Mathematical modelling and optimal control strategies of the transmission of enterovirus

by

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(February 16, 2022)

Declaration 1 - Plagiarism

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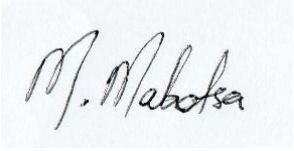
I declare that "Mathematical modeling and optimal control strategies for the transmission of enterovirus " is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references.

I further declare that I have not previously submitted this work, or part of it, for examination at Unisa for another qualification or at any other higher education institution.



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Declaration 2 - Publications

Papers published

- Mathematical modelling and optimal control of the transmission of dynamics of enterovirus

Papers in preparation

- none.

Dedication

I dedicate this thesis to my son Bokang Phatela.

Acknowledgements

Above all, I thank God for making it all possible for me to pursue this study and for giving me the strength to see it through. Many thanks to my supervisors, Prof. Munganga and Dr. Hassan, who guided me through it all, thank you so much for your patience and unwavering support.

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Abstract

We propose a mathematical model for the transmission dynamics of enterovirus. We prove that if the basic reproduction number $\mathcal{R}_0 \leq 1$, a suitable Lyapunov function is used to establish the global stability of the disease free equilibrium, in which case the infection will die out over time. Our analysis further establish the global stability of the endemic equilibrium based on the approach of Volterra-Lyapunov matrices if $\mathcal{R}_0 > 1$. Our findings show that when $\mathcal{R}_0 > 1$, the endemic equilibrium is globally asymptotically stable. In this case, the enterovirus will invade the population. It is shown that by reducing direct transmission rate by 80%, the basic reproduction number can be reduced below one and thus controlling the infection. Using optimal control with hygiene and sanitation campaigns as control measures, it is shown that the disease can be controlled within a shorter period of time as compared to minimizing the direct contact rate by 80%. Numerical simulations are provided to illustrate the results.

Key terms: Mathematical modelling, Enterovirus, basic reproduction number, Next generation matrix method, Lyapunov functions, Volterra-Lyapunov matrices, optimal control, Pontrayagin's Maximum principle.

Chapter 1

Introduction

Enteroviruses are single-stranded positive ribonucleic acid (RNA) viruses associated with several human diseases all over the world, including hand-foot-and-mouth disease (HFMD), respiratory infections, etc. [26]. Many serotypes have been discovered in the past, for instance, EV-D68 made its first appearance in 1962 and was identified as a respiratory pathogen when it caused an outbreak in many countries including Japan, the Philippines, Netherlands and North America [9]. EV71 was first discovered in 1969 and has been identified as a cause of outbreaks of HFMD in Asia-pacific region [12]. Patients usually show mild symptoms such as sore throat, runny nose, sneezing, fever, coughing, nausea and vomiting, diarrhea, trouble breathing, sores in the mouth, and on the palms of the hands and soles of the feet. However, some infected people, especially infants and people with compromised immune system may have serious illness. Complications from enteroviral infection are not common, but if they occur, can cause serious problems such as severe illness in the lungs, inflammation of membrane around the brain and spinal cord (meningitis), inflammation of the liver (hepatitis), and more. Enterovirus enters the human body through the gastrointestinal tract and thrives there. Later on, it spreads to other organs such as the skin and nervous system [4, 21, 34]. The virus can be transmitted directly from human to human through effective human contacts. It can also be transmitted indirectly from environment to human

through viral shedding from gastrointestinal or upper respiratory tract, by faecal-oral or respiratory mode, respectively [12, 21]. The average incubation period of enterovirus is 7 days and the contagious period starts about 3 days after the infection and lasts for about 10 days after symptoms developed [12, 30]. Infected individuals can shed virus without showing any symptoms of infection, and this makes the control more challenging. Currently, there is no antiviral medication to cure enteroviral infection, however, other drugs and antibiotics can be taken to relieve the pain of sores in the mouth, in addition to having bed rest. Preventive measures include but not limited to avoiding contact with infected persons, regular washing of hands with sanitizer and cleaning surfaces regularly with disinfectants.

In the past, some mathematical models have been developed to get insight and find control strategies that can be used to manage an outbreak of enterovirus and its variants. For example, Cao and Hongwu [14] studied the transmission dynamics of a hand-foot-mouth disease (HFMD) model in a population of children below 10 years of age with two infectious stages and optimal control with two control measures. Nandi Roy [32] also presented a model of HFMD, with the aim of analytically evaluating the effectiveness of quarantine as a control strategy, with reinfection of recovered population. Aihara et al [15], experimental-mathematical analyses were conducted to estimate the burst size and the basic reproductive number of a novel enterovirus 71 (EV71). In order to better inform vaccination policy, Takahashi *et al.* [35] used mathematical models to evaluate the effect of prospective vaccination against enterovirus (EV-A71) responsible for HFMD in China. Furthermore, a Susceptible-Infected-Recovered (SIR) model was adopted by S. Hu et al [24] to study the transmissibility and interactions of 3 enterovirus pathogens. Using data from Changsha city in China, they estimated three basic reproduction numbers for the viruses. Other related mathematical models include the Optimal control analysis of hepatitis B virus with treatment and vaccination presented by Alrabaiah et al [3]. Alqarni et al [2] presented the mathematical modelling of Novel corona virus and control, and Bera et al [18] presented mathematical analysis of the global dynamics of HTLV-I infection. Also closely related to our study is the impact

of media awareness and optimal control strategy on the prevalence of tuberculosis by Das et al [7], and the stability analysis of a mathematical for Glioma-Immune interaction under optimal therapy presented by Khajanchi et al [17].

In this dissertation, we intent to extend many models of enterovirus by incorporating indirect transmission of infection from the environment and the consideration of optimal control strategy. The rest of the dissertation is organized as follows: Chapter 2 focuses on preliminaries, which include the terminology, theories and laws used in the dissertation. In Chapter 3, we present the formulation for basic mathematical model for transmission dynamics of enterovirus, its mathematical analysis. The numerical simulations that confirm the results of the analysis are presented in Chapter 4. In Chapter 5 , we extend the basic model to incorporate optimal control, its analysis and numerics, with hygiene and sanitation as control measures. Finally, in Chapter 6, we present the concluding remarks.

Chapter 2

Preliminaries

This chapter covers the terminology and some laws or theorems used in this dissertation.

2.1 Definitions

Definition 2.1.1. ***Incubation period*** *is the time between infection or contact with the agent and the onset of symptoms of infection [28].*

Definition 2.1.2. ***Contagious period*** *is the time during which an infectious agent can be spread [28].*

Definition 2.1.3. ***Latent period*** *is the time between exposure and the onset of contagious period [28].*

Definition 2.1.4. ***A compact set*** $S \subset \mathbb{R}^n$ *is a set that is closed and bounded [37].*

Definition 2.1.5. ***Lyapunov function*** *is a non-negative function that decreases in time along the orbits of a dynamical system. It is useful in studying the stability of the equilibrium points [19].*

Definition 2.1.6. - *A* ***symmetric matrix*** *is one for which* $A = A^T$.

- *A* ***symmetric positive (negative) definite matrix*** *is a symmetric matrix for*

which all the eigenvalues are positive (negative).

- *We write matrix $A > 0 (< 0)$ if A is symmetric positive (negative).*

Definition 2.1.7. *We say that a non-singular $n \times n$ matrix A is* ***Volterra-Lyapunov stable*** *if there exists a positive diagonal $n \times n$ matrix M such that $MA + A^T M^T < 0$. [23]*

Definition 2.1.8. *A* ***convex set*** *is a set of elements from a vector space such that all the points on the straight line between any two points of the set are also contained in the set. That is, for any $x, y \in A$ it follows that $tx + (1-t)y \in A$ for any $t \in [0,1]$ [5].*

2.2 Laws, principles, theorems/lemmas and equations

Definition 2.2.1. ***Mass action law*** *states that when substances A and B react with each other, the reaction rate is proportional to the concentration of A, denoted by $[A]$, and the concentration of B, $[B]$.*

$$reaction\ rate = c[A][B],$$

where c is a constant of reaction [38].

Definition 2.2.2. ***Michaelis-Menten equation*** *arises from enzymatic reaction, it states that the initial velocity of reaction is given by*

$$V_0 = V_{max}\left(\frac{[S]}{\kappa + [S]}\right),$$

where V_{max} is the maximum velocity of the reaction, $[S]$ is the concentration of substrate S and κ is the Michaeli-Menten constant. The constant κ measures the kinetics of enzyme reaction, it is equivalent to the concentration of the substrate at which the reaction takes place at half of its maximum rate [27]. In the context of infectious dis-

ease modelling, $V_{max} = \beta_e S$, where β_e is the rate of indirect transmission rate and S is the class of susceptible individuals. The substrate concentration is B which represents the concentration of virus in the environment. $V_0 = \frac{dS}{dt}$ is the rate at which susceptible individuals are exposed to virus from the environment.

Theorem 2.2.3 (LaSalle's Invariance Principle)**.** *Suppose there is a neighbourhood D of O and continuously differentiable (time-independent) positive definite function $V : D \to \mathbb{R}$ whose orbital derivative $\dot{V}$ is negative semi-definite. Let I be the union of all complete orbits contained in $\{x \in D | \dot{V}(x) = 0\}$. Then there is a neighbourhood U of O such that for every $x_0 \in U$, $\omega(x_0) \subseteq I$ [20].*

Theorem 2.2.4 (**Pontryagin's Principle**)**.** *Necessary conditions that (x^*, u^*) be an optimal solution for the optimal control problem are the existence of a non-zero k-dimensional vector λ and an n-dimensional vector function $P(t)$ such that for $t \in [t_0, t_1]$:*

$$\dot{P(t)} = -P(t) f(t, x^*, u^*),$$

and

$$P(t) f(t, x, u) = H(t, x, u) = \max_{u \in U} \{H(t, x, u)\}.$$

Theorem 2.2.5 (**Next generation matrix method**)**.** *[33] In compartmental models for infectious disease transmission, individuals are categorized into several compartments: some are called disease compartments if the individuals therein are infected, while others are called non-disease compartments. Suppose that there are $n > 0$ disease compartments and $m > 0$ non-disease compartments. Then a general compartmental disease transmission model can be written as*

$$X' = \mathcal{F}(x, y) - \mathcal{V}(x, y), \quad y' = g(x, y),$$

with $g = (g_1, ..., g_m)^T$. Here $'$ denotes differentiation with respect to time; $x = (x_1, ..., x_n)^T \in$

$\mathbb{R}^n$ *and* $y = (y_1, ..., y_m)^T \in \mathbb{R}^m$ *represent the populations in disease compartments and non-disease compartments, respectively;* $F = (F_1, ..., F_n)^T$ *and* $V = (V_1, ..., V_n)^T$ *, where* F_i *represents the rate of new infections in the* i^{th} *disease compartment; and* V_i *represents the transition terms, for example, death and recovery in the* i^{th} *disease compartment. Assume that* $F_i(0, y) = 0, V_i(0, y) = 0, F_i(x, y) \geq 0, V_i(x, y) \leq 0$ *whenever* $x_i = 0$*, and* $\sum_{1=1}^{n} \mathcal{V}_i(x, y) \geq 0$ *for all* $x, y \geq 0, i = 1, ..., n$*. Also assume that the disease-free system* $y' = g(0, y)$ *has a unique equilibrium* $y = y_0 > 0$ *that is locally asymptotically stable within the disease-free space. Define two* $n \times n$ *matrices*

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(0, y_0)\right], \quad V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(0, y_0)\right].$$

Assume that $F \geq 0$ *and* $V^{-1} \geq 0$*, which are biologically reasonable. Then the next-generation matrix is* $K = FV^{-1}$*, and the basic reproduction number* $\mathcal{R}_0$ *can be defined as the spectral radius of* K *that is,*

$$\mathcal{R}_0 = \rho(FV^{-1}).$$

Lemma 2.2.6. *Let* $D = \begin{bmatrix} d_{11} & d_{22} \\ d_{33} & d_{44} \end{bmatrix}$ *be a* 2×2 *matrix. Then* D *is Volterra-Lyapunov stable if and only if* $d_{11} < 0, d_{22} < 0$ *and* $\det(D) > 0$*. [23]*

Chapter 3

Mathematical Modelling and analysis of the model

3.1 Mathematical modelling

In this section, we construct a mathematical model consisting of four human compartments and concentration of enterovirus in the environment to form a system of five ordinary differential equations in describing the dynamics of enterovirus infection. The human population at any time t, consists of four mutually-exclusive compartments namely the susceptible $S(t)$, exposed $E(t)$, infected $I(t)$, and recovered $R(t)$, so that the total population $N(t)$ is given by

$$N(t) = S(t) + E(t) + I(t) + R(t). \tag{3.1.1}$$

We consider a constant population and assume that death and birth rates denoted by μ are equal. The transmission dynamics of enterovirus infection are illustrated by the flow diagram in Figure 3.1. The concentration of enterovirus in the environment at time t, is denoted $B(t)$. The susceptible sub-population is generated by influx from newly born babies at the rate of μ, which is also the death rate of all human sub-populations. Susceptible population acquire enterovirus in two ways, through effective contacts with human to human at the

rate of β_h, or through environment to human transmission at the rate of β_e. The human to human transmission obeys the mass action law, thus the total number of susceptible individuals who get the infection or exposed is $\beta_h \frac{SI}{N}$. The environment to human transmission obeys Michaelis-Menten formulation. Thus, the total number of susceptible individuals who join the exposed class after exposure is $\beta_e \frac{BS}{\kappa+B}$, where κ is the Michaelis-Menten constant, representing the concentration of enterovirus at which the rate of infection is half the maximum rate of infection. The maximum rate of infection is attained when the concentration of enterovirus has reached its saturation level. Hence, the dynamics of this compartment is described by equation 3.1.2. Susceptible humans give rise to exposed individuals. The exposed population is decreased by becoming infectious at the rate γ and natural death at rate μ, so that the dynamics is given by equation 3.1.3. Infectious individuals class is decreased by shedding virus to environment at the rate ϵ, and natural death at the rate μ. Therefore, the equation describing I is given by equation 3.1.4. Finally for human population, the infectious individuals get recovered and die naturally at the rates α and μ respectively. The equation describing the dynamics of recovered humans is thus given by equation 3.1.6. On the other hand, the population of enterovirus in the environment is formed by infectious individuals shedding the virus at the rate ϵ. Concentration of the virus is decreased if the environment is sanitized, and the virus loses virulence at the rate δ. Dynamics of the virus in the environment is therefore given by equation 3.1.5. We therefore have the following flow diagram.

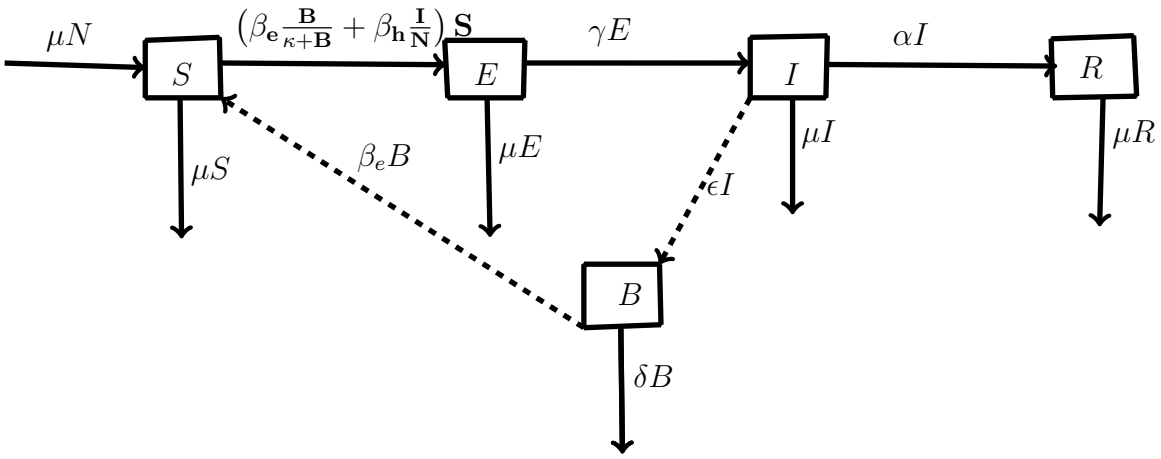

Figure 3.1: Transmission of enterovirus

From the mathematical description of the transmission dynamics, we obtain the following dynamical system.

$$\begin{aligned}
\frac{dS}{dt} &= \mu N - \mu S - \left(\beta_e \frac{B}{\kappa + B} + \beta_h \frac{I}{N}\right) S, && (3.1.2)\\
\frac{dE}{dt} &= \left(\beta_e \frac{B}{\kappa + B} + \beta_h \frac{I}{N}\right) S - (\mu + \gamma)E, && (3.1.3)\\
\frac{dI}{dt} &= \gamma E - (\mu + \alpha)I, && (3.1.4)\\
\frac{dB}{dt} &= \epsilon I - \delta B, && (3.1.5)\\
\frac{dR}{dt} &= \alpha I - \mu R, && (3.1.6)
\end{aligned}$$

with non-negative initial conditions

$$(S(0) \geq 0, E(0) \geq 0, I(0) \geq 0, B(0) \geq 0, R(0) \geq 0) = (S_0, E_0, I_0, B_0, R_0). \qquad (3.1.7)$$

We define the domain of model (3.1.2) - (3.1.6), the compact invariant set

$$\tau = \left\{(S, E, I, B, R) \in \mathbb{R}^5_+ | \mathrm{S} + \mathrm{E} + \mathrm{I} + \mathrm{R} = \mathrm{N}, \quad \mathrm{B} \leq \frac{\mathrm{N}\epsilon}{\delta}\right\}. \qquad (3.1.8)$$

3.2 Well-posedness of the system

In this section, we show that the model has a unique, non-negative solution that is bounded, and thus can be used to handle real life outbreaks. Let $X(t) = (S(t), E(t), I(t), B(t), R(t))$ and $f : X \to S'$ such that $f = (f_1, f_2, f_3, f_4, f_5)$, where

$$\begin{aligned} f_1(X) &= \mu N - \mu S - \left(\beta_e \tfrac{B}{\kappa+B} + \beta_h \tfrac{I}{N}\right) S, \\ f_2(X) &= \left(\beta_e \tfrac{B}{\kappa+B} + \beta_h \tfrac{I}{N}\right) S - (\mu+\gamma)E, \\ f_3(X) &= \gamma E - (\mu+\alpha)I, \\ f_4(X) &= \epsilon I - \delta B, \\ f_5(x) &= \alpha I - \mu R. \end{aligned}$$

So, equations (3.1.2) -(3.1.6) can be written as

$$X' = f(X(t)); \quad X(0) = (S_0, E_0, I_0, B_0, R_0). \tag{3.2.1}$$

Theorem 3.2.1. *If $f(X(t))$ is as given in (3.2.1), and the initial condition $X(0) = N = S + E + I + R > 0$, is non-negative, then system (3.1.2)-(3.1.6) has a unique solution that is non-negative and bounded.*

Proof. We notice that $f_i s$ are continuous functions and $\frac{\partial f_i}{\partial X_j}, \quad 1 \le i, j \le 5$ exist and are continuous functions as well, so $f(X(t))$ is locally Lipschitz continuous. $X(0) = N = S+E+I+R > 0$, thus at least one compartment is non-empty. Hence, there exists a unique solution $X(t)$ of the system, defined in some time interval containing $t = 0$ [25]. Let t_0 be the smallest t such that $S(t_0) = 0$ or $E(t_0) = 0$ or $I(t_0) = 0$ or $B(t_0) = 0$. By continuity of $S(t), E(t), I(t)$ and $B(t)$, $\exists\ t^* > t_0$ such that if $S(t_0) = 0$, then from (3.1.2) we get that $\frac{dS}{dt} = \mu N \ge 0, \quad \forall t \in [t_0, t^*]$. This means that S is an increasing function on the interval $[t_0, t^*]$, which in turn means that $S(t) \ge 0 \quad \forall t \in [t_0, t^*]$. Similarly, if $E(t_0) = 0$, then from (3.1.3) we get that $\frac{dE}{dt} = \left(\beta_e \frac{B}{\kappa+B} + \beta_h \frac{I}{N}\right) S \ge 0 \implies E(t) \ge 0 \quad \forall t \in [t_0, t^*]$. If $I(t_0) = 0$, then from (3.1.4), $\frac{dI}{dt} = \gamma E \ge 0 \implies I(t) \ge 0 \quad \forall t \in [t_0, t^*]$. If $B(t_0) = 0$, then from (3.1.5), $\frac{dB}{dt} = \epsilon I \ge 0 \implies B(t) \ge 0 \quad \forall t \in [t_0, t^*]$.If $R(t_0) = 0$, then from (3.1.6), $\frac{dR}{dt} = \alpha I \ge 0 \implies R(t) \ge 0 \quad \forall t \in [t_0, t^*]$. Thus, the solution to the system is

non-negative [25]. To establish that the unique solution exist globally, it is sufficient to show that the dissipativity condition of theorem 2.3.6 of [1] is satisfied.

$$
\begin{aligned}
f(X)\cdot X &= (f_1, f_2, f_3, f_4, f_5)\cdot(S, E, I, B, R)\\
&= Sf_1 + Ef_2 + If_3 + Bf_4 + Rf_5\\
&= \mu NS - \mu S^2 - \left(\beta_e\frac{B}{\kappa + B} + \beta_h\frac{I}{N}\right)S^2\\
&+ \left(\beta_e\frac{B}{\kappa + B} + \beta_h\frac{I}{N}\right)SE - (\mu+\gamma)E^2\\
&+ \gamma EI - (\mu+\alpha)I^2 + \epsilon IB - \delta B^2 + \alpha IR - \mu R^2\\
&\leq \mu N^2 - \mu S^2 + \left(\beta_e\frac{N\epsilon}{\kappa\delta} + \beta_h\right)(N^2 - S^2) - (\mu+\gamma)E^2\\
&+ \gamma N^2 - (\mu+\alpha)I^2 + \frac{\epsilon^2 N^2}{\delta} - \delta B^2 + \alpha N^2 - \mu R\\
&\leq \mu N^2 + \mu S^2 + \left(\beta_e\frac{N\epsilon}{\kappa\delta} + \beta_h\right)(N^2 - S^2) + (\mu+\gamma)E^2\\
&+ \gamma N^2 + (\mu+\alpha)I^2 + \frac{N^2\epsilon^2}{\delta} + \delta B^2 + \alpha N^2 + \mu R^2\\
&\leq \left(\mu + \gamma + \alpha + \frac{\epsilon^2}{\delta} + \beta_h + \beta_e\frac{N\epsilon}{\kappa\delta}\right)N^2\\
&+ \left(\mu + \gamma + \alpha + \delta + \beta_h + \beta_e\frac{N\epsilon}{\kappa\delta}\right)(S^2 + E^2 + I^2 + B^2 + R^2)\\
&\leq h|X|^2 + q,
\end{aligned}
$$

where $h = \left(\mu + \gamma + \alpha + \delta + \beta_h + \beta_e\frac{N\epsilon}{\kappa\delta}\right)$ and $q = \left(\mu + \gamma + \alpha + \frac{\epsilon^2}{\delta} + \beta_h + \beta_e\frac{N\epsilon}{\kappa\delta}\right)N^2$. Hence there exists a unique solution X(t) of the system defined for all $t \geq 0$ [25]. Finally, $S \leq N$, $E \leq N$, $I \leq N$ and $B \leq \frac{\epsilon N}{\delta}$ $\forall t \geq 0$, where $\frac{\epsilon N}{\delta}$ is the saturation level for the concentration of enterovirus in the environment, thus the solution is bounded [25]. ■

3.3 Equilibrium points

Since R can be determined once S, E and I are known, equation (3.1.6) is left out in the following analysis. At equilibrium point, all the variables (classes) do not change with time, that is, $\frac{dS}{dt} = \frac{dE}{dt} = \frac{dI}{dt} = \frac{dB}{dt} = 0$. From (3.1.5), we get

$$I = \frac{\delta}{\epsilon} B. \tag{3.3.1}$$

From (3.1.4) and using (3.3.1), we have

$$E = \frac{(\mu + \alpha)\delta}{\epsilon\gamma} B. \tag{3.3.2}$$

Substituting (3.3.1) and (3.3.2) into (3.1.3) and factorizing we get

$$\left(\beta_e \frac{1}{\kappa + B} + \beta_h \frac{\delta}{N\epsilon}\right) S - \frac{(\mu + \gamma)(\mu + \alpha)\delta}{\epsilon\gamma} = 0, \tag{3.3.3}$$

$$B = 0. \tag{3.3.4}$$

The case where $B = 0$ and the condition $S+E+I+R = N$ give us the Disease-free equilibrium (DFE) $X_0 = (N, 0, 0, 0, 0) \in \tau = \left\{(S, E, I, B, R) \in \mathbb{R}^5_+ | \mathrm{S} + \mathrm{E} + \mathrm{I} + \mathrm{R} = \mathrm{N}, \quad \mathrm{B} \leq \frac{\mathrm{N}\epsilon}{\delta}\right\}$ [25]. For (3.3.3), see detailed calculation in Lemma 3.4.3.

3.4 Stability analysis

In this section we study the stability of the DFE and the endemic equilibrium, using the basic reproduction number as a threshold parameter.

3.4.1 The basic reproduction number

We compute the basic reproduction number using the Next Generation Matrix method described in [39]. We consider only the disease compartments $E, I,$ and B and let $x =$

$(E, I, B)^T$. We set $\mathcal{F} = (\mathcal{F}_E, \mathcal{F}_I, \mathcal{F}_B)^T$ and $\mathcal{V} = (\mathcal{V}_E, \mathcal{V}_I, \mathcal{V}_B)^T$, where $\mathcal{F}_j, \quad j = E, I, B$, is the rate of appearance of new infection in compartment j. $\mathcal{V}_j = V_j^- - V_j^+$, where V_j^- is the rate of transfer out of compartment j and V_j^+ is the rate of transfer into compartment j. So we have

$$\mathcal{F} = \begin{bmatrix} \left(\beta_e \frac{B}{\kappa+B} + \beta_h \frac{I}{N}\right) S \\ 0 \\ 0 \end{bmatrix}, \tag{3.4.1}$$

$$\mathcal{V} = \begin{bmatrix} (\mu+\gamma)E \\ (\mu+\alpha)I - \gamma E \\ \delta B - \epsilon I \end{bmatrix}. \tag{3.4.2}$$

Assuming that X_0 is the DFE for the model, we have

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(X_0)\right] = \begin{bmatrix} 0 & \beta_h & \beta_e \frac{N}{\kappa} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \tag{3.4.3}$$

$$V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(X_0)\right] = \begin{bmatrix} \mu+\gamma & 0 & 0 \\ -\gamma & \mu+\alpha & 0 \\ 0 & -\epsilon & \delta \end{bmatrix}. \tag{3.4.4}$$

Taking the inverse of V gives

$$V^{-1} = \begin{bmatrix} \frac{1}{\mu+\gamma} & 0 & 0 \\ \frac{\gamma}{(\mu+\gamma)(\mu+\alpha)} & \frac{1}{\mu+\alpha} & 0 \\ \frac{\gamma\epsilon}{(\mu+\gamma)(\mu+\alpha)\delta} & \frac{\epsilon}{(\mu+\alpha)\delta} & \frac{1}{\delta} \end{bmatrix}.$$

We therefore have

$$FV^{-1} = \begin{bmatrix} \frac{\beta_h\gamma}{(\mu+\gamma)(\mu+\alpha)} + \frac{\beta_e\gamma\epsilon N}{(\mu+\gamma)(\mu+\alpha)\kappa\delta} & \frac{\beta_h}{(\mu+\alpha)} + \frac{\beta_e\epsilon N}{(\mu+\alpha)\kappa\delta} & \frac{\beta_e\epsilon N}{\kappa\delta} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

The basic reproduction number $\mathcal{R}_0$ is equal to the spectral radius of FV^{-1}, thus

$$\begin{aligned} \mathcal{R}_0 &= \frac{\gamma(\beta_h\kappa\delta + \beta_e N\epsilon)}{(\mu+\gamma)(\mu+\alpha)\kappa\delta} \\ &= \frac{\gamma}{\gamma+\mu}\left[\frac{\beta_h}{\mu+\alpha} + \frac{\beta_e N\epsilon}{(\mu+\alpha)\kappa\delta}\right]. \end{aligned} \tag{3.4.5}$$

The basic reproduction number is the expected number of secondary cases produced by a single infection in a completely susceptible population. The first term represents the basic reproduction number of human-to-human infection and the second term is the reproduction number for environment-to-human infection. $\frac{\gamma}{\gamma+\mu}$ is the probability of surviving the exposed period [25].

3.4.2 Stability of DFE

Theorem 3.4.1. *Given that $X_0 = (N, 0, 0, 0, 0)$ is a DFE for the model, then X_0 is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

Proof. See prove of Theorem 2 in [39]. ■

Theorem 3.4.2. *If $\mathcal{R}_0 \leq 1$, the DFE of system (3.1.2)-(3.1.5) is globally asymptotically stable in $\tau = \{(S, E, I, B, R) \in \mathbb{R}^5_+ | \mathrm{S} \geq 0, \mathrm{E} \geq 0, \mathrm{I} \geq 0, \mathrm{B} \geq 0, \mathrm{R} \geq 0, \mathrm{S} + \mathrm{E} + \mathrm{I} + \mathrm{R} = \mathrm{N} \quad and \quad \mathrm{B} \leq \frac{\epsilon \mathrm{N}}{\delta}\}$. If $\mathcal{R}_0 > 1$, the DEF is unstable.*

Proof. We use the matrix theoretic method described in [33]. In general, the dynamics

of the disease compartments for the model can be written as

$$\frac{dx}{dt} = \mathcal{F}(x, y) - \mathcal{V}(x, y),$$

where $x = (E, I, B)^T, \quad y = S$, and $\mathcal{F}$ and $\mathcal{V}$ are given by (3.4.1) and (3.4.2) respectively. We rewrite the dynamics of x (infected compartments) as

$$\frac{dx}{dt} = (F - V)x - f(x, y), \tag{3.4.6}$$

where F and V are given by (3.4.3) and (3.4.4) respectively, and

$$f(x, y) = (F - V)x - \mathcal{F}(x, y) + \mathcal{V}(x, y) = \begin{bmatrix} \beta_h I\left(1 - \frac{S}{N}\right) + \beta_e B\left(\frac{N}{\kappa} - \frac{S}{\kappa+B}\right) \\ 0 \\ 0 \end{bmatrix}.$$

Multiplying matrices V^{-1} and F gives

$$V^{-1}F = \begin{bmatrix} 0 & \frac{\beta_h}{\mu+\gamma} & \frac{\beta_e N}{(\mu+\gamma)\kappa} \\ 0 & \frac{\beta_h \gamma}{(\mu+\gamma)(\mu+\alpha)} & \frac{\beta_e N\gamma}{(\mu+\gamma)(\mu+\alpha)\kappa} \\ 0 & \frac{\beta_h \gamma\epsilon}{(\mu+\gamma)(\mu+\alpha)\delta} & \frac{\beta_e N\gamma\epsilon}{(\mu+\gamma)(\mu+\alpha)\kappa\delta} \end{bmatrix}.$$

We notice that $f(x, y) \geq 0$ in $\tau \subset \mathbb{R}^5_+, \mathrm{F} \geq 0$, and $V^{-1} \geq 0$. But $V^{-1}F$ is reducible, so we cannot use the conclusion from Theorem 2.2 of [33]. Instead, we use Theorem 2.1 of [33] to construct the Lyapunov function for this model. Let $w^T = (w_1, w_2, w_3)$ be the left eigenvector of $V^{-1}F$ corresponding to $\rho(FV^{-1}) = \rho(V^{-1}F) = \mathcal{R}_0$. We therefore have

$$(w_1, w_2, w_3)V^{-1}F = \mathcal{R}_0(w_1, w_2, w_3).$$

Solving the above equation, we get: $w_1 \cdot 0 + w_2 \cdot 0 + w_3 \cdot 0 = \mathcal{R}_0 w_1 \implies w_1 = 0$

$$w_2 \frac{\beta_h \gamma}{(\mu+\gamma)(\mu+\alpha)} + w_3 \frac{\beta_h \gamma \epsilon}{(\mu+\gamma)(\mu+\alpha)\delta} = \mathcal{R}_0 w_2, \tag{3.4.7}$$

$$w_2 \frac{\beta_e N \gamma}{(\mu+\gamma)(\mu+\alpha)\kappa} + w_3 \frac{\beta_e N \epsilon \gamma}{(\mu+\gamma)(\mu+\alpha)\kappa\delta} = \mathcal{R}_0 w_3. \tag{3.4.8}$$

Substituting the value of $\mathcal{R}_0$ in (3.4.7) and (3.4.8), both equations simplify to

$$w_3 = \frac{N\beta_e}{\beta_h \kappa} w_2.$$

So we have the general solution as $w_1 = 0, w_2 = p$ and $w_3 = \frac{N\beta_e}{\beta_h\kappa} p$, where p is a parameter. If we let $p = 1$, then $(w_1, w_2, w_3) = (0, 1, \frac{N\beta_e}{\beta_h\kappa})$. The function Q is given by

$$Q = w^T V^{-1} x = \frac{\gamma[\beta_h\kappa\delta + N\epsilon\beta_e]}{(\mu+\gamma)(\mu+\alpha)\delta\beta_h\kappa} E + \frac{\beta_h\kappa\delta + N\epsilon\beta_e}{(\mu+\alpha)\delta\beta_h\kappa} I + \frac{N\beta_e}{\delta\beta_h\kappa}.$$

Differentiating along solutions of the system gives

$$\begin{aligned} Q' =& (\mathcal{R}_0 - 1) w^T x - w^T V^{-1} f(x, y) \\ =& (\mathcal{R}_0 - 1)\left(I + \frac{N\beta_e}{\beta_h\kappa} B\right) - \frac{\gamma[\beta_h\kappa\delta + N\epsilon\beta_e]}{(\mu+\gamma)(\mu+\alpha)\delta\beta_h\kappa}\left[\beta_h I\left(1 - \frac{S}{N}\right) + N\beta_e B\left(\frac{N}{\kappa} - \frac{S}{\kappa+B}\right)\right]. \end{aligned} \tag{3.4.9}$$

Since $S \leq N$ and $\kappa \leq \kappa + B$ imply that $1 - \frac{S}{N} \geq 0$ and $\frac{N}{\kappa} - \frac{S}{\kappa+B} \geq 0$, we have

$$-\frac{\gamma[\beta_h\kappa\delta + N\epsilon\beta_e]}{(\mu+\gamma)(\mu+\alpha)\delta\beta_h\kappa}\left[\beta_h I\left(1 - \frac{S}{N}\right) + N\beta_e B\left(\frac{N}{\kappa} - \frac{S}{\kappa+B}\right)\right] \leq 0.$$

If $\mathcal{R}_0 < 1$, then $Q' \leq 0$ in τ. Therefore Q is the Lyapunov function for the system [25]. We use LaSalle's invariance principle [20] to prove global stability of DFE, and we

proceed as follows. $Q' = 0$ implies that

$$\frac{\gamma[\beta_h\kappa\delta + N\epsilon\beta_e]}{(\mu+\gamma)(\mu+\alpha)\delta\beta_h\kappa}\left[\beta_h I\left(1-\frac{S}{N}\right) + N\beta_e B\left(\frac{N}{\kappa} - \frac{S}{\kappa+B}\right)\right] = (\mathcal{R}_0 - 1)\left(I + \frac{N\beta_e}{\beta_h\kappa}B\right).$$

Since $\mathcal{R}_0 < 1$, we have

$$\frac{\gamma[\beta_h\kappa\delta + N\epsilon\beta_e]}{(\mu+\gamma)(\mu+\alpha)\delta\beta_h\kappa}\left[\beta_h I\left(1-\frac{S}{N}\right) + N\beta_e B\left(\frac{N}{\kappa} - \frac{S}{\kappa+B}\right)\right] \leq 0.$$

Since $\frac{\gamma[\beta_h\kappa\delta + N\epsilon\beta_e]}{(\mu+\gamma)(\mu+\alpha)\delta\beta_h\kappa} > 0$, we have

$$\begin{aligned} &\left[\beta_h I\left(1-\frac{S}{N}\right) + N\beta_e B\left(\frac{N}{\kappa} - \frac{S}{\kappa+B}\right)\right], \leq 0 \\ \implies &\beta_h I\left(1-\frac{S}{N}\right) \leq N\beta_e B\left(\frac{S}{\kappa+B} - \frac{N}{\kappa}\right). \end{aligned} \tag{3.4.10}$$

Since $\frac{S}{\kappa+B} - \frac{N}{\kappa} \leq 0$, we have

$$\beta_h I\left(1-\frac{S}{N}\right) \leq 0.$$

Since $\beta_h I \geq 0$, we have $\left(1 - \frac{S}{N}\right) \leq 0 \implies N \leq S$.

This result together with the condition that $S \leq N$, imply that $S = N$, which in turn implies that $E = I = R = 0$ since $S + E + I + R = N$. Going back to (3.4.10), exchanging the roles of the first and second term, the same argument can be made to show that $B = 0$. Therefore $\{(N, 0, 0, 0, 0)\}$ is the only invariant set in τ which satisfies $Q' = 0$ when $\mathcal{R}_0 < 1$. Thus, by LaSalle's invariance principle, the DFE is globally asymptotically stable in τ when $\mathcal{R}_0 < 1$ [25].

When $\mathcal{R}_0 = 1$, the first term of (3.4.9) is zero and $Q' \leq 0$ in τ. $Q' = 0$ implies that

$$\begin{aligned} \frac{\gamma[\beta_h\kappa\delta + N\epsilon\beta_e]}{(\mu+\gamma)(\mu+\alpha)\delta\beta_h\kappa}\left[\beta_h I\left(1-\frac{S}{N}\right) + N\beta_e B\left(\frac{N}{\kappa} - \frac{S}{\kappa+B}\right)\right] &= 0, \\ \implies \left[\beta_h I\left(1-\frac{S}{N}\right) + N\beta_e B\left(\frac{N}{\kappa} - \frac{S}{\kappa+B}\right)\right] &= 0, \end{aligned} \tag{3.4.11}$$

$$\implies \beta_h I\left(1-\frac{S}{N}\right) = N\beta_e B\left(\frac{S}{\kappa+B}-\frac{N}{\kappa}\right).$$

Since $0 \leq S \leq N$ and $0 < \kappa \leq \kappa + B$ imply that $\frac{S}{\kappa+B} - \frac{N}{\kappa} \leq 0$, we have

$$\beta_h I\left(1-\frac{S}{N}\right) \leq 0.$$

Since $\beta_h I \geq 0$, we have $\left(1-\frac{S}{N}\right) \leq 0 \implies N \leq S$.

This result together with the condition that $S \leq N$, imply that $S = N$, which in turn implies that $E = I = R = 0$ since $S + E + I + R = N$. Therefore $\{(N, 0, 0, 0, 0)\}$ is the only invariant set in τ which satisfies $Q' = 0$ when $\mathcal{R}_0 = 1$. Thus, by LaSalle's invariance principle, the DFE is globally asymptotically stable in τ when $\mathcal{R}_0 = 1$ [25].

We now show that when $\mathcal{R}_0 > 1$, $Q' > 0$ in a neighbourhood of X_0, making X_0 unstable. For $\mathcal{R}_0 > 1$, the first term of equation (3.4.9) is positive, and the second term is zero when $S = N$ and $B = 0$, thus $Q' > 0$. By continuity Q' remains positive in a small neighbourhood of X_0 [25]. ■

Global asymptotic stability of DFE rules-out the existence of backward bifurcation when $\mathcal{R}_0 \leq 1$. Using uniform persistence result from [11] and an argument in the proof of proposition 3.3 of [22], it can be shown that when $\mathcal{R}_0 > 1$ instability of X_0 implies that the system is uniformly persistent. Uniform persistence and positive invariance of the compact set τ imply the existence of at least one positive equilibrium.

3.4.3 Global stability of the endemic Equilibrium

Lemma 3.4.3. *When $\mathcal{R}_0 > 1$, there exists a unique endemic equilibrium X_* given by $B^* = \frac{-b+\sqrt{b^2-4ac}}{2a}$, where $a = (\beta_e N\epsilon + \beta_h\kappa\delta)\beta_h\delta$,*
$b = (\beta_e N\epsilon+\beta_h\kappa\delta)^2-\mu N\epsilon\left[\beta_h\kappa\delta(\mathcal{R}_0-1)-\beta_e N\epsilon\right]$, and $c = -\mu N\epsilon\kappa(\beta_e N\epsilon+\beta_h\kappa\delta)(\mathcal{R}_0-1)$.
When $\mathcal{R}_0 \leq 1$, there is no endemic equilibrium.

Proof. Substituting (3.3.1) and (3.3.2) into (3.1.2) we get

$$0 = \mu N - \mu S - \left(\beta_e \frac{B}{\kappa + B} + \beta_h \frac{\delta B}{N\epsilon}\right) S. \tag{3.4.12}$$

From (3.3.3), and (3.4.5)

$$S = \frac{N(\beta_e N\epsilon + \beta_h \kappa\delta)(\kappa + B)}{\mathcal{R}_0(\beta_e N\epsilon + \beta_h(\kappa + B)\delta)\kappa}. \tag{3.4.13}$$

Substituting (3.4.13) into (3.4.12) and simplifying, we get

$$0 = aB^2 + bB + c,$$

where

$$a = (\beta_e N\epsilon + \beta_h \kappa\delta)\beta_h\delta \tag{3.4.13$'$}$$

$$b = (\beta_e N\epsilon + \beta_h \kappa\delta)^2 - \mu N\epsilon\left[\beta_h\kappa\delta(\mathcal{R}_0 - 1) - \beta_e N\epsilon\right], \tag{3.4.13$''$,}$$

$$c = -\mu N\epsilon\kappa(\beta_e N\epsilon + \beta_h\kappa\delta)(\mathcal{R}_0 - 1). \tag{3.4.13$'''$}$$

We therefore have at most two endemic equilibria given by

$$B_1^* = \frac{-b + \sqrt{b^2 - 4ac}}{2a} \quad \text{and} \quad B_2^* = \frac{-b - \sqrt{b^2 - 4ac}}{2a}.$$

We consider the following cases:

1. When $\mathcal{R}_0 > 1$;

   $a > 0$, $c < 0$, and $b > 0$ if $(\beta_e N\epsilon + \beta_h\kappa\delta)^2 + \mu N\epsilon(\beta_h\kappa\delta + \beta_e N\epsilon) > N\epsilon\beta_h\kappa\delta\mu\mathcal{R}_0$. In which case $b^2 - 4ac > b^2$. If $(\beta_e N\epsilon + \beta_h\kappa\delta)^2 + \mu N\epsilon(\beta_h\kappa\delta + \beta_e N\epsilon) < N\epsilon\beta_h\kappa\delta\mu\mathcal{R}_0$, then $b < 0$ and $b^2 - 4ac > b^2$. If $(\beta_e N\epsilon + \beta_h\kappa\delta)^2 + \mu N\epsilon(\beta_h\kappa\delta + \beta_e N\epsilon) = N\epsilon\beta_h\kappa\delta\mu\mathcal{R}_0$, then $b = 0$ and $b^2 - 4ac = -4ac > 0$.

2. When $\mathcal{R}_0 = 1$;

$a > 0$, $c = 0$ and $b > 0$, thus $b^2 - 4ac = b^2$.

3. When $\mathcal{R}_0 < 1$;

   $a > 0$, $c > 0$, and $b > 0$, thus we have $b^2 - 4ac < 0$.

Table 3.1 below summarizes the analysis of the solutions of the above quadratic equation in relation to $\mathcal{R}_0$.

$\mathcal{R}_0$	c	4ac	b	$b^2 - 4ac$	$-b + \sqrt{b^2 - 4ac}$	$-b - \sqrt{b^2 - 4ac}$	Comment
> 1	< 0	< 0	$= 0$	$-4ac > 0$	> 0	< 0	1 EE
			< 0	$> b^2$	> 0	< 0	1 EE
			> 0	$> b^2$	> 0	< 0	1 EE
$= 1$	$= 0$	$= 0$	> 0	$= b^2$	$= 0$	< 0	no EE
< 1	> 0	$\in (0, b^2)$	> 0	$\in (0, b^2)$	< 0	< 0	no EE
		$\in (b^2, \infty)$	> 0	< 0	complex	complex	no EE

Table 3.1: Analysis of solutions of the quadratic equation

Thus when $\mathcal{R}_0 < 1$, there is no endemic equilibrium, and when $\mathcal{R}_0 > 1$, we have a unique endemic equilibrium obtained when

$$B^* = B_1^* = \frac{-b + \sqrt{b^2 - 4ac}}{2a}.$$

[25] ■

Theorem 3.4.4. *If $\mathcal{R}_0 > 1$, the unique endemic equilibrium is globally asymptotically stable in τ.*

Proof. We use an approach based on Volterra-Lyapunov stable matrices as described in [23]. We define the Lyapunov function as follows;

$$L = m_1(S - S^*)^2 + m_2(E - E^*)^2 + m_3(I - I^*)^2 + m_4(B - B^*)^2,$$

where m_1, m_2, m_3 and m_4 are positive constants. Differentiating L along the trajectories

of our system gives

$$\begin{aligned}
L' &= 2m_1(S-S^*)\left[\mu N - \mu S - \left(\beta_e \frac{B}{\kappa+B} + \beta_h \frac{I}{N}\right) S\right] \\
&+ 2m_2(E-E^*)\left[\left(\beta_e \frac{B}{\kappa+B} + \beta_h \frac{I}{N}\right) S - (\mu+\gamma)E\right] \\
&+ 2m_3(I-I^*)\left[\gamma E - (\mu+\alpha)I\right] + 2m_4(B-B^*)\left[\epsilon I - \delta B\right].
\end{aligned}$$

At the endemic equilibrium, $S' = E' = I' = B' = 0$. Also $\beta_h \frac{S^*I}{N} - \beta_h \frac{S^*I}{N} = 0$ and $\beta_e \frac{BS^*}{\kappa+B} - \beta_e \frac{BS^*}{\kappa+B} = 0$. Substituting in the appropriate brackets and factoring gives

$$\begin{aligned}
L' &= -2m_1(S-S^*)^2\left[\mu + \beta_e \frac{B}{\kappa+B} + \beta_h \frac{I}{N}\right] \\
&- 2m_1(S-S^*)(I-I^*)\beta_h \frac{S^*}{N} \\
&- 2m_1(S-S^*)(B-B^*)\beta_e \frac{S^*\kappa}{(\kappa+B)(\kappa+B^*)} \\
&+ 2m_2(E-E^*)(S-S^*)\left[\beta_e \frac{B}{\kappa+B} + \beta_h \frac{I}{N}\right] \\
&- 2m_2(E-E^*)^2(\mu+\gamma) \\
&+ 2m_2(E-E^*)(I-I^*)\beta_h \frac{S^*}{N} \\
&+ 2m_2(E-E^*)(B-B^*)\beta_e \frac{S^*\kappa}{(\kappa+B)(\kappa+B^*)} \\
&+ 2m_3(I-I^*)(E-E^*)\gamma \\
&- 2m_3(I-I^*)^2(\mu+\alpha) \\
&+ 2m_4(B-B^*)(I-I^*)\epsilon \\
&- 2m_4(B-B^*)^2\delta \\
&= Y(MA + A^T M^T)Y^T.
\end{aligned}$$

Where $Y = (S - S^*, E - E^*, I - I^*, B - B^*)$, $M = \text{diag}(m_1, m_2, m_3, m_4)$ and

$$A = \begin{bmatrix} -\mu - \beta_e \frac{B}{\kappa+B} - \beta_h \frac{I}{N} & 0 & -\beta_h \frac{S^*}{N} & -\beta_e \frac{S^*\kappa}{(\kappa+B)(\kappa+B^*)} \\ \beta_e \frac{B}{\kappa+B} + \beta_h \frac{I}{N} & -(\mu+\gamma) & \beta_h \frac{S^*}{N} & \beta_e \frac{S^*\kappa}{(\kappa+B)(\kappa+B^*)} \\ 0 & \gamma & -(\mu+\alpha) & 0 \\ 0 & 0 & \epsilon & -\delta \end{bmatrix} \tag{3.4.14}$$

$\det(A) = \det(-A) = (\mu + \beta_e \frac{B}{\kappa+B} + \beta_h \frac{I}{N})(\mu+\gamma)(\mu+\alpha)\delta - \mu\gamma(\delta\beta_h \frac{S^*}{N} + \epsilon\beta_e \frac{S^*\kappa}{(\kappa+B)(\kappa+B^*)})$

Let $T_1 = \beta_e \frac{B}{\kappa+B} + \beta_h \frac{I}{N}$ and $T_2 = \delta\beta_h \frac{S^*}{N} + \epsilon\beta_e \frac{S^*\kappa}{(\kappa+B)(\kappa+B^*)}$. Then

$\det(A) = \delta(\mu+\alpha)(\mu+\gamma)(\mu+T_1) - \mu\gamma T_2$.

From (3.1.3), (3.1.4) and (3.1.5), we notice that at the endemic equilibrium (S^*, E^*, I^*, B^*) we have

$$\beta_e \frac{B^*S^*}{\kappa + B^*} + \beta_h \frac{I^*S^*}{N} - (\mu+\gamma)E^* = 0 \tag{3.4.15}$$

$$\gamma E^* - (\mu+\alpha)I^* = 0 \implies E^* = (\mu+\alpha)\frac{I^*}{\gamma} \tag{3.4.16}$$

$$\epsilon I^* - \delta B^* = 0 \implies B^* = \frac{\epsilon I^*}{\delta} \tag{3.4.17}$$

Substituting (3.4.16) and (3.4.17) into (3.4.15) gives

$$\gamma\left(\delta\beta_h \frac{S^*}{N} + \epsilon\beta_e \frac{S^*}{\kappa + B^*}\right) = \delta(\mu+\alpha)(\mu+\gamma). \tag{3.4.18}$$

Since $B \geq 0$ and $B = 0$ gives us the DFE X_0. For any $X \neq X_0$, we have $B > 0$, and $\frac{\kappa}{\kappa+B} < 1$. From (3.4.18) we get that

$$\begin{aligned} (\mu+\gamma)(\mu+\alpha)\delta &< \gamma\left(\delta\beta_h \frac{S^*}{N} + \epsilon\beta_e \frac{S^*\kappa}{(\kappa+B)(\kappa+B^*)}\right) \\ \implies \det(A) &> T_1\delta(\mu+\alpha)(\mu+\gamma) \geq 0 \end{aligned}$$

$$(-A)^{-1} = \frac{1}{\det(A)} \begin{bmatrix} T_6 & -\gamma T_2 & (\mu+\gamma)T_2 & -(\mu+\gamma)T_3 \\ \delta(\mu+\alpha)T_1 & \delta(\mu+\alpha)(\mu+T_1) & \mu T_2 & -\mu T_3 \\ \gamma\delta T_1 & \gamma\delta(\mu+T_1) & \delta(\mu+\gamma)(\mu+T_1) & T_4 \\ \gamma\epsilon T_1 & \gamma\epsilon(\mu+T_1) & \epsilon(\mu+\gamma)(\mu+T_1) & -T_5 \end{bmatrix},$$

where

$$\begin{aligned} T_3 &= (\mu+\alpha)\beta_e \frac{S^*\kappa}{(\kappa+B)(\kappa+B^*)}, \\ T_4 &= \gamma\mu\beta_e \frac{S^*\kappa}{(\kappa+B)(\kappa+B^*)}, \\ T_5 &= \gamma\mu\beta_h \frac{S^*}{N} - (\mu+\alpha)(\mu+\gamma)(\mu+T_1), \\ T_6 &= \delta(\mu+\gamma)(\mu+\alpha) - \gamma T_2. \end{aligned}$$

For any $n \times n$ matrix B, let $\widetilde{B}$ denote $(n-1)\times(n-1)$ matrix obtained from B by removing the last row and column of B.

Let $U = \widetilde{(-A)^{-1}}$ and $E = U^{-1} = \widetilde{(-A)}$. Then

$$U = \frac{1}{\det(A)} \begin{bmatrix} \delta(\mu+\gamma)(\mu+\alpha) - \gamma T_2 & -\gamma T_2 & (\mu+\gamma)T_2 \\ \delta T_1(\mu+\alpha) & \delta(\mu+T_1)(\mu+\alpha) & \mu T_2 \\ \delta\gamma T_1 & \delta\gamma(\mu+T_1) & \delta(\mu+\gamma)(\mu+T_1) \end{bmatrix},$$

and

$$E = \begin{bmatrix} \mu+T_1 & 0 & \beta_h\frac{S^*}{N} \\ -T_1 & \mu+\gamma & -\beta_h\frac{S^*}{N} \\ 0 & -\gamma & \mu+\alpha \end{bmatrix}.$$

To establish the global stability of the endemic equilibrium, we show that matrix A defined in (3.4.14) is Volterra-Lyapunov stable through the following steps;

step 1 Use lemma 2.4 of [23] to conclude that there exists a 2×2 matrix $D = \mathrm{diag}(m_1, m_2)$

such that $\widetilde{D}(\widetilde{-U}) + (\widetilde{D}(\widetilde{-U}))^T < 0$, which will then imply that $\widetilde{D}\widetilde{U} + (\widetilde{D}\widetilde{U})^T > 0$. Show that $\widetilde{D}\widetilde{E} + (\widetilde{D}\widetilde{E})^T > 0$ as well.

step 2 Then use Lemma 2.8 of [23] and the results of step 1 to conclude that there exists a 3×3 matrix $\widetilde{M} = D = \text{diag}(m_1, m_2, m_3)$ such that $\widetilde{M}U + (\widetilde{M}U)^T = \widetilde{M}\widetilde{(-A)^{-1}} + (\widetilde{M}\widetilde{(-A)^{-1}})^T > 0$. Show that $\widetilde{M}(U^{-1}) + (\widetilde{M}(U^{-1}))^T = \widetilde{M}E + (\widetilde{M}E)^T = \widetilde{M}\widetilde{(-A)} + (\widetilde{M}\widetilde{(-A)})^T > 0$ as well.

step 3 Then use Lemma 2.8 of [23] and the results of step 2 to conclude that there exists a 4×4 matrix $M = \text{diag}(m_1, m_2, m_3, m_4)$ such that $M(-A) + (M(-A))^T > 0$. Which will then imply that $MA + (MA)^T < 0$, and thus proving that A is Volterra-Lyapunov stable.

Now,

$$\widetilde{-U} = \frac{1}{\det(A)} \begin{bmatrix} \gamma T_2 - \delta(\mu+\alpha)(\mu+\gamma) & \gamma T_2 \\ -\delta T_1(\mu+\alpha) & -\delta(\mu+\alpha)(\mu+T_1) \end{bmatrix}.$$

Notice that $(\widetilde{-U})_{11} < 0$, $(\widetilde{-U})_{22} < 0$ and $\det(\widetilde{-U}) => 0$.

By Lemma 2.4 of [23], $\widetilde{-U}$ is Volterra-Lyapunov stable. This mean that there exists a 2×2 positive diagonal matrix $\tilde{D} = \text{diag}(m_1, m_2)$ such that

$$\begin{aligned} \widetilde{D}(\widetilde{-U}) + (\widetilde{D}(\widetilde{-U}))^T < 0, \\ \implies \widetilde{D}\widetilde{U} + (\widetilde{D}\widetilde{U})^T > 0. \end{aligned}$$

Specifically

$$Q = \widetilde{D}\widetilde{U} + (\widetilde{D}\widetilde{U})^T = \begin{bmatrix} 2m_1\left[\delta(\mu+\alpha)(\mu+\gamma) - \gamma T_2\right] & m_2\delta T_1(\mu+\alpha) - m_1\gamma T_2 \\ m_2\delta T_1(\mu+\alpha) - m_1\gamma T_2 & 2m_2\delta(\mu+\alpha)(\mu+T_1) \end{bmatrix},$$

and

$$\begin{aligned}\det(A)\det(Q) = \delta^2(\mu+\alpha)^2\left[4m_1m_2(\mu+\gamma)(\mu+T_1) - (m_2T_1)^2\right] \\ - 2m_1m_2\delta(\mu+\alpha)(\mu+T_1)\gamma T_2 \\ - 2m_1m_2\delta(\mu+\alpha)\mu\gamma T_2 - (m_1\gamma T_2)^2.\end{aligned} \tag{3.4.19}$$

Since $Q > 0, \quad \det(Q) > 0$. On the other hand,

$$P = \widetilde{D}(\widetilde{E}) + (\widetilde{D}(\widetilde{E}))^T = \begin{bmatrix} 2m_1(\mu+T_1) & -m_2T_1 \\ -m_2T_1 & 2m_2(\mu+\gamma) \end{bmatrix}.$$

Notice that all the diagonal entries of P are positive, and

$$\det(P) = 4m_1m_2(\mu+T_1)(\mu+\gamma) - (m_2T_1)^2.$$

From (3.4.19), we notice that

$$\begin{aligned}\det(A)\det(Q) &= \delta^2(\mu+\alpha)^2\det(P) \\ &\quad - 2m_1m_2\delta(\mu+\alpha)(\mu+T_1)\gamma T_2 \\ &\quad - 2m_1m_2\delta(\mu+\alpha)\mu\gamma T_2 - (m_1\gamma T_2)^2, \\ \implies \det(P) > 0 \qquad &\text{since} \quad \det(A)\det(Q) > 0.\end{aligned}$$

Thus $P = \widetilde{D}(\widetilde{E}) + (\widetilde{D}(\widetilde{E}))^T > 0$ as well [25]. Moreover, $\widetilde{(-A)^{-1}} = U_{33} = \delta(\mu+\gamma)(\mu+T_1) > 0$. Therefore by lemma 2.8 of [23], there exists a 3×3 matrix $\tilde{M} = D = \text{diag}(m_1, m_2, m_3)$ such that $\widetilde{MU} + (\widetilde{MU})^T = \widetilde{M}\widetilde{(-A)^{-1}} + (\widetilde{M}\widetilde{(-A)^{-1}})^T > 0$. Specifically

$$\begin{aligned}H =& \widetilde{M}\widetilde{(-A)^{-1}} + (\widetilde{M}\widetilde{(-A)^{-1}})^T \\ =& \frac{1}{\det(A)}\begin{bmatrix} 2m_1[\delta(\mu+\alpha)(\mu+\gamma)-\gamma T_2] & m_2\delta T_1(\mu+\alpha)-m_1\gamma T_2 & m_3\gamma\delta T_1 - m_1T_2(\mu+\gamma) \\ m_2\delta T_1(\mu+\alpha)-m_1\gamma T_2 & 2m_2\delta(\mu+\alpha)(\mu+T_1) & m_2\mu T_2 + m_3\gamma\delta(\mu+T_1) \\ m_3\gamma\delta T_1 - m_1T_2(\mu+\gamma) & m_2\mu T_2 + m_3\gamma\delta(\mu+T_1) & 2m_3\delta(\mu+\gamma)(\mu+T_1) \end{bmatrix},\end{aligned}$$

and

$$\begin{aligned}\det(A)\det(H) =&\delta^2\det(A)\left[2m_1(\mu+T_1)\left[4m_2m_3(\mu+\alpha)(\mu+\gamma)-(m_3\gamma)^2\right]\right.\\ &-4m_1m_2m_3\gamma\beta_h\frac{S^*}{N}(\mu+T_1)+2m_1m_2m_3\gamma T_1\beta_h\frac{S^*}{N}\\ &-2m_1\mu\left(m_2\beta_h\frac{S^*}{N}\right)^2-2m_3(m_2T_1)^2(\mu+\alpha)]\\ &\left.-2m_2(\mu+\gamma)\left(m_1\beta_h\frac{S^*}{N}\right)^2\right] \qquad (3.4.20)\\ &-2m_1\mu m_2^2\left[2\delta\epsilon\beta_h\frac{S^*}{N}\beta_e\frac{\kappa S^*}{(\kappa+B)(\kappa+B^*)}+\left(\epsilon\beta_e\frac{\kappa S^*}{(\kappa+B)(\kappa+B^*)}\right)^2\right]\\ &-2m_2(\mu+\gamma)m_1^2\left[2\delta\epsilon\beta_h\frac{S^*}{N}\beta_e\frac{\kappa S^*}{(\kappa+B)(\kappa+B^*)}+\left(\epsilon\beta_e\frac{\kappa S^*}{(\kappa+B)(\kappa+B^*)}\right)^2\right]\\ &-2m_1m_2m_3T_1\gamma\epsilon\beta_e\frac{\kappa S^*}{(\kappa+B)(\kappa+B^*)}\delta\det(A)\\ &-4m_1m_2m_3\mu\gamma\epsilon\beta_e\frac{\kappa S^*}{(\kappa+B)(\kappa+B^*)}\delta\det(A).\end{aligned}$$

On the other hand

$$\begin{aligned}R =&\widetilde{M}(\widetilde{-A})+(\widetilde{M}(\widetilde{-A}))^T\\ =&\begin{bmatrix}2m_1(\mu+T_1) & -m_2T_1 & m_1\beta_h\frac{S^*}{N}\\ -m_2T_1 & 2m_2(\mu+\gamma) & -\left(m_3\gamma+m_2\beta_h\frac{S^*}{N}\right)\\ m_1\beta_h\frac{S^*}{N} & -\left(m_3\gamma+m_2\beta_h\frac{S^*}{N}\right) & 2m_3(\mu+\alpha)\end{bmatrix},\end{aligned}$$

and

$$\begin{aligned}\det(R) =&\,2m_1(\mu+T_1)\left[4m_2m_3(\mu+\alpha)(\mu+\gamma)-(m_3\gamma)^2\right]\\ &-4m_1m_2m_3\gamma\beta_h\frac{S^*}{N}(\mu+T_1)+2m_1m_2m_3\gamma T_1\beta_h\frac{S^*}{N}\\ &-2m_1\mu\left(m_2\beta_h\frac{S^*}{N}\right)^2-2m_3(m_2T_1)^2(\mu+\alpha)\\ &-2m_2(\mu+\gamma)\left(m_1\beta_h\frac{S^*}{N}\right)^2.\end{aligned}$$

Note that all the diagonal entries of R are positive. We also notice from (3.4.20) that

$$\begin{aligned}\det(A)\det(H) = \delta^2 \det(A)\det(R) \\ - 2m_1\mu m_2^2\left[2\delta\epsilon\beta_h\frac{S^*}{N}\beta_e\frac{\kappa S^*}{(\kappa+B)(\kappa+B^*)} + \left(\epsilon\beta_e\frac{\kappa S^*}{(\kappa+B)(\kappa+B^*)}\right)^2\right] \\ - 2m_2(\mu+\gamma)m_1^2\left[2\delta\epsilon\beta_h\frac{S^*}{N}\beta_e\frac{\kappa S^*}{(\kappa+B)(\kappa+B^*)} + \left(\epsilon\beta_e\frac{\kappa S^*}{(\kappa+B)(\kappa+B^*)}\right)^2\right] \\ - 2m_1m_2m_3T_1\gamma\epsilon\beta_e\frac{\kappa S^*}{(\kappa+B)(\kappa+B^*)}\delta\det(A) \\ - 4m_1m_2m_3\mu\gamma\epsilon\beta_e\frac{\kappa S^*}{(\kappa+B)(\kappa+B^*)}\delta\det(A).\end{aligned}$$

$\implies \det(R) > 0 \quad \text{since} \quad \det(A) > 0 \quad \text{and} \quad \det(H) > 0.$

Thus $\widetilde{M(-A)} + (\widetilde{M(-A)})^T > 0$ as well [25]. Moreover, $(-A)_{44} = \delta > 0$. Then lemma 2.8 of [23] guarantees that there exists a positive diagonal
$M = \text{diag}(m_1, m_2, m_3, m_4)$ such that $M(-A) + (M(-A))^T > 0$
Which directly implies that matrix A is Volterra-Lyapunov stable.

Since we have assumed that matrix M is a constant matrix, we can then conclude that

when $\mathcal{R}_0 > 1$, the endemic equilibrium of the system is globally asymptotically stable in τ [25]. ■

In the next chapter, we will present the numerical simulations to demonstrate the findings of our mathematical analysis.

Chapter 4

Numerical Simulations

4.1 Sensitivity analysis of parameters

To ascertain the contribution of each parameter in the endemicity of enterovirus, in this section, we carry sensitivity analysis of parameters in basic reproduction number $\mathcal{R}_0$ using the baseline values as shown in Table 4.1. The main novelty of this study is the incorporation of the environment contamination in the contribution to the enterovirus transmission.

4.1.1 Estimation of parameter values

We consider a constant population of 1000 individuals. We estimate the human life expectancy in our population of study to be 55 years. Since humans become infectious after 3 days of exposure, the rate at which they become infectious $\gamma = \frac{1}{3}$. The incubation period is 7 days and the infectiousness lasts for 10 days after the first symptoms developed. So, the recovery rate $\alpha = \frac{1}{(7-3)+10} = \frac{1}{14}$. Some baseline parameter values given in Table 4.1 are obtained from [6, 31]. Direct transmission rate is estimated based on the relevant values from [6] as $\beta_h = 0.3605$. Our simulations are consistent with numerical simulations of other infectious diseases in the literature, showing the number of new infections rising in the first phase and reaching a peak, then in the second phase cases decline as individuals start to

recover.

Parameter	Description	Baseline value	Value range per day and references
μ	human birth or death rate	$\frac{55}{365} = 0.1507$	0.10 to 0.20
β_e	Ingestion rate environment to human	1×10^{-6}	1.2×10^{-6} to 1.5×10^{-6} [6]
κ	Michaelis-Menten constant	542×10^{-6}	540×10^{-6} to 546×10^{-6} [6]
β_h	Contact rate human to human	0.3605	0.229 to 0.492 [6]
α	Recovery rate of infectious	0.0714	0.0667 to 0.0770 [30]
γ	Progression rate of exposed to infectious	0.333	0.25 to 0.5 [30]
ϵ	Shedding rate of infectious to environment	22.443	19 to 33 [31]
δ	Decay rate of enterovirus	698.077	600 to 700 [31]

Table 4.1: Table of baseline parameter values and sources [25]

4.1.2 Elasticity indices

The elasticity index for parameter, say p is given by $\frac{p\partial\mathcal{R}_0}{\mathcal{R}_0\partial p}$. It measures ratio of the relative change in $\mathcal{R}_0$ to the relative change in p [13]. The parameter whose elasticity index has the largest magnitude in absolute terms, affects $\mathcal{R}_0$ the most and hence affects the transmission dynamics of enterovirus as shown in Theorem 3.4.2 and Theorem 3.4.4. Table 4.2 below shows the elasticity indices of parameters calculated using baseline values given in Table 4.1, with human population $N = 1000$. The indices are arranged in descending order in terms of magnitude. We notice that the direct infection rate (β_h) has the largest magnitude, and thus affects the disease dynamics the most, followed by other parameters.

Parameter	Formula $\left(\frac{p\partial\mathcal{R}_0}{\mathcal{R}_0\partial p}\right)$	Elasticity index
β_h	$\frac{\beta_h\kappa\delta}{\beta_h\kappa\delta+N\beta_e\epsilon}$	0.9838
α	$\frac{-\alpha}{\mu+\alpha}$	-0.6503
β_e	$\frac{N\beta_e\epsilon}{\beta_h\kappa\delta+N\beta_e\epsilon}$	0.6220
κ	$-\frac{N\beta_e\epsilon}{\beta_h\kappa\delta+N\beta_e\epsilon}$	-0.6220
ϵ	$\frac{N\beta_e\epsilon}{\beta_h\kappa\delta+N\beta_e\epsilon}$	0.6220
δ	$-\frac{N\beta_e\epsilon}{\beta_h\kappa\delta+N\beta_e\epsilon}$	-0.6220
μ	$-\mu\left(\frac{1}{\mu+\alpha}+\frac{1}{\mu+\gamma}\right)$	-0.4531
γ	$\frac{\mu}{\mu+\gamma}$	0.1034

Table 4.2: Table elasticity indices of parameters in $\mathcal{R}_0$ [25].

4.1.3 Numerical simulations for model analysis

In this part, we present the numerical simulations to illustrate the results of our model analysis obtained in the previous sections. The system of equations (3.1.2)-(3.1.6) is numerically solved using baseline values given in Table 4.1. With these parameter values, the basic reproduction number is obtained to be $\mathcal{R}_0 \approx 3.43 > 1$. In Figures 4.1 and 4.2 , one can observe that the trajectories approach the unique endemic equilibrium $(S^*, E^*, I^*, B^*, R^*) \approx (340, 70, 210, 5, 380)$. Furthermore, in order to illustrate the global stability for the DFE, we reduced the value of β_h to 0.0721, to obtained the basic reproduction number $\mathcal{R}_0 = 0.484 < 1$. As can be seen from Figures 4.3 and 4.4, the trajectories of the solution approach the DFE, depicting stability of DFE.

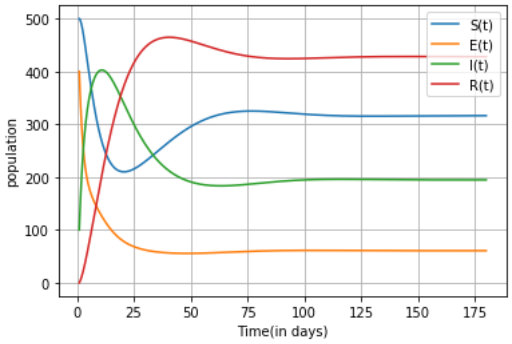

Figure 4.1: The number of humans in each compartment using parameter values in Table 3.1 with $S_0 = 500, E_0 = 400, I_0 = 100, B_0 = 0.5, N = 1000$, resulting in approximated equilibrium values $S^* = 315, E^* = 60, I^* = 195, R^* = 430$ and $\mathcal{R}_0 = 3.43$ [25].

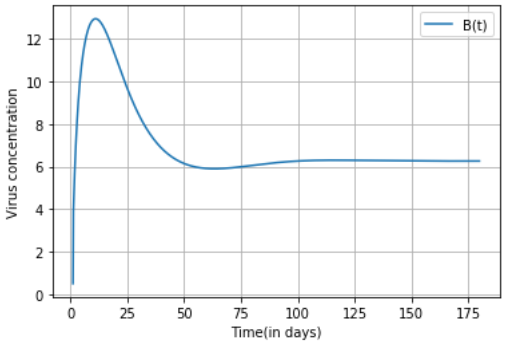

Figure 4.2: Virus concentration in compartment B using parameter values in Table 3.1 with $S_0 = 500, I_0 = 100, E_0 = 400, B_0 = 0.5, N = 1000$ and $\mathcal{R}_0 = 3.43$. The approximated equilibrium value is $B^* = 6.3$ [25].

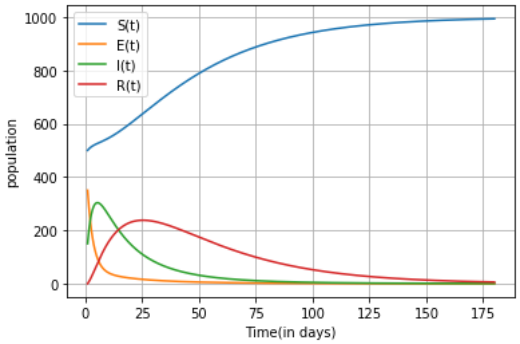

Figure 4.3: The number of humans in each compartment using parameter values in Table 3.1 with $S_0 = 500, I_0 = 150, E_0 = 350, B_0 = 1.5, N = 1000$ and $\mathcal{R}_0 = 0.484$. The approximated equilibrium values are $S^* = 1000, E^* = 0, I^* = 0, R^* = 0$ [25].

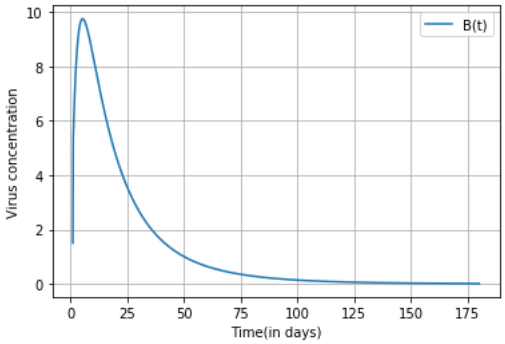

Figure 4.4: Virus concentration in compartment B using parameter values in Table 3.1 with $S_0 = 500, I_0 = 150, E_0 = 350, B_0 = 1.5, N = 1000$ and $\mathcal{R}_0 = 0.484$. The approximated equilibrium value is $B^* = 0$ [25].

Chapter 5

Optimal control applied to enterovirus model

We extend the basic model $(3.1.2)$ -$(3.1.6)$ to include the effects of hygiene and sanitation. Enterovirus illness are mostly mild and resolve on their own over time. According to the Center of Disease Control and Prevention, there in no specific treatment for enterovirus infection. People with mild symptoms like muscle ache and fever may take over-the-counter medication to fight the symptoms.

5.1 Introduction of controls

From Table 4.2, the rate of direct transmission β_h has the highest elasticity index, followed by the recovery rate α and then the rate of indirect transmission rate β_e. We thus consider personal hygiene as one of the control measures, which will reduce the direct transmission rate β_h. Since there is currently no specific treatment for enteroviral infection, there is no control measure that can help us to effectively increase the recovery rate α. We also consider sanitation as a control measure, it removes virus from the environment and thus reducing the indirect transmission rate β_e.

- **Hygiene**

  Let $h \in [0,1]$ be a time dependent and Lebesgue measurable control that represents efforts of personal hygiene that reduce the risk of infection transmission between infectious and susceptible individuals. Efforts of personal hygiene include washing body and frequent washing of hands especially after using the toilet, turning away from other people and covering mouth or nose when coughing or sneezing. The set of admissible hygiene controls is

$$H = \{h(t) : [0,T] \to [0,1] \quad \text{and} \quad h \quad \text{is Lebesgue measurable}\}.$$

- **Sanitation**

  Let $q \in [0,1]$ be a time dependent and Lebesgue measurable control that represents sanitation efforts that cause virus on sanitized environment to lose virulence. Efforts of sanitation include proper sewage disposal, sterilization of surfaces and drinking water. The admissible set of sanitation controls is

$$Q = \{q(t) : [0,T] \to [0,1] \quad \text{and} \quad q \quad \text{is Lebesgue measurable}\}.$$

For simplicity, we denote the control $u = (q,h)$ and the set of admissible controls $U = Q \times H$.

5.2 The extended mathematical model

The portion of susceptible individuals who practice personal hygiene is $h\beta_h \frac{SI}{N}$ and qB represents the concentration of virus lost due to sanitation. The extended model is thus presented as follows;

$$\frac{dS}{dt} = \mu N - \mu S - \beta_e \frac{BS}{\kappa + B} - (1-h)\beta_h \frac{SI}{N}, \tag{5.2.1}$$

$$\frac{dE}{dt} = \beta_e \frac{BS}{\kappa + B} + (1-h)\beta_h \frac{SI}{N} - (\mu + \gamma)E, \tag{5.2.2}$$

$$\frac{dI}{dt} = \gamma E - (\mu + \alpha)I, \tag{5.2.3}$$

$$\frac{dB}{dt} = \epsilon I - (\delta + q)B, \tag{5.2.4}$$

$$\frac{dR}{dt} = \alpha I - \mu R. \tag{5.2.5}$$

With initial conditions

$$S(0) = S_0, E(0) = E_0, I(0) = I_0, B(0) = B_0, R(0) = R_0. \tag{5.2.6}$$

A successful intervention is one that minimizes the number of new cases and the cost of implementing the controls. Possible costs of implementing hygiene and sanitation as control measures include expenses for fuel or electricity used for boiling drinking water, consumption of water, soap and sanitizers. The control $u = (q, h)$ is considered optimal if it minimizes the objective function defined as

$$J = \int_0^T \left(A_1 \left[\beta_e \frac{BS}{\kappa + B} + (1 - h)\beta_h \frac{SI}{N} \right] + A_2 q^2 + A_3 h^2 \right) dt, \tag{5.2.7}$$

where A_1 is unit cost of new infection per person, and $A_2 = A_3$ is unit cost of implementing the controls per time unit. A_1, A_2 and A_3 are balancing coefficients which transform the integrand into cost per time unit. The terms $A_1 \left[\beta_e \frac{BS}{\kappa+B} + (1 - h)\beta_h \frac{SI}{N} \right]$ represent the cost of new cases. Obviously, when individuals get sick, they are not as productive as they usually are under normal conditions, we interpret this as the cost of the infection. The remaining terms represent the cost of implementing the control measures. The quadratic terms indicate non-linearity of the costs. We state the optimal control problem as follows:

$$\min_{u \in U} J(u), \tag{5.2.8}$$

subject to equations $(5.2.1)$-$(5.2.5)$ and initial conditions $(5.2.6)$.

5.3 Existence of optimal control

Theorem 5.3.1. *There exists an optimal control u^* and the corresponding solution $(S^*, E^*, I^*, B^*, R^*)$ to the initial value problem given by (5.2.1)-(5.2.6) that minimizes the objective function given by (5.2.7) on U.*

Proof. The initial value problem (5.2.1)-(5.2.6) can be written as

$$X' = f(t, X, u),$$
$$\text{with} \quad X(0) = X_0.$$

We establish the existence of optimal control using the result of Theorem 4.1 of [10]. For this, we check that the following conditions are met.

1. There exist C_1 and C_2 such that
   (a) $|f(t, X, u)| \leq C_1(1 + X)$ and
   (b) $|f(t, X_1, u) - f(t, X_2, u)| \leq C_2|X_1 - X_2|$,
   for all $t \geq 0$, $X_1, X_2 \in \left\{(S, E, I, B, R) \in \mathbb{R}^5_+ | \mathrm{S} + \mathrm{E} + \mathrm{I} + \mathrm{R} = \mathrm{N}, \quad \mathrm{B} \leq \frac{\mathrm{N}\epsilon}{\delta}\right\}$
   and $u \in U$, where $U = \{u = (q, h) : 0 \leq q, h \leq 1\}$
2. The set of controls and corresponding state variables is non-empty.
3. The control set U is convex and closed, $f(t, X, u) = \alpha_1(t, X) + \beta_1(t, X)u$ and L is convex on U, where $L = A_1\left[\beta_e \frac{BS}{\kappa+B} + (1 - h(t))\beta_h \frac{SI}{N}\right] + A_2 q(t)^2 + A_3 h(t)^2$ is the integrand in (5.2.7).
4. There exist $C_3 > 0, C_4 > 1$ and $C_5 \geq 0$ such that

$$L(t, X, u) \geq C_3|u|^{C_4} - C_5.$$

Since f is C^1, conditions 1(a) and 1(b) are implied by suitable bounds on partial derivatives of f and on $f(t, 0, 0)$. Since f is continuous and bounded on a finite time interval,

Theorem 9.2.1 of [8] guarantees the existence of at least one local solution. The set $U = \{(q, h) : q \in [0, 1] \quad \text{and} \quad h \in [0, 1]\}$ is closed.

By definition, the set $Q = \{q : q \in [0, 1] \quad \text{is Lebesgue measurable}\}$ is convex if $q_1, q_2 \in Q$ and $\gamma_1 \in [0, 1]$ imply that $[(1 - \gamma_1)q_1 + \gamma_1 q_2] \in Q$

$$(1 - \gamma_1)q_1 + \gamma_1 q_2 \geq 0 \quad \text{since} \quad \gamma_1, q_1, q_2 \in [0, 1],$$

and

$$\begin{aligned}(1 - \gamma_1)q_1 + \gamma_1 q_2 &\leq (1 - \gamma_1) + \gamma_1 \quad \text{since} \quad q_1, q_2 \leq 1 \\ &= 1.\end{aligned}$$

Thus, $(1-\gamma_1)q_1+\gamma_1 q_2$ lies in Q meaning that Q is convex. In the same way, H is convex. Since the Cartesian of convex sets is convex [16], $U = Q \times H$ is a convex set [25].
The function f is linear in each control variable q and h, thus it can be written as $f(t, X, u) = \alpha_1(t, X) + \beta_1(t, X)u$. L is convex on U since it is quadratic in u and the constants A_3 and A_5 are positive. For the last condition,

$$\begin{aligned}L &= A_1 \left[\beta_e \frac{BS}{\kappa + B} + (1 - h)\beta_h \frac{SI}{N}\right] + A_2 q^2 + A_3 h^2 \\ &\geq A_2 q^2 + A_3 h^2 + A_1 \left[\beta_e \frac{BS}{\kappa + B} + (1 - h)\beta_h \frac{SI}{N}\right] \quad \text{since} \quad q \geq 0, h \geq 0. \qquad (5.3.1)\end{aligned}$$

Note that

$$\begin{aligned}A_1 \left[\beta_e \frac{BS}{\kappa + B} + (1 - h(t))\beta_h \frac{SI}{N}\right] &\leq A_1 \left[\beta_e \frac{BS}{\kappa + B} + \beta_h \frac{SI}{N}\right] \quad \text{since} \quad q \leq 1 \quad \text{and} \quad h \leq 1. \\ &\leq A_1 \left[\beta_e \frac{BS}{\kappa} + \beta_h \frac{SI}{N}\right] \quad \text{since} \quad \frac{B}{\kappa + B} \leq \frac{B}{\kappa}. \\ &\leq A_1 \left[\beta_e \frac{\epsilon N^2}{\kappa \delta} + \beta_h N\right] \quad \text{since} \quad S, I \leq N \quad \text{and} \quad B \leq \frac{\epsilon N}{\delta}\end{aligned}$$

Since both sides of the inequality are non-negative, we have

$$A_1\left[\beta_e\frac{BS}{\kappa+B}+(1-h(t))\beta_h\frac{SI}{N}\right]\geq -A_1\left[\beta_e\frac{\epsilon N^2}{\kappa\delta}+\beta_h N\right].$$

Substituting this result into (5.3.1) gives

$$\begin{aligned}L &\geq A_2q(t)^2+A_3h(t)^2-A_1\left[\beta_e\frac{\epsilon N^2}{\kappa\delta}+\beta_h N\right]\\ &\geq C_3|u|^{C_4}-C_5\end{aligned}$$

where $C_3=\min\{A_2,A_3\}$, $C_4=2$ and $C_5=A_1\left(\beta_e\frac{\epsilon N^2}{\kappa\delta}+\beta_h N\right)$ [25] ■

5.4 Characterization of the controls

We use Pontryagin's principle stated in Theorem 5.1 of [10] to find the best possible control for the system. We define the Hamiltonian H as follows;

$$\begin{aligned}H(X,u,p) &= p\cdot f(t,X,u)+L(t,X,u)\\ &= p_1f_1+p_2f_2+p_3f_3+p_4f_4+p_5f_5+L\\ &= p_1\left[\mu N-\mu S-\beta_e\frac{BS}{\kappa+B}-(1-h)\beta_h\frac{SI}{N}\right]\\ &+ p_2\left[\beta_e\frac{BS}{\kappa+B}+(1-h)\beta_h\frac{SI}{N}-(\mu+\gamma)E\right]\\ &+ p_3\left[\gamma E-(\mu+\alpha)I\right]+p_4[\epsilon I-(\delta+q)B]+p_5[\alpha I-\mu R]\\ &+ A_1\left[\beta_e\frac{BS}{\kappa+B}+(1-h)\beta_h\frac{SI}{N}\right]\\ &+ A_2q^2+A_3h^2,\end{aligned}$$

where $p=(p_1,p_2,p_3,p_4,p_5)$ and p_1,p_2,p_3,p_4,p_5 are adjoint variables for the state variable S,E,I,B and R.

Theorem 5.4.1. *Given an optimal solution (X^*,u^*) of the control problem (5.2.8),*

there exist p_1, p_2, p_3, p_4 *and* p_5*, a solution set to the adjoint system*

$$\begin{aligned}
\dot{p_1} &= -\frac{\partial H}{\partial S} = \left[\beta_e \frac{B}{\kappa + B} + (1-h)\beta_h \frac{I}{N}\right](p_1 - p_2 - A_1) + \mu p_1, \\
\dot{p_2} &= -\frac{\partial H}{\partial E} = p_2(\mu + \gamma) - \gamma p_3, \\
\dot{p_3} &= -\frac{\partial H}{\partial I} = (1-h)\beta_h \frac{S}{N}(p_1 - p_2 - A_1) + p_3(\mu + \alpha) - p_4\epsilon - p_5\alpha, \\
\dot{p_4} &= -\frac{\partial H}{\partial B} = \beta_e \frac{\kappa S}{(\kappa + B)^2}(p_1 - p_2 - A_1) + p_4(\delta + q), \\
\dot{p_5} &= -\frac{\partial H}{\partial R} = \mu p_5,
\end{aligned}$$

with transversality condition

$$p_1(T) = 0, \quad p_2(T) = 0, \quad p_3(T) = 0, \quad p_4(T) = 0, \quad p_5(T) = 0$$

such that $u^* = \min_{u \in U} H(X, p, u), \quad t \in [0, T]$*. Furthermore, the controls can be characterized as*

$$\begin{aligned}
q^* &= \min\left(1, \max\left(0, \frac{p_4 B}{2A_2}\right)\right) \qquad \textit{and} \\
h^* &= \min\left(1, \max\left(0, \frac{1}{2A_3}\left[\beta_h \frac{SI}{N}(p_2 + A_1 - p_1)\right]\right)\right).
\end{aligned}$$

Proof. The optimal control is derived from the optimality condition $\left.\frac{\partial H}{\partial u}\right|_{u^*} = 0$.

$$\begin{aligned}
\left.\frac{\partial H}{\partial q}\right|_{q^*} &= -p_4 B + 2A_2 q^* = 0. \qquad (5.4.1) \\
\implies q^* &= \frac{p_4 B}{2A_2}
\end{aligned}$$

and

$$\left.\frac{\partial H}{\partial h}\right|_{h^*} = p_1 \beta_h \frac{SI}{N} + p_2 \beta_h \frac{SI}{N} - A_1 \beta_h \frac{SI}{N} + 2A_3 h^* = 0 \qquad (5.4.2)$$

$$\Longrightarrow h^* = \frac{1}{2A_3}\left[\beta_h \frac{SI}{N}(p_2 + A_1 - p_1)\right].$$

Considering the properties of the control space, we have

$$q^* = \begin{cases} 0, & \text{if} \quad \frac{p_4 B}{2A_2} \leq 0, \\ \frac{p_4 B}{2A_2}, & \text{if} \quad 0 < \frac{p_4 B}{2A_2} < 1, \\ 1, & \text{if} \quad \frac{p_4 B}{2A_2} \geq 1. \end{cases}$$

Therefore q^* can be characterized as [25]

$$q^* = \min\left(1, \max\left(0, \frac{p_4 B}{2A_2}\right)\right).$$

Similarly, h^* can be characterized as

$$h^* = \min\left(1, \max\left(0, \frac{1}{2A_3}\left[\beta_h \frac{SI}{N}(p_2 + A_1 - p_1)\right]\right)\right).$$

In addition, we note from (5.4.1) and (5.4.2) respectively that

$\left.\frac{\partial^2 H}{\partial q^2}\right|_{q^*} = 2A_2 > 0$ and

$\left.\frac{\partial^2 H}{\partial h^2}\right|_{h^*} = 2A_3 > 0$, since A_2 and A_3 are positive constants introduced in (5.2.7),

indicating that $u^* = (q^*, h^*)$ minimizes the Hamiltonian function $H(X, p, u)$ [25]. ■

5.5 Numerical simulations for optimal control

The optimal control problem in (5.2.8) was solved numerically using parameter values in Table 4.1. In the following figures, we compare numerical solutions with optimal control and without any intervention. We compare virus concentration and the number of humans in

each compartment in the presence and absence of control measures $q \in [0, 1]$ and $h \in [0, 1]$, with $S_0 = 500, E_0 = 400, I_0 = 100, B_0 = 0.5, N = 1000$.

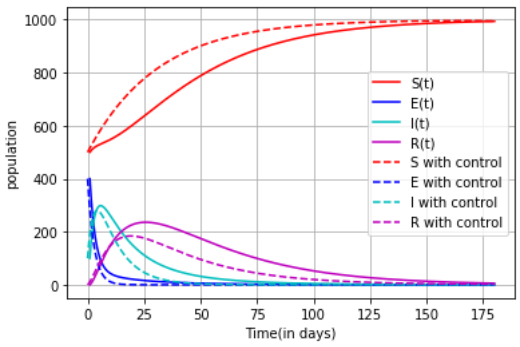

Figure 5.1: Population dynamics in the presence of control and absence of control with the direct transmission rate β_h reduced by 80% [25].

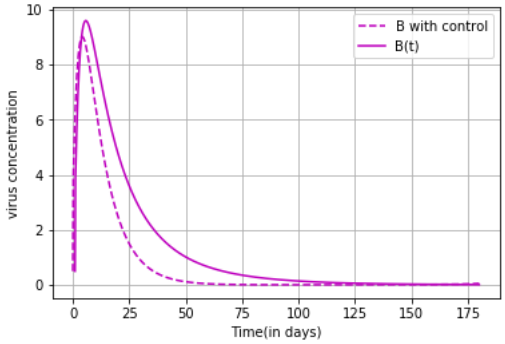

Figure 5.2: Virus concentration in the presence of control and absence of control with the direct transmission rate β_h reduced by 80% [25].

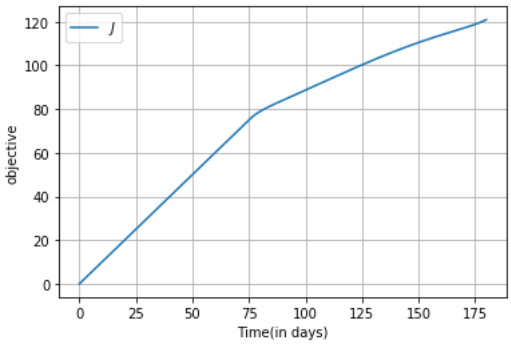

Figure 5.3: Daily cost of new infections and of implementing hygiene and sanitation measures [25].

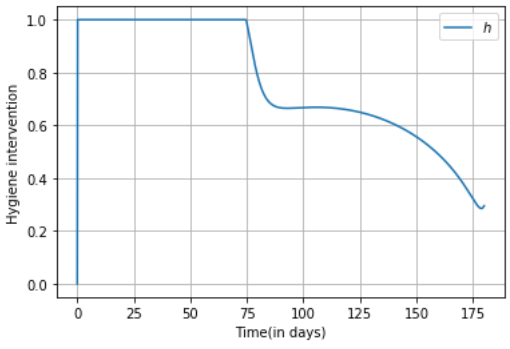

Figure 5.4: Numerical simulation of hygiene efforts using parameter values in Table 4.1 [25].

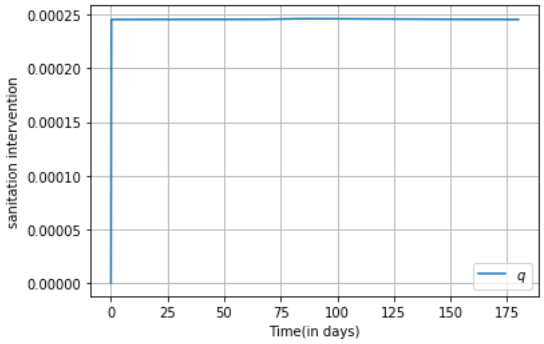

Figure 5.5: Numerical simulation of sanitation efforts using parameter values in Table 4.1 [25]

In Figures 5.1 and 5.2, numerical simulations are conducted to compare results in the presence and absence of the combined controls. The solid lines represent the case where the infection is eradicated by decreasing the value of β_h by 80% in the absence of control. In the presence of control measures, the peaks of trajectories for susceptibles and recovered humans are higher (indicating more people) compared to the ones with no control measures. In the Exposed Infected cases, however, the trajectories are lower (indicating less people) with controls compared to when there are none. Similarly, with controls, the peak for concentration of enterovirus is lower, compared to when there is none as can be seen from Figure 5.2. Moreover, in all the two populations, the trajectories with controls converge faster then the ones without control measures. Figures 5.5 and 5.4 confirm that direct transmission rate affects disease dynamics the most. For the first 75 days, hygiene measures, which reduce direct transmission rate, shoot to the maximum value, while sanitation measures do not even get close to a quarter of the maximum value of the control [25].

From day 1 to day 75, the increase of daily cost is about 133% as shown in Figure 5.3. After approximately 13 to 14 days, the virus concentration reaches its maximum level and the number of infectious individuals is at its peak. During this period, the sanitation efforts are kept at a steady level of 0.00025 and hygiene efforts are maximized. After day 14, the virus concentration as well as the number of infectious individuals begin to decline. This result is

in line with the one obtained in Nandi *et al* [29]. After about 75 days, the virus concentration is zero, there is a decline in the efforts of hygiene and as a result, the increase in daily costs reduces from 133% to about 50%. After about 150 days, the disease is eradicated and at this point, the daily cost is 110 units [25].

Chapter 6

Concluding remarks

In line with global organizations in curving the spread of infectious diseases in human populations, in this article, we extend the standard $SEIR$ model by adding a compartment for the concentration of enterovirus in the environment. This coincide with the campaign for sanitizing, disinfecting and cleaning of surfaces that are frequently touched. Furthermore, the model is extended to consider the effects of hygiene in the susceptible population and disinfection of virus in the environment. Subsequently, we study the optimal control strategy on the extended model to determine the minimum cost of applying the control strategies.

For the basic model, we proved the well-posedness properties which include existence, positivity and boundedness of solution in a defined domain. Further, we carry out stability analysis on the equilibria, disease free and endemic, both of which are globally asymptotically stable when the basic reproduction number $\mathcal{R}_0 \leq 1$ and $\mathcal{R}_0 \geq 1$, respectively. The implication of these results is enterovirus can be eradicated if $\mathcal{R}_0 \leq 1$, or established in the population if $\mathcal{R}_0 \geq 1$. Sensitivity analysis is conducted to determine elasticity indices of parameters that contribute most for endemicity of the virus. As shown in Table 4.2, the direct infection rate affects the transmission dynamics of the infection the most, followed by recovery rate [25]. We notice that decreasing the direct transmission rate to 0.0721 brings the value of the basic reproduction number to $0.484 \leq 1$ [25], thus putting the infection under control. We

conclude that one of the many approaches that can be used to control the infection is to decrease the direct transmission rate by about 80% [25].

For the extended model, we established the existence of optimal control that minimizes the number of new cases of enterovirus with minimal cost of implementing the controls (sanitation and hygiene). The results are further presented numerically as shown in Figures 5.1 - 5.3. Amongst other advantages, the control measures shorten the time scale for the infection. For example, while it takes about 113 days for virus to be eliminated from the environment in the absence of control, it only takes 53 days in the presence of controls.

In general, our work extended many models of enterovirus [15, 24, 32, 35, 36] with novelty of incorporating indirect transmission of infection from the environment and the consideration of optimal control strategy. For further work on this topic, mathematical modeling of more that one serotype, where reinfection is possible, may be considered.

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