Stability and sensitivity analysis of Be-CoDiS, an epidemiological model to predict the spread of human diseases between countries. Validation with data from the 2014-16 West African Ebola Virus Disease epidemic.

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Abstract

Ebola virus disease is a lethal human and primate disease that requires a particular attention from the international health authorities due to important recent outbreaks in some Western African countries and isolated cases in European and North-America continents. Regarding the emergency of this situation, various decision tools, such as mathematical models, were developed to assist the authorities to focus their efforts in important factors to eradicate Ebola. In a previous work, we have proposed an original deterministic spatial-temporal model, called Be-CoDiS (Between-Countries Disease Spread), to study the evolution of human diseases within and between countries by taking into consideration the movement of people between geographical areas. This model was validated by considering numerical experiments regarding the 2014-16 West African Ebola Virus Disease epidemic. In this article, we propose to perform a stability analysis of Be-CoDiS. Our first objective is to study the equilibrium states of simplified versions of this model, limited to the cases of one an two countries, and to determine their basic reproduction ratios. Then, in order to give some recommendations for the allocation of resources used to control the disease, we perform a sensitivity analysis of those basic reproduction ratios regarding the model parameters. Finally, we validate the obtained results by considering numerical experiments based on data from the 2014-16 West African Ebola Virus Disease epidemic.

keywords: Epidemiological modelling, Deterministic models, Stability analysis, Sensitivity analysis, Ebola Virus Disease.

1 Introduction

Modeling and simulation are important decision tools that can be used to control human and animal diseases [1, 18, 26, 31]. However, as each disease exhibits its own biological characteristics, the considered simulation models need to be adapted to each specific case in order to handle real situations [5].

In a previous work published in [19], we have presented a spatial-temporal epidemiological model, called Be-CoDiS (Between-Countries Disease Spread), to the study of the spread of human diseases between and within countries. This model was an adaptation of a previous software, called Be-FAST (Between Farm Animal Spatial Transmission), which simulates the spread of animal diseases between and within farms [18, 26, 24, 25, 23]. Be-CoDiS is based on the combination of a deterministic Individual-Based model (where the countries are considered as individuals) [9], simulating the between-country interactions (here, migratory flux) and disease spread, with a deterministic compartmental model [5] (a system of ordinary differential equations), simulating the within-country disease spread. At the end of a simulation, Be-CoDiS returns outputs referring to outbreaks characteristics (for instance, the epidemic magnitude, the risk of disease introduction or diffusion per country, etc.). The principal characteristic of this approach is the consideration of the following effects at the same time: migratory flux between countries, control measure effects and dynamic model parameters fitted to each country. Then, as a second part of this work, Be-CoDiS was validated by considering the case of the 2014-16 West African Ebola Virus Disease (EVD) epidemic [13, 6, 14, 39]. EVD is a human and primates virus disease that causes a high mortality rate (between 50% and 90%) [12, 28]. During the period from December 2013 to March 2016, several important outbreaks have been reported in West Africa (Guinea, Liberia, Sierra Leone and Nigeria). Furthermore, 16 isolated cases were detected in Mali, Senegal, the USA, the United Kingdom, Italy and Spain. The main pandemic was considered over at December 2015. Currently, the disease remains active in Guinea and Liberia with some sporadic cases (the last cases were reported at 24 ^{rmth} April 2016). It is estimated that the around 28616 persons were infected during those outbreaks and 11310 deaths have been reported. Starting with data from December 2013, our model predicted a total of 28475 infected persons, 11797 deaths and that the epidemic will end at April 19$^{\text{th}}$, 2016.

Here, we are interested in performing a stability analysis of continuous simplified versions of Be-CoDiS. To this aim, we first analyze the equilibrium states of the model by considering only one country. More precisely, we estimate an analytical expression of the disease basic reproductive ratio [3, 10, 11] according to the model parameters. The basic reproduction ratio, denoted by R_0, is a threshold used in epidemiology to determine the behavior of an epidemic. It is defined as the average number of new infections caused by one infected individual in an entirely of susceptible population [1, 5]. It is generally observed that if $R_0 > 1$ then the epidemic becomes endemic, whereas if $R_0 \leq 1$ then the epidemic disappears [1, 3]. We note that the mathematical definition of R_0 used in this paper is specific to deterministic finite dimensional systems such as the ones considered here [32]. Then, we extend this study to the case of two countries, when one country send infected persons to other country. Finally, we validate and illustrate the obtained theoretical results by presenting numerical experiments based on data from the 2014-16 West African Ebola virus epidemic. In particular, we perform a sensitivity analysis of the estimated basic reproductive ratio regarding the model parameters. One of the objective of this work is to propose a methodology to give some recommendations when allocating the resources for fighting a disease, such as the EVD, in cases of future outbreaks.

This work is organized as follows. In Section 2, we recall the formulation of the Be-CoDiS model presented in [19]. In Section 3, we study the equilibrium states of simplified versions of this model for one and two countries with movement of people. In Section 4, considering data from the 2014-16 West African Ebola virus epidemic, we validate and illustrate the theoretical results with numerical experiments and perform a sensitivity analysis of the basic reproductive ratio with respect to the model parameters. Finally, in Section 5, we discuss the obtained conclusions and present some perspectives of this work.

2 Be-CoDiS model formulation

We consider a disease with the following states for persons (see [20, 27, 28, 39]):

- Susceptible (denoted by S): The person is not infected by the disease pathogen.
- Infected (denoted by E): The person is infected by the disease pathogen but cannot infect other people and has no visible clinical signs (e.g., fever, hemorrhages, etc.). Then after an incubation period, the person passes to the infectious state.
- Infectious (denoted by I): The person can infect other people and start developing clinical signs. The mean duration of a person in this state is called infectious period. After this period, infectious persons are taken in charge by sanitary authorities and we classify them as Hospitalized.
- Hospitalized (denoted by H): The person is hospitalized and can still infect other people. At the end of this state, the person can pass either to the Recovered state or to the Dead state. We point out that state H does not include hospitalized persons which cannot infect other people any more. This last category of persons is included in the Recovered state explained below.
- Dead (denoted by D): The person has not survived to the disease. The cadaver of infected persons can infect other people until they are buried. After a fixed mean period, the body is buried.
- Buried (denoted by B): The person is dead because of the disease. Its cadaver is buried and can no longer infect other people.
- Recovered (denoted by R): The person has survived to the disease, is no longer infectious and develop a natural immunity to the disease pathogen.

Once an infected person is hospitalized, the authorities may apply various control measures in order to control the disease spread (see [13, 16]):

- Isolation: Infected people are isolated from contact with other people. Only sanitary professionals are in contact with them. However, depending on the considered disease, contamination of those professionals may also occur (see [13]). Isolated persons receive an adequate medical treatment that reduces the disease fatality rate.
- Quarantine: Movement of people in the area of origin of an infected person is restricted an controlled (e.g., quick sanitary check-points at the airports) to avoid that possible infected persons spread the disease.
- Tracing: The objective of tracing is to identify potential infectious contacts which may have infected a person or spread the disease to other people.
- Increase of sanitary resources: The number of operational beds and sanitary personal available to detect and treat affected persons is increased, producing a decrease in the infectious period. When necessary, the funerals of infected cadavers are controlled by sanitary personal in order to reduce the contacts between the dead bodies and susceptible persons.

Considering those general disease and control measures, the Be-CoDiS model is used to evaluate the spread of a human disease within and between countries during a fixed time interval.

At the beginning of the simulation, the model parameters are set by the user. At the initial time ($t = 0$), only susceptible people live in the countries that are free of the disease, whereas the number of persons in states S, E, I, H, R, D and B of the infected countries are set to their corresponding values. Then, during the time interval $[0, T_{\max}]$, with $T_{\max} \in \mathbb{N}$ being the maximum number of simulation days, the within-country and between-country daily spread procedures, detailed above, are applied. If at the end of a simulation day t, the number of persons in state E, I, H and D is lower than a fixed threshold, the simulation is stopped. Else, the simulation ends when $t = T_{\max}$. Furthermore, the control measures are also implemented and they can be activated or deactivated, when starting the model, in order to quantify their effectiveness to reduce the magnitude and duration of an epidemic.

The dynamic of the disease spread within a particular contaminated country is modeled by using a deterministic compartmental model (see [5]). We consider that the people in a country are characterized to be in one of those states: Susceptible (S), Infected (E), Infectious (I), Hospitalized (H), Recovered (R), Dead (D) or Buried (B). For the sake of simplicity, we assume that, at each time, the population inside a country is homogeneously distributed and constant. Thus, the spatial distribution of the epidemic inside a country can be omitted. We also suppose that new births are susceptible persons and the birth rate is equal to the death rate (due to the disease or other causes).

The disease spread between countries is modeled by using a spatial deterministic Individual-Based model (see [9]). We consider that the flow of people between countries i and j at time t (i.e., persons traveling per day from i to j at time t), is the only way to introduce the disease from country i, infected by the disease, to country j. To do so, we consider the matrix $(\tau(i,j))_{i,j=1}^{N_{\mathrm{CO}}}$, where $\tau(i,j) \in [0,1]$ is the rate of transfer (day^{-1}) of persons from country i to country j, which is expressed in % of population in i per unit of time. Furthermore, we assume that only persons in the S and E sates can travel, as other categories are not in condition to perform trips due to the clinical signs or to quarantine. Moreover, as a result of control measures in countries i and j, we assume that those rates can vary in time and are multiplied by a function denoted by $m_{\mathrm{tr}}(i,j,t)$.

Under those assumptions, the evolution of $S(i,t)$, $E(i,t)$, $I(i,t)$, $H(i,t)$, $R(i,t)$, $D(i,t)$ and $B(i,t)$, denoting the number of susceptible, infected, infectious, hospitalized, recovered, dead and buried persons in country i at time t, respectively, could be modeled by the following system of ordinary differential equations [19]

$$
\begin{aligned}
\frac{\mathrm{d}S(i,t)}{\mathrm{d}t} &= -\frac{S(i,t)\Big(m_I(i,t)\beta_I(i)I(i,t)+m_H(i,t)\beta_H(i)H(i,t)\Big)}{NP(i,t)} - \frac{S(i,t)\Big(m_D(i,t)\beta_D(i)D(i,t)\Big)}{NP(i,t)} \\
&\quad -\mu_m(i)S(i,t) + \mu_n(i)\Big(S(i,t)+E(i,t)+I(i,t)+H(i,t)+R(i,t)\Big) \\
&\quad + \textstyle\sum_{i\neq j} m_{\mathrm{tr}}(j,i,t)\tau(j,i)S(j,t) - \sum_{i\neq j} m_{\mathrm{tr}}(i,j,t)\tau(i,j)S(i,t), \\
\frac{\mathrm{d}E(i,t)}{\mathrm{d}t} &= \frac{S(i,t)\Big(m_I(i,t)\beta_I(i)I(i,t)+m_H(i,t)\beta_H(i)H(i,t)\Big)}{NP(i,t)} + \frac{S(i,t)\Big(m_D(i,t)\beta_D(i)D(i,t)\Big)}{NP(i,t)} \\
&\quad -\mu_m(i)E(i,t) + \textstyle\sum_{i\neq j} m_{\mathrm{tr}}(j,i,t)\tau(j,i)\mathcal{X}_{\epsilon_{\mathrm{fit}}}(E(j,t)) \\
&\quad - \textstyle\sum_{i\neq j} m_{\mathrm{tr}}(i,j,t)\tau(i,j)\mathcal{X}_{\epsilon_{\mathrm{fit}}}(E(i,t)) - \gamma_E\mathcal{X}_{\epsilon_{\mathrm{fit}}}(E(i,t)), \\
\frac{\mathrm{d}I(i,t)}{\mathrm{d}t} &= \gamma_E\mathcal{X}_{\epsilon_{\mathrm{fit}}}(E(i,t)) - (\mu_m(i)+\gamma_I(i,t))I(i,t), \\
\frac{\mathrm{d}H(i,t)}{\mathrm{d}t} &= \gamma_I(i,t)I(i,t) - \Big(\mu_m(i) + (1-\omega(i,t))\gamma_{HR}(i,t) + \omega(i,t)\gamma_{HD}(i,t)\Big)H(i,t), \\
\frac{\mathrm{d}R(i,t)}{\mathrm{d}t} &= (1-\omega(i,t))\gamma_{HR}(i,t)H(i,t) - \mu_m(i)R(i,t), \\
\frac{\mathrm{d}D(i,t)}{\mathrm{d}t} &= \omega(i,t)\gamma_{HD}(i,t)H(i,t) - \gamma_D D(i,t), \\
\frac{\mathrm{d}B(i,t)}{\mathrm{d}t} &= \gamma_D D(i,t),
\end{aligned}
\tag{1}
$$

where

- $i \in \{1, \ldots, N_{CO}\}$,
- $N_{\text{CO}} \in \mathbb{N}$ is the number of countries,
- $NP(i,t) = S(i,t) + E(i,t) + I(i,t) + H(i,t) + R(i,t) + D(i,t) + B(i,t)$ is the number of persons (alive and also died or buried because of the disease) in country i at time t,
- $\mu_n(i) \in [0,1]$ is the birth rate (day^{-1}) in country i: the number of births per day and per capita,
- $\mu_m(i) \in [0,1]$ is the mortality rate (day^{-1}) in country i: the number of deaths per day and per capita (or, equivalently, the inverse of the mean life expectancy (day) of a person),
- $\omega(i,t) \in [0,1]$ is the disease fatality percentage in country i at time t: the percentage of persons who do not survive the disease,
- $\beta_I(i) \in \mathbb{R}^+$ is the disease effective contact rate (day^{-1}) of a person in state I in country i: the mean number of effective contacts (i.e., contacts sufficient to transmit the disease) of a person in state I per day before applying control measures,
- $\beta_H(i) \in \mathbb{R}^+$ is the disease effective contact rate (day^{-1}) of a person in state H in country i,
- $\beta_D(i) \in \mathbb{R}^+$ is the disease effective contact rate (day^{-1}) of a person in state D in country i,
- $\gamma_E(i,t)$, $\gamma_I(i,t)$, $\gamma_{HR}(i,t)$, $\gamma_{HD}(i,t)$, $\gamma_D(i,t) \in (0, +\infty)$ denote the transition rate (day^{-1}) from a person in state E, I, H, H or D to state I, H, R, D or B, respectively: the number of persons per day and per capita passing from one state to the other (or, equivalently, the inverse of the mean duration of one of those persons in state E, I, H, H, or D, respectively). We note that $\gamma_I(i,t)$, $\gamma_{HR}(i,t)$ and $\gamma_{HD}(i,t)$ are time and country dependent, since, due to the applied control measures in country i, their value could vary in time,
- $m_I(i,t)$, $m_H(i,t)$, $m_D(i,t) \in [0,1]$ (%) are functions representing the efficiency of the control measures applied to non-hospitalized persons, hospitalized persons and infected cadavers respectively, in country i at time t to eradicate the outbreaks. Focusing on the application of the control measures, we multiply the disease contact rates (i.e., $\beta_I(i)$, $\beta_H(i)$ and $\beta_D(i)$) by decreasing functions simulating the reduction of the number of effective contacts as the control measures efficiency is improved. Here, we have considered the functions (see [21]):

$$m_I(i,t) = m_H(i,t) = m_D(i,t) = \exp\Big(-\kappa(i) \max(t - \lambda(i), 0) \Big), \tag{2}$$

  where $\kappa(i) \in [0, +\infty)$ (day^{-1}) simulates the efficiency of the control measures (greater value implies lower value of disease contact rates) and $\lambda(i) \in \mathbb{R} \cup \{+\infty\}$ (day) denotes the first day of application of those control measures,
- $\mathcal{X}_{\epsilon_{\text{fit}}}(x) = x$ if $x \geq \epsilon_{\text{fit}}$, $\mathcal{X}_{\epsilon_{\text{fit}}}(x) = 2x - \epsilon_{\text{fit}}$ if $(\epsilon_{\text{fit}}/2) \leq x \leq \epsilon_{\text{fit}}$, and 0 elsewhere, with $\epsilon_{\text{fit}} \geq 0$ (i.e., a small tolerance parameter). This function is a filter used to avoid artificial spread of the epidemic due to negligible values of x.

System (1) is completed with initial data $S(i,0)$, $E(i,0)$, $I(i,0)$, $H(i,0)$, $R(i,0)$, $D(i,0)$ and $B(i,0)$ given in $[0, +\infty)$; for i=1,.., N_{CO}.

This full model (1) is summarized in Figure 1.

Remark 1. *We note that the Be-CoDiS model proposed here is not only limited to the study of the EVD but also can tackle other diseases such as the Middle East respiratory syndrome coronavirus or the Severe acute respiratory syndrome coronavirus [7], by adapting the model parameters.*

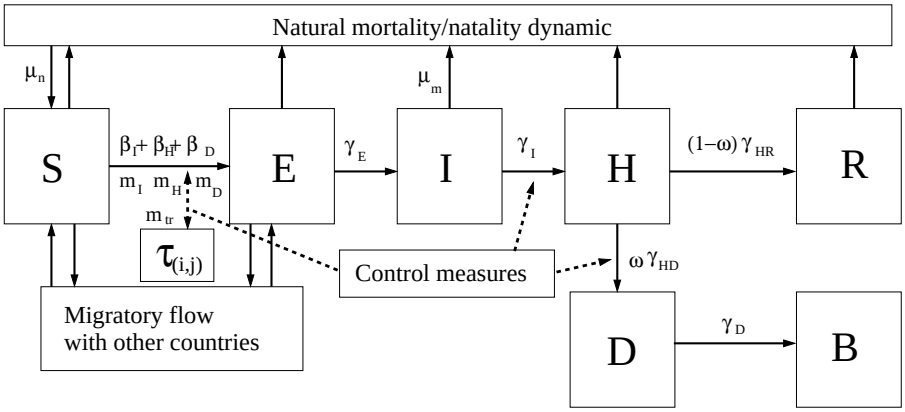

Figure 1: Diagram summarizing the complete version of the Be-CoDiS model.

3 Analytical behavior of the Be-CoDiS model

Here, we are interested in studying the equilibrium states and in estimating the basic reproductive ration of simplified versions of the Be-CoDiS model presented in Section 2. First, we focus on the case of one country with an emigration flow of infected persons. Then, we extend the study to the case of two countries, when one country send persons to the other one. The main notations used in this work are summarized in Table 1. A diagram summarizing both models is presented in Figure 2.

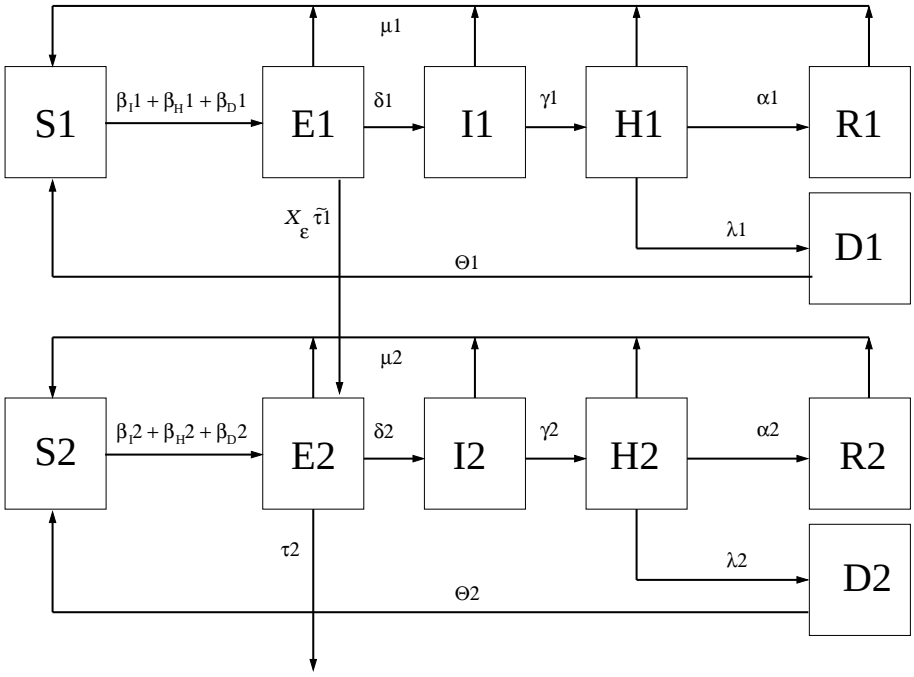

Figure 2: Diagram summarizing the simplified model considered in Section 3.

Table 1: Summary of the main notations used in this work. A brief description (**Description**) and the range of the considered values (**Value**) used in Section 4 are also reported.

Notation	**Value**	**Description**
β_{Ii}	[0.0494,0.2671]	Disease contact rate of persons in state I (day^{-1}.person^{-1}) in country i
β_{Hi}	[0.020,0.0107]	Disease contact rate of persons in state H(day^{-1}.person^{-1}) in country i
β_{Di}	[0.0494,0.2671]	Disease contact rate of persons in state D (day^{-1}.person^{-1}) in country i
δ_i	[0.0120,0.0230]	Transition rate of a person in state E (day^{-1}) in country i,
γ_i	[0.2000,0.5000]	Transition rate of a person in state I (day^{-1}) in country i,
α_i	[0.148,0.1050]	Transition rate of a person in state H to state R (day^{-1}) in country i,
λ_i	[0.0328,0.1282]	Transition rate of a person in state H to state D (day^{-1}) in country i,
θ_i	[0.5000,1.0000]	Transition rate of a person in state D (day^{-1}) in country i at time t,
μ_i	[0.012,0.023]	Natural mortality rate in country i (day^{-1})
τ_i	[0,2.4$\cdot 10^{-5}$]	Daily rate (%) of the movement of people exiting country i (day^{-1})
N_i	[10,20]$\cdot 10^6$	Number of persons in country i
$S_i(t)/E(t)/I_i(t)$ $H_i(t)/R_i(t)/D_i(t)$	[0,1]	Proportion of persons in state S, E, I, H, R, D in country i at time t

3.1 Simplified model for 1 country

Here, we are interested in studying the behavior of the epidemic inside one single country. For the sake of simplicity, we assume that the population size in the considered country is constant and equals to $N \in \mathbb{N}$ (i.e., emigration or death flows are compensated by birth flows entering the susceptible state). This hypothesis is reasonable as, due to the size of the population in a country (generally greater than a million of persons) and the time scale of the study (generally lower than five years) considered here, the global variation of the population size during a simulation is negligible [17]. Furthermore, to simplify notations during the following computations, we consider that S, E, I, H, R and D now denotes the proportion of persons in each state in the considered country. Additionally, we assume that the model coefficients are constant and no control measures are applied. As no other country is considered, the filter $\mathcal{X}_{\epsilon_{\text{fit}}}$ is omitted.

Under those assumptions, the evolution of the epidemic, is modeled by

$$\begin{cases} \dfrac{\mathrm{d}S(t)}{\mathrm{d}t} &= -S(t)\Big(\beta_I I(t) + \beta_H H(t) + \beta_D D(t)\Big) + \tau E(t) \\ & \quad +\mu\Big(E(t) + I(t) + H(t) + R(t)\Big) + \theta D(t), \\ \dfrac{\mathrm{d}E(t)}{\mathrm{d}t} &= S(t)\Big(\beta_I I(t) + \beta_H H(t) + \beta_D D(t)\Big) - (\mu + \delta + \tau)E(t), \\ \dfrac{\mathrm{d}I(t)}{\mathrm{d}t} &= \delta E(t) - (\mu + \gamma)I(t), \\ \dfrac{\mathrm{d}H(t)}{\mathrm{d}t} &= \gamma I(t) - \big(\mu + \lambda + \alpha\big)H(t), \\ \dfrac{\mathrm{d}R(t)}{\mathrm{d}t} &= \alpha H(t) - \mu R(t), \\ \dfrac{\mathrm{d}D(t)}{\mathrm{d}t} &= \lambda H(t) - \theta D(t), \end{cases} \tag{3}$$

where

- $\mu \in [0, 1]$ is the mortality rate (day^{-1}),
- $\omega \in [0, 1]$ is the disease fatality percentage,
- $\beta_I \in \mathbb{R}^+$ is the disease effective contact rate ($\text{day}^{-1}.\text{person}^{-1}$) of persons in state I,
- $\beta_H \in \mathbb{R}^+$ is the disease effective contact rate ($\text{day}^{-1}.\text{person}^{-1}$) of persons in state H,
- $\beta_D \in \mathbb{R}^+$ is the disease effective contact rate ($\text{day}^{-1}.\text{person}^{-1}$) of persons in state D,
- δ, γ, α and λ denote the transition rates (day^{-1}) from a person in state E to I, I to H, H to R, H to D and D to S, respectively.

Before starting with the estimation of equilibrium states of System (3), we first want to prove that

Theorem 1. *The set* $\Omega = \{(S, E, I, H, R, D) \in \mathbb{R}^{6,+}/S + E + I + H + R + D = 1\}$ *is positively invariant for the System (3).*

Proof. We consider the following result (see proof in [29])

Lemma 1. *Let* $Z : \mathbb{R}^n \to \mathbb{R}$ *be a differential function,* $a \in \mathbb{R}$ *and* $\nabla Z(x) \neq 0$ *for all* $x \in Z^{-1}(a) = \{x \in \mathbb{R}^n/Z(x) = a\}$. *Let* $G = \{x \in \mathbb{R}^n/Z(x) \leq a\}$. *If* $\langle \nabla Z(x), X(x)\rangle \leq 0$ *for all* $x \in Z^{-1}(a)$, *then* G *is a positive invariant set of the system* $\dot{x} = X(x)$.

Let $Z : \mathbb{R} \to \mathbb{R}$ defined by $Z(x_1, x_2, x_3, x_4, x_5, x_6) = x_1 + x_2 + x_3 + x_4 + x_5 + x_6$, $a = 1$ and $\dot{x} = X(x)$ corresponding to System (3).

We have that $\nabla Z(x) \neq 0$ for all $x \in Z^{-1}(a)$ and $\langle \nabla Z(x), X(x)\rangle = 0$ for all $x \in Z^{-1}(a)$. Thus, $\Omega \subset \{x \in \mathbb{R}^n/Z(x) \leq a\}$ is a positive invariant set of System (3). □

Considering System (3), we obtain the following stability results

Theorem 2. *System* (3) *has two positive equilibrium states:*

1. *a disease free equilibrium state* $x_1 = (S_1^0, E_1^0, I_1^0, H_1^0, R_1^0, D_1^0) = (1, 0, 0, 0, 0, 0)$ *which is globally asymptotically stable if* $R_0 \leq 1$ *and unstable if* $R_0 > 1$,

2. *a disease endemic equilibrium state* $x_2 = (S_2^0, E_2^0, I_2^0, H_2^0, R_2^0, D_2^0)$ *which is locally asymptotically stable if* $R_0 > 1$,

where

$$R_0 = \frac{\delta(\alpha\theta\beta_i + \gamma\lambda\beta_3 + \gamma\theta\beta_2 + \lambda\theta\beta_i + \mu\theta\beta_i)}{(\mu+\delta+\tau)(\mu+\gamma)(\mu+\lambda+\alpha)\theta)}$$

is the basic reproductive ration associated to System (3)*; and* $S_2^0 = \dfrac{1}{R_0}$, $E_2^0 = \theta\mu\,(\mu+\gamma)\,(\mu+\alpha+\lambda)\,\phi$, $I_2^0 = \delta\theta\mu\,(\mu+\alpha+\lambda)\,\phi$, $H_2^0 = \delta\theta\gamma\mu\phi$, $R_2^0 = \delta\theta\alpha\gamma\phi$, $D_2^0 = \delta\gamma\lambda\mu\phi$ *with*

$$\phi = \frac{1}{(\delta\gamma\lambda(\mu-\theta) + (\mu+\delta+\tau)(\mu+\gamma)(\mu+\lambda+\alpha)\theta)}\left(1 - \frac{1}{R_0}\right).$$

Proof. **1.-** First, we determine the positive equilibrium states (3) by considering (we note that, as the population size is constant, the first line of this system can be omitted)

$$\begin{cases} 0 &= S(t)\Big(\beta_I I(t) + \beta_H H(t) + \beta_D D(t)\Big) - (\mu+\delta+\tau)E(t), \\ 0 &= \delta E(t) - (\mu+\gamma)I(t), \\ 0 &= \gamma I(t) - \big(\mu+\lambda+\alpha\big)H(t), \\ 0 &= \alpha H(t) - \mu R(t), \\ 0 &= \lambda H(t) - \theta D(t), \end{cases} \tag{4}$$

After computation, we obtain that x_1 and x_2, defined previously in the enunciate, are the only positives equilibrium states.

2.- Next, following the steps proposed in [11, 10], we compute the basic reproductive ratio of the considered system, denoted by R_0. To do so, let $x = (S, E, I, H, R, D)$. System (3) can be written in a matrix form as

$$\begin{cases} \begin{pmatrix} \dot{S} \\ \dot{R} \end{pmatrix} &= A \begin{pmatrix} S-1 \\ R \end{pmatrix} + B(x) \begin{pmatrix} E \\ I \\ H \\ D \end{pmatrix}, \\ \begin{pmatrix} \dot{E} \\ \dot{I} \\ \dot{H} \\ \dot{D} \end{pmatrix} &= C(x) \begin{pmatrix} E \\ I \\ H \\ D \end{pmatrix}, \end{cases} \tag{5}$$

where

$$A = \begin{pmatrix} 0 & \mu \\ 0 & -\mu \end{pmatrix},\ B(x) = \begin{pmatrix} \mu & \mu - \beta_I S & \mu - \beta_H S & \theta - \beta_D S \\ 0 & 0 & \alpha & 0 \end{pmatrix} \text{ and}$$

$$C(x) = \begin{pmatrix} -(\mu+\delta+\tau) & \beta_I S & \beta_H S & \beta_D S \\ \delta & (\mu+\gamma) & 0 & 0 \\ 0 & \gamma & -(\mu+\lambda+\alpha) & 0 \\ 0 & 0 & \lambda & -\theta \end{pmatrix}.$$

The Jacobian matrix of this system at the disease free equilibrium state $x_1 = (1, 0, 0, 0, 0, 0)$ is given by

$$J(x_1) = \begin{pmatrix} A & B(x_1) \\ 0 & C(x_1) \end{pmatrix}, \tag{6}$$

where $C(x_1) = F + V$ is a Metzler matrix (see [22]) with

$$F = \begin{pmatrix} 0 & \beta_I & \beta_H & \beta_D \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \text{ and } V = \begin{pmatrix} -(\mu+\delta+\tau) & 0 & 0 & 0 \\ \delta & (\mu+\gamma) & 0 & 0 \\ 0 & \gamma & -(\mu+\lambda+\alpha) & 0 \\ 0 & 0 & \lambda & -\theta \end{pmatrix}.$$

We note that F is a positive Matrix and V is a Metzler Matrix.

Thus, $R_0 = \rho(-FV^{-1})$, where $\rho(.)$ is the spectral radius of a matrix, and we obtain that

$$R_0 = \frac{\delta(\alpha\theta\beta_I + \gamma\lambda\beta_H + \gamma\theta\beta_D + \lambda\theta\beta_I + \mu\theta\beta_I)}{(\mu+\delta+\tau)(\mu+\gamma)(\mu+\lambda+\alpha)\theta}.$$

3.- Now, we assume that $R_0 \leq 1$:
We use the method developed in [30] to determine a Lyapunov function of the disease free equilibrium. Let $Y = (S, R)^t$, $X = (E\ I\ H\ D)^t$. The model can rewritten as

$$\begin{cases} \dot{Y} &= g(X, Y) \\ \dot{X} &= C(x_1)X - f(X, Y) \end{cases} \tag{7}$$

where

$$g(X,Y) \begin{pmatrix} -S(t)\Big(\beta_I I(t) + \beta_H H(t) + \beta_D D(t)\Big) + \tau E(t) + \mu\Big(E(t) + I(t) + H(t) + R(t)\Big) + \theta D(t) \\ \alpha H(t) - \mu R(t) \end{pmatrix} \text{ and}$$

$$f(X,Y) = \begin{pmatrix} -S(t)\Big(\beta_I I(t) + \beta_H H(t) + \beta_D D(t)\Big) + \beta_I I + \beta_H H + \beta_D D \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

Let $w = \begin{pmatrix} 0 & \frac{\beta_I}{\beta_D} & \frac{\beta_H}{\beta_D} & 1 \end{pmatrix}$ the left eigenvector of the matrix $-V^{-1}F$ associated with the eigenvalue R_0. We define $L(x) = -wV^{-1}x$ which leads to

$$L(x) = \left(\frac{\beta_I\delta}{\beta_D\,(\mu+\gamma)\,(\mu+\delta+\tau)} + \frac{\beta_H\gamma\,\delta}{\beta_D\,(\mu+\delta+\tau)\,(\mu+\lambda+\alpha)\,(\mu+\gamma)} + \frac{\lambda\,\gamma\,\delta}{(\mu+\lambda+\alpha)\,(\mu+\gamma)\,(\mu+\delta+\tau)\,\theta}\right)E$$

$$\left(+\frac{\beta_I}{\beta_D\,(\mu+\gamma)} + \frac{\beta_H\gamma}{\beta_D\,(\mu+\gamma)\,(\mu+\lambda+\alpha)} + \frac{\lambda\,\gamma}{(\mu+\lambda+\alpha)\,(\mu+\gamma)\,\theta}\right)I + \left(\frac{\beta_H}{\beta_D\,(\mu+\lambda+\alpha)} + \frac{\lambda}{(\mu+\lambda+\alpha)\,\theta}\right)H + \frac{D}{\theta}.$$

We note that L is positive in the set $\{(S,E,I,H,R,D)/0 \leq S,E,I,H,R,D \leq 1\}$, $L(1,0,0,0,0) = 0$ and

$$\begin{aligned}
\dot{L}(x) &= -wV^{-1}\dot{x} \\
&= -wV^{-1}(C(x^*)x - f(X,Y)) \\
&= -wV^{-1}((F+V)x - f(X,Y) \\
&= -wV^{-1}(F+V)x + wV^{-1}f(X,Y) \\
&= -wV^{-1}Fx - wV^{-1}Vx + wV^{-1}f(X,Y) \\
&= R_0wx - wx + wV^{-1}f(X,Y) \\
&= (R_0-1)wx + wV^{-1}f(X,Y).
\end{aligned}$$

Additionally, since $R_0 \leq 1$, $f \geq 0$ and $V^{-1} \leq 0$, then $\dot{L}(x) \leq 0$. Hence, L is a Lyapunov function of System (3) at the equilibrium state $x_1 = (1,0,0,0,0)$ and, thus, the equilibrium x_1 is globally stable.

To show that x_1 is globally asymptotically stable, we use the Lasalle principle [15].

Let $\Gamma = \{x \in \Omega/\dot{L}(x) = 0\}$. Since $R_0 \leq 1$, $f \geq 0$ and $V^{-1} \leq 0$, we have that $\dot{L}(x) = 0$ if and only if $(R_0-1)wx = 0$ and $wV^{-1}f(X,Y) = \Big(-\frac{\beta_I\delta}{\beta_D\,(\mu+\gamma)\,(\mu+\delta+\tau)} - \frac{\beta_H\gamma\,\delta}{\beta_D\,(\mu+\delta+\tau)\,(\mu+\lambda+\alpha)\,(\mu+\gamma)} - \frac{\lambda\,\gamma\,\delta}{(\mu+\lambda+\alpha)\,(\mu+\gamma)\,(\mu+\delta+\tau)\,\theta}\Big) \times \Big(\beta_I I(t)\big(1-S(t)\big) + \beta_H H(t)\big(1-S(t)\big) + \beta_D D(t)\big(1-S(t)\big)\Big) = 0$. This implies that $S = 1$ or $I = H = D = 0$. Thus, $\Gamma = \{(S,E,I,H,R,D) \in \Omega/I = H = D = 0\}$ and System (3) is then reduced in Γ to

$$\begin{cases}
\dfrac{\mathrm{d}S(t)}{\mathrm{d}t} &= \tau E + \mu E + \mu R(t)\ , \\
\dfrac{\mathrm{d}E(t)}{\mathrm{d}t} &= -\mu E(t) - \delta E - \tau E\ , \\
\dfrac{\mathrm{d}R(t)}{\mathrm{d}t} &= -\mu R(t).
\end{cases} \tag{8}$$

Furthermore, in Γ, $\dfrac{\mathrm{d}S(t)}{\mathrm{d}t} + \dfrac{\mathrm{d}E(t)}{\mathrm{d}t} + \dfrac{\mathrm{d}R(t)}{\mathrm{d}t} = -\delta E(t) = 0$. As $\delta > 0$, this leads to $E(t) = 0$ in Γ and System (8) can be rewritten as

$$\frac{\mathrm{d}S(t)}{\mathrm{d}t} = \mu R(t) \text{ and } \frac{\mathrm{d}R(t)}{\mathrm{d}t} = -\mu R(t).$$

If $0 < R(t) < 1$, then $\dfrac{\mathrm{d}S(t)}{\mathrm{d}t} > \mu R^2(t) \Rightarrow \dfrac{\mathrm{d}S(t)}{\mathrm{d}t} > -R(t)\dfrac{\mathrm{d}R(t)}{\mathrm{d}t} \Rightarrow \dfrac{\mathrm{d}S(t)}{\mathrm{d}t}(t) + R(t)\dfrac{\mathrm{d}R(t)}{\mathrm{d}t} > 0 \Rightarrow \dfrac{\mathrm{d}S(t)}{\mathrm{d}t} + \dfrac{\mathrm{d}R(t)}{\mathrm{d}t} > 0$, which is absurd as $\dfrac{\mathrm{d}S(t)}{\mathrm{d}t} + \dfrac{\mathrm{d}R(t)}{\mathrm{d}t} = 0$. Thus, $\Gamma = \{(S,E,I,H,R,D) \in \Omega/E = I = H = D = 0, R = 0 \text{or } R = 1\}$.

Let Γ_0 the largest invariant set of the System (3) in Γ. In our case, as $R = 1$ leads to a non invariant point, Γ_0 is reduced to the singleton $\{x_1\}$.

Due to the Lasalle principle, we conclude that x_1 is globally and asymptotically stable.

4.- Next, we assume that $R_0 > 1$:

Since $C(x_1) = F + V$ is a Metzler matrix, if $R_0 = \rho(-FV^{-1}) > 1$ then Matrix $C(x_1)$ is unstable [22]. This means that the Jacobian matrix $J(x_1)$, defined by (6), is unstable and, thus, x_1 is unstable [2].

We now focus on the study of the second equilibrium state x_2, which corresponds to the endemic equilibrium. Since $S(t) + E(t) + I(t) + H(t) + R(t) + D(t) = 1$, we can remove the second equation of System (3) and consider

$$\left\{\begin{array}{rcl} \dfrac{\mathrm{d}S(t)}{\mathrm{d}t} & = & \mu - S(t)\Big(\mu + \tau + \beta_I I(t) + \beta_H H(t) + \beta_D D(t)\Big) \\ & & +\tau\Big(1 - I(t) - H(t) - R(t) - D(t)\Big) + (\theta - \mu)D(t), \\ \dfrac{\mathrm{d}I(t)}{\mathrm{d}t} & = & \delta\Big(1 - S(t) - I(t) - H(t) - R(t) - D(t)\Big) - (\mu + \gamma)I(t), \\ \dfrac{\mathrm{d}H(t)}{\mathrm{d}t} & = & \gamma I(t) - \big(\mu + \lambda + \alpha\big)H(t), \\ \dfrac{\mathrm{d}R(t)}{\mathrm{d}t} & = & \alpha H(t) - \mu R(t), \\ \dfrac{\mathrm{d}D(t)}{\mathrm{d}t} & = & \lambda H(t) - \theta D(t). \end{array}\right. \tag{9}$$

The linearized system at x_2 is given by

$$\dot{X}(t) = MX(t), \tag{10}$$

where $X = (S, I, H, R, D)^t$ and

$$M = \begin{bmatrix} -D_2^0\beta_D - H_2^0\beta_H - I_2^0\beta_I - \mu - \tau & -S_2^0\beta_I - \tau & -S_2^0\beta_H - \tau & -\tau & -S_2^0\beta_D - \mu - \tau + \theta \\ -\delta & -\mu - \gamma - \tau & -\delta & -\delta & -\delta \\ 0 & \gamma & -\mu - \lambda - \alpha & 0 & 0 \\ 0 & 0 & \alpha & -\mu & 0 \\ 0 & 0 & \lambda & 0 & -\theta \end{bmatrix}.$$

System (10) can be written as

$$\left\{\begin{array}{rcl} \dot{S} & = & -(D_2^0\beta_D + H_2^0\beta_H + I_2^0\beta_I + \mu + \tau)S + (S_2^0\beta_I + \tau)I \\ & & -(S_2^0\beta_H + \tau)H - \tau R - (S_2^0\beta_D + \mu - \tau + \theta)D, \\ \begin{pmatrix} \dot{I} \\ \dot{H} \\ \dot{R} \\ \dot{D} \end{pmatrix} & = & V_1 \begin{pmatrix} I \\ H \\ R \\ D \end{pmatrix} - \begin{pmatrix} \delta(S + H + R + D) \\ 0 \\ 0 \\ 0 \end{pmatrix}, \end{array}\right. \tag{11}$$

where

$$V_1 = \begin{bmatrix} -\mu-\gamma-\tau & 0 & 0 & 0 \\ \gamma & -\mu-\lambda-\alpha & 0 & 0 \\ 0 & \alpha & -\mu & 0 \\ 0 & \lambda & 0 & -\theta \end{bmatrix}.$$

We have that $V_1^{-1} \leq 0$. We denote by $w^1 = (1,0,0,0)$ the left eigenvector vector of V_1 associated to the eigenvalue $-\mu-\tau-\gamma$.

Following the ideas introduced in [30], we define $L^1(y) = -w^1 V_1^{-1} y$, where $Y = (I,H,R,D)^t$. This function satisfies that $L^1(0) = 0$ and $L^1(y) \geq 0$, for all $y \geq 0$. Furthermore,

$$\begin{aligned} \dot{L}^1(y) &= -w^1 V_1^{-1} \dot{y} \\ &= -w^1 V_1^{-1} \left(V_1 \begin{pmatrix} I \\ H \\ R \\ D \end{pmatrix} - \begin{pmatrix} \delta(S+H+R+D) \\ 0 \\ 0 \\ 0 \end{pmatrix} \right) \\ &= -I + w^1 V_1^{-1} \begin{pmatrix} \delta(S+H+R+D) & 0 & 0 & 0 \end{pmatrix}^t \\ &= -I - \tfrac{\delta}{\mu+\gamma+\tau}(S+H+R+D). \end{aligned}$$

Hence, L^1 is a Lyapunov function for the linearized System (10) at the equilibrium 0. Thus, 0 is stable for this system.

Let $\Gamma_1 = \{x \in \mathbb{R}^5_+ \ / \ \dot{L}^1(x) = 0\}$. We note that $\Gamma_1 = \{0\}$. Due to the Lasalle principle, we conclude that 0 is asymptotically stable for System (10).

Hence, the endemic equilibrium state x_2 is locally and asymptotically stable for system (3). □

3.2 Simplified model for 2 countries

In this section, we are interested in studying the epidemiological behavior of a country (denoted by Country 2) receiving infected persons from another country (denoted by Country 1). To do so, we limit our analysis to the spread of the considered disease between two countries with movement of people from Country 1 to Country 2. We note that the methodology presented here can be adapted to the case of more than two countries.

We take into account the same assumptions and notations (but indexed by $i = 1,2$, according to the country) than the ones introduced in Section 3.1. Furthermore, following the idea described in [19], to avoid unrealistic spread of the epidemic due to unrealistic negligible values of movement of people in the state E from one country to another, we only consider the reception of infected individuals from a Country 1 to a Country 2 when the proportion of infected individuals in Country 1 is greater than a given threshold $\epsilon > 0$.

Thus, considering those hypothesis, we now consider the following system

$$
\begin{cases}
\dfrac{\mathrm{d}S_1(t)}{\mathrm{d}t} &= -S_1(t)\Big(\beta_{I_1}I_1(t)+\beta_{H_1}H_1(t)+\beta_{D_1}D_1(t)\Big)+ \\
&\quad \tau_1E_1(t)+\mu_1\Big(E_1(t)+I_1(t)+H_1(t)+R_1(t)\Big)+\theta_1D_1(t), \\
\dfrac{\mathrm{d}S_2(t)}{\mathrm{d}t} &= -S_2(t)\Big(\beta_{I_2}I_2(t)+\beta_{H_2}H_2(t)+\beta_{D_2}D_2(t)\Big)-\tilde{\tau}_1\mathcal{X}_\epsilon(E_1(t))+ \\
&\quad \tau_2E_2(t)+\mu_2\Big(E_2(t)+I_2(t)+H_2(t)+R_2(t)\Big)+\theta_2D_2(t), \\
\dfrac{\mathrm{d}E_1(t)}{\mathrm{d}t} &= S_1(t)\Big(\beta_{I_1}I_1(t)+\beta_{H_1}H_1(t)+\beta_{D_1}D_1(t)\Big)-(\mu_1+\delta_1+\tau_1)E_1(t), \\
\dfrac{\mathrm{d}E_2(t)}{\mathrm{d}t} &= S_2(t)\Big(\beta_{I_2}I_2(t)+\beta_{H_2}H_2(t)+\beta_{D_2}D_2(t)\Big)-(\mu_2+\delta_2+\tau_2)E_2(t)+\tilde{\tau}_1\mathcal{X}_\epsilon(E_1(t)), \\
\dfrac{\mathrm{d}I_1(t)}{\mathrm{d}t} &= \delta_1E_1(t)-(\mu_1+\gamma_1)I_1(t), \\
\dfrac{\mathrm{d}I_2(t)}{\mathrm{d}t} &= \delta_2E_2(t)-(\mu_2+\gamma_2)I_2(t), \\
\dfrac{\mathrm{d}H_1(t)}{\mathrm{d}t} &= \gamma_1I_1(t)-\big(\mu_1+\lambda_1+\alpha_1\big)H_1(t), \\
\dfrac{\mathrm{d}H_2(t)}{\mathrm{d}t} &= \gamma_2I_2(t)-\big(\mu_2+\lambda_2+\alpha_2\big)H_2(t), \\
\dfrac{\mathrm{d}R_1(t)}{\mathrm{d}t} &= \alpha_1H_1(t)-\mu_1R_1(t), \\
\dfrac{\mathrm{d}R_2(t)}{\mathrm{d}t} &= \alpha_2H_2(t)-\mu_2R_2(t), \\
\dfrac{\mathrm{d}D_1(t)}{\mathrm{d}t} &= \lambda_1H_1(t)-\theta_1D_1(t), \\
\dfrac{\mathrm{d}D_2(t)}{\mathrm{d}t} &= \lambda_2H_2(t)-\theta_2D_2(t),
\end{cases}
\tag{12}
$$

where $\tilde{\tau}_1 = \dfrac{\tau_1 N_1}{N_2}$; $N_i \in \mathbb{N}$ is the population size in country i; and $\mathcal{X}_\epsilon(x) = x$ if $x \geq \epsilon$, and 0 elsewhere. We consider

$$
R_0^i = \frac{\delta_i(\alpha_i\theta_i\beta_{I_i}+\gamma_i\lambda_i\beta_{D_i}+\gamma_i\theta_i\beta_{H_i}+\lambda_i\theta_i\beta_{I_i}+\mu_i\theta_i\beta_{I_i})}{(\mu_i+\delta_i+\tau_i)(\mu_i+\gamma_i)(\mu_i+\lambda_i+\alpha_i)\theta_i}, \text{ with } i=1,2.
$$

Now, we enunciate and prove the following result regarding the stability of System (12)

Theorem 3. *We consider System* (12).

1. *if $R_0^1 \leq 1$ and $R_0^2 \leq 1$, the system admits a disease free equilibrium which is globally and asymptotically stable,*

2. *if* $R_0^1 \leq 1$ *and* $R_0^2 > 1$, $(S_1, E_1, I_1, H_1, R_1, D_1)$ *tends globally asymptotically to* $(1,0,0,0,0,0)$ *and* $(S_2, E_2, I_2, H_2, R_2, D_2)$ *tends locally asymptotically to* $(S_2^0, E_2^0, I_2^0, H_2^0, R_2^0, D_2^0)$.

3. *if* $R_0^1 > 1$ *and, for all* $t > 0$, $E_1(t) > \epsilon$, $(S_1, E_1, I_1, H_1, R_1, D_1)$ *converges locally and asymptotically to* $(S_1^0, E_1^0, I_1^0, H_1^0, R_1^0, D_1^0)$ *and* $(S_2, E_2, I_2, H_2, R_2, D_2)$ *does not converges to the disease free equilibrium.*

where $S_i^0 = \dfrac{1}{R_0^2}$, $E_i^0 = \theta_i\mu_i\left(\mu_i+\gamma_i\right)\left(\mu_i+\alpha_i+\lambda_i\right)\phi_i$, $I_i^0 = \delta_i\theta_i\mu_i\left(\mu_i+\alpha_i+\lambda_i\right)\phi_i$, $H_i^0 = \delta_i\theta_i\gamma_i\mu_i\phi_i$, $R_i^0 = \delta_i\theta_i\alpha_i\gamma_i\phi_i$, $D_i^0 = \delta_i\gamma_i\lambda_i\mu_i\phi_i$, $\phi_i = \dfrac{1}{(\delta_i\gamma_i\lambda_i(\mu_i-\theta_i)+(\mu_i+\delta_i+\tau_i)(\mu_i+\gamma_i)(\mu_i+\lambda_i+\alpha_i)\theta_i)}\left(1-\dfrac{1}{R_0^2}\right)$, *with* $i = 1, 2$.

Proof. **1.-** We first assume that $R_0^1 \leq 1$:

As the equations describing the evolution of $(S_1, E_1, I_1, H_1, R_1, D_1)$ are independent from the values of $(S_2, E_2, I_2, H_2, R_2, D_2)$ and are similar to System (3), due to Theorem 2, $(S_1, E_1, I_1, H_1, R_1, D_1)$ converges globally and asymptotically to the disease free equilibrium $(1,0,0,0,0,0)$.

This implies that it exists a time $t_\epsilon > 0$, such that $E_1(t) < \epsilon$, for all $t > t_\epsilon$. Thus, for all $t > t_\epsilon$, $\mathcal{X}_\epsilon(E_1(t)) = 0$ and the second and fourth lines of System (12) are of the form

$$\begin{cases} \dfrac{\mathrm{d}S_2(t)}{\mathrm{d}t} &= -S_2(t)\Big(\beta_{I_2}I_2(t)+\beta_{H_2}H_2(t)+\beta_{D_2}D_2(t)\Big) \\ & \quad +\tau_2E_2(t)+\mu_2\Big(E_2(t)+I_2(t)+H_2(t)+R_2(t)\Big)+\theta_2D_2(t), \\ \dfrac{\mathrm{d}E_2(t)}{\mathrm{d}t} &= S_2(t)\Big(\beta_{I_2}I_2(t)+\beta_{H_2}H_2(t)+\beta_{D_2}D_2(t)\Big)-(\mu_2+\delta_2+\tau_2)E_2(t), \end{cases}$$

In that case, the system describing the evolution of $(S_2, E_2, I_2, H_2, R_2, D_2)$ is equivalent to System (3).

Hence, due to Theorem 2

- if $R_0^2 \leq 1$, , $(S_2, E_2, I_2, H_2, R_2, D_2)$ converges globally and asymptotically to the disease free equilibrium $(1,0,0,0,0,0)$,
- if $R_0^2 \geq 1$, $(S_2, E_2, I_2, H_2, R_2, D_2)$ converges locally and asymptotically to the endemic equilibrium $(S_2^0, E_2^0, I_2^0, H_2^0, R_2^0, D_2^0)$.

2.- We consider $R_0^1 \geq 1$:

From Theorem 2, we deduce that $(S_1, E_1, I_1, H_1, R_1, B_1, D_1)$ converges locally and asymptotically to the endemic equilibrium $(S_1^0, E_1^0, I_1^0, H_1^0, R_1^0, D_1^0)$.

Now, we assume that for all $t > 0$, $E_1(t) > \epsilon$. By the absurd, if $\lim_{t\to+\infty} E_2(t) = 0$, it exists $t_1 > 0$ such that for all $t > t_1$, $E_2(t) < \dfrac{\tilde{\tau}_1\epsilon}{2(\mu_2+\delta_2+\tau_2)}$. Additionally, due to the fourth equation in System 12, $\dfrac{\mathrm{d}E_2(t)}{\mathrm{d}t} > \dfrac{\tilde{\tau}_1\epsilon}{2}$ for all $t > t_1$. This implies that $\lim_{t\to+\infty} E_2(t) = +\infty$, which is not possible. Thus, $(S_1, E_1, I_1, H_1, R_1, B_1, D_1)$ does not converge to the disease free equilibrium. □

Remark 2. *From Theorem 3, we can define a basic reproduction ratio for the disease described by System* (12) *as* $R_0 = \max(R_0^1, R_0^2)$. *Indeed, if* $R_0 \leq 1$, *System* (12) *converges globally and asymptotically to the disease free equilibrium* $(1,1,0,0,0,0,0,0,0,0,0,0)$, *else, under reasonable hypothesis, it does not converges to this disease free state. This result means that the worst basic reproduction ratio of the disease in all considered countries define the basic reproduction ratio of the global system.*

Table 2: Minimum and maximum values of the parameters of System (3) for the 2014-2016 West African EVD case.

Parameters	Mininmum	Maximum
μ	0.0120	0.0230
τ	0	2.4×10^{-5}
β_I	0.0494	0.2671
β_H	0.0020	0.0107
β_D	0.0494	0.2671
δ	0.0476	0.5000
θ	0.5000	1.0000
γ	0.2000	0.5000
λ	0.0328	0.1272
α	0.0148	0.1050

4 Application to the 2014-2016 West African EVD epidemics

In this section, in order to validate and illustrate the interest of the theoretical results obtained previously, we present some numerical experiments based on data from the 2014-2016 West African EVD epidemics [13, 6, 14, 27, 39]. To do so, in Section 4.1, we perform a sensitivity analysis of the basic reproduction ratio, estimated in Section 3.1, regarding the model parameters and propose some recommendations to allocate the resources for fighting EVD. Next, in section 4.2, we present the evolution of the epidemic between two countries by considering several sets of parameters.

4.1 Sensitivity analysis of the basic reproductive ratio

In Table 2, we show the maximum and minimum values of the parameters of System (3) proposed in [19] for the 2014-2016 West African EVD case.

Considering those values, we study the impact of variations in each model parameter on the value of the basic reproductive ratio

$$R_0 = \frac{\delta(\alpha\theta\beta_I + \gamma\lambda\beta_D + \gamma\theta\beta_H + \lambda\theta\beta_I + \mu\theta\beta_I)}{(\mu+\delta+\tau)(\mu+\gamma)(\mu+\lambda+\alpha)\theta)},$$

given in Theorem 2. To do so, we first compute $R_0^{\min}$, R_0^{mean} and $R_0^{\max}$, the basic reproduction ratio obtained by considering the minimum, mean and maximum values of the model parameters, respectively. We obtain $R_0^{\min} = 0.1171$, $R_0^{\max} = 0.5440$ and $R_0^{\max} = 1.0957$.

Then, for each model parameter, indexed by $i \in \mathbb{N}$, we compute $R_{\min,i}^{\min}$, $R_{\min,i}^{\text{mean}}$, $R_{\min,i}^{\max}$, $R_{\text{mean},i}^{\min}$, $R_{\text{mean},i}^{\text{mean}}$, $R_{\text{mean},i}^{\max}$, $R_{\max,i}^{\min}$, $R_{\max,i}^{\text{mean}}$ and $R_{\max,i}^{\max}$, the basic reproduction ratios obtained considering the minimum, mean and maximum value of parameter i and the other model parameters set to their minimum, mean and maximum values, respectively. Next, we calculate the following percentile differences

$$\frac{R_{\min,i}^j - R_0^j}{R_0^j}, \frac{R_{\text{mean},i}^j - R_0^j}{R_0^j}, \frac{R_{\max,i}^j - R_0^j}{R_0^j},$$

with $j \in \{\text{min, mean, max}\}$. During those experiments, we note that the values of the basic reproduction ratios were included in the interval [0.0957,1.5537] and their mean value was 0.5838.

For each parameter, we report on Table 3 the maximum and minimum values of the computed percentile differences and the mean absolute value of those differences. We observe on this table that parameter τ has a negligible influence on R_0. Additionally, parameters λ and θ have a limited impact on the basic reproduction ratio with variations lower than 10%. Changes on α, μ, β_H, β_D and δ produce moderated modifications on R_0 of 10%, but may produce differences up to 47% for extreme cases. Finally, β_I and γ are the most

Table 3: Minimum, mean absolute and maximum values of the percentile differences computed in Section 4.1 when studying the sensitivity analysis of R_0 with respect to each parameters of System (3) and considering data from the 2014-2016 West African EVD epidemic.

Parameters	Minimum	Mean absolute value	Maximum
μ	-5	6	27
τ	-10^{-4}	10^{-4}	10^{-4}
β_I	-60	80	355
β_H	-5	10	47
β_D	-19	12	39
δ	-22	14	42
θ	-10	5	9
γ	-41	32	113
λ	-4	3	8
α	-9	8	30

Table 4: Values of the parameters in Set 1 and Set 2 used in during the experiments presented in Section 4.2. The basic reproduction ratio (R_0) generated by those values is also reported.

Parameters	Set 1	Set 2
μ	0.0197	0.0120
τ	2.4×10^{-5}	2.4×10^{-5}
β_I	0.1147	0.2671
β_H	0.0046	0.0107
β_D	0.1147	0.2671
δ	0.3643	0.0476
θ	0.8500	0.5000
γ	0.4100	0.2000
λ	0.0564	0.1272
α	0.0693	0.0148
R_0	0.3291	1.3910

sensitive parameters with mean variations greater than 30% and reaching percentile differences up to 355% for the worst scenarios.

4.2 Disease evolution between 2 countries

We now focus on the case of System (12), when Country 1 send infected persons to Country 2.

To study some representative numerical examples, we consider two set of parameters, denoted by Set 1 and Set 2 and detailed on Table 4, corresponding to basic reproductive ratios of 0.3291 and 1.3910, respectively. Furthermore, we assume that the population sizes are $N_1 = 2 \cdot 10^7$ and $N_2 = 10^7$ in Country 1 and Country 2, respectively. The initial conditions are set to $S_1(0) = 0.999$, $E_1(0) = 0.001$, $S_2(0) = 1$ and all other proportions set to 0. Additionally, $\epsilon = 1/N_1$ to consider emigration flow from Country 1 to Country 2 only in the case that it exists at least one infected individual in Country 1. The model is discretized by considering an explicit Euler scheme with a step size of 0.1 day. The simulation is stopped after a maximum number of 3650 days; or if the evolution of people in state S from one iteration to other is lower than 10^{-9} for both countries; or if the proportion of contaminated persons (e.g., persons either in the state E, I, H or D) in each country is lower than the inverse of the population size.

Taking into account those parameters and numerical methods, we perform the following four experiments:

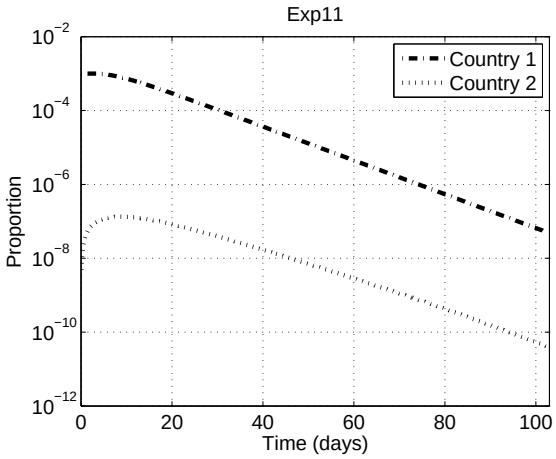

Figure 3: Evolution of the proportion of contaminated persons in Countries 1 and 2 simulated during experiment **Exp11** presented in Section 4.2.

- **Country 1 with Set 1 and Country 2 with Set1 (Exp11):** The proportion of contaminated persons in both countries is presented in Figure 3. In this case, this proportion is decreasing in Country 1. In Country 2, the maximum proportion of contaminated persons is $1.3\times10^{-5}\%$ and is reached after 8.9 days of simulation. The initial outbreak in Country 2 is due to the transportation of infected people from Country 1 occurring during the first 77.5 days of the simulation. The simulation stops after 102.7 days due to the low proportion of contaminated persons in both countries.
- **Country 1 with Set 1 and Country 2 with Set2 (Exp12):** The evolution of the proportions of contaminated and safe (i.e., persons either in the state S or R) persons are depicted in Figure 4. We can see on this figure, that the proportion of contaminated people decreases in Country 1. On the opposite, in Country 2 the epidemic starts due to the movement of infected people from Country 1 during 77.5 days and, then, reaches an endemic equilibrium with 23% of contaminated people. The simulation stops after 1238 days due to the stabilization of the numerical solutions.
- **Country 1 with Set 2 and Country 2 with Set1 (Exp21):** The evolution of the proportions of contaminated and safe persons are shown in Figure 5. We can see that the epidemic reaches an endemic equilibrium of 23% of contaminated people in Country 1. For Country 2, due to the continuous movement of infected persons coming from Country 1, the epidemic starts and remains endemic with an equilibrium of 0.01% of contaminated persons in the population. The simulation stops after 1149 days due to the stabilization of the numerical solutions. We note that, as spotted in Theorem 3, despite the fact that the basic reproduction ratio of country 2 is lower than 1, the emigration of persons from Country 1 maintains a non disease free state in Country 2.
- **Country 1 with Set 2 and Country 2 with Set2 (Exp22):** In Figure 6, we report the proportions of contaminated persons in both countries. Endemic states of 23.28% and 23.36% of contaminated people are reached in Countries 1 and 2, respectively. The epidemic in Country 2 suffers a delay, regarding Country 1, due to the time required to move infected people from Country 1 to Country 2. The simulation stop after 1436 days due to the stabilization of the numerical solutions.

5 Discussion and Conclusions

In this paper, we have performed an analysis of the equilibrium states of simplified versions of the Be-CoDiS model proposed in [19]. This model aims to study the spread of human diseases between countries.

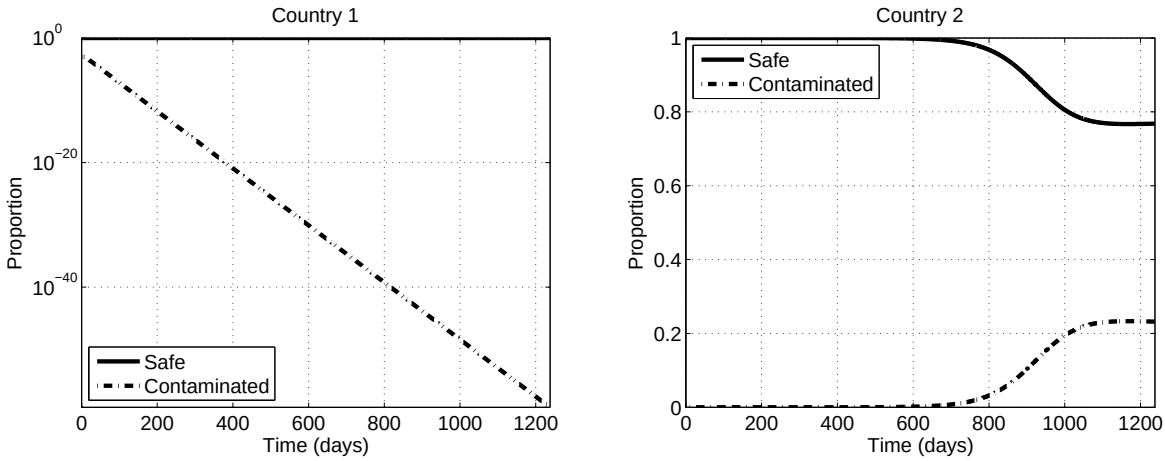

Figure 4: Evolution of the proportions of contaminated and safe persons in Countries 1 and 2 simulated during experiment **Exp12** presented in Section 4.2.

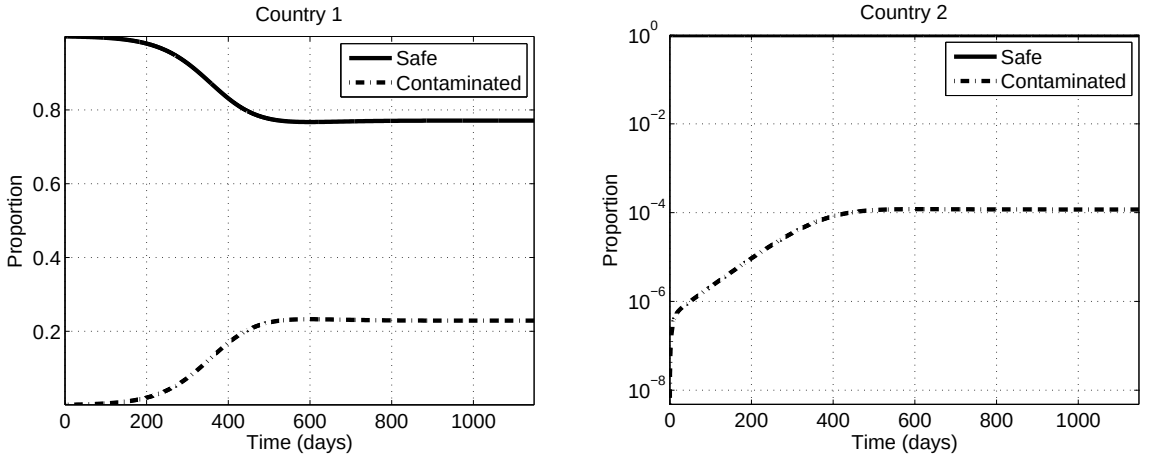

Figure 5: Evolution of the proportions of contaminated and safe persons in Countries 1 and 2 simulated during experiment **Exp21** presented in Section 4.2.

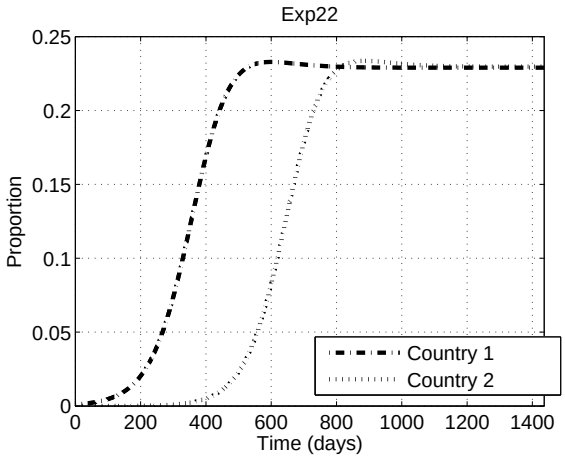

Figure 6: Evolution of the proportions of contaminated persons in Countries 1 and 2 simulated during experiment **Exp22** presented in Section 4.2.

First, in Section 3.1, we have estimated a basic reproduction ratio (denoted by R_0) of a version of the model for one country. In particular, we have obtained in Theorem 2 an analytical expression of R_0 according to the model parameters. Additionally we have proven that if $R_0 \leq 1$, then the disease free equilibrium is globally and asymptotically stable which is a desirable biological situation because the epidemic will disappear. When $R_0 > 1$, we shown that the disease free equilibrium is unstable and the endemic equilibrium is locally stable. This leads to the persistence of the epidemic in the considered population.

Then, starting from this R_0 expression and data from the 2014-16 West African Ebola epidemic, we have performed a sensitivity analysis of the basic reproductive ratio regarding the model parameters. We note that due to biological reasons, one generally does not have control on parameters μ (the mortality rate) and δ (transition from E to I). Taking into account this observation, due to the control measures applied by the authorities in order to eradicate the EVD spread (i.e., Isolation, Quarantine, Tracing and Increase of sanitary resources, see [33, 34, 13]), other model parameters can be regulated according to the technical limitations of those control measures. In particular, this sensitivity analysis seems to indicate that decreasing the time of detection of infectious persons ($1/\gamma$, the inverse of the transition rate from I to H) and the contact rate with infectious persons (β_I) are the most efficient way to reduce the epidemic evolution. During the 2014-16 EVD epidemic, both variables were controlled, for instance, by surveying the population in areas of EVD risk with healthcare workers, by performing information campaigns about the disease and by isolating suspicious cases [8, 6, 38]. For example, considering the case of Guinea, it was estimated that β_I and γ have been controlled from 0.1944 and 0.2000, at December 2013, to 0.0871 and 0.3333, at October 2015, respectively [19]. Additionally, controlling contact with hospitalized persons (β_H) and dead body (β_D), should have an impact on the EVD magnitude, although lower than reducing β_I and $1/\gamma$. In particular, it was observed that, during the first months of this EVD epidemic, around 20% of the infections were due to contacts with dead bodies [38, 35]. Additionally, the reported number of health workers infected due to contact with hospitalized persons was around 815 in May 2015, which correspond to 4% of the total number of EVD cases [37]. For these variables, control measures, such as the increase of sanitary conditions in hospitals and the supervision of funerals, have allowed to reduce those risk factors. It was estimated that, those contact rates were both reduced by two from the beginning to the end of the epidemic [19]. The increase of sanitary resources in hospitals also have allowed to increase the value of α (transition from H to R), for instance, in Guinea from 0.0847 to 0.1250 [19]. Regarding θ and λ, both parameters were controlled by reducing the duration of the funerals and the death rate (e.g., by improving the healthcare system). In particular, for Guinea, Θ passes from 0.5 to 1 and λ from 0.2381 to 0.1707 [19]. We note that the classification of the importance of the model parameters in EVD control proposed here is coherent with the response plan proposed by the international

community to fight the EDV outbreaks [36]. All those results seem to validate the interest of using System (3) and its R_0 value to identify the most important factors of an epidemic evolution.

Next, in Section 3.2, we have described the behavior of the epidemic evolution when two countries are connected by an emigration flow. From Theorem 3, we conclude that when the disease is controlled (i.e., $R_0^1 \leq 1$, where R_0^1 is computed from Theorem 2) in the country sending infected people (i.e., Country 1), the evolution of the disease in the reception country (i.e., Country 2) only depends on each countries characteristics. More precisely, if $R_0^2 \leq 1$ the epidemic disappears in Country 2, whereas if $R_0^2 > 1$ it may remain endemic in Country 2. On the opposite, in cases when the epidemic is not controlled in Country 1 (i.e., $R_0^1 > 1$), the epidemic may remain active in Country 2. This behavior was illustrated in Section 4.2 by performing four particular numerical experiments with several sets of parameters estimated from the 2014-16 EVD epidemic. Obtained numerical results were consistent with those found theoretically. Those outcomes tend to show the necessity to control the emigration flows from countries with serious epidemic scenarios. This recommendation was also proposed in the literature for the case of the 2014-16 EVD epidemic [4].

In future works, we will perform the stability analysis of the model proposed here for the case of collateral movements of people between countries. We will also apply the methodology proposed here and in [19] to the case of other diseases such as the Middle East respiratory syndrome coronavirus or the Severe acute respiratory syndrome coronavirus [7].

References

[1] M. Anderson. Population biology of infectious diseases: Part 1. *Nature*, 280:361–367, 1979.

[2] N.P. Bhatia, G.P. Szegö, and G.P. Szegö. *Stability Theory of Dynamical Systems*. Classics in Mathematics. Springer Berlin Heidelberg, 2002.

[3] D. Bichara, A. Iggidr, and G. Sallet. Global analysis of multi-strains sis, sir and msir epidemic models. *Journal of Applied Mathematics and Computing*, 44(1):273–292, 2014.

[4] I.I. Bogoch, M.I. Creatore, M.S. Cetron, J.S. Brownstein, N. Pesik, J. Miniota, T. Tam, W. Hu, A. Nicolucci, S. Ahmed, J.W. Yoon, I. Berry, S.I. Hay, A. Anema, A.J. Tatem, D. MacFadden, M. German, and K. Khan. Assessment of the potential for international dissemination of ebola virus via commercial air travel during the 2014 west african outbreak. *The Lancet*, 9962:29–35, 2016.

[5] F. Brauer and C. Castillo-Chávez. *Mathematical Models in Population Biology and Epidemiology*. Texts in applied mathematics. Springer, 2001.

[6] C.D.C. Ebola disease. *Centers for Disease Control*, 2014.

[7] G. Chowell, F. Abdirizak, S. Lee, J. Lee, E. Jung, H. Nishiura, and C. Viboud. Transmission characteristics of mers and sars in the healthcare setting: a comparative study. *BMC Medicine*, 13(1):1–12, 2015.

[8] G. Chowell and H. Nishiura. Transmission dynamics and control of ebola virus disease (evd): a review. *BMC Medecine*, 12(196), 2014.

[9] D.L. DeAngelis and L.J. Gross. *Individual-based Models and Approaches in Ecology: Populations, Communities, and Ecosystems*. Chapman & Hall, 1992.

[10] O. Diekmann, H. Heesterbeek, and T. Britton. *Mathematical Tools for Understanding Infectious Disease Dynamics:*. Princeton Series in Theoretical and Computational Biology. Princeton University Press, 2012.

[11] O. Diekmann, J. A. P. Heesterbeek, and J. A. J. Metz. On the definition and the computation of the basic reproduction ratio r0 in models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biology*, 28(4):365–382, 1990.

[12] R.T.D. Emond, B. Evans, E.T.W. Bowen, and G. Lloyd. A case of ebola virus infection. *Br Med J.*, 2:541–544, 1977.

[13] D. Fisman, E. Khoo, and A. Tuite. Early epidemic dynamics of the west african 2014 ebola outbreak: Estimates derived with a simple two-parameter model. *PLOS Currents Outbreaks*, 1, 2014.

[14] M.F.C. Gomes, A. Pastore y Piontti, L. Rossi, D. Chao, I. Longini, M.E. Halloran, and A. Vespignani. Assessing the international spreading risk associated with the 2014 west african ebola outbreak. *PLOS Currents Outbreaks*, 1, 2014.

[15] W.M. Haddad and V.S. Chellaboina. *Nonlinear Dynamical Systems and Control: A Lyapunov-Based Approach*. Princeton University Press, 2011.

[16] N. Hernandez-Ceron, Z. Feng, and C. Castillo-Chavez. Discrete epidemic models with arbitrary stage distributions and applications to disease control. *Bulletin of Mathematical Biology*, 75(10):1716–1746, 2013.

[17] H.W. Hethcote. The mathematics of infectious diseases. *SIAM Review*, 42(4):599–653, 2000.

[18] B. Ivorra, B. Martínez-López, J.M. Sánchez-Vizcaíno, and A.M. Ramos. Mathematical formulation and validation of the Be-FAST model for classical swine fever virus spread between and within farms. *Annals of Operations Research*, 219(1):25–47, 2014.

[19] B. Ivorra, D. Ngom, and A. M. Ramos. Be-codis: A mathematical model to predict the risk of human diseases spread between countries—validation and application to the 2014–2015 ebola virus disease epidemic. *Bulletin of Mathematical Biology*, 77(9):1668–1704, 2015.

[20] J. Legrand, R.F Grais, P.Y. Boelle, A.J. Valleron, and A. Flahault. Understanding the dynamics of ebola epidemics. *Med. Hypotheses.*, 135(4):610–621, 2007.

[21] P.E. Lekone and B.F. Finkenstädt. Statistical inference in a stochastic epidemic seir model with control intervention: Ebola as a case study. *Biometrics*, 62(4):1170–1177, 2006.

[22] D.G. Luenberger. *Introduction to Dynamic Systems: Theory, Models, and Applications*. Wiley, 1979.

[23] B. Martínez-López, B. Ivorra, E. Fernández-Carrión, A.M. Perez, A. Medel-Herrero, F. Sánchez-Vizcaíno, C. Gortázar, A.M. Ramos, and J.M. Sánchez-Vizcaíno. A multi-analysis approach for space-time and economic evaluation of risks related with livestock diseases: The example of fmd in Peru. *Preventive Veterinary Medicine*, 114(1):47–63, 2014.

[24] B. Martínez-López, B. Ivorra, D. Ngom, A.M. Ramos, and J.M. Sánchez-Vizcaíno. A novel spatial and stochastic model to evaluate the within and between farm transmission of classical swine fever virus. II. Validation of the model. *Veterinary Microbiology*, 155(1):21 – 32, 2012.

[25] B. Martínez-López, B. Ivorra, A.M. Ramos, E. Fernández-Carrión, T. Alexandrov, and J. M. Sánchez-Vizcaíno. Evaluation of the risk of classical swine fever spread from backyard pigs to other domestic pigs by using the spatial stochastic disease spread model Be-FAST: The example of Bulgaria. *Veterinary Microbiology*, 165(1–2):79 – 85, 2013.

[26] B. Martínez-López, B. Ivorra, A.M. Ramos, and J.M. Sánchez-Vizcaíno. A novel spatial and stochastic model to evaluate the within- and between-farm transmission of classical swine fever virus. I. General concepts and description of the model. *Veterinary Microbiology*, 147(3–4):300 – 309, 2011.

[27] M.I. Meltzer, C.Y. Atkins, S. Santibanez, B. Knust, B.W. Petersen, E.D. Ervin, S.T. Nichol, I.K. Damon, and M.L. Washington. Estimating the future number of cases in the ebola epidemic - Liberia and Sierra Leone, 2014–2015. *Centers for Disease Control. MMWR / Early Release*, 63, 2014.

[28] C. J. Peters and J. W. Peters. An introduction to ebola: The virus and the disease. *Journal of Infectious Diseases*, 179(Supplement 1):ix–xvi, 1999.

[29] M. Quincampoix. Differential inclusions and target problems. *SIAM Journal on Control and Optimization*, 30(2):324–335, 1992.

[30] Z. Shuai and P. Van den Driessche. Global stability of infectious disease models using lyapunov functions. *SIAM Journal on Applied Mathematics*, 73(4):1513–1532, 2013.

[31] H.R. Thieme. *Mathematics in Population Biology*. Mathematical Biology Series. Princeton University Press, 2003.

[32] P. Van den Driesschej and J. Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences*, 180(1-2):29–48, 2002.

[33] W.H.O. Fact sheet n^{o}103: Ebola virus disease. *World Health Organization*, 2014.

[34] W.H.O. Global alert and response: Ebola virus disease. *World Health Organization*, 2014.

[35] W.H.O. New who safe and dignified burial protocol - key to reducing ebola transmission. *World Health Organization*, 2014.

[36] W.H.O. 2015 - strategic response plan- west africa ebola outbreak. *World Health Organization*, 2015.

[37] W.H.O. Health worker ebola infections in guinea, liberia and sierra leone. *World Health Organization*, 2015.

[38] W.H.O. Ebola publications: Case management, infection prevention and control. *World Health Organization*, 2016.

[39] W.H.O. Response Team. Ebola virus disease in west africa - the first 9 months of the epidemic and forward projections. *New England Journal of Medicine*, 371:1481–1495, 2014.