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New concepts for the old challenge of African relapsing fever borreliosis

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Abstract

Relapsing fever, caused by spirochaetes belonging to the genus *Borrelia*, was once the cause of worldwide epidemic disease. This was largely through infection with the louse-borne form of the disease, caused by *Borrelia recurrentis* (louse-borne relapsing fever (LBRF)). During the last century, we have witnessed the demise of this infection, largely owing to improved standards of living and the introduction of the insecticide DDT, resulting in a reduction in the incidence of the body louse, the vector for relapsing fever. In areas of extreme poverty this disease persists, causing a significant burden of disease. It is now looking probable that this infection is caused by a louse-adapted variant of *Borrelia duttonii*, transmitted by *Ornithodoros moubata* 'soft' ticks in East Africa. Like LBRF, infection still causes impact, particularly affecting young children and pregnant women. Over recent years, the true burden of relapsing fever caused by infection with the closely related *Borrelia crocidurae*, transmitted by *Ornithodoros sonrai* ticks, has only just begun to emerge. Here, the current state of knowledge concerning relapsing fever in Africa is reviewed.

Keywords: *Borrelia*, louse-borne relapsing fever, spirochaetes, tick-borne relapsing fever
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Background

In countries such as Ethiopia, infestation with clothing lice remains commonplace; for example, 66.8% of schoolchildren were found to be infested in a study by Tesfayohannes [1]. Transmission may be further increased through habitual crushing of lice between fingers, thus liberating spirochaete-infected material (Fig. 1). The tick-borne form of the disease persists in endemic foci around the world (tick-borne relapsing fever (TBRF)). Despite the general reduction worldwide, the disease remains a significant burden in several African nations. Indeed, TBRF has been reported to be the most common bacterial infection in Senegal [2], and is usually listed among the top ten causes of mortality in children under 5 years of age in Tanzania [3]. Here, it is responsible for alarming perinatal mortality, with rates of 463/1000 in endemic regions [3,4]. In Ethiopia, louse-borne relapsing fever (LBRF) is, again, among the top ten reasons for hospital admission (countrywide), is associated with significant morbidity and mortality (Table 1), and is largely perpetuated by poverty. Although a decline has been reported in some regions [5], in others, LBRF can account for 27% of hospital admissions [6].

Traditional Concepts

Nomenclature has traditionally involved a combination of the disease vector and the geographical region in which infection was acquired. In Africa, relapsing fever has classically been assumed to result from *Borrelia crocidurae* in the west and *Borrelia hispanica* in the north, whereas the tick-borne *Borrelia duttonii* and the louse-borne *Borrelia recurrentis* persist in the east. These assumptions could not be tested in the absence of diagnostic methods with discriminatory power sufficient to identify or type the causative spirochaetes.

All four agents result in relapsing fever; however, subtle clinical differences have been correlated with infecting species. This is particularly evident with epitasis among patients with LBRF (Table 1), whereas *B. duttonii* results in a particularly poor prognosis during pregnancy [4]. *B. crocidurae* and *B. hispanica* account for high fever, frequent neurological complications and up to nine recurrences over several months, but mortality appears to be much lower with these two species than with *B. duttonii* and *B. recurrentis*. In Senegal, no deaths occurred among 521 patients from various areas, and only one of 16 infections that arose in pregnant women

FIG. 1. Mother delousing her child in Ethiopia.

provoked early delivery [2,7]. Among case reports of patients hospitalized for TBRF in Dakar since 1934, only a single death has been reported [8] among the several hundred patients who were included in these studies [9–14].

LBRF reached epidemic proportions during the first half of the last century, devastating populations as it ravaged the globe. In Africa, the most dramatic epidemics occurred after World Wars I and II, when French and British colonial soldiers returned to their countries. The first epidemic, in West Africa, lasted from 1921 to 1929, and was responsible for 60 000 deaths [15]. During World War II, 400 000 cases were observed in Algeria, 400 000 in Tunisia, 180 000 in Morocco, and 1 300 000 in Egypt [16–18]. In the following years, the epidemic reached at least 15 additional African countries, from Senegal to Sudan. Associated mortality was high, resulting in the documentation of this form of the disease as having greater severity than its tick-borne counterparts. However, patients rarely succumbed to more than four episodes of fever, whereas more numerous, albeit less severe, febrile episodes followed TBRF, with anything up to 13 relapses occurring [19]. Mortality from the louse-borne form of the disease can be high, in excess of 30% of untreated cases; however, with appropriate treatment, this can be reduced to 2% to 6% [6,20] (Fig. 2). Shaving the hair of cases, coupled with boiling of their clothes immediately after diagnosis, can reduce further transmission of infection. Treatment itself can be problematic, with up to 76% of cases exhibiting a Jarisch–Herxheimer reaction, particularly when spirochaete numbers are high [6]. The dogma that LBRF shows seasonality, typically manifesting during the rainy season, has been challenged by studies of infection in more rural settings. Here, significantly more infection is seen in the dry season, coinciding with the coffee-harvesting period, probably associated with temporary migration of highlanders seeking employment [20].

TABLE 1. Major presenting signs of LBRF among a cohort of 106 cases [6]

Clinical Signs	Number (n=106)	Percentage
Fever	106	100
Tachycardia	104	98
Headache	101	95.3
Myalgia	98	92.5
Arthralgia	98	92.5
Hepatosplenomegaly	71	67
Epistaxis	32	30.2
Peticheal rash	8	7.6
Other*	3	2.8
Jaundice	1	0.9

*Other symptoms included pneumonia; still-birth; and unconsciousness.

The characteristic gene conversion leading to multiphasic antigenic variation of these spirochaetes is pivotal in the aetiology of recurrent febrile episodes, and has attracted significant research interest over recent years. Indeed, it now appears that antigenic variation is mediated through gene conversion events at a unique telomeric expression site. This has been shown to be on the 23-kb linear plasmid of *B. recurrentis* [21] and a plasmid of equivalent size in *B. duttonii* [22]. Pivotal to gene conversion events are an upstream homology sequence proximal to the expression start codon and an extragenic downstream homology sequence through which recombination cross-over events occur [19,23]. During antigenic switching, the expressed gene is displaced by an achieved copies of variable antigen genes, usually residing on the linear plasmids of these spirochaetes.

Epidemiological Investigations

Obtaining sound epidemiological information is challenging, in part because of the dogma that all febrile episodes are a result of malaria. Indeed, many cases of relapsing fever present as 'treatment-resistant malaria', as reported in studies from Togo, where patients are often misdiagnosed as malaria cases [24,25]. Malaria co-infection with relapsing fever has been reported from Ethiopia and Tanzania [26]. Generally, only LBRF is a reportable infection; however, the reported data are likely to represent a vast underestimation of the true burden of disease. Despite this, in Ethiopia, LBRF is listed in a recent Ministry of Health report (2004) as the seventh most common reason for hospital admission (2.5% of total; 3777 cases) and the fifth most common cause of death (0.9%; 42 cases). Furthermore, epidemics of variable scales occurred during 2004 and 2005 in Oromia and southern regions of Ethiopia (2004 and 2005, Ministry of Health Reports).

Data concerning the prevalence of TBRF are difficult to obtain, with most estimates being made on the basis of

FIG. 2. Clinical case of louse-borne relapsing fever.

sporadic localized studies. These, however, have suggested that, in East Africa, the major burden of disease particularly affects the young, the elderly, and pregnant women. Estimates of impact during pregnancy are high, especially associated with *B. duttonii* infection, with 6.4% of cases being reported among hospital admissions of pregnant women, often associated with adverse outcomes, in the Democratic Republic of Congo [27]. Studies from Tanzania have reported total pregnancy loss rates of 475 per 1000 births in endemic areas, with 58% of those infected during pregnancy having premature deliveries [28].

In West Africa, *B. crocidurae*, a zoonotic relapsing fever spirochaete, predominates, and the human burden of infection has been determined to be the most significant of all bacterial infections affecting the human population. In a study conducted in a dispensary near Dakar (Fig. 3), *Borrelia* infections were observed in 4% of children of between 5 and 14 years of age, 2% of children between 2 and 4 years of age, and 0.5% of children between birth and 1 year of age [29]. During population follow-up over 14 years in a Senegalese village, the average incidence of TBRF was 11 per 100 person-years, and

FIG. 3. Relapsing fever investigations in Mali.

FIG. 4. *Ornithodoros sonrai*, the soft tick vector of *Borrelia crocidurae* in West Africa.

all age groups were afflicted with a high incidence of the disease [2]. In some years, up to 25% of this community suffered from the disease. In areas endemic for *Ornithodoros sonrai* in Senegal, Mali, Mauritania, and The Gambia, between 2% and 70% of animal burrows are inhabited by this tick vector, and an average of 31% of individual ticks are infected by *B. crocidurae* (Fig. 4) [2,30,31]. Rodent burrows are found in almost all households, with burrows opening inside bedrooms of both traditional mud-built huts and houses with cement floors and walls (Fig. 5). Transmission is mainly nocturnal, with ticks biting humans during their sleep. The bite is painless, and blood meals last from a few minutes to half an hour. Principle reservoirs for this spirochaete include at least 11 species of wild rodents and insectivores; the most important epidemiologically are the multimammate rats *Mastomys erythroleucus* and *Mastomys huberti*, the Nile rat *Arvicanthis niloticus*, and the giant Gambian rat *Cricetomys gambianus* [7,11,32].

B. hispanica TBRF is endemic to Morocco, Algeria, and Tunisia, mainly occurring along the coast and among the Tell

FIG. 5. Rodent burrows in human dwellings being investigated for the presence of *Ornithodoros sonrai* ticks.

mountains. It is transmitted by *Ornithodoros erraticus*, which inhabits the burrows of a number of rodents and other small mammals [18]. In endemic regions of Morocco, up to 50% of the rodent burrows are colonized by either *O. erraticus* or by *O. sonrai* [33]. Exposure appears to correlate with sleeping in the open, whereby contact is facilitated through proximity to rodent burrows and their ticks. The incidence in humans is poorly documented, but seems to be much lower than the incidence in West Africa of *B. crocidurae*, probably because of better quality of housing. Several cases are detected each year as part of malaria surveillance programmes, but the true incidence of the disease remains unknown.

On a more cautionary note, it must be remembered that microscopy is primarily used for diagnosis, and is a technique with low sensitivity that does not distinguish among infecting species (Fig. 6). Consequently, assumptions as to the causative species for relapsing fever are usually based on geographical location and vectors. Vector competence studies were undertaken during the 1950s; however, these were hampered by the lack of cultivable strains and of diagnostic tools able to discriminate among species. In addition, the sensitivity of microscopy varies according to *Borrelia* species. The blood density of spirochaetes of febrile patients is particularly low for *B. crocidurae* and *B. hispanica*, with 95% of samples possessing <200 *Borrelia* organisms per microlitre of blood, mostly with <20/μL. Conversely, the spirochaete density for *B. duttonii* is often ten times higher, and that for *B. recurrentis* is higher still; this might, in part, explain the differences in severity of the disease.

Despite the epidemic potential of the louse-borne form of disease, adaptation to louse-borne transmission may represent an evolutionary bottleneck, resulting in the recently observed demise of LBRF. Indeed, it is now believed that disease persists only in Ethiopia, occasionally spilling into neighbouring countries, possibly in association with the recurrent famines and drought affecting these areas. Vector transmission studies from the 1950s suggested that LBRF retained its potential for tick-borne transmission; however, this remains to be substantiated in a natural setting. Intriguingly, recent phylogenetic studies have shown identical intragenic spacer types in both lice and ticks; however, further validation of these findings through sequencing of other gene targets remains to be performed [34].

FIG. 6. Laboratory diagnosis at a health clinic in Jimma, Ethiopia.

Emerging Challenges to Conventional Paradigms

The finding of overlapping genotypes between *B. recurrentis* and *B. duttonii*, based on intragenic spacer typing, challenges the dogma that these are separate species [35]. Indeed, complete genomic sequencing provided further evidence that *B. recurrentis* is a louse-adapted variant of *B. duttonii* [22]. It is tempting to speculate that tick-borne ancestral strains may exist where these diseases geographically overlap. Currently used diagnostics would be unlikely to discriminate among these infections. Furthermore, if LBRF were to be eliminated through sustained delousing of the population (Fig. 1), what would prevent a parallel evolutionary event?

Transmission of LBRF has, until recently, been considered to necessitate the crushing of infected lice into skin abrasions, thus facilitating contact of infected haemolymph from the louse with its human host. This dogma has now been challenged through the findings of Houhamdi and Raoult, who demonstrated that *B. recurrentis* could be detected in louse feeding following experimental infection [36]. Excretion in faeces continued over a prolonged period of the louse lifespan, thus providing a more efficient means of transmission, through excretion of *B. recurrentis*, than transmission via crushing of lice alone. This route has also been described for the louse-borne *Rickettsia prowazekii* and *Bartonella quintana* [36]. In agreement with earlier literature, there was not, however, transmission from infected lice to their progeny, unlike with infection in ticks.

East African relapsing fever has been considered to be a disease of humans alone, with the arthropod vector serving as a disease reservoir. Conversely, other relapsing fever borreliae have a broader host range, typically involving small mammals. By analogy with this, an extended vertebrate host range for East African relapsing fever has been sought. As the ticks reside in and close to human dwellings (Fig. 5), it appeared reasonable to investigate other vertebrates living within typical traditional housing. Preliminary investigations of rats and chickens as alternative reservoirs of infection

failed to produce conclusive evidence of expansion of infection beyond the human host, possibly because of small study sample sizes (unpublished findings). More recently, some evidence has been provided, with the finding of *B. duttonii* DNA in chickens and swine living close to their human owners [37]; however, no attempt was made to demonstrate transmission competence from these hosts, and this may merely reflect 'accidental spill-over' from human infection.

Analysis of ticks from endemic regions of Tanzania has revealed a surprising finding of another *Borrelia* species [26,38]. These findings have been corroborated by other groups investigating ticks from the same region [34]. Phylogenetic analysis suggested greater resemblance to relapsing fever species present in the USA than to isolates from cases of Old World relapsing fever. Despite their presence in ticks collected from local dwellings and in some healthy children, these *Borrelia* species have only rarely been detected in clinical samples from symptomatic individuals [26,34]; thus, their pathogenic potential remains to be established.

The characteristic gene conversion leading to multiphasic antigenic variation of these spirochaetes is pivotal in the aetiology of recurrent febrile episodes, and has attracted significant research interest over recent years [19,23]. It was held that blood persistence on the part of these spirochaetes was entirely a result of their ability to undergo multiphasic antigenic variation; however, it now appears that a combination of factors, such as the ability to bind factor H and factor - H-like proteins, among other mechanisms, collectively assist prolonged survival within the blood [39–41].

Post-genomic Insights into African Relapsing fever

The recent publication of full genome sequences for *B. recurrentis* and *B. duttonii* relapsing fever spriochaetes has provided opportunities to gain insights into the relationship between these organisms, with *B. recurrentis* appearing as a louse-borne derivative of *B. duttonii* [22]. Furthermore, several intriguing features were noted for *B. recurrentis*, such as the apparent truncation of *recA*, required for DNA repair; similarly, *mutS* and *smf*, which work in conjunction with *recA*, appeared to be non-functional, possibly hastening evolution in this spirochaete. The absence of any unique features within *B. recurrentis* that were not already present in *B. duttonii* strongly supports its ancestral lineage from within *B. duttonii*. Furthermore, the reduced numbers of variable membrane protein genes detected within *B. recurrentis*, as compared with its tick-borne counterpart, is in concordance with clinical observations of fewer relapses among patients with LBRF.

Full genomic sequencing has also enabled comparison of these relapsing fever spirochaetes with the phylogenetically related Lyme borreliosis spirochaetes over a total of 773 parologous chromosomal genes [22]. This revealed significant conservation of not only gene content, but also localization. Only 13 genes were specific to Lyme-associated spirochaetes, whereas 17 were unique to the relapsing fever borreliae. This is likely to form the genetic basis for the cross-reactivity frequently observed in serological assays (excluding the *GlpQ* assay mentioned below). Significant divergence became apparent when the plasmid contents of these spirochaetes were compared [22].

We have explored the relationship among these spirochaetes circulating in both Tanzania and Ethiopia by sequencing an intragenic spacer region [34]. Previously reported groupings among these species described for cultivated spirochaetes and those detected among arthropod vectors were confirmed using 123 sera from patients from Ethiopia and Tanzania (unpublished observations). Similarly, the geographical demarcation of these spirochaetes was called into question, with the finding of intragenic spacer region types resembling *B. crocidurae* normally found in West Africa.

It has been hypothesized that full genomic sequencing of two similar strains, one louse-borne and the other tick-borne, might disclose the basis of louse adaptation as opposed to tick-borne transmission. At this stage, the genetic basis for vectorial specificity remains elusive. The basis of vector specificity has fascinated spirochaetologists for many years [42].

Along parallel lines, it was anticipated that the apparent greater severity of LBRF than of its tick-borne counterpart might be explained by the results of full genomic sequencing. Currently, it is difficult to extract such information from these sequences to determine the factors governing differential virulence; however, significant reduction of variable membrane protein genes is evident for *B. recurrentis*, as compared to their tick-borne counterparts, with only one variable membrane protein gene every 18 kb and one every 9.5 kb, respectively, suggesting a reductive evolutionary path [22]. The high numbers of pseudogenes further support this theory of evolutionary decay [22].

Future Perspectives

Arguably, the most significant area for development in order to understand African relapsing fever is improved detection and typing of this spirochaete. Currently used microscopy-based diagnostics could be improved in terms of sensitivity

FIG. 7. Significant milestones for relapsing fever.

through concentration of the pathogen by light centrifugation, to assist visualization of spirochaetes. Diagnosis is too frequently missed through erroneous labelling of these febrile patients as malaria cases, leading to the assumption that the disease is a microbiological curiosity.

Increasing levels of business travel and tourism to destinations such as Africa have been associated with subsequent infection, often manifesting once the travellers are back in their country of residence [43,44]. Reliance upon automated diagnostics can present subsequent challenges for detection of such cases. Serological methods for diagnosis have been developed, based on the *Glp*Q gene product, which is present in relapsing fever spirochaetes, but absent in their close relatives, the Lyme borreliosis spirochaetes [45].

Our understanding of the biology of these organisms is still in its infancy. Persistence within the blood of an infected patient is an essential prerequisite for successful transmission to uninfected arthropod vectors. Whether antigenic variation and currently disclosed pathophysiological interactions are sufficient alone to sustain the numbers of spirochaetes in the blood needed to infect, for example, a louse remains to be tested. It is similarly plausible that, as with American relapsing fever, variable membrane protein expression may influence tissue tropisms of these spirochaetes. However, unlike for their American counterparts, animal models have proven difficult to establish, or even refractory to infection, as in the case of *B. recurrentis*, thus making investigation of host–microbial interactions challenging.

Phenomena such as 'rosetting' have been described for these spirochaetes [46,47], originally hypothesized to be an additional means of host evasion; however, more recent investigations have suggested that spirochaetes may be harvesting essential hypoxanthine purine metabolites from red blood cells, for which the *purA*, *purB* and *hpt* genes are essential [48,49]. This trait has been described for both *B. crocidurae* and *B. duttonii*, but not for *B. recurrentis*.

In summary, our understanding of African relapsing fever spirochaetes is increasing (Fig. 7). The causative borreliae have shown marked changes in their distributions and prevalence, but they remain significant and largely ignored infections on a global level. Improved education and awareness of these infections, coupled with better detection and typing of the spirochaetes, are essential if we are to manage relapsing fever effectively. Although control of those species with animal reservoirs is more challenging, infections with those species prevalent in East Africa could be reduced through prevention of louse infestations and reduction of the exposure to tick vectors of the disease.

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Transparency Declaration

The authors declare no conflicts of interest.

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