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Theoretical Assessment of Environmental Factors and Untreated Infectious Individuals in the Transmission Dynamics of *Buruli ulcer*

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Abstract

Buruli ulcer is the third most common mycobacterial disease worldwide, posing a significant public health burden, especially in impoverished regions of West and Central Africa, such as Benin. The management of *Buruli ulcer* (BU) in Africa is often hindered by limited resources, delays in treatment, and inadequate medical facilities. Additionally, a portion of the population does not seek hospital care, which facilitates the continued presence of the pathogen in the environment. This paper aims to investigate the role of environmental factors in the transmission of *Buruli ulcer*. We develop a mathematical model to describe the dynamics of *Buruli ulcer* transmission, incorporating the presence of the bacterium in the environment. Theoretical results are presented to demonstrate that the model is well-posed. We compute the equilibria, including the disease-free equilibrium and the endemic equilibrium, and study their stability. To achieve this, we derive a threshold parameter called the basic reproduction number $\mathcal{R}_0$, which determines whether the disease will persist in a human population. If $\mathcal{R}_0$ is less than one, the disease will eventually die out; if $\mathcal{R}_0$ is greater than one, the disease will persist. Sensitivity analysis is performed to understand the impact of various parameters on the dynamics of *Buruli ulcer* transmission and to identify the parameters that influence the basic reproduction number $\mathcal{R}_0$. Finally, numerical simulations are conducted to validate the theoretical results obtained from the mathematical analysis.

Keywords

Buruli Ulcer, Mathematical Models, Equilibria, Stability

1. Introduction

Mathematical models constructed for epidemic diseases are to study the nonlinear process involved in the dynamics of infectious diseases and to determine the best possible way for its control. Among other infectious diseases, one can cite the *Buruli ulcer* (BU). The World Health Organization (WHO) defines *Buruli ulcer* (BU) as "an infectious disease involving the skin, caused by *Mycobacterium ulcerans*, characterized by a painless nodule, papule, plaque or edema, evolving into a painless ulcer with undermined edges, often leading to invalidating sequelae. Sometimes bones are destroyed" [1]. After tuberculosis and leprosy, BU is the third most common mycobacterial disease. Incidences have increased recently, especially in West Africa [2] [3].

In 1997, WHO recognized BU as an emerging public health problem. In West Africa countries, the prevalence of *Buruli ulcer* has been increasing in recent years [1] [3]. *Buruli ulcer*-endemic foci are regularly associated with stagnant bodies of water (ponds, backwaters, and swamps). The disease takes various clinical forms, including ulcers, nodules, plaques, and oedematous indurations. Surgical excision followed by skin grafting is the recommended treatment [4]. *M. ulcerans* is an environmental mycobacterium associated with wetlands, especially slow-flowing or stagnant water [5] [6]. Aquatic insects may play a role in transmitting BU to humans [7] [8]. Naturally, acquired *M. ulcerans* infection in wild animals [9] suggests that the etiologic agent is an environmental organism. Bone lesions also exist [10]. Trauma is probably the most frequent means by which *M. ulcerans* is introduced deep into the skin or subcutaneous tissue [11], where a toxin is produced, causing massive necrosis of the skin. *Buruli ulcer* is therefore clinically primarily a disease of the skin. *M. ulcerans* also cause osteomyelitis: in Benin, patients have been reported to suffer from severe forms of osteomyelitis as a consequence of an *M. ulcerans* infection, sometimes necessitating amputation [12].

The mode of transmission of the disease in humans is attributed to an environmental bacterium *Mycobacterian ulcerans*. However, this mode of transmission, remains uncertain because of the mysterious character of the bacterium. One possibility is that the disease is transmitted to humans by certain insects found in water. Nowadays, there is no established correlation between infection of humans and animals. For the treatment of the most serious cases, hospitalization is necessary. Indeed, hospitalization is generally prolonged thereafter, reaching on average 3 months per patient, but can reach 18 months or more. Antibiotic treatment is unfortunately unsatisfactory.

Several mathematical models are developed in order to better understand the evolution of *Buruli ulcer* within a human population. In [13], the authors formulate a system governed by nonlinear mathematical equations. Analytical results show that the elimination of certain taxa, notably Oligochaeta worms, can effectively reduce mycobacterial transmission in aquatic ecosystems, unlike the elimination of the most abundant taxa. In [14], a mathematical model of *Buruli ulcer* with a saturated processing function is developed with the aim of theoreti-

cally modeling the possible impact of challenges associated with the treatment and management of BU, such as delays in accessing treatment, limited resources and few medical facilities to deal with the very complex treatment of ulcer. Other authors such as [15] propose a mathematical model of *Buruli ulcer* transmission integrating optimal control strategies. [16] proposes a model of leprosy, a disease of the same category as UB.

Despite the numerous efforts already made, *Buruli ulcer* remains a public health issue in several countries, including Benin. Diagnosed patients are hospitalized for the entire duration of their treatment.

However, how do environmental factors and individuals' loss of follow-up influence the understanding of *Buruli ulcer* transmission dynamics, and what are the potential impacts of this integration on disease prevention and control strategies?

This work introduces a new mathematical model and intervention strategies that integrate the environment as well as individuals lost to follow-up (those who, due to lack of resources or for cultural reasons, do not return to the hospital) to explore the dynamics of *Buruli ulcer*.

Section-wise, the paper is summarized as follows: The *Buruli ulcer* model is formulated in section 2 taking into account individuals lost to follow-up. The basic properties, stability and sensitivity analysis of the model as well as some numerical simulations to validate the theoretical results obtained are given in section 3. Basic control of *Buruli ulcer* using the different mortality thresholds and of bacterial shedding in section 4. The final section 5 concludes the paper and provides some discussions that highlight some relevant perspectives.

2. Model Formulation

In this section, we proceed with the formulation of a mathematical model for the environmental transmission of *Buruli ulcer* within a human population.

We propose a deterministic compartmental model on the environmental transmission of *Buruli ulcer*. The population under consideration is grouped into disjoint classes or compartments. We divide the human population into four states representing disease status. At any time t, there are the following epidemiological statuses.

1) *Susceptible individuals S*. This class contains human individuals who are susceptible to *Buruli ulcer*.

2) *Exposed individuals E*. This class contains individuals who have come into contact with the contaminated environment but show no symptoms of the disease. They can after some time develop into illness or heal. Once sick, they can either decide to go to the hospital for treatment or to treat themselves at home.

3) *Infectious humans I*. The class of human infectious humans contains individuals who, after contracting the infection, progressed to the disease. They went to the hospital to be diagnosed and were isolated for treatment.

4) *Lost individuals J*. This class contains individuals who, after contracting the infection, progressed to the disease. After being diagnosed with the disease, they

left the hospital and decided to treat themselves by other means.

5) *Recovered individuals R*. This class comprises human cases that recover from the infection, because recovery is accompanied with the acquisition of partial immunity so that this class of individuals is partially protected against further infection and they join the class of susceptible individuals after a period

Thus, the total human population alive at time t is

$$N(t)=S(t)+E(t)+I(t)+J(t)+R(t). \tag{1}$$

Also, there is an environment class (P), which represents the concentration of *Mycobacterium ulcerans* in the environment. The environmental class represents the reservoir of contamination in the community associated with individuals lost to follow-up who have decided to seek treatment by means other than the hospital.

The model is based on the following assumptions:

We assume each sub-population of humans is submitted to the natural death rate μ. Susceptible individuals are recruited into the population at rate Λ. Transmission of *Buruli ulcer* disease within the human population occurs through contact between individuals susceptible to *Mycobacterium ulcerans* and the *Mycobacterium ulcerans* concentration in the environment.

We assume that the transmission of *Buruli ulcer* is modeled by the mass action. Thus, human susceptible individuals are infected at rate $\lambda(P)S(t)$ where $\lambda(P)$ is the force of infection given by

$$\lambda(P)=\gamma P(t), \tag{2}$$

where γ is the effective contact rate for *Mycobacterium ulcerans* in the environment.

A flow diagram characterizing the full model is depicted in Figure 1. In the diagram, solid lines represent flow between compartments, the dashed lines represent the infected classes contaminating the environment, and new infections coming from the interaction of susceptibles with the environment.

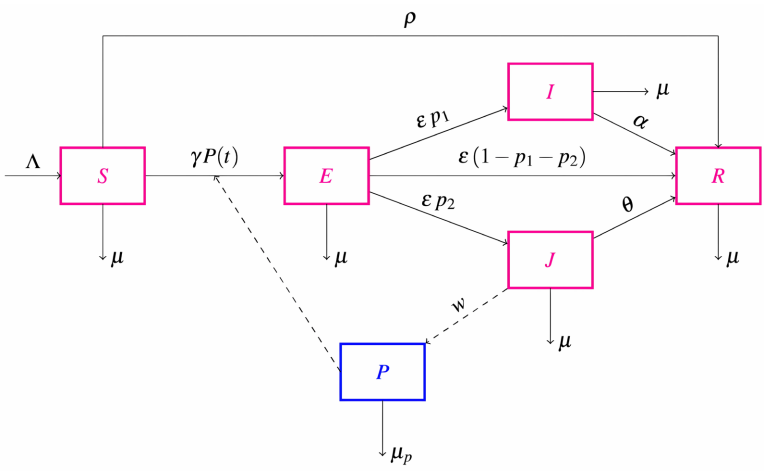

Figure 1. Structure of the model.

This transmission model is expressed by the following deterministic system of nonlinear ordinary differential equations:

$$\begin{cases} \dot{S}(t) = \Lambda + \rho R(t) - \gamma S(t) P(t) - \mu S(t), \\ \dot{E}(t) = \gamma S(t) P(t) - (\varepsilon + \mu) E(t), \\ \dot{I}(t) = \varepsilon p_1 E(t) - (\mu + \alpha) I(t), \\ \dot{J}(t) = \varepsilon p_2 E(t) - (\mu + \theta) J(t), \\ \dot{R}(t) = \varepsilon (1 - p_1 - p_2) E(t) + \alpha I(t) + \theta J(t) - (\mu + \rho) R(t) \\ \dot{P}(t) = \omega J(t) - \mu_p P(t). \end{cases} \tag{3}$$

A complete list and description of all variables and parameters in system (3) is summarized in Table 1 and Table 2, respectively. For biological reasons, all the parameters are assumed nonnegative.

Table 1. Variables with units for system (3).

Symbols	Description	Units
S	Susceptible human	indiv
E	Exposed human	indiv
I	Infectious human	indiv
J	Lost human	indiv
R	Recovered human	indiv
P	Free *M. ulcerans* concentration in the environment	cell·ml^{-1}
N	Total number of human population	indiv

Table 2. Parameters with units for system (3).

Symbols	Description	Units
Λ	Recruitment into susceptible humans	indiv·day^{-1}
β	*Buruli ulcer* disease transmission rate from	day^{-1}
ρ	Rate of loss of immunity	day^{-1}
p_1	Proportion of exposed individuals who become infectious and go to the hospital	day^{-1}
p_2	Proportion of exposed individuals who are non diagnostic in the hospital. They are lost infectious	day^{-1}
α	Recovery rate of infectious humans	day^{-1}
θ	Recovery rate of lost infectious humans	day^{-1}
μ	Natural mortality in the human population	day^{-1}
μ_P	Natural mortality rate of *Mycobacterium ulceran* in the environment	day^{-1}
ω	Shedding rate of infected humans to the environment	day^{-1}
γ	Environmental infection rate	day^{-1}
ε	Proportion of exposure that becomes infectious	day^{-1}

3. Model Analysis

In this section, we present all the theoretical results of the system (3). We study the basic properties which are essential in the proof of stability results and determine the asymptotic behaviour of our model.

3.1. Basic Properties

We start by proving that the model is well-defined and respects a biological reality. The right-hand side of System (3) is a continuously differentiable map $\mathcal{C}^1$. Then, by the Cauchy Lipschitz theorem, system (3) has a unique local positive solution.

Theorem 1. *Let* $\left(t_0=0, X_0=\left(S(0), E(0), I(0), J(0), R(0), P(0)\right)\right) \in \mathbb{R} \times \mathbb{R}_+^6$ *and for* $T \in]0,+\infty]$, $\left([0, T[, X=\left(S(t), E(t), I(t), J(t), R(t), P(t)\right)\right)$ *the maximal solution of the Cauchy problem associated to System* (3). *Then,* $\forall t \in [0; T[$, $X(t) \in \mathbb{R}_+^6$.

Proof. Let $X(t)$ be a solution of system (3). Suppose $X(0)>0$ and prove $X(t)>0$ for all $t \geq 0$.

Since $X(t)$ is continuous and $X(0)>0$, there exists $t_1>0$ such that $X(t)>0$ for all $t \in]0, t_1[$. Let us prove that $t_1=\infty$.

Let us suppose $t_1<\infty$, there exists $t_2 \geq t_1$ such that at least one of components of X is equal to 0 in time t_1. Let us pose

$$\begin{aligned} t^* = \inf \{ & t_1 \geq 0 / S(t_2)=0 \text{ or } E(t_2)=0 \text{ or } I(t_2)=0 \\ & \text{or } J(t_2)=0 \text{ or } R(t_2)=0 \text{ or } P(t_2)=0 \} \end{aligned}$$

Let us suppose $S(t^*)=0$, from the first equation of system (3), one has:

$$\begin{aligned} & \Lambda+\rho R(t)>0 \Rightarrow \dot{S}(t)>-(\mu+\gamma P(t)) S(t) \text{ for all } t \in [0, t^*], \\ & \Rightarrow S(t^*)>S(0) \exp\left[-\mu t^*-\int_0^{t^*} \gamma P(s) \mathrm{ds}\right]. \end{aligned} \tag{4}$$

Since $S(0)>0$, one has $S(t)>0$, this is absurd $S(t^*)=0$. Thus, $S(t)$ remains positive. Similarly, we prove that all components $X(t)$ are always positive.

Theorem 2. *The following sets are positively invariant and attractive for the System* (3)

$$\Omega_N=\left\{N \in \mathbb{R}^+, N \leq \frac{\Lambda}{\mu}\right\} \text{ and } \Omega_P=\left\{P \in \mathbb{R}^+, P \leq \frac{w \Lambda}{\mu \mu_p}\right\} \tag{5}$$

Proof. The dynamic of the total human population satisfies

$$\dot{N}(t)=\Lambda-\mu N(t). \tag{6}$$

Then, solving the equation, we get

$$N(t)=\frac{\Lambda}{\mu}+\left(N(0)-\frac{\Lambda}{\mu}\right) \mathrm{e}^{-\mu t}, \forall t \geq 0,$$

where $N(0)$ is the initial value of $N(t)$. It implies that

$$N(t) \leq \frac{\Lambda}{\mu}, \forall t \in \mathbb{R}^+, \text{ if } N(0) \leq \frac{\Lambda}{\mu}.$$

The dynamic of the pathogenic population also satisfies

$$\begin{aligned} \dot{P}(t) &= wJ(t) - \mu_p P(t) \\ &\leq \frac{w\Lambda}{\mu} - \mu_p P(t). \end{aligned} \tag{7}$$

Then, using Gronwall Lemma (Appendix A), we get

$$P(t) \leq \frac{w\Lambda}{\mu\mu_p} + \left(P(0) - \frac{w\Lambda}{\mu\mu_p} \right) e^{-\mu_p t}, \forall t \geq 0,$$

where $P(0)$ is the initial value of $P(t)$. It implies that

$$P(t) \leq \frac{w\Lambda}{\mu\mu_p}, \forall t \in \mathbb{R}^+, \text{ if } P(0) \leq \frac{w\Lambda}{\mu\mu_p}.$$

This achieves the proof. □

Corollary 1. *System* (3) *is a dynamical system in the biological feasible compact set*

$$\Omega = \left\{ (S, V, R, I_d, I_u, P) \in \mathbb{R}_+^6 \mid N \leq \frac{\Lambda}{\mu} \text{ and } P \leq \frac{w\Lambda}{\mu\mu_p} \right\} \tag{8}$$

□

Proof. It is a straightforward consequence of Theorem 1 and Theorem 2.

3.2. Determination of Equilibrium Points and Study of Stabilities

Herein, we determine equilibria of system (3) and we study their stability.

The Disease Free Equilibrium (DFE) and Its Stability

The disease-free equilibrium point is obtained by solving all equations of system (3) equal to zero with $I = J = 0$. Note that $I = J = 0$ implies $E = R = P = 0$ and $S = S^* = \frac{\Lambda}{\mu}$. So, the disease free equilibrium is given by:

$$Q_0 = \left(S^*, 0, 0, 0, 0, 0 \right) \tag{9}$$

Now, let us study the stability of the DFE. The stability of the DFE depends on the basic reproduction number. In epidemiology, the basic reproduction number $\mathcal{R}_0$ is one of the most important quantities for disease control, which is defined as the expected number of secondary case produced, in a completely susceptible population, by a typical infective individual. We use the method of Van den Driessche and Watmough [17] to compute the basic reproduction number of system (3).

Infected humans and Mycobacterium in the environment of system (3) can be rewritten as follows:

$$\frac{dX}{dt} = \mathcal{F}(X) - \mathcal{V}(X), \tag{10}$$

where $X = (E, I, J, R, P)^T$, $\mathcal{F}(X)$ is the incidence rate of new infections, and

$\mathcal{V}(X)$ is the transfer rate of individuals into, and out of, each sub-population defined as follows:

$$\mathcal{F}=\begin{bmatrix}\gamma PS\\0\\0\\0\\0\end{bmatrix} \text{ and } \mathcal{V}=\begin{bmatrix}(\mu+\varepsilon)E\\-\varepsilon p_1 E+I\\-\varepsilon p_2 E+(\mu+\theta)J\\-\varepsilon(1-p_1-p_2)E+(\mu+\rho)R\\-wJ+\mu_p P\end{bmatrix}$$

The Jacobian matrices of F and V at the disease-free equilibrium Q_0 are, respectively,

$$F=\begin{bmatrix}0&0&0&0&\dfrac{\Lambda\gamma}{\mu}\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\end{bmatrix}$$

and

$$V=\begin{bmatrix}\varepsilon+\mu&0&0&0&0\\-p_1\varepsilon&\mu+\alpha&0&0&0\\-p_2\varepsilon&0&\mu+\theta&0&0\\-(1-p_1-p_2)\varepsilon&0&0&\mu+\rho&0\\0&0&-w&0&\mu_p\end{bmatrix}$$

The next generation matrix FV^{-1} is

$$FV^{-1}=\begin{bmatrix}\dfrac{\Lambda p_2\gamma\varepsilon w}{\mu\mu_p(\mu+\theta)(\mu+\varepsilon)}&0&\dfrac{\Lambda\gamma w}{\mu\mu_p(\mu+\theta)}&0&\dfrac{\Lambda\gamma}{\mu\mu_p}\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\\0&0&0&0&0\end{bmatrix}$$

The basic reproduction number is the spectral radius of the next generation matrix, FV^{-1}:

$$\mathcal{R}_0=\rho\left(FV^{-1}\right)=\frac{\Lambda p_2\gamma\varepsilon w}{\mu\mu_p(\mu+\theta)(\mu+\varepsilon)}=\frac{p_2\gamma\varepsilon wS^*}{\mu_p(\mu+\theta)(\mu+\varepsilon)} \tag{11}$$

Following Van den Driessche and Watmough [17], we have the following result about the local stability of the pest free equilibrium Q_0.

Proposition 3. The disease free equilibrium Q_0 is locally asymptotically stable when $R_0\le 1$ and unstable when $\mathcal{R}_0>1$.

3.3. Sensitivity Analysis

Mathematical models are useful to understand the behaviour of an infection when it enters a community and investigates under which conditions it will be

wiped out or continued. *Buruli ulcer*, is a disease that is increasingly of interest researchers with the aim of reducing the morbidity and costs associated with the disease and to prevent long-term disabilities. After formulation of our model, it is important to study the relationship between parameters and variables of our model through sensitivity analysis.

Sensitivity analysis on a model aims to identify the most influential input factors on the output(s) of interest, whether in direct effect or in interaction effect with other factors. The input factors of the sensitivity analysis are most often model parameters whose precise values are uncertain.

In this part, we examine the effect of system parameters (3) on the basic reproduction number $\mathcal{R}_0$ to confirm their impact on *Buruli ulcer* transmission. To do this, the sensitivity index of each parameter of the model which is linked to the $\mathcal{R}_0$ reproduction number will be calculated. We use the formula presented in [18],

$$\Gamma_p^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial p} \times \frac{p}{\mathcal{R}_0} \tag{12}$$

From this formula, we can deduce that sensitivity indices are useful for assessing the relative change of a state variable in response to a variation of a parameter. We will now calculate the sensitivity indices with respect to the model parameters using Equation (12).

$$\begin{aligned}
\Gamma_\gamma^{\mathcal{R}_0} &= \frac{\partial \mathcal{R}_0}{\partial \gamma} \times \frac{\gamma}{\mathcal{R}_0} = 1 > 0, \\
\Gamma_\omega^{\mathcal{R}_0} &= \frac{\partial \mathcal{R}_0}{\partial \omega} \times \frac{\omega}{\mathcal{R}_0} = 1 > 0, \\
\Gamma_{\mu_p}^{\mathcal{R}_0} &= \frac{\partial \mathcal{R}_0}{\partial \mu_p} \times \frac{\mu_p}{\mathcal{R}_0} = -1 < 0, \\
\Gamma_\xi^{\mathcal{R}_0} &= \frac{\partial \mathcal{R}_0}{\partial \xi} \times \frac{\xi}{\mathcal{R}_0} = \frac{\mu}{\mu + \xi} > 0, \\
\Gamma_\theta^{\mathcal{R}_0} &= \frac{\partial \mathcal{R}_0}{\partial \theta} \times \frac{\theta}{\mathcal{R}_0} = -\frac{\theta}{\mu + \theta} < 0,
\end{aligned} \tag{13}$$

The analytical expression of the sensitivity indices for the parameters of model (3) is presented in (13). We found that the γ, ω, ξ parameters all have positive sensitivity indices, meaning that $\mathcal{R}_0$ are increased by an increase in parameters. The other parameters θ, μ_p all have negative values, meaning there is a decrease in $\mathcal{R}_0$ as the parameters increase.

We will analyze the sensitivity of the variables *S*, *E*, *I*, *J*, *R* and *P* using the E-fast method. This method identifies which parameter uncertainties most influence the variability of model outputs. It highlights first-order effects (main effects) and total effects (which include interactions between parameters) by decomposing the variance of the model results into individual effect components as well as their interaction.

In **Table 3**, page 13, we provide value ranges for the model parameters.

Table 3. Parameters values used for numerical simulations of the system (3).

Symbols	Values used for sensitivity analysis	Values used for numerical simulations	References
Λ	$[0.001;0.2]$	0.1	Assumed
γ	$[0.0001;0.0015]$	0.0001	Assumed
ρ	$\left[0;1.1\times10^{-2}\right]$	0.011	[14]
p_1	$[0.01;0.3]$	0.2	Assumed
p_2	$[0.01;0.1]$	0.1	Assumed
a	$\left[1.6\times10^{-5};0.5\right]$	0.5	[19]
θ	$[0.1;0.25]$	0.25	Assumed
μ	4.5×10^{-5}	4.5×10^{-5}	[20]
μ_p	$[0.1;0.8]$	0.2 - 0.75	[20]
ε	$[0.01;0.022]$	0.011	Assumed
w	$[30;100]$	40 - 100	Assumed

Figure 2 presents the sensitivity analysis (E-fast method) of all system variables (3). The gray part of Figure 2 shows the first-order sensitivity index (main index), while the sum of the two parts (gray and blue) shows the total sensitivity index. It illustrates the sensitivity of the parameters on the output variables *S*, *E*, *I*, *J*, *R* and *P*. We see that the parameters γ and μ are the most sensitive parameters for all the output variables except *S*. *xi* is the most sensitive parameter for the population of those exposed *E* of the infected *I* and the infected lost to follow-up *J*. For the aquatic ecosystem *M. ulcerans* ω and μ_p are the most sensitive parameters

It is important to always have $\mathcal{R}_0 \leq 1$, in this case, *Buruli ulcer* no longer spreads within the human population. Now, to determine parameters that impact negatively or positively the basic reproduction number $\mathcal{R}_0$ and to complete the results obtained in (13) we will use the Latin Hypercube Sampling (LHS) method and Partial Rank Correlation Coefficient (PRCC) compared to $\mathcal{R}$. The PRCCs provide indications on the relative importance and nature (positive or negative) of the impact of each parameter on the model outputs.

Parameters with high PRCCs (in absolute value) are identified as having a significant influence on the model.

Figure 3, page 11 shows the LHS-PRCC analysis on basic reproduction numbers $\mathcal{R}_0$. One can observe that $\mathcal{R}_0$ is more impacted specifically by parameters Λ, γ, ω which have positive effect on $\mathcal{R}_0$ while μ, μ_p and θ which have a negative effect. Since μ_p, represents bacterial mortality rate, keeping $\mathcal{R}_0$ below 1 amounts to increasing the mortality of free bacteria in the environment and reducing the infection rate.

The local asymptotic stability of the disease-free equilibrium Q_0 does not guarantee the complete elimination of the disease within a human population. Only the global asymptotic stability of the disease-free equilibrium Q_0 ensures that the disease either dies out or persists within a human population. We are now going to

study the global asymptotic stability of the disease-free equilibrium Q_0.

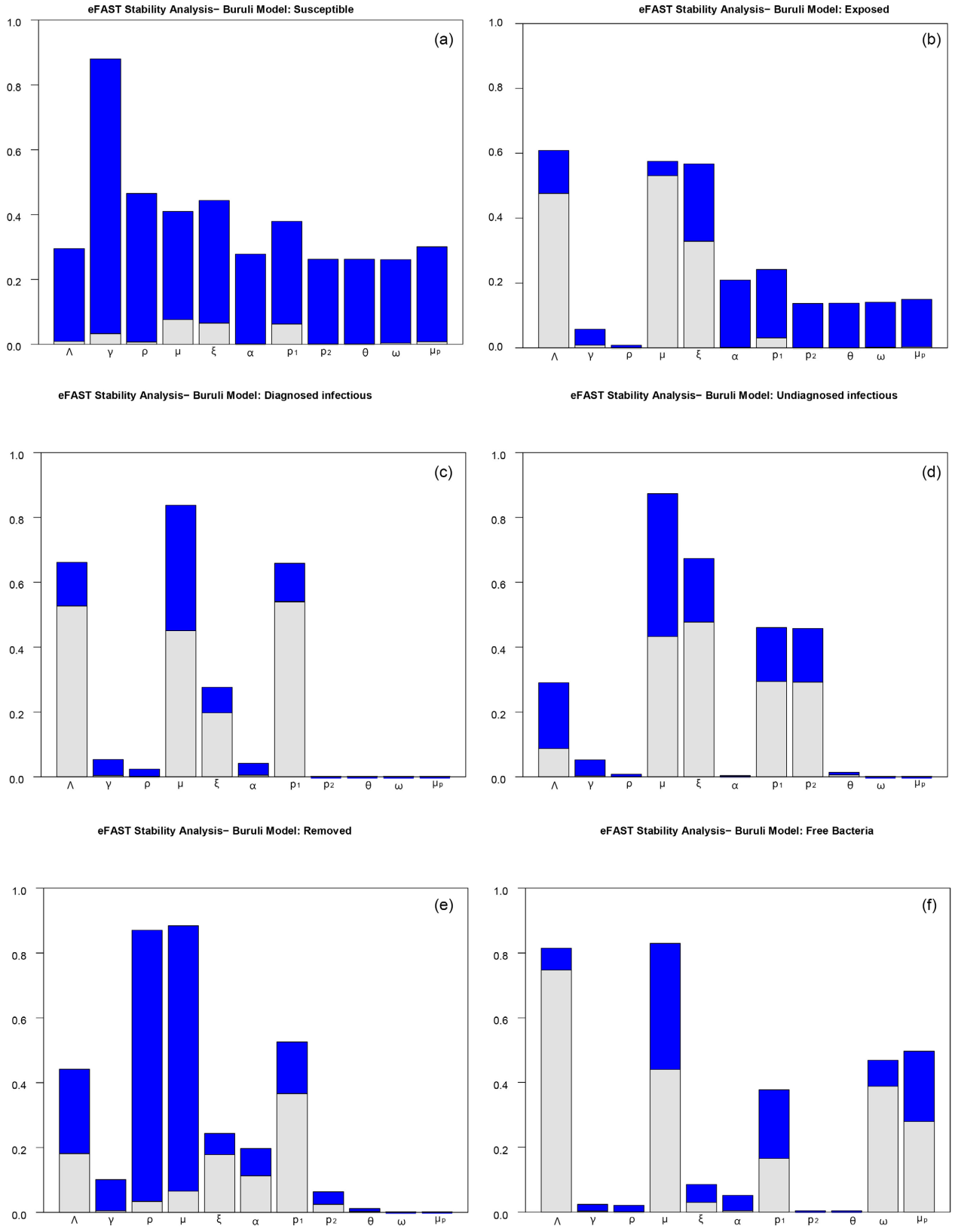

Figure 2. Efast sensitivity analysis of *Buruli ulcer* model.

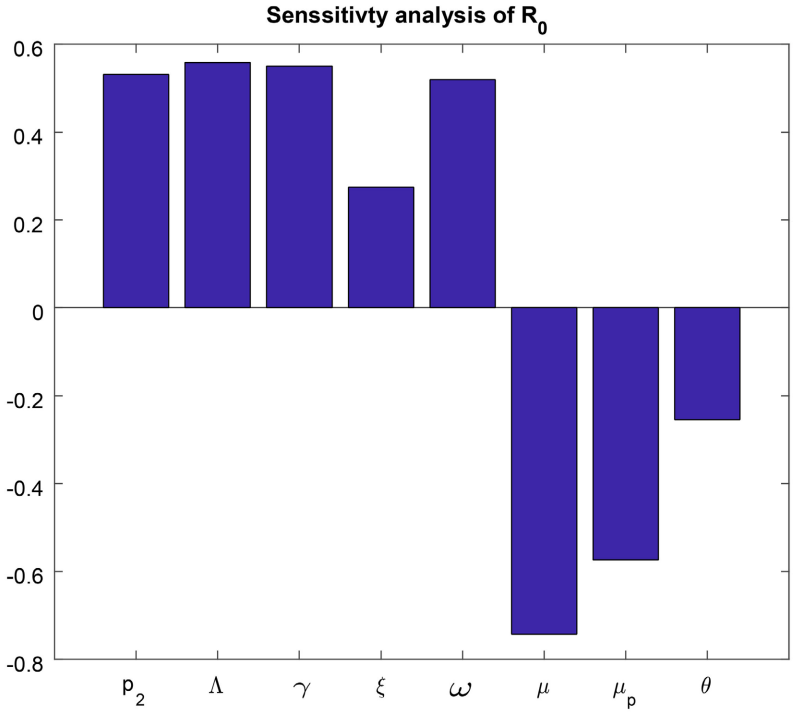

Figure 3. PRCC sensitivity analysis of $\mathcal{R}_0$.

Theorem 4 The disease-free equilibrium Q_0 is globally asymptotically stable if $\mathcal{R}_0 \le 1$.

Proof. Let $\boldsymbol{X} = (S, E, I, J, R, P)^{\mathrm{T}}$ and consider a Lyapunov function,

$$V(\boldsymbol{X}) = \frac{p_2 \varepsilon w}{\mu + \varepsilon} E + wJ + (\mu + \theta) P. \tag{14}$$

Direct calculation leads to

$$\begin{aligned} \dot{V} &= \frac{p_2 \varepsilon w}{\mu + \varepsilon} \dot{E} + w\dot{J} + (\mu + \theta)\dot{P} \\ &= \frac{p_2 \varepsilon w}{\mu + \varepsilon} \left(\gamma PS - (\mu + \varepsilon) E \right) - w\left(\varepsilon p_2 E - (\mu + \theta) J \right) + (\mu + \theta)\left(wJ - \mu_p P \right) \\ &= \mu_p (\mu + \theta) P \left[\frac{p_2 \gamma \varepsilon w S}{\mu_p (\mu + \theta)(\mu + \varepsilon)} - 1 \right] \end{aligned}$$

Therefore

$$\begin{aligned} \dot{V} &\le \mu_p (\mu + \theta) P \left[\frac{p_2 \gamma \varepsilon w S^*}{\mu_p (\mu + \theta)(\mu + \varepsilon)} - 1 \right] \text{ since } S \in \Omega \\ &= \mu_p (\mu + \theta) P (\mathcal{R}_0 - 1) \text{ whenever } \mathcal{R}_0 \le 1. \end{aligned}$$

Furthermore,

$$\dot{V} = 0 \Leftrightarrow P = 0 \text{ or } S = S^* \text{ and } \mathcal{R}_0 = 1$$

Thus the largest invariant set $\mathcal{H}$ such as $\mathcal{H} \subseteq \{ X \in \Omega, \dot{V}(X) = 0 \}$ is the singleton Q_0. By LaSalle's Invariance Principle, Q_0 is globally asymptotically stable in Ω.

This achieves the proof.

Theorem 4 completely determines the global dynamics of system (3) in Ω when $\mathcal{R}_0 \le 1$. It establishes the basic reproduction number as a threshold parameter. If $\mathcal{R}_0 \le 1$, all the solutions in the feasible region converge to the disease free equilibrium Q_0, and the *Buruli ulcer* will die out from the population irrespective of the initial conditions. If $\mathcal{R}_0 > 1$, the disease free equilibrium Q_0 is unstable and the system is uniformly persistent, and a *Buruli ulcer* epidemic will become endemic.

Now, we will illustrate our theoretical results by numerical simulations.

For numerical simulations, we use parameters values consigned in Table 3. Initial conditions are $S(0)=300$, $E(0)=200$, $I(0)=150$, $J(0)=100$, $R(0)=100$ and $P(0)=100$. Figure 4, page 14 presents the trajectories of system (3) when $\Lambda=0.1$; $\gamma=0.0001$; $\rho=0.011$; $p_1=0.2$; $p_2=0.1$; $\alpha=0.5$; $\theta=0.25$; $\mu=0.00045$; $\mu_p=0.5$; $\varepsilon=0.011$; $w=30$ so that $\mathcal{R}_0=0.531\le 1$. From this figure, it clearly appears that the trajectories of system (3) converge to the disease free equilibrium Q_0 as shown in Theorem 4. This means that the disease disappears within a human population.

3.4. Endemic Equilibrium (EE) and Its Stability

Endemic equilibrium is obtained by solving the following system:

$$\begin{cases} \Lambda+\rho\bar{R}-\gamma\bar{S}\bar{P}-\mu\bar{S}=0 \\ \gamma\bar{S}\bar{P}-(\varepsilon+\mu)\bar{E}=0 \\ \varepsilon p_1\bar{E}-(\mu+\alpha)\bar{I}=0 \\ \varepsilon p_2\bar{E}-(\mu+\theta)\bar{J}=0 \\ \varepsilon(1-p_1-p_2)\bar{E}+\alpha\bar{I}+\theta\bar{J}-(\mu+\rho)\bar{R}=0 \\ w\bar{J}-\mu_p\bar{P}=0 \end{cases} \tag{15}$$

The resolution of Equation (15) leads to $\bar{Q}=(\bar{S},\bar{E},\bar{I},\bar{J},\bar{R},\bar{P})$ where

$$\bar{S}=\frac{\Lambda+\rho\bar{R}}{\mu+\gamma\bar{P}},\quad \bar{E}=\frac{\mu\mu_p(\mu+\theta)^2(\mu+\alpha)(\mu+\rho)(\mu+\varepsilon)(\mathcal{R}_0-1)}{\mathcal{D}},$$

$$\bar{I}=\frac{\varepsilon p_1\bar{E}}{\mu+\alpha},\quad \bar{J}=\frac{\varepsilon p_2\bar{E}}{\mu+\theta},\quad \bar{R}=\frac{\varepsilon(1-p_1-p_2)\bar{E}+\alpha\bar{I}+\theta\bar{J}}{\mu+\rho},\quad \bar{P}=\frac{w\bar{J}}{\mu_p}$$

where

$$\mathcal{D}=\gamma w\varepsilon p_2\mu_p\left[\mu^4+\mu^3(\rho+\alpha+\theta+\varepsilon)+\mu^2\left(\rho\varepsilon(1+p_1+p_2)+\alpha(\rho+\varepsilon+\theta)+\theta(\varepsilon+\rho)\right)\right]$$

So, we have the following result:

Theorem 5. *System* (3) *has a unique endemic equilibrium when* $\mathcal{R}_0>1$.

Now, let us study the stability [21] of the endemic equilibrium $\bar{Q}$.

Theorem 6. *Endemic equilibrium* $\bar{Q}$ *is globally asymptotically stable when* $\mathcal{R}_0>1$.

Proof. The proof of this Theorem is given in Appendix B.

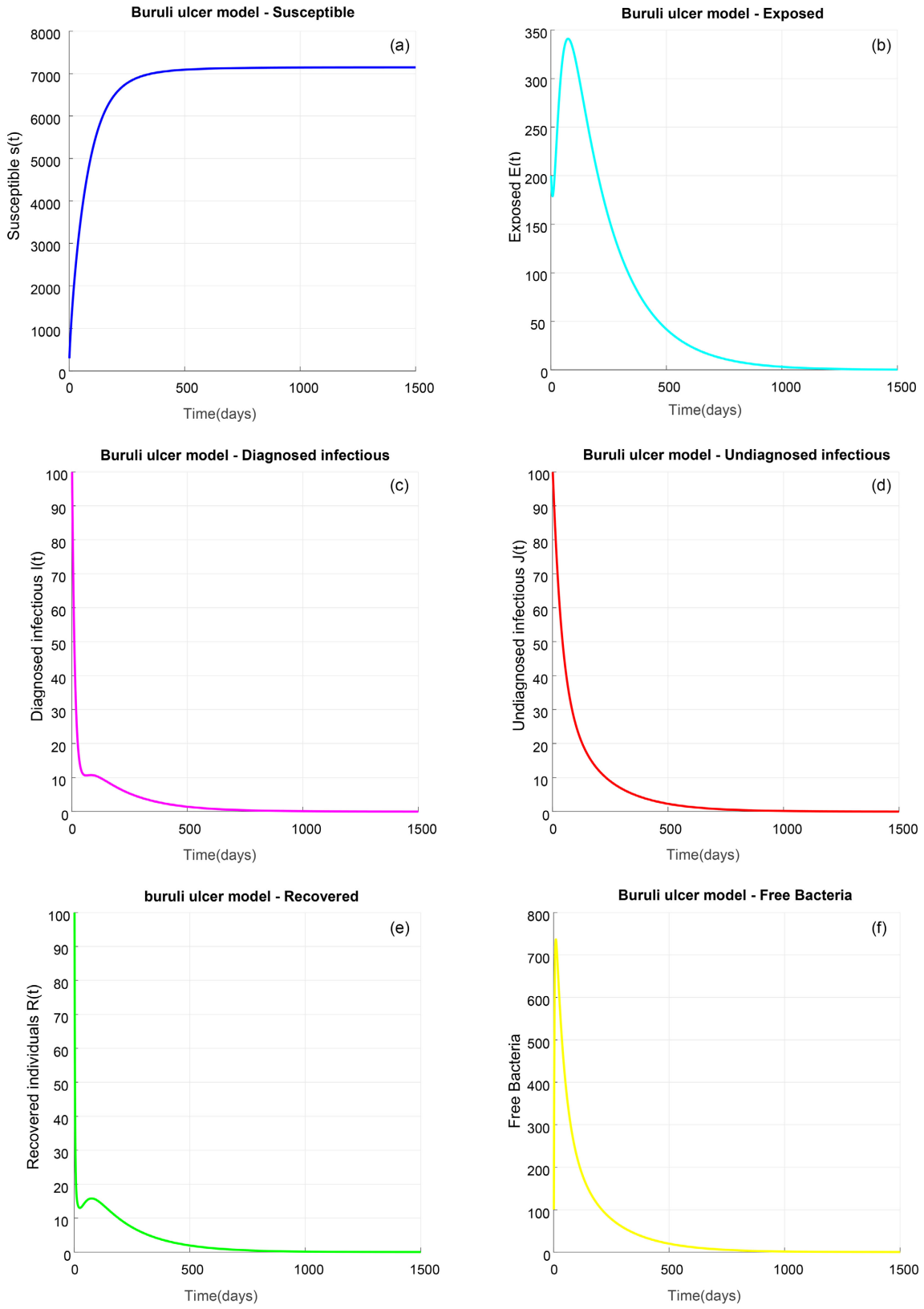

Figure 4. Numerical simulations for system (3) when $\Lambda = 0.1$; $\gamma = 0.0001$; $\rho = 0.011$; $p_1 = 0.2$; $p_2 = 0.1$; $\alpha = 0.5$; $\theta = 0.25$; $\mu = 0.00045$; $\mu_p = 0.5$; $\varepsilon = 0.011$; $w = 30$ so that $\mathcal{R}_0 = 0.531 \leq 1$.

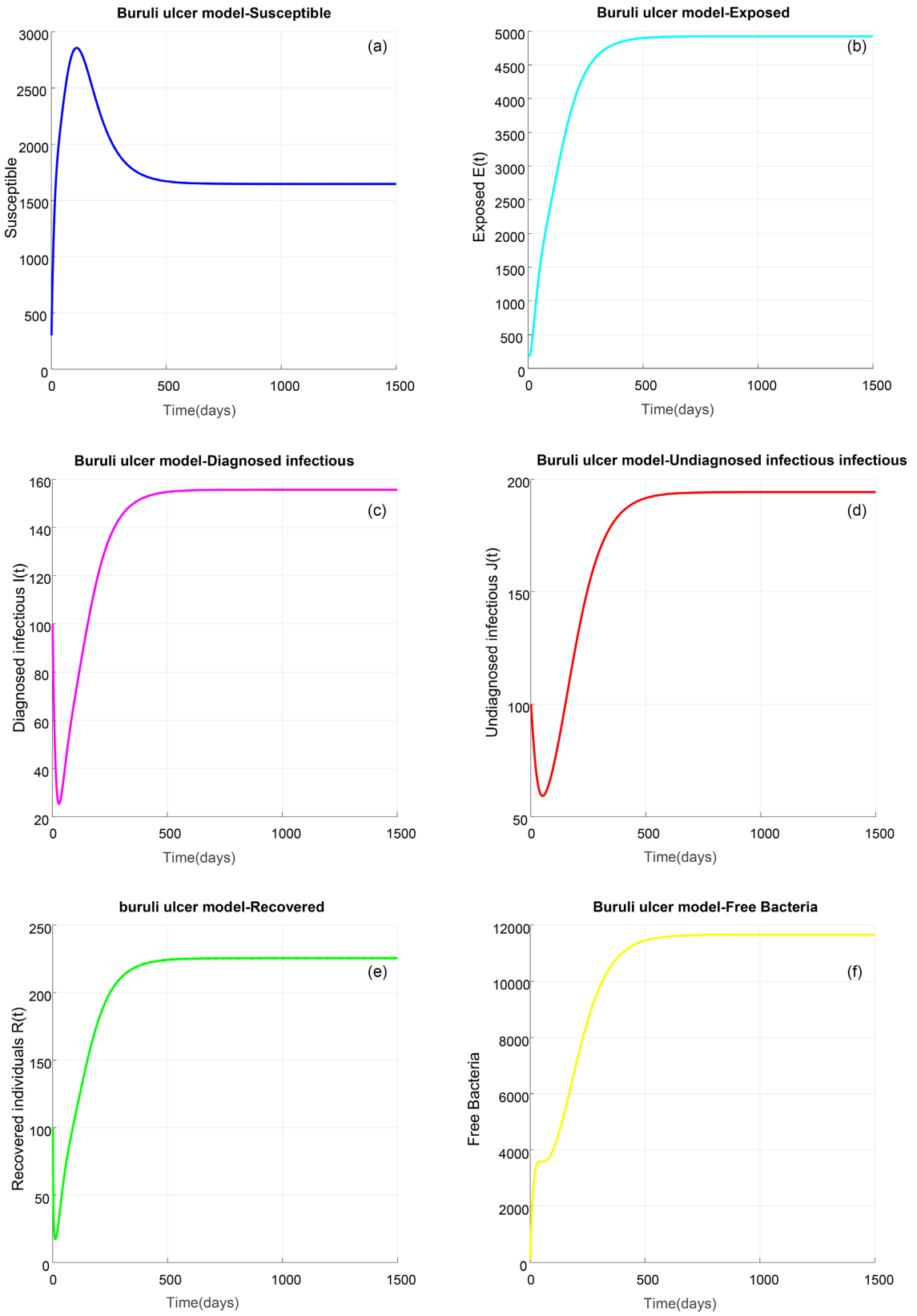

Figure 5. Numerical simulations for system (3) when $\Lambda = 0.1$; $\gamma = 0.0001$; $\rho = 0.011$; $p_1 = 0.2$; $p_2 = 0.1$; $\alpha = 0.5$; $\theta = 0.25$; $\mu = 0.014$; $\mu_p = 0.1$; $\varepsilon = 0.011$; $w = 40$ so that $\mathcal{R}_0 = 3.54 \geq 1$.

Figure 5, page 16 presents the trajectories of system (3) when $\Lambda = 0.1$; $\gamma = 0.0001$; $\rho = 0.011$; $p_1 = 0.2$; $p_2 = 0.1$; $\alpha = 0.5$; $\theta = 0.25$; $\mu = 0.014$; $\mu_p = 0.1$; $\varepsilon = 0.011$; $w = 40$ so that $\mathcal{R}_0 = 3.54 \geq 1$ From this figure, it clearly appears that the trajectories of system (3) converge to the endemic equilibrium $\overline{Q}$ as shown in Theorem 6. This means that the disease persists within a human population.

4. Impact of Bacterial Mortality and Excretion Rates on the Dynamics of *Buruli ulcer* Transmission

The aim of this section is to study how the mortality rate and excretion of bacteria into the environment impacts the dynamics of *Buruli ulcer* transmission.

Figure 6 presents the time evolution of basic reproduction number as function of the bacteria in the environment mortality and shedding rate respectively. Ones can see in this figure that the values of the basic reproduction number less or greater than one depends strongly on these two parameters of the model. For the values taken for our numerical simulations, we can estimate a mortality threshold value above which the basic reproduction number R_0 is always less than one: this corresponds to a situation of disease free equilibrium. Biological or chemical control in an aquatic ecosystem can be a means of having a bacterial mortality rate in the environment higher than this threshold value. On the other hand, we have a threshold value for the excretion rate: this means that if we educate the population to be screened and accept hospitalization during treatment, we can limit the excretion rate of the bacteria. in the environment and therefore better control the disease.

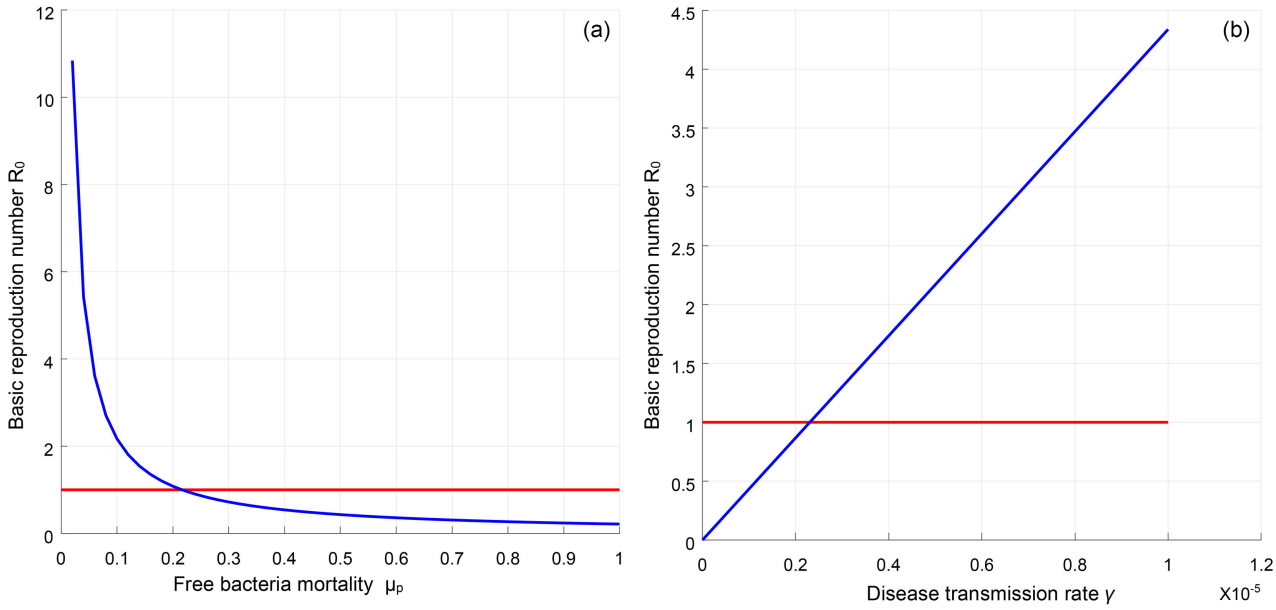

Figure 6. Basic reproduction number $\mathcal{R}_0$ as a function of μ_p and ω when $\Lambda = 500$; $\gamma = 0.0001$; $\rho = 0.011$; $p_1 = 0.2/30$; $p_2 = 0.1/30$; $\alpha = 0.5/30$; $\theta = 0.25/30$; $\mu = 0.014$; $\varepsilon = 0.001$; $\omega = 100/30$ (when we plot the basic reproduction number as function of ω; $\mu_p = 0.08$).

More informing the population about the disease, the importance of getting tested, and receiving treatment in hospital, along with biological or chemical control measures, are two approaches that will help us better control the spread of *Buruli ulcer* among the human population. Thus, to opt for a chemical control method to eliminate the bacteria in the environment, it would be ideal to assess the environmental impact of this measure using the approach proposed in [22].

5. Conclusion and Discussion

In the present work, we present a deterministic mathematical model for the transmission of *Buruli ulcer* whose aim was to highlight the impact of bacteriumpresent in the environment on the spread of the disease within a human population. Model uses nonlinear differential equations and regroups each human according to their epidemiological status. The particularity of this model is that it considers that once diagnosed, the patient is hospitalized until complete recovery. But the socio-economic nature of our study environment leads people to avoid hospitals even if it means treating themselves: it is this class of population considered as patients lost to sight who therefore contribute to the spread of the infection releasing bacterium into the environment. The obtained model is analysed by determining the steady states. We show that the model analysis is carried out in terms of the basic reproduction number R_0, which summarizes the dynamics of the system: If it is less than one, the disease disappears within a human population; when it is greater than one, the disease is endemic. We use sensitivity analysis that highlights how parameters affects the basic reproduction number R_0 and how parameters affects the output of the variables. Numerical simulations were made to validate the mathematical results obtained. As we observe in **Figure 4** and **Figure 5**, the numerical results are in agreement with the theoretical results.

Our main result is that the control of the spread of *Buruli ulcer* within a human population depends mostly on the environmental management and sensitisation of the human population. Lack of knowledge of the disease plays an important role in its spread. the human population must know that, faced with this disease, they must go to the hospital and agree to remain hospitalize until complete recovery: awareness campaigns must be multiplied in this direction. Controlling the spread of the epidemic within the human population remains a challenge. At the end of our study, it suffices to maintain a basic reproduction number $\mathcal{R}_0$ lower than 1. We carry out sensitivity analysis of $\mathcal{R}_0$ to find out the degree to which the parameters influence the basic reproduction number $\mathcal{R}_0$. We show a monotonic decrease of $\mathcal{R}_0$ when μ_p increase. This means that the clearance of the environment will reduce the spread of *Buruli ulcer* epidemic. According to **Figure 6**, we have identified a threshold for the excretion rate below which we can control the progression of the disease, and a threshold for bacterial mortality above which we can also control the spread of *Buruli ulcer*

among the human population. However, the complete eradication of Mycobacterium in the aquatic ecosystem is not feasible in practice. An approach in our future work could involve combining these factors with the control of water bugs in an optimal control model to determine the best strategy for controlling *Buruli ulcer* in the population.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix A. Classical Differential Version of Gronwall Lemma

Lemma 7. Suppose that a function x of class $\mathscr{C}^1(I,\mathbb{R})$, where I is an interval of $\mathbb{R}$, verifies

$$\dot{x}(t) \le a(t)x(t) + b(t), \tag{16}$$

where a and b are continuous functions from I into $\mathbb{R}$, and $x(t) = x_0$ for $t_0 \in I$. Then we have the inequality

$$x(t) \le x(t_0)\exp\left(\int_{t_0}^{t} a(s)\mathrm{d}s\right) + \int_{t_0}^{t} b(s)\exp\left(\int_{s}^{t} a(\sigma)\mathrm{d}\sigma\right)\mathrm{d}s \tag{17}$$

Appendix B. Proof of Theorem 6

Let $\boldsymbol{X} = (S,E,I,J,R,P)^{\mathrm{T}}$ and consider a Lyapunov function,

$$\begin{aligned} V(\boldsymbol{X}) = {} & \left(S - \overline{S} - \overline{S}\ln\left(\frac{S}{\overline{S}}\right)\right) + a_1\left(E - \overline{E} - \overline{E}\ln\left(\frac{E}{\overline{E}}\right)\right) \\ & + a_2\left(I - \overline{I} - \overline{I}\ln\left(\frac{I}{\overline{I}}\right)\right) + a_3\left(J - \overline{J} - \overline{J}\ln\left(\frac{J}{\overline{J}}\right)\right) \\ & + a_4\left(R - \overline{R} - \overline{R}\ln\left(\frac{R}{\overline{R}}\right)\right) + a_5\left(P - \overline{P} - \overline{P}\ln\left(\frac{P}{\overline{P}}\right)\right). \end{aligned} \tag{18}$$

A direct computation leads to

$$\begin{aligned} \dot{V} = {} & \left(1 - \frac{\overline{S}}{S}\right)\dot{S} + a_1\left(1 - \frac{\overline{E}}{E}\right)\dot{E} + a_2\left(1 - \frac{\overline{I}}{I}\right)\dot{I} + a_3\left(1 - \frac{\overline{J}}{J}\right)\dot{J} \\ & + a_4\left(1 - \frac{\overline{R}}{R}\right)\dot{R} + a_5\left(1 - \frac{\overline{P}}{P}\right)\dot{P} \\ = {} & \left(1 - \frac{\overline{S}}{S}\right)\left[\Lambda + \rho R - \gamma PS - \mu S\right] + a_1\left(1 - \frac{\overline{E}}{E}\right)\left[\gamma PS - (\mu+\varepsilon)E\right] \\ & + a_2\left(1 - \frac{\overline{I}}{I}\right)\left[\varepsilon p_1 E - (\mu+\alpha)I\right] + a_3\left(1 - \frac{\overline{J}}{J}\right)\left[\varepsilon p_2 E - (\mu+\theta)J\right] \\ & + a_4\left(1 - \frac{\overline{R}}{R}\right)\left[\varepsilon(1-p_1-p_2)E + \alpha I + \theta J - (\mu+\rho)R\right] \\ & + a_5\left(1 - \frac{\overline{P}}{P}\right)\left[wJ - \mu_p P\right]. \end{aligned}$$

At the endemic equilibrium point, we have the following relations:

$$\begin{cases} \Lambda = -\rho\overline{R} + \gamma\overline{SP} + \mu\overline{S}, \\ \gamma\overline{SP} = (\varepsilon+\mu)\overline{E}, \\ \varepsilon p_1\overline{E} = (\mu+\alpha)\overline{I}, \\ \varepsilon p_2\overline{E} = (\mu+\theta)\overline{J}, \\ \varepsilon(1-p_1-p_2)\overline{E} + \alpha\overline{I} + \theta\overline{J} = (\mu+\rho)\overline{R}, \\ w\overline{J} = \mu_p\overline{P}. \end{cases} \tag{19}$$

Using relations (19), we have

$$\begin{aligned}\dot{V} &= \left(1-\frac{\bar{S}}{S}\right)\left[\mu\bar{S}\left(1-\frac{S}{\bar{S}}\right)+\gamma\bar{P}\bar{S}\left(1-\frac{PS}{\bar{P}\bar{S}}\right)+\rho\bar{R}\left(\frac{R}{\bar{R}}-1\right)\right]\\ &+a_1\left(1-\frac{\bar{E}}{E}\right)\left[\gamma\bar{P}\bar{S}\left(\frac{PS}{\bar{P}\bar{S}}-\frac{E}{\bar{E}}\right)\right]\\ &+a_2\left(1-\frac{\bar{I}}{I}\right)\left[\varepsilon p_1\bar{E}\left(\frac{E}{\bar{E}}-\frac{I}{\bar{I}}\right)\right]+a_3\left(1-\frac{\bar{J}}{J}\right)\left[\varepsilon p_2\bar{E}\left(\frac{E}{\bar{E}}-\frac{J}{\bar{J}}\right)\right]\\ &+a_4\left(1-\frac{\bar{R}}{R}\right)\left[\varepsilon\left(1-p_1-p_2\right)\bar{E}\left(\frac{E}{\bar{E}}-\frac{R}{\bar{R}}\right)+\alpha\bar{I}\left(\frac{I}{\bar{I}}-\frac{R}{\bar{R}}\right)+\theta\bar{J}\left(\frac{J}{\bar{J}}-\frac{R}{\bar{R}}\right)\right]\\ &+a_5\left(1-\frac{\bar{P}}{P}\right)\left[w\bar{J}\left(\frac{J}{\bar{J}}-\frac{P}{\bar{P}}\right)\right].\end{aligned}$$

Let

$$x=\frac{S}{\bar{S}},\quad y=\frac{E}{\bar{E}},\quad z=\frac{I}{\bar{I}},\quad t=\frac{J}{\bar{J}},\quad u=\frac{R}{\bar{R}},\quad v=\frac{P}{\bar{P}},$$

$$\begin{aligned}\dot{V} &= \left(1-\frac{1}{x}\right)\left[\mu\bar{S}\left(1-x\right)+\gamma\bar{P}\bar{S}\left(1-vx\right)+\rho\bar{R}\left(u-1\right)\right]\\ &+a_1\left(1-\frac{1}{y}\right)\left[\gamma\bar{P}\bar{S}\left(vx-y\right)\right]\\ &+a_2\left(1-\frac{1}{z}\right)\left[\varepsilon p_1\bar{E}\left(y-z\right)\right]+a_3\left(1-\frac{1}{t}\right)\left[\varepsilon p_2\bar{E}\left(y-t\right)\right]\\ &+a_4\left(1-\frac{1}{u}\right)\left[\varepsilon\left(1-p_1-p_2\right)\bar{E}\left(y-u\right)+\alpha\bar{I}\left(z-u\right)+\theta\bar{J}\left(t-u\right)\right]\\ &+a_5\left(1-\frac{1}{v}\right)\left[w\bar{J}\left(t-v\right)\right]\\ &=\mu\bar{S}\left(\frac{\left(1-x\right)^2}{x}\right)+G\left(x,y,z,t,u,v\right)\end{aligned}$$

where

$$\begin{aligned}G\left(x,y,z,t,u,v\right) &= \left(1-\frac{1}{x}\right)\left[b_1\left(1-vx\right)+b_2\left(u-1\right)\right]+a_1\left(1-\frac{1}{y}\right)\left[b_1\left(vx-y\right)\right]\\ &+a_2\left(1-\frac{1}{z}\right)\left[b_3\left(y-z\right)\right]+a_3\left(1-\frac{1}{t}\right)\left[b_4\left(y-t\right)\right]\\ &+a_4\left(1-\frac{1}{u}\right)\left[b_5\left(y-u\right)+b_6\left(z-u\right)+b_7\left(t-u\right)\right]\\ &+a_5\left(1-\frac{1}{v}\right)\left[b_8\left(t-v\right)\right]\\ &=\mu\bar{S}\left(\frac{\left(1-x\right)^2}{x}\right)+G\left(x,y,z,t,u,v\right)\end{aligned}$$

and

$$b_1=\gamma\bar{P}\bar{S},\quad b_2=\rho\bar{R},\quad b_3=\varepsilon p_1\bar{E},\quad b_4=\varepsilon p_2\bar{E}$$

$$b_5=\varepsilon\left(1-p_1-p_2\right)\bar{E},\quad b_6=\alpha\bar{I},\quad b_7=\theta\bar{J},\quad b_8=w\bar{J}$$

The development of $G\left(x,y,z,t,u,v\right)$ leads to

$$\begin{aligned}G(x,y,z,t,u,v) &= vx(-b_1+a_1b_1)+y(-a_1b_1+a_2b_2+a_3b_4+a_4b_5)\\ &+z(-a_2b_3+a_4b_6)+t(-a_3b_4+a_4b_7+a_5b_8)+v(b_1-a_5b_8)\\ &+u(-a_4b_5-a_4b_6-a_4b_7+b_2)+b_1-b_2+a_1b_1+a_2b_3\\ &+a_4b_5+a_4b_6+a_4b_7+a_5b_8+\frac{b_2}{x}(1-u)-\frac{a_1b_1vx}{y}-\frac{b_1}{x}\\ &-\frac{a_1b_1vx}{z}-\frac{a_3b_4y}{t}-\frac{a_4b_5y}{u}-\frac{a_4b_6z}{u}-\frac{a_4b_7t}{u}-\frac{a_5b_8t}{v}\end{aligned}$$

The positive constants a_1, a_2, a_3, a_4 and a_5 are chosen such that:

$$\begin{cases}-b_1+a_1b_1=0,\\ -a_1b_1+a_2b_3+a_3b_4+a_4b_5=0,\\ -a_2b_3+a_4b_6=0,\\ -a_3b_4+a_4b_7+a_5b_8=0,\\ b_1-a_5b_8=0.\end{cases} \tag{20}$$

The resolution of system (20) gives:

$$a_1=1,\quad a_2=a_4=0,\quad a_3=\frac{b_1}{b_2},\quad a_5=\frac{b_1}{b_8}$$

and $G(x,y,z,t,u,v)$ becomes

$$G(x,y,z,t,u,v)=b_1\left[4-\frac{vx}{y}-\frac{1}{x}-\frac{y}{x}-\frac{t}{v}\right]-b_2\left[1-u-\frac{1}{x}+\frac{u}{x}\right],$$

and

$$\dot{V}=-\mu\bar{S}\left(\frac{(1-x)^2}{x}\right)+b_1\left[4-\frac{vx}{y}-\frac{1}{x}-\frac{y}{x}-\frac{t}{v}\right]-b_2\left[1-u-\frac{1}{x}+\frac{u}{x}\right],$$

where

$$b_1=\gamma\bar{P}\bar{S},\quad b_2=\rho\bar{R}.$$

Using the arithmetic-geometric means inequality leads to

$$b_1\left[4-\frac{vx}{y}-\frac{1}{x}-\frac{y}{x}-\frac{t}{v}\right]\le 0$$

and $b_2\left[1-u-\frac{1}{x}+\frac{u}{x}\right]>0$. Consequently $\dot{V}\le 0$. By LaSalle's invariance principle, one can conclude that the endemic equilibrium is globally asymptotically stable in Ω. Since Ω is absorbing, this proves the global asymptotically stability in the nonnegative orthant.

This concludes the proof.