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Mini Review

Epidemiology of Relapsing Fever *Borreliae* in Uganda

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Abstract

Borrelia spp. include the agents of Lyme disease and the relapsing fever group; tickborne and louse-borne relapsing fever in humans and animals. They are Gram-negative spirochaetes. There are 42 species in the Borrelia genus: 21 in the tickborne relapsing fever (TBRF) group, 20 in the Lyme-Borreliosis (LB) group, and one (B. turcica) associated with reptiles with unknown pathology in wildlife, domestic animals, or humans. The LB groups are split into B. burgdorferi sensu stricto (s. s.) causes disease in both humans and animals and B. burgdorferi sensu lato (s. l.) mainly causes disease in humans. Relapsing fever borreliae are a group of ectoparasite-borne, fastidious bacteria causing a variety of febrile presentations, notably malaria-like symptoms. Borrelia spirochetes transmit to humans tick-borne endemic relapsing fever (TBRF) and lice-borne epidemic relapsing fever. East African Relapsing Fever Borrelia spp. includes: endemic East African tick-borne relapsing fever Borrelia duttonii spirochetes and epidemic louse-borne relapsing fever (LBRF) B. recurrentis spirochetes. The management of febrile illnesses represents a big challenge in sub-Saharan Africa. Until recently most of them were considered as malaria. However, it was shown that a large part of non-malarial febrile diseases in African rural regions may be caused by tick-borne infections. Pathogenic bacteria are responsible for many infectious diseases like Rickettsia (spotted fevers), Borrelia (relapsing fevers), Anaplasma, Ehrlichia (ehrlichiosis and anaplasmosis) and Coxiella burnetii (Q fever). As in other sub-Saharan African countries, tick-borne diseases may be considered as a health care problem in Uganda.

Keywords: Borrelia, Lice, Relapsing fever, Ticks, Uganda.

Introduction

Ticks are a major group of the hematophagous arthropods, and they are a concern for both public and veterinary health because they infest a wide variety of mammals all over the world, including domestic animals, ruminants, wild animals, and humans. Ticks feed on the blood of mammals, and they can transmit diseases to humans (Adenubi *et al*., 2018). They are prevalent in semiarid regions, bushes, and forests, and are known to harbor a wide variety of disease-causing pathogens (Wu *et al*., 2013). *Borrelia hispanica*, *Borrelia crocidurae*, *Borrelia duttonii*, and *Borrelia recurrentis* were given their own classifications based on geography and the vector they were associated with, along with the unproven hypothesis that each species was only associated with a single vector. In the study of epidemiology, hosts and ectoparasites in Africa, as well as the vector association of these pathogens for Africans and visitors to Africa, are taken into consideration. Relapsing fever *borreliae* can present itself in a number of different ways, the most common of which are symptoms similar to those of malaria (Cutler *et al*., 2009). Arnould, a French Army doctor working in Algeria in March 1866, was the first person to describe the disease in a clinical setting in prison inmates (Ministe´re de la Guerre, 1931). This was then followed by the detection of the bacteria by microscopic means in the blood of febrile patients two years later (Obermeier, 1873), and confirmation (Cook, 1904). Additional evidence of confirmation comes from the finding in *Ornithodoros moubata* ticks (Dutton and Todd, 1905). Nicolle and colleagues (1913) demonstrated that relapsing fever could be transmitted by lice (Mackie, 1907; Nicolle *et al*., 1913). Ornithodoros ticks are responsible for the transmission of the endemic tick-borne relapsing fever spirochetes; *O. sonrai* serve as the principal vector for *Borrelia crocidurae* in West Africa, and *O. moubata* complex ticks effectively maintain these spirochetes in East Africa (Cutler *et al*., 2009). Studies have shown that *Borrelia recurrentis*, the bacteria responsible for louse-borne relapsing fever, and *Borrelia duttonii*, the bacteria responsible for East African tick-borne relapsing fever, are similar (Ras *et al*., 1996; Scott and Wright, 2005; Cutler and Scott, 2008).

In the year 1868, Berlin was struck by a widespread epidemic of recurrent fever. Borrelia was found in the blood of febrile patients while being examined by Dr. Otto Obermeier, a young physician 25 years old who worked at the Berlin Charité Hospital (Burgdorfer 2001). In 1873, Obermeier published the results of his research (Obermeier 1873). Five years after his discovery of relapsing fever (RF), he passed away as a result of injecting himself with blood taken from a patient who was on their deathbed. The human body louse Pediculus humanus humanus was shown to be the vector of relapsing fever spirochetes by the French microbiologists Sergent and Foley (Sergent and Foley 1910). Later on, in 1904 and 1905, a number of researchers, including Cook in Uganda, Ross and Milne in the same region, and Dutton and Todd in the Congo, independently discovered that spirochetes were the cause of Dr. Livingstone's tick fever. They presumed that it was the same pathogen as *Spirochaeta obermeieri*, which is carried by the *Ornithodoros moubata* tick (Ross and Milne 1904; Dutton and Todd 1905). Dutton passed away as a result of becoming unintentionally infected while working on the autopsy. In his honour, the species *B. duttonii* was given its name. It wasn't until 1981 that the agent that causes Lyme disease, *B. burgdorferi*, was identified. It was found in the midgut of *Ixodes dammini* ticks while researchers were looking for *Rickettsia*, which causes spotted fever (Burgdorfer, Barbour, *et al.* 1982). During the epidemic that lasted from 1843 until 1948 in Edinburgh, the term "relapsing fever" was first used (Southern and Sanford 1969). Spirochetes which are a part of the genus *Borrelia* are the pathogens that cause relapsing fever. The bacteria have a shape similar to waves and measure approximately 10 micrometers in length. The flagellae of the spirochetes are located in the periplasmic space, which is connected to the cytoplasmic membrane and the outer membrane by a hook-shaped basal body. This allows the spirochetes to move very quickly.

Borrelia recurrentis is thought to be a louse-adapted form of *B. duttonii* (Lescot *et al*., 2008). *Borrelia recurrentis*, a spirochaete that causes relapsing fever, is a pathogen that only infects humans and is transmitted via the human body louse, *Pediculus humanus humanus*. Infestations are associated with congestion, poverty, and lack of attention to personal cleanliness. There is a high mortality rate associated with this illness, ranging from 10% to 40% in untreated cases to 2-5% in people who have received therapy. Antibiotic therapy can trigger a Jarisch-Herxheimer response, which can be life-threatening if left untreated.

The human *Pediculus humanus* louse has been eradicated from most of the world except for Ethiopia and a few other countries. According to the Ethiopian Department of Health, it was the seventh leading cause of hospital admission (2.5% of the total; 3,777 cases) and the fifth leading cause of death (0.9%; 42 cases) in 2004. (Cutler *et al*., 2009). Five sequences from Tanzania, two sequences from Zaire, one sequence from Rwanda, and three sequences with an unknown origin can be found in GenBank for *B. duttonii* 16S rRNA.

Ethiopia, Rwanda, Sudan, and Zaire all have confirmed cases of *Borrelia recurrentis* (Cobey *et al*., 2001; De Jong *et al*., 1995). The disease used to be widespread throughout the world, but it has since diminished and is now primarily found in Africa. Both Ethiopia and Sudan continue to be hot spots. Relapsing fever species have a wide range of genetic diversity. Patients with fevers often have their diagnoses determined by testing their blood.

Aetiology and Disease Transmission

Borreliosis aetiology includes the agents of Lyme disease and tickborne relapsing fever in humans and animals. The causative agents are Gram-negative spirochaetes belonging to *Borrelia* genus composed of 42 species: 21 in the tickborne relapsing fever (TBRF) group, 20 in the Lyme-Borreliosis (LB) group, and one (B. turcica) associated with reptiles. The LB groups are split into *B. burgdorferi* sensu stricto (s. s.) and *B. burgdorferi* sensu lato (s. l.). The former can cause disease in both humans and animals while the latter include *B. burgdorferi* s. s. mainly causes disease in humans. Pathological disease in the LB group for both humans and animals is mainly caused by *B. burgdorferi* s. s. *Borrelia turcica* has unknown pathology in reptiles, wildlife, domestic animals, or humans. Borreliosis is vectored by several tick species. These transmit these bacteria to wildlife, domestic animals, and humans; clinical disease in wildlife is limited with Lyme and TBRF. The primary tick species that spread *Borrelia spp*. infecting and causing clinical diseases in wildlife are *Ixodes* and *Argas.* The soft-bodied ticks - *Argas* and *Ornithodoros spp*.

Ixodes spp., one of the vectors for *B. burgdorferi*, are three-host ticks. The larval and nymphal ticks feed on the reservoir host and acquire the pathogen. Nymphal ticks then feed on humans or other animals and spread the pathogen to their hosts. As adults, *Ixodes* spp. are maintained on deer. Regarding the soft-bodied ticks *Argas* and *Ornithodoros* spp.; wild rodents and birds can serve as reservoir hosts for the bacteria. Bovine borreliosis in domestic cattle can be caused by *Rhipicephalus spp.* (e.g., *R. annulatus*, *R. microplus*) are one-host tick species that spread *B. Theileri*. Infected ticks transmit bacteria to their hosts via coxal secretions or saliva from bite. Outbreaks of *B. anserina* in birds have occurred due to coprophagia and cannibalism. Also spread by faeces, excreta, and tissues from infected birds. *B. burgdorferi* may be spread by direct or indirect co-feeding on host. Louse-borne relapsing fever (LBRF) is a vector-borne disease caused by the spirochaete *Borrelia recurrentis,* a human-restricted pathogen transmitted by the body louse *Pediculus humanus humanus*.

Distribution

Several Lyme and TBRF *Borrelia* spp. have regional and tick host specificities. Lyme borreliosis was first detected in humans in Lyme, Connecticut, in 1975, when an epidemiological investigation revealed an abnormally high incidence of rheumatoid arthritis in children, some of whom presented with a characteristic erythema migrans rash. *Ixodes* spp. were subsequently detected as potential vectors, and *Borrelia* was detected as the infective agent in 1981. *B. burgdorferi* occurs in Japan, Europe, Russia, and New South Wales (Australia). In the United States, *B. burgdorferi* exists on the Pacific Coast, Wisconsin, Minnesota, and the Atlantic Coast. *Ixodes ricinus* transmits the bacteria throughout northern Africa, the United Kingdom, parts of Russia, Scandinavian countries, and Mediterranean countries. *I. persulcatus* is another vector in Japan and Eastern European countries. *B. afzelii* and *B. garinii* are more prevalent in Asia than *B. burgdorferi*. Seabirds harbour *B. garinii* which is spread by *I. uriae,* a tick that primarily feeds on seabirds. Worldwide, it is thought that the spread of Lyme disease is secondary to tick habitat expansion due to climate change. In the United States, the movement of people to rural areas and a rise in deer populations is thought to contribute to Lyme disease spread due to increased interaction between deer and humans. Wild avian species spread both ticks and bacteria to new geographic locations via their migration routes. In the western United States, the western fence lizard (*Sceloporus occidentalis*) is a host to the larval and nymphal stages of the western black-legged tick (*Ixodes pacificus*). However, it is not a reservoir host for the bacteria, which is thought to be due to the borreliacidal activity of its blood. Tickborne Relapsing Fever *B. anserina* was first identified in Russia as goose septicemia in 1891. The bacterium is present in captive and domestic birds in subtropical and tropical areas of the world, such as South America (Brazil, Ecuador, Argentina, Colombia, Venezuela), the southwestern United States, the Middle East, Australia, West and North Africa, India, Central America, and Indonesia. In Europe, other TBRF *Borrelia* spp. are mainly found in Mediterranean countries.

Prevention and Control

Prophylaxis can be sanitary or medical. Tick control with acaricides, vegetation management, leaf litter removal, biological agents, soaps, and desiccants. Tick preventive medication for captive animals. Wildlife management, including permethrin-treated deer feeding stations and adequate livestock fencing. Several vaccines for borreliosis in the different host species have been developed.

Risks to Public Health: *B. burgdorferi* can be transmitted to humans directly from infected ticks. There is no evidence that the bacteria can be spread directly from animals to humans. *B. burgdorferi* is the main cause of Lyme disease in humans in North America. *B. garinii* and *B. afzelii* are considered emerging Lyme disease pathogens. *B. duttonii* causes TBRF in eastern and central Africa; *B. crocidurae* causes TBRF in western Africa. These are spread by *Ornithodoros* tick spp. *B. miyamotoi* and *B. recurrentis* cause relapsing fever in humans; the latter is transmitted to humans via *Pediculus humanus* lice.

Risks to Agriculture: Hens infected with *B. anserina* may experience decreased egg production. Ruminants infected with *B. theileri* (causing TBRF, spread by *Rhipicephalus* spp.) and cows infected with *B. burgdorferi* may experience decreased milk production.

Economic Impact

The economic impact of TBRF in some areas such as Uganda and the rest of Africa is not clearly quantified most probably because of limited diagnostic facilities, hence, they are likely to be missed. Although TBRF is rarely reported to be of veterinary importance, there are sporadic reports of canine infection, some of which have been reported as fatal (Baneth *et al*., 2022, Baneth *et al*., 2016). The infection in canines is often complicated by co-infection with other haemoparasites such as *Babesia* (Baneth *et al.*, 2016).

In livestock, TBRF causes fever, haemoglobinuria, loss of appetite, diarrhoea, pale mucous membranes, enlarged superficial lymph nodes, and rough hair coats leading to reduced productivity (Faccini-Martínez *et al*., 2022). Co-infection of *Borrelia* and *Babesia* was reported in cattle in South Sudan, Zambia, and Botswana, and implicated as the cause of low productivity (Qiu *et al*., 2021).

In horses, TBRF can be fatal through probable cause of abortion. Previous report of equine abortion due to TBRF spirochaete (*B. parkeri*) was observed and was thought to be as a result of the horse as an incidental host for an infected tick (Elelu, 2018).

To have a full understanding of the economic impacts of TBRF, there is a need for future efforts using field and laboratory surveys to determine its pathogenesis, vector competence and distribution, and impact on animal health and productivity. This will be crucial in order to prevent further spillover to the human population, which is already a public health problem in some parts of the world.

Methods

Laboratory Diagnosis

Those who live in or visit endemic African countries are at risk of contracting a relapsing fever. They are still not reliably diagnosed in most cases because there are no standard diagnostic procedures for them and doctors are not aware of their existence. Care facility-based diagnosis is done using in-house real-time PCR assays, validated by an external lab.

The definitive method for diagnosing *borreliae*-related relapsing fever is direct microscopic detection in Giemsa-stained thick blood smears (Mediannikov *et al*., 2014; Trape *et al*., 1991). Diagnosis at the point-of-care, and confirmation of *Borrelia* via molecular typing allows for precise species identification and a final, confirmatory diagnosis at the reference laboratory. Molecular typing is used for species identification of *Borrelia* in epidemiological studies (Haitham *et al*., 2012; Schwan *et al*., 2012; Scott, 2005). Since *borreliae* that cause relapsing fever are transmitted by vectors, the aetiology of *Borrelia* can be identified in the vector via xenodiagnosis. Presently, isolation and culture screening tests currently consist of microscopic examination and culture of midgut tissues dissected from live vectors of relapsing fever *borreliae* (Gustafson *et al*., 1989). Infection with *Borrelia* cannot be reliably diagnosed using specific serology. There is not much value in using serology as a diagnostic tool because specific antibodies are needed for a proper diagnosis. It is not sensitive enough to spot subclinical infections, active infections, species differences, or species specificity.

Relapsing fever borreliosis is characterised by repeated bouts of fever interspersed with periods of normal body temperature. Besides these, there are a few other *B. recurrentis* fever symptoms such as rapid heart rate, headache, muscle aches, and joint pain; hepatosplenomegaly, epistaxis, a petechial rash, and jaundice occur, but are less common. For the tick-borne *B. crocidurae*, some people get a high fever, feel weak, and vomiting. There is no correlation between age or sex and the number of times an infected person relapses after treatment. Immunity cannot be assumed; subsequent infections are possible. In Tanzania, the disease was responsible for 2.3% of deaths (Mayegga *et al*., 2005). In addition, conjunctivitis, orange urine, and perinatal mortality can be caused by *B. duttonii* in 436 per thousand births (Jongen *et al.,* 1997).

Tetracycline, doxycycline, and penicillin are used to treat relapsing fever borrelioses (Ramos *et al*., 2008). Up to 5% of people who receive antibiotic treatment will develop the Jarisch-Herxheimer reaction, which includes symptoms like rapid breathing and low blood pressure (Bryceson *et al*., 1970; Warrell *et al*., 1970). This response is linked to cytokine production during *Borreliae* blood clearance (Cooper *et al*., 2000).

To our knowledge, no prior research on *Borrelia* has been conducted in Uganda. Ticks in Uganda were tested for *Borrelia* using genus-specific primers by Nakayima *et al*. (2014), but no positive results were found. Therefore, we plan to undertake further research on Ugandan ticks to screen for *Borrelia*.

Conclusion

Since most Ugandans work in agriculture and live in rural areas, tick-borne diseases pose a serious problem to the population. In addition, tourism is the top foreign exchange earner in Uganda, with many foreign tourists visiting national conservation game parks and potentially getting exposed to tick-borne diseases. There is a lack of awareness of relapsing fever borreliosis in Ugandan public health management, which could be misdiagnosed as malaria. Therefore, there is a need for surveillance and control measures against potential tick-borne diseases for public health and livestock production.

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Contribution by Authors

Equal contribution

Conflict of Interests

There is no conflict of interest.

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