

Prevalence of aquatic insects and arsenic concentration determine the geographical distribution of *Mycobacterium ulcerans* infection

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A modified SIR model is used to explain the transmission of *Mycobacterium ulcerans* (MU) and its dependence on arsenic (As) environments. Some studies have suggested that As plays a major role in the spread and prevalence of buruli ulcer (BU). In addition, it has been hypothesized that a vector in the form of a water-bug plays a key role in the epidemiology of BU. We develop an epidemiological model based on these assumptions for the dynamics and prevalence of BU and show that As positively induces the growth and spread of MU.

Keywords: *Mycobacterium ulcerans*; Buruli Ulcer; Water-bugs; Arsenic

1. Introduction

Mycobacterium ulcerans (MU), a pathogenic bacterium that causes dermal ulcers known as “buruli ulcers” (BU), is fast becoming a debilitating affliction in many countries worldwide. The incidence of BU is not limited solely to tropical environments. In fact, occurrence of BU has been well documented in subtropical and temperate regions of Australia and the possibility of the disease spreading beyond its current confines into temperate climatic zones of other continents cannot be entirely dismissed. The impact of BU on affected communities is devastating since BU causes permanent disabilities in over 25% of its victims [1–3]. By 1999, cases of BU had been reported in more than twenty five countries worldwide [4]. Within the next year, the number increased to over thirty countries and cases spanning races have been recorded at the University of Ibadan campus in Western Nigeria [5].

The disease infects the skin and subcutaneous tissues, resulting in indolent ulcers, with lesions appearing mainly in the limbs. In 2001, Small and her group at University of Tennessee isolated a toxin produced by the causative organism. The toxin is thought to be the source of BU [6]. Named Mycolatone, it is a class of polyketides derived from manolides. The toxin quickly destroys large areas of the skin after manifesting itself in the form of painless dermal nodules. This proceeds to the destruction of tissues and even bones. When the ulcer heals, it leads to significant and permanent scarring.

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No cure has yet been found for BU since the bacterium has resisted available antibiotics. The only treatment remains the removal of the lesion and subsequent skin grafting. As such, though the mortality rate of BU is very low, the economic implications are significant globally. In most endemic areas, access to modern health services is restricted. Owing to inadequate information and education about the disease, patients often seek treatment late. This usually leads to severe complications and costly treatment methods. In such areas, treatment cost per patient usually far exceeds annual per capita health spending. In the West African country of Ghana, for example, the average cost of treatment is estimated at USD780 per patient [7] whereas the per capita health spending is estimated by the World Health Organization (WHO) as USD10.92 [8]. Comparatively, it has been reported that patients who seek early treatment for lesions in general reduce cost to about USD20–30 per patient with very limited hospitalization. With an increasing number of cases and associated complications, the long-term economic and social impact of BU on affected populations could be substantial.

The emergence of BU in various localities has been linked to slow flowing water bodies and swamps, especially the type that emerge after major environmental and topographical disturbance, such as occur after construction of artificial lakes and irrigation canals [2,3,5,9,10]. This has implications on water recreation in the affected areas. Even for developed countries with better health services, the socioeconomic impact of BU could still be significant. Recreational activities near rivers where MU persists could lead to costly BU infection. Considering the fact that the cost of swimming related illnesses in only two beaches of Orange County in California, for example, is estimated to be over USD 3 million per year [11], an outbreak of BU could lead to substantially higher health costs since water recreation is enjoyed by a greater proportion of the population in developed countries.

A disturbing feature of BU is that scientists have not been able to identify the exact mode of transmission of the disease, even though the relationship between outbreaks and the existence of swampy environments has long been established [12]. Because of acute lack of knowledge of how the bacterium thrives in nature and of a transmission vector, the epidemiology of BU is not completely understood. Specifically, the mode of transmission remains elusive. Thus, effective methods of control have not been designed to eliminate, or at least reduce, the scourge.

Studies in West Africa and elsewhere have implicated certain aquatic insects as likely candidate transmission vectors from a natural source to humans [9,13–15]. These recent studies reveal that aquatic bugs of the genus *Naucoris* (family Naucoridae) and *Diplonicus* (family Belostomatidae) are the probable candidates in the transmission of MU to humans. In addition, it has been established that most of MU are introduced into the human body by means of physical damage to the skin [5]. Person to person transmission has not been completely ruled out yet, but is considered unlikely. Similar studies completed recently have led to a better understanding of the toxins produced by MU that sustain the ulcers [16,17]. In addition, these studies have left very little doubt that BU is prevalent mainly in swampy areas.

An aquatic environment is not the only factor that has been linked to the prevalence of MU. It has been observed that if, in addition, high levels of arsenic (As) concentration prevail in such environments, the occurrence of MU is enhanced. Duker *et al.* [18] have advanced the hypothesis that As may play a significant role in the spatial distribution of BU [19]. Concentration of As in surface and ground water in areas where BU is a serious health threat has been noted to be higher than average. Incidentally, in Ghana, West Africa, the Amansie West District which accounts for most of the BU cases coincides with the highest levels of As, possibly released into rivers and lakes and ground water by intensive gold mining activities. It has not been confirmed whether higher levels of As in water help to nurture MU

microbes in water or whether As causes skin lesions which are infected when the nodes come into contact with MU [20].

Even though a vector and the concentration of As in water have been linked with the spread of BU, neither of these two factors have been fully investigated and proven yet. Emerging science suggests that a vector infects exposed limbs, making individuals who are scantily clothed highly vulnerable to this flesh eating disease. In tropical environments where BU mostly prevails, researchers believe that people working in fields where the water-bugs breed are more exposed to the bites from insect vectors. Thus, a comprehensive study of the epidemiology of BU needs to include the role of a vector. Since the aquatic bug that has been identified has not been fully investigated, its transmission cycle is not known.

With the spread of tropical diseases such as Ebola, West Nile virus and Gambian plague into temperate regions of the world, cases of BU can easily spread to cooler climatic regions. The WHO estimates that MU might surpass tuberculosis and leprosy if not checked [6,13,21]. At this stage, all possible methods of evaluation and analysis must be employed to separate all the facts from fiction so that BU can be better understood, in order to facilitate research into its cure and stop its spread globally. In this paper, we use a mathematical model that exploits the dynamics of infectious diseases to investigate the epidemiology of BU.

2. Modified SIR model

Since understanding the epidemiology of BU has so far proved elusive to scientists, we present a mathematical model that seeks to use a quantitative analysis to understand the epidemiology and etiology of BU. For a disease such as BU, the number of parameters to include in a mathematical model is difficult to determine since there is a complete lack of informative studies on the disease. Basically, we consider the role of As and the vector (water-bug) in our model. Even though including seasonal dynamics of the water-bug will be more informative [22] we will not consider details such as the seasonal variation of the vector at this stage. Hopefully, this will have a minimal effect on the predictions of the model.

2.1 Model assumptions

The following assumptions are considered:

1. MU is not passed on from humans to water-bugs.
2. Person to person transmission is excluded.
3. Seasonal variations in the life cycle of the water-bug are negligible.
4. Homogeneity of human and water-bug populations.
5. Whenever humans are within the vicinity of the breeding grounds of the water-bugs, they are randomly bitten by the bugs.
6. Humans who develop BU become immune to any further attack.
7. No incubation period is considered here because of the assumption that human to human transmission is not valid.
8. Infected individuals do not recover to be re-infected with MU.

BU is a micro parasitic disease in which host–parasite interaction basically occurs within isolated communities. We assume that the host population is of fixed size containing susceptible individuals who are not yet infected with MU. This leads us to consider the SIR

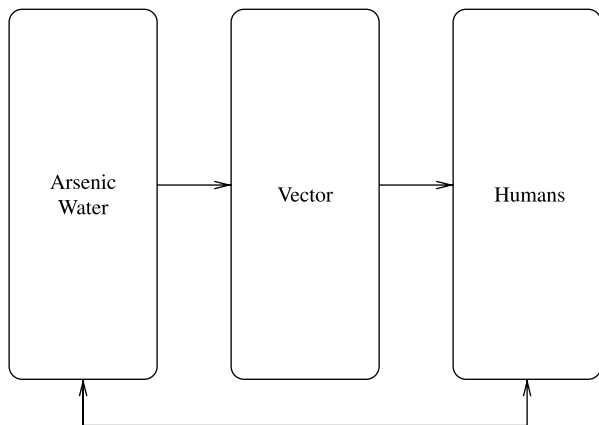


Figure 1. Possible transmission cycle of MU through the vector (water-bugs) and the influence of environmental arsenic concentration. While the detailed gonotrophic cycle of the aquatic bugs is not known, it is assumed that a swampy environment with a high As concentration enhances its survival and its ability to transmit MU.

type model to analyze the epidemiology of BU. We incorporate the roles played by the vector and levels of As into an SIR model. We begin with a possible life cycle of MU illustrated in a schematic model in figure 1 [23] and the chain links between humans, water-bugs that transmit MU and As levels in the environment. Figure 2 demonstrates the possible interrelationships between these variables.

2.2 Model variables and parameters

- m —Density of water-bugs (number of water-bugs per human host)
- a —bite frequency (biting rate of humans by a single water-bug)
- a_1 —Rate of ingestion of MU by water-bugs
- b —Proportion of infected bites on humans that produce infection
- α —Relative concentration of As in water
- μ —Mortality rate of water-bugs
- x —Proportion of humans infected by MU
- y —Proportion of water-bugs infected by MU
- r —Death rate of humans

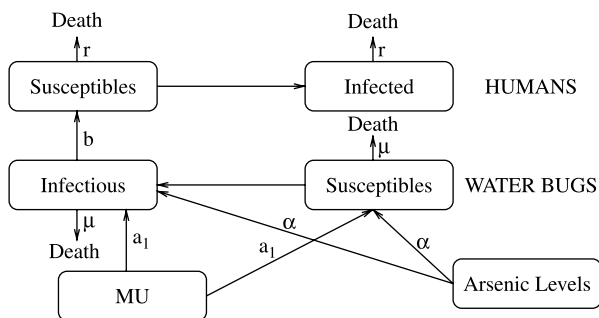


Figure 2. Schematic representation showing interrelations between the compartmented sections of human and water-bug populations and the role of As concentration in the epidemiology of BU.

The model equations describing the proportion of humans infected by MU and the corresponding proportion of water-bugs are given by:

$$\frac{dx}{dt} = maby(1 - x) - rx \quad (1)$$

$$\frac{dy}{dt} = a_1x(1 - y) - (\mu - \alpha)y \quad (2)$$

$$x(t_0) + y(t_0) = 1. \quad (3)$$

Here, $\alpha = \bar{\alpha}/\alpha_0$ where α_0 is the highest As concentration in water recorded in studies in Taiwan [24] and $\bar{\alpha}$ is the As concentration in water measured in a particular location.

For steady states solutions:

$$maby(1 - x) - rx = 0 \quad (4)$$

$$a_1x(1 - y) - (\mu - \alpha)y = 0 \quad (5)$$

Equation (4) leads to:

$$y = \frac{rx}{mab(1 - x)} \quad (6)$$

Substituting this in the second equation we have:

$$a_1x \left(1 - \frac{rx}{mab(1 - x)} \right) = (\mu - \alpha) \frac{rx}{mab(1 - x)} \quad (7)$$

$$x = \frac{maa_1b - (\mu - \alpha)r}{maa_1b + ra}, \quad x \neq 0 \quad (8)$$

$$= \frac{1 - ((\mu - \alpha)r/maa_1b)}{1 + (r/ma_1b)} \quad (9)$$

Let

$$R_0 = \frac{maa_1b}{(\mu - \alpha)r} \quad (10)$$

then

$$x = \frac{R_0 - 1}{R_0 + (a/\mu - \alpha)} \quad (11)$$

Intuitively, the transmission of BU depends on a high density of water-bugs as well as their biting frequency, the high rate of ingestion of MU by water-bugs and a high rate of infectiousness. Inversely, a lower level of μ and a relatively higher level of α will lead to propagation rate of MU. In addition, the spread of BU is enhanced by a lower death rate of humans. Equation (11) shows that the prevalence of BU in humans depends on the biting rate of water-bugs, their mortality rate and As concentration in the environment. For BU,

α is relatively smaller than μ , thus the prevalence of BU (see equation (11)) in humans and MU in waterbugs (equation (15)) increases for $R_0 > 1$ and decreases for $R_0 < 1$ (see figure 3).

The effect of reproductive number on the prevalence levels of both infected humans and aquatic bugs is captured in figure 3. The prevalence of infected humans increases more rapidly even though the prevalence of water-bugs is generally higher than that of humans. The prevalence of humans overtakes that of the vector at relatively low reproductive numbers (between 5 and 10, see figure 3). This is an indication that if the ingestion of MU by water-bugs is not checked, then in the presence of high As concentration the prevalence of BU in human population will rise.

Substituting (9) in (6) we have:

$$y = \frac{r\{maa_1 - (\mu - \alpha)r\}/maa_1b + ra}{mab(1 - (ma^2b - (\mu - \alpha)r)/maa_1b + ra)} \quad (12)$$

$$= \frac{maa_1b - (\mu - \alpha)r}{mab\{(\mu - \alpha) + a\}} \quad (13)$$

$$= \frac{1 - ((\mu - \alpha)r/maa_1b)}{mab((\mu - \alpha/maa_1b) + (a/maa_1b))} \quad (14)$$

$$= \frac{R_0 - 1}{R_0} \cdot \left(\frac{a_1/(\mu - \alpha)}{1 + (a/(\mu - \alpha))} \right) \quad (15)$$

3. Numerical results

In this section we present the numerical results of the model presented in section 2. For this simulation, we used a death rate r of 0.0003 (*i.e.* three deaths per 10,000 humans per year) and infection rate b of 70% [9]. The biting rate a and the density of water-bugs m were taken

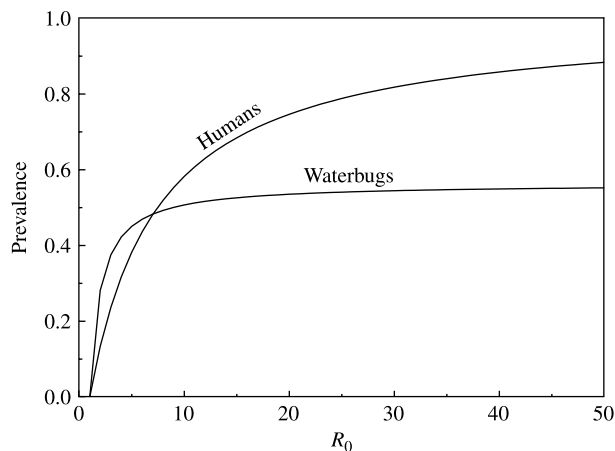


Figure 3. Effect of reproductive number R_0 on the prevalence levels of both infected humans and water-bugs. The concentration of As used for this simulation is $10 \mu\text{g/l}$. Notice that the prevalence of humans exceeds water-bugs for $5 < R_0 < 10$.

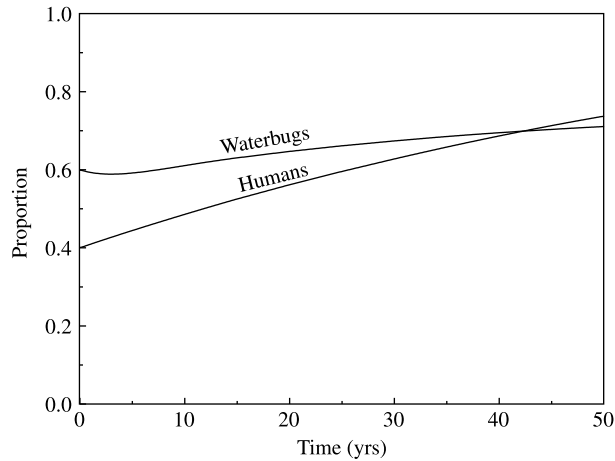


Figure 4. Time evolution of the proportion of infected water-bugs and humans. Here, $x(0) = 0.4$, $y(0) = 0.6$. The value of α is $10 \mu\text{g/l}$, the WHO accepted level of As concentration. Over time, there is a steady increase in the population of infected humans.

as 75 and 5%, respectively, while we used a mortality rate of water-bugs of 15% [23] and their ingestion rate of MU as 50%. Figure 4 shows the time evolution of the proportion of both infected water-bugs and humans.

From figure 4 it can be seen that the proportion of infected water-bugs initially decreases in the first five years or so of the incidence of MU. After this, there is an increase above the level of the initial proportion. The proportion of infected humans, on the other hand, increases continuously from the first year.

The effect of higher than accepted As level in the environment on the epidemiology of BU is investigated. Three levels of As concentration in the environment are chosen. The choices of 10, 50 and $80 \mu\text{g/l}$ are based on WHO accepted levels of As in water, nationally allowed levels in water for some countries, and a third chosen higher value to capture the role played

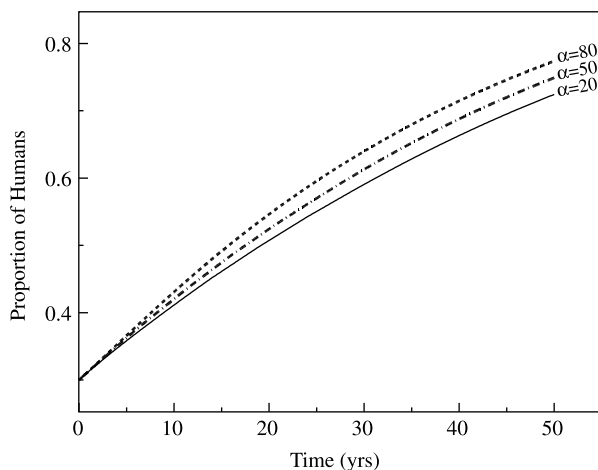


Figure 5. The role of As in the distribution of BU infection in a human population. As the level of As concentration increases, the proportion of humans infected with BU increases over time. Values of α used here are 10, 50 $\mu\text{g/l}$, 80 $\mu\text{g/l}$.

by As levels. As levels in water have been used here instead of the general environmental levels because it is the easiest way for both humans and water-bugs to ingest As. An extension of these values to environmental levels will therefore be in order. Figure 5 shows an increase in the density of infected humans as levels of As in the environment increase.

It can easily be seen from figure 6a that halving m , a , a_1 or b reduces R_0 by a factor of two. On the other hand, halving both As concentration and mortality rate or the death rate of water bugs results in an increase of the reproductive number by a factor of two.

4. Discussion and conclusion

We have considered the role of certain aquatic bugs and levels of As in the environment in the spread of BU. We have shown that higher levels of As concentration in water lead to more

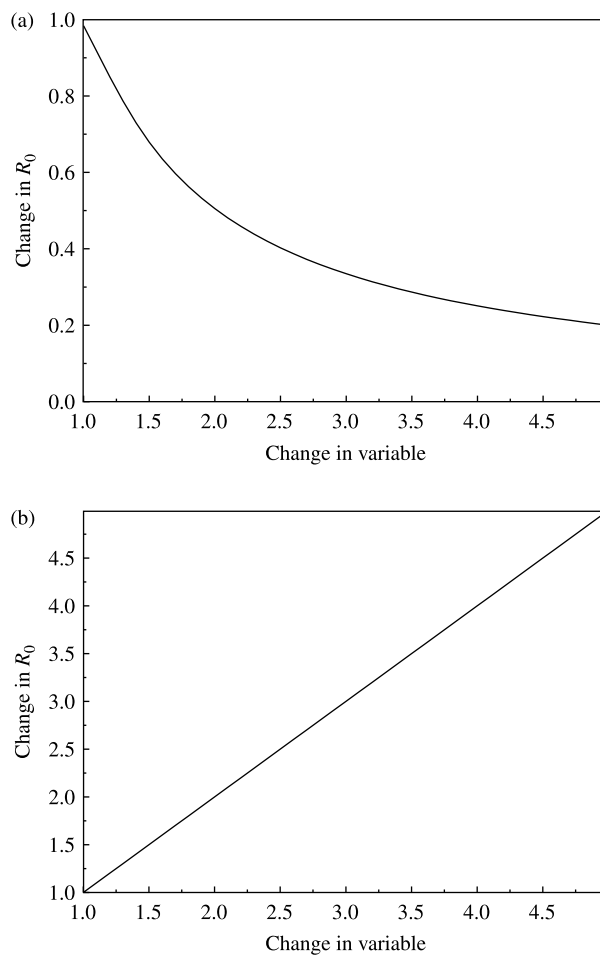


Figure 6. Sensitivity analysis for the parameters of the reproductive number for $\alpha = 10 \mu\text{g/l}$. (a) A value of 2 for $m(a_1, a, b)$ represents a two-fold decrease in the parameter and this causes a two-fold decrease in the reproductive number, since all the parameters are linearly related to R_0 . (b) Similarly, a two-fold decrease in the value of r causes a two-fold increase in the value of the reproductive number.

BU cases within a population that comes into contact with water-bugs that are infected with MU. While our model clearly points out that As concentration is likely to influence the prevalence and spread of BU, it is not known for sure whether water with high As concentration offers a perfect breeding ground for MU, or whether drinking or bathing predisposes the skin to MU infection.

Based on the assumption that there is a vector, our paper has alluded to Duker *et al.*'s [18] hypothesis that As plays an active role in the spread and dynamics of BU. From figure 5, when As concentration is increased from 10 to 80 $\mu\text{g/l}$, the density of infected humans increases. In a nutshell, the lower the environmental As concentration the less likely it is that BU will thrive. This was clearly manifested in Australia, where BU was eradicated after some swamps were completely drained out [5]. It must be noted that As is found in higher levels in groundwater and mining areas in Australia. The real problem may not have been the drains but rather the combination with higher than normal levels of As. It was not then known that BU thrives in As rich environments.

There is a nonlinear relationship between the basic reproductive number R_0 and the prevalence of infection of both infected water-bugs and infected humans (see figure 3). Moreover, a small increase in the reproductive number leads to a large change in both the prevalence levels of humans and water-bugs (see figure 3). Judging from the graph, higher levels of R_0 will lead to increases in cases of BU for $R_0 > 1$. Thus, clearly if BU is not controlled it will continue to spread in regions with conducive conditions. More importantly, if the R_0 value of BU is determined and the parameter values of BU are determined accurately for any region, better decisions toward controlling the spread of BU could be made.

Finally, our model indirectly points to the fact that other factors that have not as yet been revealed or studied could play key roles in the transmission of BU. Hence, at this stage of uncertainty about the epidemiology of BU, prevention remains the key measure in fighting the disease. Such preventive measures include draining As rich water bodies in environments with known high prevalence of BU; wearing protective clothing against water-bugs while working outdoors in fields; and non-exposure to As contaminated environments.

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