

An Age- Structured Model for the spread of Buruli ulcer: Analysis and Simulation in Ghana

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) [5]. The disease usually begins as a painless nodule or papule and may progress to massive skin ulceration [9]. It also appears that different modes of transmission occur in different geographical and epidemiological setting [18]. 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 [12]. Buruli ulcer causes serious pain as 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 continue. The study of Buruli ulcer continues to pose a public health challenge [1]. 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 [12, 13]. The modes of transmission vary with geographical and epidemiological settings [18]. In Africa, it is estimated that almost 30, 000

36 | cases were reported between 2005 and 2010 [14]. Buruli ulcer is a severe, disfiguring disease
37 | which affects all age groups but particularly children less than 15 years of age in many tropical
38 | and subtropical countries [17]. The disease has emerged over the past two or more decades,
39 | especially in Central and West Africa and has been confirmed by laboratory test in 26 countries
40 | with reports in other countries around the world [18].

41 | The known common model for the spread of an infectious disease is the Susceptible-Infected-
42 | Recovered (*SIR*) model, which is based on the categorization of individuals in the classes of
43 | susceptible (those at risk of getting the infection), infected (those with the ulcer) and recovered
44 | (those cured of the ulcer). The *SIR* models of Buruli ulcer developed at the moment are time
45 | dependent models which lead to system of ordinary differential equations (ODEs), see [2]. In
46 | order to model the pathway of infection clearly, we propose a model which considers the role of
47 | *M. ulcerans* introduced to the water reservoirs by disturbed environment and stratify the
48 | population with age.

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50 | Age is an important consideration in the modeling infectious disease that depends on age. Different age groups of populations may have different reproduction and
51 | survival capacities. A disease may vary with respect to infection and mortality for different age groups [3]. In reality, individuals of varying age groups may exhibit different
52 | behaviours and immunological competencies. Behavioural and immunological changes are vital
53 | in control and prevention of many infectious diseases and in particular the Buruli ulcer. Young
54 | individuals are known to be more active in interacting with or between populations, and the
55 | disease. This paper therefore, intends to use an age-structured model to study the spread of
56 | Buruli ulcer.

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60 | At the heart of an age-structured model, is a coupled system of hyperbolic partial differential
61 | equations (PDEs). The introduction of a system of PDEs instead of a system of ODEs gives rise
62 | to the interconnectivity of the problem greatly. Although using age-structured models to study
63 | the spread of diseases is not something new, to the best of our knowledge, no such model has
64 | been proposed for the Buruli ulcer. The equations which account for the growth of the *M.*
65 | *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 [19, 21]. The earliest models of age structured populations, due to [19] and [21] 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 [16] for nonlinear age structured models. Barbu [15] developed mathematical theory behind age-structured populations [3] 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.

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83

2.0 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

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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 [23, 24]. 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 (Figure 1).

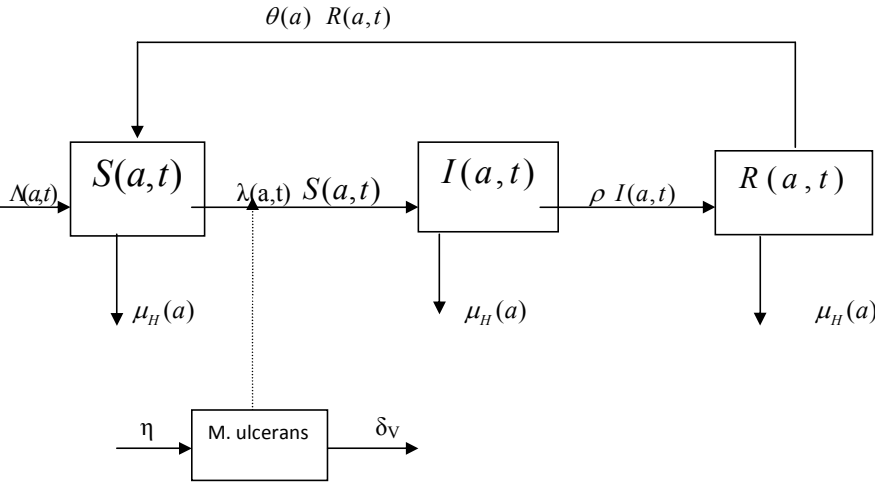


Figure 1: Proposed transmission dynamics of the Buruli ulcer between humans and M. ulcerans in the environment.

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

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123 mortality rate $\mu_H(a)$. Individuals recover from BU at a rate $\theta(a)$ which depends on age. M.
 124 ulcerans bacteria experience a natural removal rate of δ_V due to death or predation. A strategy
 125 $g(a, t)$ that can help reduce the spread of BU that represent antibiotic treatment was included in
 126 the model. This reduces the duration and quantity of infected humans concentration to the
 127 concentration of M.ulcerans bacteria in the environment. We study the age-time domain
 128 $P = (0, A) \times (0, T)$ with intervention-intervention $g(a)$. With the above notations, we study the
 129 following infected-age- structured model with Mycobacterium ulcerans transmission.

$$130 \quad \frac{\partial S}{\partial t} + \alpha \frac{\partial S}{\partial a} = \Lambda(a, t) - \beta_H(a) \frac{B_H(t)}{k_H(a) + B_H(t)} S(a, t) - \mu_H(a) S(a, t) + \theta(a) R(a, t), \quad (2a)$$

$$131 \quad \frac{\partial I}{\partial t} + \alpha \frac{\partial I}{\partial a} = \beta_H(a) \frac{B_H(t)}{k_H(a) + B_H(t)} S(a, t) - \mu_H(a) I(a, t) - \rho_1(1 - g(a, t)) I(a, t) - \rho_2 g(a, t) I(a, t) \quad ,$$

132 (2b)

$$133 \quad \frac{\partial R}{\partial t} + \alpha \frac{\partial R}{\partial a} = \rho_1(1 - g(a, t)) I(a, t) + \rho_2 g(a, t) I(a, t) - \mu_H(a) R(a, t) - \theta(a) R(a, t), \quad (2c)$$

$$134 \quad \frac{dB_H}{dt} = \int_0^\infty \eta I(a, t) da - \delta_V B_H(t) . \quad (2d)$$

135 For the above equations $\alpha = \frac{1 \text{ week}}{7 \text{ days}}$ is the coefficient introduced to balance the units of age a
 136 in weeks and time t in days. With respect to infected class, the multiplicative factors $\rho_1(1 - g)$
 137 and $\rho_2 g$ represent the rates of recovery for the individuals who have had no antibiotic treatment
 138 and those who have undergone such treatment respectively.
 139

140 The boundary and initial conditions

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

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145 $S(0,t) = 0, I(0,t) = 0, R(0,t) = \int_0^A (S(a,t) + I(a,t) + R(a,t))f(a)da,$

146

147 $(2e)$

148 where the fecundity function f is stated as

149
$$f(a) = \begin{cases} \frac{1}{5} \sin^2 \left(\pi \frac{(a-15)}{30} \right) & \text{if } 15 \leq a \leq 40 \\ 0 & \text{otherwise} \end{cases}$$

150 The fecundity function $f(.)$ is stated here in units of per year for easier readability and assumes
151 that from age 15 to 40 years a woman will give generally give birth to three children, since

152 $\int_0^{a^+} f(a)da = 3$, where $a^+ = 60$ is the largest age allowed for the simulation [25].

153 The initial conditions are stated as

154 $S(a,0) = S_0(a), I(a,0) = I_0(a), R(a,0) = R_0(a)$ and $0 \leq B_{H0} \leq B$. (2f)

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 a
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

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age – specific contribution of infected humans to the environment

ance rate of MU in the environment

Table 1: Model parameters and the state variables

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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)

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(4) The functions- $\rho_1(a), \rho_2(a), \eta(a) \in L^\infty(0, \infty)$, where $i = 1, 2, 3$.

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(2) The function- $\phi(a)$ is nonnegative and integrable.

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Abstract Cauchy problem

In this section we seek to deal with quantitative properties of (2a)-(2d) as in [25, 26]. In order to undertake this, we consider the Banach spaces. Characterize the space of functions

$$Y = \square \times L^1(0, \infty) \times \times L^1(0, \infty) \times \times L^1(0, \infty),$$

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

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

$$A\phi = -\phi' - \mu_H \phi, \text{ with the domain}$$

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

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

$$175 \quad F_1 \begin{pmatrix} \phi_1 \\ \phi_2 \\ \phi_3 \end{pmatrix} = \begin{pmatrix} \Lambda - \beta_H \frac{B_H}{k_H + B_H} \phi_1 - \mu_H \phi_1 + \theta \phi_3 \\ \beta_H \frac{B_H}{k_H + B_H} \phi_1 - \mu_H \phi_2 - \rho_1(1-g)\phi_2 - \rho_2 g \phi_2 \\ \rho_1(1-g)\phi_2 + \rho_2 g \phi_2 - (\mu_H + \theta)\phi_3 \end{pmatrix}.$$

$$176 \quad F_2 = \int_0^{+\infty} \eta \phi_1 da$$

177

178 Let us consider that

$$179 \quad \overline{DA} = X_0.$$

180 Now by carefully observing $(S(t, \cdot), I(t, \cdot), R(t, \cdot), B_H(t))$ in (2a)-(2d) together with

$$181 \quad u(t) = (0, 0, 0, S(t, \cdot), I(t, \cdot), R(t, \cdot), B_H(t))^T,$$

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

$$183 \quad \frac{du}{dt} = Au(t) + F(ut), \quad t > 1, \quad (2.21a)$$

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

185 We also take into account the positive cones

$$186 \quad Y_+ = \left[\square^+ \right]^3 \times \left[L_+^1(0, \infty) \right]^3, \quad Y_{0+} = Y_0 \cap Y_+.$$

187 Theorem 1 : *There exists a continuous semiflow $\{U(t)\}_{t \geq 0}$ on Y_{0+} into itself such that for each*

188 *$y \in Y_{0+}$, the map $t \rightarrow U(t)y$ is the unique integrated solution of (2.21a) with initial data y ,*

189 *namely $t \rightarrow U(t)y$ satisfies*

$$190 \quad (i) \quad \int_0^t U(s)y ds \in D(A), \quad \forall t \geq 0,$$

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

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

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

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

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

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

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

On the other hand one has

$$\frac{dQ(t)}{dt} = \Lambda - \mu_H Q(t)$$

$$\geq \Lambda - \mu_H.$$

So that

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

211

212 This completes the proof of the result.

213 2.23 Equilibria and their stabilities

214 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
 215 invariant for the system (2a-d)

$$216 \quad W = (S, I, R, B_H) \left| \left(\int_0^\infty S(a, t) + \int_0^\infty I(a, t) + \int_0^\infty R(a, t) \right) da \leq \frac{\Lambda}{\mu_H}, B_H(t) \leq \frac{\bar{\eta}\Lambda}{\mu_H \delta_V} \right. \quad (2.23a)$$

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

$$219 \quad \pi(a) = e^{-u(a)} e^{-\int_0^a (\rho_1(v) + g(v)) dv}.$$

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

$$222 \quad \frac{dS^*(a)}{da} = \Lambda(a, t) - \beta_H(a) \frac{B_H^*}{k_H(a) + B_H^*} S^*(a) - \mu_H(a) S^*(a) + \theta(a) R^*(a), \quad (2.4a)$$

$$223 \quad \frac{dI^*(a)}{da} = \beta_H(a) \frac{B_H^*}{k_H(a) + B_H^*} S^*(a) - \mu_H(a) I^*(a) - \rho_1(1 - g(a)) I^*(a) - \rho_2 g(a) I^*(a) \quad (2.4b)$$

$$224 \quad \frac{dR^*(a)}{da} = \rho_1(1 - g(a)) I^*(a) + \rho_2 g(a, t) I^*(a) - \mu_H(a) R^*(a) - \theta(a) R^*(a) \quad (2.4c)$$

$$225 \quad \int_0^\infty \eta I^*(a) da - \delta_V B_H^* = 0, \quad (2.4d)$$

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

$$227 \quad I^*(a) = I^*(0) \pi(a),$$

$$228 \quad B_H^* = \frac{1}{\delta_V} \int_0^{+\infty} \eta I^*(a) da.$$

229 Let

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

According to [24] 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

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

3.0 Existence of the solution to the state system by method of characteristics

We determine solution of the system applying the method of characteristics [8]. By using Banach contraction mapping principle, we prove the existence and uniqueness of the solutions of the

251 system. To compute the solution representation for the system (2a)-(2b), we add new notation to
 252 the right hand side of the partial differential equation (PDEs): a is age and t is time expressed in
 253 weeks and days respectively. $S(a,t)$ deals with susceptible humans of age a at time t divided
 254 uniformly over all ages with a unit of human per week. $I(a,t)$ has to do with infected humans of
 255 age a at time t of human per week. The $R(a,t)$ represents removed and immune humans of age
 256 a at time t of human per week. The Mycobacterium ulcerans population is represented by
 257 $B_H(t)$ of cells per ml. α is the proportionality factor and $\Lambda(a,t)$ is the recruitment rate of
 258 susceptible human population of age a at time t per week. $k_H(a)$ is the saturation constant of M
 259 ulcerans age a one per day. $\mu(a)$ is the natural mortality rate of humans at age t of one per day.
 260 $\theta(a)$ also deals with rate of waning of immunity from recovered humans at age a per day. ρ_1
 261 and ρ_2 are rate of untreated and treated Buruli ulcer per day. δ_v also explains clearance rate of
 262 M ulcerans in the environment per day. The antibiotic rate of treatment is denoted by $g(a, t)$ for
 263 humans of age a at time t . η is the age – specific contribution of infected individuals to the M
 264 ulcerans population in the environment.

265 The method of characteristics to determine the existence of a solution of system state was
 266 applied. The Banach contraction mapping principle to prove the existence and uniqueness of
 267 solution was applied. In order to find solution representation for the system (2a--d), the following
 268 notation for the right hand sides of the partial differential equation (PDEs) was created:

$$269 \quad f_1(B_H(t), S(a, t), R(a, t)) = \Lambda(a, t) - \beta_H(a) \frac{B_H(t)}{k_H(a) + B_H(t)} S(a, t) + \theta(a) R(a, t)$$

270 (3a)

$$271 \quad f_2(B_H(t), S(a, t), I(a, t), g(a, t)) = \beta_H(a) \frac{B_H(t)}{k_H(a) + B_H(t)} S(a, t) - \rho_1(1 - g(a, t)) I(a, t) - \rho_2 g(a, t) I(a, t)$$

272 (3b)

$$273 \quad f_3(S(a, t), I(a, t), R(a, t), g(a, t)) = \rho_1(1 - g(a, t)) I(a, t) + \rho_2 g(a, t) I(a, t) - \theta(a) R(a, t). \quad (3c)$$

274

275 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
 276 $i = 1, 2, 3$ terms. They were added in the left side of the three partial differential equations (2a-c)
 277 to make use in the representation of the solution based on characteristics.

278 Let B be chosen such that

$$279 \quad \int_0^A S_0(a)da \leq B, \int_0^A I_0(a)da \leq B, \int_0^A R_0(a)da \leq B, \quad \text{and } 0 \leq B_{H0} \leq B,$$

280 The state solution is defined as

$$281 \quad Y = \{(S, I, R, B_H) \in (L^\infty(0, T; L^1(0, A)))^3 \times (L^\infty(0, T))\}$$

$$282 \quad \sup_t \int_0^A |S(a, t)|da \leq 2B, \sup_t \int_0^A |I(a, t)|da \leq 2B,$$

$$\sup_t \int_0^A |R(a, t)|da \leq 2B, |B_H(t)| \leq 2B\}$$

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

286 $L : Y \rightarrow Y$ such that

$$287 \quad L(S, I, R, B_H) = (L_1(S, I, R, B_H), L_2(S, I, R, B_H), L_3(S, I, R, B_H), L_4(S, I, R, B_H))$$

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

$$\begin{aligned}
289 \quad L_1(S, I, R, B_H)(a, t) = & \begin{cases} e^{-\int_0^t \mu_H(\alpha\tau - \alpha t + a) d\tau_{S_0(a-\alpha t)}} \\ + \int_0^t e^{-\int_s^t \mu_H(\alpha\tau - \alpha t + a) d\tau} \times \\ (f_1(B_H(s), S(\alpha s + a - \alpha t, s), \\ R(\alpha s + a - \alpha t, s))) ds \\ \text{if } a > \alpha t \\ \left(\frac{1}{\alpha} \right) \int_0^a e^{-\int_s^a \frac{\mu_H(\tau)}{\alpha} d\tau} \times \\ (f_1(B_H(\frac{s + \alpha t - a}{\alpha}), S(s, \frac{s + \alpha t - a}{\alpha}), R(s, \frac{s + \alpha t - a}{\alpha}))) ds \\ \text{if } a < \alpha t, \end{cases} \quad (3d)
\end{aligned}$$

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

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

with

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

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

$$L : Y \rightarrow Y$$

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

$$310 \int_0^A |L_i(S, I, R, B_H)| (a, t) da \leq D_1 BW + B \leq 2B$$

311 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

$$312 \int_0^A R_0(a) da, \text{ respectively for } i = 1, 2, 3. \text{ By the fact } W \text{ is sufficiently minimal, then the above}$$

313 estimate is less than or equal to $2B$. In an addition for $j = 1, 2, 3$

314 $|L_j(S, I, R, B_H)| \leq \sup\{B_{H0}\} + D_2 BW \leq 2B$ was obtained. The constants D_1 and D_2 hinge upon
 315 the coefficients and the parameters in the model. Also for D to be sufficiently small, we get the
 316 estimates above and hence, the L maps Y into Y . Note that for the contraction property, for

317
 318 $i = 1, 2, 3$ this contraction property was taken into account

$$319 \int_0^A |L_i(S_1, I_1, R_1, B_{H1}) - L_i(S_2, I_2, R_2, B_{H2})| (a, t) da. \text{ There is a need to examine some of the terms on}$$

320 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, the

321 expression (4) below was investigated

$$322 \frac{B_{H1}(t)}{k_H(a) + B_H(t)} |S_1 - S_2| (a, t) + \frac{S_2(a, t) k_H |B_{H1} - B_{H2}| (t)}{k_H + B_{H1}(t) (k_H + B_{H2}(t))} \quad (4)$$

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

$$325 \int_0^A \int_0^A e^{-\int_0^t \mu_H(\alpha\tau - \alpha t + a) d\tau} \times$$

$$326 B_H(\alpha s + a - \alpha t, s) \left(\frac{B_{H2}(s)}{k_H + B_{H2}(s)} |S_2 - S_1| (\alpha s + a - \alpha t, s) \right)$$

$$\begin{aligned}
& + \frac{S_1(\alpha s + a - \alpha t, s) k_H |B_{H2} - B_{H1}|(s)}{(k_H + B_{H1}(s))(k_H + B_{H2}(s))} \\
& + \theta(\alpha s + a - \alpha t, s)(R_2 - R_1)(\alpha s + a - \alpha t, s) |ds da
\end{aligned}$$

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

$$\begin{aligned}
& \int_0^T \int_0^A D_3 |S_2 - S_1|(s_1, s_2) + D_4 |R_2 - R_1|(s_1, s_2) ds_1 ds_2 \\
& + D_5 \int_0^T \int_0^A |S_1(s_1, s_2)| ds_1 \{ |B_{H2}(s_2) - B_{H1}(s_2)| ds_2 \} \\
& \leq D_6 W \sup_t \int_0^A (|S_2 - S_1| + |R_2 - R_1|)(a, t) da \\
& + D_7 N W \sup_t [|B_{H2} - B_{H1}|(t)]
\end{aligned}$$

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 leads~~ these estimates which lead

$$\begin{aligned}
& \int_0^A |L_1(S_1, I_1, R_1, B_{H1}) - L_1(S_2, I_2, R_2, B_{H2})|(a, t) da \\
& \leq D_8 W \sup_t \int_0^A (|S_2 - S_1| + |R_2 - R_1|)(a, t) da + D_9 N \Omega \sup_t [|B_{H2} - B_{H1}|(t)].
\end{aligned}$$

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

$$\begin{aligned}
& \left| L_j(S_1, I_1, R_1, B_{H1}) - L_j(S_2, I_2, R_2, B_{H2}) \right|(t) \\
& \leq W \sup_t \int_0^A |I_1 - I_2|(a, t) da + D_{10} \Omega \sup_t |B_{H1} - B_{H2}|(t) \\
& \left| L_j(S_1, I_1, R_1, B_{H1}) - L_j(S_2, I_2, R_2, B_{H2}) \right|(t) \\
& \leq W \sup_t \int_0^A |I_1 - I_2|(a, t) da + D_{10} W \sup_t |B_{H1} - B_{H2}|(t)
\end{aligned}$$

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 [17]. 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 [17] 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. We note that any explicit scheme is only conditionally stable [17]. The stability of our scheme is achieved by applying Courant-Friedrich-Levy (CFL) condition [17] to ensure a necessary and sufficient condition and satisfies that

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

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

370

371

372 **5 Simulations with no infected individuals**

373

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

376

$$377 \quad \theta(a) = \begin{cases} 1/365 & \text{for } a \leq 15 \text{ year}(s) \\ 1/2.363 & \text{for } a > 15 \text{ year}(s) \end{cases}.$$

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

379

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

$$387 \quad S(a, 0) = \begin{cases} 0 & \text{if } 0 \leq a \leq 40 \text{ weeks} \\ d & \text{if } a > 40 \text{ weeks} \end{cases}$$

$$388 \quad R(a, 0) = \begin{cases} 0 & \text{if } 0 \leq a \leq 40 \text{ weeks} \\ d & \text{if } a > 40 \text{ weeks} \end{cases}.$$

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

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

$$394 \quad d = \frac{20,000 \text{ (humans)}}{50 \text{ (weeks / year)} \times 60 \text{ (year)}} \approx 8.33 \text{ humans / weeks}$$

395

396

397

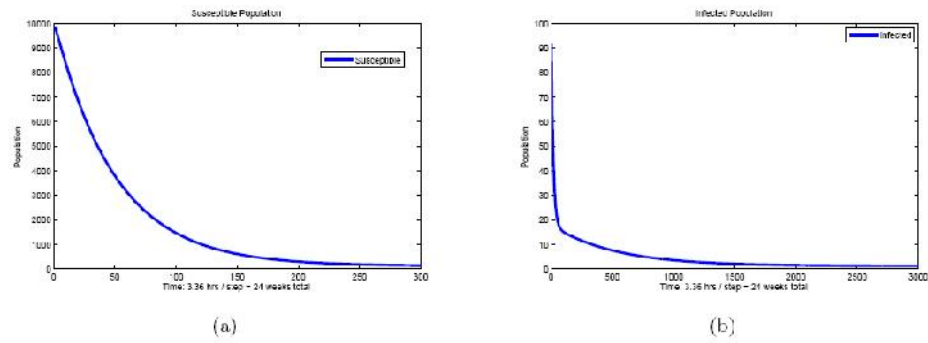
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Parameter	Value/Range	Sources
$\Lambda(a, t)$	0	Estimated
$g(a, t)$	0.8	Estimated
B_H	1.5/7	[2]
k_H	10^5	Estimated
β_H	0.00065	[2]
$\mu_H(a)$	0.45	[2]
ρ_1	1/5	Estimated
ρ_2	1/3	Estimated
η	0.04	Estimated
δ_V	1/5	Estimated

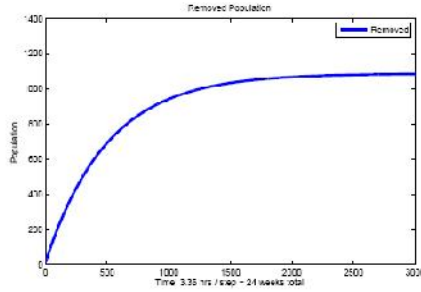
401 **Table 2:** These are the values of the model parameters in the simulation.

402
403 This provides the values of d in the initial conditions for $S(a, 0)$ and $R(a, 0)$. Given the age
404 resolution of 1 week, that at the initial time with constant density d , this leads 40 to 333 humans
405 of each age a . In other words, we are saying that 20, 000 total humans are distributed to the ages
406 0 to 60 uniformly as $20,000 / 60 \approx 333$ humans

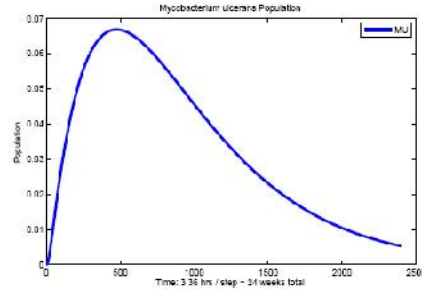
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(c)



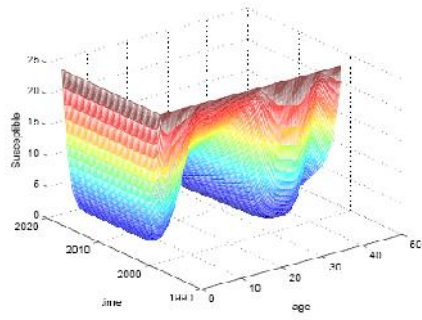
(d)

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

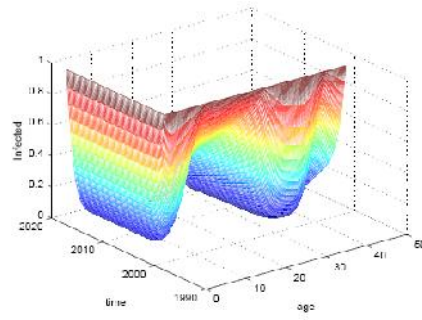
In Figure 2 above, we show the dynamics in the total population, susceptible population, infected population, and recovered population over time. We note here, the decrease in the susceptible population, which is attributed to humans who died of natural causes during the period-line of the simulation. 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 Figure 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 Figure3 depict the advantages of this age-structured model even in this basic simulation. Each plot in Figure3 indicates the number of humans at an age a in years at time t in weeks; the color 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

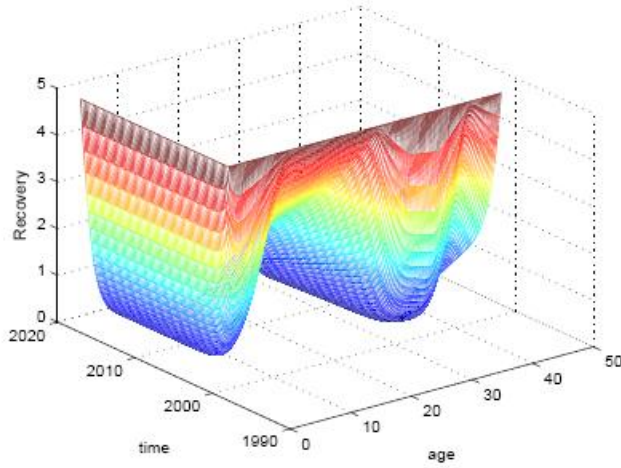
$a + 1$ years by $\int_a^{a+1} S(\bar{a},t)d\bar{a}$ constituting the basic apprehension that humans from age a to $a + 1$



(a)



(b)



(c)

Figure 3: Shows simulation of BU with susceptible, infected population and recovered population dynamics as function of age and 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 Figures 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 Figure 3 which indicate how the quantities vary over time across different age groups. For instance, in Figure 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 Figure 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 Figure 3(c) as a result of high recovery rate based on natural and antibiotic medications.

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 [1]. 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-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.

7. References

- [1] Asiedu K, Etuafu S. Socio-economic implications of Buruli ulcer in Ghana: a three- year review. *AmJ Trop Med Hyg.* 1998; 59(6):1015-1022.

472 [2] Aidoo AY, Osei B. Prevalence of aquatic insects and arsenic concentration deter- mine the
 473 geographical distribution of Mycobacterium ulcerans. Computational
 474 and Mathematical Methods in Medicine. 2007 ; 8:235-244.
 475
 476
 477 [3] Anderson RM, May RM. Infectious disease of humans, dynamics and control. Oxford
 478 university press, infection. Computational and Mathematical Methods in Medicine 1991; 8:235-
 479 244.
 480
 481 [4] Ainseba B, Langlais M. On a population dynamics control problem with age dependence and
 482 spatial structure, J. Math. Anal. Appl. 2005; 248 (2): 455474
 483
 484 [5] Duker AA, Portaels F, Hale M. Pathways of Mycobacterium ulcerans infection: A review.
 485 Environment International. 2006; 32: 567573.
 486
 487 [6] Cushing JM. The dynamics of hierarchical age-structured populations, Journal of
 488 Mathematical Biology . 1994;32:705-729
 489
 490
 491
 492 [7] John C. Strikwerda. Finite Difference Schemes and Partial Differential Equations. Society for
 493 Industrial and Applied Mathematics (SIAM), Philadelphia, PA, second edition. 2004
 494
 495 [8] Webb GF. Theory of Nonlinear Age-Dependent Population Dynamics . Marcel Dekker: New
 496 York and Basel. 1985.
 497
 498 [9] Bonyah E, Owusu-Sekyere E. Modelling of Buruli Ulcer Prevalence in Amansie West
 499 District, Ghana. International Journal of Sciences. 2012 ;1:2305-3925.
 500
 501 [10] Saleem M. Predator-prey relationships: indiscriminate predation dynamics, J. Math.Biol.
 502 1984;21:2534.
 503
 504 [11] Venturino E. Age-structured predator-prey models, Math. Modelling. (1984);5:117128.
 505
 506 [12] Jacobsen KH, Padgett JJ. 2010. Risk factors for Mycobacterium ulcerans infection. Int J
 507 Infect Dis. 2010;14(8):677.
 508
 509 [13] Debacker M, Portaels F, Aguiar J, Steunou C, Zinsou C, Meyers W. Risk factors for Buruli
 510 ulcer, Benin. Emerg Infect Dis. 2006; 12:1325.
 511
 512 [14] World Health Organization. Buruli ulcer: Number of new cases of Buruli ulcer reported
 513 (per year). http://apps.who.int/neglected_diseases/ntddata/buruli/buruli.html. 2011.
 514
 515 [15] Barbu V. Mathematical methods in optimization of differential systems, Kluwer Academic
 516 Publishers, Dordrecht. 1994.
 517

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518
519 [16] Gurtin ME, MacCamy RC. Non-linear age-dependent population dynamics. Arch. Rat.
520 Mech. Anal.1974;3:281–300.

521
522 [17] Janssens P, Pattyn SR, Meyers WM, Portaels F. Buruli ulcer: a historical overview with
523 updating . Bull Seances Acad R Sci Outre Mer. 2005; 51:265-299.

524
525 [18] World Health Organization. Buruli Ulcer. Diagnosis of Mycobacterium ulcerans. Portaels
526 F, Johnson P, Meyers WM, eds. Geneva: World Health Organization.
527 WHO/CDS/CPE/GBUI/2001.4.

528
529 [19] Sharpe F, Lotka A. A population in age distribution, Philosophical Magazine.1911; 6:435-
530 438

531
532 [20] Gopalsamy K. Age-specific coexistence in two species competition, Math.
533 Biosci.1982;61:101–122.

534
535 [21] McKendrick. Application of Mathematics to medical problems. Proc. Edinburgh Math. Soc.
536 1926; 44:98-130.

537 [22] Marston BJ, Diallo MO, Horsburgh CR. Emergence of Buruli ulcer disease in the Daloa
538 region of Cote d'Ivoire. Am J Trop Med Hyg.1995; 52:219-24.

539
540 [23] Amofah GK, Sagoe-Moses C, Adjei-Acquah C, Frimpong EH. Epidemiology of Buruli
541 ulcer in Amansie West District, Ghana. Trans Roy Soc Trop Med Hyg. 1993; 87: 644-645.

542
543 [24] Diekmann O, Heesterbeek JAP, Metz, JAJ. On the definition and the computation of the
544 basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations. J.
545 Math. Biol.1990, 28:365-382.

546
547 [25] Demasse RD, Tewa JJ, Bowong S. Analysis of an Age-structured SIL model with
548 demographics process and vertical transmission. ARIMA Journal.2014; 17:23-52

549
550 [26] Kouakep TY, Houpa DDE, Ducrot A. A Model for Hepatitis B with Chronological and
551 Infection Ages. Applied Mathematical Sciences.2013;7:5977 – 5993.

552
553
554 [1] Asiedu K, Etuafu S. Socio-economic implications of Buruli ulcer in Ghana: a three-year
555 review. Am J Trop Med Hyg. 1998; 59(6):1015–1022.

556
557 [2] Aidoo A.Y., Osei, B. Prevalence of aquatic insects and arsenic concentration deter- mine the
558 geographical distribution of Mycobacterium ulcerans, Computational
559 and Mathematical Methods in Medicine. 2007; 8: 235-244.

560
561

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[3] Anderson R.M., May R.M. Infectious disease of humans, dynamics and control. Oxford university press, 1991. infection, Computational and Mathematical Methods in Medicine 8, 235-244.

[4] Ainseba B., Langlais M. 2005. On a population dynamics control problem with age dependence and spatial structure, J. Math. Anal. Appl. 248 (2), 455-474.

[5] Duker A.A., Portaels F., Hale M. (2006) Pathways of Mycobacterium ulcerans infection: A review. Environment International 32: 567-573.

[6] Cushing, J. 1988. An Introduction to Structured Population Dynamics, Society for Industrial and Applied Mathematics.

[7] Strikwerda J. 2004. Finite difference schemes and partial differential equations, 2nd edition, Society for Industrial and Applied Mathematics.

[8] Webb, G. 1985. Theory of Non-linear Age Dependent Population Dynamics, Marcel Dekker, New York.

[9] Bonyah E., Owusu Sekyere E. 2012. Modelling of Buruli Ulcer Prevalence in Amansie West District, Ghana. International Journal of Sciences ISSN 2305-3925, vol 1.

[10] Saleem, M. 1984. Predator-prey relationships: indiscriminate predation dynamics, J. Math. Biol. 21, 253-4.

[11] Venturino, E. 1984. Age structured predator-prey models, Math. Modelling 5 (1984), 117-128.

[12] Jacobsen K.H., Padgett J.J. 2010. Risk factors for Mycobacterium ulcerans infection. Int J Infect Dis. 14(8):e677.

[13] Debaecker, M., Portaels, F., Aguiar, J., Steunou, C., Zinsou, C., Meyers, W. 2006. Risk factors for Buruli ulcer, Benin. Emerg Infect Dis, 12, 1325.

[14] World Health Organization. Buruli ulcer: Number of new cases of Buruli ulcer reported (per year). http://apps.who.int/neglected_diseases/ntddata/buruli/buruli.html

[15] Barbu, V. 1994. Mathematical methods in optimization of differential systems, Kluwer Academic Publishers, Dordrecht.

[16] Gurtin, M. E., MacCamy, R. C. 1974. Nonlinear age dependent population dynamics, Arch. Rational Mech. Anal.

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[17] Janssens, P., Pattyn, S.R., Meyers, W.M., Portaels F. 2005. Buruli ulcer: a historical overview with updating to 2005. *Bull Seances Acad R Sci Outre Mer* 51: 265-299 SIAM,14

[18] World Health Organization 2001 Buruli Ulcer. Diagnosis of Mycobacterium ulcerans Disease. Portaels F, Johnson P, Meyers WM, eds. Geneva: World Health Organization, WHO/CDS/CPE/GBUI/2001.4

[19] Sharpe F., Lotka A. 1911. A population in age distribution, *Philosophical Magazine*, 6, 435-438.

[20] Gopalsamy, K. 1982. Age specific coexistence in two species competition, *Math. Biosci.* 61.

[21] McKendrick. 1926. Application of Mathematics to medical problems. *Poe. Edinburgh Math. Soc.* 44, 98-130.

[22] Marston B J., Diallo M O., Horsburgh Jr C. R., et al. 1995. Emergence of Buruli ulcer disease in the Daloa region of Cote d'Ivoire. *Am J Trop Med Hyg* 52: 219-24.

[23] Amofah, G. K., Sagoe Moses, C., Adjei Aequah, C., Frimpong, E. H. 1993. Epidemiology of Buruli ulcer in Amansie West District, Ghana. *Trans Roy Soc Trop Med Hyg* 87: 644-645.

[24] Diekmann O, Heesterbeek J.A.P., and J. A. J. Metz, J.A.J. 1990 On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations, *J. Math. Biol.*, 28 (1990), 365-382.

[25] Demasse R. D., Tewa J. J., Bowong S. 2014. Analysis of an Age-structured SH model with demographics process and vertical transmission, *ARIMA Journal*, vol. 17, pp. 23-52.

[26] Kouakep T.Y., Houpa D., D.E., Ducrot A. 2013. A Model for Hepatitis B with Chronological and Infection Ages. *Applied Mathematical Sciences*, Vol. 7, no. 120, 5977-5993.

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