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Ecology, Transmission and Seasonal Patterns of *Mycobacterium ulcerans* Disease, Buruli Ulcer

Ahor Hubert Senanu[1*], Solomon Gyabaah[1,2] and Rejoice Agyeiwaa Arthur[1]

[1]*Kwame Nkrumah University of Science and Technology, Ghana*

[2]*Komfo Anokye Teaching Hospital, Ghana*

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Abstract

Infectious diseases are observed to have their own seasonal window of occurrence and variations which differ with geographical location. Climate is well acknowledged to influence infectious disease outbreaks via changes in pathogen, reservoir and vector dynamics as well as influencing human behavior. This review looks into the ecology, transmission, and seasonal patterns of Buruli ulcer disease and its causative organism *Mycobacterium ulcerans*. The transmission of Buruli ulcer/*M. ulcerans* is via an environmental reservoir found in either the abiotic or biotic component of aquatic and or terrestrial ecosystems. However, there exist multiple transmission pathway dependent on epidemiological setting and geographical areas. Rainfall patterns especially raining seasons and periods right after the major raining seasons are known to influence the occurrence of *Mycobacterium ulcerans* in the environment and its infection among human and animal populace. As such community case search activities ought to be done during the period between the rainy season and dry season. In addition, individuals in endemic communities must ensure maximum protective measures during the raining seasons.

Keywords: Ecology; Transmission; Buruli ulcer; *Mycobacterium ulcerans*; Climate; Rainfall

Introduction

Buruli ulcer (BU) is a debilitating skin infection caused by *Mycobacterium ulcerans* [1]. It is the third most common mycobacterial infection after tuberculosis (TB) [2,3]. It is the third most common mycobacterial infection after tuberculosis (TB) and leprosy globally, but in endemic countries such as Cote d'ivore and Ghana, its prevalence rate is second to TB [2,3]. This disease is reported in over 33 countries in Africa, the Americas, Asia and Western Pacific with most cases reported from poor rural communities in West Africa [4]. Within the last decade, there have been a 64% reduction in BU cases globally with only Australia and Nigeria reporting high number of BU cases recently [1]. The clinical and epidemiological perspective of BU differ across various settings. In Africa, children below the age of 15 years are mostly affected whereas in Australia cases are frequently reported in older populations [1].

BU initially presents clinically as painless pre-ulcerative lesion forms; nodule, plaque or edema which usually ulcerate within weeks to the ulcerative form with undermined edges. Due to the painless nature of BU lesions, affected individuals presents large ulcers at treatment centers which can lead to deformities or even amputation of affected Limb [1,5]. The pathogenesis of the disease is hinged on the production of an exotoxin called mycolactone which has anti-inflammatory, cytotoxicity and analgesic effects rendering the typical lesions painless [5]. The lack of insight into the ecology and the exact mode of transmission of *M. ulcerans* hinders the prevention and control of BU worldwide [1]. The current control strategy outlined by the WHO is early detection of cases followed by prompt treatment with rifampicin and clarithromycin/streptomycin [1,6,7].

Corresponding author: **Dr. Ahor Hubert Senanu,** Kumasi Centre for Collaborative Research in Tropical Medicine, Kwame Nkrumah University of Science and Technology, Ghana

E-mail: *ahor@kccr.de* and *hubertsenanu@gmail.com*

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Infectious diseases are observed to have their own seasonal window of occurrence and variations which differ with geographical location [8]. Climate is well acknowledged to influence infectious disease outbreaks through changes in pathogen, reservoir and vector dynamics as well as influencing human behavior [8]. Seasonality patterns of infectious diseases such as tuberculosis (TB), malaria, diarrheal diseases and many more have been reported in the incidences of these diseases, necessitating the need for specific controls measures at particular periods [9-12]. With respect to TB, studies have reported the end of winter and start of summer as period for high TB incidences [9,13]. Various social, environmental and host-related risk factors such as temperature, rainfall, humidity, sunlight, indoor activity, pollution, crowding, immune suppression and delays in TB diagnosis are known to be involved in TB seasonality during the winter period [14]. Epidemiological and socio-demographic data have also been used to explain the trend and seasonality of TB [12,15]. In Buruli ulcer disease, studies have tried to elucidate the ecology of *M. ulcerans* and the possible transmission route. Few studies have noticed and reported the seasonal pattern of the occurrence of the BU and it causative organism, *M. ulcerans* in endemic countries [16-19]. As such this article reviewed works done with regard to the ecology, transmission and seasonal variation in the detection of *M. ulcerans* in the environment or *M. ulcerans* infection among human and animal population.

Search strategy and selection strategy

We searched PubMed and Google scholar with the search terms: "Buruli ulcer", "*Mycobacterium ulcerans*" in association with the term's "ecology", "transmission", "seasonality" and "rainfall". In some instances, key references within some articles were included. A systematic review of our search result was done and article relevant to the aims of this review were selected (**Figure 1**).

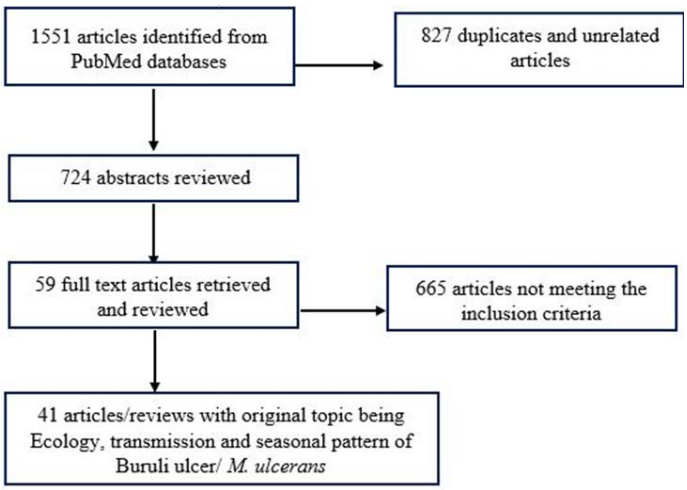

Figure 1: Illustrates how the review articles were searched and selected.

Results and Discussion

Ecology, reservoir, vectors and transmission of *Mycobacterium ulcerans*

The successful growth of *M. ulcerans* from *Gerris* sp. (Water Strider), an aquatic Hemiptera, provided a factual evidence of the present of *M. ulcerans* in the environment [20]. The use of PCR based techniques have implicated environmental agents such soil, water plants, detritus, plant/biofilms, frogs, snails, turtles, fish, water filtrates, mosquitoes (*Anopheles* sp., Aedes sp., *Coquillettidia* sp. and *Culex* sp.) and aquatic insects (Naucoridae, Hydrophilidae, Belastomatidae) in many BU endemic areas as potential reservoir or vectors of *M. ulcerans* [16,21,22-30]. This suggests that the aquatic ecosystem/habitat could be the source of *M. ulcerans* from which it is transmitted to humans and possibly the vehicle for disseminating *M. ulcerans* strains in endemic communities. However, the transmission routes of *M. ulcerans* from the environment to humans/animals is still unclear but remains very speculative.

A conceptual hypothesis described by Portaels et al. and Marion et al. have been used to explain the possible *M. ulcerans* transmission mode. According to this hypothesis, *M. ulcerans* found in water, mud, water filtrates, detritus and plant biofilms are picked and accumulated by filtering or grazing aquatic insects (such as mosquito larvae, midges and water bugs) or other invertebrates (crustaceans, snails, plankton) during feeding. The invertebrate is then fed on by predatory aquatic invertebrates (beetles, dragonfly larvae and true bugs) and vertebrates (fish, frogs), which are also fed on by aquatic insects capable of flight and Birds which disperse *M. ulcerans* to another aquatic environment. Humans are infected with *M. ulcerans* through direct contact with these potential reservoirs/vectors via skin abrasions or through insect bites [21,25,31]. BU patients living under poor hygienic conditions or those with large ulcerative lesions (category III) can help disseminate *M. ulcerans* in the environment through their activities such as bathing, washing of clothes and swimming in water bodies albeit human to human transmission is rare [29,32,33]. The occurrence of BU lesions in domestic mammal species (dogs, cats, horses) and native wildlife (koalas (*Phascolarctos cinereus*), Alpacas, ringtail (*Pseudocheirus peregrinus*) and brushtail possums (*Trichosurus cunninghami*) have been widely observed in Australia, suggesting that these animals could also be a major link between the environment and human in the transmissions of *M. ulcerans* [16]. However in endemic countries such as Ghana, Cameroon and Côte d'Ivoire where endemicity of BU is high, few cases have been found or reported in domestic mammal species such as a dog, a goat and few Mice (*Mastomys sp.*) [28,33,34].

Fyfe and his colleagues postulated that domestic animals get infected with *M. ulcerans* via contact with infected soils, environmental samples or fecal matter of wild/other domestic animals. Humans are then infected through direct contact with infected animal excreta or Animal bites. Ectoparasites of domestic animals that feed on humans can also transmit *M. ulcerans* from animals to humans. An insect vector particularly mosquitoes could transfer *M. ulcerans* from possum to humans during feeding. In addition, mosquitoes breeding sites (gutters, ponds or drains) heavily

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contaminated with possum excreta harboring *M. ulcerans* can facilitate mosquitoes (either as adults or larvae or) to be infected with *M. ulcerans* [16]. However, this hypothesis cannot be extended to Africa, as studies are yet to found evidences of adult mosquitoes harboring and possibly transmitting *M. ulcerans* to human. Also animal excreta being the vehicle for dispersing *M. ulcerans* in the environment is yet to be proven in Africa [35,36]. The prevailing dogma with regard to transmission of BU is that the environmental reservoir of *M. ulcerans* is either an abiotic or biotic component of aquatic and/terrestrial ecosystems and that there exist multiple transmission pathway dependent on epidemiological setting and geographical areas [16,33,37]

Seasonality of Buruli Ulcer Disease

Outbreaks of Buruli ulcer in humans have been linked to close proximity to aquatic systems such slow flowing or stagnant water bodies created by human activities [38]. Flooding of lakes during heavy rainfall, creation of dams/agriculture irrigation system on stream/rivers, modifying wetlands, deforestation and agriculture activities resulting in increased flooding and alluvial, pit and sand mining operations have been associated with high BU incidence in endemic communities [25,38,39]. These environmental disturbances are known to redistribute *M. ulcerans* in the environment increasing the possibility of human contact with the pathogens.

There exist an interplay between ecosystem (habitat) changes and climatic patterns which result in both functional and abiotic environmental changes in biodiversity [3]. Studies have reported climatic/rainfall patterns to result in a cyclical incidence of MU/BU in many endemic communities (**Table 1**). During heavy rainfall/flooding, *M. ulcerans* in aquatic habitat is washed into and surface run off water thereby contaminate them. In the dry season, these waterbodies moves back leading to the formation of stagnant/small water bodies near urban and agricultural areas [3]. These events lead to a cyclic transformation of the ecosystem resulting in the creation of new ecological niches characterized by stagnation of water, increased amount of light in surface water, high water temperatures and increase acidity of water. These changes are accompanied by sedimentation (turbidity), growth of aquatic plant and algal biofilm formation, decrease ultraviolet light and dissolve oxygen which favors the growth, persistence and transmission of *M. ulcerans* in the environment [3]. These changes also affect composition of aquatic ecosystem leading to a turnover of biotic communities favoring the species adapted to lentic habitats. Such aquatic systems are prone to *M. ulcerans* as well as human activities such as building, fishing, washing of clothes and hunting which increases the likelihood of human contact with *M. ulcerans* in the environment [40,41].

M. ulcerans exhibits major seasonal and intra-seasonal variations in large water bodies and temporary flooded areas with its presence less variable between seasons in permanent swamps and streams [42]. Peak incidence of *M. ulcerans* DNA in crayfish has been observed to be in the summer season which comes right after the rainy season in Japan [43]. These findings correlate with studies conducted in Northern Malawi and Cameroon [31,44]. In Louisiana, USA, *M. ulcerans* DNA was abundant in the wet seasons than in fall and winter [45]. The link between *M. ulcerans* presence in the environment and Buruli ulcer seasonal pattern in human population have been explored [17-19]. In Australia, Fyfe and his colleagues, observed a positive correlation between human BU cases and the presence of *M. ulcerans* DNA in possum feces [16]. Williamson and colleagues also reported a positive correlation between *M. ulcerans* DNA presence in the environment and BU occurrence among humans [18]. In Ghana, the months with high amount of rainfall are known to record the highest amount of *M. ulcerans* DNA in the environment which corresponds to high incidence of BU in human population compared to the dry season [17]. Genomic profiling of both *M. ulcerans* DNA detected in BU patients and environmental samples shows a very close genetic relationship of *M. ulcerans* in the same niche [16,28,30]. In addition, BU lesions in patients were source tracked to water bodies present in endemic communities in Ghana [28]. These provides evidence that BU patients are infected by *M. ulcerans* present in the environment individuals are constantly exposed to.

Place of Study	Year	Sample used	Season with peak incidence of BU or MU	Reference
Uganda	1969-1970	Clinical samples	Rainy season	[46]
Uganda	1966-1970	Clinical samples	Rainy season	[47]
Ghana	1993	Clinical samples	Rainy season	[48]
Northern Malawi	2006	Environment samples	Dry Season	[44]
Australia	1981-2008	Clinical samples	Wet season	[49]
USA	2010	Environmental samples	Wet season	[45]
Cameroon	2010	Environmental samples	Dry season	[31]
Cameroon	2002-2012	Clinical samples	Rainy season	[50]
French Guiana	1969-2012	Clinical samples	Dry season	[19]
Japan	2015	Environment samples	Rainy season	[43]
Ghana	2016	Environment samples	Rainy season	[17]
Australia	2004-2016	Clinical samples	Rainy season	[51]

Table1: Summary of studies indicating season with peaked Buruli ulcer cases or M. ulcerans DNA in respective countries

In Australia and French Guiana, it was observed that warmer and wet conditions before case emergence followed by a dry period to case emergence is a precursor to the occurrence of BU [19,49]. It was hypothesized that flooding during the raining season influence the distribution of *M. ulcerans* in the environment leading to the infection of humans with clinical signs showing at the onset of the dry season similar to an earlier observation made in Uganda by Radford [49,52]. This phenomenon of high BU cases in the subsequent dry season, and this lag phase can be attributed to the long incubation period of BU (estimated between 3-4.5 months) resulting in the delays between infection and diagnosis [49,53,54]. However, in a recent study conducted in Australia, high BU-incidents were observed in Bellarine and Mornington Peninsulas, in months with high rainfalls as compared to months with less rainfall [51]. These findings confirms observations earlier studies conducted in Cameroon and Uganda where high number of cases were also reported

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during months with high rainfall compared to others with low rainfall [46,47,50]. In Ghana, it has been revealed that BU cases peaked from September to October which are minor rainy seasons in the country [48]. A potential issue that may be a hindrance to understanding the seasonal patterns of BU in human is the difference in time between appearance of symptoms, reporting to health facilities as reflected in the size of lesion presented [19]. However, the variation of Buruli ulcer incidence by season can be associated with fluctuations of *Mycobacterium ulcerans* occurrences in the environment which are probably influenced by the dynamics of freshwater ecosystems [50]. There is trend of BU/ *M. ulcerans* peak incidence to be associated to rainfall and period just after wet season. This requiring that during these periods, BU control programs such as community case search activities in endemic communities should be intensify so as to enable early detection of cases to allow prompt treatment. This would prevent the various forms of deformities, disability or even amputation of affected Limb which commonly occur when BU lesion are not treated early. In addition, there ought to be intensive public education on BU protective measures such as Wearing of long protective cloths, washing and immediate application of alcohol at wound [17,55].

Globally, there is a downward trend (64% reduction) in the incidence of Buruli ulcer in most endemic countries with the main reason for the reduction unknown [1]. However, we can speculate that this reduction in BU cases can be as a result of global warming effect which it known to affect rainfall pattens (reduction in rainfall). This speculation is based on this review, showing high incidence of Buruli ulcer/*M. ulcerans* during period of high precipitation. However, we suggest that the seasonal patterns of BU/ *M. ulcerans* may be dependent on epidemiological setting and geographical areas similar to its transmission's mode due to the differences in climatic conditions.

Conclusion

Mode of transmission of *M. ulcerans* from the environment to humans is not known and not well established. As a result, individuals living around or visiting BU endemic areas must take precautions especially during the wet seasons or period prior to dry season as these periods are known to be associated with high incidence of BU. However, it is very important to consider any seasonal variation associated with Buruli ulcer disease in a particular endemic area in order to predict seasons for implementation of BU control programs.

Author Contributions

Ahor Hubert Senanu, Solomon Gyabaah, Rejoice Agyeiwaa Arthur: drafting and revising the article, concept and design. Ahor Hubert Senanu: Final revision of the article; concept and design.

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