and hospitalised patients.

Methodological notes

Our review summarises the most relevant recent literature following a search of PubMed, and the personal perspectives of contributing experts. Our search strings are included as Appendix 1. Articles are included at the authors discretion.

Studies investigating multiple causes of fever

Studies investigating multiple causes of fever are scarce (5), particularly outside of East Africa. When performed, the proportion of patients without an aetiological diagnosis is often large, particularly among those with fatal febrile illness (6). This is partly due to the insensitivity of reference tests to diagnose common pathogens, but may also be due to as yet

unrecognised pathogens. In addition, as few studies have enrolled healthy controls, determining whether an identified pathogen is the cause of fever is challenging, particularly when patients have evidence of infection with multiple microorganisms, or when tests used are not the reference standard and have sub-optimal specificity (7, 8). Table 1 summarises selected studies investigating multiple causes of acute febrile illness. Table 1 demonstrates the variability in tests performed, the proportion of participants in whom no microorganism was detected, and the challenges of interpreting multiple positive diagnostic tests.

Self-limited infections are a common cause of fever in ambulatory patients attending first level health facilities

Recent studies have demonstrated the high prevalence of self-limited infections, particularly respiratory viruses. Among children with fever, attending lower-level health facilities in both Tanzania and Kenya the prevalence of viral respiratory pathogens was 41% (7, 12). Arboviral infections, notably dengue, are also important causes of fever among both ambulatory and hospitalised patients (14). In one study conducted in multiple urban centres in Nigeria the prevalence of dengue virus infection was 23.4% (15). There are also reports of multiple serotypes of dengue virus infection being highly prevalent, in both rural and urban areas of West Africa (15, 16), East Africa (17), and southern Africa (18, 19). Acute HIV infection also contributes to acute febrile illness and was identified in 1.7% and 3.3% of outpatients with fever in Kenya (20), and Mozambique respectively (21).

Bacteraemia, particularly *Salmonella enterica* serovar Typhi, zoonotic bacterial infections, and HIV related opportunistic infections occur. However, these appear to be far less common among ambulatory patients than in those hospitalised with severe disease (7, 22, 23).

Multiple potential aetiologies of fever among hospitalised patients

Bacterial bloodstream infection

Bloodstream infection is a major cause of hospitalised fever in Africa. In patients with severe febrile illness, bacteraemia has been detected in 10.4% of patients in East Africa, and 12.4% of patients in West Africa (5). Immunosuppression due to HIV, and severe malnutrition remain significant risk factors for bacteraemia (24).

The most prevalent bloodstream pathogens are nontyphoidal serovars of *S. enterica* and *S. enterica* serovar Typhi (22, 25–29), together accounting for 46.2% of bacterial bloodstream isolates in Blantyre, Malawi during 1998-2016 (30). The Typhoid Surveillance in Africa Program (TSAP) study has estimated the incidence of invasive nontyphoidal *Salmonella* (iNTS) disease to exceed 100 cases per 100,000 population per year in many sites in Africa (29). Risk factors for iNTS include HIV infection, malnutrition, sickle cell disease, recent malaria infection, and severe anaemia (31–34). Declining malaria incidence and widespread availability of ART may contribute to the declining prevalence of iNTS in some areas (25, 35–39).

Longitudinal data indicate re-emergence of *S. enterica* serovar Typhi. In Malawi it was identified in 1.0% of patients with bloodstream infection during 1998-2009, and in 43.0% of

positive blood cultures during 2014-16 (30). In TSAP, the incidence of *S. enterica* serovar Typhi bacteraemia was greater than 100 cases per 100,000 population per year at multiple rural and urban sites in West Africa and East Africa. Incidence was often highest among pre-school children (29).

Streptococcus pneumoniae remains another common cause of bacteraemia, particularly among children (22, 27–29, 40). Despite some replacement by non-vaccine strains among patients with invasive pneumococcal disease (41), recent data suggest a decline in invasive pneumococcal disease associated with use of pneumococcal conjugate vaccine and ART (25, 42, 43). Other commonly identified pathogens include *Staphylococcus aureus* (7, 29, 40), which at 54% of isolates was the most prevalent bloodstream pathogen among children from Guinea-Bissau (40), and *Enterobacteriaceae* (22, 25, 29, 44).

The prevalence of antimicrobial resistance (AMR) is a growing concern. Among *Salmonella* isolates multidrug resistance (resistance to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole) has become common. In Ghana during 2010-2014, 56% of iNTS isolates and 63% of *S. enterica* serovar Typhi isolates were multi-drug resistant, and similar proportions have been seen in Burkina Faso, Kenya, and Tanzania (29, 39). In addition, there is emerging resistance to fluoroquinolones in *S. enterica* (26, 29, 30, 45), limiting oral outpatient treatment options. Reports also indicate increasing prevalence of resistance to extended-spectrum cephalosporins across Africa (29, 30), present in up to 56.5% nontyphoidal *Salmonella* bloodstream isolates in western Kenya (46). Resistance to extended spectrum cephalosporins among *Salmonella enterica* serovar Typhi remains rare, but was recently identified in the Democratic Republic of Congo (47). AMR is also increasing among other invasive bacteria (48, 49). Of concern, there has been rapid expansion of fluoroquinolone and extended-spectrum beta-lactam resistant *Enterobacteriaceae* in Malawi (30), and it is likely that there are similar trends across Africa.

Mycobacterial blood stream infections—*Mycobacterium tuberculosis* is a major cause of bloodstream infection among adults living with HIV, but less so in children. *M. tuberculosis* was the cause of bacteraemia among 0.4% of children and 13.5% of adults with HIV in a recent systematic review (50). *M. tuberculosis* persists as a major cause of bloodstream infection in Zambia and Uganda despite the availability of ART (10, 51).

Bacterial zoonoses

Bacterial zoonoses are under-recognised causes of febrile illness in Africa. Major bacterial zoonoses include brucellosis, leptospirosis, Q fever, and rickettsiosis. The close association between people, livestock, and wildlife in both rural and urban areas of many African countries is a key driver of the high prevalence of zoonotic infection.

Brucellosis—Recent studies have found a prevalence of brucellosis among febrile patients in East Africa of between 2.6% and 22.4% (8, 52, 53). In a pastoralist area of rural Tanzania, *Brucella melitensis* was the most common bloodstream isolate (54). Available data on risk factors for brucellosis in Africa suggest that birthing livestock and drinking raw milk are important in sub-Saharan Africa, as they are elsewhere (55–57).

Leptospirosis—Testing for leptospirosis is reported infrequently among febrile patients, but when sought has been diagnosed in up to 8.4% of patients hospitalised with fever (58). Countries in tropical Africa may have among the highest incidences of leptospirosis globally (59), albeit with marked variation in incidence over time (60). Leptospirosis appears to be common in both rural and urban environments. In addition to rodents, livestock may play an important role as a source for human disease in Africa (61).

Q fever—A recent systematic review identified *C. burnetii*, the cause of Q fever, among 6-9% of African patients with community acquired pneumonia, and 3-8% with undifferentiated febrile illness (62). In addition there have been reports of high prevalence of human seropositivity in Togo (63), and the Gambia (64). Cattle, goats, sheep, and camels have all been identified as having high prevalence of seroreactivity to *C. burnetii* and are likely to be important reservoirs of infection (62, 63).

Rickettsial infections—Rickettsioses are a frequent cause of fever in travellers returning from Africa (65). The major spotted fever group rickettsiosis (SFGR) in Africa is African tick-bite fever caused by *Rickettsia africae*. However, *R. conorii*, the cause of Mediterranean spotted fever, has been identified in at least nine countries in sub-Saharan Africa (66). It is accepted that rickettsioses are common in Southern Africa (67), and they may be common across the continent. A recent study from Kenya identified SFGR in 22.4% of children with fever (13), and studies from Ethiopia and Tanzania also found a high prevalence (68, 69). In West Africa, the prevalence of SFGR is less well documented, but is likely to be high, as both tick vectors and human seropositivity are common (66). In addition, *Rickettsia felis* appears prevalent in West and Central Africa. Although *R. felis* has been identified among healthy individuals, data suggest it may be a common cause of fever (70).

Relapsing fever

Borrelia spp., the cause of relapsing fever, have been identified across Africa, are rarely sought in fever aetiology studies and may be under-recognised by clinicians (71). In Senegal *B. crocidurae*, which causes tick-borne relapsing fever, was detected in 7.3% of unselected adult and paediatric patients with fever. In Ethiopia *B. recurrentis* the cause of louse-borne relapsing fever was identified using blood film in 6.1% of healthy yekolotemaries (religious students) and 4.9% of healthy street children. The high prevalence among community members highlights the challenges of determining the prevalence of relapsing fever among patients with acute febrile illness.

Protozoal infections

Visceral leishmaniasis, which can cause fever, causes substantial morbidity in some areas of East Africa, particularly among people infected with HIV (72). Human African trypanosomiasis (HAT) is endemic in parts of Central and West Africa, although control efforts aim to eliminate HAT as a public health problem are reducing incidence (73). The prevalence of these diseases in unselected patients with febrile illness is undetermined, but is likely to vary considerably by location.

Fungal Infections

Fungal infections remain an under-recognised cause of febrile illness among both HIV infected and uninfected hospitalised patients. Cryptococcal infection, which can result in disseminated disease and meningitis, remains a leading cause of death in HIV infected adults in Africa, despite increasingly widespread availability of ART. The epidemiology of cryptococcal disease is changing, while it is still most commonly identified at first presentation with HIV, presentation with cryptococcal disease is increasingly associated with treatment failure, default from treatment, and immune reconstitution early in the course of ART (74). Although there are few data, it is likely that histoplasmosis is endemic across large areas of Africa (75), and is often misdiagnosed as tuberculosis (76).

Implications for diagnosis and treatment

Management of patients presenting with fever requires appropriate supportive care, and correct antimicrobial therapy. Empiric management should be informed by knowledge of the local epidemiology of fever and AMR, HIV status of the patient, and results of malaria and HIV RDTs. In countries with a high prevalence of malaria parasitaemia, consideration of non-malaria aetiology is needed even in the presence of a positive malaria RDT, due to asymptomatic parasitaemia. Due to marked differences in disease severity and aetiology, management challenges for ambulant patients in the outpatient setting are different from those of patients hospitalised with severe febrile illness.

Management of patients in first level health facilities

The World Health Organisation (WHO) has proposed guidelines on the Integrated Management of Childhood Illness (IMCI) and the Integrated Management of Adolescent and Adult Illness (IMAAI). Such guidance informs management decisions regarding appropriate supportive care, who should be referred to a higher level health facility, and who needs anti-microbial drugs (77, 78). Updates reflecting the epidemiologic and management advances are needed to ensure the guidelines remain safe and effective. In malaria-endemic areas, the introduction of malaria RDTs has led to more rational use of antimalarial drugs (79), but surprisingly over-prescription of antibacterial drugs (80, 81). Due to the high prevalence of self-limiting viral infections at first level health facilities, the challenge in management of ambulatory patients is to identify those from whom antibacterial drugs can be safely withheld. Research efforts to reduce over-prescription include investigating refinement of clinical severity criteria, and the use of biomarkers to detect severe bacterial disease. Studies addressing biomarkers are described in a separate review within this issue.

Identification of the most severely unwell

Among hospitalised patients, there are a large number of potentially fatal causes of fever that cannot be reliably separated on clinical grounds. Management is guided by illness severity, and WHO pocketbooks help clinicians identify severe disease (82, 83). Recent attempts to improve identification of those with severe illness with prediction scores, such as the quick sequential organ failure assessment (84) and the universal vital assessment score (85), have shown ability to identify those at greatest risk of death. These scores could help clinicians

better target those needing broad-spectrum antimicrobial therapy and more intensive supportive care.

Identification of those with bacterial infections that are not susceptible to first-line antimicrobials

IMCI and IMAI handbooks recommend an extended-spectrum cephalosporin, or ampicillin plus gentamicin, as suitable broad-spectrum antimicrobial therapy for those with severe febrile illness. The diversity of pathogens and bacterial AMR in different settings raises the possibility that this generic guidance is insufficient. The WHO pocketbooks do not address severe disease due to bacterial pathogens that are not susceptible to these agents, nor in which patients with undifferentiated fever to use anti-fungal and antituberculosis drugs (82, 83). Local microbiologic data in aggregate are invaluable for tailoring of empiric management guidelines. Depending on local epidemiology, consideration should be given to additional therapies including carbapenem and tetracycline group antibacterials, antifungal agents, and antituberculosis medications. There is no clinical trial evidence currently to support empiric treatment with tetracycline in patients in Africa with severe or prolonged fever. However, the high prevalence of relapsing fever, rickettsiosis, and Q fever suggest a role. In areas with a high prevalence of ESBL-producing organisms, such western Kenya where ESBL-producing nontyphoidal *S. enterica* is the leading cause of bacteraemia (46), empiric regimens active against ESBL-producing organisms must be considered for patients with sepsis. Such escalation in antimicrobial therapy must be in concert with robust antimicrobial stewardship programmes.

Use of rapid diagnostic tests to guide empiric treatment of *M. tuberculosis* and *Cryptococcus* spp

Provider-initiated HIV testing is recommended for all patients in countries with a high prevalence of HIV (78, 83). HIV testing is invaluable for managing febrile patients in such countries, as the results inform the probability that the patient might have cryptococcal disease or disseminated tuberculosis (78, 83). Among those with HIV, the cryptococcal antigen RDTs are useful to diagnose cryptococcal disease (86). Early anti-tuberculosis therapy may improve outcomes in the most severely unwell patients infected with tuberculosis (87, 88). Although trials are needed, there is a case for further development of RDTs to diagnose disseminated tuberculosis (89), or the inclusion of anti-tuberculosis therapy as empiric treatment for adults with advanced HIV who present with sepsis (90).

Ongoing patient management: establishing a microbiological diagnosis to inform therapeutic strategy

Microbiological diagnosis informs ongoing patient management, especially when the infection is not responsive to empiric agents, requires multi-drug therapy, or prolonged treatment. The laboratory capacity to identify patients infected with the broad range of organisms that can cause fever is not available in most hospitals in sub-Saharan Africa (91). There is therefore need for either laboratory development, which may be a cost-effective approach (92), or continued development of sentinel sites to monitor both aetiology of fever and AMR.

Conclusions

The causes of non-malarial fever are diverse and yet to be fully determined. In addition to bacterial bloodstream infection, recent studies highlight the role of viral pathogens, bacterial zoonoses, disseminated tuberculosis, and cryptococcal disease, for which the antimicrobials currently recommended by the World Health Organisation for acute febrile illness may not be effective. In addition, there is evidence of increasing AMR, particularly among *Salmonella* and other gram negative bacteria. These developments highlight the critical role of sentinel surveillance sites that can inform in real-time the epidemiology of febrile illness. There is a need to incorporate the evolving complexity in causes of acute febrile illness into evidenced based algorithms to manage patients for whom reliable and relevant diagnostic services are not available.

Acknowledgments

Funding declaration

MJM received support from University of Otago scholarships: the Frances G. Cotter Scholarship and the MacGibbon Travel Fellowship. JAC was supported by the joint US National Institutes of Health (NIH:www.nih.gov)-National Science Foundation (NSF:www.nsf.gov) Ecology of Infectious Disease program (R01TW009237), the US National Institutes of Health Institute of Allergy and Infectious Disease (R01 AI121378), and the Research Councils UK, Department for International Development (UK) and UK Biotechnology and Biological Sciences Research Council (BBSRC:www.bbsrc.ac.uk) (grant numbers BB/J010367/1, BB/L018926, BB/L017679, BB/L018845).

Appendix 1. Search strategy for identifying papers for inclusion in this narrative review of the recent advances in the epidemiology of febrile illness in sub-Saharan Africa

Search Date

15 September 2017

Search terms

[African country names] AND [Fever]
 [African country names] AND [Non-malarial fever.mp] AND [Epidemiology]
 [African country names] AND [Bacteremia]
 [African country names] AND [Disseminated tuberculosis.mp OR Tuberculosis, miliary]
 [African country names] AND [Brucellosis]
 [African country names] AND [Leptospirosis]
 [African country names] AND [Coxiella burnetii OR Q fever]
 [African country names] AND [Rickettsia infections]
 [African country names] AND [Histoplasmosis]

[African country names] AND [Cryptococcosis]

[African country names] AND [Viruses]

[African country names] AND [Dengue]

[African country names] AND [Respiratory Virus]

[African country names] AND [Salmonella]

[African country names] AND [Drug resistance, bacterial]

[African country names]= Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Congo (Brazzaville) OR Congo (Democratic Republic) OR Côte d'Ivoire OR Djibouti OR Equatorial Guinea OR Eritrea OR Ethiopia OR Gabon OR The Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Réunion OR Rwanda OR Sao Tome and Principe OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa OR Sudan OR Swaziland OR Tanzania OR Togo OR Uganda OR Western Sahara OR Zambia OR Zimbabwe OR Africa, Eastern OR South Africa OR Africa OR Africa, Western OR Africa, Southern OR Africa, Central OR "Africa South of the Sahara"

Year limitation

2012-2017 (inclusive)

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Table 1
Summary of selected studies investigating the aetiology of febrile illness in Africa, published 2013-2018

	Study population	Study size	Testing	Main diagnoses	Comment and limitations
D'Acremont, Tanzania, 2006 (7)	Paediatric Outpatient District Hospital HIV prevalence: not stated	1005	Blood culture, respiratory virus and arboviral nucleic acid amplification testing (NAAT); arboviral serology; <i>Leptospira</i> , <i>Coxiella</i> , and <i>Toxoplasma</i> serology	Viral aetiology in 78% of systemic infections, 100% of nasopharyngeal infections, and 51% of lower respiratory infections Overall: 9% malaria, 4.2% bacteraemia	Challenging to determine causation due to high prevalence (76.9%) of co-infection and lack of healthy controls.
Crump, Tanzania, 2007-08 (6)	Paediatric/ adult Referral hospitals Inpatient HIV prevalence <13 years 12.2% 13 years : 39.0%	870	Antigen detection for <i>Cryptococcus</i> , <i>Histoplasma capsulatum</i> , <i>Legionella pneumophila</i> , <i>Streptococcus pneumoniae</i> ; blood culture (aerobic and mycobacterial); NAAT for arboviruses; serology for <i>Bruceella</i> , <i>Leptospira</i> , <i>Coxiella</i> , and <i>Rickettsia</i> ; thick and thin blood film for parasites	<13 years: chikungunya 10.2%, leptospirosis 7.7%, 7.4% spotted fever group rickettsiosis (SFG), 3.4% bacteraemia, 2.6% Q fever, 2.0% brucellosis, 1.3% malaria, 0.9% fungaemia, 13 years: 17.1% bacteraemia, 10.1% leptospirosis, 8.7% SFG, 7.9% Q fever, 5.3% brucellosis, 5.7% chikungunya, 5.2% fungaemia, 3.5% mycobacteraemia, 2% malaria	Large proportion of patients (64.0% aged <13 years, and 33.2% 13 years without a aetiological diagnosis. Respiratory viruses not sought.
Baba, Nigeria, 2006 (9)	Adult Referral hospital Hospitalisation and HIV status not reported	310	Serology for chikungunya, dengue, typhoid, West Nile virus (WNV), yellow fever; thick and thin film for malaria	67% dengue, 50.2% chikungunya, 32.6% typhoid, 29.4% malaria, 24.9% WNV,	The high prevalence of co-infection of malaria, serologically diagnosed typhoid, and arboviral infections highlights challenges of making diagnoses through non-reference standard tests
Jacob, Uganda, 2008-09 (10)	Adult Referral hospital Inpatients with severe sepsis HIV prevalence 100%	368	Antigen detection of <i>Cryptococcus</i> , blood culture (aerobic and mycobacterial); serology for HIV; thick and thin blood film for malaria,	23.4% <i>Mycobacterium tuberculosis</i> , 11% bacteraemia, 4% non-tuberculous mycobacteria, 2% <i>Cryptococcus neoformans</i>	Highly selected population, with limited breadth of pathogens investigated
Chipwaza, Tanzania 2013 (8, 11)	District hospital Outpatient/ Inpatient HIV prevalence not stated	370	NAAT for influenza and dengue; serology for brucellosis, chikungunya, dengue, leptospirosis, typhoid; thick and thin blood films for malaria; urine microscopy for bacteria	<5 years: 31.3% dengue, 22.9% malaria, leptospirosis 19.5%, brucellosis 13.2%, typhoid 6.8%, 5.4% chikungunya, 1% influenza 5 years: 81.1% dengue, 49.7% brucellosis, 31% leptospirosis, 22.6% malaria, typhoid 14.4%, 4.1 influenza	High prevalence of co-infection of serologically diagnosed typhoid and zoonotic infections highlights the challenges of determining causation when non-reference standard tests are used
O'Meara, Maie Kenya, 2011-12 (12, 13)	Paediatric District hospital Outpatient HIV prevalence 0.4%	370	Antigen detection for group A <i>Streptococcus</i> ; NAAT for adenovirus, influenza A and B, human metapneumovirus, parainfluenza virus 1-3, malaria, respiratory syncytial virus (RSV); serology for <i>Rickettsia</i> , <i>Coxiella</i> ; thick and thin films for parasites	22.4% SFG, * 20.3% influenza A/B, 10.5% adenovirus, 10.1% parainfluenza virus 1-3, 8.9% Q fever, 5.3% RSV 5.2% malaria 5.2%, 3.6% scrub typhus, hMNV 3.2%, group A <i>Streptococcus</i> 2.3%, 1.0% typhus group <i>Rickettsia</i>	Study notable for inclusion of healthy controls, in whom 1 pathogen was detected in 49.1%. Limitations include a limited selection of pathogens sought.