



An Age-structured Model for the Spread of Buruli Ulcer: Analysis and Simulation in Ghana

Ebenezer Bonyah^{1*}, Isaac Dontwi¹, Farai Nyabadza² and Fatmawati³

¹*Department of Mathematics, Kwame Nkumah University of Science and Technology,
Kumasi, Ghana.*

²*Department of Mathematical Science, University of Stellenbosch, Private Bag XI, Matieland,
7602, South Africa.*

³*Department of Mathematical Science, Faculty of Science and Technology, Universitas Airlangga,
Kampus C Unair, Jl. Mulyorejo Surabaya 60115, Indonesia.*

Received: 13 March 2014

Accepted: 08 May 2014

Published: 17 June 2014

Original Research Article

Abstract

Despite the advances in medical research on its treatment and intensive public education on prevention and control, the Buruli ulcer (BU) continues to be a major public health problem that continues to overwhelm authorities in Ghana. Ghana is the second most endemic country after the Ivory Coast at the global level. While it is common knowledge in literature that the disease can affect people of all ages, the mode of transmission is still evasive. The studied model is expressed as a system of hyperbolic (first order) partial differential equations. We first, employ a representation from the method of characteristics and a fixed point argument and also prove the existence and uniqueness of solutions to the nonlinear system. We establish the mathematical well-posedness of the time evolution problem using the semigroup theory approach. We then determine the basic reproduction ratio R_0 . Then we present a numerical scheme to model the dynamics of BU. The simulation results showed that Mycobacterium ulcer has peak period of spread and reduced subsequently.

Keywords: Buruli ulcer, SIR, hyperbolic transport, finite difference schemes, simulations.

1 Introduction

Buruli ulcer, also known as Bairnsdale ulcer is a chronic, indolent, and necrotizing disease of the skin tissue caused by Mycobacterium ulcerans (M. ulcerans) [1]. The disease usually begins as a painless nodule or papule and may progress to massive skin ulceration [2]. It also appears that different modes of transmission occur in different geographical and epidemiological setting [3]. Though the disease can affect people of all ages, children less the 15 years of age are particularly more vulnerable in many tropical and subtropical countries [4]. Buruli ulcer causes serious pain as

*Corresponding author: ebbonya@yahoo.com;

well as permanent physical damage. The physical signs visually mark the individual and deprive them of societal standards of beauty. Additionally, physical deformities may prevent the individual from participating in any economic and social activities.

The study of Buruli ulcer continues to be an important problem in mathematical epidemiology as outbreaks of *M. ulcerans* continues to pose a public health challenge [5]. The mode of transmission of the ulcer is not well understood, however residence near aquatic environment has been identified as a risk factor for the ulcer in Africa [4,6]. The modes of transmission vary with geographical and epidemiological settings [3]. In Africa, it is estimated that almost 30, 000 cases were reported between 2005 and 2010 [7]. Buruli ulcer is a severe, disfiguring disease which affects all age groups but particularly children less the 15 years of age in many tropical and subtropical countries [8]. The disease has emerged over the past two or more decades, especially in Central and West Africa and has been confirmed by laboratory test in 26 countries with reports in other countries around the world [3].

The known common of model for the spread of an infectious disease is the Susceptible-Infected-Recovered (*SIR*) model, which is based on the categorization of individuals in the classes of susceptible (those at risk of getting the infection), infected (those with the ulcer) and recovered (those cured of the ucler). The *SIR* models of Buruli ulcer developed at the moment are time dependent models which lead to system of ordinary differential equations (ODEs), see [9]. In order to model the pathway of infection clearly, we propose a model which considers the role of *M. ulcerans* introduced to the water reseviors by disturbed environment and stratify the population with age.

Age is an important consideration in the modeling infectious disease that depends on age. Different age groups of populations may have different reproduction and survival capacities. A disease may vary with respect to infection and mortality for different age groups [10]. In reality, individuals of varying age groups may exhibit different behaviours and immunological competencies. Behavioural and immunological changes are vital in control and prevention of many infectious diseases and in particular the Buruli ulcer. Young individuals are known to be more active in interacting with or between populations, and the disease. This paper therefore, intends to use an age-structured model to study the spread of Buruli ulcer.

At the heart of an age-structured model, is a coupled system of hyperbolic partial differential equations (PDEs). The introduction of a system of PDEs instead of a system of ODEs gives rise to the interconnectivity of the problem greatly. Although using age-structured models to study the spread of diseases is not something new, to the best of our knowledge, no such model has been proposed for the Buruli ulcer. The equations which account for the growth of the *M. ulcerans* will not be age structured and therefore, will remain as ordinary differential equations.

Further background of age-structured models, we entreat readers to see [11,12]. The earliest models of age structured populations, due to [11,12] developed a foundation for a partial differential equations approach to modeling continuum age structure in an evolving populations. A new drive of research in age structured models came up with the pioneering work of Gurtin and [13] for nonlinear age structured models. Barbu [14] developed mathematical theory behind age-structured populations [10] and studied nonlinear age-dependent population and predator prey dynamics.

The increasing mathematical complexity of biological issues, nonlinearities and age structure in biological models, has brought about new dimension of analyzing them. One of these powerful tools is method semi-groups of linear and nonlinear operators in Banach spaces.

This paper sought to develop an age-structured BU model and provide some theoretical and numerical analysis of the model. The system differential equations along with initial and boundary conditions that form the disease model will be discussed. We will further prove the existence and uniqueness of the solutions in L^1 and L^∞ to our PDE system using the fixed point theory on a representation derived from the method of characteristics. Finally the numerical simulations and its implications will be discussed.

2 The Model and Its Analysis

2.1 Model Formulation

We consider the human population divided into three subgroups: the susceptible individuals who are do not have Buruli ulcer but are at risk of getting it, infected individuals with the ulcer and the recovered, who would have been treated of the disease. Within each category, the age and population changes over time are taken into account. The number of people in each subgroup are expressed as $S = S(a, t)$, $I = I(a, t)$ and $R = R(a, t)$, each variable is a function of age a and time t . In order to use a dimensional approach in this model, we formally apply units of weeks for the age of humans a and days for the simulation time t . However, conventional units of years are also used in some instances to elucidate the age of human population. The number of

susceptible people between, say age a_1 , and a_2 at a time t is expressed as $\int_{a_1}^{a_2} S(a, t) da$ applying

convectional understanding that all humans from $a = a_0$ year to $a = a_0 + 1$ year taken a_0 year old. A similar approach is also used for the infected and recovered humans $I(a, t)$ and $R(a, t)$ respectively. There is one water bug compartment of infective M. ulcerans denoted by $B_H = B_H(t)$. The four quantities S, I, R, B_H are dependent variables of the model. Buruli ulcer is considered a water-borne disease and in most cases, transmission of the disease is through contact with contaminated water bodies ([15], [16]). To put in various factors that influence the dynamics of a BU epidemic, we have put in the model an extra coefficient function which maybe constant or may vary with age or time (or both). A disturbed environment is taken into account in the model formulation. We include a human demographic recruitment term $\Lambda(a, t)$ alongside natural death rate $\mu_H(a)$.

The possible interrelations between humans, the M. ulcerans are represented by the schematic diagram below (Fig. 1).

The susceptible individuals become infected through interacting with the environment with M. ulcerans at rate $\beta_H(a)B_H(t)/(k_H(a) + B_H(t))$ with M ulcerans concentration measured with respect to infectious dose denoted byg. The human population is suffers a natural per capita

mortality rate $\mu_H(a)$. Individuals recover from BU at a rate $\theta(a)$ which depends on age. M. ulcerans bacteria experience a natural removal rate of δ_V due to death or predation. A strategy $g(a, t)$ that can help reduce the spread of BU that represent antibiotic treatment was included in the model. This reduces the duration and quantity of infected humans concentration to the concentration of M.ulcerans bacteria in the environment. We study the age-time domain $P = (0, A) \times (0, W)$ with intervention $g(a)$. With the above notations, we study the following infected-age- structured model with Mycobacterium ulcerans transmission. See Table 1 for a complete description of the model quantities and their units.

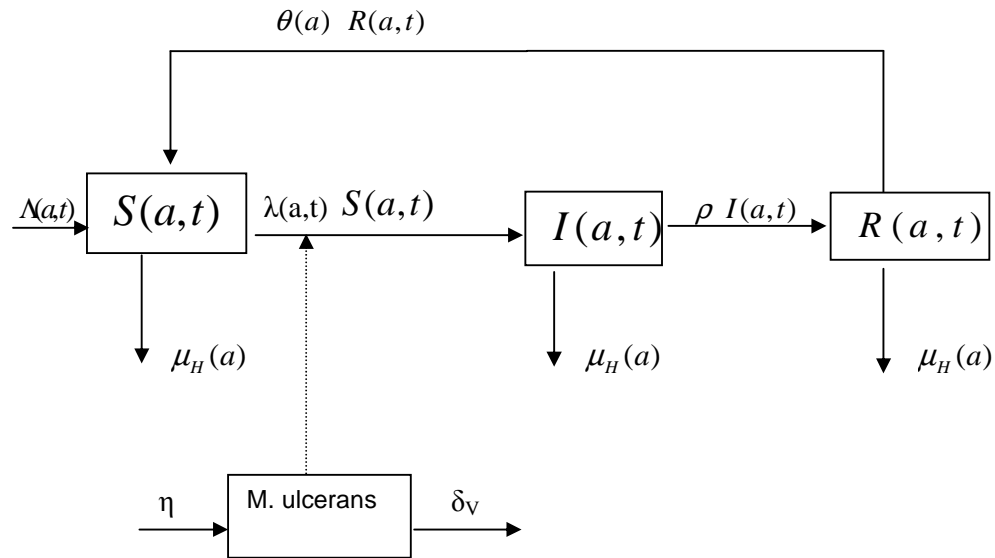


Fig. 1. Proposed transmission dynamics of the Buruli ulcer between humans and M. ulcerans in the environment

$$\frac{\partial S}{\partial t} + \alpha \frac{\partial S}{\partial a} = \Lambda(a, t) - \beta_H(a) \frac{B_H(t)}{k_H(a) + B_H(t)} S(a, t) - \mu_H(a) S(a, t) + \theta(a) R(a, t), \quad (2a)$$

$$\frac{\partial I}{\partial t} + \alpha \frac{\partial I}{\partial a} = \beta_H(a) \frac{B_H(t)}{k_H(a) + B_H(t)} S(a, t) - \mu_H(a) I(a, t) - \rho_1(1 - g(a, t)) I(a, t) - \rho_2 g(a, t) I(a, t). \quad (2b)$$

$$\frac{\partial R}{\partial t} + \alpha \frac{\partial R}{\partial a} = \rho_1(1 - g(a, t)) I(a, t) + \rho_2 g(a, t) I(a, t) - \mu_H(a) R(a, t) - \theta(a) R(a, t) \quad , \quad (2c)$$

$$\frac{dB_H}{dt} = \int_0^{\infty} \eta I(a, t) da - \delta_V B_H(t) . \quad (2d)$$

For the above equations $\alpha = \frac{1 \text{ week}}{7 \text{ days}}$ is the coefficient introduced to balance the units of age a in weeks and time t in days. With respect to infected class, the multiplicative factors $\rho_1(1-g)$ and ρ_2g represent the rates of recovery for the individuals who have had no antibiotic treatment and those who have undergone such treatment respectively.

2.1.1 The boundary and initial conditions

Buruli ulcer disease does not transmit vertically from parent to infants and therefore we can infer that children have some immunity. In this regard, newborns will appear in the R class in SIR model. This is significantly different from most S, I, R model. We translate this consideration to state the boundary conditions.

$$S(0, t) = 0, I(0, t) = 0, R(0, t) = \int_0^A (S(a, t) + I(a, t) + R(a, t)) f(a) da, \quad (2e)$$

where the fecundity function f is stated as

$$f(a) = \begin{cases} \frac{1}{5} \sin^2 \left(\pi \frac{(a-15)}{30} \right) & \text{if } 15 \leq a \leq 40 \\ 0 & \text{otherwise} \end{cases}$$

The fecundity function $f(\cdot)$ is stated here in units of per year for easier readability and assumes that from age 15 to 40 years a woman will give generally give birth to three children, since $\int_0^{a^+} f(a) da = 3$, where $a^+ = 60$ is the largest age allowed for the simulation [17].

The initial conditions are stated as

$$S(a, 0) = S_0(a), I(a, 0) = I_0(a), R(a, 0) = R_0(a) \text{ and } 0 \leq B_{H0} \leq B. \quad (2f)$$

2.2 Abstract Cauchy Problem Formulation

We assume that all the parameters are nonnegative, i.e $\Lambda_H > 0, \mu_H > 0, \delta_V > 0, \beta_H > 0$. The parameters fulfil the following assumptions.

- (1) The functions $\rho_1(a), \rho_2(a), \eta(a) \in L^\infty(0, \infty)$, where $i = 1, 2, 3$.
- (2) The function $\varphi(a)$ is nonnegative and integrable.

2.2.1 Abstract cauchy problem

In this section we seek to deal with quantitative properties of (2a)-(2d) as in [17,18]. In order to undertake this, we consider the Banach spaces. Characterize the space of functions $Y = \mathbb{R} \times L^1(0, \infty) \times \mathbb{R} \times L^1(0, \infty) \times \mathbb{R} \times L^1(0, \infty)$,

Endowed by the norm $\|\phi\|_Y = \sum_{i=1}^3 \|\phi_i\|_{L^1}$;

where $\phi = (\phi_1, \phi_2, \phi_3)^T \in Y$. Let us denote Y_+ the positive cone of Y . It is well known that $(Y, \|\cdot\|_Y)$ is a Banach space. Let $A : D(A) \subset Y \rightarrow Y$ be a operator defined by $A\phi = -\phi' - \mu_H \phi$, with the domain

Table 1. Model parameters and the state variables

| Quantity | Descriptions |
|-----------------|---|
| $S(a, t)$ | Susceptible humans of age a at time t divided uniformly over all ages |
| $I(a, t)$ | Infected humans of age a at time t |
| $R(a, t)$ | Removed and immune humans of age a at time t |
| $B_H(t)$ | Mycobacterium ulcerans population |
| $\Lambda(a, t)$ | Recruitment rate of human population of age a at time t |
| $g(a, t)$ | Antibiotic treatment rate for humans of age a at time t |
| β_H | Contact rate of MU at age a |
| $f(a)$ | Maternity rate |
| $\theta(a)$ | Rate of waning immunity of human at age |
| k_H | Saturation constant of MU at age a |
| μ_H | Natural mortality rate of human at age a |
| ρ_1 | Recovery rate of untreated Buruli ulcer |
| ρ_2 | Recovery rate of treated Buruli ulcer |
| η | Age – specific contribution of infected humans to the environment |
| δ_L | Clearance rate of MU in the environment |

$$D(A) = \left\{ \phi = (\phi_1, \phi_2, \phi_3) \in W^{1,1}(0, a^+, \mathbb{R}^3) \text{ and } \begin{pmatrix} \phi_1(0) \\ \phi_2(0) \\ \phi_3(0) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ \int_0^{a^+} |f(a)[\phi_1(a) + \phi_2(a) + \phi_3(a)] da \end{pmatrix} \right\}.$$

the function $F : \overline{DA} \rightarrow Y$ defined by

$$F_1 \begin{pmatrix} \phi_1 \\ \phi_2 \\ \phi_3 \end{pmatrix} = \begin{pmatrix} \Lambda - \beta_H \frac{B_H}{k_H + B_H} \phi_1 - \mu_H \phi_1 + \theta \phi_3 \\ \beta_H \frac{B_H}{k_H + B_H} \phi_1 - \mu_H \phi_2 - \rho_1(1-g)\phi_2 - \rho_2 g \phi_2 \\ \rho_1(1-g)\phi_2 + \rho_2 g \phi_2 - (\mu_H + \theta)\phi_3 \end{pmatrix}.$$

$$F_2 = \int_0^{+\infty} \eta \phi_1 da$$

Let us consider that

$$\overline{DA} = X_0.$$

Now by carefully observing $(S(t, \cdot), I(t, \cdot), R(t, \cdot), B_H(t))$ in (2a)-(2d) together with $u(t) = (0, 0, 0, S(t, \cdot), I(t, \cdot), R(t, \cdot), B_H(t))^\Gamma$,

One obtains that $u(t)$ satisfies the following abstract Cauchy problem

$$\frac{du}{dt} = Au(t) + F(ut), t > 1, \tag{2.21a}$$

together with the initial data $u(0) = y = (0, 0, 0, S_0, I_0, R_0)^\Gamma \in Y_0$.

We also take into account the positive cones

$$Y_+ = [\mathbb{R}^+]^3 \times [L^1_+(0, \infty)]^3, Y_{0+} = Y_0 \cap Y_+.$$

Theorem 1: *There exists a continuous semiflow $\{(U(t))\}_{t \geq 0}$ on Y_{0+} into itself such that for each $y \in Y_{0+}$, the map $t \rightarrow U(t)y$ is the unique integrated solution of (2.21a) with initial data y , namely $t \rightarrow U(t)y$ satisfies*

$$(i) \int_0^t U(s)y ds \in D(A), \forall t \geq 0,$$

$$(ii) \int_0^t U(t)y = x + A \int_0^t U(s)y ds + F \int_0^t U(s)y ds$$

Moreover we have for each $y \in Y_{0+}$.

$$\limsup_{t \rightarrow \infty} \|U(t)y\| y \leq \frac{\Lambda}{\mu_H}$$

Proof:

Let us take into consideration that for each N centered at 0 . One gets the existence of maximal positive semiflow for (2.21a) on Y_{0+} into itself. It remains to prove that this semiflow is globally defined. In order to achieve this, let $y \in Y_{0+}$ be given and recall that

$$U(t)y = (0, 0, 0, S(t, \cdot), I(\cdot, \cdot), R(\cdot, \cdot))^T.$$

Also let us consider the quantity

$$Q(t) = \|U(t)y\| y = \int_0^\infty S(t, a) da + \int_0^\infty I(t, a) da + \int_0^\infty R(t, a) da, B_H(t) \leq \frac{\bar{\eta}\Lambda}{\mu_H \delta_V}$$

the total population at time t . Then it satisfies the differential inequality

$$\limsup_{t \rightarrow \infty} \|U(t)y\| y \leq \frac{\Lambda}{\mu_H}, \forall y \in Y_{0+} - \mu_H Q(t)$$

Thus the map $t \rightarrow Q(t)$ cannot blow up in finite time and the global existence result follows. Let us in addition, notice that, from this inequality one gets

$$\limsup_{t \rightarrow \infty} \|U(t)y\| y \leq \frac{\Lambda}{\mu_H}, \forall y \in Y_{0+}.$$

One the other hand one has

$$\begin{aligned} \frac{dQ(t)}{dt} &= \Lambda - \mu_H Q(t) \\ &\geq \Lambda - \mu_H. \end{aligned}$$

So that

$$\liminf_{t \rightarrow \infty} \|U(t)y\|_y \leq \frac{\Lambda}{\mu_H}, \forall y \in Y_{0+}, B_H(t) \leq \frac{\bar{\eta}\Lambda}{\mu_H \delta_V}.$$

This completes the proof of the result.

2.3 Equilibria and Their Stabilities

Let $\bar{\eta} = \max\{\bar{\eta}\}, \bar{\eta} = \text{ess sup}_{(0, \infty)} |\bar{\eta}|$. It is easy to demonstrate the following set is positively invariant for the system (2a-d)

$$W = (S, I, R, B_H) \left| \left(\int_0^\infty S(a,t) + \int_0^\infty I(a,t) + \int_0^\infty R(a,t) \right) da \leq \frac{\Lambda}{\mu_H}, B_H(t) \leq \frac{\bar{\eta}\Lambda}{\mu_H \delta_V} \right. \quad (2.23a)$$

System of equation (2a-d) always has the disease free equilibrium $E_0(\Lambda e^{\mu_H a}, 0, 0, 0)$. To simplify expressions, we introduce the following notations

$$\pi(a) = e^{-u(a)} e^{-\int_0^a (\rho_1(v) + g(v)) dv}.$$

Let $(S^*(a), I^*(a), R^*(a), B_H^*)$ represent any arbitrary endemic equilibrium of the model (2a-d). This equilibrium satisfies the following equations

$$\frac{dS^*(a)}{da} = \Lambda(a,t) - \beta_H(a) \frac{B_H^*}{k_H(a) + B_H^*} S^*(a) - \mu_H(a) S^*(a) + \theta(a) R^*(a), \quad (2.4a)$$

$$\frac{dI^*(a)}{da} = \beta_H(a) \frac{B_H^*}{k_H(a) + B_H^*} S^*(a) - \mu_H(a) I^*(a) - \rho_1(1-g(a)) I^*(a) - \rho_2 g(a) I^*(a) \quad (2.4b)$$

$$\frac{dR^*(a)}{da} = \rho_1(1-g(a)) I^*(a) + \rho_2 g(a, t) I^*(a) - \mu_H(a) R^*(a) - \theta(a) R^*(a) \quad (2.4c)$$

$$\frac{dB_H^*}{dt} = \int_0^\infty \eta I^*(a) da - \delta_V B_H^* = 0, \quad (2.4d)$$

Solving the second and fourth equations of (2.4b)-(2.4d) respectively, leads

$$I^*(a) = I^*(0)\pi(a),$$

$$B_H^* = \frac{1}{\delta_V} \int_0^{+\infty} \eta I^*(a) da.$$

Let

$$R_0 = \frac{\beta_H \Lambda}{\mu_H \delta_V} \int_0^{\infty} [\eta_1(a) \pi(a)] da. \tag{2.4e}$$

According to [16] R_0 in (2.4e) can be regarded as the basic reproduction number of the disease and explained as follows. Since the total infectivity at time t is the sum of the infectivity in the compartment and the Mycobacterium ulcerans compartment, we define $R_0 = R_I + R_B$ where

$$R_I = \int_0^{\infty} S_0 \beta_H(a) \pi(a) da$$

is the number of secondary cases generated by individual in the infective compartment, and

$S_0 = \frac{\Lambda}{\mu_H}$ is the number of susceptible individuals in the absence of the disease. The term

$\pi(a) = e^{-\int_0^a (\mu_H(v) + \rho_1(1-g(v)) + \rho_2 g(v)) dv}$ is the survival probability as a function of age a in the infected class.

The reproduction number of the infectious caused by the free Mycobacterium ulcerans is

$$RB_H = \frac{\beta_H}{\delta_V} S_0 \int_0^{\infty} \eta(a) \pi(a) da.$$

Now we consider the existence of the endemic equilibria. From (2.4b) and (2.4d), we obtain that the equilibrium level of susceptible individual S^* satisfies the following equations

$$S^* = \frac{k_H + \frac{1}{\delta_V} \int_0^{+\infty} (\eta \pi(a))}{\frac{\beta_H}{\delta_V} \int_0^{+\infty} (\eta \pi(a))} (\mu_H(a) + \rho_1(1-g(a)) + \rho_2 g(a)) \pi(a).$$

3 Existence of the Solution to the State System by Method of Characteristics

We determine solution of the system applying the method of characteristics [19]. By using Banach contraction mapping principle, we prove the existence and uniqueness of the solutions of the system. To compute the solution representation for the system (2a)-(2b), we add new notation to the right hand side of the partial differential equation (PDEs):

$$f_1(B_H(t), S(a, t), R(a, t)) = \Lambda(a, t) - \beta_H(a) \frac{B_H(t)}{k_H(a) + B_H(t)} S(a, t) + \theta(a) R(a, t) \quad (3a)$$

$$f_2(B_H(t), S(a, t), I(a, t), g(a, t)) = \beta_H(a) \frac{B_H(t)}{k_H(a) + B_H(t)} S(a, t) - \rho_1(1 - g(a, t)) I(a, t) - \rho_2 g(a, t) I(a, t) \quad (3b)$$

$$f_3(S(a, t), I(a, t), R(a, t), g(a, t)) = \rho_1(1 - g(a, t)) I(a, t) + \rho_2 g(a, t) I(a, t) - \theta(a) R(a, t). \quad (3c)$$

A notice was made that, $\mu_H(a)S(a, t)$, $\mu_H(a)I(a, t)$ and $\mu_H(a)R(a, t)$ were not part of the f_i for $i = 1, 2, 3$ terms. They were added in the left side of the three partial differential equations (2a-c) to make use in the representation of the solution based on characteristics.

Let B be chosen such that

$$\int_0^A S_0(a) da \leq B, \int_0^A I_0(a) da \leq B, \int_0^A R_0(a) da \leq B,$$

and $0 \leq B_{H0} \leq B$,

The state solution is defined as

$$Y = \{(S, I, R, B_H) \in (L^\infty(0, T; L^1(0, A)))^3 \times (L^\infty(0, T))\} \\ \left. \begin{aligned} \sup_t \int_0^A |S(a, t)| da \leq 2B, \sup_t \int_0^A |I(a, t)| da \leq 2B, \\ \sup_t \int_0^A |R(a, t)| da \leq 2B, |B_H(t)| \leq 2B \end{aligned} \right\}$$

By applying the method of characteristics, we can determine the representation of the solution and then use that representation to construct the map to be employed in the fixed point argument for existence and uniqueness. Now we define a map

$L : Y \rightarrow Y$ such that

$$L(S, I, R, B_H) = (L_1(S, I, R, B_H), L_2(S, I, R, B_H), L_3(S, I, R, B_H), L_4(S, I, R, B_H))$$

where L_1 is associated with equation (2a) and L_2 is associated with equation (2b) and where

$$L_1(S, I, R, B_H)(a, t) = \begin{cases} e^{-\int_0^t \mu_H(\alpha\tau - \alpha t + a) d\tau} s_0(a - \alpha t) \\ + \int_0^t e^{-\int_s^t \mu_H(\alpha\tau - \alpha t + a) d\tau} \times \\ (f_1(B_H(s), S(\alpha s + a - \alpha t, s), \\ R(\alpha s + a - \alpha t, s))) ds \\ \text{if } a > \alpha t \\ \left(\frac{1}{\alpha}\right) \int_0^a e^{-\int_s^a \frac{\mu_H(\tau)}{\alpha} d\tau} \times \\ (f_1(B_H(\frac{s + \alpha t - a}{\alpha}), S(s, \frac{s + \alpha t - a}{\alpha}), R(s, \frac{s + \alpha t - a}{\alpha}))) ds \\ \text{if } a < \alpha t, \end{cases} \quad (3d)$$

$$L_2(S, I, R, B_H)(a, t) = \begin{cases} e^{-\int_0^t \mu_H(\alpha\tau - \alpha t + a) d\tau} I_0(a - \alpha t) \\ + \int_0^t e^{-\int_s^t \mu_H(\alpha\tau - \alpha t + a) d\tau} \times \\ (f_2(B_H(s), S(\alpha s + a - \alpha t, s), I(\alpha s + a - \alpha t, s) \\ g(\alpha s + a - \alpha t, s)) ds \\ \text{if } a > \alpha t \\ \left(\frac{1}{\alpha}\right) \int_0^a e^{-\int_s^a \frac{\mu_H(\tau)}{\alpha} d\tau} \times \\ (f_2(B_H(\frac{s + \alpha t - a}{\alpha}), S(s, \frac{s + \alpha t - a}{\alpha}), I(s, \frac{s + \alpha t - a}{\alpha})), ds \\ g(s, \frac{s + \alpha t - a}{\alpha})) ds \\ \text{if } a < \alpha t, \end{cases} \quad (3f)$$

$$L_3(S, I, R, B_H)(a, t) = \begin{cases} e^{-\int_0^t \mu_H(\alpha\tau - \alpha t + a) d\tau_{R_0(a-\alpha t)}} \\ + \int_0^t e^{-\int_s^t \mu_H(\alpha\tau - \alpha t + a) d\tau} \times \\ f_3(S(\alpha s + a - \alpha t, s), I(\alpha s + a - \alpha t, s), R(\alpha s + a - \alpha t, s), \\ g(\alpha s + a - \alpha t, s)) ds \\ \text{if } a > \alpha t \\ \left(\frac{1}{\alpha}\right) \int_0^a e^{-\int_s^a \frac{\mu_H(\tau)}{\alpha} d\tau} \times \\ (f_3(S(s, \frac{s + \alpha t - a}{\alpha}), I(s, \frac{s + \alpha t - a}{\alpha}), R(s, \frac{s + \alpha t - a}{\alpha})) ds \\ g(s, \frac{s + \alpha t - a}{\alpha})) ds \\ \text{if } a < \alpha t, \end{cases} \tag{3g}$$

with

$$L_4(S, I, R, B_H)(t) = B_{H0} e^{-\delta_L t} + \int_0^t \int_0^A e^{-\delta_L(t-s)} \eta I(a, t) dad s$$

A fixed point of the map L was derived, meeting the conditions

$$(S, I, R, B_H) = (L_1, L_2, L_3, L_4)(S, I, R, B_H),$$

with each one of $S(a, t), I(a, t), R(a, t)$ and B_H being positive, will be a solution $(S, I, R, B_H) = (S, I, R, B_H)(g)$ to the system of the model.

Theorem 2: (Existence and Uniqueness of solution). For $g \in W$ as defined in (2.23a) and D sufficiently small, there exists a unique solution (S, I, R, B_H) to the system (2a) –(2c) with boundary 2e and initial conditions 2f

Proof : We prove that the map

$$L : Y \rightarrow Y$$

stated above is a strict contraction. Note that the function f_1, f_2 and f_3 used in the S, I, R equations are Lipschitz in their arguments with the Lipschitz constants base on coefficients and parameters from our model and also on B , an addition to the bounds on S, I, R from the set Y . The definition of the map L , was given to show that L maps Y into Y and the definition of the L_i functions for $i = 1, 2, 3$ was expressed as

$$\int_0^A |L_i(S, I, R, B_H)|(a, t) da \leq D_1 B W + B \leq 2B$$

where the single B in the first inequality obtained from the bound of $\int_0^A S_0(a) da, \int_0^A I_0(a) da$, or

$\int_0^A R_0(a) da$, respectively for $i = 1, 2, 3$. By the fact W is sufficiently minimal, then the above estimate is less than or equal to $2B$.

In an addition for $j = 1, 2, 3$

$$|L_j(S, I, R, B_H)| \leq \sup\{B_{H0}\} + D_2 B W \leq 2B .$$

The constants D_1 and D_2 hinge upon the coefficients and the parameters in the model. Also for D to be sufficiently small, we get the estimates above and hence, the L maps Y into Y .

Note that for the contraction property, for $i = 1, 2, 3$ we take into account

$$\int_0^A |L_i(S_1, I_1, R_1, B_{H1}) - L_i(S_2, I_2, R_2, B_{H2})|(a, t) da.$$

There is a need to examine some of the terms on the model such as

$\beta_H(a) \frac{B_H(t)}{k_H(a) + B_H(t)} S(a, t)$ and in specific their differences. For instance, we have

$$\frac{B_{H1}(t)}{k_H(a) + B_H(t)} |S_1 - S_2|(a, t) + \frac{S_2(a, t) k_H |B_{H1} - B_{H2}|(t)}{k_H + B_{H1}(t))(k_H + B_{H2}(t))} \tag{4}$$

and consider from equations (3a) and (3b). In order to make things simple, we show an estimate of such a term for $a > \alpha t$ in $L_1(S, I, R, B_H)(a, t)$

$$\int_0^A \int_0^t e^{-\int_0^t \mu_H(\alpha\tau - \alpha t + a) d\tau} \times$$

$$B_H(\alpha s + a - \alpha t, s) \left(\frac{B_{H_2}(s)}{k_H + B_{H_2}(s)} |S_2 - S_1|(\alpha s + a - \alpha t, s) \right.$$

$$+ \frac{S_1(\alpha s + a - \alpha t, s) k_H |B_{H_2} - B_{H_1}|(s)}{(k_H + B_{H_1}(s))(k_H + B_{H_2}(s))}$$

$$\left. + \theta(\alpha s + a - \alpha t, s)(R_2 - R_1)(\alpha s + a - \alpha t, s) \right) ds da$$

Note that we let $s_1 = \alpha(s-t) + a$ and $s_2 = s$ then $0 < -\alpha t + a < \alpha(s-t) + a < a$ or $0 < (s-t) + a < A$ and $0 \leq s_2 < W$. In addition, the Jacobian for this transformation becomes finite. Hence, we can now bound the estimate above by

$$\int_0^T \int_0^A D_3 |S_2 - S_1|(s_1, s_2) + D_4 |R_2 - R_1|(s_1, s_2) ds_1 ds_2$$

$$+ D_5 \int_0^T \int_0^A |S_1(s_1, s_2)| ds_1 \{ |B_{H_2}(s_2) - B_{H_1}(s_2)| ds_2 \}$$

$$\leq D_6 W \sup_t \int_0^A (|S_2 - S_1| + |R_2 - R_1|)(a, t) da$$

$$+ D_7 N W \sup_t [|B_{H_2} - B_{H_1}|(t)]$$

In the above equations, we have substituted S_1 and S_2 by a and t respectively. Again, the constants D_k for $k = 3, \dots, 7$ depend on the bounds of the coefficients. For terms that consist of the fractional parts, we have employed the 2B bound for the terms made up of the S_i for $i = 1, 2$ in the second term of 7 for integrals over $(0, A) \times (0, t)$ when $a > \alpha t$ or for integrals over $(0, A) \times (0, a)$ when $a < \alpha t < \alpha T$. We can determine these estimates which lead

$$\int_0^A |L_1(S_1, I_1, R_1, B_{H1}) - L_1(S_2, I_2, R_2, B_{H2})|(a, t) da$$

$$\leq D_8 W \sup_t \int_0^A (|S_2 - S_1| + |R_2 - R_1|)(a, t) da + D_9 N W \sup_t [|B_{H2} - B_{H1}|(t)].$$

Similarly we estimate for $j = 2, 3$ and for $j = 4, 5$ we have

$$|L_j(S_1, I_1, R_1, B_{H1}) - L_j(S_2, I_2, R_2, B_{H2})|(t)$$

$$\leq W \sup_t \int_0^A |I_1 - I_2|(a, t) da + D_{10} \Omega \sup_t |B_{H1} - B_{H2}|(t),$$

where D_{10} has to do with η and δ .

By putting the work and carefully selecting W sufficiently small, we obtain the contraction result and therefore, desire fixed point to the system 2-2d.

4 Numerical Simulations

We state briefly the numerical method employed in our simulations. The equations for the quantities S , I and R from (2a) —(2c) from hyperbolic system of PDEs; in addition to these, we have one ODE for B_H from 2d. Our choice of numerical method is a forward time/ backward space finite difference [20]. For the convenience of our model, we use the scalar one- way wave equation.

$$\frac{\partial u}{\partial t} + \alpha \frac{\partial u}{\partial a} = f(a, t)$$

where α is a constant (that is the wave speed), and t and x denote time and space, respectively. The forward time/backward space scheme [20] for the above model is expressed as

$$\frac{f_m^{n+1} - f_m^n}{\Delta t} - \alpha \frac{f_m^n - f_{m-1}^n}{\Delta x} = q(x_m, x_n),$$

where n stands for the time index and m the space index in the time and space grid. The stability of our scheme is achieved by applying Courant-Friedrich-Levy (CFL) condition [20] to ensure a necessary and sufficient condition and satisfies that

$$\alpha \Delta x \leq \Delta t$$

For a given spatial discretization Δx , this produces a restriction on the time step as $\Delta t \leq \Delta x / \alpha$

5 Simulations with no Infected Individuals

Buruli ulcer disease requires more antibiotic in children than adults. We model the rate of losing immunity of humans at age a by

$$\theta(a) = \begin{cases} 1/365 & \text{for } a \leq 15 \text{ year}(s) \\ 1/2.363 & \text{for } a > 15 \text{ year}(s) \end{cases}.$$

The rate of waning is important because it influences our choice of initial conditions

We assumed a pool of 20,000 humans distributed uniformly over the age range $0 \leq a \leq A$, for all ages a at $t = 0$. Therefore, all 20,000 humans are distributed to the susceptible and removed classes. Based on the rate of losing immunity conditions for children and adult, it requires a year for a newborn baby to lose his or her immunity and become susceptible to Buruli ulcer. In this regard, we initialize everyone with age less than or equal to one year old in the removed section and everyone older than one year old in the susceptible section. This leads to the initial conditions

$$S(a, 0) = \begin{cases} 0 & \text{if } 0 \leq a \leq 40 \text{ weeks} \\ d & \text{if } a > 40 \text{ weeks} \end{cases}$$

$$R(a, 0) = \begin{cases} 0 & \text{if } 0 \leq a \leq 40 \text{ weeks} \\ d & \text{if } a > 40 \text{ weeks} \end{cases}.$$

for the susceptible and removed population, respectively. The numerical value of the age density d in the initial conditions depends on the number of humans and the numerical resolution of the age variable.

By applying numerical and having age resolution in weeks, we will then have to have a fixed density d for each age for $0 \leq a \leq 40$, given by

$$d = \frac{20,000 \text{ (humans)}}{50 \text{ (weeks/year)} \times 60 \text{ (year)}} \approx 8.33 \text{ humans / weeks}$$

This provides the values of d in the initial conditions for $S(a, 0)$ and $R(a, 0)$. Given the age resolution of 1 week, that at the initial time with constant density d , this leads 40 to 333 humans of each age a . In other words, we are saying that 20,000 total humans are distributed to the ages 0 to

60 uniformly as $20,000/60 \approx 333$ humans. See Table 2 for a complete description of the model parameters value and their sources.

Table 2. These are the values of the model parameters in the simulation

| Parameter | Value/Range | Sources |
|----------------|-------------|-----------|
| $\Lambda(a,t)$ | 0 | Estimated |
| $g(a,t)$ | 0.8 | Estimated |
| B_H | 1.5/7 | [2] |
| k_H | 10^5 | Estimated |
| β_H | 0.00065 | [2] |
| $\mu_H(a)$ | 0.45 | [2] |
| ρ_1 | 1/5 | Estimated |
| ρ_2 | 1/3 | Estimated |
| η | 0.04 | Estimated |
| δ_V | 1/5 | Estimated |

In Fig. 2 billow, we show the dynamics in the total population, susceptible population, infected population, and recovered population over time. We note here, the decrease in the susceptible population, which is attributed to humans who died of natural causes during the period-line of the simulation. Furthermore, we notice an increase in recovered population, which is partly due to antibiotic and partly due to natural recovery of MU by humans.

This however, takes sometime for human to lose immunity to get back to susceptible class and is governed by the rate of waning of immunity. In Fig. 2b we see that the infection reduced with respect to time and this could be inferred from people getting awareness of MU and antibiotic medications which are now available to BU patients. Even though there is no epidemic in this simulation, our model indicates more than just the population dynamics. Our three-dimensional surface plots in Fig. 3 depict the advantages of this age-structured model even in this basic simulation. Each plot in Fig. 3 indicates the number of humans at an age a in years at time t in weeks; the colour provides the same information as the height of surface. The number of humans at a particular age is calculated by integrating each density. For instance $S(a,t)$ from a years to

$a+1$ years by $\int_a^{a+1} S(\bar{a},t)d\bar{a}$ constituting the basic apprehension that humans from age a to $a+1$

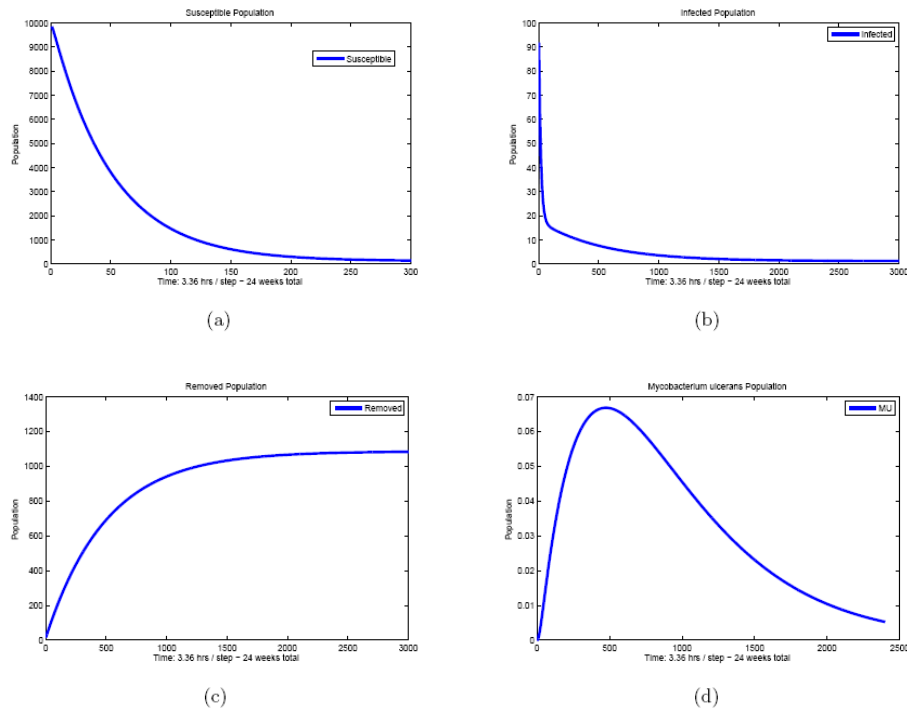


Fig. 2. Shows simulations of BU with susceptible, infected population and recovered population dynamics over time

are taken to be a years old. Notice that we use a resolution of 1 week in age, thus at the initial time with constant density d . This leads $52 \approx 120$ humans of each age a . We also examined the dynamics of B_H over time which is shown in Figs. 2(d). It depicts a peak within few days of the spread of BU and this is due to the fact that initially people do not pay attention to the environment. Hence a greater accumulation in the entire area in the curve was observed.

To make excessive use of our PDE model, we can observe at the model quantities in Fig. 3 which indicate how the quantities vary over time across different age groups. For instance, in Fig. 3, in the surface plot of the susceptible, infected and recovered population, the height (the vertical coordinate) at point (a, t) is the number of susceptible, infected and recovered people of age a at time t as the height of surface respectively. Since the susceptible and infected populations decline, as anticipated, the recovered rise over time and age. We note that owing natural recovery and antibiotic given, the recovered increase. There is a decrease in both Fig. 3(a) and 3(b) as assumed to crop up as a result of medication and long duration for humans to who have recovered to wane their immunity. We note a rise in the Fig. 3(c) as a result of high recovery rate based on natural and antibiotic medications.

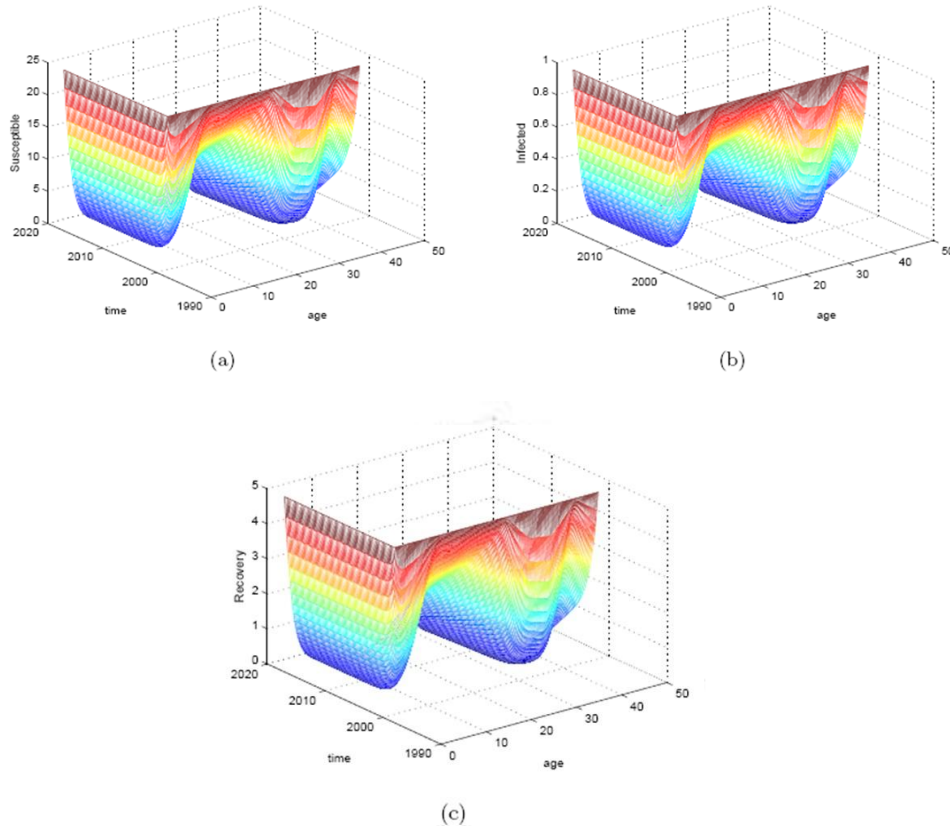


Fig. 3. Shows simulation of BU with susceptible, infected population and recovered population dynamics as function of age and time

6 Conclusion

An age-structured model can model the infection pathway of Buruli ulcer more accurately since the risk for contracting the disease has something to do with the age of a human being [5]. We observe that introducing age as another independent variable encompasses solving a system of partial differential equations instead of simpler ordinary differential equation systems and this brings in new challenges for the existence of a solution of the system, and for the numerical method. We also present our existence result for the PDE system applying a fixed point argument. We determined the reproduction number of BU disease R_0 . We present time dependent S, I, R simulation. We also present numerical simulation on both age and time the dynamics of BU disease. We also observe that Mycobacterium ulcrans spread is facilitated by the behaviour of humans as the rate of recovery untreated Buruli ulcer depend on the immunity. Treatment of Buruli ulcer at early stages reduces the epidemiology of BU disease. The inclusion of treatment

control strategies in an age-structured Buruli ulcer model will help in further explanation of the dynamics of BU.

Competing Interests

Authors have declared that no competing interests exist.

References

- [1] Duker AA, Portaels F, Hale M. Pathways of mycobacterium ulcerans infection: A review. *Environment International*. 2006;32:567-573.
- [2] Bonyah E, Owusu-Sekyere E. Modelling of buruli ulcer prevalence in Amansie West District, Ghana. *International Journal of Sciences*. 2012;1:2305-3925.
- [3] World Health Organization. Buruli Ulcer. Diagnosis of mycobacterium ulcerans. Portaels F, Johnson P, Meyers WM, eds. Geneva: World Health Organization, WHO/CDS/CPE/GBUI/2001.4.
- [4] Jacobsen KH, Padgett JJ. Risk factors for Mycobacterium ulcerans infection. *Int J Infect Dis*. 2010;14(8):677.
- [5] Asiedu K, Etuafu S, Socio-economic implications of Buruli ulcer in Ghana: A three- year review. *Am J Trop Med Hyg*. 1998;59(6):1015-1022.
- [6] Debacker M, Portaels F, Aguiar J, Steunou C, Zinsou C, Meyers W. Risk factors for buruli ulcer, Benin. *Emerg Infect Dis*. 2006;12:1325.
- [7] World Health Organization. Buruli ulcer: Number of new cases of Buruli ulcer reported (per year); 2011. Available: http://apps.who.int/neglected_diseases/ntddata/buruli/buruli.html.
- [8] Janssens P, Pattyn SR, Meyers WM, Portaels F. Buruli ulcer: A historical overview with updating . *Bull Seances Acad R Sci Outre Mer*. 2005;51:265-299.
- [9] Aidoo AY, OSei B. Prevalence of aquatic insects and arsenic concentration determine the geographical distribution of Mycobacterium ulcerans. *Computational and Mathematical Methods in Medicine*. 2007;8:235-244.
- [10] Anderson RM, May RM. Infectious disease of humans, dynamics and control. Oxford university press, infection. *Computational and Mathematical Methods in Medicine*. 1991;8:235- 244.
- [11] Sharpe F, Lotka A. A population in age distribution. *Philosophical Magazine*. 1911;6:435-438.

- [12] McKendrick. Application of Mathematics to medical problems. *Poc Edinburgh Math Soc.* 1926;44:98-130.
- [13] Gurtin ME, MacCamy RC. Non-linear age-dependent population dynamics. *Arch Rat Mech Anal.* 1974;3:281–300.
- [14] Barbu V. *Mathematical methods in optimization of differential systems.* Kluwer Academic Publishers, Dordrecht; 1994.
- [15] Amofah GK, Sagoe-Moses C, Adjei-Acquah C, Frimpong EH. Epidemiology of buruli ulcer in Amansie West District, Ghana. *Trans Roy Soc Trop Med Hyg.* 1993;87:644-645.
- [16] Diekmann O, Heesterbeek JAP, Metz, JAJ. On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations. *J Math Biol.* 1990;28:365-382.
- [17] Demasse RD, Tewa JJ, Bowong S. Analysis of an Age-structured SIL model with demographics process and vertical transmission. *ARIMA Journal.* 2014;17:23-52
- [18] Kouakep TY, Houpa DDE, Ducrot A. A model for hepatitis B with chronological and infection ages. *Applied Mathematical Sciences.* 2013;7:5977–5993.
- [19] Webb GF. *Theory of nonlinear age-dependent population dynamics.* Marcel Dekker: New York and Basel; 1985.
- [20] John C. Strikwerda. *Finite Difference Schemes and Partial Differential Equations.* Society for Industrial and Applied Mathematics (SIAM). Philadelphia, PA, second edition; 2004.

© 2014 Bonyah et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here (Please copy paste the total link in your browser address bar)

www.sciencedomain.org/review-history.php?iid=567&id=6&aid=4950