

# Environmental Hypothesis: Arsenic can be a Contributory Factor in Mycobacterium Ulcerans Infection

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**Abstract:** Buruli ulcer (BU), an often-deforming skin and bone disease caused by *Mycobacterium ulcerans* (MU), is now considered by the World Health Organisation (WHO) to be the third most widespread mycobacterial infection after Tuberculosis and leprosy. However, the reservoir of MU in the environment and the epidemiology of BU are poorly understood. This paper explores the hypothesis that arsenic in the natural environment can be a contributory factor in MU infection. A review and synthesis of the published literature shows: (a) numerous similarities between BU and arsenicosis; (b) spatial coincidences between BU rates and periodic enrichments of arsenic in the environment.

**Keywords:** *Mycobacterium ulcerans*, Buruli ulcer, aquatic ecosystem, arsenic, spatial analysis.

## 1. Introduction

Buruli ulcer (BU) is a skin and bone disease caused by *Mycobacterium ulcerans* (MU) and is rated as the third most common mycobacterial infection after tuberculosis and leprosy [1]. It begins with a painless nodule on the skin, which in the absence of appropriate therapy, causes skin ulceration so severe that it often results in a grossly deformed sequel [2,3]. The disease has been reported from West Africa, Central Africa (Democratic Republic of Congo, Congo Brazzaville), Uganda, Australia, Papua New Guinea, Indonesia, Malaysia, Mexico, French Guyana, Surinam and Peru. It afflicts mainly impoverished inhabitants living in remote areas to which the amenities of modern medical science

are not readily accessible [4]. Children are particularly afflicted: [5] reported that 76% of the BU patients from the Afram valley in the Eastern Region of Ghana were younger than 20 years; [6] reported that 70% of the BU patients from the Ashanti Region of Ghana were younger than 15 years. The increasing incidence of BU, particularly in West Africa, led the World Health organization to recognize BU as an emerging disease and called for urgent action to control it [7].

The reason for the emergence of BU and its epidemiology are poorly understood. Investigations [8,9,10] have emphasised the clinical aspects of the disease. However, environmental factors may influence its

distribution. Buruli ulcer is endemic in aquatic ecosystems [9,11] and the disease has been associated with aquatic insects [12,13] and with natural and anthropogenic environmental changes such as flooding and land-use changes [12,14]. However, the reservoir of MU in the environment is still unclear and the specific environmental factors that predispose BU infection have not yet been identified.

This paper reviews the occurrence of BU in relation to one variable in the natural environment, arsenic. It examines the symptoms of arsenicosis and considers whether these could be associated with or facilitate BU infection. It describes natural environments prone to anomalous arsenic enrichment, spatial coincidences of BU infection rates and fluctuations in concentrations of environmental arsenic.

## **2. Similarities in Disease Characteristics (BU and Arsenicosis)**

Several well-documented characteristics of arsenicosis are also found in BU. The indolent character of arsenicosis [15] is also observed in BU [1,16]. Limb gangrene is a well-documented characteristic effect of exposure to arsenic [17,18] and cases of BU in French Guyana have shown gangrene-like characteristics [19,20].

Other characteristics of arsenicosis shared by BU include injury to nerves [21,22], occlusion of blood vessels [23,24], obstruction of cutaneous lymphatics leading to oedema [25,16], microhaemorrhage [25,26] and fibrosis [27,28,16].

A study by [29] showed that mice exposed to arsenic concentrations of 4.0 – 4.8 mg/l developed lesions similar to those seen in MU infections in mice. Clinical manifestations of erythematous lesions and swellings of the paws and tail regions of the mice were also similar to

those of MU infections. Furthermore, it was observed that there was significant reduction of the white blood cells; an indication of the defect of the body's immune system, and thus susceptibility to microbial infections.

These similar characteristics suggest that some BU patients have arsenicosis 'signature', implying that the infection could be a combination of sub-clinical arsenic poisoning and BU. This raises the possibility that MU and arsenic may interact synergistically to impact adversely on health; and this in turn prompts the consideration of environmental arsenic in relation to BU causation.

### *2.1 Pathways of Arsenic Poisoning*

Oral ingestion is the most common route by which people are exposed, whereas inhalation and dermal uptake are significant in certain occupational settings [30]. There have been a large number of studies related to arsenic toxicity in both humans and animals. Studies in humans indicate that arsenates and arsenites are well absorbed across the gastrointestinal tract [31,32]. Several cases and large-scale arsenic poisoning [33] have resulted from ingestion of contaminated drinking water or food, which is absorbed through the gastrointestinal tract and into the blood stream. The absorbed arsenic is then converted into a methylated form by the liver and excreted through the urine. Long-term medium-level exposures have several effects on the body, especially the skin (e.g., hyperpigmentation, hypopigmentation, keratosis, warts), but this may further lead to damage of the vascular system, an example of which is Blackfoot disease, prevalent in some parts of Taiwan where average concentration of arsenic in water range from 170-800  $\mu\text{g l}^{-1}$  [34]. High concentration levels of arsenic in tissues was known to cause inflammation, erythema and open ulcers on the skin [29]. In both groundwater and

surface water, dissolved arsenic concentrations are normally less than  $10 \mu\text{g l}^{-1}$  [35,3]. Although several countries still maintain the maximum concentration of  $50 \mu\text{g l}^{-1}$ , adherence to the WHO minimum regulatory level (i.e.,  $10 \mu\text{g l}^{-1}$ ) may be safer when the fact that individuals vary in response to arsenic toxicity is considered [36]. At low to moderate environmental exposure levels (i.e.,  $< 100 \mu\text{g l}^{-1}$ ) arsenic tends to accumulate in the body [37,38]. In some geographical areas, however, natural mineralization of arsenic leads to much higher concentrations of arsenic in water (e.g.,  $3400 \mu\text{g l}^{-1}$ ) as in West Bengal [39], and arsenic may then accumulate in the body.

Arsenic poisoning through inhalation derives from occupational settings such as smelters and chemical plants. In such cases, airborne arsenic is predominantly fine particles of arsenic trioxide ( $\text{As}_2\text{O}_3$ ). In humans arsenic is first deposited on the lungs before being absorbed through the epithelium and into the blood stream. Several studies [40,41,42] have reported of nausea, vomiting and diarrhoea due to inhalation exposure, which is characteristic of oral ingestion mode of high doses of arsenic. Arsenic the most toxic of the arsenicals [43,44], however, is known to cause hemolysis of the blood cells, leading to haemolytic anaemia.

Research has indicated that although the human skin acts as a barrier to water, particles and other materials of high molecular weight, the stratum corneum (the principal penetration barrier) is not a perfect barrier. Thus, polar substance (i.e., metal ions) can penetrate the stratum corneum via the intercellular route and through the sebaceous gland, sweat gland and hair follicles [45]. Factors affecting dermal absorption include degree of dermal hydration, arsenic species and its concentration in water, ambient temperature, frequency and duration of exposure [45]. There has been limited number of *in vivo* and

*in vitro* studies in this area of arsenic intake involving both humans and animals [46,47,48,33,49].

## 2.2 Consequences of Arsenic Poisoning

[50] reported that about 40-60% of arsenic may be retained in the body even after exposure cessation, and that this may accumulate in the skin, hair, nails, muscles and small amounts in the teeth and bones [51,52]. The skin is known to localize and store arsenic due to its keratin content, which may explain why the skin is very sensitive to arsenic toxicity [53]. Further, the interaction of arsenite with several essential enzymes in the body [54,55] could predispose to defect the host immune system [56,57,58]. Moreover, the ability of arsenic to draw iron from ferritin [59] could enhance the adhesion of bacteria to human tissues [60,61] infection.

Arsenic impairs the host immune function [62,63], which could imply susceptibility to bacterial infections [64]. Immunosuppression due to arsenic has been found to defect antigen processing of splenic macrophages with consequent defective protective mechanism of helper T cells [65,66] and alteration of humoral response parameters (e.g., IgM) [67,68].

There have been reports of impaired resistance to viral/bacterial infection via arsenic ingestion [69,70,71,72]. Down-regulation of the immune system is known to be a risk factor for the development of BU [73,28]. In a study of cytokine profiles of BU patients, [74,75] report that the immunosuppressive properties of the mycolactone secreted by MU alone are not likely to account for the induced systemic effects in BU patients and that this could be attributed to an intrinsic immune defect predisposing the individual to MU infection. It has also been found that anaemia (or severe anemia) is a negative

predictor for survival in some infections caused by opportunistic mycobacteria [76,77,78].

Anaemia and leucopenia are common effects of arsenic poisoning in humans [79,80,81,82,38], even though this may not be observed in all cases of arsenic exposure [83]. Severe anaemia, however, disrupts the normal functioning of the macrophages and the T-cells [76].

In the case of children, there is considerable placental transfer of arsenic to the developing foetus during pregnancy [84]. Thus the foetus and infant inherit the mother's latent exposure to arsenic, which is transferred to the child prenatally [85] and postnatally [86]. Ingestion of or contact with arsenic-rich dusts and garden soils by young children [11,87], especially those living on or near mine waste areas in which arsenic concentrations can exceed 1% [88], is another route by which children are exposed to arsenic [89]. If mother, child and young adult live in the same environment, the propensity for arsenicosis is likely enhanced, and thus along with predisposition to any MU infections.

### 3. Arsenic-Enriched Environments and MU Infections

#### 3.1 Riverine Areas in Volcanic Environments

The explosive eruption of Mt. Lamington in 1951 (in Papua New Guinea) was also followed by mudflows that lasted until 1956 [90,91]. Following the eruption, floods of the Sepik and Kumusi Rivers devastated the area. The earliest report of BU in Papua New Guinea was in 1957. Most MU infections were found in settlements along the two inundated portions of the rivers [92]. Lack of scarring coupled with the absence of the disease in the older people was an indication that the disease was recent. It is not

known whether the post-eruption floodwaters contained high concentrations of arsenic. However, several studies [93,94,95,96] have shown that volcanoes are important natural sources of arsenic especially in the southern hemisphere [96,94]. At high temperatures (e.g., volcanic eruptions) arsenic is very mobile in the fluid phase and may also be present in the fumaroles as sublimates and incrustations [97,3]. Volcanic ashes are also known to contribute to or generate high arsenic concentrations in waters [98,99], probably by reason of their reactive nature, and due to acidic material as well as the fine-grained volcanic ash, which could generate low pH in surface and ground waters.

#### 3.2 Mineralized Environments

Certain sulphide ores commonly have high concentrations of arsenic [100,101,102]. The extensive Archaean West African Craton, stretching from Ghana to Sierra Leone, is underlain by the Birimian Formation (including greenstone belts), which consists of folded and metamorphosed sediments and volcanics intruded by suites of granites, associated with which are gold-bearing sulphide mineralizations. In Ghana, and other parts of West Africa, gold occurs in quartz veins accompanied by arsenopyrite and pyrite [103,104].

Exploitation of these gold ores exposes the sulphide minerals to oxidation, liberating arsenic into natural drainage systems. The oxidation process is also a focus of microbial activities in which redox reactions transfer electrons, release energy and thereby promote bacterial growth [105,106]. Some bacteria use sulphide as an electron donor to reduce arsenate [107]. Some of these bacteria also use arsenite as their sole source of energy [108].

Some reports indicate that gold mining increased considerably in the period 1980-1990 in the West African region [109]. [9] also showed that since 1980 new foci of BU emerged in West Africa.

Indeed, West Africa has borne the brunt of BU infections in the last 15 years [110,111,112,113,114]. Ghana experienced a sharp increase in the incidence of BU, with about 2000 cases recorded in the period 1993-1997 [115], coincident with the initial wave of legal registration of artisanal miners (1992-1996).

### 3.3 Agricultural Environments

Although the main source of arsenic in soils (including those favourable for agriculture) is the parent rock [98], fertilizers (especially pesticides and phosphates) can substantially enhance the concentration of arsenic in soils. Arsenic has been used and is still in use as pesticides, insecticides and in cattle and sheep dips [116], and for the control of moths in fruit crops [117,118]. Arsenate mimics certain characteristics of phosphate and, through its absorption by ligand exchange on hydrous iron and aluminum oxides [119], accumulates in soil. It is then taken up by plants and entrenched in the mammalian/insectivore food chain [120].

Irrigated lands can be enriched in arsenic [88,121]. Irrigation, especially with wastewaters, can cause a problem of build-up of mobile and potentially toxic metals in soils and in surface runoff [122,123]. In Australia BU cases appeared in 1995 following the creation of a golf terrain irrigated by used water [11]. In the Amansie West District of Ghana where BU is endemic and 44% of patients are farmers [112] irrigation of vegetable crops or food crops, especially in the dry season is by surface waters [124] containing  $>500 \mu\text{g l}^{-1}$  arsenic. A significant positive exposure-response relationship was found between BU and arsenic concentration in surface water [125]. In this same district (Amansie West District) [126] showed that mean BU prevalence in settlements along arsenic-enriched drainages and within arsenic-enriched farmlands is greater than elsewhere.

### 3.4 Lakes and Reservoirs

BU cases have been reported in lake/reservoir environments [114,127]. Arsenic concentrations in lakes compared to those in rivers or streams may be lower due to the adsorption of arsenic on iron oxides in neutral to alkaline conditions. Some lakes and reservoir environments are, however, prone to geothermal activity, which can enhance concentrations of arsenic [128]. Porewaters from shallow anoxic sediments in a lake situated in a geothermal region in New Zealand contained up to  $6.43 \text{ mg l}^{-1}$  of arsenic [128], which comprised mostly of  $\text{As}^{3+}$  that had diffused across the sediment/lake interface and which had accumulated along with dissolved Fe and Mn in the hypolimnion. Geothermal activity beneath the lakes of the East African Rift Valley [129,130] could also lead to similar arsenic enrichment in the lake waters. Lake Kyoga is one such lake, and several cases of BU occurred around its edge [131].

Arsenic concentrations in lakes and reservoir environments can also increase due to low water flow [98,132,123] and containment of water by natural or anthropogenic means. The increase in  $\text{As}^{3+}$  and mobility [133] may be linked to the depletion of  $\text{O}_2$  levels especially in the bottom of lakes due to microbial reduction [134]. Construction of dams or reservoirs on rivers can, therefore, promote enrichment of arsenic in the contained water. Although there is no corresponding report on arsenic data, there was a report in Nigeria of BU incidence among Caucasians in the campus of Ibadan University [135], which is adjacent to a small stream that was dammed to make a 2.5-hectare artificial lake. In Liberia, there were reports of BU cases after a dam construction following the introduction of swamp rice to replace upland rice [114,136]. In Côte d'Ivoire, a boy residing beside Lake Kossou, an artificial lake in the centre of the country was reported as infected with BU [137]. In Ghana, BU is clustered along the Densu River, mostly in rural settlements [138,139]. Measured

levels of arsenic concentrations from 100 m and 12 km downstream of the Weija Dam (an impoundment on the Densu River that stores water for the western part of Accra) were 19.1 mg l<sup>-1</sup> and 14.0 mg l<sup>-1</sup> respectively. BU occurred in settlements both upstream and downstream of the impoundment. Upstream and along the impoundment where wetlands have been created, BU incidences were higher than downstream of the dam where settlements were mostly at higher elevations.

### 3.5 Swamps and Related Environments

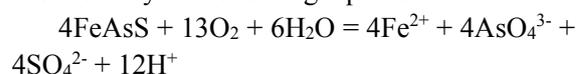
Swamps and some alluvial and deltaic environments are characterized by reducing conditions [98]. Their organic-rich sediments have a high metal-binding affinity [140], but the reducing conditions result in increased concentration of arsenic in solution, coupled with the dominance of the As<sup>3+</sup> species. Floods carry along sediments and/or contaminants that have been stored (for short periods, several decades or even a millennia) in the river beds and other sediments preserved in local low-energy environments such as behind bedrock obstructions in valley floor or alcoves developed in valley walls. Floods and/or storm waters can therefore carry along metals that contaminate the environment [141]. Flooding induces (anaerobic) reducing conditions in soils [142,143]. Under this condition, As<sup>5+</sup> is reduced to the more toxic As<sup>3+</sup> and adsorbed As<sup>5+</sup> released as As<sup>3+</sup> [144]. Trivalent arsenic is toxic to both humans and animals because of its interaction with sulfhydryl group of proteins and enzymes [18,54]. For example, alluvial soils in Thailand (plagued by arsenic lesions) could, after flooding, contain up to 5000 mg g<sup>-1</sup> of arsenic [88]. Such contaminations increase through flooding. They become severe with time and pose health hazard to both wildlife and humans [145,146]. Several references have been made to renewed outbreaks of BU after flood events [147,148,8]. The appearance of the first BU patient in 1939 in

Australia was after the occurrence of the worst flooding on record in the district of Bainsdale in 1935 [149]. The outbreak of BU cases in the Busoga district of Uganda was related to an unprecedented flooding from 1962-1964 [131]. In Cameroun, sharp increases of BU cases occurred after the flooding of the Nyong River [150,3].

## 4 Seasonal Variations and MU Infections

It is noteworthy that those arsenic-enriched and BU endemic areas mentioned above are mostly in tropical (to sub-tropical) countries. In these countries, there is a characteristic alternation of dry and wet seasons and this seasonal variation is influential to arsenic enrichment in the environment and could be a factor in BU infection.

Seasonal variation affects, in general, metal concentration and particularly arsenic speciation both in water and soil, apparently due to biologic uptake [151,152]. Temperature changes, particularly dry spells, may help to potentiate metal toxicity [153]. A drop in water levels in certain parts of the tropical world during dry seasons exposes arsenic-enriched substrate to air and oxidation [154,155]. For arsenopyrite, the aqueous oxidation by dissolved oxygen is described by the following equation:



Based on a number of studies [153,151,88] the arsenic cycle could be described as follows: (a) The dry period is a preparatory stage in which arsenic-rich beds (pyrites/arsenopyrites) are exposed to air and oxidized. (b) The rains during the wet season solubilize oxidized arsenic or secondary minerals and disseminate them into the ecosystems through floods or storm waters. (c) The concentration and thus toxic effects of arsenic is after the recession of the floods (i.e., the dry season). In Papua New Guinea and

Cameroun, for example, it was observed that the disease was on the increase during the dry season [150,92] at which time the toxicity of arsenic (increased proportion of  $As^{3+}$  to  $As^{5+}$ ) may be enhanced by the high temperatures and extreme evaporation of the season [156].

[112] and [113] found that BU incidence was at its peak in Ghana and Côte d'Ivoire respectively, towards the beginning of the dry season. In a previous study in the Ashanti Region of Ghana, [157] found that the period in which subsistence crops and fern contained the highest concentration of both species of arsenic ( $As^{3+}$ ,  $As^{5+}$ ) peaked in those same months (in which BU was at its peak). This may imply bioaccumulation of arsenic in human tissues through ingestion of arsenic-enriched food and water, which could cause, for example, immune dysfunction [57,58,158] and thereby an increased susceptibility to bacterial infection [73]. Several authors have referred to the seasonal dimension of BU infections [147]. Thus, there seems to be a temporal relation between BU incidences and relatively dry seasons.

## 5 Summary

Aside from its causative agent MU, there is also a strong association between arsenic and MU environments, which suggests that arsenic in the environment may be a contributory factor in MU infection. This is evidenced by a synergy of the following observations: (a) similarities in the characteristics of arsenicosis and BU (including stellate scars, microhaemorrhage, gangrene) (b) the occurrence of BU in several tropical to sub-tropical environments where arsenic enrichment is natural and/or anthropogenic; and (c) the temporal relation between the incidence of BU in tropical to sub-tropical countries and the end of the wet seasons, in which, according to the cycle, oxidized and toxic species of arsenic have been spread into the ecosystems. Exposure to toxic arsenic, either through ingestion or aerogenic

transmission may render one susceptible to (myco)bacterial pathogens as a result of skin disorders (making mycobacterium penetration easier) or impairment of cellular immune response [72,57,62]. Although there is the possibility of MU infection through the respiratory tract [159] some researchers [160,161] suggest direct inoculation.

Arsenic-enriched areas that are natural and where BU cases were reported are riverine, volcanic environments and mineralized environments. Arsenic-enriched areas due to anthropogenic activities and where BU cases were reported are agricultural and lake/reservoir environments. Arsenic-enriched areas that are either natural or anthropogenically-modified and where BU cases are reported are swampy environments. Therefore these arsenic-enriched environments could be potentially spatial contributory factors of BU.

Many of the arsenic-enriched environments where BU cases have been reported are periodically flooded due to natural calamities and/or anthropogenic activities. Many of the BU cases reported have occurred mostly when the floodwaters have already dried-up during the dry seasons, which indicate the seasonal dimension of MU infection.

The discussion above, which is based on spatial (not direct) association, does not presuppose that wherever arsenic exists MU is found. It does, however, indicate that arsenic makes one susceptible to bacterial infections and may predispose one to MU infection.

One of the precautionary and/or preventive measures that have been recommended is limiting contact with the environmental source of MU [14]. [113] also suggested the wearing of trousers, boots and long sleeved shirts on farms and on swamps, which is only a partial solution since infection can affect any part of the body including the face [112]. With regard, however, to what has been discussed in terms of arsenic toxicity and its impact on the body, especially the

skin, what one eats and drinks need be carefully considered since the main pathway of arsenic into the body is the oral ingestion route.

The conclusions obtained through these spatial relationships are indicative and therefore need

confirmation through further epidemiological research.

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