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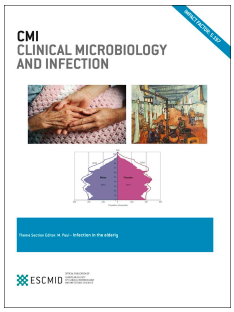

The epidemiology of febrile illness in sub-Saharan Africa: implications for diagnosis and management

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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 co-infecting 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 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.

ARTICLE

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.

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117 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; *Leptospira*, *Coxiella*, and *Toxoplasma* 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 *Cryptococcus, Histoplasma capsulatum, Legionella pneumophila, Streptococcus pneumoniae*; blood culture (aerobic and mycobacterial); NAAT for arboviruses; serology for *Brucella*, *Leptospira*, *Coxiella*, and *Rickettsia*; thick and thin blood film for parasites	<13 years: chikungunya 10.2%, leptospirosis 7.7%, 7.4% spotted fever group rickettsiosis (SFGR), 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% SFGR, 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 aetiologic 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 mlalaria, 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 *Cryptococcus,* blood culture (aerobic and mycobacterial); serology for HIV; thick and thin blood film for malaria,	23.4% *Mycobacterium tuberculosis,* 11% bacteraemia, 4% non-tuberculous mycobacteria, 2% *Cryptococcus neoformans*	Highly selected population, with limmited 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 o determining causation when non-reference standard tests are used
O'Meara , Maine Kenya, 2011-12 (12, 13)	Paediatric District hospital Outpatient HIV prevalence 0.4%	370	Antigen detection for group A *Streptococcus*, NAAT for adenovirus, influenza A and B, human metapneumovirus, parainfluenza virus 1-3, malaria, respiratory syncitial virus (RSV); serology for *Rickettsia, Coxiella*; thick and think films for parasites	22.4% SFGR, 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 *Streptococcus* 2.3%, 1.0% typhus group *Rickettsia*	Study notable for inclusion of healthy controls, in whom ≥1 pathgen was detected in 49.1%. Limitations include a limited selection of pathogens sought.

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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

214 birthing livestock and drinking raw milk are important in sub-Saharan Africa,
215 as they are elsewhere (55-57).
216
217 ***Leptospirosis***
218 Testing for leptospirosis is reported infrequently among febrile patients, but
219 when sought has been diagnosed in up to 8.4% of patients hospitalised with
220 fever (58). Countries in tropical Africa may have among the highest
221 incidences of leptospirosis globally (59), albeit with marked variation in
222 incidence over time (60). Leptospirosis appears to be common in both rural
223 and urban environments. In addition to rodents, livestock may play an
224 important role as a source for human disease in Africa (61).
225
226 ***Q fever***
227 A recent systematic review identified *C. burnetii,* the cause of Q fever, among
228 6-9% of African patients with community acquired pneumonia, and 3-8% with
229 undifferentiated febrile illness (62). In addition there have been reports of high
230 prevalence of human seropositivity in Togo (63), and the Gambia (64). Cattle,
231 goats, sheep, and camels have all been identified as having high prevalence
232 of seroreactivity to *C. burnetii* and are likely to be important reservoirs of
233 infection (62, 63).
234
235 ***Rickettsial infections***
236 Rickettsioses are a frequent cause of fever in travellers returning from Africa
237 (65). The major spotted fever group rickettsiosis (SFGR) in Africa is African
238 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 (IMAI). 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 anti-tuberculosis 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 anti-tuberculosis 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 anti-microbial 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 cryptoccal 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 algorthims to manage patients for whom reliable and relevant diagnostic services are not available.

Conflict of Interest

All authors declare they have no conflict of interest.

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REFERENCES

1. Prasad N, Sharples KJ, Murdoch DR, Crump JA. Community prevalence of fever and relationship with malaria among infants and children in low-resource areas. Am J Trop Med Hyg. 2015;93(1):178-80.

2. Global Burden of Disease Study 2015. Global Burden of Disease Study 2015 (GBD 2015) Results Seattle, United States of America: Insititute for Health Metrics and Evaluation (IHME); 2016 [7 March 2017]. Available from: http://ghdx.healthdata.org/gbd-results-tool

3. Murray CJ, Ortblad KF, Guinovart C, Lim SS, Wolock TM, Roberts DA, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2014;384(9947):1005-70.

4. Bhatt S, Weiss DJ, Cameron E, Bisanzio D, Mappin B, Dalrymple U, et al. The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015. Nature. 2015;526(7572):207-11.

5. 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(6):e0127962.

6. Crump JA, Morrissey AB, Nicholson WL, Massung RF, Stoddard RA, Galloway RL, et al. Etiology of severe non-malaria febrile illness in Northern Tanzania: a prospective cohort study. PLoS Negl Trop Dis. 2013;7(7):e2324.

7. D'Acremont V, Kilowoko M, Kyungu E, Philipina S, Sangu W, Kahama-Maro J, et al. Beyond malaria - causes of fever in outpatient Tanzanian children. N Engl J Med. 2014;370(9):809-17.

8. Chipwaza B, Mhamphi GG, Ngatunga SD, Selemani M, Amuri M, Mugasa JP, et al. Prevalence of bacterial febrile illnesses in children in Kilosa district, Tanzania. PLoS Negl Trop Dis. 2015;9(5):e0003750.

9. Baba M, Logue CH, Oderinde B, Abdulmaleek H, Williams J, Lewis J, et al. Evidence of arbovirus co-infection in suspected febrile malaria and typhoid patients in Nigeria. J Infect Dev Ctries. 2013;7(1):51-9.

10. Jacob ST, Pavlinac PB, Nakiyingi L, Banura P, Baeten JM, Morgan K, et al. *Mycobacterium tuberculosis* bacteremia in a cohort of HIV-infected patients hospitalized with severe sepsis in Uganda-high frequency, low clinical suspicion [corrected] and derivation of a clinical prediction score. PLoS One. 2013;8(8):e70305.

11. Chipwaza B, Mugasa JP, Selemani M, Amuri M, Mosha F, Ngatunga SD, et al. Dengue and Chikungunya fever among viral diseases in outpatient febrile children in Kilosa district hospital, Tanzania. PLoS Negl Trop Dis. 2014;8(11):e3335.

12. O'Meara WP, Mott JA, Laktabai J, Wamburu K, Fields B, Armstrong J, et al. Etiology of pediatric fever in western Kenya: a case-control study of falciparum malaria, respiratory viruses, and streptococcal pharyngitis. Am J Trop Med Hyg. 2015;92(5):1030-7.

13. Maina AN, Farris CM, Odhiambo A, Jiang J, Laktabai J, Armstrong J, et al. Q fever, scrub typhus, and rickettsial diseases in children, Kenya, 2011–2012. Emerging infectious diseases. 2016;22(5):883.

440 14. Amarasinghe A, Kuritsk JN, Letson GW, Margolis HS. Dengue virus
441 infection in Africa. Emerg Infect Dis. 2011;17(8):1349-54.
442 15. Onoja AB, Adeniji JA, Olaleye OD. High rate of unrecognized dengue
443 virus infection in parts of the rainforest region of Nigeria. Acta Trop.
444 2016;160:39-43.
445 16. Ridde V, Agier I, Bonnet E, Carabali M, Dabire KR, Fournet F, et al.
446 Presence of three dengue serotypes in Ouagadougou (Burkina Faso):
447 research and public health implications. Infect Dis Poverty. 2016;5:23.
448 17. Ngoi CN, Price MA, Fields B, Bonventure J, Ochieng C, Mwashigadi G,
449 et al. Dengue and chikungunya virus infections among young febrile adults
450 evaluated for acute HIV-1 infection in coastal Kenya. PLoS One.
451 2016;11(12):e0167508.
452 18. Parreira R, Conceicao C, Centeno-Lima S, Marques N, Saraiva da
453 Cunha J, Abreu C, et al. Angola's 2013 dengue outbreak: clinical, laboratory
454 and molecular analyses of cases from four Portuguese institutions. J Infect
455 Dev Ctries. 2014;8(9):1210-5.
456 19. Massangaie M, Pinto G, Padama F, Chambe G, da Silva M, Mate I, et
457 al. Clinical and epidemiological characterization of the first recognized
458 outbreak of dengue virus-type 2 in Mozambique, 2014. Am J Trop Med Hyg.
459 2016;94(2):413-6.
460 20. Sanders EJ, Mugo P, Prins HA, Wahome E, Thiong'o AN, Mwashigadi
461 G, et al. Acute HIV-1 infection is as common as malaria in young febrile adults
462 seeking care in coastal Kenya. AIDS. 2014;28(9):1357-63.
463 21. Serna-Bolea C, Munoz J, Almeida JM, Nhacolo A, Letang E,
464 Nhampossa T, et al. High prevalence of symptomatic acute HIV infection in an

outpatient ward in southern Mozambique: identification and follow-up. AIDS. 2010;24(4):603-8.

22. Hildenwall H, Amos B, Mtove G, Muro F, Cederlund K, Reyburn H. Causes of non-malarial febrile illness in outpatients in Tanzania. Trop Med Int Health. 2016;21(1):149-56.

23. Mahende C, Ngasala B, Lusingu J, Butichi A, Lushino P, Lemnge M, et al. Bloodstream bacterial infection among outpatient children with acute febrile illness in north-eastern Tanzania. BMC Res Notes. 2015;8:289.

24. Huson MA, Stolp SM, van der Poll T, Grobusch MP. Community-acquired bacterial bloodstream infections in HIV-infected patients: a systematic review. Clin Infect Dis. 2014;58(1):79-92.

25. Feasey NA, Houston A, Mukaka M, Komrower D, Mwalukomo T, Tenthani L, et al. A reduction in adult blood stream infection and case fatality at a large African hospital following antiretroviral therapy roll-out. PLoS One. 2014;9(3):e92226.

26. Feasey NA, Masesa C, Jassi C, Faragher EB, Mallewa J, Mallewa M, et al. Three epidemics of invasive multidrug-resistant *Salmonella* bloodstream infection in Blantyre, Malawi, 1998-2014. Clin Infect Dis. 2015;61 Suppl 4:S363-71.

27. Crump JA, Ramadhani HO, Morrissey AB, Msuya LJ, Yang LY, Chow SC, et al. Invasive bacterial and fungal infections among hospitalized HIV-infected and HIV-uninfected children and infants in northern Tanzania. Trop Med Int Health. 2011;16(7):830-7.

28. Crump JA, Ramadhani HO, Morrissey AB, Saganda W, Mwako MS, Yang LY, et al. Invasive bacterial and fungal infections among hospitalized

490 HIV-infected and HIV-uninfected adults and adolescents in northern Tanzania.
491 Clin Infect Dis. 2011;52(3):341-8.
492 29. Marks F, von Kalckreuth V, Aaby P, Adu-Sarkodie Y, El Tayeb MA, Ali
493 M, et al. Incidence of invasive salmonella disease in sub-Saharan Africa: a
494 multicentre population-based surveillance study. Lancet Glob Health.
495 2017;5(3):e310-e23.
496 30. Musicha P, Cornick JE, Bar-Zeev N, French N, Masesa C, Denis B, et
497 al. Trends in antimicrobial resistance in bloodstream infection isolates at a
498 large urban hospital in Malawi (1998-2016): a surveillance study. Lancet Infect
499 Dis. 2017;17(10):1042-52.
500 31. Uche IV, MacLennan CA, Saul A. A systematic review of the incidence,
501 risk factors and case fatality rates of invasive nontyphoidal *Salmonella* (iNTS)
502 Disease in Africa (1966 to 2014). PLoS Negl Trop Dis. 2017;11(1):e0005118.
503 32. Park SE, Pak GD, Aaby P, Adu-Sarkodie Y, Ali M, Aseffa A, et al. The
504 relationship between invasive nontyphoidal *Salmonella* disease, other
505 bacterial bloodstream infections, and malaria in sub-Saharan Africa. Clin
506 Infect Dis. 2016;62 Suppl 1:S23-31.
507 33. Takem EN, Roca A, Cunnington A. The association between malaria
508 and non-typhoid *Salmonella* bacteraemia in children in sub-Saharan Africa: a
509 literature review. Malar J. 2014;13:400.
510 34. Biggs HM, Lester R, Nadjm B, Mtove G, Todd JE, Kinabo GD, et al.
511 Invasive *Salmonella* infections in areas of high and low malaria transmission
512 intensity in Tanzania. Clin Infect Dis. 2014;58(5):638-47.
513 35. Scott JA, Berkley JA, Mwangi I, Ochola L, Uyoga S, Macharia A, et al.
514 Relation between falciparum malaria and bacteraemia in Kenyan children: a

515 population-based, case-control study and a longitudinal study. Lancet.
516 2011;378(9799):1316-23.
517 36. Mackenzie G, Ceesay SJ, Hill PC, Walther M, Bojang KA, Satoguina J,
518 et al. A decline in the incidence of invasive non-typhoidal *Salmonella* infection
519 in The Gambia temporally associated with a decline in malaria infection. PLoS
520 One. 2010;5(5):e10568.
521 37. Feasey NA, Everett D, Faragher EB, Roca-Feltrer A, Kang'ombe A,
522 Denis B, et al. Modelling the contributions of malaria, HIV, malnutrition and
523 rainfall to the decline in paediatric invasive non-typhoidal *Salmonella* disease
524 in Malawi. PLoS Negl Trop Dis. 2015;9(7):e0003979.
525 38. Keddy KH, Takuva S, Musekiwa A, Puren AJ, Sooka A, Karstaedt A, et
526 al. An association between decreasing incidence of invasive non-typhoidal
527 salmonellosis and increased use of antiretroviral therapy, Gauteng Province,
528 South Africa, 2003-2013. PLoS One. 2017;12(3):e0173091.
529 39. Muthumbi E, Morpeth SC, Ooko M, Mwanzu A, Mwarumba S, Mturi N,
530 et al. Invasive salmonellosis in Kilifi, Kenya. Clin Infect Dis. 2015;61 Suppl
531 4:S290-301.
532 40. Isendahl J, Manjuba C, Rodrigues A, Xu W, Henriques-Normark B,
533 Giske CG, et al. Prevalence of community-acquired bacteraemia in Guinea-
534 Bissau: an observational study. BMC Infect Dis. 2014;14:3859.
535 41. Balsells E, Guillot L, Nair H, Kyaw MH. Serotype distribution of
536 *Streptococcus pneumoniae* causing invasive disease in children in the post-
537 PCV era: A systematic review and meta-analysis. PLoS One.
538 2017;12(5):e0177113.

539 42. von Gottberg A, de Gouveia L, Tempia S, Quan V, Meiring S, von
540 Mollendorf C, et al. Effects of vaccination on invasive pneumococcal disease
541 in South Africa. N Engl J Med. 2014;371(20):1889-99.
542 43. Mackenzie GA, Hill PC, Jeffries DJ, Hossain I, Uchendu U, Ameh D, et
543 al. Effect of the introduction of pneumococcal conjugate vaccination on
544 invasive pneumococcal disease in The Gambia: a population-based
545 surveillance study. Lancet Infect Dis. 2016;16(6):703-11.
546 44. Akoua-Koffi C, Tia H, Plo JK, Monemo P, Cisse A, Yao C, et al.
547 Epidemiology of community-onset bloodstream infections in Bouake, central
548 Cote d'Ivoire. New Microbes New Infect. 2015;7:100-4.
549 45. Feasey NA, Cain AK, Msefula CL, Pickard D, Alaerts M, Aslett M, et al.
550 Drug resistance in *Salmonella enterica* ser. Typhimurium bloodstream
551 infection, Malawi. Emerg Infect Dis. 2014;20(11):1957-9.
552 46. Oneko M, Kariuki S, Muturi-Kioi V, Otieno K, Otieno VO, Williamson
553 JM, et al. Emergence of community-acquired, multidrug-resistant invasive
554 nontyphoidal *Salmonella* disease in rural western Kenya, 2009–2013. Clinical
555 Infectious Diseases. 2015;61(suppl_4):S310-S6.
556 47. Phoba M-F, Barbé B, Lunguya O, Masendu L, Lulengwa D, Dougan G,
557 et al. *Salmonella enterica* serovar Typhi producing CTX-M-15 extended
558 spectrum β-lactamase in the Democratic Republic of the Congo. Clinical
559 Infectious Diseases. 2017:cix342.
560 48. Leopold SJ, van Leth F, Tarekegn H, Schultsz C. Antimicrobial drug
561 resistance among clinically relevant bacterial isolates in sub-Saharan Africa: a
562 systematic review. J Antimicrob Chemother. 2014;69(9):2337-53.

563 49. Pons MJ, Vubil D, Guiral E, Jaintilal D, Fraile O, Soto SM, et al.
564 Characterisation of extended-spectrum β-lactamases among *Klebsiella*
565 *pneumoniae* isolates causing bacteraemia and urinary tract infection in
566 Mozambique. Journal of Global Antimicrobial Resistance. 2015;3(1):19-25.
567 50. Pavlinac P, Lokken E, Walson J, Richardson B, Crump J, John-Stewart
568 G. *Mycobacterium tuberculosis* bacteremia in adults and children: a
569 systematic review and meta-analysis. The International Journal of
570 Tuberculosis and Lung Disease. 2016;20(7):895-902.
571 51. Muchemwa L, Shabir L, Andrews B, Bwalya M. High prevalence of
572 *Mycobacterium tuberculosis* bacteraemia among a cohort of HIV-infected
573 patients with severe sepsis in Lusaka, Zambia. Int J STD AIDS. 2016.
574 52. Animut A, Mekonnen Y, Shimelis D, Ephraim E. Febrile illnesses of
575 different etiology among outpatients in four health centers in northwestern
576 Ethiopia. Jpn J Infect Dis. 2009;62(2):107-10.
577 53. Bouley AJ, Biggs HM, Stoddard RA, Morrissey AB, Bartlett JA,
578 Afwamba IA, et al. Brucellosis among hospitalized febrile patients in northern
579 Tanzania. Am J Trop Med Hyg. 2012;87(6):1105-11.
580 54. Bodenham RF, Lukambagire A-H, Buza JJ, Kazwala RR, Maro VP,
581 Mmbaga BT, et al. Brucella among febrile outpatients and their household
582 members in northern Tanzania. Royal Society of Tropical Medicine and
583 Hygeine East African research in progress meeting; 28 Sep - 1 Oct 2017;
584 Moshi, Tanzania.
585 55. John K, Fitzpatrick J, French N, Kazwala R, Kambarage D, Mfinanga
586 GS, et al. Quantifying risk factors for human brucellosis in rural northern
587 Tanzania. PLoS One. 2010;5(4):e9968.

588 56. Ducrotoy M, Bertu WJ, Matope G, Cadmus S, Conde-Alvarez R, Gusi
589 AM, et al. Brucellosis in sub-Saharan Africa: current challenges for
590 management, diagnosis and control. Acta Trop. 2017;165:179-93.
591 57. Cash-Goldwasser S, Maze MJ, Rubach MP, Biggs HM, Stoddard RA,
592 Sharples KJ, et al. Risk factors for human brucellosis in northern Tanzania.
593 Am J Trop Med Hyg. 2017.
594 58. Allan KJ, Biggs HM, Halliday JE, Kazwala RR, Maro VP, Cleaveland S,
595 et al. Epidemiology of leptospirosis in Africa: a systematic review of a
596 neglected zoonosis and a paradigm for 'One Health' in Africa. PLoS Negl Trop
597 Dis. 2015;9(9):e0003899.
598 59. Costa F, Hagan JE, Calcagno J, Kane M, Torgerson P, Martinez-
599 Silveira MS, et al. Global morbidity and mortality of leptospirosis: a systematic
600 review. PLoS Negl Trop Dis. 2015;9(9):e0003898.
601 60. Maze MJ, Biggs HM, Rubach MP, Galloway RL, Cash-Goldwasser S,
602 Allan KJ, et al. Comparison of the estimated incidence of acute leptospirosis
603 in the Kilimanjaro Region of Tanzania between 2007-08 and 2012-14. PLoS
604 Negl Trop Dis. 2016;10(12):e0005165.
605 61. Maze MJ, Cash-Goldwasser S, Rubach MP, Biggs HM, Galloway RL,
606 Sharples KJ, et al., editors. Risk factors for acute human leptospirosis in
607 northern Tanzania. In: Program and abstracts of the American Society of
608 Tropical Medicine and Hygiene 65th Annual Meeting; 2016 November 13-17,
609 2016; Atlanta, Georgia, USA.
610 62. Vanderburg S, Rubach MP, Halliday JE, Cleaveland S, Reddy EA,
611 Crump JA. Epidemiology of *Coxiella burnetii* infection in Africa: a OneHealth
612 systematic review. PLoS Negl Trop Dis. 2014;8(4):e2787.

613 63. Dean AS, Bonfoh B, Kulo AE, Boukaya GA, Amidou M, Hattendorf J, et
614 al. Epidemiology of brucellosis and Q Fever in linked human and animal
615 populations in northern Togo. PLoS One. 2013;8(8):e71501.
616 64. Bok J, Hogerwerf L, Germeraad EA, Roest HI, Faye‐Joof T, Jeng M,
617 et al. *Coxiella burnetii* (Q fever) prevalence in associated populations of
618 humans and small ruminants in The Gambia. Tropical Medicine &
619 International Health. 2017;22(3):323-31.
620 65. Jensenius M, Davis X, von Sonnenburg F, Schwartz E, Keystone JS,
621 Leder K, et al. Multicenter GeoSentinel analysis of rickettsial diseases in
622 international travelers, 1996-2008. Emerg Infect Dis. 2009;15(11):1791-8.
623 66. Parola P, Paddock CD, Socolovschi C, Labruna MB, Mediannikov O,
624 Kernif T, et al. Update on tick-borne rickettsioses around the world: a
625 geographic approach. Clin Microbiol Rev. 2013;26(4):657-702.
626 67. Raoult D, Fournier PE, Fenollar F, Jensenius M, Prioe T, de Pina JJ, et
627 al. *Rickettsia africae*, a tick-borne pathogen in travelers to sub-Saharan Africa.
628 N Engl J Med. 2001;344(20):1504-10.
629 68. Prabhu M, Nicholson WL, Roche AJ, Kersh GJ, Fitzpatrick KA, Oliver
630 LD, et al. Q fever, spotted fever group, and typhus group rickettsioses among
631 hospitalized febrile patients in northern Tanzania. Clin Infect Dis.
632 2011;53(4):e8-15.
633 69. Aarsland SJ, Castellanos-Gonzalez A, Lockamy KP, Mulu-Droppers R,
634 Mulu M, White AC, et al. Treatable bacterial infections are underrecognized
635 causes of fever in Ethiopian children. Am J Trop Med Hyg. 2012;87(1):128-33.

636 70. Mourembou G, Lekana-Douki JB, Mediannikov O, Nzondo SM, Kouna
637 LC, Essone JC, et al. Possible role of *Rickettsia felis* in acute febrile illness
638 among children in Gabon. Emerg Infect Dis. 2015;21(10):1808-15.
639 71. Elbir H, Raoult D, Drancourt M. Relapsing fever borreliae in Africa. Am
640 J Trop Med Hyg. 2013;89(2):288-92.
641 72. Diro E, Lynen L, Ritmeijer K, Boelaert M, Hailu A, van Griensven J.
642 Visceral leishmaniasis and HIV coinfection in East Africa. PLoS Negl Trop
643 Dis. 2014;8(6):e2869.
644 73. Simarro PP, Cecchi G, Franco JR, Paone M, Diarra A, Priotto G, et al.
645 Monitoring the progress towards the elimination of gambiense human African
646 trypanosomiasis. PLoS Negl Trop Dis. 2015;9(6):e0003785.
647 74. Scriven JE, Lalloo DG, Meintjes G. Changing epidemiology of HIV-
648 associated cryptococcosis in sub-Saharan Africa. Lancet Infect Dis.
649 2016;16(8):891-2.
650 75. Valero C, Gago S, Monteiro MC, Alastruey-Izquierdo A, Buitrago MJ.
651 African histoplasmosis: new clinical and microbiological insights. Med Mycol.
652 2017.
653 76. Lofgren SM, Kirsch EJ, Maro VP, Morrissey AB, Msuya LJ, Kinabo GD,
654 et al. Histoplasmosis among hospitalized febrile patients in northern Tanzania.
655 Trans R Soc Trop Med Hyg. 2012;106(8):504-7.
656 77. Integrated Management of Adolescent and Adult Illness, acute illness:
657 guidelines for first-level facility health workers at health centre and district
658 outpatient clinic. Geneva: World Health Organization; 2009.
659 78. Integrated Management of Childhood Illness Chart Booklet. Geneva:
660 World Health Organization, 2014.

79. Lubell Y, Reyburn H, Mbakilwa H, Mwangi R, Chonya S, Whitty CJ, et al. The impact of response to the results of diagnostic tests for malaria: cost-benefit analysis. BMJ. 2008;336(7637):202-5.

80. Hopkins H, Bruxvoort KJ, Cairns ME, Chandler CI, Leurent B, Ansah EK, 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.

81. Johansson EW, Selling KE, Nsona H, Mappin B, Gething PW, Petzold M, et al. Integrated paediatric fever management and antibiotic over-treatment in Malawi health facilities: data mining a national facility census. Malar J. 2016;15(1):396.

82. Organization WH. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses: World Health Organization; 2013.

83. IMAI district clinician manual: hospital care for adolescents and adults: guidelines for the management of illnesses with limited-resources. Geneva: World Health Organization, 2011.

84. Huson MA, Kalkman R, Grobusch MP, van der Poll T. Predictive value of the qSOFA score in patients with suspected infection in a resource limited setting in Gabon. Travel Medicine and Infectious Disease. 2017;15:76-7.

85. Moore CC, Hazard R, Saulters KJ, Ainsworth J, Adakun SA, Amir A, et al. Derivation and validation of a universal vital assessment (UVA) score: a tool for predicting mortality in adult hospitalised patients in sub-Saharan Africa. BMJ Global Health. 2017;2(2):e000344.

685 86. Mamuye AT, Bornstein E, Temesgen O, Blumberg HM, Kempker RR.
686 Point-of-care testing for cryptococcal disease among hospitalized Human
687 Immunodeficiency Virus–infected adults in Ethiopia. Am J Trop Med Hyg.
688 2016;95(4):786-92.
689 87. Kethireddy S, Light RB, Mirzanejad Y, Maki D, Arabi Y, Lapinsky S, et
690 al. Mycobacterium tuberculosis septic shock. Chest. 2013;144(2):474-82.
691 88. Katagira W, Walter ND, Den Boon S, Kalema N, Ayakaka I, Vittinghoff
692 E, et al. Empiric TB Treatment of Severely Ill Patients With HIV and Presumed
693 Pulmonary TB Improves Survival. J Acquir Immune Defic Syndr.
694 2016;72(3):297-303.
695 89. Manabe YC, Nonyane BA, Nakiyingi L, Mbabazi O, Lubega G, Shah M,
696 et al. Point-of-care lateral flow assays for tuberculosis and cryptococcal
697 antigenuria predict death in HIV infected adults in Uganda. PloS One.
698 2014;9(7):e101459.
699 90. Cummings MJ, O'Donnell MR. Inverting the pyramid: increasing
700 awareness of mycobacterial sepsis in sub-Saharan Africa. Int J Tuberc Lung
701 Dis. 2015;19(10):1128-34.
702 91. Schroeder LF, Amukele T. Medical laboratories in sub-Saharan Africa
703 that meet international quality standards. Am J Clin Pathol. 2014;141(6):791-
704 5.
705 92. Penno EC, Baird SJ, Crump JA. Cost-effectiveness of surveillance for
706 bloodstream infections for sepsis management in low-resource settings. Am J
707 Trop Med Hyg. 2015;93(4):850-60.
708

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)