

Review

Fever of Unknown Origin in Africa: The Causes Are Often Determined!

Fièvre d'origine indéterminée en Afrique: Les causes sont souvent identifiées

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Abstract

Introduction: In Africa, the presumptive diagnosis of malaria leads to the misdiagnosis and under diagnosis of many other infectious diseases. Certain etiologies of fever of unknown origin (FUO) have a significant prevalence in this continent but are seldom the focus of practitioners or are impossible to diagnose because of a lack of resources.

Methods: In this literature review, we focus on the causes of FUO that are not usually examined by practitioners in Africa, outside of Maghreb. Data were obtained from publications identified by PubMed searches.

Results: Among the FUO etiologies reported in the literature, we were interested by rickettsiosis, borreliosis, Q fever, leptospirosis, dengue, chikungunya, and the Zika virus.

Conclusion: These listed diseases should be part of etiologies that are systematically searched for in the African continent.

Key words: Fever of unknown origin, rickettsiosis, borreliosis, Q fever, leptospirosis, dengue, chikungunya, Zika virus, Africa

Résumé

Introduction: En Afrique, le diagnostic présomptif du paludisme conduit à des erreurs diagnostiques. Certaines étiologies de fièvre d'origine indéterminée (FOI) ont une prévalence significative dans ce continent, mais ne sont pas été évoqués par les praticiens ou impossibles à diagnostiquer en raison du manque de ressources.

Méthodes: Dans cette revue de la littérature, nous serons limités aux causes de FOI généralement non mentionnées par les praticiens en Afrique en dehors du Maghreb. Les données ont été obtenues à partir de publications identifiées dans la base de données PubMed. Nous ne parlerons pas de la fièvre Ebola qui est actuellement l'actualité médicale africaine et mondiale avec plusieurs publications.

Résultats : Parmi ces étiologies de FOI rapportées dans la littérature, nous avons retrouvé plusieurs maladies infectieuses peu diagnostiquées habituellement et nous nous sommes intéressés aux rickettsioses, borrelioses, fièvre Q, leptospirose, dengue, chikungunya et au virus Zika.

Conclusion: Les Rickettsioses, les borrelioses, la fièvre Q, la leptospirose, la dengue, le chikungunya et le virus zika doivent être pris en compte systématiquement parmi les causes de FOI en Afrique.

Mots clés: Fièvre d'origine indéterminée, rickettsiose, borreliose, fever Q, leptospirose, dengue, chikungunya, zika virus, Afrique.

INTRODUCTION

Fevers of unknown origin (FUO) are defined as prolonged febrile illness without an established etiology often despite intensive evaluation and diagnostic testing. The prevalence of different febrile states depends on the location, type of population, local microbiological factors, and available hospital services. In the international literature, causes of FUO are divided into three major groups: infectious, inflammatory, and neoplastic causes [1 – 5]. The rate of non-diagnosed cases of FUO, according to studies published since 1990, varies considerably from 9 to 51% [1, 6].

Tuberculosis is one of the most common infections in several series that deal with FUOs, especially with the advent of HIV [2, 3], followed by other causes, such as deep abscesses and endocarditis, especially if there are negative blood cultures [4].

In Africa, the presumptive diagnosis of malaria without evidence leads to the misdiagnosis and under-diagnosis many other infectious diseases [7, 8]. When the first-line tests are negative, practitioners are often unable to search for other causes of fever. However, infectious causes of fever, such as rickettsial and borreliosis, have a significant prevalence, but are often ignored or under-diagnosed. In Senegal, up to 13% of positive *Borrelia* spp. sera were diagnosed in patients following a FUO very often in association with the cutaneous manifestations [9]. The aim of this study was to make know the medical practitioners of the reality of those diseases in Africa outside the Maghreb.

METHODS

We have limited this literature review to causes of FUO usually not mentioned by practitioners in Africa, outside the Maghreb. Data were obtained

from publications identified by PubMed searches. Search items were combinations of the keywords: “fever of unknown origin”, “Africa”, “sub-Saharan Africa”, “rickettsioses,” “recurrent fever”, “Q fever”, “leptospirosis”, “viral infections”. A secondary manual search of the references cited in these articles was also performed to find relevant articles that had been reviewed. In this review, we will not talk about the Ebola fever, which is currently the focus of African and worldwide medical news with several publications.

REVIEW

In villages and even some African cities, the exploration of fever is limited to a blood smear, which itself often does not respond to the appropriate performance criteria. Some causes of FUO are not mentioned or are impossible to diagnose because of a lack of resources. Etiologies, such as rickettsiosis, borreliosis, Q fever, and leptospirosis, are reported in African studies and are not new infections on this continent. Indeed, older literature has reported cases of rickettsial disease in the Congo since 1954 [6], in west Africa since 1964 [10, 11], and in Sierra Leone and Côte d’Ivoire since 1986 [12]. Since the 1990s, interest has been reprioritized in the literature on these infections [9], and isolated cases have been reported among travelers returning from African countries [13 – 15]. This review of the literature focuses on rickettsial diseases, borreliosis, Q fever, leptospirosis, and some viral etiologies of FUO in Africa.

Rickettsioses

Tick-borne rickettsioses are caused by obligate intracellular bacteria belonging to the spotted fever group from the genus *Rickettsia*. The *Rickettsia* larva multiply frequently at the point of inoculation and produce a bed sore. Their tropism for endothelial cells in small blood vessels explains the appearance of vasculitis and perivascular inflammation. The consequence is fever and purpura around capillary damage [16 – 18].

African tick-bite fever (ATBF) is now recognized as the predominant rickettsial disease in sub-Saharan Africa [14, 15, 19, 20] and is caused by *Rickettsia africae* [21]. African tick fever is transmitted through the bite of the *Amblyomma variegatum* tick and causes multiple bedsores localized mostly in the lower limbs, as well as a mild fever and cutaneous maculopapular rash in 50% of cases, often vesicular, which can reach the palms and soles. African tick-fever is a benign infection [22]. Since 2005, *R. africae* has also been detected in *Rhipicephalus annulatus* ticks (2 to 93%) in Guinea, Senegal, and Nigeria; in *Rhipicephalus evertsi evertsi* ticks (0.4–5%) in Senegal and Nigeria [23 – 25]; in *Rhipicephalus decoloratus* ticks (5–77%) in Nigeria and Botswana

[26]; in *Rhipicephalus sanguineus* (5%) and in *Hyalomma impeltatum* (10%) ticks in Nigeria [25] and in *Rhipicephalus geigy* ticks (14%) in Liberia [27]. *R. africae* has been detected in ticks and/or humans in 22 sub-Saharan African countries. A high *R. africae* seropositivity rate is detected in indigenous populations in rural areas. The seropositivity rates in Cameroon and Senegal are reported as being between 12 and 52% [28].

Apart from *R. africae*, *R. conorii* (the agent of Mediterranean spotted fever) is also encountered in Africa and has been reported in nine sub-Saharan African countries. In a Tanzanian study, published in 2013, etiological research on 870 patients with a FUO showed that of the 528 cases (60.7%) of suspected malaria, only 14 cases (1.6%) were true cases of malaria. Instead, 36 cases (30.5%) were caused by infections from the purple *Rickettsia* group and two (1.8%) from the typhus group [7]. To minimize this inaccurate diagnosis of malaria, many African states have adopted the policy of the using rapid diagnostic tests to diagnose malaria [7]. Brise et al. reported, in 1997, that endemic typhus caused by *R. prowazekii* caused prolonged fever among prisoners of Ngozi in Burundi, with a mortality rate of 2.61% [29]. Parola et al. reported, in two studies conducted in Senegal and Kenya, cases of *Rickettsia felis* infection in patients with a FUO [30]. Between November 2008 and July 2009, Socolovschi et al. demonstrated that *R. felis* had developed in Senegalese patients suffering from a FUO [31].

The development of rapid diagnostic tests to diagnose rickettsial diseases could have an impact on the overall diagnosis of FUOs in Africa.

Treatment of rickettsial diseases is not expensive, even for African countries. It consists of administering doxycycline orally, with the duration of treatment depending on the type of rickettsial disease. In the literature, most patients with African tick-bite fever have been treated with doxycycline (200 mg/day) for 7–10 days, but treatment durations of up to 3 weeks have been reported [15, 18, 32].

Borreliosis: Tick-born relapsing fever (TBRF)

Borrelia species are responsible for relapsing fever in Africa. Three species (*Borrelia crocidurae*, *Borrelia duttonii*, *Borrelia hispanica*) are transmitted by ticks, whereas *Borrelia recurrentis* is transmitted by body lice. These *Borrelia* species result in a febrile infection that mimics malaria with varying severity, but can be particularly devastating during pregnancy when the infection will often cause miscarriage [33].

Epidemiologically, infection with *B. crocidurae* can spread through the African savannah mainly because with the advance of a drought [34].

In Zaire, in a study published in 1997, showed that relapsing fever caused by *B. duttonii* was diagnosed

in 6.4% of pregnant women, and caused morbidity and mortality within this group [35]. Trape et al. reported, in 1991, that recurrent fever caused by borreliosis was a major cause of morbidity in rural areas across much of West Africa. Indeed, they found 12 positive smears in 1340 children in rural Senegal (0.9%) [34].

In Tanzania, *Borrelia* spp. were identified in six children (11%) out of 54 who had a fever and in 13 (4%) out of 307 children who were not febrile [31]. Currently, *B. duttonii* is transmitted by a tick (*Ornithodoros moubata*) in east Africa and *B. crocidurae* is transmitted by *Ornithodoros sonrai* [34].

Among 27 positive samples assessed by PCR, only four (15%) were identified as positive for *Borrelia* by a blood smear performed at the clinic and 15 (56%) by highly skilled microscopists in Dakar [9]. This means that even experienced biologists can miss this diagnosis using only the methods used in African hospitals. Diagnosis of TBRF, as in rickettsia, requires the establishment of adequate resources in African countries and especially the development of TDR.

Several other studies have reported on recurrent fevers in Africa [35 - 38]. *B. crocidurae* has been highlighted in samples from mammals and the examination of ticks taken from 20 villages in southern Mali [38]. Epidemiological studies have shown that 26 of the 30 villages surveyed (87%) were colonized by the tick vector of *B. crocidurae*, and the incidence of relapsing fever in the community was cause of the highest bacterial disease described in Africa. The presence of the tick vector in most of the villages studied and the high infection rates suggest that relapsing fever is a common cause of fever in most rural areas of Senegal, Mauritania, and Mali [38].

Note that, in some areas of Africa, these infections are known by people empirically. In Tanzania, 198 heads of households were interviewed and, of these, 94.5% were aware of the existence of relapsing fever but that 69.5% thought that this fever had an unknown origin [39].

In Togo, between 2002 and 2004, blood samples from patients with fever were examined. Although no spirochetes were seen in blood smears, 10% of the patients were positive by PCR and 13% were seropositive for spirochetes. Most patients were treated for malaria whether or not plasmodia were observed [40].

Except for relapsing febrile episodes, this illness presents with no pathognomonic signs. Relapsing fever caused by *B. crocidurae* is generally benign but neurological or ocular complications can occur. The best treatment for relapsing fever is tetracycline or doxycycline. Western ATBRF must be systematically considered in cases of fever in these countries and if a patient has returned from an endemic area [41].

Q fever

Q fever is caused by *Coxiella burnetii*, which is a zoonotic bacterial pathogen found worldwide, except in New Zealand, and is transmitted to humans through direct contact with milk, urine, feces, or semen from infected animals, as well as from inhalation of aerosolized particles from animal placentas, parturient fluids, aborted fetuses, and environmental dust [42, 43]. While infection with *C. burnetii* in humans can be asymptomatic, symptomatic infection, known as Q fever, can present as an acute undifferentiated febrile illness with the possibility of focal manifestations, such as hepatitis and pneumonia. Acute disease can also progress to chronic forms, such as endocarditis in 0.5–2.0% of cases [44, 45], typically in individuals predisposed by valvular heart disease or immunodeficiency.

Many studies in Africa have evaluated animals carrying *C. burnetii*, but not in humans [46 – 48], and the published criteria for the diagnosis of chronic Q fever are difficult to apply in Africa and have little scientific relevance [42, 43]. In the countries of sub-Saharan Africa, the seroprevalence of antibodies reactive to *C. burnetii* varies greatly; the generally higher figures for West Africa, where stock breeding is prominent, suggest that domestic animals may be the main reservoir of infection [49]. *C. burnetii* was first reported in Africa in 1947, but since then the quantity and quality of epidemiologic research on this pathogen has been limited [50]. In Maradi, a region of Niger, 32% of goats with previous abortions were seropositive, compared to 29% of non-randomly selected goats without a history of abortion [48]. In two studies of patients admitted for community-acquired pneumonia in Yaounde and Douala (Cameroon), 6% and 9% of persons had serologically-confirmed acute Q fever [51, 52]. In these studies, Q fever was the third most common etiologic agent of pneumonia, after *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*. A review of the literature, published in April 2014 by Sky Vanderburg et al. concerning Q fever in Africa, found 17 published articles. They identified no estimates for this disease's incidence, and the majority of research undertaken had limited validity due to the nonrandom sampling procedures used. Further, only two investigations using random sampling procedures have linked human and animal-livestock populations [42, 43].

In the Republic of Guinea, the proportion of people who are sera positive to *C. burnetii* is in the range of 0.8–10.5% (or $2.4 \pm 0.3\%$) on average; in livestock, the range is 3.2–18.7% (or $8.0 \pm 0.6\%$) on average [53].

Hoek et al. report that exposure to *C. burnetii* can be considerable in the early years of life in the Gambia, with IgG and/or IgM phase-II antibodies positive in 8.3% (66/796) of children aged 1–15

years [54]. Mediannikov et al. found, in Senegal, a seroprevalence of *C. burnetii* to be as high as 24.5% (59 of the 238 people studied) in Dielmo village; the bacteria was recovered from the soft tick (*Ornithodoros sonrai*) [55]. In West Africa, there is evidence of exposure to the organism amongst patients with fever in Mali [56]: blood samples from 156 febrile patients in healthcare facilities at Bamako and Mopti showed 70% (n = 63) seropositivity for Q fever (28% in Bamako and 51% in Mopti). In a study conducted by Anna et al. in Togo, the people of Fulani ethnicity had greater contact with livestock and also had a significantly higher seroprevalence of Q fever than other ethnic groups (Fulani: 45.5%, 95%CI:37.7–53.6%; non-Fulani: 27.1%, 95%CI:20.6–34.7%) [57]. In Tanzania, Q fever was diagnosed in 24 cases (20.3%) of FUO [7].

Leptospirosis

Leptospirosis is a zoonosis caused by spirochetes from the genus *Leptospira*; these bacteria have a variety of mammalian hosts, particularly rodents. The bacterium enters the bloodstream via abrasions in the skin or through mucous membranes after contact with contaminated moist soil, water, or aerosolized droplets. Often, environmental contamination arises when leptospires are shed in the urine from infected animal reservoirs, such as rodents, cattle, pigs, and various wild animals. Leptospirosis is also transmitted to humans by direct contact with tissue or urine from infected animals. Human-to-human transmission is rare [58]. Leptospirosis complications are cardiac, renal, and pulmonary failures. Pulmonary findings for patients with leptospirosis have been reported in 17–70% of patients in several large studies and include hemoptysis, respiratory distress, cough, difficulty in breathing, and pulmonary hemorrhage [59]. Like in rickettsiosis, borreliosis and Q fever, doxycycline is the first-line treatment and is given for 7 to 10 days.

The incidence of leptospirosis is uncertain in sub-Saharan Africa [60]. Several studies in countries have shown that leptospirosis may comprise a substantial proportion of acute febrile illnesses [61 – 64, 7]. Biggs et al. estimated the incidence of leptospirosis in two districts in the Kilimanjaro region of Tanzania using data from a hospital-based surveillance of 810 households. Patients residing in the two districts were enrolled in fever surveillance over a 1-year period: 42 (7.14%) out of 588 met the case definition for confirmed or probable leptospirosis. The authors estimated that the overall incidence of leptospirosis ranged from 75–102 cases per 100,000 persons annually [65]. In the other Tanzanian study, of 870 cases of FUO; leptospirosis was diagnosed in 40 cases (33.9%) [7]. In a cross-sectional survey of rodents in the

Kibera settlement of Nairobi (Kenya): 41 (18.3%) of the 224 rodents carried pathogenic leptospires in their kidneys, and the authors showed that there was frequent contact between humans and rodents in this zone [66].

According to the World Health Organization, a leptospirosis-confirmed outbreak that occurred at two schools in western Kenya in 2004 involved more than 141 suspected cases and eight deaths [67]. Several patients assessed during an outbreak of acute febrile illness in northeastern Kenya in 2005 were positive for antibodies against *Leptospira* [68]. Other published data on leptospirosis in Kenya date back to the 1960s and 1970s, and describe cases in humans in several provinces [63, 69, 70].

Dengue and chikungunya

Chikungunya and dengue are both arboviruses responsible for febrile illnesses in sub-Saharan Africa. Human infection with either virus is associated with fever, arthralgia, malaise, headache, and cutaneous rash. *Aedes aegypti* and *Aedes albopictus* are the primary vectors in chikungunya virus (CHIKV) and dengue virus (DENV) epidemics in sub-Saharan Africa [71 – 73], but the viruses are also maintained in some parts of Africa in sylvatic cycles involving primates and forest-dwelling *Aedes* species [71].

CHIKV was first isolated and described during an epidemic in Tanzania in 1952 [74]. Since then, periodic CHIKV outbreaks have been reported across the African continent [73, 75, 76]. Although several DENV epidemics have been reported in sub-Saharan Africa [77–79] DENV infection is likely to be considerably underreported because of the limited diagnostic capacity and its misclassification as malaria [80].

The majority of studies on DENV and CHIKV have been published in countries of central and East Africa. In two hospitals in the Kilimanjaro region of Tanzania, a prospective study enrolled 870 febrile in-patients between 17 September 2007 and 31 August 2008. Among these patients, PCR testing was performed on 700 (80.5%). Of these, 55 (7.9%) had an acute CHIKV infection whereas no participants had an acute DENV infection. Anti-DENV IgM serologic testing was performed in 747 (85.9%) participants and, of these, 71 (9.5%) had a presumptive acute DENV infection. Anti-DENV IgG serologic testing was performed on 751 (86.3%) of the participants [81].

In Gabon, between 2007 and 2010, 4287 acutely febrile patients were investigated for CHIKV and DENV-2 infections, of whom 1567 were CHIKV positive, 376 were DENV 2–positive, and 37 were co-infected [82].

Ananda et al. published a literature review on the occurrence of dengue in Africa between 1960 and 2010; they found a total of 22 African countries

reported sporadic cases or outbreaks of dengue, whereas 12 other countries reported dengue only in travelers. The high prevalence of antibodies to the dengue virus is limited in the high number of serologic surveys, which suggests endemic dengue virus infection occurs in all or many parts of Africa. Dengue is likely under-recognized and under-reported in Africa because of its low awareness by health-care providers, the presence of other prevalent febrile illnesses, and the lack of diagnostic testing and systematic surveillance [83]. During the 50 years between 1960 and 2010, twenty laboratory-confirmed dengue outbreaks were reported in 15 countries in Africa; most were from eastern Africa. Nearly 300,000 cases were reported in five large epidemics in the Seychelles (1977–1979), Réunion Island (1977–1978), Djibouti (1992–1993), Comoros (1992–1993), and Cape Verde (2009) [84–87].

DENV was first isolated in Nigeria in the 1960s [88]. Subsequently, all four DENV serotypes have been isolated in Africa [89]. DENV-2 has been reported to have caused most of the epidemics, followed by DENV-1 [86, 87].

In Angola, as of May 2013, a total of 517 suspected cases of dengue fever have been reported and tested for using a rapid diagnostic test. A total of 313 (60.5%) specimens tested positive for dengue, including one from a patient who died [90].

In West Africa, epidemiological studies or case reports have been reported by travelers.

Marycelin et al. reported arbovirus co-infection was detected in 310 sera samples collected from febrile, clinically suspected malaria/typhoid patients in Borno State (Nigeria). Of the 285 samples, 193 (67.71%) had antibodies against DENV and 143 (50.17%) against CHIKV [91].

In Mali, of the 93 human serum samples tested, the prevalence of dengue, based on a dengue IgG enzyme-linked immunosorbent assay, was found in 93%. Three DENV-specific positive samples were identified by a plaque-reduction neutralization test [92]. Gautret et al. and Moi et al. also reported cases of dengue in travelers returning from Bénin [93, 94].

Other viral causes

The majority of symptoms from other viral causes are anorexia, rash, asthenia, retro-orbital eye pain, edema, lymphadenopathy, and diarrhea [95 - 99]. This non-specific clinical presentation can be confused with most other arboviruses, particularly dengue and chikungunya virus infections.

In Gabon, sample collections, including 4312 sera from patients presenting with painful febrile disease and analyses of 4665 mosquitoes belonging to nine species, were split into 247 pools (including 137 pools of *Aedes albopictus*). These were screened using molecular-biology methods. Results showed five human sera and two *A. albopictus* pools, all

sampled in an urban setting during the 2007 outbreak, were positive for the flavivirus Zika (ZIKV) [100].

In West Africa, the Zika virus was also reported in Sénégal where the authors developed a rapid, sensitive and specific test (rRT-PCR) for detection of ZIKV. This assay is a useful tool for detection of ZIKV infection in regions where a number of other clinically indistinguishable arboviruses, such as dengue or chikungunya, co-circulate. The expansion of ZIKV outside Africa shows the need to develop rapid assays and specific monitoring of this virus. Rapid detection of the virus in field-collected specimens can accelerate appropriate mosquito-control measures, which could prevent transmission of disease among the human population [101 - 102]. Importantly, we believe that the development of TDR is essential in Africa for the diagnosis of many infectious diseases, as Sokhna et al. have shown in a study in Senegal [103].

CONCLUSION

The groups of rickettsiosis, borreliosis, Q fever, leptospirosis, dengue, chikungunya, and Zika virus should become part of etiologies that are systematically searched for in the African continent. The non-expensive treatment of doxycycline can treat four of the bacterial diseases. In addition, diagnostics can be improved with the development of rapid tests. Given that malaria is still the most frequent disease in tropical countries, the practitioner must think the possibility of combination of those infectious.

COMPETING INTERESTS

The authors declare no competing interest.

AUTHORS' CONTRIBUTIONS

All the authors were involved in designing and implementing the programs that are described in this manuscript. All the authors participated in drafting this manuscript, and reviewed and approved the final draft.

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