Assessing the impact of treatment delays on the prevalence of HIV drug resistant cases: Modeling Case Study in Ecuador.

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Abstract

Human Immunodeficiency Virus (HIV-1) is a major pandemic with approximately 36.7 million people infected worldwide. Although the prevalence of HIV-1 in Latin America remains stable (around 0.5%) [UNAIDS, 2016], the epidemic is globally expanding among Men Seeking Men (MSM), independently of country or gross domestic product [Beyrer, 2010]. One of the major current public health challenges for HIV includes providing effective HIV antiretroviral therapy to affected populations centered on the relationship between access and adherence to treatment and prevalence of drug resistance. This research aims to evaluate the

impact of delay in treatment on the changes in prevalence of infectious and drug resistant populations. The study focus on spread of HIV in Ecuador where researchers has found that the estimated HIV prevalence among MSM is between 10-27%. In this work, a new mathematical model that incorporates a non-exponentially distributed infectious period and variable treatment coverage is developed and analyzed numerically to capture the HIV transmission dynamics in Ecuador. Our research suggests that (i) the introduction of early treatment (infection stage 1 and 2) prevents HIV to become large outbreak but considerably increases drug resistant cases, (ii) treatment on late stages (stage 3 and 4) has the opposite effect (increases infected population and reduce the resistant population), (iii) even under our proposed optimal conditions (i.e. high treatment coverage and efficacy with low level of transmissibility) any treatment strategy will be ineffective if there is no decrease on risky behavior of the individuals, (iv) from the global uncertainty and sensitivity analysis, it was observed that the rate of transmissibility and treatment effectiveness have significant influence on the model's prediction.

1 Introduction

The third decade of the Human Immunodeficiency Virus (HIV) epidemic have been marked by significant successes and failures in biomedical and behavioral research. By the end of 2015 approximately 36.7 million people were living with HIV (PLHIV) worldwide. Of these, 19 million were unaware that they were HIV-positive, while approximately 17 million were receiving antiretroviral therapy (ART) [UNAIDS, 2016]. Although the prevalence of human immunodeficiency virus (HIV) in Latin America remains stable (between the 0.5% range) [UNAIDS, 2016], the epidemic is globally expanding among Men Seeking Men (MSM) independent of country or gross domestic product [4]. Despite numerous control and prevention efforts targeted to MSM population, there is evidence of recurrent epidemics among this group, with alarming numbers of increments. Many authors displayed the rising prevalence levels ranging from 5 to 20% among the MSM infected population [18, 31–33, 35]. Beyrer [4] and Baral *et al.*, [3] identified high rates of HIV infection among MSM in all areas where data were available (sub-Saharan Africa, Latin America and the Caribbean, southern and Southeast Asia, China, and the Russian Federation).

In 2014, in Ecuador, there were approximately 35,000 people living with HIV (PLWH), representing a prevalence of about 0.3% of adults with ages ranging from 15 to 49. In the same year, 3,546 new HIV-positive cases were clinically detected, with the majority of the cases (74.8%) among people with ages from 20 to 64 [Health Ministry, 2014] (see Figure 1). Although it is well documented that the rates of HIV/AIDS among MSM tend to be higher than in the general population, especially in developing countries [3, 34], little is known about the prevalence rate

among MSM in Ecuador [22, 23]. Hernandez *et al*., [24] showed that the HIV estimated prevalence among MSM living in Northwestern of Ecuador was 10.5% in 2016, which is in agreement with at reported by Jacobson [29] in 2014 (11% in Quito), and Montano *et al*., [34] in 2005 (14.5% in Quito, and 27.8% in Guayaquil). According to the data reported by the Ministry of Health of Ecuador the group of MSM represents 17% among all high-risk population tested for HIV in the country (Health Ministry, 2014).

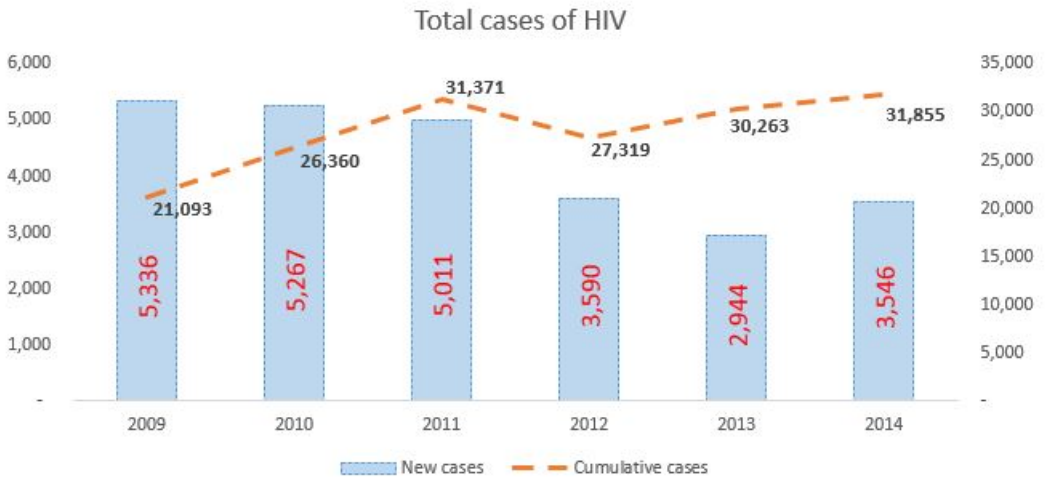

Figure 1: Newly and cumulative cases of HIV-positive cases in Ecuador from 2009 to 2014 (source: Health Ministry, 2014).

Mathematical modeling combined with experimental measurements have yielded important insights into HIV-1 pathogenesis and enhanced progress in the understanding of HIV-1 infection. Models used to study HIV-1 infection have involved viral load and infectiousness, latency and reservoir, antiretroviral (ART) response, evolution of drug resistance, among others [1, 2, 8, 13, 14,

19, 25, 27, 30, 36, 40–46, 54–58]. In order to gain more insights into the effects of behavior change or treatment on transmission dynamics, Hyman and Li 2007 [25] developed an infection-stage ODE model. They showed that the reproductive number is maximally reduced if the infectives individuals change their sexual behavior or seek treatment immediately after infection, regardless of which infection group has the highest infectivity. Pawelek *et al*., [38] in 2012 incorporated two times delays in their model to study HIV-1 dynamics. They predicted that the infection-free steady state is stable when $\Re_0 < 1$, which indicates that the infection can be cleared if antiretroviral therapy is sufficiently efficient in reducing the basic reproductive ratio below one. However, current treatment regimens cannot eradicate the virus. Likewise, they showed that including a time delay in a model comparison with experimental data can affect the estimate of model parameters. It highlights the need of more data sets for model verification and selection when times delays are incorporated into mathematical models to study virus dynamics.

Furthermore, several models have been applied to estimate HIV spreading on human population, specially in men who have sex with men, who would be considered involved to spread of the disease within the high-risk population [3–5, 9, 18, 20, 21, 26, 37, 39, 47, 53]. The challenge of this kind of modeling is the lack of data about MSM population due to social stigma and discrimination. This limitations make it very hard to make accurate predictions about HIV incidence within this population. Nevertheless, mathematical models allow us to explore the outcome under different scenarios and determine the possible consequences of having or not having any control measures. For example, how the application of appropriate treatment and precise preventive measures would help to reduce the incidence of HIV in men who have sex with men. This research aims to evalu-

ate the impact of delaying treatment on the changes in prevalence of infectious and drug resistant population. We focus on HIV transmission dynamics in Ecuador where researchers have estimated HIV prevalence among MSM between 10-27%. We developed and numerically analyzed a mathematical model that incorporates HIV transmission patterns in Ecuador with non-exponential infectious period distribution and variable treatment coverage. We intent to identify the principal factors that affect the spreading of the virus among MSM. Then, we targeted different treatment strategies to determine which one is more effective on maintaining infectious and resistant populations at the minimum.

2 Methods

2.1 Mathematical Model

We adapted a model from [17] to fit HIV dynamics among the different stages of the virus and different lines of treatment. Here we assume a gamma (specifically Erlang) distributed infectious period for the stages one through four of the disease. The model depict schematically in Figure2 describes the basic transmission dynamics of an infectious disease and includes the effects of treatment, as well as the rate at which resistance is developed to treatment. The individuals are divided into susceptible (S), infected (I), treated (T), resistant (R), finally develop AIDS (A) and die. Susceptible individuals become infected with HIV virus through a successful contact with individuals in the I, T and R compartments (with transmission parameters β). Individuals infected with the sensitive strain can move into the treated class at some per capita rate, χ, where χ is the

rate of movement to the treatment strategy of interest. Treated individuals can develop resistance (therapeutic failure) at a constant per capita rate ρ.

If mutations are developing in the virus genome to the first strategy, infected individuals can move into the second treated class at some constant per capita rate σ. These treated individuals with the second strategy can develop resistance (therapeutic failure) at some constant per capita rate ξ. Then, individuals infected developing resistance to the second strategy can move into the third treated class at some constant per capita rate θ. These treated individuals can develop resistance (therapeutic failure) at some constant per capita rate ν. Individuals in each of the seven infected classes can move into the AIDS class at some per capita rate mα, where m is the shape parameter of the Erlang distribution associated with the infectious period, which in turn is the number of sub compartments in our model, mα is the rate of horizontal movement in the different disease stages. Finally, individuals in each of the seven infected classes (Infected, treated class 1, 2, 3 and resistant class 1, 2, 3 and AIDS class) leave the system, through either death or recovery with immunity, at constant per capita rate μ

In the development of our model equations, we employed a non-exponential distribution for the infectious period and for AIDS an exponential distribution. For simplicity, we consider the total population size, as well as the rates at which individuals move from one sub-compartment to another (horizontal movement)as constant. We assume that all infected treated individuals have a 100% adherence to the treatment and that treated individuals can infect susceptibles depending on the treatment effectiveness (κ). The case when susceptible individuals become infected with a

resistant strain of the virus, i.e., from individuals in the compartment of R is also contemplated. For this case, we considered these individuals as part of the infected class (I). This is because, at the time of diagnosis, there is no way to know whether the individual is resistant to the treatment.

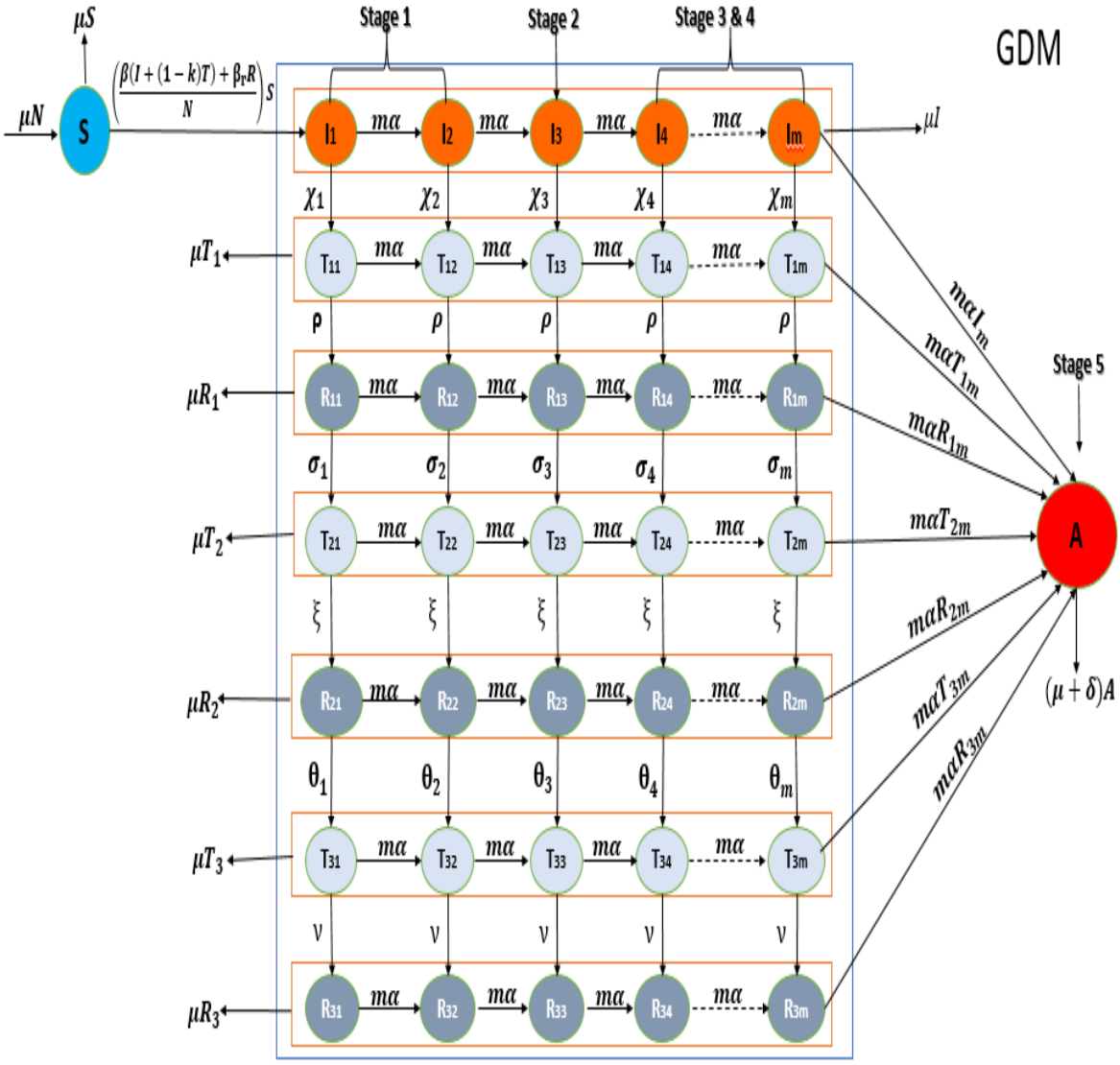

Figure 2: Schematic diagram for the progression of HIV stages, including compartments for susceptible (S), infected (I), treated (T), resistant (R), and AIDS (A).

2.2 Parameters estimate

For the calculation of the shape parameter (m) and shape parameter (ω) of the gamma distribution, we used the mean and variance for the infectious period of MSM, 136.83 months and 429.025 months, respectively [49]. With this data we calculated $m = 43$ and α= 0.028848 years^{-1}.

For the estimation of the rate at which individuals become resistant to the first (ρ), second (ξ) and third (ν) line of treatment, we first assume that the rate at which treated individuals develop resistance is constant for the three treatment scheme. We used the number of HIV positive that develop mutation related to resistance from our data (92 positive individuals). We divided the number of resistant individuals (92) by the total number of positive cases (3546) and obtained the rates ρ, ξ and ν.

We used data from [UNAIDS] to estimate the rate at which infected individuals receive treatment (χ). It is reported that 46 out 100 people receive treatment in Ecuador [50] and 64 out 100 in Latin America [51]. To convert this number to a ratio we used the total population of positive HIV cases in 2014 (3,546) [Health Ministry]. We calculated the number of individuals out of the total that will receive treatment and then divided it by the total HIV positive cases.

Previous to establish the treatment strategies, we calculated the average time that an individual will spend at every sub-compartment. For this, we let the average life-span of an HIV infected individual be 20 years and divided by the shape parameter m obtaining 24 weeks. With this infor-

mation we defined three time intervals on which individuals received treatment (categories). The first category represent a 48 week interval where individuals received treatment. For the second category the time interval is given by 24 weeks. Under the third category individuals received treatment for 960 weeks. Then we define five treatment strategies considering delay of treatment (strategies 3-5) and two strategies considering non-adherence to the treatment (strategies 1-2). For the first strategy treatment is received only the first 48 weeks (category 1) after infection follow by dropout of the treatment. The second strategy enables treatment for 24 weeks (category 2). This occur 48 weeks after infection follow by dropout after week 72. In the third strategy treatment dropout is not included and treatment is introduced at week 73 after infection to week 960 (category 3) which implies a 72 weeks delay. For the fourth strategy there is a delay of 48 weeks and treatment is introduced from week 25 to 960 (categories 2 and 3). In the fifth strategy we presented a hypothetical case, where treatment is applied on every category (no delay)(Table 1).

Table 1: Treatment strategies for non-adherence and delay treatment groups, considered the 3 different categories: 1 (48 weeks); 2 (24 weeks) and 3 (960 weeks).

	Treatment Strategies				
	Non-adherence		**Delay**		
Categories	1	2	3	4	5
1	**ON**	OFF	OFF	OFF	**ON**
2	OFF	**ON**	OFF	**ON**	**ON**
3	OFF	OFF	**ON**	**ON**	**ON**

The corresponding nonlinear ordinary differential equation (ODE) model is given by the following system:

$$
\begin{cases}
\dot{S} = \mu N - \left(\dfrac{\beta(I + (1-\kappa)T) + \beta_r R}{N} \right) S - \mu S \\
\dot{I}_1 = \left(\dfrac{\beta(I + (1-\kappa)T) + \beta_r R}{N} \right) S - (m\alpha + \chi_1 + \mu) I_1 \\
\dot{I}_j = m\alpha I_{j-1} - (m\alpha + \chi_j + \mu) I_j \\
\dot{T}_{11} = \chi_1 I_1 - (m\alpha + \rho + \mu) T_{11} \\
\dot{T}_{1j} = m\alpha T_{1j-1} + \chi_j I_j - (m\alpha + \rho + \mu) T_{1j} \\
\dot{R}_{11} = \rho T_{11} - (m\alpha + \sigma_1 + \mu) R_{11} \\
\dot{R}_{1j} = m\alpha R_{1j-1} + \rho T_{1j} - (m\alpha + \sigma_j + \mu) R_{1j} \\
\dot{T}_{21} = \sigma_1 R_1 - (m\alpha + \xi + \mu) T_{21} \\
\dot{T}_{2j} = m\alpha T_{2j-1} + \sigma_j R_j - (m\alpha + \xi + \mu) T_{2j} \qquad \forall \quad j = 2, \ldots, m \\
\dot{R}_{21} = \xi T_{21} - (m\alpha + \theta_1 + \mu) R_{21} \\
\dot{R}_{2j} = m\alpha R_{2j-1} + \sigma_j T_{2j} - (m\alpha + \xi + \mu) R_{2j} \\
\dot{T}_{31} = \theta_1 R_{21} - (m\alpha + \nu + \mu) T_{31} \\
\dot{T}_{3j} = m\alpha T_{3j-1} + \theta_j R_{2j} - (m\alpha + \nu + \mu) T_{3j} \\
\dot{R}_{31} = \nu T_{31} - (m\alpha + \mu) R_{31} \\
\dot{R}_{3j} = m\alpha R_{3j-1} + \nu T_{3j} - (m\alpha + \mu) R_{3j} \\
\dot{A} = m\alpha (I_m + T_{1m} + T_{2m} + T_{3m} + R_{1m} + R_{2m} + R_{3m}) - \mu A
\end{cases}
$$

with

$$
I = \sum_{q=1}^{m} I_q, \qquad T = \sum_{i=1}^{3} \sum_{j=1}^{m} T_{ij} \quad \text{and} \qquad R = \sum_{i=1}^{3} \sum_{j=1}^{m} R_{ij}.
$$

where $N = S+I+T+R+A$ is the total population. Table 2 provides the definition for each state variables and all model parameters used in our model.

Table 2: Definition of state variables and model parameters

Symbol	Description
	State variables
S	Number of susceptible individuals at time t.
I	Number of infected individuals at time t.
T	Number of treated individuals at time t.
R	Number of resistant individuals to the medication at time t.
A	Number of individuals in AIDS at time t.
N	Total population size (constant).
	Parameters
β	Transmission rate.
β_r	Transmission rate from resistant individuals
α	Rate of movement between all infected, treated and resistance stage.
m	shape parameter of the gamma distribution for the infectious period.
μ	Natural birth and death rate.
δ	AIDS induced mortality rate.
χ	Rate at which individuals enter the scheme of treatment 1 after infection (treated 1).
ρ	Rate at which individuals become resistant to the first line of treatment (resistant 1).
σ	Rate at which individuals enter the scheme of treatment 2 after develop resistance to the treatment 1 (treated 2).
ξ	Rate at which individuals become resistant to the second line of treatment (resistant 2).
θ	Rate at which individuals enter the scheme of treatment 3 after develop resistance to the treatment 2 (treated 3).
ν	Rate at which individuals become resistant to the third line of treatment (resistant 3).
κ	Effectiveness of treatment on reducing transmissibility

2.3 Global Uncertainty and Sensitivity analysis

The transmission coefficients between susceptible and infected (β and β_r), the effectiveness of treatment (κ) and the rates at which infected individuals enters the treated class (χ) have an im-

portant influence in the spread of HIV infection. Global uncertainty and sensitivity analysis permits to quantify how changes in the values of the input parameters alter the value of the outcome variables [7]. Using the former method via Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficient (PRCC) described by [7], we analyze the variability of the parameters β, β_r, κ, χ, α, μ, ρ, ξ, ν and their effect in our model predictions.

A probability distribution function (PDF) was assigned to each parameter and a uniform distribution $U(a, b)$ with parameters a and b for every input parameter was used, where *a* is *min value* and *b* is 2*mean value - min value*. The min and mean values of input parameters were selected from literature or taken from data available.

A sensitivity analysis for every treatment strategy was performed to determine the effect of all parameters with respect to the model, the levels of significance for the analysis were 0.001 (****), 0.01(***), 0.05 (**), 0.1(*), in which the parameters would have influence on the treatment strategy.

2.4 Graphic User Interface

We developed Matlab scripts for the implementation of the global sensitivity and uncertainty analysis to the model parameters. To facilitate the setup of the parameters, we created a graphical user interface (GUI) that is useful for those who wish to reproduce the research, especially for those who have no programming knowledge. The graphical interface consists of a window that compute

and summarize the global sensitivity and uncertainty analysis for the system's parameters from a particular treatment strategy. Also the GUI generates and stores the figures for the sensitivity analysis for the parameters with respect to infected and resistant classes that can be consulted by the user later. Similarly,the GUI also generates the corresponding graphs of uncertainty analysis for each model parameters. At the same time, it allows to adjust the parameter values to run simulations and see the results in the same window (see Appendix C Figure 22).

3 Analysis

3.1 The control reproduction number $\Re_c$

The threshold condition, $\Re_c$, represents the number of secondary infection caused by a single infective individual in a population consisting essentially only of susceptibles with control measures in place [10]. For the derivation of $\Re_c$, we use the next generation operator method [52]. We simplified our model considering only one disease stage and only a first line of treatment, obtaining the following system of equations:

$$\begin{cases} \dot{S} = \mu N - \left(\dfrac{\beta(I + (1-\kappa)T)}{N}\right) S - \mu S, \\ \dot{I} = \left(\dfrac{\beta(I + (1-\kappa)T)}{N}\right) S - (m\alpha + \chi + \mu) I, \\ \dot{T} = \chi I - (m\alpha + \rho + \mu) T, \\ \dot{R} = \rho T - (m\alpha + \mu) R, \\ \dot{A} = m\alpha(I + T + R) - \mu A. \end{cases} \tag{1}$$

Using the next generation operator we get:

$$\mathcal{F} = \begin{pmatrix} \left(\frac{\beta(I+(1-\kappa)T)S}{N}\right) \\ 0 \\ 0 \end{pmatrix} \text{ and } \mathcal{V} = \begin{pmatrix} (m\alpha+\chi+\mu)I \\ -\chi I + (m\alpha+\rho+\mu)T \\ -\rho T + (m\alpha+\mu)R \end{pmatrix}$$

$$\text{F} = \begin{pmatrix} \beta & \beta(1-\kappa) & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \text{ and V} = \begin{pmatrix} m\alpha+\chi+\mu & 0 & 0 \\ -\chi & m\alpha+\rho+\mu & 0 \\ 0 & -\rho & m\alpha+\mu \end{pmatrix}$$

When multiply both matrix

$$\text{FV}^{-1} = \begin{pmatrix} \frac{\beta}{m\alpha+\chi+\mu} + \frac{\beta(1-\kappa)\chi}{(m\alpha+\chi+\mu)(m\alpha+\rho+\mu)} & \frac{\beta(1-\kappa)}{m\alpha+\rho+\mu} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

Thus,

$$\Re_c = \frac{\beta}{m\alpha+\chi+\mu} + \frac{\beta(1-\kappa)\chi}{(m\alpha+\chi+\mu)(m\alpha+\rho+\mu)}$$

Which is a function of treatment. When there is no treatment, (i.e. when $\chi = 0$), the control reproductive number $\Re_c$ becomes a basic reproductive number $\Re_0$ given by:

$$\Re_0 = \frac{\beta}{\alpha+\mu}.$$

3.2 Equilibria and Stability

It is shown that if $\Re_c < 1$ the disease free equilibrium (DFE) $(N, 0, 0, 0)$ is locally asymptotically stable (L.A.S.) and when $\Re_c > 1$, it is unstable [52]. The endemic equilibrium (EE) of System of Equations (1) is given by (S^*, I^*, T^*, R^*).

$$\begin{aligned} S^* &= \frac{\mu N}{\lambda^* + \mu}, \\ I^* &= \frac{\mu N}{m\alpha + \chi + \mu} \frac{\lambda^*}{\lambda^* + \mu}, \\ T^* &= \frac{\mu N}{m\alpha + \chi + \mu} \frac{\chi}{m\alpha + \rho + \mu} \frac{\lambda^*}{\lambda^* + \mu}, \\ R^* &= \frac{\mu N}{m\alpha + \chi + \mu} \frac{\chi}{m\alpha + \rho + \mu} \frac{\rho}{m\alpha + \mu} \frac{\lambda^*}{\lambda^* + \mu}. \end{aligned}$$

where,the expression λ^* is then,

$$\lambda^* = \mu \left[\frac{\beta}{m\alpha + \chi + \mu} \left(1 + (1 - \kappa) \frac{\chi}{m\alpha + \rho + \mu} \right) - 1 \right] = \mu(\Re_c\text{-}1)$$

Thus, we express I^* as a function of $\Re_c$:

$$I^* = \frac{\mu N}{m\alpha + \chi + \mu} \frac{(\Re_c - 1)}{\Re_c}$$

3.3 Numerical Analysis

For the numerical analysis, we used the parameters values estimated and obtained from previous research as given in Table 3.

Table 3: Parameters and values used in our model

Symbol	Values	Unit	Reference
β	0.54 - 2.6	years^{-1}	[23]
β_r	0.026	years^{-1}	[48]
κ	0.4 - 0.6	dimensionless	[12]
μ	0.00504	years^{-1}	[15]
δ	0.0000131	years^{-1}	[15]
m	43	dimensionless	Estimated
χ	0.46 - 0.64	years^{-1}	Estimated
α	0.028848	years^{-1}	Estimated
ρ	0.026	years^{-1}	Estimated
ξ	0.026	years^{-1}	Estimated
ν	0.026	years^{-1}	Estimated

3.4 Results

The calculated uniform distribution parameters Unif(a, b) for the model parameters β, β_r, κ, χ, α, μ, ρ, ξ, ν, which are used in the uncertainty and sensitivity analysis are showed in the Table 4.

Table 4: Parameters of a uniform distribution for the uncertainty and sensitivity analysis.

Parameters	a	b
β	0.53	1.75
β_r	0.001	0.051
κ	0.4	0.6
χ	0.46	0.64
α	0.002404	0.056063
μ	0.03	0.00708
ρ	0.001	0.051
ξ	0.001	0.051
ν	0.001	0.051

Descriptive statistics obtained from the uncertainty analysis of β, β_r, κ, χ, α, μ, ρ, ξ, ν parameters are presented in Table 5.

Table 5: Descriptive statistics from the uncertainty analysis

Parameter	Min	Max	Mean
β	0.5381	1.7358	1.1407
β_r	0.0014	0.0502	0.0260
κ	0.4051	0.6980	0.5501
α	0.0024	0.0027	0.0025
μ	0.003	0.0090	0.006
ρ	0.0018	0.0503	0.026
ξ	0.0018	0.0503	0.026
ν	0.4137	1.1890	0.7991

From the Global Uncertainty and Sensitivity analysis we obtained that β and κ are the most influential parameters at a consistently 0.001 level of significance on every strategy, with β reflecting PRCCs (Partial Rank Correlation Coefficient) ranging from 0.6641 to 0.9264 and κ from -0.9465 to -0.7911. Note that β have highest proportional influence in the strategy 2 and lowest in the strategy 4, but κ has inversely proportional influence on the outcome in every strategy, being the highest inversely proportional influence on the strategy 2 and the lowest inversely proportional influence on the strategy 1 (Figure 3 and see Table 6)(for more details, see Appendix A).

Table 6: Result of β and κ from PRCCs (significance level 0.001)

Parameter	Strategy 1	Strategy 2	Strategy 3	Strategy 4	Strategy 5
β	0.7451	0.9264	0.8330	0.7709	0.6641
κ	-0.9465	-0.7911	-0.9022	-0.9289	-0.9394

With the results of the sensitivity analysis we decided to pay particular attention to the rate of infection (β) and treatment efficiency (κ) to make our simulations. During the simulation of the delay treatment strategies (3 and 4) we observed a trend were the introduction of treatment on the

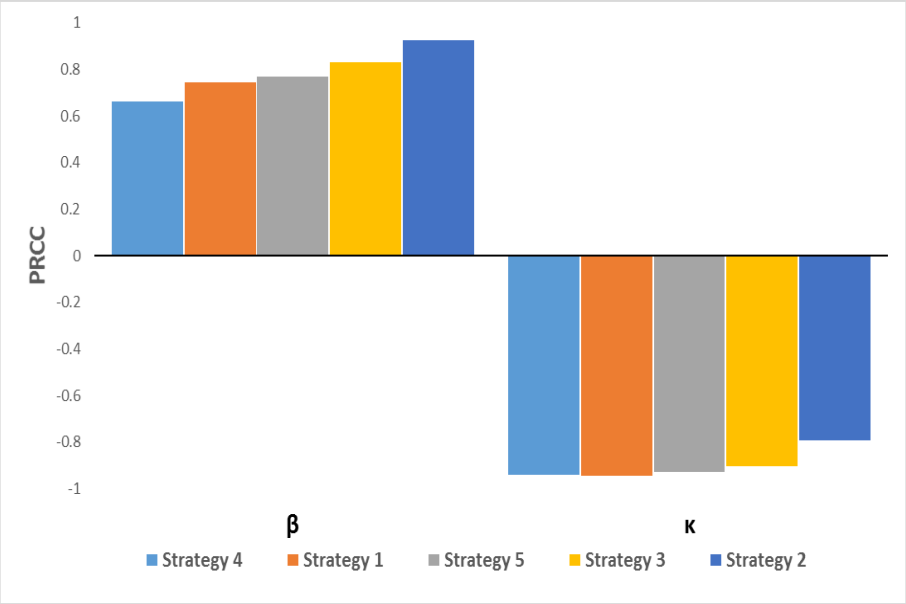

Figure 3: Plot of results to Sensitivity analysis on every strategy. Note that β have a proportional influence, but κ has inversely proportional influence on the outcome in every strategy.

very late stages produces more infectious cases but reduce the resistant cases, whereas the earlier introduction of treatment produces less infectious cases but more resistant cases (see Figures 4 and 5). With $\beta = 0.54$ the strategy 5 generate the lowest number of infected individual, and strategies 3 and 4 generate higher number of infected individuals, where strategy 3 produces the largest number of infected individuals (see Figure 4). When we compare the ratio of strategy without delay (5) with the strategies with delay (3 and 4), we observed that strategy 3 produce 0.96 more infected cases than strategy 5; otherwise, the strategy 4 generate 0.940 more infected cases than strategy 5 (see Appendix D, Figure 23). It shows that strategy 4 produces 0.328 less infected cases than strategy 3 (see Appendix D, Figure 26).

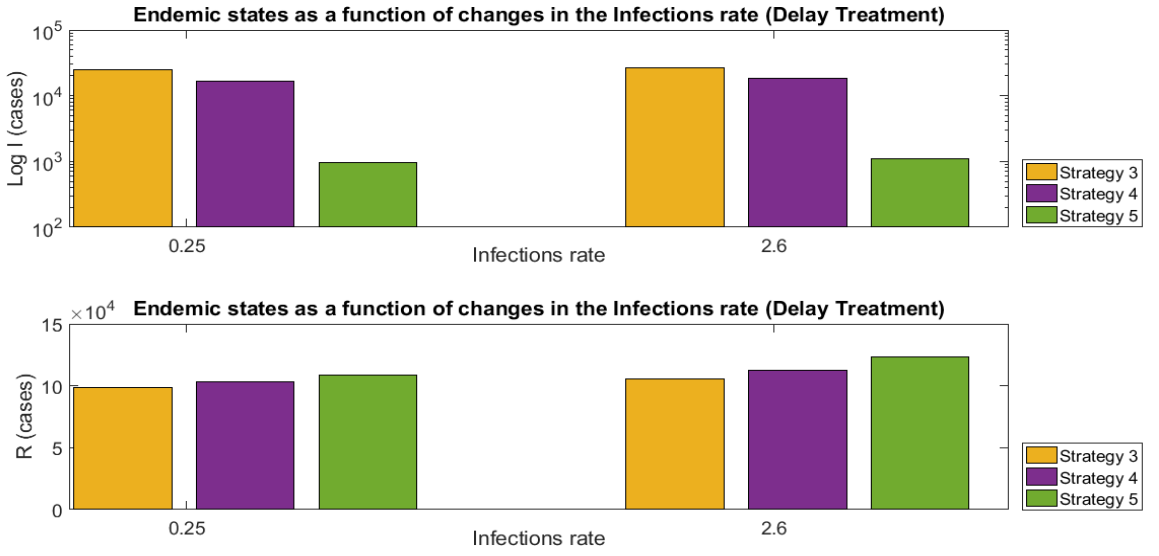

Figure 4: The effect of increasing the transmission rate (β) on infected (Top) and resistant (Bottom) cases at equilibrium for delay treatment strategies.

For $\beta = 2.6$, similar qualitative results were obtained, where strategy 5 producing the lowest number of infected individual, and strategies 3 and 4 generate higher number of infected individuals, where strategy 3 produces the largest number of infected individuals. Similarly, when we compare the ratio of strategy without delay (5) with the strategies with delay (3 and 4), we observed that strategy 3 produce 0.958 more infected cases than strategy 5; otherwise, the strategy 4 generate 0.940 more infected cases than strategy 5. It shows that strategy 4 produces 0.297 less infected cases than strategy 3 (see Figure 4). Comparing both results, $\beta = 0.54$ generate a lowest value (0.03) of infected individual than $\beta = 2.6$ with the strategy 4. Confirming that the strategy 4 is the best because it generates the fewest number of infected cases between delay strategy group.

With $\beta = 0.54$ we observed that, the onset of resistant population growth for all strategies was delayed. And the strategy 3 produce the lowest number of resistant individual and the strategy 5 the highest one, on the strategy 4 the number of individual resistant is more close to strategy 3. When we compare the ratio of strategy without delay (5) with the strategies with delay (3 and 4) we observed that strategy 3 produce 0.10 less resistant cases than strategy 5; the otherwise, the strategy 4 generate 0.05 less resistant cases than strategy 5. It shows that strategy 3 produces 0.05 less infected cases than strategy 4. For $\beta = 2.6$ similar qualitative results were obtained. The strategy 3 produce the lowest number of resistant individual and the strategy 5 the highest one, on the strategy 4 the number of individual resistant is more close to strategy 3. When we compare the ratio of strategy without delay (5) with the strategies with delay (3 and 4) we observed that strategy 3 produce 0.19 less resistant cases than strategy 5; the otherwise, the strategy 4 generate 0.10 less resistant cases than strategy 5. It shows that strategy 3 produces 0.09 less infected cases than strategy 4. Comparing both results, $\beta = 0.54$ generate a lowest value (0.022) of infected individual than $\beta = 2.6$ with the strategy 3. Confirming that the strategy 3 is the best because it generates the fewest number of resistant cases.

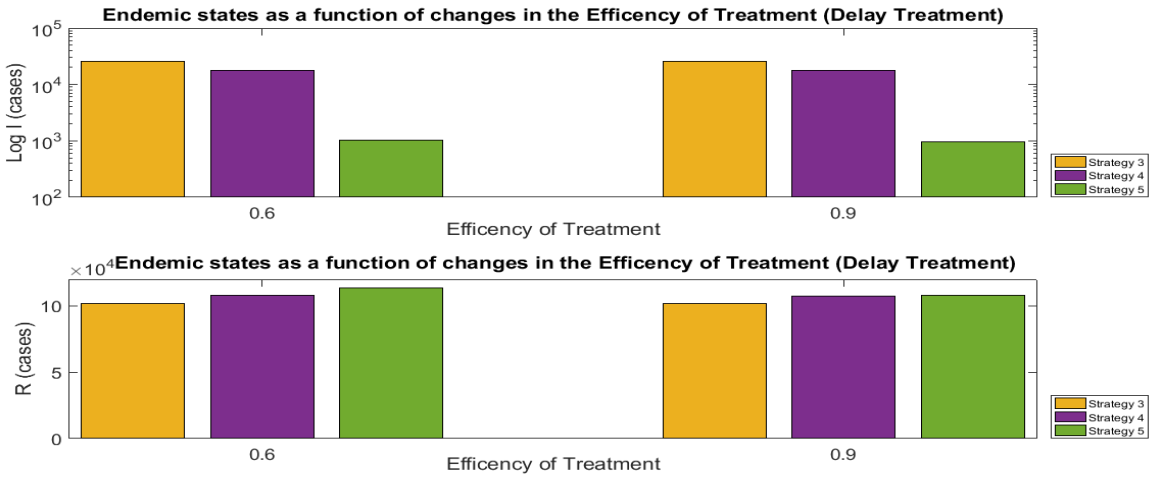

Figure 5: The effect of increasing the treatment efficiency (κ) on the infected (Top) and resistant (bottom) cases at equilibrium for delay treatment strategies

Now when we evaluate the effect of κ, we observed that when used $\kappa = 0.6$, similar time delay to reaching the epidemic were obtained for all strategies. Then, the strategy 5 generate the lowest number of infected individual, and strategies 3 and 4 generate higher number of infected individuals, where strategy 3 produces the largest number of infected individuals (see Figure 5). When we compare the ratio of strategy without delay (5) with the strategies with delay (3 and 4), we observed that strategy 3 produce 0.959 more infected cases than strategy 5; otherwise, the strategy 4 generate 0.942 more infected cases than strategy 5 (see Appendix D, Figure 24). It shows that strategy 4 produces 0.296 less infected cases than strategy 3.

For $\kappa = 0.9$, similar qualitative results were obtained, because the strategy 5 producing the lowest

number of infected individual, and strategies 3 and 4 generate higher number of infected individuals, where strategy 3 produces the largest number of infected individuals. Similarly, when we compare the ratio of strategy without delay (5) with the strategies with delay (3 and 4), we observed that strategy 3 produce 0.9619 more infected cases than strategy 5; otherwise, the strategy 4 generate 0.9445 more infected cases than strategy 5. It shows that strategy 4 produces 0.3137 less infected cases than strategy 3 (see Figure 5). Comparing both results, $\kappa = 0.9$ generate a lowest value (0.017) of infected individuals than $\kappa = 0.6$ with the strategy 4. Confirming that the strategy 4 is the best because it generates the fewest number of infected cases between delay strategy group.

With $\kappa = 0.6$ and $\kappa = 0.9$, we observed that, the onset of resistant population growth for all strategies was delayed. And the strategy 3 produce the lowest number of resistant individual and the strategy 5 the highest one, on the strategy 4 the number of individual resistant is more close to strategy 3. When we compare the ratio of strategy without delay (5) with the strategies with delay (3 and 4), we observed that strategy 3 produce 0.13 less resistant cases than strategy 5; the otherwise, the strategy 4 generate 0.05 less resistant cases than strategy 5. It shows that strategy 3 produces 0.08 less infected cases than strategy 4. For $\kappa = 0.9$ similar qualitative results were obtained. The strategy 3 produce the lowest number of resistant individual and the strategy 5 the highest one, on the strategy 4 the number of individual resistant is more close to strategy 3. When we compare the ratio of strategy without delay (5) with the strategies with delay (3 and 4) we observed that strategy 3 produce 0.06 less resistant cases than strategy 5; the otherwise, the strategy 4 generate 0.01 less resistant cases than strategy 5 (see Appendix D, Figure 24). It shows that

strategy 3 produces 0.05 less infected cases than strategy 4. Comparing both results, $\kappa = 0.9$ generate a lowest value (0.027) of resistant individuals than $\kappa = 0.6$ with the strategy 3. Confirming that the strategy 3 is the best because it generates the fewest number of resistant cases.

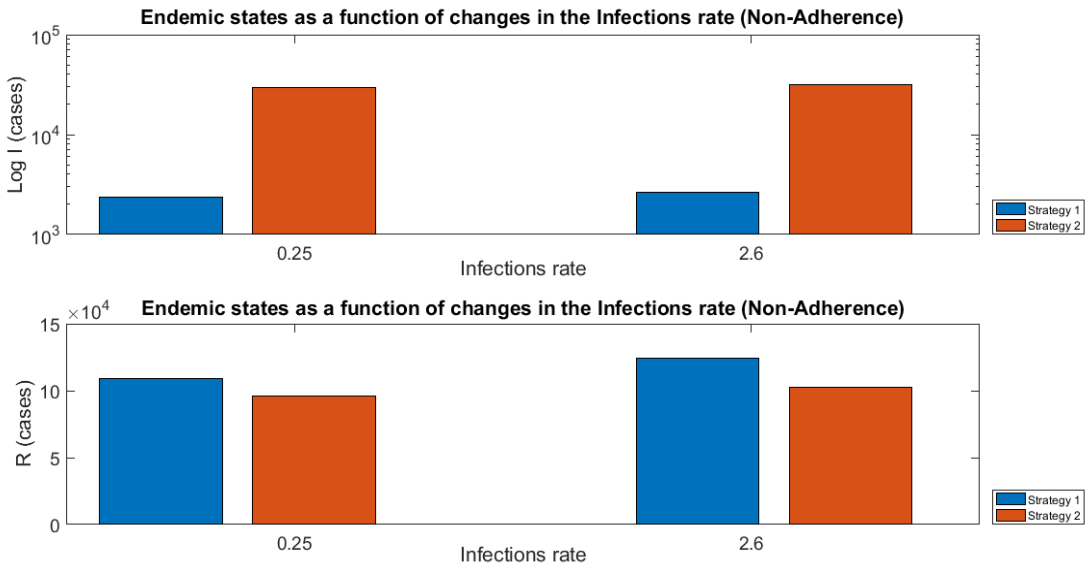

Figure 6: The effect of increasing the transmission rate (β) on infected (Top) and resistant (Bottom) cases at equilibrium for non-adherence treatment strategies.

With $\beta = 0.54$ strategy 1 generate 0.918 lower numbers of infected individuals compared with strategy 2, for $\beta = 2.6$ the same qualitative results were obtained with 0.915 lowest number of infected individuals for the strategy 1 compared with strategy 2. With $\beta = 0.54$ strategy 1 reduce in 0.135 the numbers of resistant individuals compared with strategy 2, for $\beta = 2.6$ the same

qualitative results were obtained with reduction of 0.211 the number of resistant individuals for the strategy 1 compared with strategy 2 (see Figure 6).

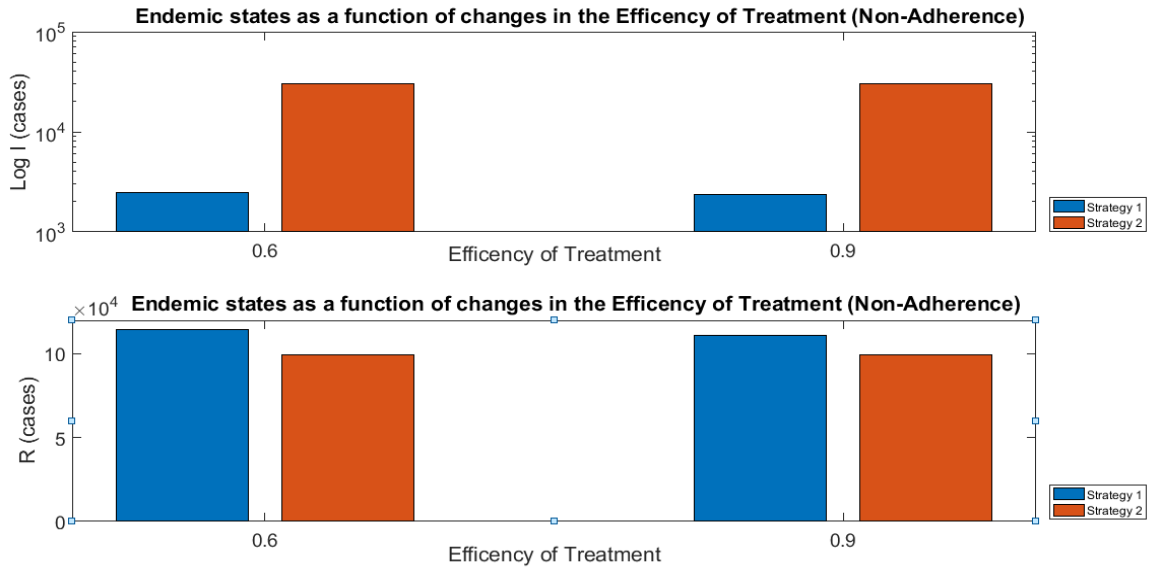

Figure 7: The effect of increasing the treatment efficiency (κ) on infected (Top) and resistant (Bottom) cases at equilibrium for non-adherence treatment strategies.

When evaluate the effect of κ, we observed that $\kappa = 0.9$ produce the lowest number of infected individual (0.921) compared with $\kappa = 0.6$ (0.919) between strategy 2 in related to strategy 1. For κ, we observed that strategy 2 compared with strategy 1 generate with $\kappa = 0.6$ the lowest the number of resistant individual (0.145) compared with $\kappa = 0.9$ (0.114)(see Figure 7).

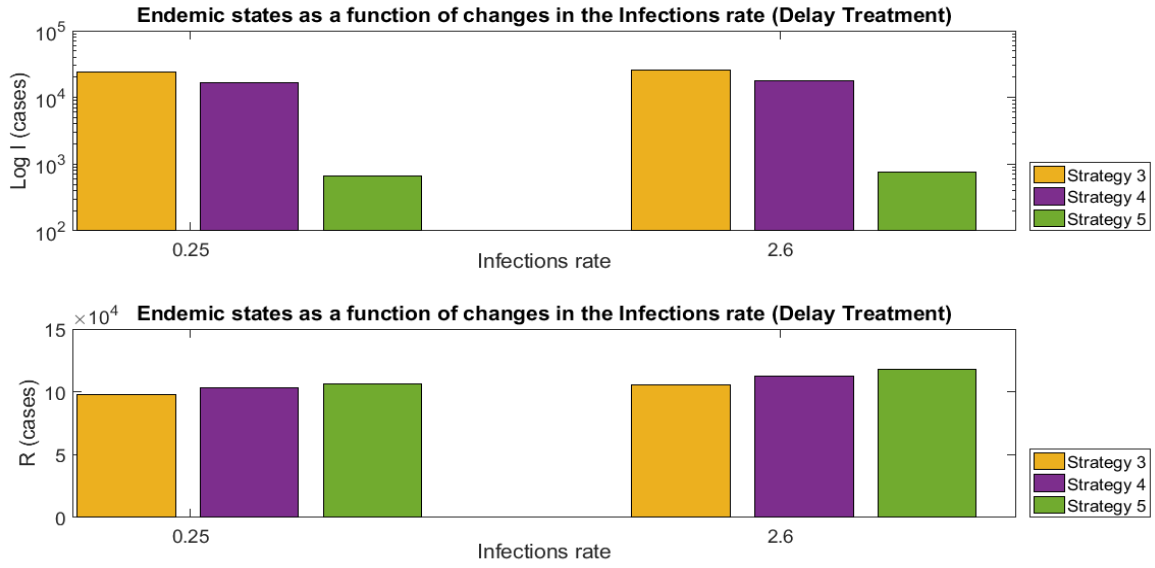

Figure 8: Implications using WHO standards (90-90-90 strategy): The effect of increasing the transmission rate (β) on infected (Top) and resistant (Bottom) cases at equilibrium for delay treatment strategies.

Evaluating the implication of using WHO strategy 90-90-90, with $\beta = 0.25$ the time delay to reaching the epidemic increase drastically for the strategy 5. Then, the strategy 5 generate the lowest number of infected individual, and strategies 3 and 4 generate higher number of infected individuals, where strategy 3 produces the largest number of infected individuals (see Figure 8). When we compare the ratio of strategy without delay (5) with the strategies with delay (3 and 4), we observed that strategy 3 produce 0.975 more infected cases than strategy 5; otherwise, the strategy 4 generate 0.97298 more infected cases than strategy 5 (see Appendix D, Figure 25). It

shows that strategy 4 produces 0.334 less infected cases than strategy 3.

Evaluating the implication of using WHO strategy 90-90-90, with $\beta = 0.25$ we observed that, the onset of resistant population growth for all strategies was delayed, which the strategy 5 have the highest delayed than others. The strategy 3 produce the lowest number of resistant individual and the strategy 5 the highest one, on the strategy 4 the number of individual resistant is more close to strategy 3. When we compare the ratio of strategy without delay (5) with the strategies with delay (3 and 4) we observed that strategy 3 produce 0.08 less resistant cases than strategy 5; the otherwise, the strategy 4 generate 0.04 less resistant cases than strategy 5. It shows that strategy 3 produces 0.03 less infected cases than strategy 4 (see Figure 8). For $\beta = 2.6$ similar qualitative results were obtained. When we compare the ratio of strategy without delay (5) with the strategies with delay (3 and 4) we observed that strategy 3 produce 0.124 less resistant cases than strategy 5; the otherwise, the strategy 4 generate 0.05 less resistant cases than strategy 5. It shows that strategy 3 produces 0.062 less infected cases than strategy 4. Comparing both results, $\beta = 0.25$ generate a lowest value (0.023) of resistant individuals than $\beta = 2.6$ with the strategy 3. Confirming that the strategy 3 is the best because it generates the fewest number of resistant cases.

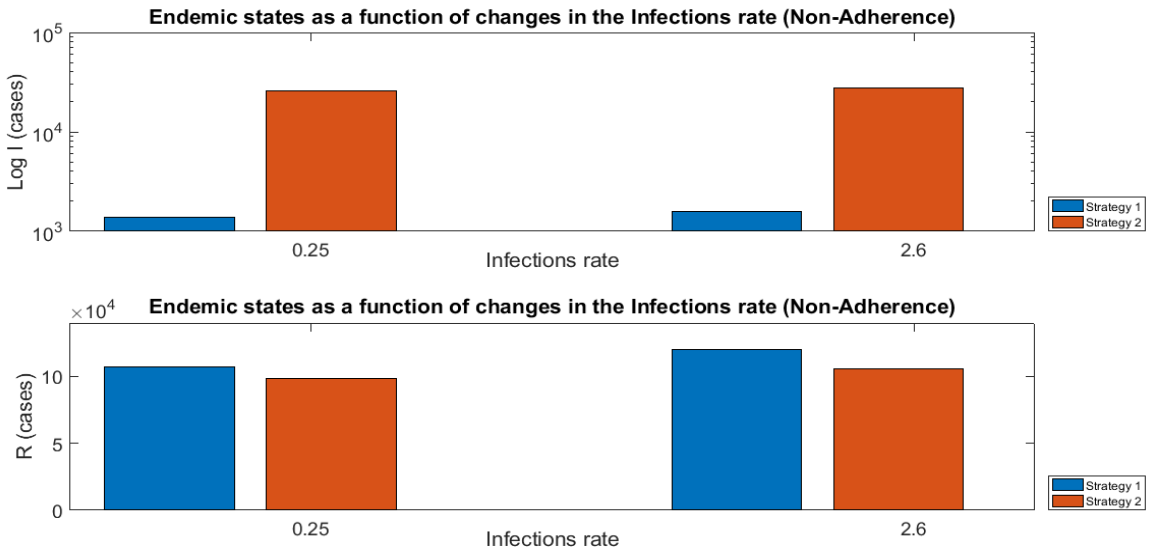

Figure 9: Implications using WHO standards (90-90-90 strategy): Implications using WHO standards (90-90-90 strategy): The effect of increasing the transmission rate (β) on infected (Top) and resistant (Bottom) cases at equilibrium for non-adherence treatment strategies.

Evaluating the implication of using WHO strategy 90-90-90, with $\beta = 0.25$ obtained lowest number of infected individual (0.946) compared with $\beta = 2.6$ (0.43) between strategy 1 and 2. Evaluating the implication of using WHO strategy 90-90-90, with $\beta = 0.25$ the strategy 2 is reduced in 0.088 the numbers of resistant individuals compared with strategy 1, for $\beta = 2.6$ the same qualitative results were obtained with reduction of 0.174 the number of resistant individuals for the strategy 2 compared with strategy 1 (see Figure 9).

4 Discussion and Conclusions

Blower [6] showed that incidence rates of HIV will fall as more HIV-positive individuals gain access to treatment (HAART), but that this public health benefit will only occur if the levels of risky behavior do not increase. Computer simulations based on a model of ordinary differential-equations for an HIV epidemic [16], contrarily, showed that treatment without reduction of risky behavior may even increase the proportion of infected individuals. Our numerical results based on simulations of ordinary differential-equations with non-exponentially distributed infectious period model showed that if HAART is introduced in early stages, it may reduce the number of infected individuals, but at the same time increases the amount of resistant individuals. Nevertheless, if the risky behavior (large values of β) increases, the proportion of infected individuals may increase more. On the other hand, strategy 3 produces the least amount of resistant individuals but increases considerably the infectious population. The former is the strategy which better exemplified the present treatment approaches.

The simulations for the ODE model in [16] showed that the combination of reduction of risky behavior together with antiretroviral drug treatment is a promising strategy in fighting the epidemic of HIV infection. In our model, we obtain similar behavior by reducing β to 0.25 and coverage (χ) to 0.9, while treatment effectiveness increase to 0.9 and 0.95. Reducing β implies a decrease on risky behavior of the infected individuals which could be possible with early detection and awareness of the impact of spreading the disease.

To the best of our knowledge, this is the first mathematical model to address HIV dynamics among MSM in Ecuador. For the simplify model we demonstrate the existence of a disease free equilibrium and an endemic equilibrium. According to the sensitivity analysis, scheme to reducing the rate of infection and increasing the effectiveness of treatment should be implemented if you want to keep the spread of the disease at lowest levels possible.

Among the delay treatment strategies, strategy 5 is better at reducing the number of infected individuals (96%) compare to strategy 3. But strategy 3 is better at lowering the number of resistant individuals (11% for β and 13% for κ) than strategy 5. Under WHO standards (90-90-90) same qualitative results were obtained (strategy 5 is best for infected individuals with 97.5% and strategy 3 is the best for resistant individuals with 10.8%.When evaluate the ratio between two delay strategies (3 and 4) compared to non-delay strategy (5), the strategy 4 is better because generate 0.328 with $\beta = 0.54$ and 0.3137 with $\kappa = 0.9$ less infected individuals than strategy 3. Under the WHO standards (90-90-90) same qualitative results were obtained, because the strategy 4 generate 0.3346 less infected individual than strategy 3.

Between non-adherence treatment strategies, strategy 1 is better at reducing the number of infected individuals (91.8%) than strategy 2. And the Strategy 2 is better at lowering the number of resistant individuals (13.5% for β and 11.4% for κ) than strategy 1. Under the WHO standards (90-90-90) same qualitative results were obtained (strategy 5 is best for infected individuals with 94.6% and strategy 3 is the best for resistant individuals with 8.8%).

Our results suggest that if we reach to implement the WHO strategy 90-90-90 is need to reduce the risky behavior of the individuals, because if the risky behavior are not reducing any treatment strategy become ineffective. This goal can be reached by educating the population and the creation of more effective drugs.

For future works, we aim to analyze the full model analytically including treatment dropout and variable adherence and contrast the predictions of the model by using different types of distribution for the infectious period. Also, consider modeling other HIV high-risk populations and determinate the impact of the risk behavior, used of physical barriers (condoms) and Injection Drug User (IDU) on HIV dynamics and finally include the most common mutations (associated to resistance) to study the impact on the different treatment schemes

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References

[1] U. L. ABBAS, R. GLAUBIUS, A. MUBAYI, G. HOOD, AND J. W. MELLORS, *Antiretroviral therapy and pre-exposure prophylaxis: combined impact on hiv transmission and drug resistance in south africa*, Journal of Infectious Diseases, (2013), p. jit150.

[2] N. BAIRAGI AND D. ADAK, *Global analysis of hiv-1 dynamics with hill type infection rate and intracellular delay*, Applied Mathematical Modelling, 38 (2014), pp. 5047–5066.

[3] S. BARAL, F. SIFAKIS, F. CLEGHORN, AND C. BEYRER, *Elevated risk for hiv infection among men who have sex with men in low-and middle-income countries 2000–2006: a systematic review*, PLoS Med, 4 (2007), p. e339.

[4] C. BEYRER, *Global prevention of hiv infection for neglected populations: men who have sex with men*, Clinical Infectious Diseases, 50 (2010), pp. S108–S113.

[5] D. BEZEMER, A. CORI, O. RATMANN, A. VAN SIGHEM, H. S. HERMANIDES, B. E. DUTILH, L. GRAS, N. R. FARIA, R. VAN DEN HENGEL, A. J. DUITS, ET AL., *Dispersion of the hiv-1 epidemic in men who have sex with men in the netherlands: A combined mathematical model and phylogenetic analysis*, PLoS Med, 12 (2015), p. e1001898.

[6] S. BLOWER, *Calculating the consequences: Haart and risky sex*, Aids, 15 (2001), pp. 1309–1310.

[7] S. M. BLOWER AND H. DOWLATABADI, *Sensitivity and uncertainty analysis of complex models of disease transmission: an hiv model, as an example*, International Statistical Review/Revue Internationale de Statistique, (1994), pp. 229–243.

[8] D. BURG, L. RONG, A. U. NEUMANN, AND H. DAHARI, *Mathematical modeling of viral kinetics under immune control during primary hiv-1 infection*, Journal of Theoretical Biology, 259 (2009), pp. 751–759.

[9] Y. CARO-VEGA, C. DEL RIO, V. D. LIMA, M. LOPEZ-CERVANTES, B. CRABTREE-RAMIREZ, S. BAUTISTA-ARREDONDO, M. A. COLCHERO, AND J. SIERRA-MADERO, *Estimating the impact of earlier art initiation and increased testing coverage on hiv transmission among men who have sex with men in mexico using a mathematical model*, PloS one, 10 (2015), p. e0136534.

[10] C. CASTILLO-CHAVEZ AND F. BRAUER, *Mathematical models in population biology and epidemiology*, Springer, 2012.

[11] S. COFFEY. Guide for HIV AIDS Clinical Care (Online). U.S. Department of Health and Human Services (HHS), Health Resources and Services Administration (HRSA), 2014.

[12] B. CORIAT, *The Political Economy of HIV/AIDS in Developing Countries: TRIPS, Public Health Systems and Free Access*, Edward Elgar Publishing, Incorporated, 2008.

[13] R. V. CULSHAW AND S. RUAN, *A delay-differential equation model of hiv infection of cd4+ t-cells*, Mathematical biosciences, 165 (2000), pp. 27–39.

[14] R. V. CULSHAW, S. RUAN, AND G. WEBB, *A mathematical model of cell-to-cell spread of hiv-1 that includes a time delay*, Journal of mathematical biology, 46 (2003), pp. 425–444.

[15] I. N. DE ESTADISTICAS Y CENSOS (INEC). Anuario de Estadisticas Vitales.Nacimientos y Defunciones 2014 (Online). Available at http://www.ecuadorencifras.gob.ec/Anuario Nacimientos y Defunciones 2014.pdf.

[16] A. DORFMAYR, *The effects of antiretroviral therapy on an hiv/aids epidemic*, Mathematics in Medicine and Pharmacy, (2002).

[17] Z. FENG, D. XU, AND H. ZHAO, *Epidemiological models with non-exponentially distributed disease stages and applications to disease control*, Bulletin of mathematical biology, 69 (2007), pp. 1511–1536.

[18] M. R. FRIEDMAN, C. WEI, M. L. KLEM, A. J. SILVESTRE, N. MARKOVIC, AND R. STALL, *Hiv infection and sexual risk among men who have sex with men and women (msmw): a systematic review and meta-analysis*, PLoS One, 9 (2014), p. e87139.

[19] T. GAO, W. WANG, AND X. LIU, *Mathematical analysis of an hiv model with impulsive antiretroviral drug doses*, Mathematics and Computers in Simulation, 82 (2011), pp. 653–665.

[20] M. C. GARCÍA, Q. LE DUONG, L. E. MERCER, S. B. MEYER, AND P. R. WARD, *'never testing for hiv'among men who have sex with men in viet nam: results from an internet-based cross-sectional survey*, BMC public health, 13 (2013), p. 1.

[21] G. B. GOMEZ, A. BORQUEZ, C. F. CACERES, E. R. SEGURA, R. M. GRANT, G. P. GARNETT, AND T. B. HALLETT, *The potential impact of pre-exposure prophylaxis for hiv prevention among men who have sex with men and transwomen in lima, peru: a mathematical modelling study*, PLoS Med, 9 (2012), p. e1001323.

[22] J. P. GUTIÉRREZ, E. E. ATIENZO, S. M. BERTOZZI, AND S. MCPHERSON, *Effects of the frontiers prevention project in ecuador on sexual behaviours and sexually transmitted infections amongst men who have sex with men and female sex workers: challenges on evaluating complex interventions*, Journal of Development Effectiveness, 5 (2013), pp. 158–177.

[23] J.-P. GUTIÉRREZ, D. MOLINA-YEPEZ, K. MORRISON, F. SAMUELS, AND S. M. BERTOZZI, *Correlates of condom use in a sample of msm in ecuador*, BMC Public Health, 6 (2006), p. 1.

[24] I. HERNANDEZ, M. REINA-ORTIZ, A. JOHNSON, C. ROSAS, V. SHARMA, S. TERAN, E. NAIK, H. M. SALIHU, E. TERAN, AND R. IZURIETA, *Risk factors associated with hiv among men who have sex with men (msm) in ecuador*, American journal of men's health, (2016), p. 1557988316646757.

[25] J. M. HYMAN AND J. LI, *Infection-age structured epidemic models with behavior change or treatment*, Journal of biological dynamics, 1 (2007), pp. 109–131.

[26] J. M. HYMAN, J. LI, AND E. A. STANLEY, *Threshold conditions for the spread of the hiv infection in age-structured populations of homosexual men*, Journal of theoretical biology, 166 (1994), pp. 9–31.

[27] ——, *Modeling the impact of random screening and contact tracing in reducing the spread of hiv*, Mathematical biosciences, 181 (2003), pp. 17–54.

[28] A. INFO. Guide for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents (Online). U.S. Department of Health and Human Services (HHS), Health Resources and Services Administration (HRSA), 2016.

[29] J. O. JACOBSON, A. SÁNCHEZ-GÓMEZ, O. MONTOYA, E. SORIA, W. TARUPI, M. C. URQUIZO, E. C. ORTIZ, S. M. MIRANDA, R. TOBAR, B. GÓMEZ, ET AL., *A continuing hiv epidemic and differential patterns of hiv-sti risk among msm in quito, ecuador: an urgent need to scale up hiv testing and prevention*, AIDS and Behavior, 18 (2014), pp. 88–98.

[30] M. Y. LI AND L. WANG, *Backward bifurcation in a mathematical model for hiv infection in vivo with anti-retroviral treatment*, Nonlinear Analysis: Real World Applications, 17 (2014), pp. 147–160.

[31] C. MAULSBY, G. MILLETT, K. LINDSEY, R. KELLEY, K. JOHNSON, D. MONTOYA, AND D. HOLTGRAVE, *A systematic review of hiv interventions for black men who have sex with men (msm)*, BMC Public Health, 13 (2013), p. 1.

[32] ——, *Hiv among black men who have sex with men (msm) in the united states: a review of the literature*, AIDS and Behavior, 18 (2014), pp. 10–25.

[33] G. MELENDEZ-TORRES, E. NYE, AND C. BONELL, *Is location of sex associated with sexual risk behaviour in men who have sex with men? systematic review of within-subjects*

studies, AIDS and Behavior, 20 (2016), pp. 1219–1227.

[34] S. M. MONTANO, J. L. SANCHEZ, A. LAGUNA-TORRES, P. CUCHI, M. M. AVILA, M. WEISSENBACHER, M. SERRA, J. VIÑOLES, J. C. RUSSI, N. AGUAYO, ET AL., *Prevalences, genotypes, and risk factors for hiv transmission in south america*, JAIDS Journal of Acquired Immune Deficiency Syndromes, 40 (2005), pp. 57–64.

[35] B. S. MUSTANSKI, M. E. NEWCOMB, S. N. DU BOIS, S. C. GARCIA, AND C. GROV, *Hiv in young men who have sex with men: a review of epidemiology, risk and protective factors, and interventions*, Journal of sex research, 48 (2011), pp. 218–253.

[36] P. W. NELSON AND A. S. PERELSON, *Mathematical analysis of delay differential equation models of hiv-1 infection*, Mathematical biosciences, 179 (2002), pp. 73–94.

[37] B. E. NICHOLS, H. M. GÖTZ, E. C. VAN GORP, A. VERBON, C. ROKX, C. A. BOUCHER, AND D. A. VAN DE VIJVER, *Partner notification for reduction of hiv-1 transmission and related costs among men who have sex with men: A mathematical modeling study*, PloS one, 10 (2015), p. e0142576.

[38] K. A. PAWELEK, S. LIU, F. PAHLEVANI, AND L. RONG, *A model of hiv-1 infection with two time delays: mathematical analysis and comparison with patient data*, Mathematical Biosciences, 235 (2012), pp. 98–109.

[39] N. S. PERRY, S. W. TAYLOR, S. ELSESSER, S. A. SAFREN, AND C. O'CLEIRIGH, *the predominant relationship between sexual environment characteristics and hiv-serodiscordant*

condomless anal sex among hiv-positive men who have sex with men (msm), AIDS and Behavior, 20 (2016), pp. 1228–1235.

[40] C. M. PINTO AND A. CARVALHO, *Mathematical model for hiv dynamics in hiv-specific helper cells*, Communications in Nonlinear Science and Numerical Simulation, 19 (2014), pp. 693–701.

[41] M. PRAGUE, *Use of dynamical models for treatment optimization in hiv infected patients: a sequential bayesian analysis approach.*, arXiv preprint math.PR/00000000, (2016).

[42] M. C. PROSPERI, R. D'AUTILIA, F. INCARDONA, A. DE LUCA, M. ZAZZI, AND G. ULIVI, *Stochastic modelling of genotypic drug-resistance for human immunodeficiency virus towards long-term combination therapy optimization*, Bioinformatics, 25 (2009), pp. 1040–1047.

[43] L. RONG, M. A. GILCHRIST, Z. FENG, AND A. S. PERELSON, *Modeling within-host hiv-1 dynamics and the evolution of drug resistance: trade-offs between viral enzyme function and drug susceptibility*, Journal of Theoretical biology, 247 (2007), pp. 804–818.

[44] L. RONG AND A. S. PERELSON, *Modeling hiv persistence, the latent reservoir, and viral blips*, Journal of theoretical biology, 260 (2009), pp. 308–331.

[45] P. K. ROY, A. N. CHATTERJEE, D. GREENHALGH, AND Q. J. KHAN, *Long term dynamics in a mathematical model of hiv-1 infection with delay in different variants of the basic drug therapy model*, Nonlinear Analysis: Real World Applications, 14 (2013), pp. 1621–1633.

[46] G. SAMANTA, *Permanence and extinction of a nonautonomous hiv/aids epidemic model with distributed time delay*, Nonlinear Analysis: Real World Applications, 12 (2011), pp. 1163–1177.

[47] S. W. SORENSEN, S. L. SANSOM, J. T. BROOKS, G. MARKS, E. M. BEGIER, K. BUCHACZ, E. A. DINENNO, J. H. MERMIN, AND P. H. KILMARX, *A mathematical model of comprehensive test-and-treat services and hiv incidence among men who have sex with men in the united states*, PloS one, 7 (2012), p. e29098.

[48] B. TAIWO, *Understanding transmitted {HIV} resistance through the experience in the {USA}*, International Journal of Infectious Diseases, 13 (2009), pp. 552 – 559.

[49] W. TAN AND H. WU, *Deterministic and Stochastic Models of AIDS Epidemics and HIV Infections with Intervention*, 2005.

[50] UNAIDS, *The gap report*. The GAP report 2014 (Online). Available a http://www.unaids.org, 2014.

[51] ——, *Fact sheet 2016*. Fact sheet 2016 (Online). Available athttp://www.aids2016.org/Portals/0/File/UNAIDS FactSheet en.pdf, 2016.

[52] P. VAN DEN DRIESSCHE AND J. WATMOUGH, *Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission*, Mathematical biosciences, 180 (2002), pp. 29–48.

[53] A. VAN SIGHEM, B. VIDONDO, T. R. GLASS, H. C. BUCHER, P. VERNAZZA, M. GEBHARDT, F. DE WOLF, S. DERENDINGER, A. JEANNIN, D. BEZEMER, ET AL., *Resurgence of hiv infection among men who have sex with men in switzerland: mathematical modelling study*, PloS one, 7 (2012), p. e44819.

[54] X. WANG, A. ELAIW, AND X. SONG, *Global properties of a delayed hiv infection model with ctl immune response*, Applied Mathematics and Computation, 218 (2012), pp. 9405–9414.

[55] X. WANG AND X. SONG, *Global stability and periodic solution of a model for hiv infection of cd4+ t cells*, Applied Mathematics and Computation, 189 (2007), pp. 1331–1340.

[56] D. P. WILSON, M. G. LAW, A. E. GRULICH, D. A. COOPER, AND J. M. KALDOR, *Relation between hiv viral load and infectiousness: a model-based analysis*, The Lancet, 372 (2008), pp. 314–320.

[57] Y. XIAO, H. MIAO, S. TANG, AND H. WU, *Modeling antiretroviral drug responses for hiv-1 infected patients using differential equation models*, Advanced drug delivery reviews, 65 (2013), pp. 940–953.

[58] Y. YAN AND C. KOU, *Stability analysis for a fractional differential model of hiv infection of cd4+ t-cells with time delay*, Mathematics and Computers in Simulation, 82 (2012), pp. 1572–1585.

6 Appendix

6.1 Appendix A

For the Global Uncertainty and Sensitivity analysis, we evaluated the influence of parameters on infected (I), and resistant (R) populations and the ratio I/R for each strategy.

In Figures 10 - 11, we show the results of Uncertainty and Sensitivity analysis for the strategy 1. Note that β, κ, ρ, ξ and χ have different influence levels, it shows that β and κ have an important influence on this strategy. In Figures 12 - 13, we show the results of Uncertainty and Sensitivity analysis for the strategy 2. Note that β, κ and χ have different influence levels, it shows that β and κ have an important influence on this strategy. In the figures 14 - 15, we showed the results of Uncertainty and Sensitivity analysis for the strategy 3. β and κ, were the only parameters which have an important influence on this strategy. In Figures 16 - 17, we show the results of Uncertainty and Sensitivity analysis for strategy 4. Note that β, κ, α have different influence levels, it shows that β and κ have an important influence on this strategy. In Figures 18 - 19, we show the results of Uncertainty and Sensitivity analysis for strategy 5. Note that β, κ, ν have different influence levels, it shows that β and κ have an important influence on this strategy.

Sensitivity analyses for Infected class

	Parameter	PRCC	Significance
1	Kappa	-0.9465	****
2	Beta	0.7451	****
3	Rho_2	-0.6109	***
4	Treatment Le...	-0.3734	**
5	Rho_1	-0.3314	*

Sensitivity analyses for Resistent class

	Parameter	PRCC	Significance
1	Kappa	-0.9465	****
2	Beta	0.7451	****
3	Rho_2	-0.6109	***
4	Treatment Le...	-0.3734	**
5	Rho_1	-0.3314	*

Sensitivity analyses for Ratio I / R

	Parameter	PRCC	Significance
1	Kappa	-0.9465	****
2	Beta	0.7451	****
3	Rho_2	-0.6109	***
4	Treatment Le...	-0.3734	**
5	Rho_1	-0.3314	*

Figure 10: PRCC results of Uncertainty and Sensitivity analysis of infected (I), resistant (R) individuals and the ratio I/R for strategy 1. The levels of significance for the analysis were represented by 0.001 (****), 0.01(***), 0.05 (**), and 0.1(*)

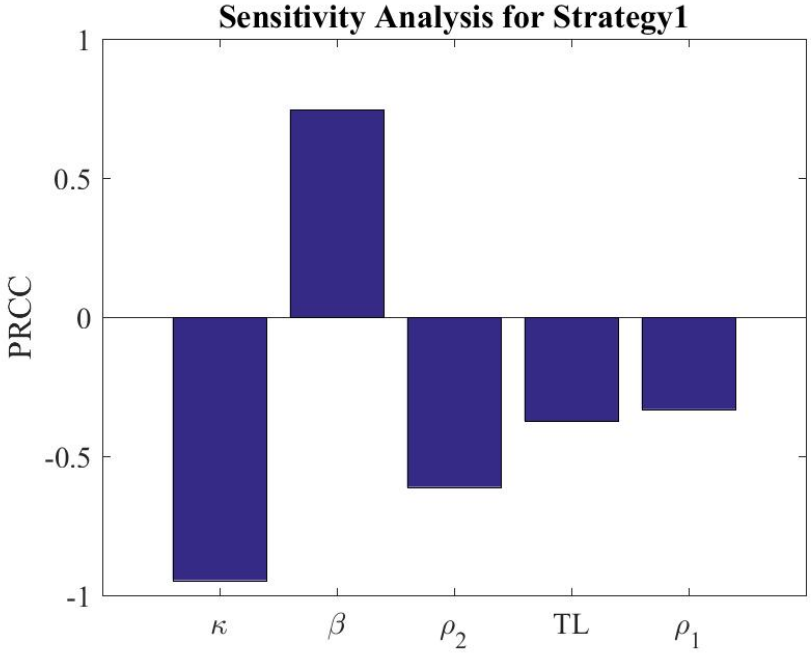

Figure 11: Plot of result to Sensitivity analysis on strategy 1. β has a proportional influence. κ, ρ_1, ρ_2, and TL (χ) have inversely proportional influence on the outcome in this strategy.

Sensitivity analyses for Infected class

	Parameter	PRCC	Significance
1	Beta	0.9264	****
2	Kappa	-0.7911	****
3	Treatment Le...	-0.5455	***

Sensitivity analyses for Resistent class

	Parameter	PRCC	Significance
1	Beta	0.9264	****
2	Kappa	-0.7911	****
3	Treatment Le...	-0.5455	***

Sensitivity analyses for Ratio I / R

	Parameter	PRCC	Significance
1	Beta	0.9264	****
2	Kappa	-0.7911	****
3	Treatment Le...	-0.5455	***

Figure 12: PRCC results of Uncertainty and Sensitivity analysis of infected (I), resistant (R) individuals and the ratio I/R for strategy 2. The levels of significance for the analysis were represented by 0.001 (****), 0.01(***), 0.05 (**), and 0.1(*)

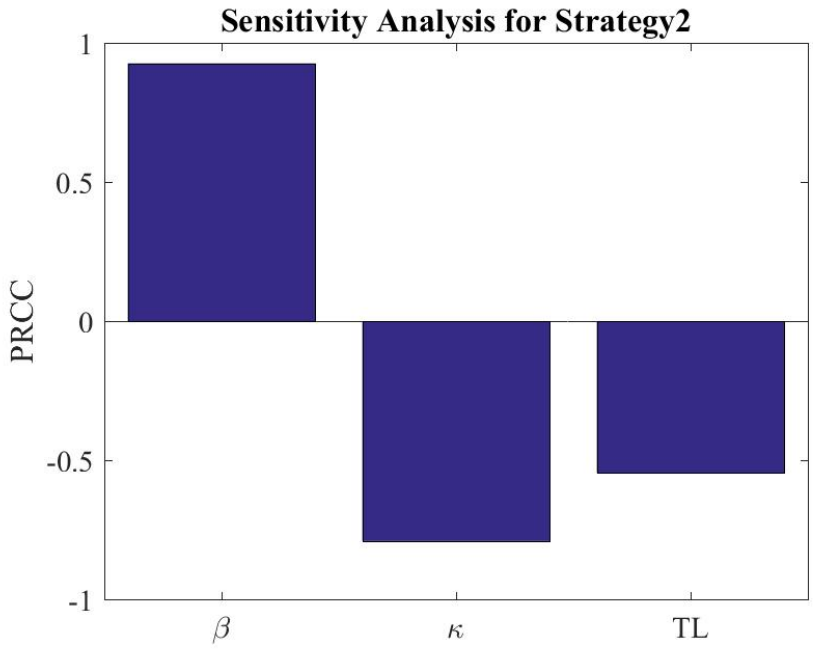

Figure 13: Plot of results to Sensitivity analysis on strategy 2. β has a proportional influence but κ and TL (χ) have inversely proportional influence on the outcome in this strategy.

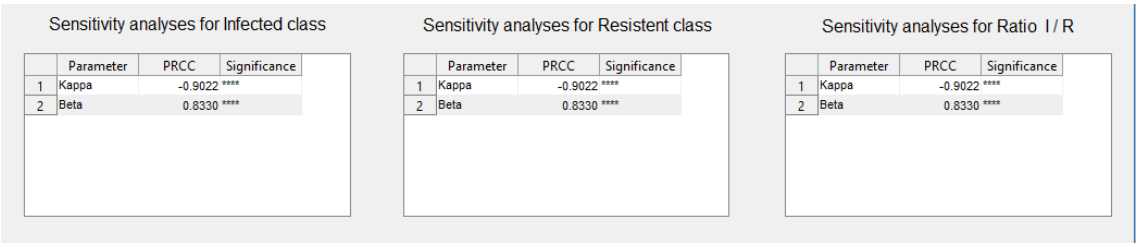

Figure 14: PRCC results of Uncertainty and Sensitivity analysis of infected (I), resistant (R) individuals and the ratio between I/R for strategy 3. The levels of significance for the analysis were represented by 0.001 (****), 0.01(***), 0.05 (**), and 0.1(*)

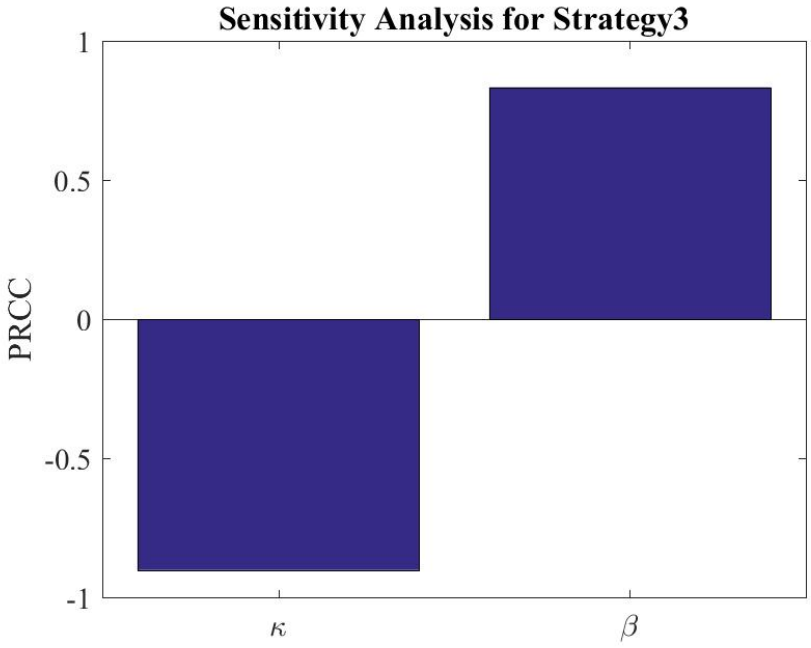

Figure 15: Plot of results to Sensitivity analysis on the strategy 3. β has a proportional influence but κ has inversely proportional influence on the outcome in this strategy.

Sensitivity analyses for Infected class

	Parameter	PRCC	Significance
1	Kappa	-0.9394	****
2	Beta	0.6641	****
3	Alpha	0.2628	**

Sensitivity analyses for Resistent class

	Parameter	PRCC	Significance
1	Kappa	-0.9394	****
2	Beta	0.6641	****
3	Alpha	0.2628	**

Sensitivity analyses for Ratio I / R

	Parameter	PRCC	Significance
1	Kappa	-0.9394	****
2	Beta	0.6641	****
3	Alpha	0.2628	**

Figure 16: PRCC results of Uncertainty and Sensitivity analysis for infected (I), resistant (R) populations and the ratio between I/R for strategy 4. The levels of significance for the analysis were represented by 0.001 (****), 0.01(***), 0.05 (**), and 0.1(*)

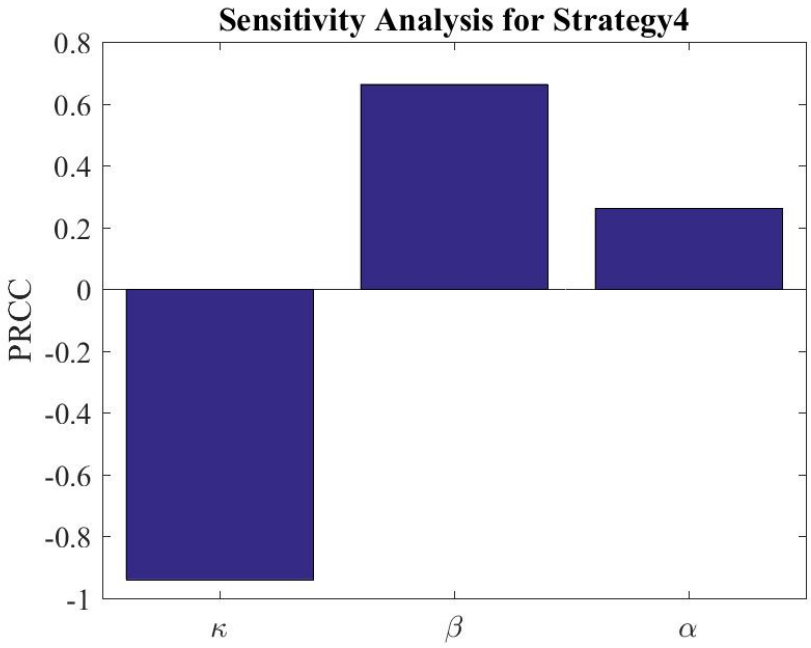

Figure 17: Plot of results to Sensitivity analysis on strategy 4. β and α have a proportional influence, but κ has inversely proportional influence on the outcome in this strategy.

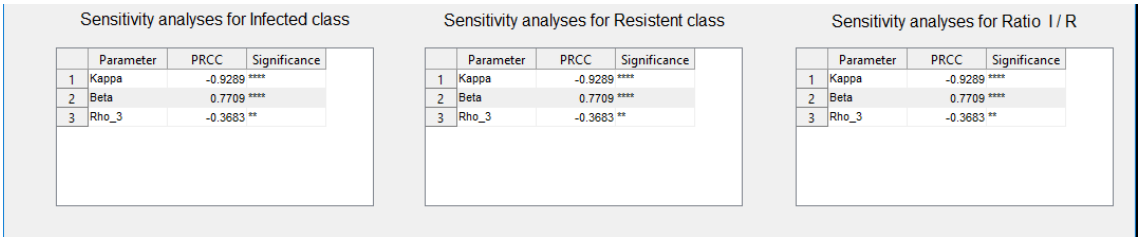

Figure 18: PRCC results of Uncertainty and Sensitivity analysis for infected (I), resistant (R) populations and the ratio between I/R for strategy 4. The levels of significance for the analysis were represented by 0.001 (****), 0.01(***), 0.05 (**), and 0.1(*)

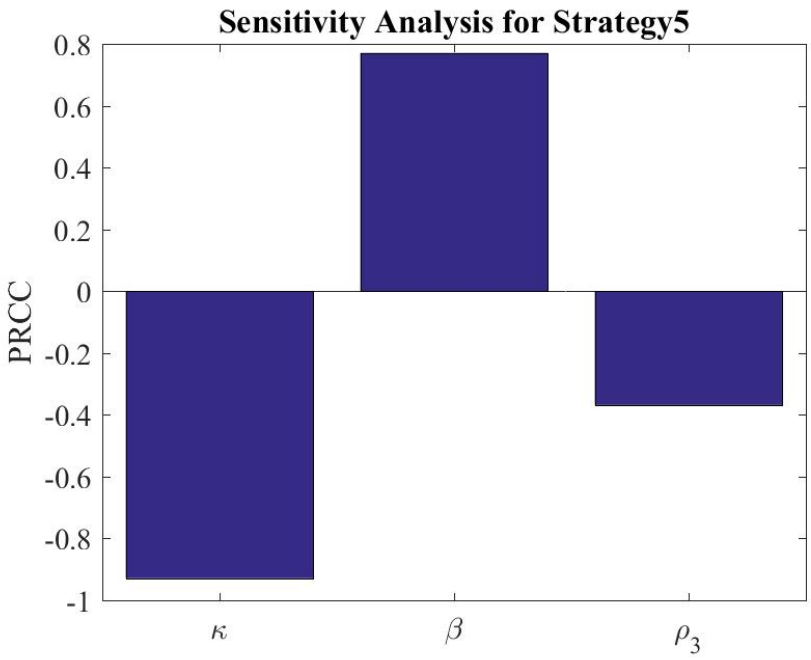

Figure 19: Plot of results to Sensitivity analysis on strategy 5. β and α have a proportional influence, but κ has inversely proportional influence on the outcome in this strategy.

6.2 Appendix B

Analyzing the effect of χ on the infected and resistant populations (strategies 1 and 4) shows an increase in the time at which the resistant population begins to grow proportional to the increase of χ . Also its should be noted that the maximum infected population is also delayed in the same way.

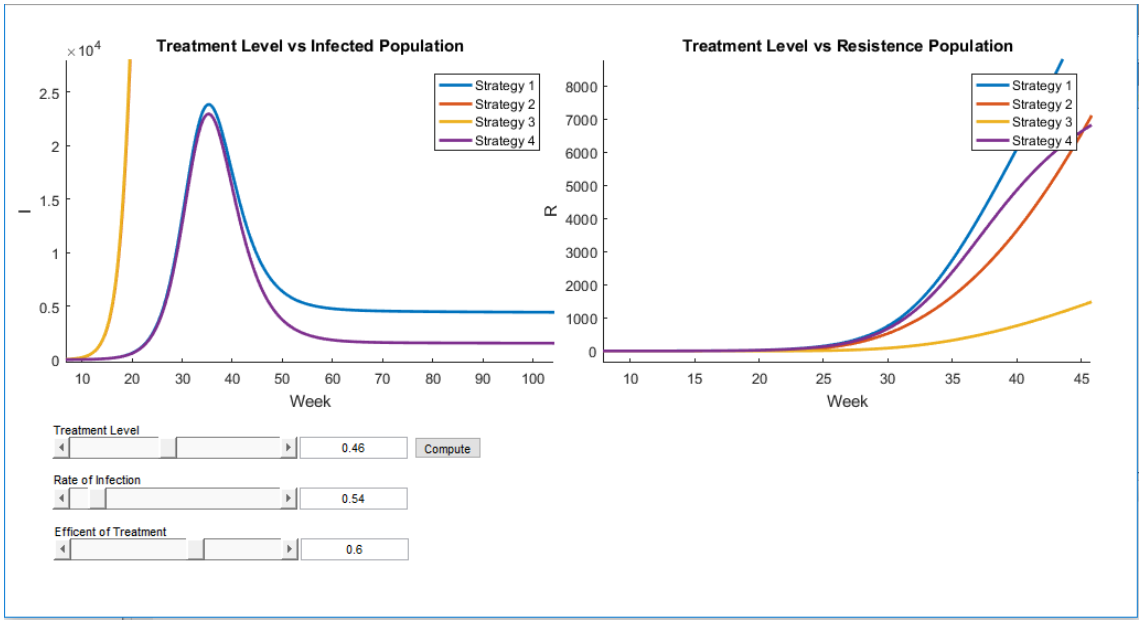

Figure 20: Effect of χ in the infected and resistant populations $\chi = 0.46$, Maximum Infected Population = 25,000 at 35 weeks. Onset of resistant population = 25 weeks.

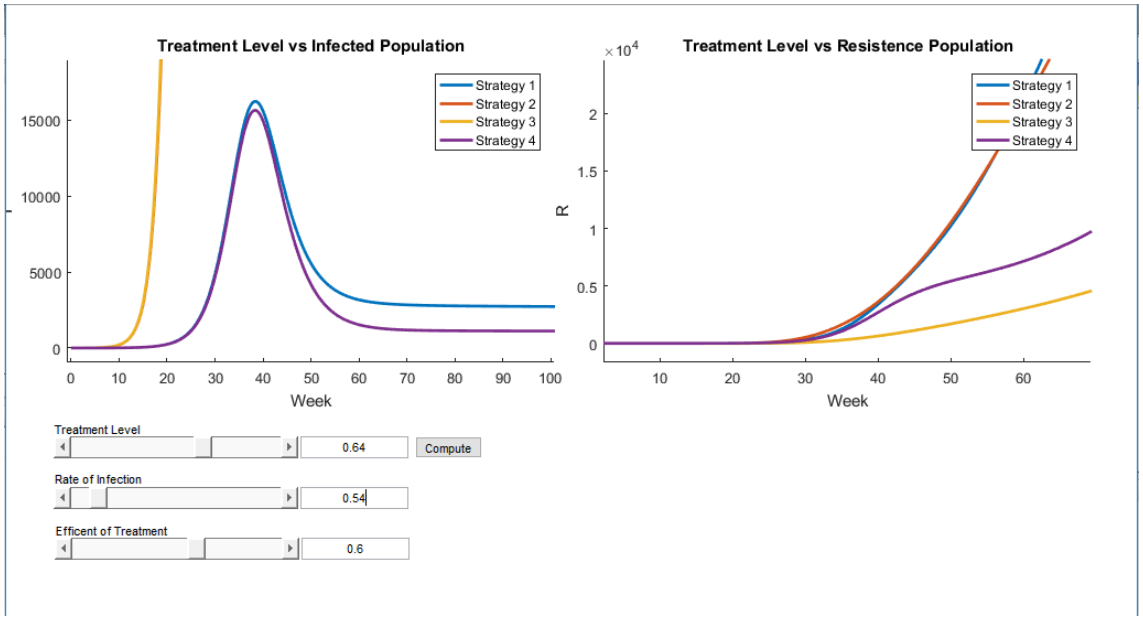

Figure 21: Effect of χ in the infected and resistant populations $\chi = 0.64$, Maximum Infected Population = 15,000 at 40 weeks. Onset of resistant population = 30 weeks.

6.3 Appendix C

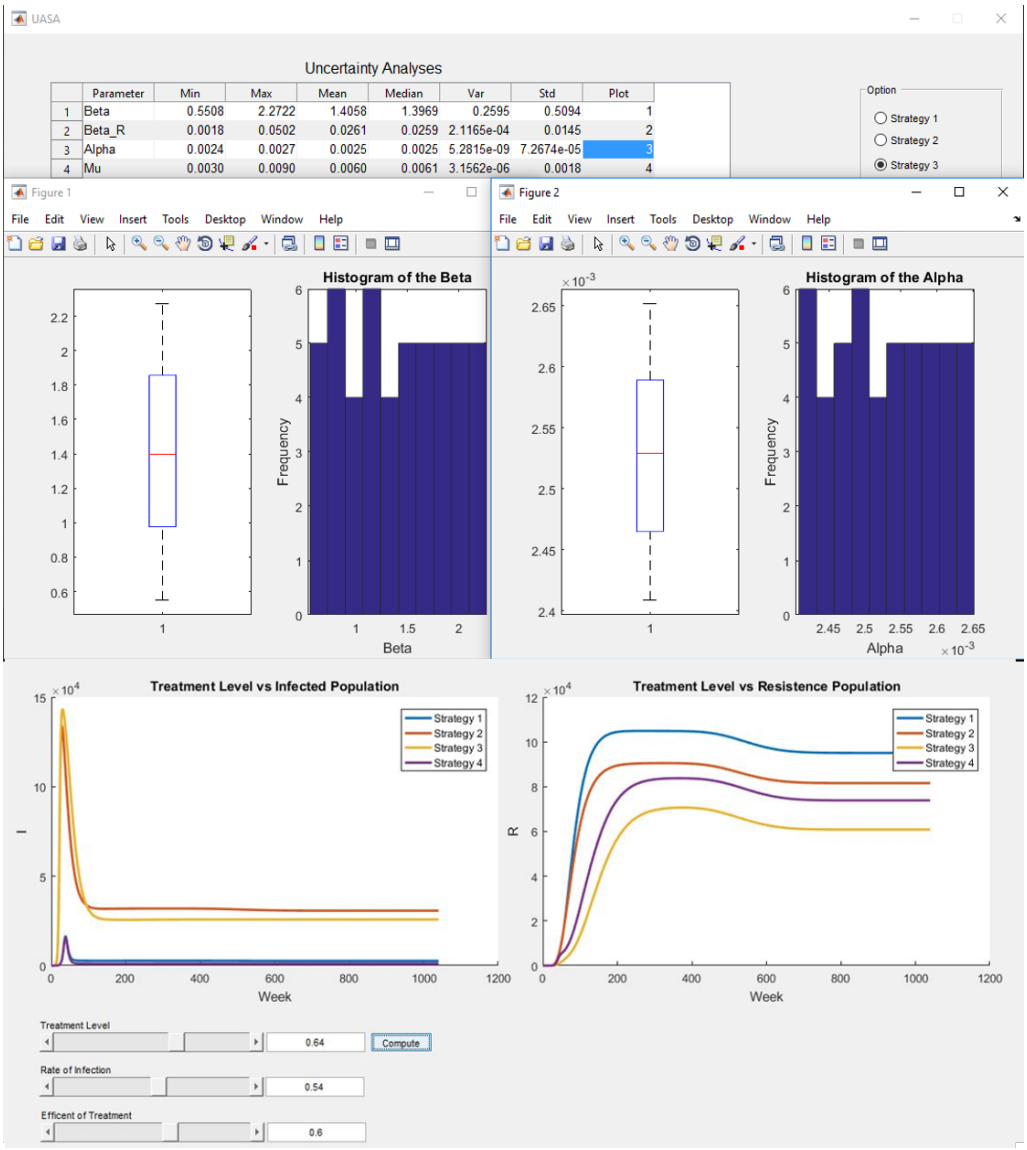

Figure 22: Graphic user interface develop for simulations and analysis of sensitivity and uncertainty to the model parameters.

6.4 Appendix D

Figure 23: Proportion of strategies 3 and 4 vs strategy 5 for β.

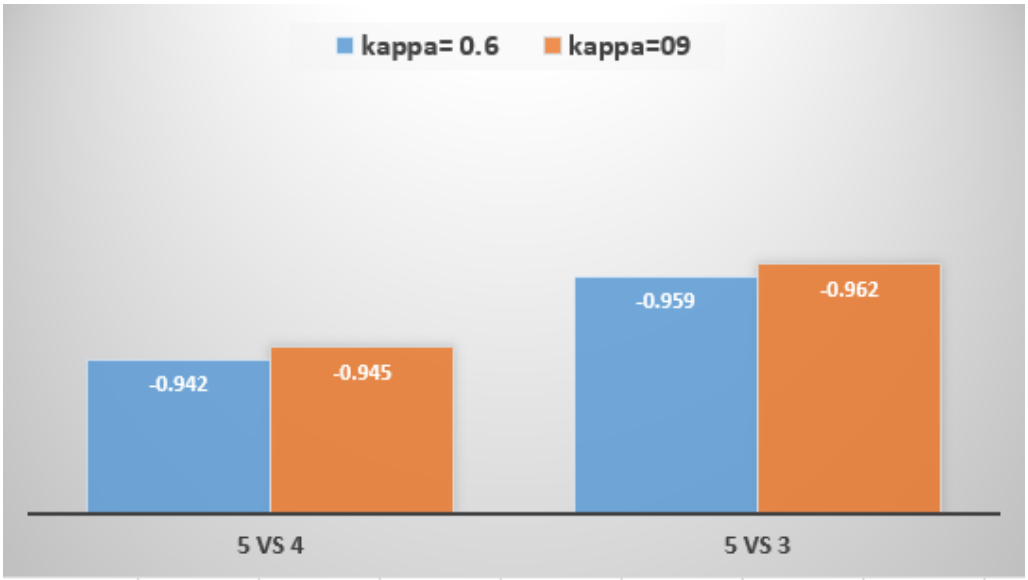

Figure 24: Proportion of strategies 3 and 4 vs strategy 5 for κ.

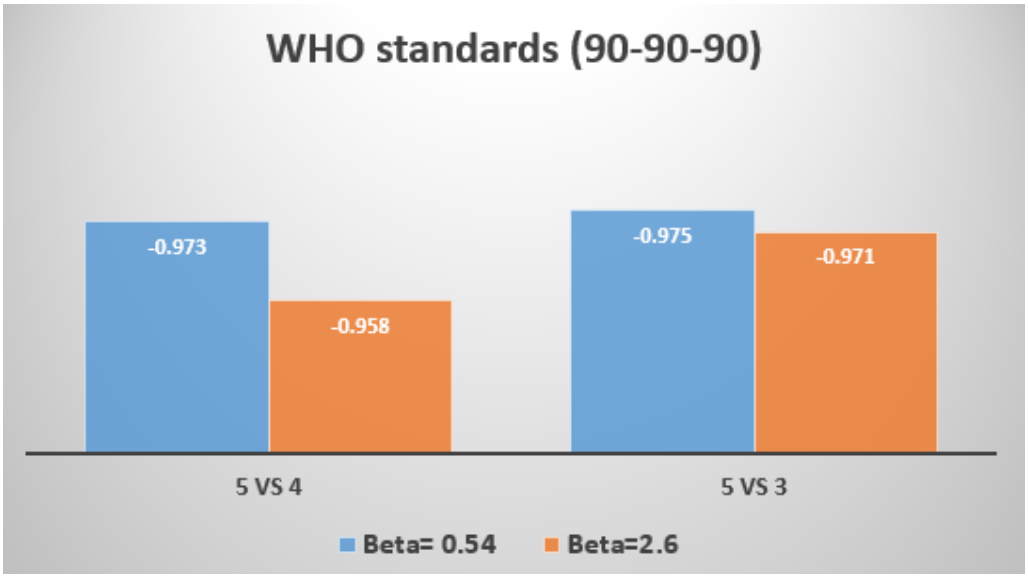

Figure 25: Proportion of strategies 3 and 4 vs strategy 5 under WHO standards (90-90-90) for β.

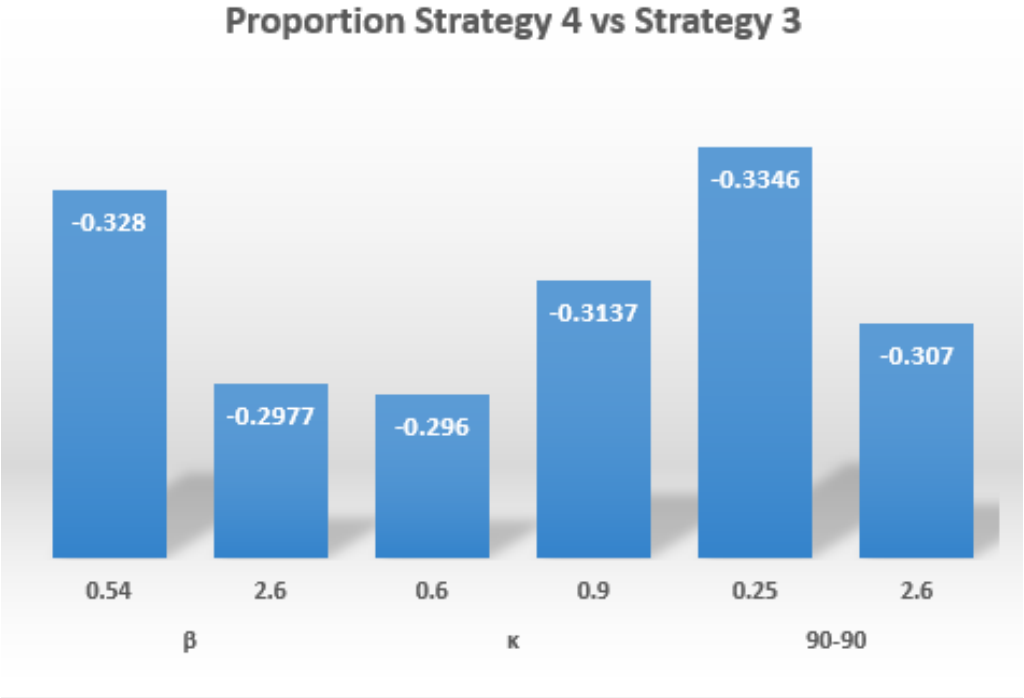

Figure 26: Ratio between strategy 4 and 3 for β, κ, and β under WHO standards.