ABSTRACT

ACQUESTA, ERIN CAROLYN SOLFIELL. Cost and Benefit Analysis of Vaccination Strategies for the HIV Virus. (Under the direction of Prof. Negash Medhin.)

For decades the human immunodeficiency virus (HIV), which left untreated leads to the acquired immunodeficiency syndrome (AIDS), has plagued societies from both developed and developing countries alike. Although there have been many successful intervention campaigns for controlling the spread of the infection the fight to eradicate the virus continues. As an important part of that fight, mathematical models of infectious diseases have been used to better understand the spread of infection from an epidemiological perspective, as well as for the purpose of analyzing the economic evaluation of intervention programs. An approach that is not commonly applied considers the results from the epidemiological analysis in the economic evaluation of intervention programs for the purpose of optimizing a strategy for intervention that will control the spread of infections. For the research presented, we will consider an existing HIV-transmission model, presented by Edwards *et al.* in the late 1990's, that evaluated the costs and benefits of vaccine programs. The original authors considered the economic evaluation of vaccines with varying efficacy and duration to determine a minimum requirement for each that will result with an outcome where the benefits, measured in quality-adjusted life years (QALYs), have a broader impact than the introduction of adverse effects. In our research we will build on Edwards *et al.*'s findings and consider optimizing a strategy for administering the vaccines in the event that both vaccines are available.

Considering the success that various HIV vaccines have had in clinical trials, scientist are very optimistic about the development of a vaccine in the future. This puts an emphasis on the importance for understanding further analysis regarding the cost and benefits of various vaccine programs, the impact that adverse effects can have, and the methods for comparing the benefits to competing intervention programs. Therefore, the current research will start on the path of exploring the epidemiological analysis of the HIV-transmission model with vaccine intervention programs for the purpose of understanding more about the impact the vaccines will have on controlling the spread of the virus. From a mathematical perspective this implies studying the properties of the dynamics governing the projections of the model for the equilibria and their stability. Then the consideration for how the vaccines are administered can be made in a way that will result with an efficient balance between the multiobjective optimization for minimizing monetary cost and increasing QALYs. To do so, we will utilize principles from optimal control theory and multiobjective optimization, then apply appropriate numerical methods to derive the solutions. Confirming that the result will generate a 'better' outcome will be done by comparing the cost-effective analysis to alternative strategies and evaluate that it will meet the appropriate

criterion for optimality from the principles defined by optimal control theory.

To conclude a well-rounded analysis of the infectious disease model, the use of the adjoint variable method will allow us to determine the impact that the variations in the parameters will have on results for the objective function. Then consideration for the impact that the most highly sensitive parameter will have on the outcome for the optimal intervention strategy is further explored.

The results of the research as a whole indicate the importance of analyzing the dynamics of an infectious disease model whenever the consideration for economic evaluation of intervention programs is made. This will give researchers a full picture of the impact each program will have on the spread of the infection, while highlighting primary areas of concern.

Cost and Benefit Analysis of Vaccination Strategies for the HIV Virus

by
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DEDICATION

- To my parents, Eline Whitehead and Warren Solfiell, for all of your love and support.

- To my maternal grandmother, Ernestene Young Christensen, seeing the strength and courage in you helped me find the courage to move 700 miles from home to pursue my PhD at North Carolina State University.

BIOGRAPHY

Written by: Kara Solfiell Otis

Erin Acquesta grew up in Union Springs, a small town in rural upstate New York, located on Cayuga Lake in the beautiful Finger Lakes region of the state. The second of three girls Erin developed a reputation in the family for being talkative and it was even suggested by her grandmother that she become a lawyer because she "liked to argue so much".

Taking her grandmothers advice Erin attended the National Youth Leadership Forum on Law in her senior year of high school where she unanimously won a debate with her position to defend the separation of church and state. Erin continued this path toward a career in law by taking criminal justice and debate classes in her freshman year of college at SUNY Albany. Interestingly, Erin was assigned the argument against the division of church and state in a debate and again won. The fact that she was able to effectively argue opposing sides of an issue did not make Erin feel victorious, it made her question the career path she had chosen. At nineteen years old Erin was unsettled with the subjectivity and ambiguity of the law and instead craved something with more clarity.

She left SUNY Albany and returned home to take time to reevaluate the direction of her education. In that year Erin recalled an influential teacher from high school. Mr. OLeary, a calculus instructor, always encouraged her to pursue a future in mathematics, seeing a natural talent in her. Erin returned to SUNY Albany to continue her education for two years before she transferred to Ithaca College, where her passion for the field of mathematics bloomed.

Under the advisement of Professor David Brown and Professor John Maceli in the math department of Ithaca College Erin decided to pursue her PhD in applied mathematics.

After researching programs across the country to find the right fit, Erin started her graduate career at North Carolina State University in the fall of 2006. In her time at NC State Erin has experienced an exponential growth in her passion for the rigorous methods of analysis that the field of mathematics provides, which will continue in her work at Sandia National Laboratories.

As a Senior Member of the Technical Staff, Mathematician, at Sandia National Laboratories, Erin will be addressing state of the art challenges in multi-dimensional data analysis; especially associated with populations of imagery, uncertainty quantification and propagation in advanced data analytics structures. In addition to the career path she has chosen, Erin will also continue to collaborate with others on infectious disease models for the economic evaluation of intervention strategies.

The pursuit of a PhD has been a very personal experience for Erin and she looks forward to the opportunity to apply this work in the next chapter of her career.

ACKNOWLEDGEMENTS

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Chapter 1

Introduction

For decades the human immunodeficiency virus (HIV), which left untreated leads to the acquired immunodeficiency syndrome (AIDS), has plagued societies from both developed and developing countries alike. According to the National Institute of Allergies and Infectious Diseases (NIAID), a component of the National Institute of Health (NIH), there are 50,000 new infections in the United States each year and over 34 million people worldwide currently living with HIV [40]. At the local, federal, and global levels, efforts have been made to both manage and treat those who are already infected as well as addressing ways to prevent new infections from occurring. Although researchers have been making significant progress in both areas, there is still much more that needs to be done in the fight against HIV and AIDS.

A key component to this fight is the use of mathematical modeling. For HIV research there are two primary types of models used. The first type of modeling, we will refer to as HIV-pathogen models, are used to interpret the interaction between the virus and the human immune system. Researchers will refer to this type of modeling when they are interested in understanding the immunology of the HIV virus as a pathogen [26]. The second type of modeling, is HIV-transmission models. These models interpret the likelihood that the virus will transfer from one individual to another. Researchers interested in understanding the epidemiology of the virus will refer to these types of models instead. The research we are presenting will focus on an HIV-transmission model. The purpose is to understand the impact that various intervention strategies will have on an infected society.

The model under consideration was developed, by Edwards *et al.* in the late 1990's, to determine what the expectations should be for both preventative and therapeutic vaccines to be considered cost-effective [13]. For the preventative vaccine the researchers allowed both the efficacy and duration of the vaccine to vary. This allowed them to evaluate the impact adverse effects could have on cost-effectiveness. For the therapeutic vaccine, the primary parameters were reduction to infectivity and duration in the asymptomatic phase of infection. They then

considered how cost-effective a therapeutic vaccine would be for various infectivity rates and duration.

The contributions we make to the existing model include the dynamical analysis of four variations of the model: ① the baseline HIV-transmission model without an intervention; ② the impact of a therapeutic vaccine only, ③ the impact of a preventative vaccine only; and ④ the analysis of the system when the combination of both vaccines is offered during the same time period. This leads to the consideration of optimizing an intervention strategy, related to the timing and duration for each, utilizing methods from control theory and multi-objective optimization. To evaluate the validity of the results from the analysis it is also necessary to address the sensitivity of the output relative to the parameters of the model.

The organization of the subsequent chapters will be as follows. In chapter 2 we offer more detail regarding the motivation for the current research, and provide the reader an understanding of the policies and prevention methods currently in place to reduce the number of new infections as well as manage the symptoms and infectivity of those already infected. Then in chapter 3, we give a full description of the model under consideration as it was defined by the original authors, along with the trajectories for each of the four possible state spaces of the model and the cost-effective analysis of each. This leads us to chapter 4, where we determine the physically relevant equilibria for each variation of the model and asses the stability for each using the Routh-Hurwitz criterion.

Once we have determined the cost-effective analysis for the three intervention strategies, as they relate to the baseline HIV-transmission model, as well as the dynamical analysis for each state space, we can consider methods for optimizing an intervention strategy. In chapter 5 we introduce fundamental definitions, concepts and principles of optimal control theory and multi-objective optimization, allowing us to structure a statement for the problem of optimizing an intervention strategy. This implies that numerical methods for solving fundamental optimal control problems can be applied to optimize an intervention strategy. While taking into consideration the physical boundaries of the model, including the implications for the solution that satisfies the optimality conditions we implement a direct numerical method that results in a locally optimal solution. If the solution satisfies the necessary conditions for optimality, we can then verify that the solution is also globally optimal. By comparing the results to the earlier cost-effective analysis, we can further validate the solution as a more cost-effective strategy.

Up to this point, all of the analysis applied to the HIV-transmission model under consideration took into account the assumptions for the parameters made by the original authors. In chapter 6, we consider the sensitivity of the output for the model relative to its parameters. Implementing the adjoint variable method for sensitivity analysis, we can quantify the impact variations that the parameters have on the objective function as it relates to each interpretation of the model. Comparing the results of the sensitivities for each of the model variations, we will

be able to evaluate the impact that variations from each of the parameters has on the overall solution to the optimal intervention strategy.

We conclude in chapter 7 with a summary for the research completed. Once we have completed the analysis of the HIV-transmission model and the optimization strategy, we will have insight into areas for future research.

Chapter 2

The Fight Against HIV and AIDS

Since the onset of the HIV/AIDS epidemic in the early 1980s efforts made by medical doctors, scientists, researchers, and policy makers in the fight against HIV and AIDS have led to a decrease in the number of new infections and an increase in life expectancy for those infected. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) 2015 Facts Sheet, there has been a 35% decrease in new infections since 2000 and a 42% decrease in AIDS related deaths since 2004 [41]. Between prevention programs and treatment therapies the epidemic has been on the decline for the last 10 to 15 years. Although there has been great success in combating the virus, experts believe that progress will need to continue through 2030 before we can expect to see an end to the HIV/AIDS epidemic. In joining the fight, we focus on analyzing a deterministic HIV-transmission model for the purpose of optimizing cost-effective intervention strategies with the intent to aid decision makers in allocating resources in an efficient manor.

2.1   Modeling the Spread and Control of Infectious Diseases

There are countless publications referencing mathematical modeling of infectious diseases. Some are written for the purpose of defining the standards of modeling infectious diseases as well as highlighting areas for development that will result with better accuracy [3, 4, 22, 26, 27]. Many more focus on a particular disease, offering methods for deriving thresholds that characterize conditions for model parameters that will result in an epidemic [2, 12, 37, 54, 38, 39]. This mostly refers to epidemic models, where the analysis is restricted to the projections for a single year [22]. The most notable development of analyzing epidemic models is known as the R_0 threshold. In epidemiological terms, R_0 defines the number of secondary infections expected for each infected individual. As an expression defined by the parameters of the model, mathematically R_0 is a bifurcation for which the stability of a disease-free equilibrium transfers to the endemic equilibrium [22]. If $R_0 < 1$, then the disease-free equilibrium is considered

asymptotically stable and the disease is not considered a threat to the population. Otherwise, when $R_0 > 1$ the endemic equilibrium is asymptotically stable and the disease is expected to persist, resulting with an epidemic and a need for controlling new infections.

To offer a more detailed description of the R_0 threshold we will introduce a simple SIR (Susceptible, Infected, Recovery) model and give a brief description for the mathematical analysis of the secondary infection rate, as it is presented by Hethcote in *The Mathematics of Infectious Diseases* [22]. Consider the following system of differential equations,

$$\frac{dS(t)}{dt} = \mu N - \mu S(t) - \beta \frac{I(t)S(t)}{N} \tag{2.1a}$$

$$\frac{dI(t)}{dt} = \beta \frac{I(t)S(t)}{N} - \gamma I(t) - \mu I(t) \tag{2.1b}$$

$$\frac{dR(t)}{dt} = \gamma I(t) - \mu R(t), \tag{2.1c}$$

where $S(t)$ is the number of susceptible individuals at time t, $I(t)$ is the number of infected individuals, $R(t)$ is the number of individuals who have recovered from infection, and $N = S(t) + I(t) + R(t)$ is the total population size. For the model described by (2.1) there is an assumption made that the inflow of newborns into the susceptible class, μN, is equal to the death rate for the total population, $\mu S(t)$, $\mu I(t)$ and $\mu R(t)$. This implies that the size of the total population is constant for all $t \geq 0$ and if we let $S(0) = S_0$, $I(0) = I_0$ and $R(0) = R_0$, then $N = S_0 + I_0 + R_0$ for $t \geq 0$. The parameter μ can be better described in terms of its reciprocal, where $1/\mu$ is the average life expectancy for the population. The number of new infections, $\beta I(t)S(t)/N$, can be described further in detail as the average number of contacts a susceptible individual has with the infected population, $\beta I(t)/N$, where β is the average number of adequate contacts. We will emphasize that in a more descriptive model the average number of adequate contacts is typically broken down further into two distinct parameters for infectivity separate from the number of contacts. For our current objective, to use the SIR model to briefly describe the R_0 threshold, assuming β to be the number of adequate contacts will be sufficient. The final component of the model, $\gamma I(t)$, is the rate at which infected individuals recover from the infection. As a more descriptive interpretation of the parameter γ, its reciprocal $1/\gamma$, represents the average infectious period.

To introduce the R_0 threshold, Hethcote choses to reduce the system of differential equations (2.1) by dividing the equations by N and only considering the dynamics for the resulting state space with $s(t)$ defining the proportion of the susceptible population at time t and $i(t)$ is the proportion of the infected population. Then we can assume the proportion of the population that has recovered is $r(t) = 1 - s(t) - i(t)$. Thus, the system of differential equations we will use to describe the secondary infection rate, R_0, that still holds all of the same properties as (2.1), is defined by

$$\frac{ds(t)}{dt} = \mu - \mu s(t) - \beta i(t)s(t) \tag{2.2a}$$

$$\frac{di(t)}{dt} = \beta i(t)s(t) - (\gamma i(t) + \mu)i(t), \tag{2.2b}$$

with the initial conditions $s(0) = s_0$ and $i(0) = i_0$. The two equilibria of system (2.2) are defined in terms of the parameters as the following,

$$(s_{df}, i_{df}) = (1, 0)$$

$$(s_e, i_e) = \left(\frac{(\mu + \gamma)}{\beta}, \frac{\mu(\beta - (\mu + \gamma))}{\beta(\mu + \gamma)} \right).$$

In epidemiological terms, (s_{df}, i_{df}) is the *disease-free equilibrium* and (s_e, i_e) is the *endemic equilibrium*. For this model we will not give the full analysis to derive R_0, instead we will present Hethcote's findings along with a brief examination of the properties of the equilibria with various parameter selections. For the infectious disease model, described by (2.2), the secondary infection rate is defined as

$$R_0 = \frac{\beta}{(\mu + \gamma)},$$

where $1/(\mu + \gamma)$ is described as the average death-adjusted infectious period. Therefore, if we reconsider the endemic equilibrium point for the system in terms of R_0 we get

$$(s_e, i_e) = \left(\frac{1}{R_0}, \frac{\mu(R_0 - 1)}{\beta} \right).$$

As we mentioned earlier, in mathematical terms the R_0 threshold defines a bifurcation at which the stability of the disease-free equilibrium transfers to the endemic equilibrium. To check that this condition is met we will make a couple of couple of parameter selections so that we can evaluate the stability for each equilibrium. The fixed assumptions we will make include the following: ① the average life expectancy is 60 years $(1/\mu = 60 \Rightarrow \mu = 1/60)$ and ② the average infectious period is 3 years $(1/\gamma = 3 \Rightarrow \gamma = 1/3)$. We will chose β to be defined such that $\beta = R_0(\mu + \gamma)$, allowing us to consider each case for $R_0 < 1$ and $R_0 > 1$. To determine the stability for each equilibria with particular parameter selections, we begin by linearizing system (2.2) to get the following Jacobian matrix,

$$J = \begin{bmatrix} -\beta i - \mu & -\beta s - \mu \\ \beta i & \beta s - (\mu + \gamma) \end{bmatrix}, \tag{2.3}$$

and the corresponding characteristic polynomial,

$$p(x) = x^2 + (\beta(i - s) + 2\mu + \gamma)x + (\beta i + \mu)((\mu + \gamma) - \beta s) - \beta i(\beta s + \mu). \qquad (2.4)$$

Thus, the roots of (2.4) can be solved at each of the equilibrium points, (s_{df}, i_{df}) and (s_e, i_e), giving us the eigenvalues for the system in a neighborhood of each equilibrium, which can then be used to determine their stability. Therefore when we check each case, $R_0 < 1$ and $R_0 > 1$, we will make the parameter selections such that $R_0 = 1 \pm \delta$ for $0 < \delta$. In table 2.1 we set $\delta = 0.001$ and evaluate the roots to the characteristic polynomial at each of the equilibrium points. From the choice of the δ in these two cases the results show a stable disease-free equilibrium when $R_0 < 1$ and a stable endemic equilibrium when $R_0 > 1$.

Table 2.1: Roots to the characteristic polynomial for an si infectious disease model for $R_0 < 1$ and $R_0 > 1$.

	$R_0 = 0.999$	$R_0 = 1.001$
(s_{df}, i_{df})	$x \approx -0.01667$ $x \approx -0.00035$	$x \approx -0.01667$ $x \approx 0.00035$
(s_e, i_e)	$x \approx -0.01701$ $x \approx 0.00036$	$x \approx -0.01631$ $x \approx -0.00037$

We will emphasize that the simple SIR model has been presented to give a sufficiently reasonable understanding for the R_0 threshold for those that may not be familiar with the mathematical analysis of infectious disease models. We will also note that, although a solution for an R_0 threshold cannot be evaluated for the model used in the current research, the importance for having a preliminary understanding is essential whenever the discussion of infectious disease models is presented from an epidemiological perspective.

In addition to the epidemiological implication of a virus, infectious disease models are also used quite extensively in the economic evaluation of intervention programs for controlling the spread of infectious diseases [2, 10, 12, 13, 14, 15, 20, 28, 50, 53]. For the past century the most successful means of controlling an infectious disease is by means of vaccinating [14]. Although vaccinations have controlled the spread of infectious diseases like influenza, pertussis and the human papillomavirus (HPV), to name a few, not all vaccines can be considered cost-effective.

This is where transmission models are useful in determining which ones are not before they are made available to the population. Taking into consideration the possibility of introducing adverse effects, analyzing the cost-effectiveness of new and emerging vaccines is essential in understanding when the benefits will out weigh the costs. To measure benefits of vaccinating, researcher use a utility assessment for each health status, as they relate to a particular infectious disease, known as quality-adjusted life years (QALYs) [45, 43]. The utility for each disease related health status is defined on an interval between 0 and 1, where 0 indicates death and the uninfected population will assume the value 1 since this is the standard of good health for which all other health status' will be measured against. After the introduction of QALYs in the 1970s they have become the most commonly used parameters for measuring the undesirable health consequences of acquiring an infection, allowing researchers a quantifiable means to measure the benefits as they relate to the human factor of vaccinating the population [45].

Of the publications referenced thus far only two address the implications that the epidemiological analysis has on optimizing intervention programs to control the spread of infections. Castillo-Chavez and Feng defined an age-structured model to determine an optimal vaccination strategy for a tuberculosis (TB) vaccine that determined the ideal age for which individuals should be vaccinated [12]. Alister *et al.* analyzed a standard susceptible, infected, recovery (SIT) model to evaluate optimal allocation of prevention and treatment resources for populations with and without mixing [2]. A similar method for optimizing a strategy was implemented in both cases. The group of researchers first determined the R_0 threshold for their model then used this as the objective to be minimized while considering constraints defined by the limited resources available to do so. By targeting the R_0 threshold to be minimized the conclusion that the optimal result will define the best control for reducing the spread of the infection is a direct result from the original interpretation of the dynamics. Although minimizing R_0 results with a reduction to the number of secondary infections it does not capture the full benefits of an intervention. Alister *et al.* addresses this fact when they consider sensitivity analysis and consider the alternative measure for QALYs gained. This leads to the possibility that optimization methods can be applied with the objective of maximizing QALYs, especially for models that do not define an R_0 threshold.

Today the means to controlling the spread of HIV does not include any form of vaccination, but progress is being made with regards to both preventative and therapeutic vaccine research. In anticipation for the future availability of a preventative vaccine and in consideration that current therapies for infected individuals offer similar benefits to that of a therapeutic vaccine, the research we will present in the subsequent chapters offers detailed analysis for an HIV-transmission model with vaccine intervention for the purpose of optimizing the timing of interventions.

2.2 Controlling the Spread of HIV

2.2.1 Preventative Vaccine Research and Current Prevention Programs

As the worlds leading researcher in HIV/AIDS, the NIH has sponsored over 80 clinical trials of more than 50 preventative vaccine candidates, both individually and in combination [1]. The vaccine known as RV144, the first to demonstrate modest prevention, is the most notable and only HIV vaccine tested in a Phase III clinical trial. Although the modest results were not sufficient to receive FDA approval for production to the general public, it did give researchers insight into developing a vaccine that one day will be. This led to HTVN 100, the latest preventative vaccine candidate currently in Phase I/II clinical trials in South Africa. Building from the successes of RV144 there is great anticipation that HVTN 100 will show more potential for preventing HIV infection.

In the meantime, in the absence of a preventative vaccine, policy makers have had to consider alternatives for preventing the spread of HIV. These efforts include screening for infected individuals, running HIV awareness campaigns, and early education programs. Noting again that there has been a decrease by 35% of new infections since 2000 implies these efforts have been effective, most notably in developed countries.

2.2.2 Therapeutic Vaccine Research and Antiretroviral Therapies

The prospects of developing a therapeutic vaccine have proven to be even more challenging than the preventative vaccine. By definition, a therapeutic vaccine is a treatment that is designed to stimulate the body's immune system for the purpose of controlling an infection. The problem with developing a therapeutic HIV vaccine relates to the virus' ability to hide in particular cells and going undetected for decades. By eluding researchers the development of a vaccine that produces an effective immune response has been close to impossible. This does not imply, however, that researchers have given up hope.

As an alternative to a therapeutic HIV vaccine the FDA has approved of more than 35 antiretroviral therapies. This form of treatment differs from a vaccine because they do not enhance the immune system for fighting the virus. Instead, an antiretroviral therapy suppresses the virus from replicating, thus mitigating the effects on the individuals system. Although the antiretroviral therapies can be reasonable responses to the infection, when only one treatment is administered the virus is capable of becoming immune. This leads to treatment plans known as highly active antiretroviral therapy (HAART). HAART is the combination of three or more drugs that can be used by newly infected individuals as well as patients with AIDS.

Chapter 3

HIV-Transmission Model with Vaccine Intervention Programs

The model that we will use as the focus of our analysis defines a deterministic compartmental model for HIV-transmission for the homosexual male population of San Francisco, CA during the early to mid 1990s [13]. Introduced by Edwards *et al.* in the late 1990s, the model was generated for the purpose of analyzing how cost-effective vaccine programs will be with varying efficacy and duration, resulting with minimal requirements each vaccine must meet to be considered a dominant program.

To begin the analysis of the model for the purpose of optimizing an intervention strategy we will introduce the HIV-transmission model with vaccine intervention in detail, then evaluate the short term projections for four variations of the model.

Table 3.1: HIV-transmission model with vaccine intervention programs: compartment classifications.

$Y_{i,j}(t)$	Disease Status, i	Vaccination Status, j
$Y_{0,0}(t)$	Susceptible	Unvaccinated
$Y_{0,1}(t)$		Vaccinated (Preventative)
$Y_{1,0}(t)$	Asymptomatic	Unvaccinated
$Y_{1,1}(t)$	Unaware	Vaccinated (Preventative)
$Y_{2,0}(t)$	Asymptomatic	Unvaccinated
$Y_{2,1}(t)$	Aware	Vaccinated (Therapeutic)
$Y_{3,0}(\text{t})$	Symptomatic	Unvaccinated
$Y_{4,0}(\text{t})$	AIDS	Unvaccinated

3.1 Model Description

The dynamics for HIV-transmission with vaccine intervention is given as the following system of ordinary differential equations:

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - \nu_p(t)Y_{0,0}(t) - \mu Y_{0,0}(t) - p_0\lambda(t)Y_{0,0}(t) + \omega Y_{0,1}(t)$$

$$\frac{dY_{0,1}(t)}{dt} = \nu_p(t)Y_{0,0}(t) - \mu Y_{0,1}(t) - \omega Y_{0,1}(t) - p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}(t)$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0\lambda(t)Y_{0,0}(t) - \sigma\xi Y_{1,0}(t) - \nu_p(t)Y_{1,0}(t) + \omega Y_{1,1}(t) - \mu_{1,0}Y_{1,0}(t) - \mu Y_{1,0}(t)$$

$$\frac{dY_{1,1}(t)}{dt} = p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}(t) + \nu_p(t)Y_{1,0}(t) - \omega Y_{1,1}(t) - \sigma\xi Y_{1,1}(t) - \mu_{1,1}Y_{1,1}(t) - \mu Y_{1,1}(t)$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) - \nu_t(t)Y_{2,0}(t) - \mu_{2,0}Y_{2,0}(t) - \mu Y_{2,0}(t)$$

$$\frac{dY_{2,1}(t)}{dt} = \nu_t(t)Y_{2,0}(t) - \mu_{2,1}Y_{2,1}(t) - \mu Y_{2,1}(t)$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{j=0}^{j=1}\sum_{i=1}^{i=2}\mu_{i,j}Y_{i,j}(t) - \mu_{3,0}Y_{3,0}(t) - \mu Y_{3,0}(t)$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - \mu_{4,0}Y_{4,0}(t) - \mu Y_{4,0}(t).$$

The initial population is distributed amongst the unvaccinated states according to the initial prevalence and the average duration for each stage of infection. Both vaccine programs will be initiated at time $t = 0$, therefore all three states related to the vaccinated populations are initially set to zero. This gives us the following initial populations for each compartment of the model,

$$Y_{0,0}(0) = (1 - \phi_0)Y_0$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{k=1}^{k=4}1/\mu_{k,0}}\phi_0 Y_0, \text{ for } i = 1,2,3,4$$

$$Y_{i,1}(0) = 0, \text{ for } i = 0,1,2,$$

such that $Y_0 = \sum_{i=0}^{i=4}Y_{i,0}(0)$ and denotes the total size of the initial population. The state variables $Y_{i,j}(t)$ represent the total population for each compartment of the model corresponding to a classification for disease status i and vaccination status j. Each of the 8 compartments of the model are defined in table 3.1. The fixed parameters, as well as the numerical assumptions for each, can be found in tables 3.2 and 3.3.

In the dynamics there are two distinct representation for the rate of infection. The first, $\lambda(t)$, relative to the likelihood an unvaccinated susceptible individual becomes infected and the

Table 3.2: HIV-transmission model with vaccine intervention programs: state dependent parameters and the numerical value for each.

State variable	Immigration $I_{i,0}$	Infectivity $\beta_{i,j}$	Mean duration of disease stage $1/\mu_{i,j}$ (years)	Contact rate p_i (per year)
$Y_{0,0}$	$0.9(\mu Y_0)$	-	-	2
$Y_{0,1}$	-	-	-	2
$Y_{1,0}$	$0.04(\mu Y_0)$	0.066	7.1	2
$Y_{1,1}$	-	0.066	7.1	2
$Y_{2,0}$	$0.04(\mu Y_0)$	0.066	8.1	2
$Y_{2,1}$	-	$(0.066\cdot(1-\beta_t))$ $0.25 \le \beta_t \le 0.9$	$(8.1+d_t)$ $5 \le d_t \le 20$	2
$Y_{3,0}$	$0.02(\mu Y_0)$	0.147	2.7	2
$Y_{4,0}$	-	0.147	2.1	0.667

Table 3.3: HIV-transmission model with vaccine intervention programs: state independent parameters and the numerical value for each.

Description	Parameter	Value
Percent of susceptible and asymptomatic-unaware populations that receives the preventative vaccine at time t	$\nu_p(t)$	0.75
Percent of the asymptomatic-aware population that receives the therapeutic vaccine at time t	$\nu_t(t)$	0.75
Initial size of total population	Y_0	$55,816$
Initial prevalence of the disease	ϕ_0	0.493
Non-AIDS-related annual death rate	μ	0.0222
Fraction of population screened annually for HIV	σ	0.15
True-positive rate of screening process	ξ	0.983
Efficacy of preventative vaccine	ε	$0.75 \le \varepsilon \le 0.9$
Mean duration, in years, of preventative vaccine	$1/\omega$	$10 \le 1/\omega \le 20$

second, $\lambda_\nu(t)$, for the likelihood a vaccinated susceptible individual will acquire the infection,

$$\lambda(t) = \frac{\sum_{j=0}^{j=1} \sum_{i=1}^{i=4} p_i \beta_{i,j} \eta_{00,ij} Y_{i,j}(t)}{\sum_{j=0}^{j=1} \sum_{i=0}^{i=4} p_i Y_{i,j}(t)} \quad \lambda_\nu(t) = \frac{\sum_{j=0}^{j=1} \sum_{i=1}^{i=4} p_i \beta_{i,j} \eta_{01,ij} Y_{i,j}(t)}{\sum_{j=0}^{j=1} \sum_{i=0}^{i=4} p_i Y_{i,j}(t)}.$$

As a means to model the adverse effects of vaccinating, Edwards *et al.* introduced an additional parameter $\eta_{\ell k,ij}$ defining the probability that a partnership, between an individual in disease status ℓ with vaccination status k and an individual in disease status i and vaccination status j, is not protected by a condom. Resulting with the distinction for the rate of infection between susceptible individuals who are not vaccinated and those that are. The adverse effect addressed by the model is the concern that vaccinated individuals will not practice the same precautions that unvaccinated individuals do, by assuming vaccinated individuals reduce their condom use by 25%. To emphasize the impact the individual behavioral changes will have on the partnerships that result in transmission of the disease, the authors started with the individuals probability for condom use $(h_{i,j})$ as they relate to each compartment of the model, presented in table 3.4. In defining $g_{\ell k,ij}$, the maximum of the two individuals probabilities for using a condom, $h_{\ell,k}$ and $h_{i,j}$ results with the probability that a condom is used in a partnership between an individual in disease status ℓ and vaccination status k with an individual in disease status i and vaccination status j,

$$g_{\ell k,ij} := \max(h_{\ell,k}, h_{i,j}).$$

Table 3.4: HIV-transmission model with vaccine intervention programs: individuals probability of using a condom.

	$Y_{0,0}$	$Y_{0,1}$	$Y_{1,0}$	$Y_{1,1}$	$Y_{2,0}$	$Y_{2,1}$	$Y_{3,0}$	$Y_{4,0}$
$h_{i,j}$	0.55	0.415	0.55	0.415	0.77	0.5775	0.85	0.85

Concluding with the probability that a partnership with a susceptible individual is not protected by a condom, $\eta_{00,ij}$ and $\eta_{01,ij}$, is the sum between the two mutually exclusive events that the partnership can result in transmission of the virus: ① the condom is used, but fails to work (which is assumed to occur 10% of the time); or ② a condom was not used at all. This description gives us the following expressions,

$$\eta_{0k,ij} := (0.1)g_{0k,ij} + (1 - g_{0k,ij}) \quad \text{for } k = 0, 1,$$

along with table 3.5 where the probability for each partnership has been calculated.

Table 3.5: HIV-transmission model with vaccine intervention programs: probability that a partnership is NOT protected by a condom.

	$Y_{0,0}$	$Y_{0,1}$	$Y_{1,0}$	$Y_{1,1}$	$Y_{2,0}$	$Y_{2,1}$	$Y_{3,0}$	$Y_{4,0}$
$Y_{0,0}$	0.505	0.505	0.505	0.505	0.307	0.4803	0.235	0.235
$Y_{0,1}$	0.505	0.6287	0.505	0.6287	0.307	0.4803	0.235	0.235

We will point out that the adverse effects of vaccinating is not simply restricted to susceptible population that is vaccinated. Notice that the probability that the partnership between a susceptible individual and an asymptomatic and aware individual is not protected by a condom increases when individuals from the asymptomatic and aware population become vaccinated, regardless of whether or not their susceptible partner has been vaccinated. Alternatively, the adverse effects for administering a preventative vaccine only occur when there is a partnership between an individual that has received the preventative vaccine with an individual that is unaware that they are infected with the virus. According to the calculations presented in table 3.5 we can see that the likelihood that the partnership between two individuals that are both susceptible and vaccinated also goes up, but since there is no danger of this contact resulting in a new infection it does not contribute to the adverse effects of vaccinating.

This concludes the introduction to the variable and parameter definitions of the HIV-transmission model with vaccine intervention programs and leads us to a brief description of the analysis presented by Edwards *et al.* to evaluate the cost-effectiveness of various vaccine programs; where analyzing the preventative vaccine independently from the therapeutic vaccine. For the preventative vaccine there are three parameters in the HIV-transmission model that relate directly to introducing the vaccine to the system: ① the percent of susceptible and unaware-asymptomatic populations that receive the vaccine at time t $(\nu_p(t))$; ② mean duration of the vaccine, in years, $(1/\omega)$; and ③ vaccine efficacy, (ε). The first of the three parameters was assumed to be fixed, while the focus of their analysis was to allow both duration and efficacy to vary. Similarly, the model introduces three therapeutic vaccine specific parameters: ① the percent of the aware-asymptomatic population that receives the vaccine at time t, $(\nu_t(t))$; ② average additional years added to the asymptomatic stage of the infection, $(1/\mu_\nu)$; and ③ change in infectivity $(1 - \beta_\nu)$. Again, the first of the three parameters was fixed and the other two were allowed to vary for evaluating the cost effective analysis for alternative therapeutic vaccine programs.

To evaluate the cost-effectiveness of each vaccine program two integral equations were defined. The first to quantify the expected accumulated cost, for both direct and indirect monetary costs. As well as a second integral equation to measure the accumulated QALYs over a specified time horizon,

$$C(T) = \int_0^T \left[\kappa_p \nu_p(t)(Y_{0,0}(t) + Y_{1,0}(t)) + \kappa_t \nu_t(t) Y_{2,0}(t) \right] e^{-rt} dt + \int_0^T \sum_{j=0}^{j=1} \sum_{i=0}^{i=4} c_i Y_{i,j} e^{-rt} dt$$

$$Q(T) = \int_0^T \sum_{j=0}^{j=1} \sum_{i=0}^{i=4} q_i Y_{i,j}(t) e^{-rt} dt.$$

This introduces additional parameters related to the costs and benefits of vaccinating that are presented and defined with their numerical values in table 3.6.

Table 3.6: HIV-transmission model with vaccine intervention programs: cost and benefit parameters and the numerical value for each.

Description	Parameter	Value
Per-person cost of preventative vaccine	κ_p	$\$1,000$
Per-person cost of therapeutic vaccine	κ_t	$\$1,000$
Annual discount rate	r	0.05
Time horizon	T	20
Average annual medical expenses:		
Susceptible population	c_0	$\$3,307$
Unaware-asymptomatic population	c_1	$\$5,467$
Aware-asymptomatic population	c_2	$\$5,467$
Symptomatic population	c_3	$\$12,586$
AIDS population	c_4	$\$35,394$
Quality-adjustment for a year of life:		
Susceptible population	q_0	1
Unaware-asymptomatic population	q_1	1
Aware-asymptomatic population	q_2	0.83
Symptomatic population	q_3	0.42
AIDS population	q_4	0.17

For the purposes of the research that we will present in the subsequent sections and the

following chapters we will consider only dominant vaccine programs. A *dominant vaccine program* is one that will save money and increases QALYs. The conclusion from the original authors analysis, on a 20 year time horizon, resulted with two cases that a preventative vaccine program is considered dominant: ① the efficacy of the vaccine is at least 75% and the mean duration is at least 10 years; or ② the efficacy is at least 50% and the mean duration is at least 50 years. With regards to the therapeutic vaccine program there are three cases that result with a dominant program: ① the vaccine adds at least 10 years to the asymptomatic stage of infection; ② the vaccine decreases infectivity by at least 50%; or ③ the vaccine adds at least 5 years to the asymptomatic stage of infection and decreases infectivity by at least 25%.

Based on these results we will make the following assumptions for the analysis regarding optimization for the timing of vaccine strategies that minimizes cost and maximizes QALYs.

Assumptions:

- 75% of the respective population will be vaccinated, whenever either vaccine is administered.

- The efficacy of the preventive vaccine is 75%.

- The mean duration of the preventative vaccine is 10 years.

- The therapeutic vaccine adds 5 years to the asymptomatic stage of the infection.

- The therapeutic vaccine reduces infectivity by 25%.

Thus, initiating our analysis of the model we begin by evaluating the projected outcomes and cost-effectiveness on a time horizon of 20 years for each variation of the model: ① the baseline HIV-transmission model without an intervention; ② the impact of a therapeutic vaccine only, ③ the impact of a preventative vaccine only; and ④ the analysis of the system when the combination of both vaccines is offered during the same time horizon. Then concluding the current chapter by comparing the results for each and determining which of the four alternatives is the most cost-effective.

3.1.1 HIV-Transmission Dynamics without an Intervention

To apply the cost-effective analysis for each of the vaccine programs we begin with introducing the baseline analysis for the system without an intervention. Removing all of the vaccine related compartments and parameters we have the following system of ordinary differential equations:

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\mu + p_0\lambda(t))Y_{0,0}(t) \tag{3.1a}$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0\lambda(t)Y_{0,0}(t) - (\sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) \tag{3.1b}$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi Y_{1,0}(t) - (\mu_{2,0} + \mu)Y_{2,0}(t) \tag{3.1c}$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{i=1}^{i=2}\mu_{i,0}Y_{i,0}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t) \tag{3.1d}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t), \tag{3.1e}$$

with the initial value

$$Y_{0,0}(0) = (1 - \phi_0)Y_0 \tag{3.2a}$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{k=1}^{k=4} 1/\mu_{k,0}}\phi_0 Y_0, \text{ for } i = 1, 2, 3, 4. \tag{3.2b}$$

Resulting with just one of the two rate of infection functions,

$$\lambda(t) = \frac{\sum_{i=1}^{i=4} p_i\beta_{i,0}\eta_{00,i0}Y_{i,0}(t)}{\sum_{i=0}^{i=4} p_iY_{i,0}(t)}, \tag{3.3}$$

and the integral functions for the accumulated cost and QALYs simplify to the following,

$$C(T) = \int_0^T \left(\sum_{i=0}^{i=4} c_iY_{i,0}(t)\right)e^{-rt}dt \tag{3.4a}$$

$$Q(T) = \int_0^T \left(\sum_{i=0}^{i=4} q_iY_{i,0}(t)\right)e^{-rt}dt. \tag{3.4b}$$

For the model without an intervention program we get a base understanding for the costs of doing nothing. The accumulated monetary cost, $C(T)$, represents the general medical expenses for the population as a whole. The accumulated QALYs, $Q(T)$, without an intervention present, gives us a projection for the quality of life for the total population if nothing is done to control the spread of infections.

To determine the expected cost for not implementing an intervention strategy we will turn to numerical solvers to evaluate the initial value problem and corresponding integrals. Setting up the problem in MatLab we add the two integrand expressions, (3.4a) and (3.4b), as additional equations to the system (3.1). By applying the second fundamental theorem of calculus, given $\left(\sum_{i=0}^{i=4} c_iY_{i,0}(t)\right)e^{-rt}$ and $\left(\sum_{i=0}^{i=4} q_iY_{i,0}(t)\right)e^{-rt}$ are each continuous on the open interval $(0, T)$,

for all $T > 0$, then the following holds true for any $t \in (0, T)$

$$\frac{dC(t)}{dt} = \Big(\sum_{i=0}^{i=4} c_i Y_{i,0}(t)\Big) e^{-rt} \tag{3.5a}$$

$$\frac{dQ(t)}{dt} = \Big(\sum_{i=0}^{i=4} q_i Y_{i,0}(t)\Big) e^{-rt}. \tag{3.5b}$$

By adding (3.5a) and (3.5b) to system (3.1) and setting $C(0) = Q(0) = 0$ we have the following initial value problem:

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\mu + p_0 \lambda(t)) Y_{0,0}(t) \tag{3.6a}$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0 \lambda(t) Y_{0,0}(t) - (\sigma\xi + \mu_{1,0} + \mu) Y_{1,0}(t) \tag{3.6b}$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi Y_{1,0}(t) - (\mu_{2,0} + \mu) Y_{2,0}(t) \tag{3.6c}$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{i=1}^{i=2} \mu_{i,0} Y_{i,0}(t) - (\mu_{3,0} + \mu) Y_{3,0}(t) \tag{3.6d}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0} Y_{3,0}(t) - (\mu_{4,0} + \mu) Y_{4,0}(t) \tag{3.6e}$$

$$\frac{dC(t)}{dt} = \Big(\sum_{i=0}^{i=4} c_i Y_{i,0}(t)\Big) e^{-rt} \tag{3.6f}$$

$$\frac{dQ(t)}{dt} = \Big(\sum_{i=0}^{i=4} q_i Y_{i,0}(t)\Big) e^{-rt}, \tag{3.6g}$$

with the initial values

$$Y_{0,0}(0) = (1 - \phi_0) Y_0 \tag{3.7a}$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{k=1}^{k=4} 1/\mu_{k,0}} \phi_0 Y_0, \text{ for } i = 1, 2, 3, 4 \tag{3.7b}$$

$$C(0) = 0 \tag{3.7c}$$

$$Q(0) = 0. \tag{3.7d}$$

Setting $T = 20$ and the parameters to their numerical values as they are defined in section 3.1 we applied the Runge-Kutta(4,5) algorithm using MatLab to generate the following projections. For the expected cost and accumulated QALYs when no intervention is introduced during a time horizon of 20 years we get the results presented in table 3.7. These values will be the bases from which we will measure any gains and losses that each intervention program is projected

to produce.

Table 3.7: Model without an intervention: expected accumulated cost and QALYs over a 20 year time horizon.

Monetary Cost, $C(20)$	Accumulated QALYs, $Q(20)$
$3,778,541,557	495,630

Evaluating accumulated cost and QALYs only gives us part of the story, without an intervention and an initial prevalence of 49.3%, over the course of 20 years, the total population is projected to drop from 55,816 to a population of 35,714. In addition, we can expect to see a drop in the prevalence of infection from 49.3% to 20%. Noting that the time horizon and the total expected duration of infection, $\sum_{k=1}^{k=4} 1/\mu_{k,0}$, are both equal to 20 years and the initial prevalence of the infection is 49.3% implies that at the end of only 20 years 49.3% of the initial population is expected to die from AIDS related causes. We point this out with the purpose of emphasizing the overall impact the infection has already had on the population. Alternatively, with constant immigration into both uninfected and infected states, the population is continually replenishing guaranteeing that a distribution to all compartments of the model exists for all time.

To get more detail about the mixing of the population, new infections, and the expected trajectories for each compartment of the model we now address the graphs showen in figure 3.2.
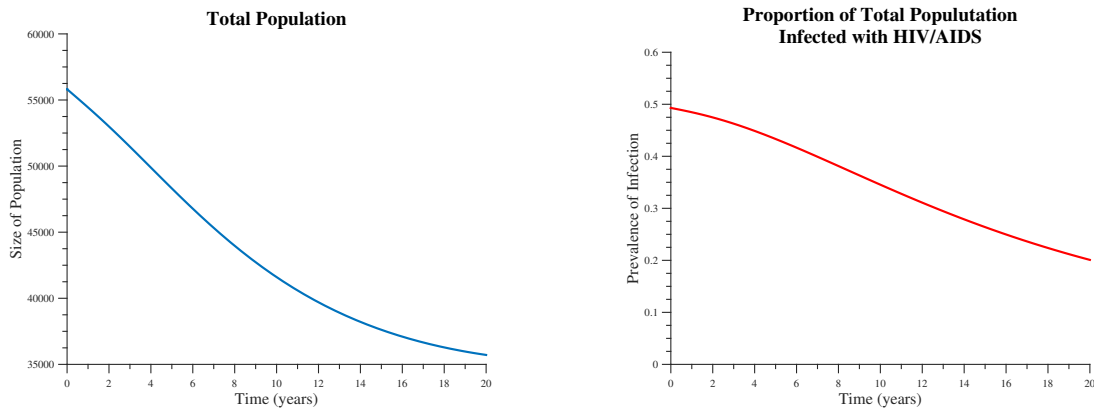
Figure 3.1: Model without an intervention: total population projections for a 20 year time horizon.

It is noted that each of the asymptomatic states are strictly decreasing, unlike the other three states where we see more interesting behavior. For the first 4-6 years both the symptomatic and AIDS populations are growing fairly consistently, while the susceptible population is strictly de-
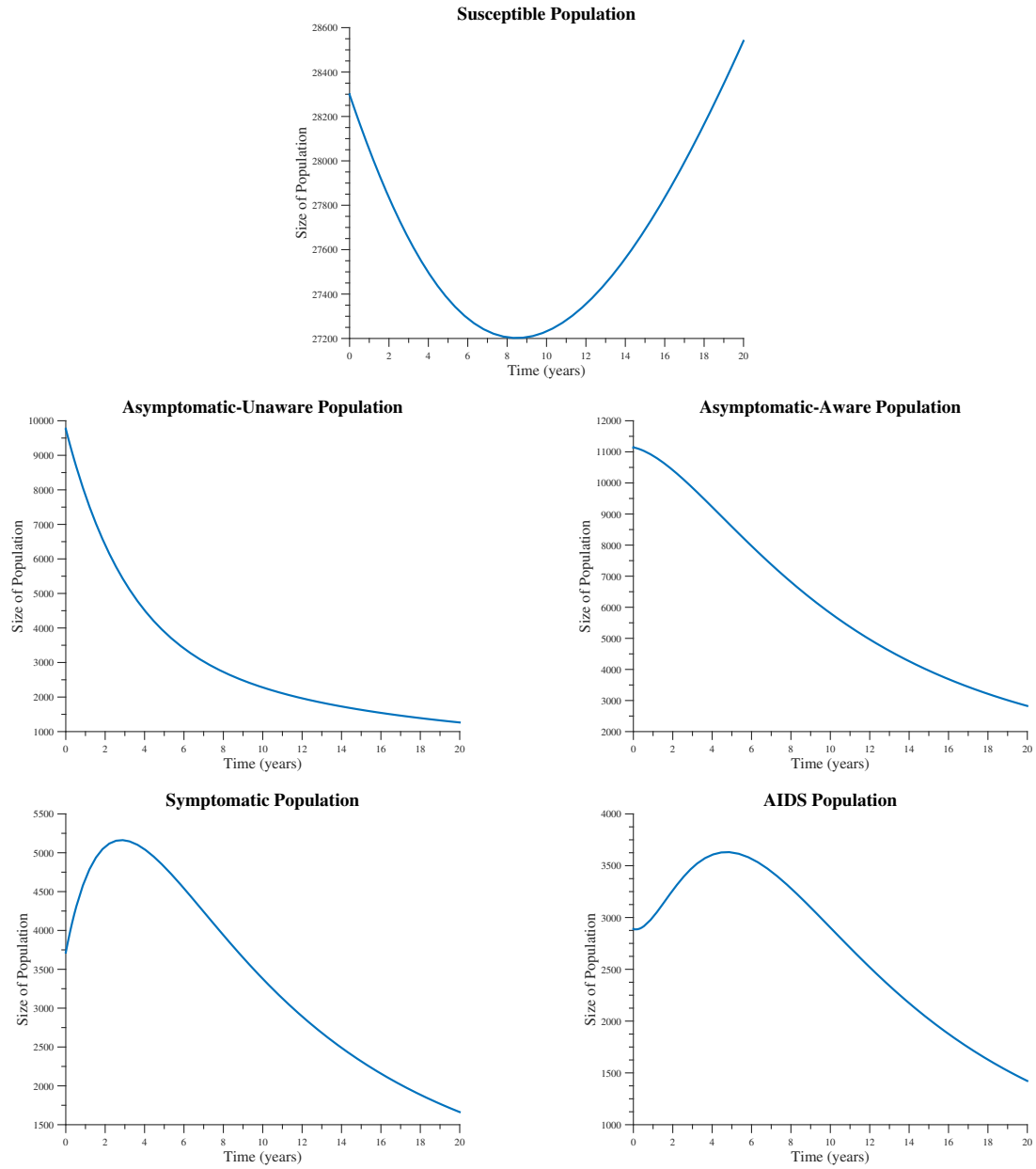
Figure 3.2: Model without an intervention: projections for each classe over a 20 year time horizon.

creasing. At the end of 6th year, even without an intervention, both the symptomatic and AIDS population start to decrease, which is due to the already decreasing asymptomatic populations. The impact the trajectories of the infectious states has on $\lambda(t)$, the probability of acquiring the infection at time t from any one partner, is shown in figure 3.3. Comparing the results for $\lambda(t)$ to the projections for the susceptible population, we can see that once the rate of infection drops below about .009 (less than a 1% chance of acquiring the infection) the susceptible population starts to increase. Even though it appears as though the system seems to correct itself, we need to keep in mind the major impact the disease has already had on the population. Recall, by the end of the 20 years, if nothing is done to intervene against the spread of the virus the population is expected to decrease by 36%, with at least 46% of the initial population passing away due to AIDS related causes.
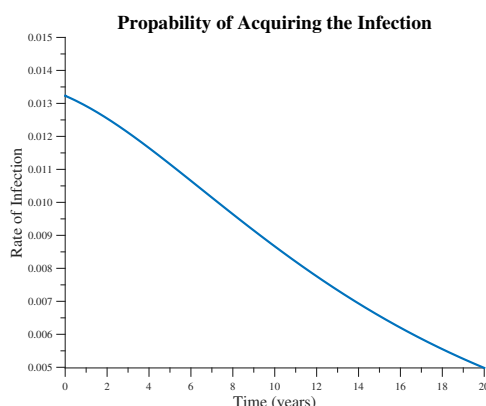
Figure 3.3: Model without an intervention: probability of acquiring the infection.

The results from analyzing the projections for the system without an intervention highlight the need for a program that will control the spread of HIV. In the subsequent sections of this chapter we will evaluate the predictions the model makes for each of the vaccine programs independently then as a combined strategy, allowing the comparison to the made between each alternative.

3.1.2   Therapeutic Vaccine Program

Introducing a vaccine program to the analysis of the model results in the addition of one state, $Y_{2,1}(t)$ representing the asymptomatic, aware and vaccinated population. Recall, from section 3.1 we made the assumption that a therapeutic vaccine is administered to 75% of the asymptomatic and aware population. Setting the percentage of the population that receives the

vaccine as a fixed parameter we will remove the time dependency from the notation, $\nu_t = \nu_t(t) = 0.75$ for all $t \in [0, 20]$. For those that receive the vaccine their infectivity will be reduced by 25% and an increase of 5 years added to the asymptomatic stage of the infection. By receiving the vaccine there is also the assumption that the likelihood partnerships with the susceptible population is not protected by a condom increases. After the vaccination wears off it is assumed that infected individuals will transfer directly to the symptomatic stage of the infection. This results with the following initial value problem governing the projections for each trajectory of the model:

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\mu + p_0\lambda(t))Y_{0,0}(t) \tag{3.8a}$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0\lambda(t)Y_{0,0}(t) - (\sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) \tag{3.8b}$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi Y_{1,0}(t) - (\nu_t + \mu_{2,0} + \mu)Y_{2,0}(t) \tag{3.8c}$$

$$\frac{dY_{2,1}(t)}{dt} = \nu_t Y_{2,0}(t) - (\mu_{2,1}(t) + \mu)Y_{2,1}(t) \tag{3.8d}$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{j=0}^{j=1}\sum_{i=1}^{i=2}\mu_{i,j}Y_{i,j}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t) \tag{3.8e}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t), \tag{3.8f}$$

with the initial values

$$Y_{0,0}(0) = (1 - \phi_0)Y_0 \tag{3.9a}$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{k=1}^{k=4} 1/\mu_{k,0}}\phi_0 Y_0, \text{ for } i = 1, 2, 3, 4, \tag{3.9b}$$

$$Y_{2,1}(0) = 0. \tag{3.9c}$$

We will now use the original expression for the rate of infection function that was introduced in the beginning of the chapter,

$$\lambda(t) = \frac{\sum_{j=0}^{j=1}\sum_{i=1}^{i=4} p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)}{\sum_{j=0}^{j=1}\sum_{i=0}^{i=4} p_iY_{i,j}(t)}. \tag{3.10}$$

Regarding the integral equations we will account for the additional cost of the therapeutic vaccine in the accumulated cost equation,

$$C(T) = \int_0^T \left(\kappa_t \nu_t Y_{2,0}(t) + \sum_{j=0}^{j=1} \sum_{i=0}^{i=4} c_i Y_{i,j}(t) \right) e^{-rt} dt \tag{3.11a}$$

$$Q(T) = \int_0^T \left(\sum_{i=0}^{i=4} q_i Y_{i,0}(t) \right) e^{-rt} dt. \tag{3.11b}$$

Following the approach we took for solving the state trajectories in addition to the accumulated cost and QALYs for the model without an intervention, we will add the corresponding expressions for $\dfrac{dC(t)}{dt}$ and $\dfrac{dQ(t)}{dt}$ to system (3.8), resulting with the following initial value problem:

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\mu + p_0 \lambda(t)) Y_{0,0}(t) \tag{3.12a}$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0 \lambda(t) Y_{0,0}(t) - (\sigma\xi + \mu_{1,0} + \mu) Y_{1,0}(t) \tag{3.12b}$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi Y_{1,0}(t) - (\nu_t + \mu_{2,0} + \mu) Y_{2,0}(t) \tag{3.12c}$$

$$\frac{dY_{2,1}(t)}{dt} = \nu_t Y_{2,0}(t) - (\mu_{2,1}(t) + \mu) Y_{2,1}(t) \tag{3.12d}$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{j=0}^{j=1} \sum_{i=1}^{i=2} \mu_{i,j} Y_{i,j}(t) - (\mu_{3,0} + \mu) Y_{3,0}(t) \tag{3.12e}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0} Y_{3,0}(t) - (\mu_{4,0} + \mu) Y_{4,0}(t) \tag{3.12f}$$

$$\frac{dC(t)}{dt} = \left(\kappa_t \nu_t Y_{2,0}(t) + \sum_{j=0}^{j=1} \sum_{i=0}^{i=4} c_i Y_{i,j}(t) \right) e^{-rt} \tag{3.12g}$$

$$\frac{dQ(t)}{dt} = \left(\sum_{i=0}^{i=4} q_i Y_{i,0}(t) \right) e^{-rt}, \tag{3.12h}$$

with the initial values,

$$Y_{0,0}(0) = (1 - \phi_0) Y_0 \tag{3.13a}$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{k=1}^{k=4} 1/\mu_{k,0}} \phi_0 Y_0, \text{ for } i = 1, 2, 3, 4 \tag{3.13b}$$

$$Y_{2,1}(0) = 0 \tag{3.13c}$$

$$C(0) = 0 \tag{3.13d}$$

$$Q(0) = 0. \tag{3.13e}$$

Setting $T = 20$ and the parameters as they are defined in section 3.1 we again used the

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Runge-Kutta(4,5) algorithm in MatLab to generate the following projections. In table 3.8 the outcomes related to the accumulated cost and QALYs for the therapeutic vaccine program are presented in comparison to the outcomes when no intervention is introduced. The results show a savings of $31,138,862 and an increase of 11,178 QALYs when the therapeutic vaccine program is offered. This confirms the conclusions of Edwards *et al.* that a therapeutic vaccine that decreases infectivity by 25% and prolongs the asymptomatic stage of infection by 5 years will result with a dominant program.

Table 3.8: Therapeutic vaccine program: expected accumulated cost and QALYs over a 20 year time horizon.

	No Intervention	Therapeutic Vaccine Program
Cost, $C(20)$	$3,778,541,557	$3,747,402,695
QALYs, $Q(20)$	495,630	506,808

Taking the analysis of the therapeutic vaccine program a step further we consider the projections for the population trajectories shown in figures 3.4 and 3.5. At the end of 20 years the total population is 37,218 with a 26% prevalence of the infected individuals. This is an increase in the size of the total population and prevalence of the infection compared to the results for the population over 20 years when no intervention is introduced. Intuitively a vaccine that decreases infectivity and prolonged life expectancy for the infected asymptomatic population benefits both
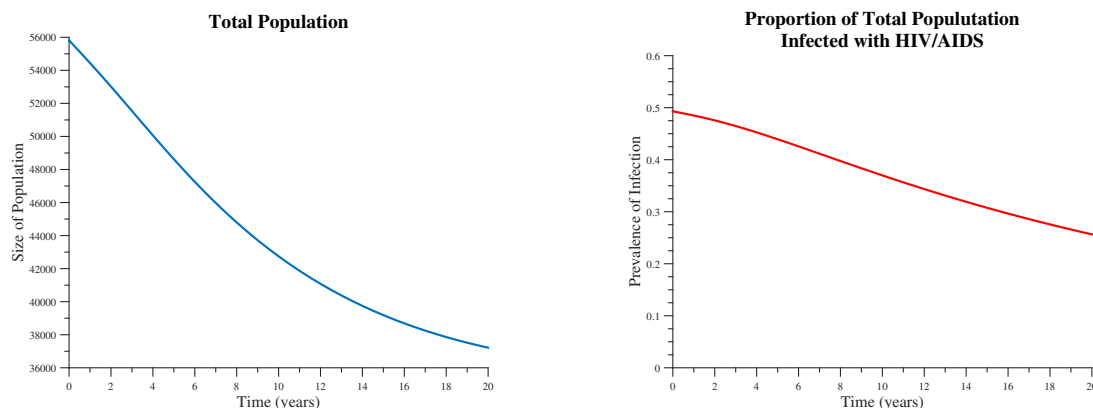
Figure 3.4: Therapeutic vaccine program: total population projections for a 20 year time horizon.

the susceptible and infected populations, but taking into consideration the adverse effects of vaccinating we find that the results of the therapeutic vaccine for the susceptible population are actually undesirable. This is apparent from the trajectory for the susceptible population presented in figure 3.5. After decreasing for the first 10 years the susceptible population starts to increase, but only recovering to about half the size of the initial susceptible population. For the projections when nothing was done to intervene with the spread of infections the susceptible population decreased for the first 9 years, then recovered to a susceptible population size larger than its initial population. Exploring the properties of the model a bit further to determine the impact the adverse effects has on the spread of the infection we will start by considering $\beta_{2,0}\eta_{00,20}$, representing the likelihood that an asymptomatic and aware individual infects a susceptible individual. Referencing tables 3.2 and 3.5, $\beta_{2,0} = 0.066$ and $\eta_{00,20} = 0.307$ resulting with $\beta_{2,0}\eta_{00,20} = 0.020262$. Implying there is approximately a 2% chance the disease will spread from partnerships between the asymptomatic, aware and unvaccinated population with the susceptible population. Alternatively, when an asymptomatic and aware individual receives the therapeutic vaccine their infectivity is reduced by 25%, resulting with $\beta_{2,1} = 0.066 * 0.75 = 0.0495$. From table 3.5 the probability that their partnerships with a susceptible individual is not protected by a condom was evaluated to be $\eta_{00,21} = 0.4803$. Therefore, $\beta_{2,1}\eta_{00,21} = 0.0495 * 0.4803 = 0.02377485$ which implies there is approximately a 2.38% chance that a susceptible individual will become infected by means of a partnership with an asymptomatic and aware individuals that have received the vaccination. Although the therapeutic vaccine reduces infectivity, the impact the adverse effect has on the population has a much greater impact. Resulting with an increase of 17.34% for the likelihood the asymptomatic and aware population will spread the infection after they become vaccinated. Not only does the introduction of the therapeutic vaccine increase the likelihood that the disease will spread, but it also extends the period of time for which this population is unknowingly more dangerous than they were before they were vaccinated. All of which resulting in an undesirable outcome for the susceptible population.

This leads us to considering the outcome for $\lambda(t)$ with the therapeutic vaccine program and how it relates to to the results when no intervention is introduced. Referring to figure 3.6, the graph of the function shows an initial increase to the probability of acquiring the infection when the therapeutic vaccine is first offered. This peak is directly attributed to the adverse effects that out weigh the benefits of vaccinating for reduction to infectivity. After the initial increase, the probability for the spread of infection begins to decline. In figure 3.7 we take the combined asymptomatic and aware population for the therapeutic vaccine program and compare it to the respective population for the projections when no intervention was introduced. In both cases we see the asymptomatic and aware population is strictly decreasing, offering the therapeutic vaccine only slows the rate at which it goes down. This defines the rather quick change in the

probability for acquiring the infection from increasing to decreasing.
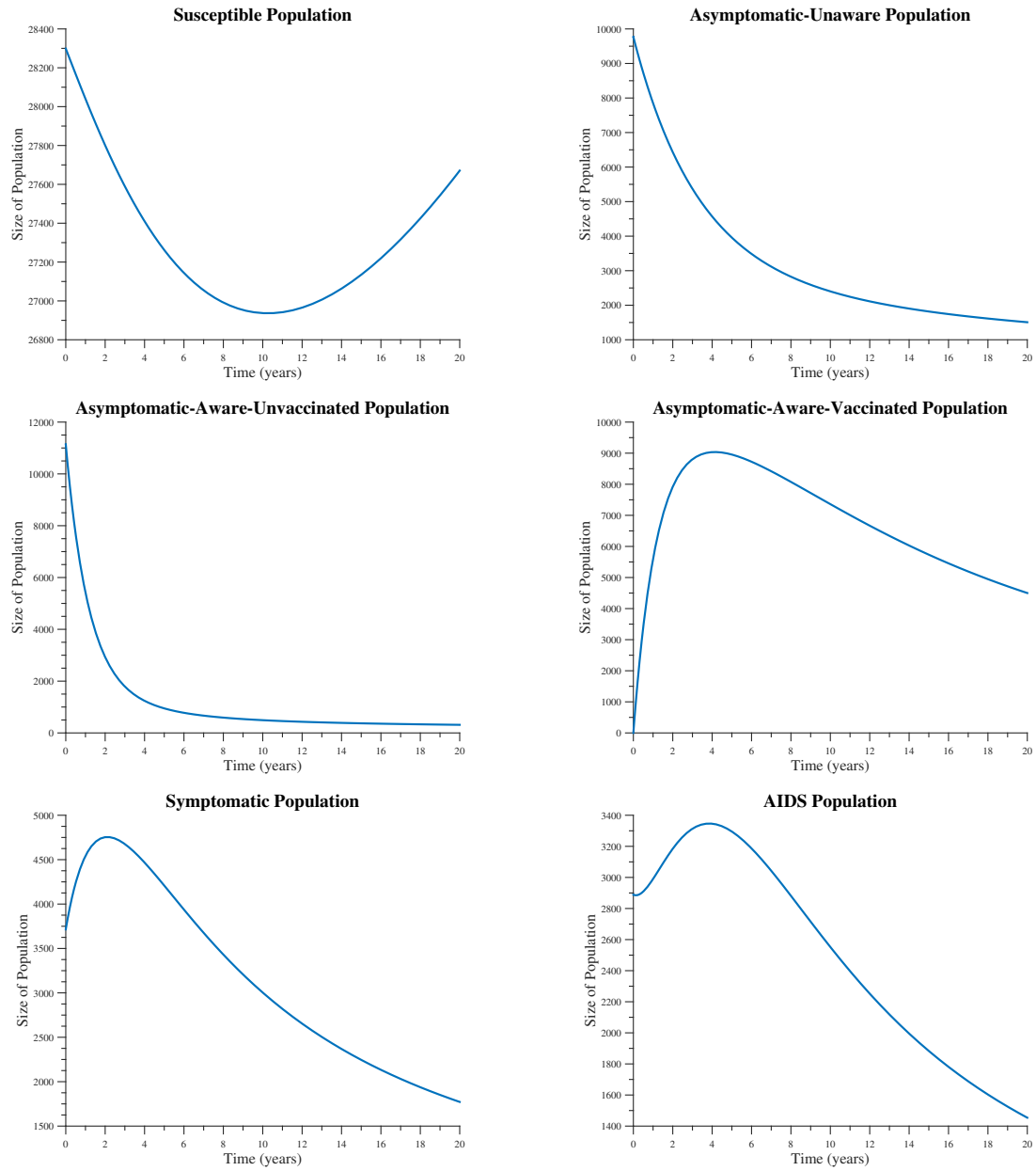
Figure 3.5: Therapeutic vaccine program: projections for each class over a 20 year time horizon.

| Therapeutic Vaccine Program | No Intervention Program |

Propability of Acquiring the Infection

Propability of Acquiring the Infection
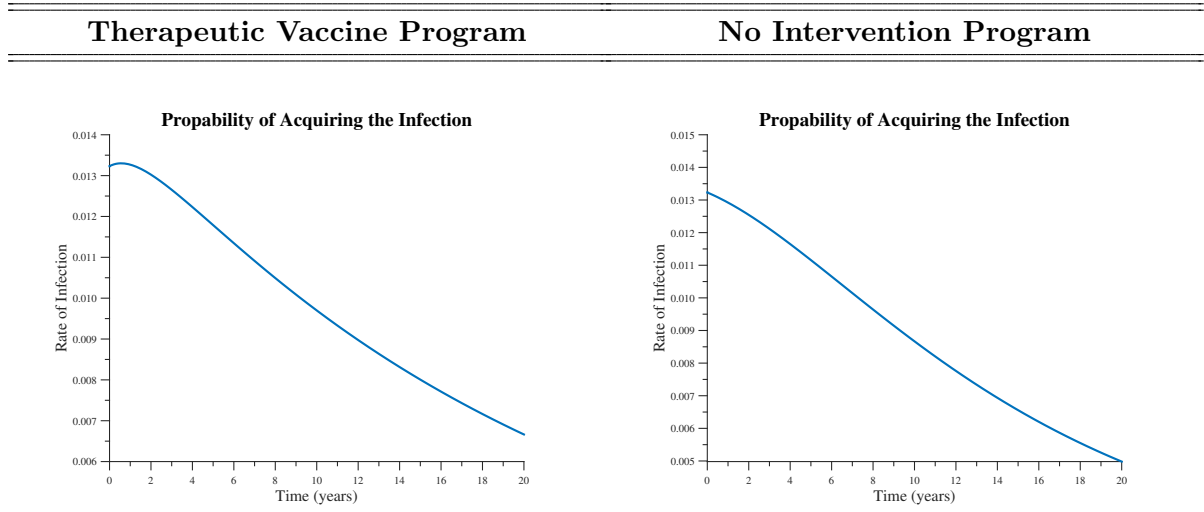
Figure 3.6: Therapeutic vaccine program: comparison for the rate of infection function with the projections found when no intervention was made.

| Therapeutic Vaccine Program | No Intervention Program |

**Asymptomatic-Aware Population
(Unvaccinated + Vaccinated)**

Asymptomatic-Aware Population
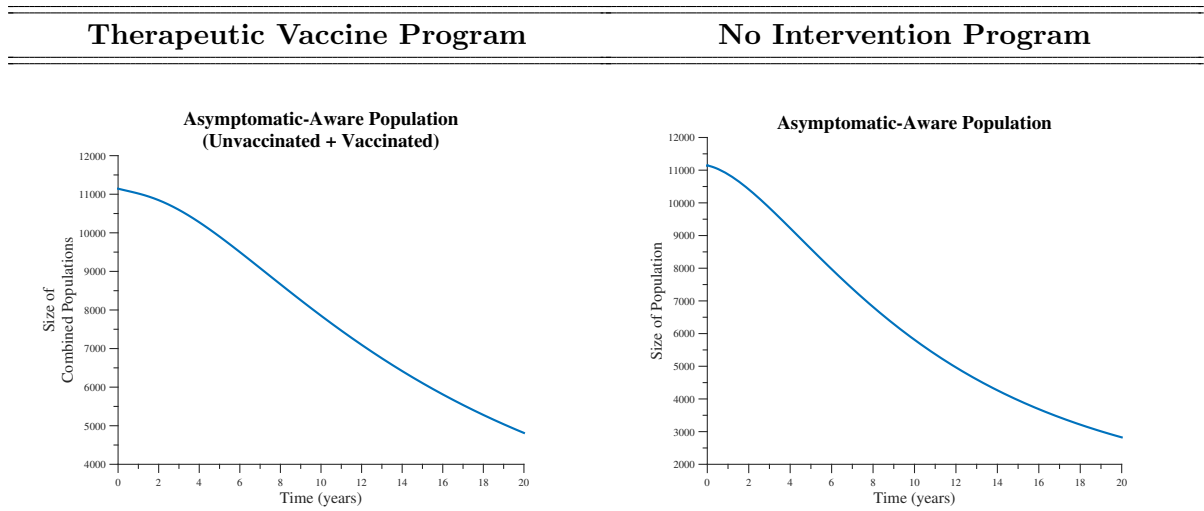
Figure 3.7: Therapeutic vaccine program: comparison for the total asymptomatic-aware population with the projections found when no intervention was made.

In conclusion, the therapeutic vaccine does offer a better cost-effective strategy in comparison to doing nothing for controlling the spread of the disease. Although, regarding the results we've seen for the susceptible population, it is not a desirable vaccine program for the total population.

3.1.3 Preventative Vaccine Program

Now we consider the analysis for the impact the preventative only vaccine program will have on the population and how it compares to the baseline analysis from section 3.1.1. In the beginning of this chapter we made the assumption that vaccines are administered to 75% of the population. By fixing the percentage of the population that receives the preventive vaccine we will remove the time dependency from the notation, $\nu_p = \nu_p(t) = 0.75$ for all $t \in [0, 20]$. Introducing the preventative vaccine to the system adds two additional states to the dynamics, the susceptible and vaccinated population $(Y_{0,1}(t))$ and the asymptomatic, unaware and vaccinated population $(Y_{1,1}(t))$. The dominant preventative vaccine program we chose to analyze has an efficacy of 75% and a mean duration of 10 years. Emphasizing that the vaccine is not 100% effective and a portion of the population being vaccinated are already infected results with the need for the second force of infection rate, $\lambda_\nu(t)$, which takes into account for the likelihood that vaccinated individuals reduce their condom use by 25%. Once the vaccine wears off the vaccinated populations return to their respective unvaccinated states. This results with the following initial value problem governing the projections for each trajectory of the model when only a preventative vaccine is administered:

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\nu_p + \mu + p_0\lambda(t))Y_{0,0}(t) + \omega Y_{0,1}(t) \tag{3.14a}$$

$$\frac{dY_{0,1}(t)}{dt} = \nu_p Y_{0,0}(t) - (\mu + \omega + p_0(1-\varepsilon)\lambda_\nu(t))Y_{0,1}(t) \tag{3.14b}$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0\lambda(t)Y_{0,0}(t) - (\sigma\xi + \nu_p + \mu_{1,0} + \mu)Y_{1,0}(t) + \omega Y_{1,1}(t) \tag{3.14c}$$

$$\frac{dY_{1,1}(t)}{dt} = p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}(t) + \nu_p Y_{1,0}(t) - (\omega + \sigma\xi + \mu_{1,1} + \mu)Y_{1,1}(t) \tag{3.14d}$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) - (\mu_{2,0} + \mu)Y_{2,0}(t) \tag{3.14e}$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{j=0}^{j=1}\sum_{i=1}^{i=2}\mu_{i,j}Y_{i,j}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t) \tag{3.14f}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t), \tag{3.14g}$$

with the initial values

$$Y_{0,0}(0) = (1 - \phi_0)Y_0 \tag{3.15a}$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{k=1}^{k=4} 1/\mu_{k,0}} \phi_0 Y_0, \text{ for } i = 1, 2, 3, 4 \tag{3.15b}$$

$$Y_{i,1}(0) = 0, \text{ for } i = 0, 1. \tag{3.15c}$$

We now have the representation for both rate of infection functions, $\lambda(t)$ defines the probability that a susceptible and unvaccinated individual becomes infected and $\lambda_\nu(t)$ defines that probability that a susceptible vaccinated individual will acquire the infection,

$$\lambda(t) = \frac{\sum_{j=0}^{j=1} \sum_{i=1}^{i=4} p_i \beta_{i,j} \eta_{00,ij} Y_{i,j}(t)}{\sum_{j=0}^{j=1} \sum_{i=0}^{i=4} p_i Y_{i,j}(t)} \tag{3.16a}$$

$$\lambda_\nu(t) = \frac{\sum_{j=0}^{j=1} \sum_{i=1}^{i=4} p_i \beta_{i,j} \eta_{01,ij} Y_{i,j}(t)}{\sum_{j=0}^{j=1} \sum_{i=0}^{i=4} p_i Y_{i,j}(t)}. \tag{3.16b}$$

Accounting for the additional cost for the preventative vaccine in the accumulated cost equation we have the following two integral functions,

$$C(T) = \int_0^T \left(\kappa_p \nu_p (Y_{0,0}(t) + Y_{1,0}(t)) + \sum_{j=0}^{j=1} \sum_{i=0}^{i=4} c_i Y_{i,j}(t) \right) e^{-rt} dt \tag{3.17a}$$

$$Q(T) = \int_0^T \left(\sum_{j=0}^{j=1} \sum_{i=0}^{i=4} q_i Y_{i,j}(t) \right) e^{-rt} dt. \tag{3.17b}$$

Following the same method used in the analysis for the model without an intervention and the therapeutic vaccine strategy we will again add $\dfrac{dC(t)}{dt}$ and $\dfrac{dQ(t)}{dt}$ to the dynamics to give us the following initial value problem we will solve using numerical methods:

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\nu_p + \mu + p_0 \lambda(t))Y_{0,0}(t) + \omega Y_{0,1}(t) \tag{3.18a}$$

$$\frac{dY_{0,1}(t)}{dt} = \nu_p Y_{0,0}(t) - (\mu + \omega + p_0(1-\varepsilon)\lambda_\nu(t))Y_{0,1}(t) \tag{3.18b}$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0 \lambda(t)Y_{0,0}(t) - (\sigma\xi + \nu_p + \mu_{1,0} + \mu)Y_{1,0}(t) + \omega Y_{1,1}(t) \tag{3.18c}$$

$$\frac{dY_{1,1}(t)}{dt} = p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}(t) + \nu_p Y_{1,0}(t) - (\omega + \sigma\xi + \mu_{1,1} + \mu)Y_{1,1}(t) \tag{3.18d}$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) - (\mu_{2,0} + \mu)Y_{2,0}(t) \tag{3.18e}$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{j=0}^{j=1} \sum_{i=1}^{i=2} \mu_{i,j} Y_{i,j}(t) - (\mu_{3,0} + \mu) Y_{3,0}(t) \tag{3.18f}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0} Y_{3,0}(t) - (\mu_{4,0} + \mu) Y_{4,0}(t) \tag{3.18g}$$

$$\frac{dC(t)}{dt} = \Big(\kappa_p \nu_p (Y_{0,0}(t) + Y_{1,0}(t)) + \sum_{j=0}^{j=1} \sum_{i=0}^{i=4} c_i Y_{i,j}(t)\Big) e^{-rt} \tag{3.18h}$$

$$\frac{dQ(t)}{dt} = \Big(\sum_{j=0}^{j=1} \sum_{i=0}^{i=4} q_i Y_{i,j}(t)\Big) e^{-rt}, \tag{3.18i}$$

with the initial values

$$Y_{0,0}(0) = (1 - \phi_0) Y_0 \tag{3.19a}$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{k=1}^{k=4} 1/\mu_{k,0}} \phi_0 Y_0, \text{ for } i = 1,2,3,4 \tag{3.19b}$$

$$Y_{i,1}(0) = 0, \text{ for } i = 0,1 \tag{3.19c}$$

$$C(0) = 0 \tag{3.19d}$$

$$Q(0) = 0. \tag{3.19e}$$

Applying the Runge-Kutta(4,5) algorithm, using Matlab, we get the following projections for the current model.

Table 3.9: Preventative vaccine program: expected accumulated cost and QALYs over a 20 year time horizon.

	No Intervention	Preventative Vaccine Program
Cost, $C(20)$	$3,778,541,557	$3,711,111,604
QALYs, $Q(20)$	495,630	508,220

From the projections of the dominant preventative vaccine program we see a reduction to cost by $67,429,953 and an increase to QALYs by an additional 12,590. For the population as whole, at the end of 20 years, the size of the population drops to 37,862 with 12% prevalence of the infection.

The impact that the preventative vaccine has on the population is apparent by the drastic drop in the prevalence of the infection compared to the initial prevalence of 49.3%, the resulting

Total Population / **Proportion of Total Populutation Infected with HIV/AIDS**
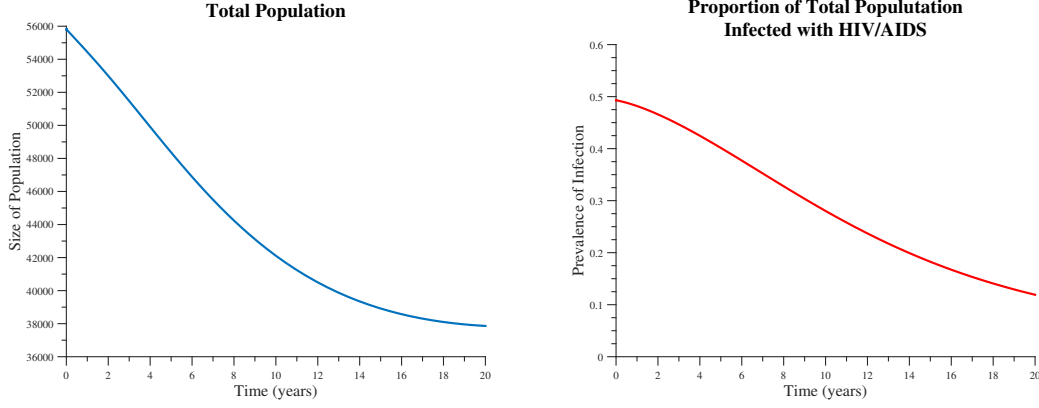
Figure 3.8: Preventative vaccine program: total population projections for a 20 year time horizon.

prevalence from the therapeutic vaccine program, 26%, and the prevalence of infection from the model without an intervention at the end of 20 years, 20%. For the terminal size of the total population we still have a result below 38,000, which can again be attributed to the fact that the mean total duration of infection is equal to the time horizon of 20 years. This implies the total initial population of infected individuals are expected to die due to AIDS related causes before the end of the 20 years. Although the preventative vaccine has been shown to have a major impact on controlling the spread of the virus, it lacks in consideration for benefiting those that are already infected.

Considering the impact these results have on the projections for both rate of infection functions we refer to figure 3.10 where we compare the the results from the preventative vaccine program to the results we found when we analyzed the system without an intervention. The impact the adverse effect of vaccinating has on the over all spread of the infection is over shadowed by the efficacy of vaccinating. For the unvaccinated population the rate of infection, $\lambda(t)$, for the preventative vaccine program is closely related to the projections for $\lambda(t)$ when no intervention is offered. Alternatively, $(1 - \varepsilon)\lambda_\nu(t)$, the probability of acquiring the infection for the susceptible and vaccinated population, is significantly lower than the projections made for unvaccinated susceptible population. This results with projections for the combined susceptible population to only drop very subtly for the first year then strictly increase for the rest of the time horizon. The asymptomatic and unaware population, as a whole, follows a similar trajectory as the system when no intervention is present with the exception that there is greater decline to the population when a preventative vaccine program is administered.

31
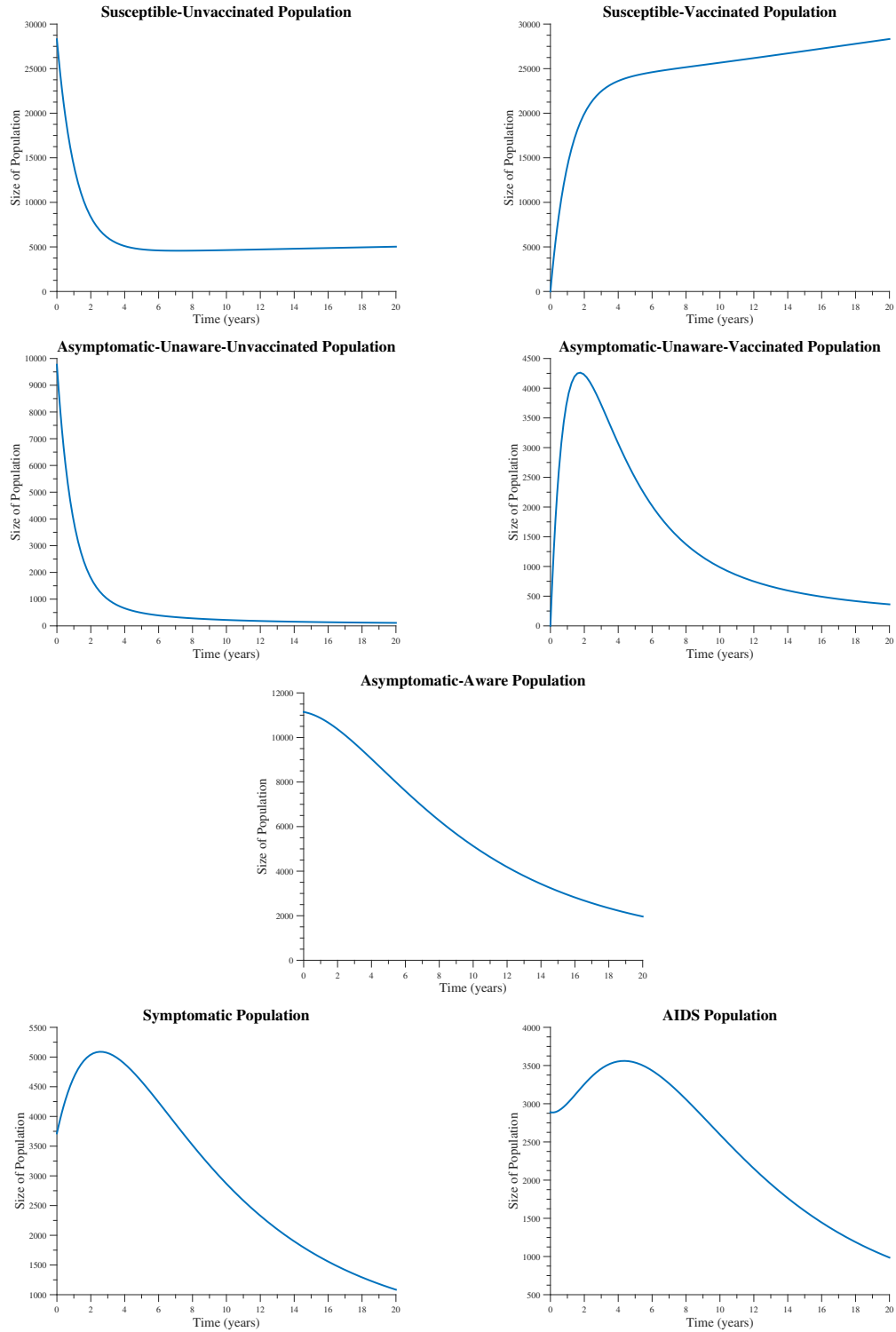
Figure 3.9: Preventative vaccine program: projections for each class over a 20 year time horizon.

Preventative Vaccine Program

Propability of Acquiring the Infection
Unvaccinated Susceptible Population

Propability of Acquiring the Infection
Vaccinated Susceptible Population
(Accounting for the Efficacy of Vaccinating)

No Intervention
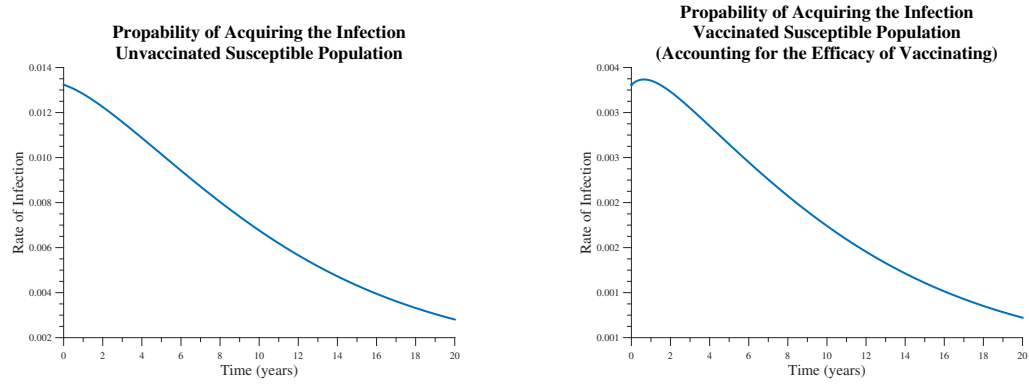
Propability of Acquiring the Infection
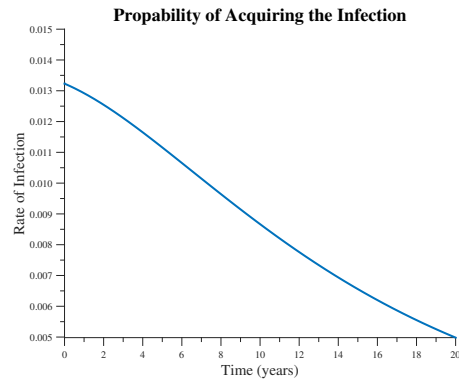
Figure 3.10: Preventative vaccine program: comparison for the rate of infection functions with the projections found when no intervention was made.
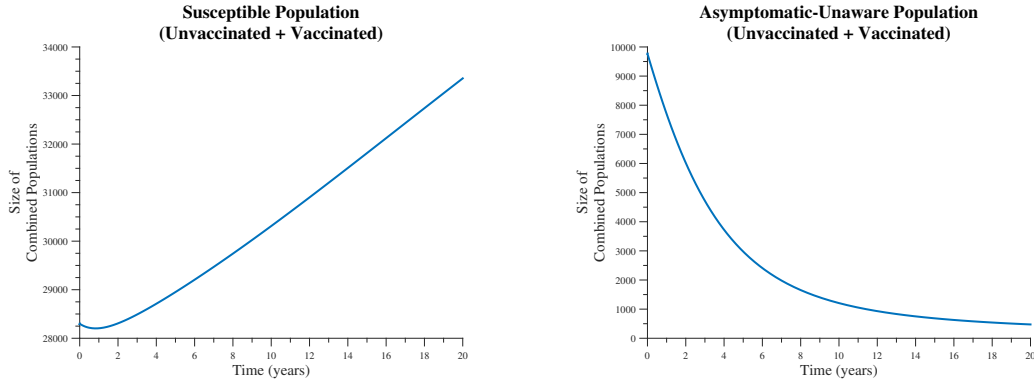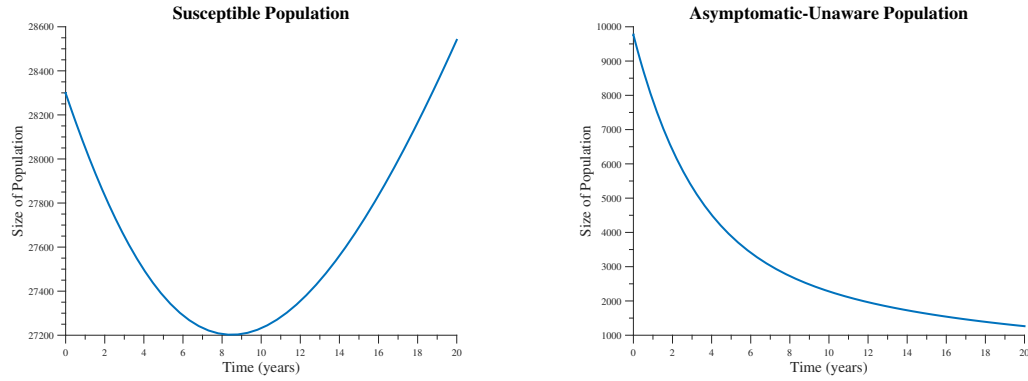
Figure 3.11: Preventative vaccine program: comparison for the total susceptible and total asymptomatic-unaware populations with the model when no intervention is offered.

In conclusion the preventative vaccine program resulted with a dominate strategy that decreases cost and increases QALYs, but still does not contribute to the overall well being for the population as a whole.

3.1.4 Combined, Preventative and Therapeutic, Vaccine Program

Taking into consideration the third possible vaccine program, where the therapeutic and preventative vaccine programs are both offered for the duration of the 20 year time horizon, the dynamics are presented as they were originally defined in the beginning of the chapter. We will

emphasize that both of the parameters for each of the vaccines is assumed to be administered to 75% of their respective populations. Since we are also assuming that both vaccines are administered to the population for the full duration of the time horizon we will again drop the time dependency from each parameter, $\nu_p = \nu_p(t) = 0.75$ and $\nu_t = \nu_t(t) = 0.75$ for all $t \in [0, 20]$. Therefore, we have the following initial value problem that governs the state trajectories for the full model description:

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\nu_p + \mu + p_0\lambda(t))Y_{0,0}(t) + \omega Y_{0,1}(t) \tag{3.20a}$$

$$\frac{dY_{0,1}(t)}{dt} = \nu_p Y_{0,0}(t) - (\mu + \omega + p_0(1-\varepsilon)\lambda_\nu(t))Y_{0,1}(t) \tag{3.20b}$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0\lambda(t)Y_{0,0}(t) - (\sigma\xi + \nu_p + \mu_{1,0} + \mu)Y_{1,0}(t) + \omega Y_{1,1}(t) \tag{3.20c}$$

$$\frac{dY_{1,1}(t)}{dt} = p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}(t) + \nu_p Y_{1,0}(t) - (\omega + \sigma\xi + \mu_{1,1} + \mu)Y_{1,1}(t) \tag{3.20d}$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) - (\nu_t + \mu_{2,0} + \mu)Y_{2,0}(t) \tag{3.20e}$$

$$\frac{dY_{2,1}(t)}{dt} = \nu_t Y_{2,0}(t) - (\mu_{2,1} + \mu)Y_{2,1}(t) \tag{3.20f}$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{j=0}^{j=1}\sum_{i=1}^{i=2}\mu_{i,j}Y_{i,j}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t) \tag{3.20g}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t), \tag{3.20h}$$

with the initial values

$$Y_{0,0}(0) = (1-\phi_0)Y_0 \tag{3.21a}$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{k=1}^{k=4}1/\mu_{k,0}}\phi_0 Y_0, \text{ for } i = 1, 2, 3, 4 \tag{3.21b}$$

$$Y_{i,1}(0) = 0, \text{ for } i = 0, 1, 2. \tag{3.21c}$$

$$\tag{3.21d}$$

Including both rate of infection functions, $\lambda(t)$, the probability that a susceptible and unvaccinated individual becomes infected, and $\lambda_\nu(t)$, the probability that a susceptible vaccinated individual will acquire the infection,

$$\lambda(t) = \frac{\sum_{j=0}^{j=1}\sum_{i=1}^{i=4}p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)}{\sum_{j=0}^{j=1}\sum_{i=0}^{i=4}p_iY_{i,j}(t)} \tag{3.22a}$$

$$\lambda_\nu(t) = \frac{\sum_{j=0}^{j=1} \sum_{i=1}^{i=4} p_i \beta_{i,j} \eta_{01,ij} Y_{i,j}(t)}{\sum_{j=0}^{j=1} \sum_{i=0}^{i=4} p_i Y_{i,j}(t)}. \tag{3.22b}$$

Accounting for the cost of the preventative and therapeutic vaccines in the accumulated cost, we have the following two integral functions,

$$C(T) = \int_0^T \left(\kappa_p \nu_p (Y_{0,0}(t) + Y_{1,0}(t)) + \kappa_t \nu_t Y_{2,0}(t) + \sum_{j=0}^{j=1} \sum_{i=0}^{i=4} c_i Y_{i,j}(t) \right) e^{-rt} dt \tag{3.23a}$$

$$Q(T) = \int_0^T \left(\sum_{j=0}^{j=1} \sum_{i=0}^{i=4} q_i Y_{i,j}(t) \right) e^{-rt} dt. \tag{3.23b}$$

Taking the same approach from the earlier three variations of the model, the equations for $\frac{dC(t)}{dt}$ and $\frac{dQ(t)}{dt}$ are included in system (3.20) for the following initial value problem that can be solved numerically:

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\nu_p + \mu + p_0 \lambda(t)) Y_{0,0}(t) + \omega Y_{0,1}(t) \tag{3.24a}$$

$$\frac{dY_{0,1}(t)}{dt} = \nu_p Y_{0,0}(t) - (\mu + \omega + p_0(1 - \varepsilon)\lambda_\nu(t)) Y_{0,1}(t) \tag{3.24b}$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0 \lambda(t) Y_{0,0}(t) - (\sigma\xi + \nu_p + \mu_{1,0} + \mu) Y_{1,0}(t) + \omega Y_{1,1}(t) \tag{3.24c}$$

$$\frac{dY_{1,1}(t)}{dt} = p_0(1 - \varepsilon)\lambda_\nu(t) Y_{0,1}(t) + \nu_p Y_{1,0}(t) - (\omega + \sigma\xi + -\mu_{1,1} + \mu) Y_{1,1}(t) \tag{3.24d}$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) - (\nu_t + \mu_{2,0} + \mu) Y_{2,0}(t) \tag{3.24e}$$

$$\frac{dY_{2,1}(t)}{dt} = \nu_t Y_{2,0}(t) - (\mu_{2,1} + \mu) Y_{2,1}(t) \tag{3.24f}$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{j=0}^{j=1} \sum_{i=1}^{i=2} \mu_{i,j} Y_{i,j}(t) - (\mu_{3,0} + \mu) Y_{3,0}(t) \tag{3.24g}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0} Y_{3,0}(t) - (\mu_{4,0} + \mu) Y_{4,0}(t) \tag{3.24h}$$

$$\frac{dC(t)}{dt} = \left(\kappa \nu_p(t)(Y_{0,0}(t) + Y_{0,1}(t)) + \kappa_t \nu_t + \sum_{j=0}^{j=1} \sum_{i=0}^{i=4} c_i Y_{i,j}(t) \right) e^{-rt} \tag{3.24i}$$

$$\frac{dQ(t)}{dt} = \left(\sum_{j=0}^{j=1} \sum_{i=0}^{i=4} q_i Y_{i,j}(t) \right) e^{-rt}, \tag{3.24j}$$

with the initial values

$$Y_{0,0}(0) = (1 - \phi_0)Y_0 \tag{3.25a}$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{k=1}^{k=4} 1/\mu_{k,0}} \phi_0 Y_0, \text{ for } i = 1, 2, 3, 4 \tag{3.25b}$$

$$Y_{i,1}(0) = 0, \text{ for } i = 0, 1, 2 \tag{3.25c}$$

$$C(0) = 0 \tag{3.25d}$$

$$Q(0) = 0. \tag{3.25e}$$

Setting $T = 20$ and the parameters as they are defined in section 3.1 then implementing the Runge-Kutta(4,5) algorithm from MatLab results with the following projections for the combined vaccination program.

Table 3.10: Combined vaccine program: expected accumulated cost and QALYs over a 20 year time horizon.

	No Intervention	Combined Vaccine Program
Cost, $C(20)$	\$3,778,541,557	\$3,674,411,240
QALYs, $Q(20)$	495,630	519,572
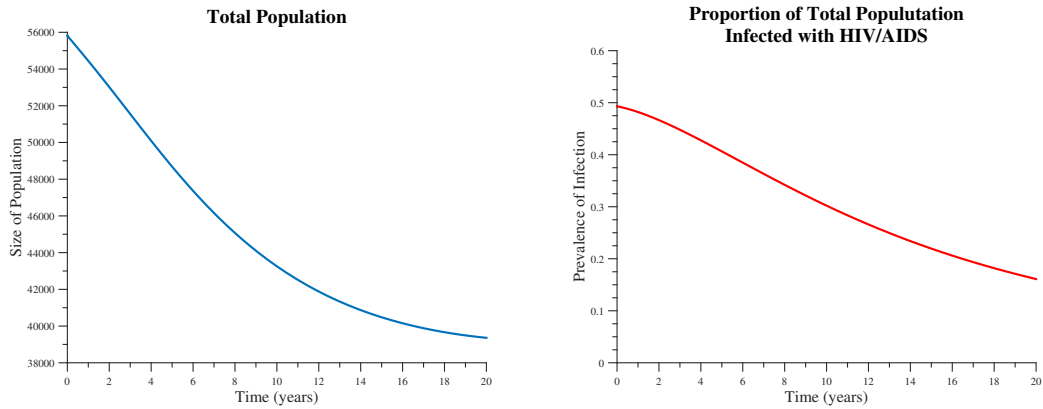
Figure 3.12: Combined, preventative and therapeutic, vaccine program: total population projections for a 20 year time horizon.

From table 3.10 implementing both vaccines over the course of 20 years results with a savings of $104,130,318 and a gain of 23,942 in QALYs. Both the greatest savings and highest gain in QALYs between the three vaccination programs considered in this chapter. There is still a consistent decline in the total population, at the end of 20 years the population drops to 39,359 with a prevalence of 16%.

For controlling the spread of the infection, when the two vaccine programs were considered independently, the results showed that the adverse effects of the therapeutic vaccine had a significant impact on increasing the spread of the infection. Alternatively, the preventative vaccine, while accounting for the adverse effects, resulted with a significant impact on reducing the spread of the infection. The impact of adding the therapeutic vaccine to the system for the preventative vaccine program introduces similar results to the ones obtained when the therapeutic vaccine program was introduced to the system when no intervention was introduced. For each there was an increase of approximately 2,000 in the final total population and a 30% increase to the prevalence of the infection at the end of 20 years. As a combined strategy the benefits of offering the preventative vaccine out weigh the adverse effects introduced by the therapeutic vaccine. In administering both generates the most desirable outcome with regards to the total population as well as begin the most cost-effective strategy.
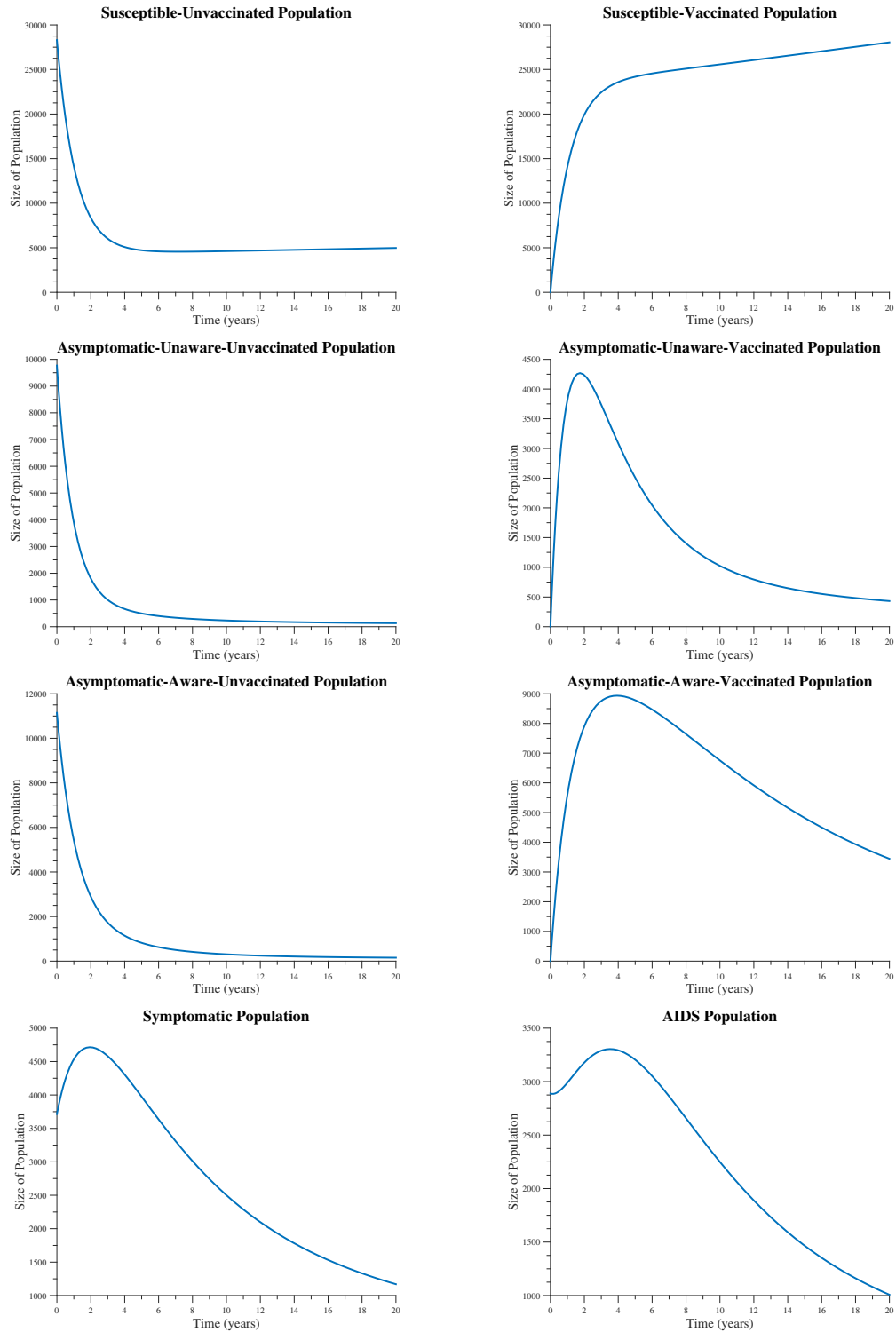
Figure 3.13: Combined, preventative and therapeutic, vaccine program: projections for each class over a 20 year time horizon.
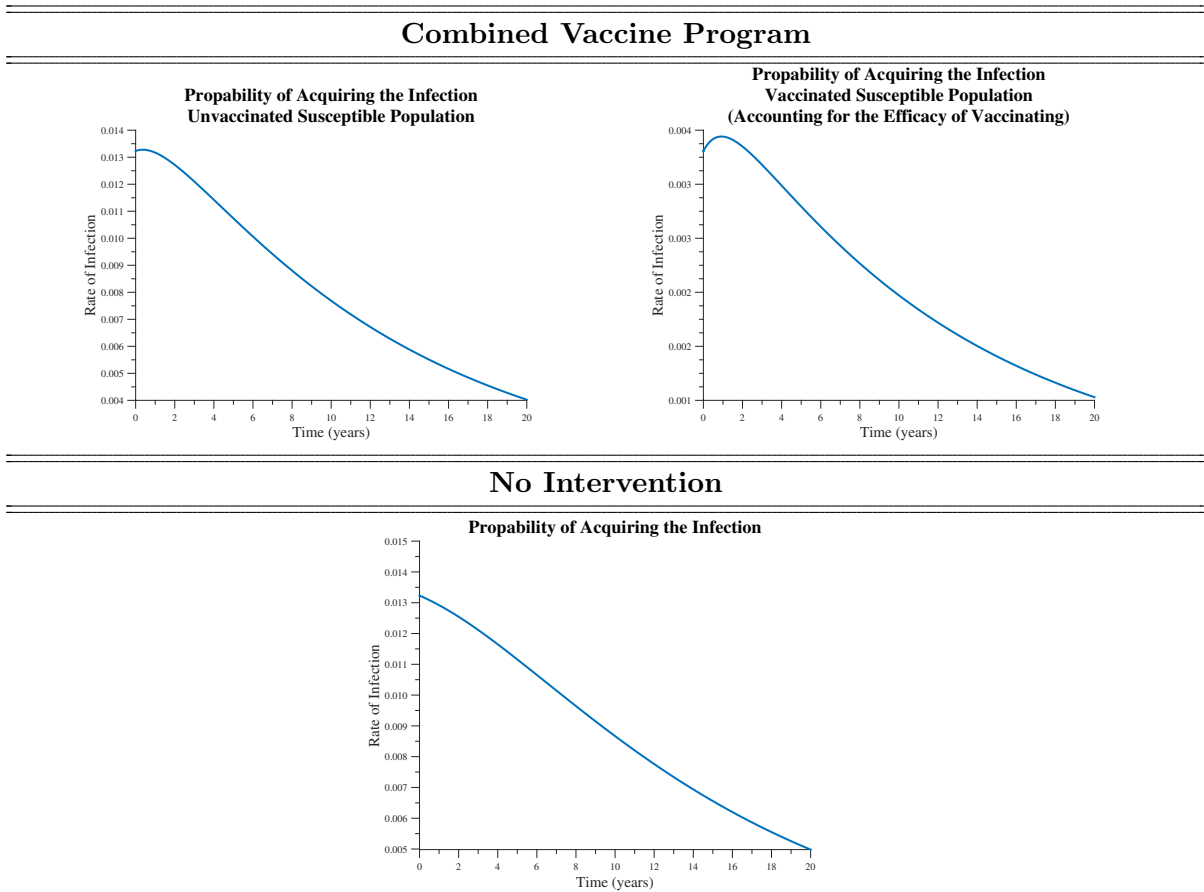
Figure 3.14: Combined, preventative and therapeutic, vaccine program: comparison for the rate of infection functions with the results when no intervention was made.

Combined
Vaccine Program
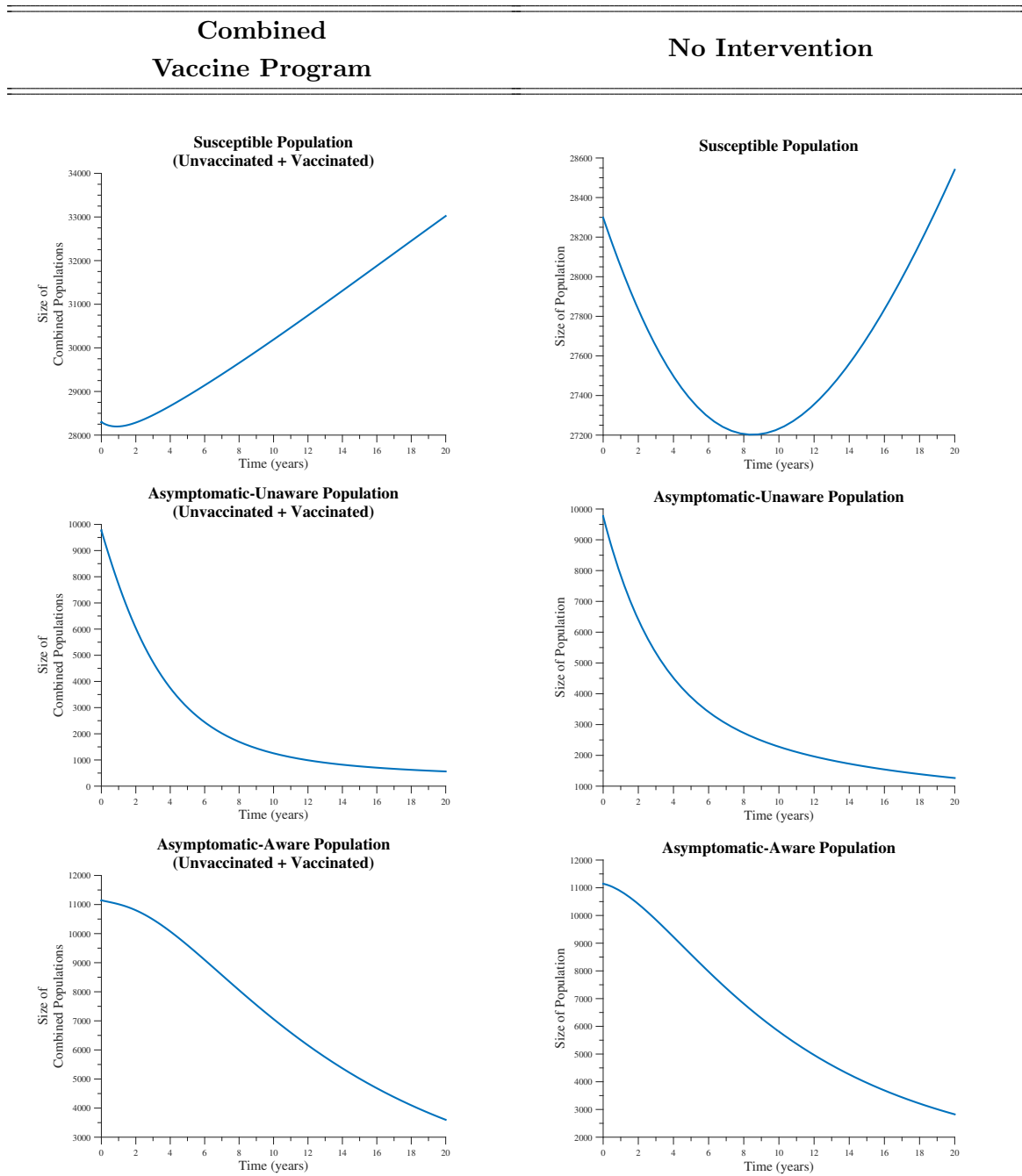
No Intervention

Figure 3.15: Combined, preventative and therapeutic, vaccine program: comparison of the total susceptible, total asymptomatic-unaware and the total asymptomatic populations with the projections found when no intervention is made.

Concluding with the combined vaccination program, the results indicate a significant decrease to cost with a substantial increase in QALYs and benefits the population as a whole. Following the analysis of each vaccine program, in the next section a comparative analysis for all four possible outcomes is evaluated.

3.2   Cost-Effective Analysis of Intervention Strategies

Concluding the analysis for the projections defined on a fixed time horizon for each of the four possible variations of the model a brief discussion of the results in direct comparison to each alternative is presented.

Considering the incremental cost of each scenario in table 3.11 we can see how much of an impact each strategy will have. Independently the therapeutic vaccine strategy is expected to result with a savings of \$229/QALY and the preventative vaccine is projected to save \$321/QALY. Implying, between the two, the preventative vaccine is a slightly better alternative with a savings of an additional \$92/QALY. Alternatively, the strategy of administering both vaccine options will result with an expected savings of \$551/QALYs, more than a \$230/QALY in savings compared to each vaccine program as a stand alone option.

Table 3.11:   Projected accumulated cost and QALYs, as well as the cost/QALY, for each of the four variations of the model over a 20 year time horizon.

	Accumulated Cost	Accumulated QALYs	Cost/QALY
No Intervention	\$3,778,541,557	495,630	\$7623/QALY
Therapeutic Vaccine	\$3,747,402,695	506,808	\$7394/QALY
Preventative Vaccine	\$3,711,111,604	508,220	\$7302/QALY
Combination Both Vaccines	\$3,674,411,239	519,572	\$7072/QALY

After the detailed analysis for the state trajectories for each of the four possible variations of the model, presented in sections 3.1.1 - 3.1.4, we learned that the cost-effective analysis only highlighted part of the story regarding the benefits of intervention strategies. Due to the adverse effects of vaccinating the therapeutic vaccine made the asymptomatic and aware population riskier than before for spreading the infection. To evaluate the results for the total population and each of the sub populations, figures 3.16 - 3.21 show a direct comparison of the four alternative scenarios, with the combination of the unvaccinated and vaccinated populations graphed when needed. From the graphs we can see that there is a variation to the trajectories between alternative scenarios. Considering that the ultimate purpose of analyzing infectious disease models is to understand the spread and control of infections, this puts an emphasis on the importance in understanding the projections of the susceptible population for evaluating the rate of success each intervention program has for controlling the spread of the disease. Recall, based on the assumptions of the model and the fixed 20 year time horizon for analysis, the life expectancy after acquiring the infection is the same as the time horizon for analysis. This explains the marginal impact to the trajectories for the total population as well as each of the infected populations. Unfortunately there is no intervention that can reverse the impact the epidemic has already had on the population.

In conclusion, we have already shown that offering both vaccines has a significantly better cost-effective outcome for a 20 year time horizon in comparison the projections for offering either one of the vaccines on their own. To determine if we can find an even better strategy, regarding the timing for offering each vaccine, will be the focus of the next couple of chapters. Starting in chapter 4 with the long run analysis for each of the four state spaces of the model to characterize the dynamical properties of the system and the expectations for the state trajectories.
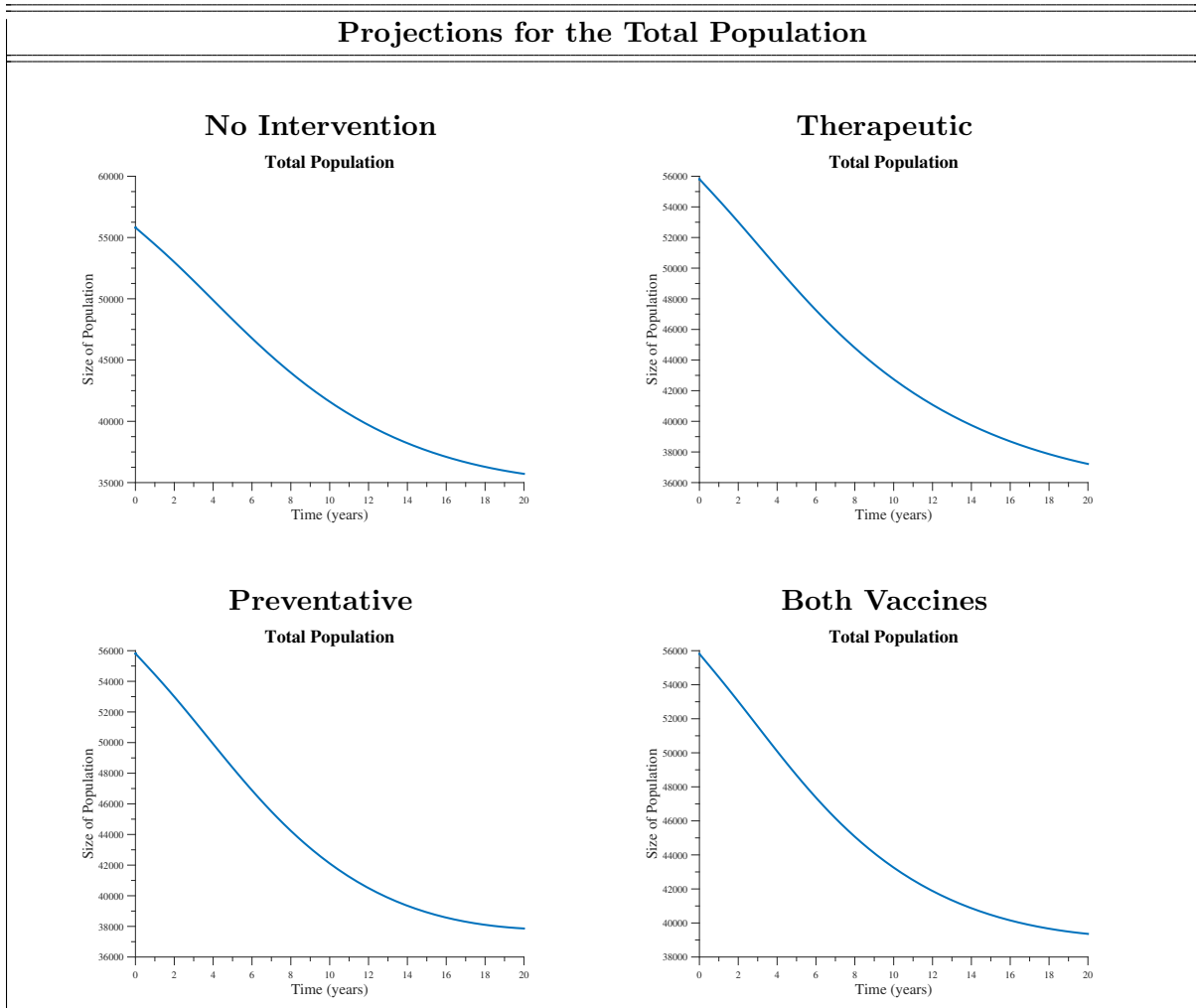
Figure 3.16: Total population projections for each of the four variation of the model; no intervention, therapeutic only, preventative only, and the combined vaccination strategy.
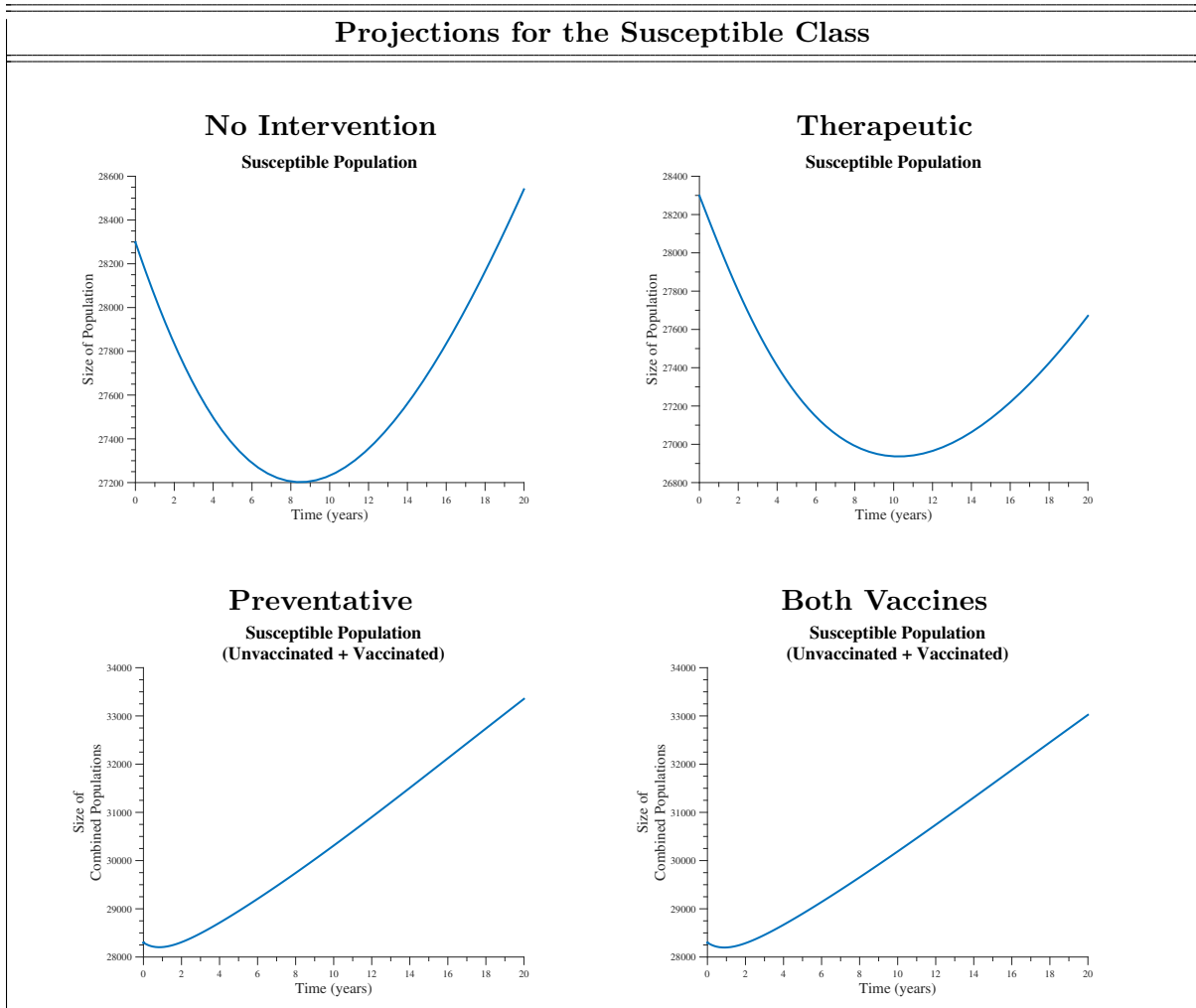
Figure 3.17: Susceptible population projections for each of the four variation of the model; no intervention, therapeutic only, preventative only, and the combined vaccination strategy.
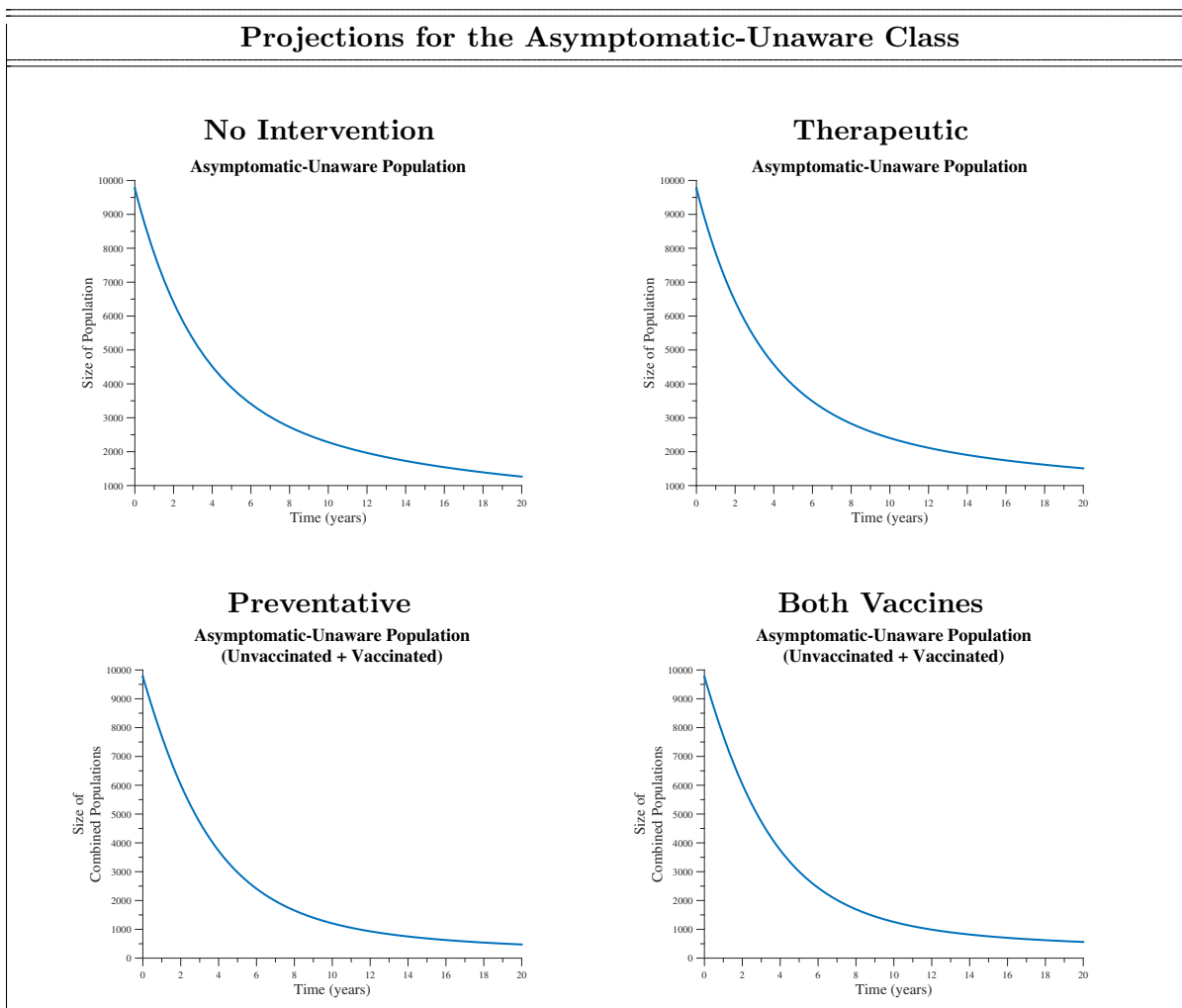
Figure 3.18: Asymptomatic-unaware population projections for each of the four variation of the model; no intervention, therapeutic only, preventative only, and the combined vaccination strategy.

Projections for the Asymptomatic-Aware Class

No Intervention

Asymptomatic-Aware Population

Therapeutic

Asymptomatic-Aware Population
(Unvaccinated + Vaccinated)

Preventative

Asymptomatic-Aware Population

Both Vaccines

Asymptomatic-Aware Population
(Unvaccinated + Vaccinated)
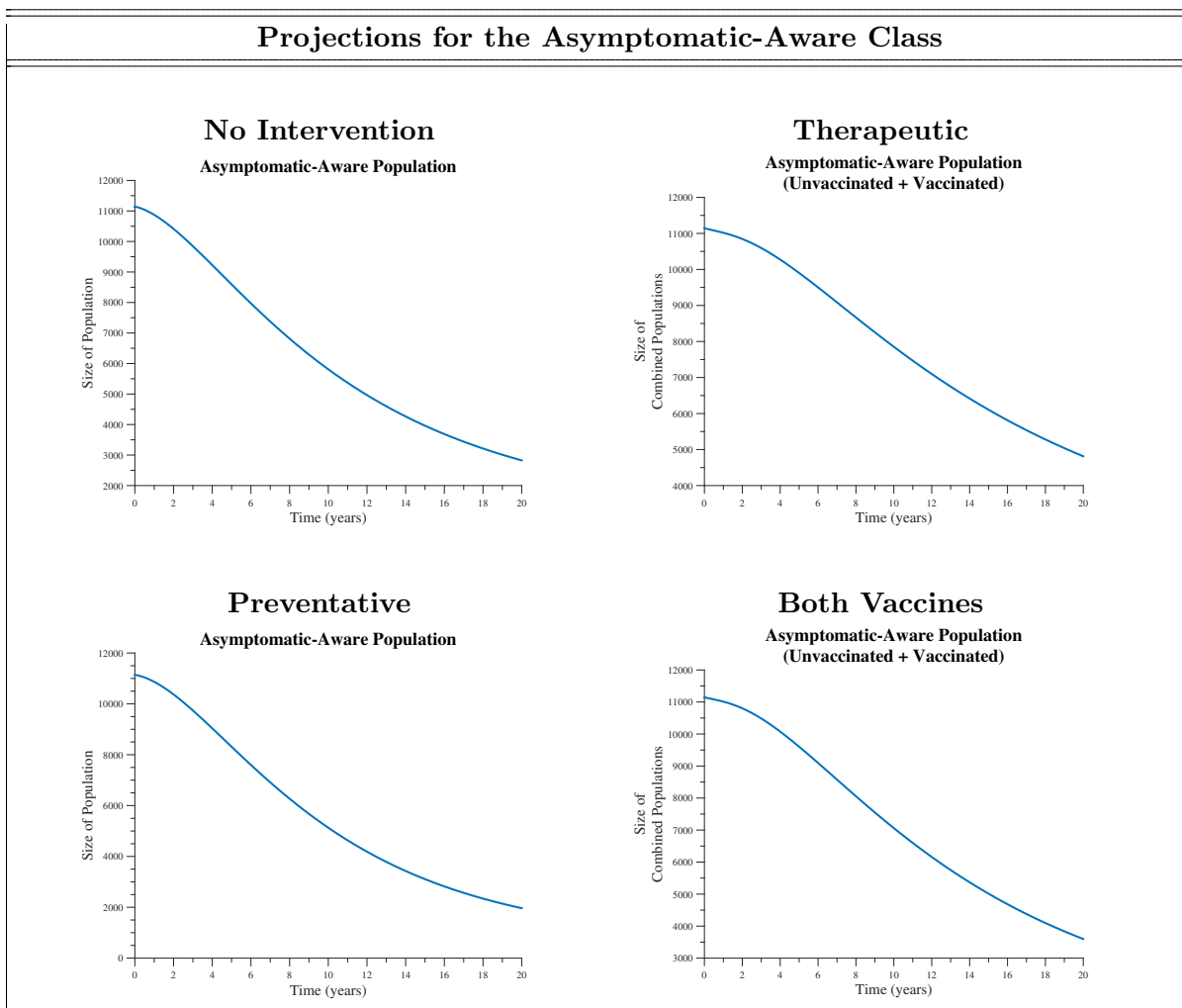
Figure 3.19: Asymptomatic-aware population projections for each of the four variation of the model; no intervention, therapeutic only, preventative only, and the combined vaccination strategy.
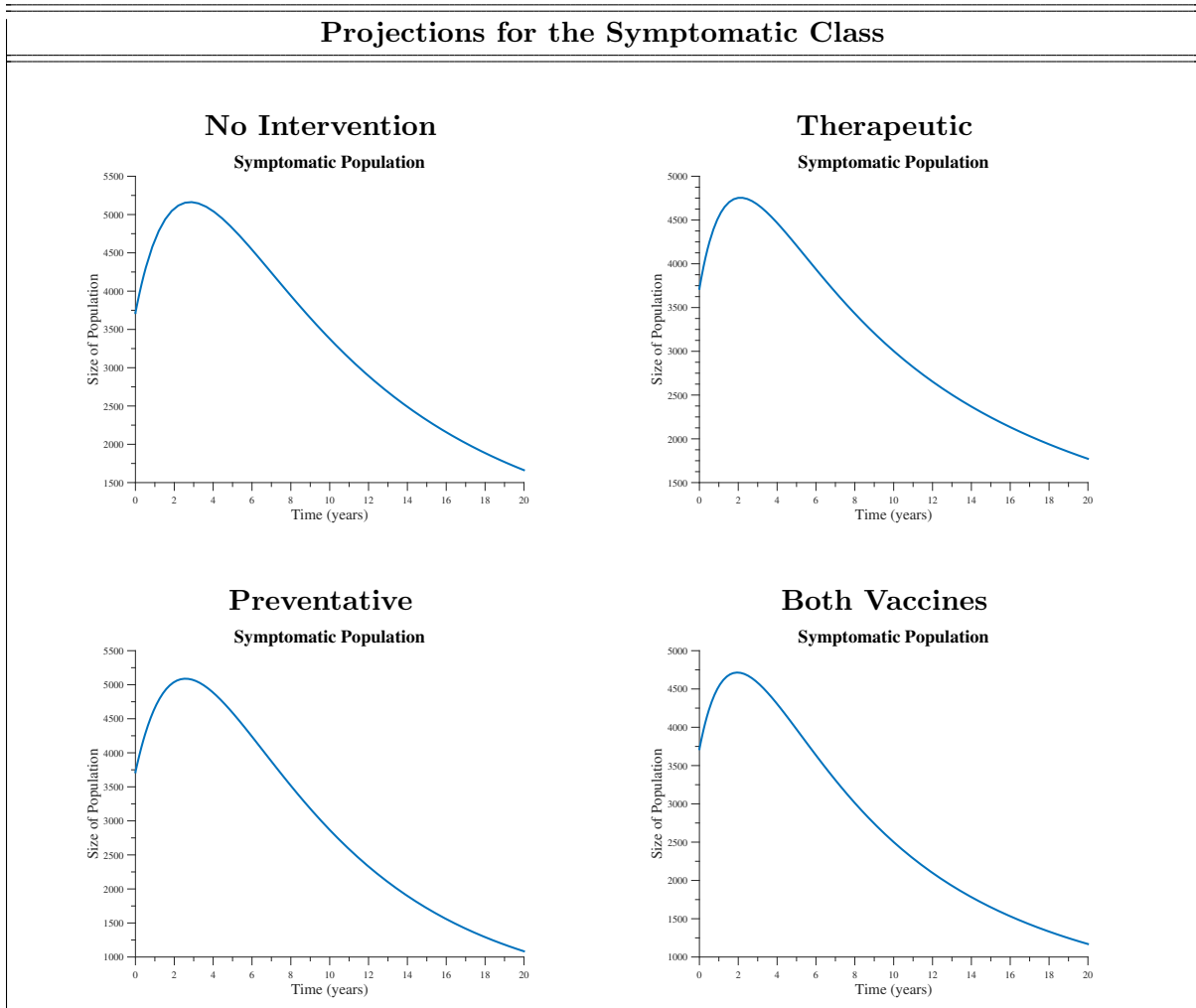
Figure 3.20: Symptomatic population projections for each of the four variation of the model; no intervention, therapeutic only, preventative only, and the combined vaccination strategy.
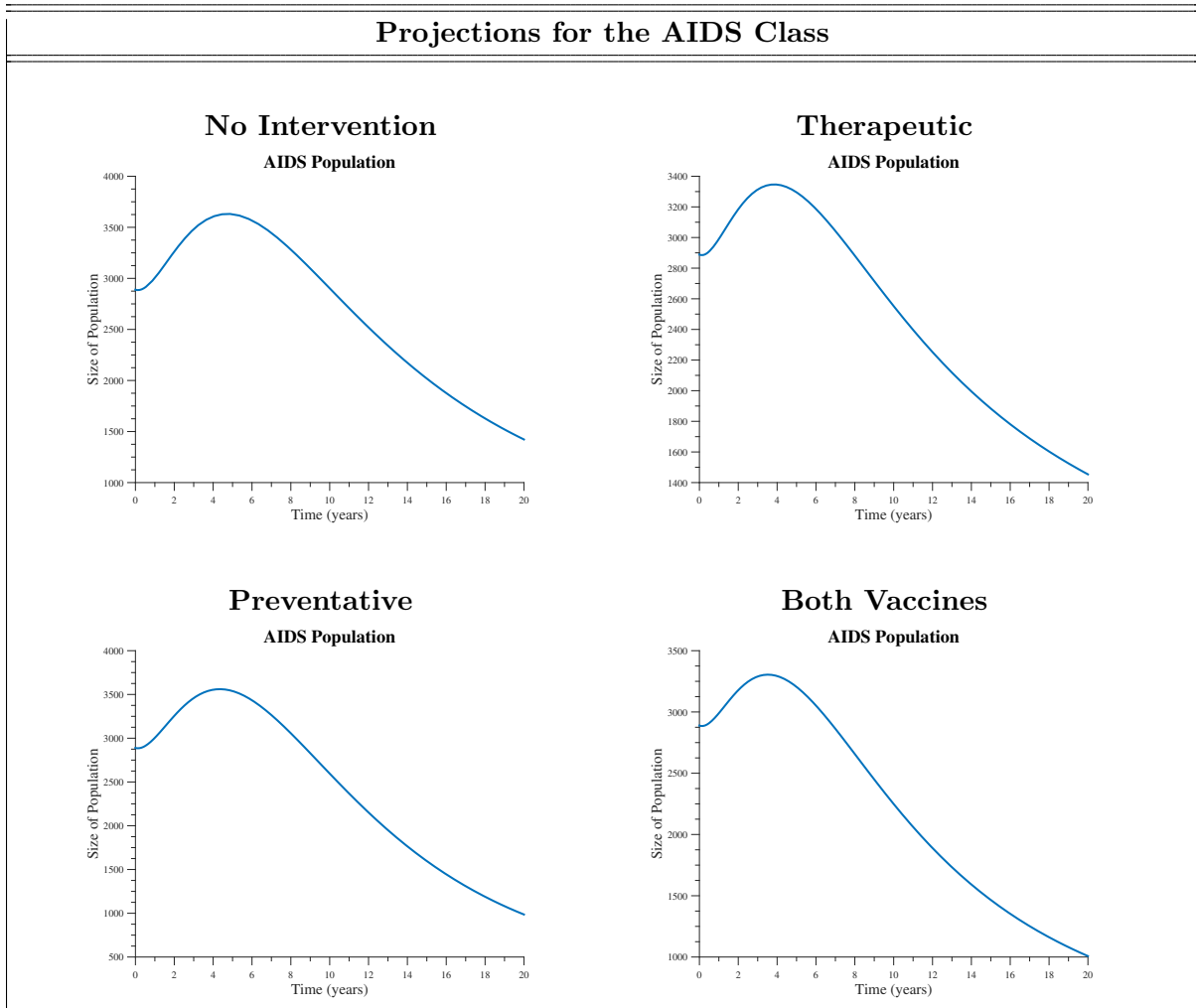
Figure 3.21: AIDS population projections for each of the four variation of the model; no intervention, therapeutic only, preventative only, and the combined vaccination strategy.

Chapter 4

Equilibria and Stability Analysis

Equilibrium stability analysis is a critical part of analyzing deterministic compartment epidemic models. The importance of doing such can lead to the characterization for the R_0 threshold in terms of the parameters of the model. As a bifurcation defining the point in the parameter space that the stability of the disease free equilibrium is transferred to an endemic equilibrium implies that the dynamics should have both equilibrium points, for the variation of the model without an intervention. We will find with the HIV-transmission model we described and analyzed in chapter 3 the dynamics for each variation of the model have exactly one equilibrium and it's the endemic equilibrium. This is a result of the assumption that constant immigration into the infected population is independent of the population size or prevalence of the infection. Therefore, we will not derive a symbolic representation for R_0 in terms of the parameters of the model. Instead we consider the stability of the equilibrium to understand the expectations for the trajectories and their behavior in the neighborhood of each equilibrium for the purposes of controlling the system.

4.1   Routh-Hurwitz Criterion for Stability

To determine the stability of the equilibrium points the Routh-Hurwitz Criterion will be verified. Before proceeding with the equilibrium and stability analysis for each variation of model we will begin by introducing necessary definitions for the Routh-Hurwitz criterion, as it was stated by Gantmacher in 1959 [19]. For the polynomial

$$c(x) = c_0 x^n + c_1 x^{n-1} + c_2 x^{n-2} + \cdots + c_{n-1}x + c_n \quad (c_0 \neq 0 \text{ and } n \in \mathbb{N})$$

of degree n we have the following definitions.

Definition 4.1.1. The *Hurwitz matrix* is a square matrix of order n defined by the coefficients of the polynomial $c(x)$ as the following:

$$H = \begin{bmatrix} c_1 & c_3 & c_5 & \cdots & \cdots & \cdots & 0 & 0 & 0 \\ c_0 & c_2 & c_4 & & & & \vdots & \vdots & \vdots \\ 0 & c_1 & c_3 & & & & \vdots & \vdots & \vdots \\ \vdots & c_0 & c_2 & \ddots & & 0 & & \vdots & \vdots \\ \vdots & 0 & c_1 & & \ddots & & c_n & \vdots & \vdots \\ \vdots & \vdots & c_0 & & & \ddots & c_{n-1} & 0 & \vdots \\ \vdots & \vdots & 0 & & & & c_{n-2} & c_n & \vdots \\ \vdots & \vdots & \vdots & & & & c_{n-3} & c_{n-1} & 0 \\ 0 & 0 & 0 & \cdots & \cdots & \cdots & c_{n-4} & c_{n-2} & c_n \end{bmatrix}.$$

For even n: $c_k = 0$ when $k > \dfrac{n}{2}$.

For odd n: $c_k = 0$ when $k > \dfrac{n-1}{2}$.

Definition 4.1.2. The *Hurwitz determinants* are the principle minors of the Hurwitz matrix,

$$\Delta_1(c) = c_1, \Delta_2(c) = \begin{vmatrix} c_1 & c_3 \\ c_0 & c_2 \end{vmatrix}, \Delta_3(c) = \begin{vmatrix} c_1 & c_3 & c_5 \\ c_0 & c_2 & c_4 \\ 0 & c_1 & c_3 \end{vmatrix}, \ldots, \Delta_n(c) = \det(H).$$

Therefore the Criterion of Routh-Hurwiz for Stability is given by the following statement.

Criterion 4.1.3 (Routh-Hurwitz)**.** All the roots of the real polynomial $c(x)$ have negative real parts if and only if the following inequalities hold,

$$c_0\Delta_1(c) > 0, \Delta_2(c) > 0, c_0\Delta_3(c) > 0, \Delta_4(c) > 0, \ldots, \begin{cases} c_0\Delta_n(c) > 0 & \text{(for odd } n) \\ \Delta_n(c) > 0 & \text{(for even } n) \end{cases}.$$

Thus, checking if all the roots for the characteristic polynomial at an equilibrium point have negative real parts implies that the equilibrium is asymptotically stable. The benefit that is gained by using the Routh-Hurwitz criterion for stability is the ability to define a threshold in terms of the parameters that will define when an equilibrium is stable or unstable.

4.2 Endemic Equilibria

As we have already mentioned, the model as it was originally defined will have only one physically relevant equilibrium point for each of the four variations. In each case, with the constant immigration of infected individuals the only equilibrium for the system will be endemic equilibria.

4.2.1 HIV-Transmission Dynamics without an Intervention

Starting with the HIV-transmission dynamics without an intervention we reintroduce the system of differential equations to the following:

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\mu + p_0\lambda(t))Y_{0,0}(t) \tag{4.1a}$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0\lambda(t)Y_{0,0}(t) - (\sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) \tag{4.1b}$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi Y_{1,0}(t) - (\mu_{2,0} + \mu)Y_{2,0}(t) \tag{4.1c}$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{i=1}^{i=2} \mu_{i,0}Y_{i,0}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t) \tag{4.1d}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t) \tag{4.1e}$$

were

$$\lambda(t) = \frac{\sum_{i=1}^{i=4} p_i\beta_{i,0}\eta_{00,i0}Y_{i,0}(t)}{\sum_{i=0}^{i=4} p_iY_{i,0}(t)}. \tag{4.2}$$

Equilibrium Calculations

To solve for the equilibria of the system without an intervention we set $\frac{dY_{i,0}(t)}{dt} = 0$ for $i = 0, 1, \ldots, 4$ and solve for $Y^\star(t) = [Y_{0,0}^\star(t), Y_{1,0}^\star(t), Y_{2,0}^\star(t), Y_{3,0}^\star(t), Y_{4,0}^\star(t)]^\mathsf{T}$. Thus,

$$0 = I_{0,0} - (\mu + p_0\lambda(t))Y_{0,0}^\star(t) \tag{4.3a}$$

$$0 = I_{1,0} + p_0\lambda(t)Y_{0,0}^\star(t) - (\sigma\xi + \mu_{1,0} + \mu)Y_{1,0}^\star(t) \tag{4.3b}$$

$$0 = I_{2,0} + \sigma\xi Y_{1,0}^\star(t) - (\mu_{2,0} + \mu)Y_{2,0}^\star(t) \tag{4.3c}$$

$$0 = I_{3,0} + \sum_{i=1}^{i=2} \mu_{i,0}Y_{i,0}^\star(t) - (\mu_{3,0} + \mu)Y_{3,0}^\star(t) \tag{4.3d}$$

$$0 = \mu_{3,0}Y_{3,0}^\star(t) - (\mu_{4,0} + \mu)Y_{4,0}^\star(t). \tag{4.3e}$$

Note that equation (4.3a) can be written as the following expression for $\lambda(t)$, defined only at an equilibrium,

$$\lambda(t) = \frac{I_{0,0} - \mu Y_{0,0}^\star(t)}{p_0 Y_{0,0}^\star(t)}. \tag{4.4}$$

Using the expression for $\lambda(t)$ defined by equation (4.4) in (4.3b) we can solve for $Y_{1,0}^\star(t)$ in terms of $Y_{0,0}^\star(t)$. In doing so,

$$0 = I_{1,0} + p_0 \left(\frac{I_{0,0} - \mu Y_{0,0}^\star(t)}{p_0 Y_{0,0}^\star(t)} \right) Y_{0,0}^\star(t) - (\sigma\xi + \mu_{1,0} + \mu) Y_{1,0}^\star(t)$$

$$0 = I_{1,0} + I_{0,0} - \mu Y_{0,0}^\star(t) - (\sigma\xi + \mu_{1,0} + \mu) Y_{1,0}^\star(t)$$

implies,

$$Y_{1,0}^\star(t) = \frac{I_{1,0} + I_{0,0}}{(\sigma\xi + \mu_{1,0} + \mu)} - \left[\frac{\mu}{(\sigma\xi + \mu_{1,0} + \mu)} \right] Y_{0,0}^\star(t). \tag{4.5}$$

Next, substituting the right side of equation (4.5) into equation (4.3c), $Y_{2,0}(t)$ can also be defined in terms of $Y_{0,0}(t)$, such that

$$0 = I_{2,0} + \sigma\xi \left(\frac{I_{1,0} + I_{0,0}}{(\sigma\xi + \mu_{1,0} + \mu)} - \left(\frac{\mu}{(\sigma\xi + \mu_{1,0} + \mu)} \right) Y_{0,0}^\star(t) \right) - (\mu_{2,0} + \mu) Y_{2,0}^\star(t)$$

$$0 = I_{2,0} + \frac{\sigma\xi(I_{1,0} + I_{0,0})}{(\sigma\xi + \mu_{1,0} + \mu)} - \left(\frac{\sigma\xi\mu}{(\sigma\xi + \mu_{1,0} + \mu)} \right) Y_{0,0}^\star(t) - (\mu_{2,0} + \mu) Y_{2,0}^\star(t)$$

implies,

$$Y_{2,0}^\star(t) = \frac{I_{2,0}}{(\mu_{2,0} + \mu)} + \frac{\sigma\xi(I_{1,0} + I_{0,0})}{(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)} - \left[\frac{\sigma\xi\mu}{(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)} \right] Y_{0,0}^\star(t). \tag{4.6}$$

Continuing with evaluating each of the infectious states in terms of $Y_{0,0}^\star(t)$, the right side of equations (4.5) and (4.6) can be substituted into equation (4.3d) to get the following expression for $Y_{3,0}(t)$,

$$0 = I_{3,0} + \mu_{1,0}\left(\frac{I_{1,0} + I_{0,0}}{(\sigma\xi + \mu_{1,0} + \mu)} - \left[\frac{\mu}{(\sigma\xi + \mu_{1,0} + \mu)}\right]Y^\star_{0,0}(t)\right)$$

$$+ \mu_{2,0}\left(\frac{I_{2,0}}{(\mu_{2,0} + \mu)} + \frac{\sigma\xi(I_{1,0} + I_{0,0})}{(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}\right.$$

$$\left. - \left[\frac{\sigma\xi\mu}{(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}\right]Y^\star_{0,0}(t)\right) - (\mu_{3,0} + \mu)Y^\star_{3,0}(t)$$

$$0 = I_{3,0} + \frac{\mu_{1,0}(I_{1,0} + I_{0,0})}{(\sigma\xi + \mu_{1,0} + \mu)} + \frac{\mu_{2,0}I_{2,0}}{(\mu_{2,0} + \mu)} + \frac{\mu_{2,0}\sigma\xi(I_{1,0} + I_{0,0})}{(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$- \left(\frac{\mu_{1,0}\mu}{(\sigma\xi + \mu_{1,0} + \mu)} + \frac{\mu_{2,0}\sigma\xi\mu}{(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}\right)Y^\star_{0,0}(t) - (\mu_{3,0} + \mu)Y^\star_{3,0}(t)$$

results with,

$$Y^\star_{3,0}(t) = \frac{I_{3,0}}{(\mu_{3,0} + \mu)} + \frac{\mu_{1,0}(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)} + \frac{\mu_{2,0}I_{2,0}}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)}$$

$$+ \frac{\mu_{2,0}\sigma\xi(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$- \left[\frac{\mu_{1,0}\mu}{(\mu_{3,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}\right.$$

$$\left. + \frac{\mu_{2,0}\sigma\xi\mu}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}\right]Y^\star_{0,0}(t). \qquad (4.7)$$

Finally plugging equation (4.7) into equation (4.3e) the last infectious state, $Y^\star_{4,0}(t)$, will be defined by the following,

$$0 = \mu_{3,0}\left(\frac{I_{3,0}}{(\mu_{3,0} + \mu)} + \frac{\mu_{1,0}(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)} + \frac{\mu_{2,0}I_{2,0}}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)}\right.$$

$$+ \frac{\mu_{2,0}\sigma\xi(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$- \left[\frac{\mu_{1,0}\mu}{(\mu_{3,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}\right.$$

$$\left.\left. + \frac{\mu_{2,0}\sigma\xi\mu}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}\right]Y^\star_{0,0}(t)\right) - (\mu_{4,0} + \mu)Y^\star_{4,0}(t)$$

$$0 = \frac{\mu_{3,0}I_{3,0}}{(\mu_{3,0} + \mu)} + \frac{\mu_{3,0}\mu_{1,0}(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)} + \frac{\mu_{3,0}\mu_{2,0}I_{2,0}}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)}$$

$$+ \frac{\mu_{3,0}\mu_{2,0}\sigma\xi(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$- \left(\frac{\mu_{3,0}\mu_{1,0}\mu}{(\mu_{3,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)} + \frac{\mu_{3,0}\mu_{2,0}\sigma\xi\mu}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)} \right) Y^{\star}_{0,0}(t)$$

$$- (\mu_{4,0} + \mu)Y^{\star}_{4,0}(t)$$

implies,

$$Y^{\star}_{4,0}(t) = \frac{\mu_{3,0}I_{3,0}}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)} + \frac{\mu_{3,0}\mu_{1,0}(I_{1,0} + I_{0,0})}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$+ \frac{\mu_{3,0}\mu_{2,0}I_{2,0}}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)}$$

$$+ \frac{\mu_{3,0}\mu_{2,0}\sigma\xi(I_{1,0} + I_{0,0})}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$- \left[\frac{\mu_{3,0}\mu_{1,0}\mu}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)} \right.$$

$$\left. + \frac{\mu_{3,0}\mu_{2,0}\sigma\xi\mu}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)} \right] Y^{\star}_{0,0}(t). \qquad (4.8)$$

The expressions derived for the infectious disease states in terms of the susceptible population can now be used to express the rate of infection function $\lambda(t)$ in terms of $Y^{\star}_{0,0}(t)$. To simplify the notation we introduce the following vector notation,

$$P := \begin{bmatrix} p_0 \\ p_1 \\ p_2 \\ p_3 \\ p_4 \end{bmatrix} \qquad B := \begin{bmatrix} 0 \\ p_1\beta_{1,0}\eta_{00,10} \\ p_2\beta_{2,0}\eta_{00,20} \\ p_3\beta_{3,0}\eta_{00,30} \\ p_4\beta_{4,0}\eta_{00,40} \end{bmatrix} \qquad \Phi := \begin{bmatrix} \phi_{0,0} \\ \phi_{1,0} \\ \phi_{2,0} \\ \phi_{3,0} \\ \phi_{4,0} \end{bmatrix} \qquad M := \begin{bmatrix} m_{0,0} \\ m_{1,0} \\ m_{2,0} \\ m_{3,0} \\ m_{4,0} \end{bmatrix}, \text{ such that}$$

$$\phi_{0,0} := 0$$

$$\phi_{1,0} := \frac{I_{1,0} + I_{0,0}}{(\sigma\xi + \mu_{1,0} + \mu)}$$

$$\phi_{2,0} := \frac{I_{2,0}}{(\mu_{2,0} + \mu)} + \frac{\sigma\xi(I_{1,0} + I_{0,0})}{(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$\phi_{3,0} := \frac{I_{3,0}}{(\mu_{3,0} + \mu)} + \frac{\mu_{1,0}(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)} + \frac{\mu_{2,0}I_{2,0}}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)}$$

$$+ \frac{\mu_{2,0}\sigma\xi(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$\phi_{4,0} := \frac{\mu_{3,0}I_{3,0}}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)} + \frac{\mu_{3,0}\mu_{1,0}(I_{1,0} + I_{0,0})}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$+ \frac{\mu_{3,0}\mu_{2,0}I_{2,0}}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)}$$

$$+ \frac{\mu_{3,0}\mu_{2,0}\sigma\xi(I_{1,0} + I_{0,0})}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)},$$

$$m_{0,0} := 1$$

$$m_{1,0} := -\frac{\mu}{(\sigma\xi + \mu_{1,0} + \mu)}$$

$$m_{2,0} := -\frac{\sigma\xi\mu}{(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$m_{3,0} := -\frac{\mu_{1,0}\mu}{(\mu_{3,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)} - \frac{\mu_{2,0}\sigma\xi\mu}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$m_{4,0} := -\frac{\mu_{3,0}\mu_{1,0}\mu}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)} - \frac{\mu_{3,0}\mu_{2,0}\sigma\xi\mu}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}.$$

Therefore the rate of infection function defined by equation (4.2) can be expressed as the ratio of two linear combinations of $Y^\star_{0,0}(t)$,

$$\lambda(t) = \frac{B'\Phi + B'MY^\star_{0,0}(t)}{P'\Phi + P'MY^\star_{0,0}(t)}. \tag{4.9}$$

Given two expressions for $\lambda(t)$, defined only at an equilibrium point, we will set each expression

from (4.4) and (4.9) equal to each other to get an equation in terms of only $Y_{0,0}^\star(t)$. The solution to the following equation can then be solved to get the symbolic representation for the susceptible population defined at the equilibria,

$$\frac{B'\Phi + B'MY_{0,0}^\star(t)}{P'\Phi + P'MY_{0,0}^\star(t)} = \frac{I_{0,0} - \mu Y_{0,0}^\star(t)}{p_0 Y_{0,0}^\star(t)}. \tag{4.10}$$

By cross-multiplying and combining like terms in equation (4.10) we will get the following quadratic equation for $Y_{0,0}^\star(t)$,

$$(\mu P'M + p_0 B'M)(Y_{0,0}^\star(t))^2 + (p_0 B'\Phi + \mu P'\Phi - I_{0,0}P'M)Y_{0,0}^\star(t) - I_{0,0}P'\Phi = 0. \tag{4.11}$$

Considering the graph of the quadratic function corresponding to (4.11), written in standard form,

$$f(Y_{0,0}^\star(t)) = (\mu P'M + p_0 B'M)\left(Y_{0,0}^\star(t) + \frac{p_0 B'\Phi + \mu P'\Phi - I_{0,0}P'M}{2(\mu P'M + p_0 B'M)}\right)^2$$
$$- I_{0,0}P'\Phi - \frac{(p_0 B'\Phi + \mu P'\Phi - I_{0,0}P'M)^2}{4(\mu P'M + p_0 B'M)},$$

we can determine conditions for the parameters that will result with either 0, 1, or 2 roots. Thus, the existence of a solution and the number of roots will depend on the sign of $(\mu P'M + p_0 B'M)$ and $\left(- I_{0,0}P'\Phi - \dfrac{(p_0 B'\Phi + \mu P'\Phi - I_{0,0}P'M)^2}{4(\mu P'M + p_0 B'M)}\right)$[1]. Assuming that $(\mu P'M + p_0 B'M) \neq 0$ we have the following conditions for solutions.

- When $\left(- I_{0,0}P'\Phi - \dfrac{(p_0 B'\Phi + \mu P'\Phi - I_{0,0}P'M)^2}{4(\mu P'M + p_0 B'M)}\right)$ and $(\mu P'M + p_0 B'M)$ have the same sign, there are no solutions to (4.11).

- When $I_{0,0}P'\Phi = -\dfrac{(p_0 B'\Phi + \mu P'\Phi - I_{0,0}P'M)^2}{4(\mu P'M + p_0 B'M)}$ there is exactly one solution to equation (4.11).

- When $\left(- I_{0,0}P'\Phi - \dfrac{(p_0 B'\Phi + \mu P'\Phi - I_{0,0}P'M)^2}{4(\mu P'M + p_0 B'M)}\right)$ and $(\mu P'M + p_0 B'M)$ have opposite signs, there are exactly two solutions to (4.11).

---

[1]Recall that most of the components of M are negative.

For the parameter values presented in chapter 3,

$$\mu P'M + p_0 B'M \approx \ 0.0115792 > 0$$

$$-I_{0,0}P'\Phi - \frac{(p_0 B'\Phi + \mu P'\Phi - I_{0,0}P'M)^2}{4(\mu P'M + p_0 B'M)} \approx -\ 25,155,561 < 0.$$

Therefore there are exactly two roots to equation (4.11) and using MatLab to find the numerical solution to each we get

$$Y_{0,0}^{\star}(t) \approx -47,847 \tag{4.12a}$$

$$Y_{0,0}^{\star}(t) \approx 45,371. \tag{4.12b}$$

This implies from equations (4.5) - (4.8) and the solutions in (4.12) we get the following two equilibrium points for the system,

$$E^{\dagger} \approx \begin{bmatrix} -47,847 \\ 7,183 \\ 7,589 \\ 5,027 \\ 3,736 \end{bmatrix} \qquad E^{\star} \approx \begin{bmatrix} 45,372 \\ 508 \\ 853 \\ 514 \\ 382 \end{bmatrix}.$$

Although there are two mathematical solutions for system (4.3), only one is considered physically relevant for the model. Requiring that the solution to the dynamics stay non-negative, $E^{\dagger}$ is not considered a feasible solution. Therefore the infectious disease model without an intervention only has an endemic equilibrium that we will denote by $E_b^{\star}$. Here we make the distinction that this is the endemic equilibrium with respect to the base dynamics without an intervention (b). This is important because we will also need to evaluate the equilibrium points as they are defined when we introduce each strategy; the therapeutic progam (t), the preventative program (p), and the combined vaccine strategy (c).

$$E_b^{\star} \approx \begin{bmatrix} 45,372 \\ 508 \\ 853 \\ 514 \\ 382 \end{bmatrix}$$

This implies that in the long run we should expect the total population to stay around 47,629 with a consistent prevalence of infected individuals at approximately 5%.

Equilibrium Stability

The full description of the Jacobian along with the derivation of the characteristic polynomial in symbolic form is presented in appendix A. For the purpose of determining the stability of the endemic equilibrium we will use the solution to the characteristic polynomial and the endemic equilibrium to evaluate the numerical approximation for the characteristic polynomial at $E_b^\star$,

$$c(x) = c_0 x^5 + c_1 x^4 + c_2 x^3 + c_3 x^2 + c_4 x + c_5 \tag{4.13}$$

with each of the coefficients approximated by,

$c_0 = 1$

$c_1 \approx 1.36886129999$

$c_2 \approx 6.06507381914\text{e-}01$

$c_3 \approx 1.43752973349\text{e-}01$

$c_4 \approx 1.17082002872\text{e-}02$

$c_5 \approx 1.96150810432\text{e-}04.$

If the objective is to solely determine whether or not the system (4.1) with the fixed parameters values defined in section 3.1 is stable then solving for the roots of (4.13) and verifying that they all have negative real parts would be sufficient. This refers to determining the sign of the eigenvalues. In doing so, we used the 'root' function in MatLab to find the numerical approximations for each of the roots of (4.13), resulting with the following solutions,

$x \approx -0.824$

$x \approx -0.209 + 0.242i$

$x \approx -0.209 - 0.242i$

$x \approx -0.104$

$x \approx -0.022.$

Since all of the eigenvalues have negative real parts implies that $E_b^\star$ is a local asymptotically stable equilibrium. To evaluate how stable the equilibrium is in terms of the assumptions regarding the parameter values we will consider validating the stability using the Routh-Hurwitz

criterion 4.1.3 with the following Hurwitz determinants[2],

$$\Delta_1(c) = c_1$$
$$\Delta_2(c) = c_2\Delta_1 - c_0c_3$$
$$\Delta_3(c) = c_3\Delta_2 - c_4c_1^2 + c_5c_1c_0$$
$$\Delta_4(c) = c_4\Delta_3 - c_5c_2\Delta_2 + c_5c_4c_1c_0 - c_5^2c_0^2$$
$$\Delta_5(c) = c_5\Delta_4.$$

For the numerical approximations to the characteristic polynomial (4.13) the Hurwitz determinants are each evaluated to be the following,

$$\Delta_1(c) \approx 1.368861299993612$$

$$\Delta_2(c) \approx 6.864701859278965\text{e-}01$$

$$\Delta_3(c) \approx 7.701293620277477\text{e-}02$$

$$\Delta_4(c) \approx 8.231208565862636\text{e-}04$$

$$\Delta_5(c) \approx 1.614558231066645\text{e-}07.$$

Noting that some of the results for the Hurwitz determinants are defined within a 'small' neighborhood of zero it is important that we address the accuracy for which the calculations were made. We will first emphasize that the derivation for the endemic equilibria and characteristic polynomial were each done analytically. The derivation for the endemic equilibrium was done in this section of the current chapter and the derivation for the characteristic polynomial can be found in appendix A. Given the size and complexity of each, MatLab was used to derive the numerical approximations to both the equilibrium point and then the coefficients of the characteristic polynomial. We will note that MatLab stores numbers and computes to the equivalent of 16 decimal places [23]. This implies, that the numerical approximations to each of the coefficients for the characteristic polynomial at the endemic equilibrium is accurate to about 16 decimal places. Since the Hurwitz determinants are defined analytically in terms of the coefficients to the characteristic polynomials in appendix B, we can state that the solutions we have found for the Hurwitz determinants are within the order of accuracy expected for the numerical solver we used.

Given the approximations for the Hurwitz determinants and $c_0 = 1$, we can verify that the equilibrium point $E_b^\star$ satisfies the Routh-Hurwitz criterion for stability,

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[2]The detailed calculations for deriving each of the Hurwitz determinants is presented in appendix B.

$$c_0 \Delta_1(c) \approx 1.368861299993612 > 0$$

$$\Delta_2(c) \approx 6.864701859278965\text{e-}01 > 0$$

$$c_0 \Delta_3(c) \approx 7.701293620277477\text{e-}02 > 0$$

$$\Delta_4(c) \approx 8.231208565862636\text{e-}04 > 0$$

$$c_0 \Delta_5(c) \approx 1.614558231066645\text{e-}07 > 0.$$

From these results we have confirmed that the endemic equilibrium for the system without an intervention is asymptotically stable. By verifying the conditions for stability defined by the Routh-Hurwitz criterion we have realized that the stability of the equilibrium could possibly change if the assumptions for the values of the parameters are altered. This insight can lead to another are for consideration when determining the sensitivity of the model with regards to the parameters. An area of research that would be far more interesting to explore when the dynamics introduce both the disease-free equilibrium along with the endemic equilibrium.

For the purpose of optimizing an intervention strategy, the results of an asymptotically stable endemic equilibrium leads us on the investigation for alternative outcomes when various intervention programs are introduced.

4.2.2 Therapeutic Vaccine Program

The first intervention program we will analyze for the corresponding equilibria and stability is the therapeutic vaccine program. For the model with only the therapeutic vaccine we have following system of ordinary differential equations:

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\mu + p_0 \lambda(t))Y_{0,0}(t) \tag{4.14a}$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0 \lambda(t)Y_{0,0}(t) - (\sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) \tag{4.14b}$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi Y_{1,0}(t) - (\nu_t + \mu_{2,0} + \mu)Y_{2,0}(t) \tag{4.14c}$$

$$\frac{dY_{2,1}(t)}{dt} = \nu_t Y_{2,0}(t) - (\mu_{2,1} + \mu)Y_{2,1}(t) \tag{4.14d}$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{j=0}^{j=1}\sum_{i=1}^{i=2} \mu_{i,j}Y_{i,j}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t) \tag{4.14e}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t) \tag{4.14f}$$

were

$$\lambda(t) = \frac{\sum_{i=1}^{i=4} \sum_{j=0}^{j=1} p_i \beta_{i,j} \eta_{00,ij} Y_{i,j}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)}. \tag{4.15}$$

Equilibrium Calculations

To solve for the equilibria of the system when the therapeutic vaccine only is admistered we set $\dfrac{dY_{i,j}(t)}{dt} = 0$ for $i = 0, 1, \ldots, 4$ and $j = 0, 1$ then solve for $Y^\star(t) = [Y_{0,0}^\star(t), Y_{1,0}^\star(t), Y_{2,0}^\star(t), Y_{2,1}^\star(t), Y_{3,0}^\star(t), Y_{4,0}^\star(t)]^\intercal$. This gives us the following system of equations:

$$0 = I_{0,0} - (\mu + p_0 \lambda(t)) Y_{0,0}^\star(t) \tag{4.16a}$$

$$0 = I_{1,0} + p_0 \lambda(t) Y_{0,0}^\star(t) - (\sigma\xi + \mu_{1,0} + \mu) Y_{1,0}^\star(t) \tag{4.16b}$$

$$0 = I_{2,0} + \sigma\xi Y_{1,0}^\star(t) - (\nu_t + \mu_{2,0} + \mu) Y_{2,0}^\star(t) \tag{4.16c}$$

$$0 = \nu_t Y_{2,0}^\star(t) - (\mu_{2,1} + \mu) Y_{2,1}^\star(t) \tag{4.16d}$$

$$0 = I_{3,0} + \sum_{j=0}^{j=1} \sum_{i=1}^{i=2} \mu_{i,j} Y_{i,j}^\star(t) - (\mu_{3,0} + \mu) Y_{3,0}^\star(t) \tag{4.16e}$$

$$0 = \mu_{3,0} Y_{3,0}^\star(t) - (\mu_{4,0} + \mu) Y_{4,0}^\star(t). \tag{4.16f}$$

In adding the therapeutic vaccine to the dynamics we will note that nothing changes with regards to the first two equations. This implies that equation (4.4) for the second expression for $\lambda(t)$ at the equilibrium and equation (4.5) for $Y_{1,0}^\star(t)$ in terms of $Y_{0,0}^\star(t)$ still hold,

$$\lambda(t) = \frac{I_{0,0} - \mu Y_{0,0}^\star(t)}{p_0 Y_{0,0}^\star(t)} \tag{4.17}$$

$$Y_{1,0}^\star(t) = \frac{I_{1,0} + I_{0,0}}{(\sigma\xi + \mu_{1,0} + \mu)} - \left[\frac{\mu}{(\sigma\xi + \mu_{1,0} + \mu)}\right] Y_{0,0}^\star(t). \tag{4.18}$$

For the rest of the infectious populations the following expressions take into consideration the additional parameters for the therapeutic vaccine and the additional state $Y_{2,1}(t)$. Therefore, we have the following expressions for the rest of the infected populations in terms of the susceptible population,

$$Y_{2,0}^\star(t) = \frac{I_{2,0}}{(\nu_t + \mu_{2,0} + \mu)} + \frac{\sigma\xi(I_{0,0} + I_{1,0})}{(\nu_t + \mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$
$$- \left[\frac{\sigma\xi\mu}{(\nu_t + \mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}\right] Y_{0,0}^\star(t) \tag{4.19}$$

$$Y_{2,1}^{\star}(t) = \frac{I_{2,0}\nu_t}{(\mu_{2,1}+\mu)(\nu_t+\mu_{2,0}+\mu)} + \frac{\sigma\xi(I_{0,0}+I_{1,0})\nu_t}{(\mu_{2,1}+\mu)(\nu_t+\mu_{2,0}+\mu)(\sigma\xi+\mu_{1,0}+\mu)}$$
$$- \left[\frac{\sigma\xi\mu\nu_t}{(\mu_{2,1}+\mu)(\nu_t+\mu_{2,0}+\mu)(\sigma\xi+\mu_{1,0}+\mu)}\right]Y_{0,0}^{\star}(t) \qquad (4.20)$$

$$Y_{3,0}^{\star}(t) = \frac{I_{3,0}}{(\mu_{3,0}+\mu)} + \frac{\mu_{2,0}I_{2,0}}{(\mu_{3,0}+\mu)(\nu_t+\mu_{2,0}+\mu)} + \frac{\mu_{2,0}I_{2,0}\nu_t}{(\mu_{3,0}+\mu)(\mu_{2,1}+\mu)(\nu_t+\mu_{2,0}+\mu)}$$
$$+ \frac{\mu_{1,0}(I_{0,0}+I_{1,0})}{(\mu_{3,0}+\mu)(\sigma\xi+\mu_{1,0}+\mu)} + \frac{\mu_{2,0}\sigma\xi(I_{0,0}+I_{1,0})}{(\mu_{3,0}+\mu)(\nu_t+\mu_{2,0}+\mu)(\sigma\xi+\mu_{1,0}+\mu)}$$
$$+ \frac{\mu_{2,0}\sigma\xi\nu_t}{(\mu_{3,0}+\mu)(\mu_{2,1}+\mu)(\mu_{2,0}+\mu)(\sigma\xi+\mu_{1,0}+\mu)}$$
$$- \left[\frac{\mu_{1,0}\mu}{(\mu_{3,0}+\mu)(\sigma\xi+\mu_{1,0}+\mu)} + \frac{\mu_{2,0}\sigma\xi\mu}{(\mu_{3,0}+\mu)(\nu_t+\mu_{2,0}+\mu)(\sigma\xi+\mu_{1,0}+\mu)}\right.$$
$$\left.+ \frac{\mu_{2,0}\mu\sigma\xi\nu_t}{(\mu_{3,0}+\mu)(\mu_{2,1}+\mu)(\nu_t+\mu_{2,0}+\mu)(\sigma\xi+\mu_{1,0}+\mu)}\right]Y_{0,0}^{\star}(t) \qquad (4.21)$$

and

$$Y_{4,0}^{\star}(t) = \frac{\mu_{3,0}I_{3,0}}{(\mu_{4,0}+\mu)(\mu_{3,0}+\mu)} + \frac{\mu_{3,0}\mu_{2,0}I_{2,0}}{(\mu_{4,0}+\mu)(\mu_{3,0}+\mu)(\nu_t+\mu_{2,0}+\mu)}$$
$$+ \frac{\mu_{3,0}\mu_{2,0}I_{2,0}\nu_t}{(\mu_{4,0}+\mu)(\mu_{3,0}+\mu)(\mu_{2,1}+\mu)(\nu_t+\mu_{2,0}+\mu)}$$
$$+ \frac{\mu_{3,0}\mu_{1,0}(I_{0,0}+I_{1,0})}{(\mu_{4,0}+\mu)(\mu_{3,0}+\mu)(\sigma\xi+\mu_{1,0}+\mu)}$$
$$+ \frac{\mu_{3,0}\mu_{2,0}\sigma\xi(I_{0,0}+I_{1,0})}{(\mu_{4,0}+\mu)(\mu_{3,0}+\mu)(\nu_t+\mu_{2,0}+\mu)(\sigma\xi+\mu_{1,0}+\mu)}$$
$$+ \frac{\mu_{3,0}\mu_{2,0}\sigma\xi\nu_t}{(\mu_{4,0}+\mu)(\mu_{3,0}+\mu)(\mu_{2,1}+\mu)(\mu_{2,0}+\mu)(\sigma\xi+\mu_{1,0}+\mu)}$$
$$- \left[\frac{\mu_{3,0}\mu_{1,0}\mu}{(\mu_{4,0}+\mu)(\mu_{3,0}+\mu)(\sigma\xi+\mu_{1,0}+\mu)}\right.$$
$$+ \frac{\mu_{3,0}\mu_{2,0}\sigma\xi\mu}{(\mu_{4,0}+\mu)(\mu_{3,0}+\mu)(\nu_t+\mu_{2,0}+\mu)(\sigma\xi+\mu_{1,0}+\mu)}$$
$$\left.+ \frac{\mu_{3,0}\mu_{2,0}\mu\sigma\xi\nu_t}{(\mu_{4,0}+\mu)(\mu_{3,0}+\mu)(\mu_{2,1}+\mu)(\nu_t+\mu_{2,0}+\mu)(\sigma\xi+\mu_{1,0}+\mu)}\right]Y_{0,0}^{\star}(t).$$
$$(4.22)$$

Thus, we will again introduce vector notation to simplify our calculations in solving for the equilibrium points,

$$P := \begin{bmatrix} p_0 \\ p_1 \\ p_2 \\ p_2 \\ p_3 \\ p_4 \end{bmatrix} \qquad B := \begin{bmatrix} 0 \\ p_1\beta_{1,0}\eta_{00,10} \\ p_2\beta_{2,0}\eta_{00,20} \\ p_2\beta_{2,1}\eta_{00,21} \\ p_3\beta_{3,0}\eta_{00,30} \\ p_4\beta_{4,0}\eta_{00,40} \end{bmatrix} \qquad \Phi := \begin{bmatrix} \phi_{0,0} \\ \phi_{1,0} \\ \phi_{2,0} \\ \phi_{2,1} \\ \phi_{3,0} \\ \phi_{4,0} \end{bmatrix}, \qquad M := \begin{bmatrix} m_{0,0} \\ m_{1,0} \\ m_{2,0} \\ m_{2,1} \\ m_{3,0} \\ m_{4,0} \end{bmatrix}, \text{ such that}$$

$\phi_{0,0} := 0$

$$\phi_{1,0} := \frac{I_{1,0} + I_{0,0}}{(\sigma\xi + \mu_{1,0} + \mu)}$$

$$\phi_{2,0} := \frac{I_{2,0}}{(\nu_t + \mu_{2,0} + \mu)} + \frac{\sigma\xi(I_{1,0} + I_{0,0})}{(\nu_t + \mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$\phi_{2,1} := \frac{I_{2,0}\nu_t}{(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)} + \frac{\sigma\xi(I_{1,0} + I_{0,0})\nu_t}{(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$\phi_{3,0} := \frac{I_{3,0}}{(\mu_{3,0} + \mu)} + \frac{\mu_{1,0}(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)} + \frac{\mu_{2,0}I_{2,0}}{(\mu_{3,0} + \mu)(\nu_t + \mu_{2,0} + \mu)}$$

$$+ \frac{\mu_{2,0}\sigma\xi(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)(\nu_t + \mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$+ \frac{\mu_{2,0}I_{2,0}\nu_t}{(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)}$$

$$+ \frac{\mu_{2,0}\sigma\xi\nu_t}{(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$\phi_{4,0} := \frac{\mu_{3,0}I_{3,0}}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)} + \frac{\mu_{3,0}\mu_{1,0}(I_{1,0} + I_{0,0})}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$+ \frac{\mu_{3,0}\mu_{2,0}I_{2,0}}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\nu_t + \mu_{2,0} + \mu)}$$

$$+ \frac{\mu_{3,0}\mu_{2,0}\sigma\xi(I_{1,0} + I_{0,0})}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\nu_t + \mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$+ \frac{\mu_{3,0}\mu_{2,0}I_{2,0}\nu_t}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)}$$

$$+ \frac{\mu_{3,0}\mu_{2,0}\sigma\xi\nu_t}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)},$$

$$m_{0,0} := 1$$

$$m_{1,0} := -\frac{\mu}{(\sigma\xi + \mu_{1,0} + \mu)}$$

$$m_{2,0} := -\frac{\sigma\xi\mu}{(\nu_t + \mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$m_{2,1} := -\frac{\sigma\xi\mu\nu_t}{(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$

$$m_{3,0} := -\frac{\mu_{1,0}\mu}{(\mu_{3,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)} - \frac{\mu_{2,0}\sigma\xi\mu}{(\mu_{3,0} + \mu)(\nu_t + \mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$
$$- \frac{\mu_{2,0}\sigma\xi\mu\nu_t}{(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}.$$

$$m_{4,0} := -\frac{\mu_{3,0}\mu_{1,0}\mu}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$
$$- \frac{\mu_{3,0}\mu_{2,0}\sigma\xi\mu}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\nu_t + \mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}$$
$$- \frac{\mu_{3,0}\mu_{2,0}\sigma\xi\mu\nu_t}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)(\sigma\xi + \mu_{1,0} + \mu)}.$$

Using the vector notation implies that we will have the same rate of infection function that was defined in the previous section when we considered the dynamics without an intervention,

$$\lambda(t) = \frac{B'\Phi + B'MY_{0,0}^{\star}(t)}{P'\Phi + P'MY_{0,0}^{\star}(t)}. \tag{4.23}$$

With both expressions for $\lambda(t)$ defined as they were when we solved for the equilibria in section 4.2.1 results with the same quadratic function in terms of $Y_{0,0}(t)$. Therefore,

$$\frac{B'\Phi + B'MY_{0,0}^{\star}(t)}{P'\Phi + P'MY_{0,0}^{\star}(t)} = \frac{I_{0,0} - \mu Y_{0,0}^{\star}(t)}{p_0 Y_{0,0}^{\star}(t)} \tag{4.24}$$

implies

$$(\mu P'M + p_0 B'M)(Y_{0,0}^{\star}(t))^2 + (p_0 B'\Phi + \mu P'\Phi - I_{0,0}P'M)Y_{0,0}^{\star}(t) - I_{0,0}P'\Phi = 0. \tag{4.25}$$

Emphasizing the only difference between equation (4.25) and the same equation (4.11) in section 4.2.1 is how each of the vectors, P, B, Φ, and M are defined. We will still check the standard notation,

$$f(Y_{0,0}^{\star}(t)) = (\mu P'M + p_0 B'M)\left(Y_{0,0}^{\star}(t) - \frac{p_0 B'\Phi + \mu P'\Phi - I_{0,0}P'M}{2(\mu P'M - p_0 B'M)}\right)^2$$

$$- I_{0,0}P'\Phi - \frac{(p_0 B'\Phi + \mu P'\Phi - I_{0,0}P'M)^2}{4(\mu P'M + p_0 B'M)},$$

and determine whether the quadratic equation (4.25) has 0, 1, or 2 roots. Yet again, the existence of a solution and the number of roots will depend on the sign of $(\mu P'M + p_0 B'M)$ and $\left(-I_{0,0}P'\Phi - \frac{(p_0 B'\Phi + \mu P'\Phi - I_{0,0}P'M)^2}{4(\mu P'M + p_0 B'M)}\right)^3$. Assuming that $(\mu P'M + p_0 B'M) \neq 0$ we have the following conditions for solutions.

- When $\left(-I_{0,0}P'\Phi - \frac{(p_0 B'\Phi + \mu P'\Phi - I_{0,0}P'M)^2}{4(\mu P'M + p_0 B'M)}\right)$ and $(\mu P'M + p_0 B'M)$ have the same sign, there are no solutions to (4.11).

- When $I_{0,0}P'\Phi = -\frac{(p_0 B'\Phi + \mu P'\Phi - I_{0,0}P'M)^2}{4(\mu P'M + p_0 B'M)}$ there is exactly one solution to equation (4.11).

- When $\left(-I_{0,0}P'\Phi - \frac{(p_0 B'\Phi + \mu P'\Phi - I_{0,0}P'M)^2}{4(\mu P'M + p_0 B'M)}\right)$ and $(\mu P'M + p_0 B'M)$ have opposing signs, there are exactly two solutions to (4.11).

For the parameter values presented in chapter 3 and the vector notation defined by equations (4.18) - (4.22),

$$\mu P'M + p_0 B'M \approx 0.0070660 > 0$$

$$-I_{0,0}P'\Phi - \frac{(p_0 B'\Phi + \mu P'\Phi - I_{0,0}P'M)^2}{4(\mu P'M + p_0 B'M)} \approx -32,820,709 < 0.$$

Therefore there are exactly two roots to equation (4.25) and using MatLab to find the numerical solution to each we get the following,

$$Y_{0,0}^{\star}(t) \approx -92,687 \tag{4.26a}$$

$$Y_{0,0}^{\star}(t) \approx 43,619 \tag{4.26b}$$

resulting with the following two equilibrium points,

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[3] Recall that most of the components of M are negative.

$$E^{\dagger} \approx \begin{bmatrix} -92,687 \\ 10,393 \\ 1,761 \\ 13,405 \\ 6,952 \\ 5,167 \end{bmatrix} \qquad E^{\star} \approx \begin{bmatrix} 43,619 \\ 634 \\ 159 \\ 1,213 \\ 576 \\ 428 \end{bmatrix}.$$

Noting again that one of the two mathematical solutions to the equilibrium points does not satisfy the physical limitation for the interpretation of the model (i.e. all of the compartments of the model are strictly non-negative), we are left with only one equilibrium point for the therapeutic model,

$$E_t^{\star} \approx \begin{bmatrix} 43,619 \\ 634 \\ 159 \\ 1,213 \\ 576 \\ 428 \end{bmatrix}.$$

This result implies that the long run expectation for the population as a whole when a therapeutic vaccine is administered is that the total population will stay around 46,629, with a steady prevalence of the infection around 6.5%.

Equilibrium Stability

The Jacobian and the derivation for the characteristic polynomial in symbolic form are both presented in appendix A. As a numerical approximation to the symbolic solution to the characteristic polynomial, at the endemic equilibrium we get the following,

$$c(x) = c_0 x^6 + c_1 x^5 + c_2 x^4 + c_3 x^3 + c_4 x^2 + c_5 x + c_6 \tag{4.27}$$

with the coefficients,

$$c_0 = 1$$

$$c_1 \approx 2.217397865783052$$

$$c_2 \approx 1.802908824781624$$

$$c_3 \approx 6.747477931309361\text{e-}01$$

$$c_4 \approx 1.160699718272295\text{e-}01$$

$$c_5 \approx 7.616996330660597\text{e-}03$$

$$c_6 \approx 1.188495639018756\text{e-}04.$$

For the fixed parameter values of the model we can verify that the endemic equilibrium is stable if all of the solutions to (4.27) have negative real parts. Solving for the roots numerically we get the following,

$$x \approx -8.956574588109634\text{e-}01$$

$$x \approx -4.983781016846317\text{e-}01$$

$$x \approx -3.925958681080570\text{e-}01$$

$$x \approx -3.100305547497526\text{e-}01$$

$$x \approx -9.853594264602114\text{e-}02$$

$$x \approx -2.219993978362754\text{e-}02.$$

Given all eigenvalues have negative real parts we can conclude that the equilibrium is asymptotically stable. To verify the stability we will also confirm the results by checking the conditions for Routh-Hurwitz criterion 4.1.3. For a 6th degree polynomial the Hurwitz determinants are defined by the following[4],

$$\Delta_1(c) = c_1$$

$$\Delta_2(c) = c_2\Delta_1 - c_0 c_3$$

$$\Delta_3(c) = c_3\Delta_2 - c_4 c_1^2 + c_5 c_1 c_0$$

$$\Delta_4(c) = c_4\Delta_3 - c_5 c_2\Delta_2 + c_5 c_4 c_1 c_0 - c_5^2 c_0^2 + c_6 c_2 c_1^2 - c_6 c_3 c_1 c_0$$

$$\Delta_5(c) = c_5\Delta_4 - c_6 c_3\Delta_3 + c_6 c_5 c_1\Delta_2 - c_6^2 c_1^3$$

$$\Delta_6(c) = c_6\Delta_5.$$

Using the numerical approximations to the characteristic polynomial (4.27) the approximations

---

[4]The derivation for each of the Hurwitz determines can be found in appendix B.

to the Hurwitz determinants are each evaluated to be the following,

$\Delta_1(c) \approx 2.217397865783052$

$\Delta_2(c) \approx 3.323018387141267$

$\Delta_3(c) \approx 1.688390211214303$

$\Delta_4(c) \approx 1.531153542540695\text{e-}01$

$\Delta_5(c) \approx 1.037397690930284\text{e-}03$

$\Delta_6(c) \approx 1.232942631598769\text{e-}07.$

Again we will address the accuracy for which the results of the calculations can be reliable. Noting that the derivation for the endemic equilibrium, the characteristic polynomial, and the Hurwitz determinants were all done analytically in symbolic form and each can be found either in this section, appendix A, or appendix B, respectively, the numerical approximations will therefore rely on the precision that MatLab evaluates the calculations. As we already mentioned in the previous section, MatLab stores and computes all numbers to the equivalent 16 digit value [23]. Therefore, it can again be concluded that the accuracy for each of the solutions to the Hurwitz determinants are all defined within machine precision.

Given the approximations for the Hurwitz determinants, as well as $c_0 = 1$, we can verify that the equilibrium point $E_t^\star$ just nearly satisfies the Criterion of Routh-Hurwitz for stability,

$c_0\Delta_1(c) \approx 2.217397865783052 > 0$

$\Delta_2(c) \approx 3.323018387141267 > 0$

$c_0\Delta_3(c) \approx 1.688390211214303 > 0$

$\Delta_4(c) \approx 1.531153542540695\text{e-}01 > 0$

$c_0\Delta_5(c) \approx 1.037397690930284\text{e-}03 > 0$

$\Delta_6(c) \approx 1.232942631598769\text{e-}07 > 0.$

To conclude with the equilibria and stability analysis for the therapeutic vaccine program there is only one physically relevant equilibrium point and based on the parameters values, as they are defined in section 3.1, it is asymptotically stable.

4.2.3 Preventative Vaccine Program

Continuing with the dynamical analysis for each of the intervention strategies we will introduce the dynamics as they are defined for the model when only the preventative vaccine is available:

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\nu_p + \mu + p_0\lambda(t))Y_{0,0}(t) + \omega Y_{0,1}(t) \tag{4.28a}$$

$$\frac{dY_{0,1}(t)}{dt} = \nu_p Y_{0,0}(t) - (\mu + \omega + p_0(1 - \varepsilon)\lambda_\nu(t))Y_{0,1}(t) \tag{4.28b}$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0\lambda(t)Y_{0,0}(t) - (\nu_p + \sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) + \omega Y_{1,1}(t) \tag{4.28c}$$

$$\frac{dY_{1,1}(t)}{dt} = \nu_p Y_{1,0}(t) + p_0(1 - \varepsilon)\lambda_\nu(t)Y_{0,1}(t) - (\omega + \sigma\xi + \mu_{1,1} + \mu)Y_{1,1}(t) \tag{4.28d}$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) - (\mu_{2,0} + \mu)Y_{2,0}(t) \tag{4.28e}$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{j=0}^{j=1}\sum_{i=1}^{i=2}\mu_{i,j}Y_{i,j}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t) \tag{4.28f}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t) \tag{4.28g}$$

where

$$\lambda(t) = \frac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1}p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)} \tag{4.29a}$$

$$\lambda_\nu(t) = \frac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1}p_i\beta_{i,j}\eta_{01,ij}Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)}. \tag{4.29b}$$

Equilibrium Calculations

To solve for the equilibria of the system when the preventative vaccine only is administered we set $\dfrac{dY_{i,0}(t)}{dt} = 0$ for $i = 0, 1, \ldots, 4$ and $j = 0, 1$ then solve for $Y^\star(t) = [Y_{0,0}^\star(t), Y_{0,1}^\star(t), Y_{1,0}^\star(t),$ $Y_{1,1}^\star(t), Y_{2,0}^\star(t), Y_{3,0}^\star(t), Y_{4,0}^\star(t)]^\intercal$. Therefore, the system of equations defined at the equilibria is given as:

$$0 = I_{0,0} - (\nu_p + \mu + p_0\lambda(t))Y_{0,0}^\star(t) + \omega Y_{0,1}^\star(t) \tag{4.30a}$$

$$0 = \nu_p Y_{0,0}^\star(t) - (\mu + \omega + p_0(1 - \varepsilon)\lambda_\nu(t))Y_{0,1}^\star(t) \tag{4.30b}$$

$$0 = I_{1,0} + p_0\lambda(t)Y_{0,0}^\star(t) - (\sigma\xi + \nu_p + \mu_{1,0} + \mu)Y_{1,0}^\star(t) + \omega Y_{1,1}^\star(t) \tag{4.30c}$$

$$0 = p_0(1 - \varepsilon)\lambda_\nu(t)Y_{0,1}^\star(t) + \nu_p Y_{1,0}^\star(t) - (\omega + \sigma\xi + \mu_{1,1} + \mu)Y_{1,1}^\star(t) \tag{4.30d}$$

$$0 = I_{2,0} + \sigma\xi(Y_{1,0}^\star(t) + Y_{1,1}^\star(t)) - (\mu_{2,0} + \mu)Y_{2,0}^\star(t) \tag{4.30e}$$

$$0 = I_{3,0} + \sum_{j=0}^{j=1}\sum_{i=1}^{i=2}\mu_{i,j}Y_{i,j}^\star(t) - (\mu_{3,0} + \mu)Y_{3,0}^\star(t) \tag{4.30f}$$

$$0 = \mu_{3,0}Y_{3,0}^\star(t) - (\mu_{4,0} + \mu)Y_{4,0}^\star(t). \tag{4.30g}$$

Recall from the introduction to the model in chapter 3, Edwards *et al.* introduced the model to analyze the impact that adverse effects of vaccinating can have on the effectiveness of various vaccination programs. To model this behavioral impact the introduction for two rate of infection functions was made: ① for the susceptible population that is unvaccinated (the primary rate of infection) and ② for the susceptible population that is vaccinated (accounting for the adverse effects). This implies when we consider the method we have already used for deriving the equilibrium for the model without an intervention and the therapeutic vaccine program this time we will need to take into consideration setting up two equations for each of the force of infection rates. Just as we derived in the previous sections, equation (4.30a) defines a second expression for the primary rate of infection, defined only at an equilibrium point,

$$\lambda(t) = \frac{I_{0,0} - (\nu_p + \mu)Y_{0,0}^{\star}(t) + \omega Y_{0,1}^{\star}(t)}{p_0 Y_{0,0}^{\star}(t)}. \tag{4.31}$$

Similarly, we also get a second expression for $\lambda_\nu(t)$ from equation (4.30b),

$$\lambda_\nu(t) = \frac{\nu_p Y_{0,0}^{\star}(t) - (\omega + \mu)Y_{0,1}^{\star}(t)}{p_0(1 - \varepsilon)Y_{0,1}^{\star}(t)}. \tag{4.32}$$

Plugging (4.31) and (4.32) into equations (4.30c) and (4.30d) respectively we get the following equivalent system of equations:

$$0 = \frac{I_{0,0} - (\nu_p + \mu)Y_{0,0}^{\star}(t) + \omega Y_{0,1}^{\star}(t)}{p_0 Y_{0,0}^{\star}(t)} - \lambda(t) \tag{4.33a}$$

$$0 = \frac{\nu_p Y_{0,0}^{\star}(t) - (\omega + \mu)Y_{0,1}^{\star}(t)}{p_0(1 - \varepsilon)Y_{0,1}^{\star}(t)} - \lambda_\nu(t) \tag{4.33b}$$

$$0 = I_{1,0} + I_{0,0} - (\nu_p + \mu)Y_{0,0}^{\star}(t) + \omega Y_{0,1}^{\star}(t) - (\sigma\xi + \nu_p + \mu_{1,0} + \mu)Y_{1,0}^{\star}(t) + \omega Y_{1,1}^{\star}(t) \tag{4.33c}$$

$$0 = \nu_p Y_{0,0}^{\star}(t) - (\omega + \mu)Y_{0,1}^{\star}(t) + \nu_p Y_{1,0}^{\star}(t) - (\omega + \sigma\xi + \mu_{1,1} + \mu)Y_{1,1}^{\star}(t) \tag{4.33d}$$

$$0 = I_{2,0} + \sigma\xi(Y_{1,0}^{\star}(t) + Y_{1,1}^{\star}(t)) - (\mu_{2,0} + \mu)Y_{2,0}^{\star}(t) \tag{4.33e}$$

$$0 = I_{3,0} + \sum_{j=0}^{j=1}\sum_{i=1}^{i=2}\mu_{i,j}Y_{i,j}^{\star}(t) - (\mu_{3,0} + \mu)Y_{3,0}^{\star}(t) \tag{4.33f}$$

$$0 = \mu_{3,0}Y_{3,0}^{\star}(t) - (\mu_{4,0} + \mu)Y_{4,0}^{\star}(t). \tag{4.33g}$$

Considering the method used before, where we defined each of the infectious states in terms of the susceptible population, we will again define each of the infectious states in terms of the susceptible populations. For the preventative vaccine only dynamics this implies that we will need to define each of the infectious states in terms of both the susceptible and unvaccinated

as well as the susceptible and vaccinated states. Thus, the objective now is to reduce the above system of equations (4.33) to a system of two equations defining the relationship between $Y_{0,0}^\star(t)$ and $Y_{0,1}^\star(t)$.

Starting with equation (4.33d)

$$Y_{1,1}^\star(t) = \frac{\nu_p}{(\sigma\xi + \omega + \mu_{1,1} + \mu)}Y_{0,0}^\star(t) - \frac{\omega + \mu}{(\sigma\xi + \omega + \mu_{1,1} + \mu)}Y_{0,1}^\star(t) + \frac{\nu_p}{(\sigma\xi + \omega + \mu_{1,1} + \mu)}Y_{1,0}^\star(t)$$

$$(4.34)$$

and plugging into equation (4.33c) we get the following representation for $Y_{1,0}^\star(t)$,

$$Y_{1,0}^\star(t) = \frac{(\sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}$$

$$+ \left[\frac{\omega\nu_p - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}\right]Y_{0,0}^\star(t)$$

$$+ \left[\frac{\omega(\sigma\xi + \mu_{1,1})}{(\sigma\xi + \nu_p + \mu_{1,0})(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}\right]Y_{0,1}^\star(t). \qquad (4.35)$$

Using (4.35) to express $Y_{1,1}^\star(t)$ in terms of $Y_{0,0}^\star(t)$ and $Y_{0,1}^\star(t)$, we get the following

$$Y_{1,1}^\star(t) = \frac{\nu_p(I_{1,0} + I_{0,0})}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}$$

$$+ \left[\frac{\nu_p(\sigma\xi + \mu_{1,0})}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}\right]Y_{0,0}^\star(t)$$

$$+ \left[\frac{\omega\nu_p - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}\right]Y_{0,1}^\star(t). \qquad (4.36)$$

Continuing to the following infectious state equations, we input (4.35) and (4.36) into equation (4.33e) to define $Y_{2,0}^\star(t)$ in terms of $Y_{0,0}^\star(t)$ and $Y_{0,1}^\star(t)$,

$$Y_{2,0}^\star(t) = \frac{I_{2,0}}{(\mu_{2,0} + \mu)} + \frac{\sigma\xi(\nu_p + \sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \left[\frac{\sigma\xi\big(\nu_p(\omega + \sigma\xi + \mu_{1,0}) - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)\big)}{(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}\right]Y_{0,0}^\star(t)$$

$$+ \left[\frac{\sigma\xi\big(\omega(\nu_p + \sigma\xi + \mu_{1,1}) - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)\big)}{(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}\right]Y_{0,1}^\star(t). \qquad (4.37)$$

Then (4.35), (4.36), and (4.37) input into (4.33f) results with

$$Y_{3,0}^{\star}(t) = \frac{I_{3,0}}{(\mu_{3,0} + \mu)} + \frac{\mu_{2,0}I_{2,0}}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)}$$

$$+ \frac{\mu_{2,0}\sigma\xi(\nu_p + \sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \frac{(\mu_{1,0}(\sigma\xi + \omega + \mu_{1,1} + \mu) + \mu_{1,1}\nu_p)(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \bigg[\frac{\mu_{2,0}\sigma\xi\big(\nu_p(\omega + \sigma\xi + \mu_{1,0}) - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)\big)}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \frac{\mu_{1,0}(\omega\nu_p - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)) + \mu_{1,1}\nu_p(\sigma\xi + \mu_{1,0})}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)} \bigg] Y_{0,0}^{\star}(t)$$

$$+ \bigg[\frac{\mu_{2,0}\sigma\xi\big(\omega(\nu_p + \sigma\xi + \mu_{1,1}) - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)\big)}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \frac{\mu_{1,0}\omega(\sigma\xi + \mu_{1,1}) + \mu_{1,1}(\omega\nu_p - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu))}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)} \bigg] Y_{0,1}^{\star}(t). \qquad (4.38)$$

Finally, we have $Y_{4,0}^{\star}(t)$ defined as the following

$$Y_{4,0}^{\star}(t) = \frac{\mu_{3,0}I_{3,0}}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)} + \frac{\mu_{3,0}\mu_{2,0}I_{2,0}}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)}$$

$$+ \frac{\mu_{3,0}\mu_{2,0}\sigma\xi(\nu_p + \sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \frac{\mu_{3,0}\big((\mu_{1,0}(\sigma\xi + \omega + \mu_{1,1} + \mu) + \mu_{1,1}\nu_p)(I_{1,0} + I_{0,0})\big)}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \bigg[\frac{\mu_{3,0}\mu_{2,0}\sigma\xi\big(\nu_p(\omega + \sigma\xi + \mu_{1,0}) - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)\big)}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \frac{\mu_{3,0}\big(\mu_{1,0}(\omega\nu_p - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)) + \mu_{1,1}\nu_p(\sigma\xi + \mu_{1,0})\big)}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)} \bigg] Y_{0,0}^{\star}(t)$$

$$+ \bigg[\frac{\mu_{3,0}\mu_{2,0}\sigma\xi\big(\omega(\nu_p + \sigma\xi + \mu_{1,1}) - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)\big)}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \frac{\mu_{3,0}\big(\mu_{1,0}\omega(\sigma\xi + \mu_{1,1}) + \mu_{1,1}(\omega\nu_p - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu))\big)}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)} \bigg] Y_{0,1}^{\star}(t).$$

$$(4.39)$$

Again, we will use vector notation to represent each of the infection rate functions, as they are originally defined in the model. In consideration that each of the infectious states are now defined in terms of the two distinct susceptible populations, we will define M for the coefficients of $Y_{0,0}^{\star}(t)$ and M_ν for the coefficients to $Y_{0,1}^{\star}(t)$. All other vector notation will be notated as before with the correct representation for the preventative vaccine model.

$$
P := \begin{bmatrix} p_0 \\ p_0 \\ p_1 \\ p_1 \\ p_2 \\ p_3 \\ p_4 \end{bmatrix}
\quad
B := \begin{bmatrix} 0 \\ 0 \\ p_1\beta_{1,0}\eta_{00,10} \\ p_1\beta_{1,1}\eta_{00,11} \\ p_2\beta_{2,0}\eta_{00,20} \\ p_3\beta_{3,0}\eta_{00,30} \\ p_4\beta_{4,0}\eta_{00,40} \end{bmatrix}
\quad
B_\nu := \begin{bmatrix} 0 \\ 0 \\ p_1\beta_{1,0}\eta_{01,10} \\ p_1\beta_{1,1}\eta_{01,11} \\ p_2\beta_{2,0}\eta_{01,20} \\ p_3\beta_{3,0}\eta_{01,30} \\ p_4\beta_{4,0}\eta_{01,40} \end{bmatrix}
\quad
\Phi := \begin{bmatrix} \phi_{0,0} \\ \phi_{0,1} \\ \phi_{1,0} \\ \phi_{1,1} \\ \phi_{2,0} \\ \phi_{3,0} \\ \phi_{4,0} \end{bmatrix}
$$

$$
M := \begin{bmatrix} m_{0,0} \\ m_{0,1} \\ m_{1,0} \\ m_{1,1} \\ m_{2,0} \\ m_{3,0} \\ m_{4,0} \end{bmatrix}
\quad
M_\nu := \begin{bmatrix} m_{0,0}^{\nu} \\ m_{0,1}^{\nu} \\ m_{1,0}^{\nu} \\ m_{1,1}^{\nu} \\ m_{2,0}^{\nu} \\ m_{3,0}^{\nu} \\ m_{4,0}^{\nu} \end{bmatrix}
\quad , \text{ such that}
$$

$\phi_{0,0} := 0$

$\phi_{0,1} := 0$

$$
\phi_{1,0} := \frac{(\sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0)})}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}
$$

$$
\phi_{1,1} := \frac{\nu_p(I_{1,0} + I_{0,0)})}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}
$$

$$
\phi_{2,0} := \frac{I_{2,0}}{(\mu_{2,0} + \mu)} + \frac{\sigma\xi(\nu_p + \sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}
$$

$$\phi_{3,0} := \frac{I_{3,0}}{(\mu_{3,0} + \mu)} + \frac{\mu_{2,0}I_{2,0}}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)}$$

$$+ \frac{\mu_{2,0}\sigma\xi(\nu_p + \sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \frac{(\mu_{1,0}(\sigma\xi + \omega + \mu_{1,1} + \mu) + \mu_{1,1}\nu_p)(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$\phi_{4,0} := \frac{\mu_{3,0}I_{3,0}}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)} + \frac{\mu_{3,0}\mu_{2,0}I_{2,0}}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)}$$

$$+ \frac{\mu_{3,0}\mu_{2,0}\sigma\xi(\nu_p + \sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \frac{\mu_{3,0}\big((\mu_{1,0}(\sigma\xi + \omega + \mu_{1,1} + \mu) + \mu_{1,1}\nu_p)(I_{1,0} + I_{0,0})\big)}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$m_{0,0} := 1$$

$$m_{0,1} := 0$$

$$m_{1,0} := \frac{\omega\nu_p - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}$$

$$m_{1,1} := \frac{\nu_p(\sigma\xi + \mu_{1,0})}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}$$

$$m_{2,0} := \frac{\sigma\xi\big(\nu_p(\omega + \sigma\xi + \mu_{1,0}) - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)\big)}{(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$m_{3,0} := \frac{\mu_{2,0}\sigma\xi\big(\nu_p(\omega + \sigma\xi + \mu_{1,0}) - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)\big)}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \frac{\mu_{1,0}(\omega\nu_p - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)) + \mu_{1,1}\nu_p(\sigma\xi + \mu_{1,0})}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$m_{4,0} := \frac{\mu_{3,0}\mu_{2,0}\sigma\xi\big(\nu_p(\omega + \sigma\xi + \mu_{1,0}) - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)\big)}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \frac{\mu_{3,0}\big(\mu_{1,0}(\omega\nu_p - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)) + \mu_{1,1}\nu_p(\sigma\xi + \mu_{1,0})\big)}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$m_{0,0}^{\nu} := 0$$

$$m_{0,0}^{\nu} := 1$$

$$m_{1,0}^{\nu} := \frac{\omega(\sigma\xi + \mu_{1,1})}{(\sigma\xi + \nu_p + \mu_{1,0})(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}$$

$$m_{1,1}^{\nu} := \frac{\omega\nu_p - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}$$

$$m_{2,0}^{\nu} := \frac{\sigma\xi\big(\omega(\nu_p + \sigma\xi + \mu_{1,1}) - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)\big)}{(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$m_{3,0}^{\nu} := \frac{\mu_{2,0}\sigma\xi\big(\omega(\nu_p + \sigma\xi + \mu_{1,1}) - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)\big)}{(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \frac{\mu_{1,0}\omega(\sigma\xi + \mu_{1,1}) + \mu_{1,1}(\omega\nu_p - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu))}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$m_{4,0}^{\nu} := \frac{\mu_{3,0}\mu_{2,0}\sigma\xi\big(\omega(\nu_p + \sigma\xi + \mu_{1,1}) - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)\big)}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \frac{\mu_{3,0}\big(\mu_{1,0}\omega(\sigma\xi + \mu_{1,1}) + \mu_{1,1}(\omega\nu_p - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu))\big)}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}.$$

With the vector notation we can now express each of the rate of infection functions as

$$\lambda(t) = \frac{B'\Phi + B'MY_{0,0}^{\star}(t) + B'M_{\nu}Y_{0,1}^{\star}(t)}{P'\Phi + P'MY_{0,0}^{\star}(t) + P'M_{\nu}Y_{0,1}^{\star}(t)} \tag{4.40}$$

$$\lambda_{\nu}(t) = \frac{B_{\nu}'\Phi + B_{\nu}'MY_{0,0}^{\star}(t) + B_{\nu}'M_{\nu}Y_{0,1}^{\star}(t)}{P'\Phi + P'MY_{0,0}^{\star}(t) + P'M_{\nu}Y_{0,1}^{\star}(t)}. \tag{4.41}$$

Setting equations (4.40) and (4.41) equal to (4.31) and (4.32) respectively, will result with the two equations needed for evaluating $Y_{0,0}^{\star}(t)$ and $Y_{0,1}^{\star}(t)$ at the equilibria,

$$\frac{I_{0,0} - (\nu_p + \mu)Y_{0,0}^{\star}(t) + \omega Y_{0,1}^{\star}(t)}{p_0 Y_{0,0}^{\star}(t)} = \frac{B'\Phi + B'MY_{0,0}^{\star}(t) + B'M_{\nu}Y_{0,1}^{\star}(t)}{P'\Phi + P'MY_{0,0}^{\star}(t) + P'M_{\nu}Y_{0,1}^{\star}(t)} \tag{4.42}$$

$$\frac{\nu_p Y_{0,0}^{\star}(t) - (\omega + \mu)Y_{0,1}^{\star}(t)}{p_0(1 - \varepsilon)Y_{0,1}^{\star}(t)} = \frac{B_{\nu}'\Phi + B_{\nu}'MY_{0,0}^{\star}(t) + B_{\nu}'M_{\nu}Y_{0,1}^{\star}(t)}{P'\Phi + P'MY_{0,0}^{\star}(t) + P'M_{\nu}Y_{0,1}^{\star}(t)}. \tag{4.43}$$

After simplifying equations (4.42) and (4.43) we have the following system of equations

$$0 = \left[(P'M)(\nu_p + \mu) + (B'M)p_0 \right] (Y^{\star}_{0,0}(t))^2$$
$$+ \Bigg[\big((B'M_\nu)p_0 + (P'M_\nu)(\nu_p + \mu) - (P'M)\omega \big) Y^{\star}_{0,1}(t)$$
$$+ \big((B'\Phi)p_0 + (P'\Phi)(\nu_p + \mu) - (P'M)I_{0,0} \big) \Bigg] Y^{\star}_{0,0}(t)$$
$$- \left[(P'M_\nu)\omega (Y^{\star}_{0,1}(t))^2 + \big((P'\Phi)\omega + (P'M_\nu)I_{0,0} \big) Y^{\star}_{0,1}(t) + (P'\Phi)I_{0,0} \right] \qquad (4.44)$$

$$0 = \left[(P'M_\nu)(\omega + \mu) + (B'_\nu M_\nu)p_0(1 - \varepsilon) \right] (Y^{\star}_{0,1}(t))^2$$
$$+ \Bigg[\big((P'M)(\omega + \mu) - (P'M_\nu)\nu_p + (B'_\nu M)p_0(1 - \varepsilon) \big) Y^{\star}_{0,0}(t)$$
$$+ \big((P'\Phi)(\omega + \mu) + (B'_\nu \Phi)p_0(1 - \varepsilon) \big) \Bigg] Y^{\star}_{0,1}(t)$$
$$- \left[(P'M)\nu_p (Y^{\star}_{0,0}(t))^2 + (P'\Phi)\nu_p Y^{\star}_{0,0}(t) \right]. \qquad (4.45)$$

To consolidate the calculations we will introduce the following parameters and continue with solving the system. For equation (4.44)

$$a_{00,2} := (P'M)(\nu_p + \mu) + (B'M)p_0$$
$$b_{00,1} := (B'M_\nu)p_0 + (P'M_\nu)(\nu_p + \mu) - (P'M)\omega$$
$$b_{00,2} := (B'\Phi)p_0 + (P'\Phi)(\nu_p + \mu) - (P'M)I_{0,0}$$
$$c_{00,0} := -(P'M_\nu)\omega$$
$$c_{00,1} := -(P'\Phi)\omega - (P'M_\nu)I_{0,0}$$
$$c_{00,2} := -(P'\Phi)I_{0,0}$$

and for equation (4.45) let

$$a_{01,2} := (P'M_\nu)(\omega + \mu) + (B'_\nu M_\nu)p_0(1 - \varepsilon)$$
$$b_{01,1} := (P'M)(\omega + \mu) - (P'M_\nu)\nu_p + (B'_\nu M)p_0(1 - \varepsilon)$$
$$b_{01,2} := (P'\Phi)(\omega + \mu) + (B'_\nu \Phi)p_0(1 - \varepsilon)$$
$$c_{01,0} := -(P'M)\nu_p$$
$$c_{01,1} := -(P'\Phi)\nu_p$$

then the system of equations can be more simply written as

$$0 = a_{00,2}(Y_{0,0}^{\star}(t))^2 + (b_{00,1}Y_{0,1}^{\star}(t) + b_{00,2})Y_{0,0}^{\star}(t) + c_{00,0}(Y_{0,1}^{\star}(t))^2 + c_{00,1}Y_{0,1}^{\star}(t) + c_{00,2} \qquad (4.46a)$$

$$0 = a_{01,2}(Y_{0,1}^{\star}(t))^2 + (b_{01,1}Y_{0,0}^{\star}(t) + b_{01,2})Y_{0,1}^{\star}(t) + c_{01,0}(Y_{0,0}^{\star}(t))^2 + c_{01,1}Y_{0,0}^{\star}(t). \qquad (4.46b)$$

From equation (4.46b), the quadratic formula can be used to define a solution for $Y_{0,1}^{\star}(t)$ in terms of $Y_{0,0}^{\star}(t)$,

$$Y_{0,1}^{\star}(t) = \frac{-b_{01,1}Y_{0,0}^{\star}(t) - b_{01,2} \pm \sqrt{(b_{01,1}Y_{0,0}^{\star}(t) + b_{01,2})^2 - 4a_{01,2}(c_{01,0}(Y_{0,0}^{\star}(t))^2 + c_{01,1}Y_{0,0}^{\star}(t))}}{2a_{01,2}}.$$

Focusing now on just the radicand we derive another quadratic expression in terms of $Y_{0,0}^{\star}(t)$,

$$(b_{01,1}Y_{0,0}^{\star}(t) + b_{01,2})^2 - 4a_{01,2}(c_{01,0}(Y_{0,0}^{\star}(t))^2 + c_{01,1}Y_{0,0}^{\star}(t))$$
$$= \left[(b_{01,1})^2 - 4a_{01,2}c_{01,0}\right](Y_{0,0}^{\star}(t))^2 + \left[2b_{01,1}b_{01,2} - 4a_{01,2}c_{01,1}\right]Y_{0,0}^{\star}(t) + (b_{01,2})^2.$$

Introducing another set of parameters to consolidate our calculations,

$$\alpha_{01,0} := (b_{01,1})^2 - 4a_{01,2}c_{01,0}$$

$$\alpha_{01,1} := 2b_{01,1}b_{01,2} - 4a_{01,2}c_{01,1}$$

$$\alpha_{01,2} := (b_{01,2})^2$$

and setting

$$Y_{0,1}^{\star}(t) = \frac{-b_{01,1}Y_{0,0}^{\star}(t) - b_{01,2} \pm \sqrt{\alpha_{01,0}(Y_{0,0}^{\star}(t))^2 + \alpha_{01,1}Y_{0,0}^{\star}(t) + \alpha_{01,2}}}{2a_{01,2}} \qquad (4.47)$$

we plug (4.47) into (4.44) to get,

$$0 = 4(a_{01,2})^2 a_{00,2}(Y_{0,0}^{\star}(t))^2 + 4(a_{01,2})^2 b_{00,2}Y_{0,0}^{\star}(t) + 4(a_{01,2})^2 c_{00,2}$$

$$+ 2(a_{01,2}b_{00,1})\left(-b_{01,1}Y_{0,0}^{\star}(t) - b_{01,2} \pm \sqrt{\alpha_{01,0}(Y_{0,0}^{\star}(t))^2 + \alpha_{01,1}Y_{0,0}^{\star}(t) + \alpha_{01,2}}\right)Y_{0,0}^{\star}(t)$$

$$+ c_{00,0}\left(-b_{01,1}Y_{0,0}^{\star}(t) - b_{01,2} \pm \sqrt{\alpha_{01,0}(Y_{0,0}^{\star}(t))^2 + \alpha_{01,1}Y_{0,0}^{\star}(t) + \alpha_{01,2}}\right)^2$$

$$+ 2a_{01,2}c_{00,1}\left(-b_{01,1}Y_{0,0}^{\star}(t) - b_{01,2} \pm \sqrt{\alpha_{01,0}(Y_{0,0}^{\star}(t))^2 + \alpha_{01,1}Y_{0,0}^{\star}(t) + \alpha_{01,2}}\right).$$

Expanding and reorganizing the expressions results with

$$\Big(\big(2a_{01,2}b_{00,1} - 2c_{00,0}b_{01,1} \big) Y_{0,0}^{\star}(t) + 2a_{01,2}c_{00,1} - 2c_{00,0}b_{01,2} \Big)$$

$$\times \Big(\pm \sqrt{\alpha_{01,0}(Y_{0,0}^{\star}(t))^2 + \alpha_{01,1}Y_{0,0}^{\star}(t) + \alpha_{01,2}} \Big)$$

$$= \Big(4(a_{01,2})^2 a_{00,2} - 2a_{01,2}b_{00,1}b_{01,1} + c_{00,0}\alpha_{01,0} \Big)(Y_{0,0}^{\star}(t))^2$$

$$+ \Big(4(a_{01,2})^2 b_{00,2} - 2a_{01,2}b_{00,1}b_{01,2} - 2a_{01,2}c_{00,1}b_{01,1}$$

$$+ 2c_{00,0}b_{01,1}b_{01,2} + c_{00,0}\alpha_{01,1} \Big) Y_{0,0}^{\star}(t)$$

$$+ 4(a_{01,2})^2 c_{00,2} - 2a_{01,2}c_{00,1}b_{01,2} + c_{00,0}(b_{01,2})^2 + c_{00,0}\alpha_{01,2}.$$

And, yet again, we will introduce our last set of parameters for the purpose of consolidating the calculations as we work toward a solution to the equilibrium,

$$\phi_1 := 2a_{01,2}b_{00,1} - 2c_{00,0}b_{01,1}$$
$$\phi_2 := 2a_{01,2}c_{00,1} - 2c_{00,0}b_{01,2}$$
$$\gamma_0 := 4(a_{01,2})^2 a_{00,2} + c_{00,0}(b_{01,1})^2 + c_{00,0}\alpha_{01,0} - 2a_{01,2}b_{00,1}b_{01,1}$$
$$\gamma_1 := 4(a_{01,2})^2 b_{00,2} + 2c_{00,0}b_{01,1}b_{01,2} + c_{00,0}\alpha_{01,1} - 2a_{01,2}b_{00,1}b_{01,2} - 2a_{01,2}c_{00,1}b_{01,1}$$
$$\gamma_2 := 4(a_{01,2})^2 c_{00,2} + c_{00,0}(b_{01,2})^2 + c_{00,0}\alpha_{01,2} - 2a_{01,2}c_{00,1}b_{01,2},$$

implies,

$$\left[\big(\phi_1 Y_{0,0}^{\star}(t) + \phi_2 \big) \Big(\pm \sqrt{\alpha_{01,0}(Y_{0,0}^{\star}(t))^2 + \alpha_{01,1}Y_{0,0}^{\star}(t) + \alpha_{01,2}} \Big) \right]^2$$

$$= \left[\gamma_0(Y_{0,0}^{\star}(t))^2 + \gamma_1 Y_{0,0}^{\star}(t) + \gamma_2 \right]^2.$$

Upon squaring each side of the equation, we see that the solution for $Y_{0,0}^{\star}(t)$ is independent of the sign for the radical expression. After expanding and combining like terms we get the following quartic equation for $Y_{0,0}^{\star}(t)$,

$$0 = \left[\gamma_0^2 - \phi_1^2 \alpha_{01,0} \right](Y_{0,0}^{\star}(t))^4 + \left[2\gamma_0\gamma_1 - \phi_1^2 \alpha_{01,1} - 2\phi_1\phi_2\alpha_{01,0} \right](Y_{0,0}^{\star}(t))^3$$

$$+ \left[\gamma_1^2 + 2\gamma_0\gamma_2 - 2\gamma_1\gamma_2\alpha_{01,1} - \phi_1^2\alpha_{01,2} - \phi_2^2\alpha_{01,0} \right](Y_{0,0}^{\star})^2$$

$$+ \left[2\gamma_1\gamma_2 - 2\phi_1\phi_2\alpha_{01,2} - \phi_2^2\alpha_{01,1} \right]Y_{0,0}^{\star}(t) + \left[\gamma_2^2 - \phi_2^2\alpha_{01,2} \right].$$

Now, going to a numerical solver we input the original parameter assumptions along with each of the defined parameters we introduced into the calculations and solve for the roots of the quartic expression to the get the following solutions,

$$Y_{0,0}^{\star}(t) \approx 178,153$$

$$Y_{0,0}^{\star}(t) \approx 6,903$$

$$Y_{0,0}^{\star}(t) \approx 4,073$$

$$Y_{0,0}^{\star}(t) \approx -1,177.$$

For each solution to $Y_{0,0}^{\star}(t)$ we get two solutions for $Y_{0,1}^{\star}(t)$. In table 4.1 we let $b(Y_{0,0}^{\star}(t)) = -b_{01,1}Y_{0,0}^{\star}(t) - b_{01,2}$ and $\alpha(Y_{0,0}^{\star}(t)) = \alpha_{01,0}(Y_{0,0}^{\star}(t))^2 + \alpha_{01,1}Y_{0,0}^{\star}(t) + \alpha_{01,2}$.

Table 4.1: Solutions to $Y_{0,1}^{\star}(t)$ evaluated from the quadratic expression for each solution to $Y_{0,0}^{\star}(t)$ for the preventative vaccine only model.

$Y_{0,0}^{\star}(t)$	$Y_{0,1}^{\star}(t) = \dfrac{b(Y_{0,0}^{\star}(t)) + \sqrt{\alpha(Y_{0,0}^{\star}(t))}}{2a_{01,2}}$	$Y_{0,1}^{\star}(t) = \dfrac{b(Y_{0,0}^{\star}(t)) - \sqrt{\alpha(Y_{0,0}^{\star}(t))}}{2a_{01,2}}$
178,153	1,128,273	-193,515
6,903	42,246	-21,937
4,073	24,508	-19,312
-1,177	-5,677	-17,160

Before moving on to define the equilibrium points to the dynamical system we will first verify that the solutions to $Y_{0,0}^{\star}(t)$ and $Y_{0,1}^{\star}(t)$ in table 4.1 satisfy equations (4.46a) and (4.46b). In doing so, we found for each solution for $Y_{0,0}^{\star}(t)$ there is only one corresponding solution to $Y_{0,1}^{\star}(t)$ that satisfies the original system. Thus, after checking all solutions found in table 4.1 we are left with only the four $(Y_{0,0}^{\star}(t), Y_{0,1}^{\star}(t))$ pairs in table 4.2 that satisfy equations (4.46a) and (4.46b). Thus, using the verified solutions for $Y_{0,0}^{\star}(t)$ and $Y_{0,1}^{\star}(t)$, along with the expressions for each of the infectious states defined by equations (4.35) - (4.39) we get the following four solutions for the equilibrium points to the dynamical system used to defined the infectious disease model when a preventative vaccine is introduced.

Table 4.2: Verified solutions to $Y_{0,1}^\star(t)$ for each solution of $Y_{0,0}^\star(t)$ for the preventative vaccine only model.

$Y_{0,0}^\star(t)$	$Y_{0,1}^\star(t) = \dfrac{b(Y_{0,0}^\star(t)) + \sqrt{\alpha(Y_{0,0}^\star(t))}}{2a_{01,2}}$	$Y_{0,1}^\star(t) = \dfrac{b(Y_{0,0}^\star(t)) - \sqrt{\alpha(Y_{0,0}^\star(t))}}{2a_{01,2}}$
178,153	1,128,273	**-193,515**
6,903	**42,246**	-21,937
4,073	24,508	**-19,312**
-1,177	-5,677	**-17,160**

$$
E_1^\dagger \approx \begin{bmatrix} 178,153 \\ -193,515 \\ -133,849 \\ 138,706 \\ 5,242 \\ 3,454 \\ 2,567 \end{bmatrix}
\qquad
E^\star \approx \begin{bmatrix} 6,903 \\ 42,246 \\ 71 \\ 166 \\ 580 \\ 331 \\ 246 \end{bmatrix}
\qquad
E_2^\dagger \approx \begin{bmatrix} 4,073 \\ -19,312 \\ -2,954 \\ 7,802 \\ 5,233 \\ 3,448 \\ 2,562 \end{bmatrix}
\qquad
E_3^\dagger \approx \begin{bmatrix} -1,177 \\ -17,160 \\ 745 \\ 4,324 \\ 5,457 \\ 3,598 \\ 2,674 \end{bmatrix}
$$

Just as we have seen in the analysis of the previous models, we again have only one physically relevant equilibrium point. Therefore, to continue our analysis of the dynamical system when a preventative vaccine is present we will only need to evaluate the stability of the one endemic equilibrium point,

$$
E_p^\star \approx \begin{bmatrix} 6,903 \\ 42,246 \\ 71 \\ 166 \\ 580 \\ 331 \\ 246 \end{bmatrix}.
$$

Equilibrium Stability

In referencing appendix A where the full symbolic representation for the Jacobian matrix is presented we will again evaluate the eigenvalues of the system and determine the stability of the equilibria $E_c^\star$. Given the size of the system the calculations required to derive the characteristic

polynomial in symbolic form are far to computationally intensive and will not be evaluated. Instead the numerical approximation to the coefficients of the characteristic polynomial was derived using the 'poly' function in MatLab,

$$c(x) = c_0 x^7 + c_1 x^6 + c_2 x^5 + c_3 x^4 + c_4 x^3 + c_5 x^2 + c_6 x + c_7 \qquad (4.48)$$

with the coefficients,

$c_0 = 1$

$c_1 \approx 3.376272183437085$

$c_2 \approx 4.387961784494099$

$c_3 \approx 2.800292114176461$

$c_4 \approx 9.265143626371679\text{e-}01$

$c_5 \approx 1.515818025675994\text{e-}01$

$c_6 \approx 1.018052814755124\text{e-}02$

$c_7 \approx 1.607176324024748\text{e-}04.$

For the fixed parameter values of the model we can verify that the endemic equilibrium is stable if all of the solutions to (4.64) have negative real parts. Solving for the roots numerically we get the following,

$x \approx -1.159622474835404$

$x \approx -8.734244681842751\text{e-}01$

$x \approx -4.816493409460326\text{e-}01$

$x \approx -4.289209890026219\text{e-}01$

$x \approx -2.918423857965558\text{e-}01$

$x \approx -1.186262672926165\text{e-}01$

$x \approx -2.218625737957888\text{e-}02.$

Given all eigenvalues have negative real parts we can conclude that the equilibrium is asymptotically stable. To verify the stability we will also confirm the results by checking the conditions for Routh-Hurwitz criterion 4.1.3. For a 7th degree polynomial the Hurwitz determinants are defined by the following[5]

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[5]The derivation for each of the Hurwitz determinants can be found in appendix B.

$$\Delta_1(c) = c_1$$

$$\Delta_2(c) = c_2\Delta_1 - c_0 c_3$$

$$\Delta_3(c) = c_3\Delta_2 - c_4 c_1^2 + c_5 c_1 c_0$$

$$\Delta_4(c) = c_4\Delta_3 - c_5 c_2\Delta_2 + c_5 c_4 c_1 c_0 - c_5^2 c_0^2 + c_6 c_2 c_1^2 - c_6 c_3 c_1 c_0 - c_7 c_2 c_1 c_0 + c_7 c_3 c_0^2$$

$$\Delta_5(c) = c_5\Delta_4 - c_6 c_3\Delta_3 + (c_6 c_5 c_1 + c_7 c_3 c_2 - c_7 c_4 c_1)\Delta_2 - c_6^2 c_1^3 + c_6 c_7 c_1^2 c_0$$
$$\qquad\qquad - c_7 c_3 c_4 c_1 c_0 + c_7 c_3 c_5 c_0^2 + c_7 c_6 c_1^2 c_0 - c_7^2 c_1 c_0^2$$

$$\Delta_6(c) = c_6\Delta_5 - c_7 c_4\Delta_4 + c_7 c_6 c_2\Delta_3 + (c_7^2 c_4 c_0 - c_7^2 c_2^2 - c_7 c_6 c_5 c_0)\Delta_2$$
$$\qquad\qquad + c_7 c_6^2 c_1^2 c_0 - c_7^2 c_6 c_1 c_0^2 + c_7^2 c_2 c_4 c_1 c_0 - c_7^2 c_2 c_5 c_0^2 - c_7^2 c_6 c_1 c_0^2 + c_7^3 c_0^3$$

$$\Delta_7(c) = c_7\Delta_6.$$

Thus, to verify the stability of the endemic equilibrium point, $E_p^\star$, for the preventative vaccine model we will again use a numerical solver to evaluate the approximation to each of the Hurwitz determinants,

$$\Delta_1(c) \approx 3.376272183437085$$

$$\Delta_2(c) \approx 12.01466120079592$$

$$\Delta_3(c) \approx 44.71787779957474$$

$$\Delta_4(c) \approx 34.30261806001776$$

$$\Delta_5(c) \approx 4.003863356067739$$

$$\Delta_6(c) \approx 3.556684851783046\text{e-}02$$

$$\Delta_7(c) \approx 5.716219685803183\text{e-}06.$$

Noting that the solutions to the Hurwitz determinants are not as 'small' as they were in the cases for the model without an intervention and the therapeutic only variations, they are 'small' enough to address again the accuracy of the calculations. One major difference in the calculations for the Hurwitz determinants in the preventative only variation of the model, was the need to use the built-in function 'poly' in MatLab to solve for the characteristic polynomial. The concern that a numerical method for deriving the coefficients to the characteristic polynomial could reduce the accuracy for the solution is alleviated by the fact that 'poly' uses the summation algorithm for which the error depends on the floating-point precision [24]. Therefore, the accuracy for the numerical solution to the Hurwitz determinants are within machine precision.

Given the approximations for the Hurwitz determinants, as well as $c_0 = 1$, we can verify at the endemic equilibrium point $E_p^\star$ the Criterion of Routh-Hurwitz for stability is just nearly

satisfied,

$$c_0\Delta_1(c) \approx 3.376272183437085 > 0$$
$$\Delta_2(c) \approx 12.01466120079592 > 0$$
$$c_0\Delta_3(c) \approx 44.71787779957474 > 0$$
$$\Delta_4(c) \approx 34.30261806001776 > 0$$
$$c_0\Delta_5(c) \approx 4.003863356067739 > 0$$
$$\Delta_6(c) \approx 3.556684851783046\text{e-}02 > 0$$
$$c_0\Delta_7(c) \approx 5.716219685803183\text{e-}06 > 0.$$

Thus we have found that the endemic equilibrium point for the preventative vaccine program dynamics, $E_p^\star$ is locally asymptotically stable. By checking the conditions from Routh-Hurwitz criterion for stability we find that the conditions are just nearly met, but we can say that $E_p^\star$ is more stable than $E_b^\star$ and $E_t^\star$.

4.2.4 Combined, Preventative and Therapeutic, Vaccine Program

We conclude the equilibrium and stability analysis for each of the intervention strategies with the dynamics for the combined vaccination strategy. For the full model with both vaccines, the preventative and therapeutic, we have the following system of ordinary differential equations:

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\nu_p + \mu + p_0\lambda(t))Y_{0,0}(t) + \omega Y_{0,1}(t) \tag{4.49a}$$

$$\frac{dY_{0,1}(t)}{dt} = \nu_p Y_{0,0}(t) - (\mu + \omega + p_0(1-\varepsilon)\lambda_\nu(t))Y_{0,1}(t) \tag{4.49b}$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0\lambda(t)Y_{0,0}(t) - (\nu_p + \sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) + \omega Y_{1,1}(t) \tag{4.49c}$$

$$\frac{dY_{1,1}(t)}{dt} = \nu_p Y_{1,0}(t) + p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}(t) - (\omega + \sigma\xi + \mu_{1,1} + \mu)Y_{1,1}(t) \tag{4.49d}$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) - (\nu_t + \mu_{2,0} + \mu)Y_{2,0}(t) \tag{4.49e}$$

$$\frac{dY_{2,1}(t)}{dt} = \nu_t Y_{2,0}(t) - (\mu_{2,1} + \mu)Y_{2,1}(t) \tag{4.49f}$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{j=0}^{j=1}\sum_{i=1}^{i=2}\mu_{i,j}Y_{i,j}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t) \tag{4.49g}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t) \tag{4.49h}$$

with

$$\lambda(t) = \frac{\sum_{i=1}^{i=4} \sum_{j=0}^{j=1} p_i \beta_{i,j} \eta_{00,ij} Y_{i,j}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)} \tag{4.50a}$$

$$\lambda_\nu(t) = \frac{\sum_{i=1}^{i=4} \sum_{j=0}^{j=1} p_i \beta_{i,j} \eta_{01,ij} Y_{i,j}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)}. \tag{4.50b}$$

Equilibrium Calculations

To solve for the equilibria of the system with the combined intervention strategy we set $\frac{dY_{i,0}(t)}{dt} = 0$ for $i = 0, 1, \ldots, 4$ and $j = 0, 1$ then solve for $Y^\star(t) = [Y_{0,0}^\star(t), Y_{0,1}^\star(t), Y_{1,0}^\star(t), Y_{1,1}^\star(t),$ $Y_{2,0}^\star(t), Y_{2,1}^\star(t), Y_{3,0}^\star(t), Y_{4,0}^\star(t)]^\mathsf{T}$. This results with the following system of equations:

$$0 = I_{0,0} - (\nu_p + \mu + p_0\lambda(t))Y_{0,0}^\star(t) + \omega Y_{0,1}^\star(t) \tag{4.51a}$$

$$0 = \nu_p Y_{0,0}^\star(t) - (\mu + \omega + p_0(1-\varepsilon)\lambda_\nu(t))Y_{0,1}^\star(t) \tag{4.51b}$$

$$0 = I_{1,0} + p_0\lambda(t)Y_{0,0}^\star(t) - (\sigma\xi + \nu_p + \mu_{1,0} + \mu)Y_{1,0}^\star(t) + \omega Y_{1,1}^\star(t) \tag{4.51c}$$

$$0 = p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}^\star(t) + \nu_p Y_{1,0}^\star(t) - (\omega + \sigma\xi + \mu_{1,1} + \mu)Y_{1,1}^\star(t) \tag{4.51d}$$

$$0 = I_{2,0} + \sigma\xi(Y_{1,0}^\star(t) + Y_{1,1}^\star(t)) - (\nu_t + \mu_{2,0} + \mu)Y_{2,0}^\star(t) \tag{4.51e}$$

$$0 = \nu_t Y_{2,0}^\star(t) - (\mu_{2,1} + -\mu)Y_{2,1}^\star(t) \tag{4.51f}$$

$$0 = I_{3,0} + \sum_{j=0}^{j=1} \sum_{i=1}^{i=2} \mu_{i,j} Y_{i,j}^\star(t) - (\mu_{3,0} + \mu)Y_{3,0}^\star(t) \tag{4.51g}$$

$$0 = \mu_{3,0} Y_{3,0}^\star(t) - (\mu_{4,0} + \mu)Y_{4,0}^\star(t). \tag{4.51h}$$

The approach for evaluating the equilibria for the system with the combined vaccine strategy is the same method we used to solve for the equilibria for the preventative vaccine program. Noting that the addition of the therapeutic vaccine to the preventative only system implies that the first four equations of the current system, (4.51a) - (4.51d), are the same as the first four equations from the preventative vaccine analysis, (4.30a) - (4.30d). This results with the same expressions for each of the infection rate functions, as well as the two distinct states for the asymptomatic and unaware populations,

$$\lambda(t) = \frac{I_{0,0} - (\nu_p + \mu)Y_{0,0}^\star(t) + \omega Y_{0,1}^\star(t)}{p_0 Y_{0,0}^\star(t)} \tag{4.52}$$

$$\lambda_\nu(t) = \frac{\nu_p Y_{0,0}^\star(t) - (\omega + \mu)Y_{0,1}^\star(t)}{p_0(1-\varepsilon)Y_{0,1}^\star(t)} \tag{4.53}$$

$$Y_{1,0}^\star(t) = \frac{(\sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}$$

$$+ \left[\frac{\omega\nu_p - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p} \right] Y_{0,0}^\star(t)$$

$$+ \left[\frac{\omega(\sigma\xi + \mu_{1,1})}{(\sigma\xi + \nu_p + \mu_{1,0})(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p} \right] Y_{0,1}^\star(t) \qquad (4.54)$$

$$Y_{1,1}^\star(t) = \frac{\nu_p(I_{1,0} + I_{0,0})}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}$$

$$+ \left[\frac{\nu_p(\sigma\xi + \mu_{1,0})}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p} \right] Y_{0,0}^\star(t)$$

$$+ \left[\frac{\omega\nu_p - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p} \right] Y_{0,1}^\star(t). \qquad (4.55)$$

Next, evaluating the rest of the infectious states using the expressions defined for $Y_{1,0}^\star(t)$ and $Y_{1,1}^\star(t)$, as well as each of the following expressions for the next consecutive populations, we get the following

$$Y_{2,0}^\star(t) = \frac{I_{2,0}}{(\nu_t + \mu_{2,0} + \mu)}$$

$$+ \frac{\sigma\xi(\nu_p + \sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \left[\frac{\sigma\xi\big(\nu_p(\omega + \sigma\xi + \mu_{1,0}) - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)\big)}{(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)} \right] Y_{0,0}^\star(t)$$

$$+ \left[\frac{\sigma\xi\big(\omega(\nu_p + \sigma\xi + \mu_{1,1}) - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)\big)}{(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)} \right] Y_{0,1}^\star(t) \qquad (4.56)$$

$$Y_{2,1}^{\star}(t) = \frac{\nu_t I_{2,0}}{(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)}$$

$$+ \frac{\nu_t \sigma\xi(\nu_p + \sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \left[\frac{\nu_t \sigma\xi\big(\nu_p(\omega + \sigma\xi + \mu_{1,0}) - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)\big)}{(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}\right] Y_{0,0}^{\star}(t)$$

$$+ \left[\frac{\nu_t \sigma\xi\big(\omega(\nu_p + \sigma\xi + \mu_{1,1}) - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)\big)}{(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}\right] Y_{0,1}^{\star}(t)$$

$$\tag{4.57}$$

$$Y_{3,0}^{\star}(t) = \frac{I_{3,0}}{(\mu_{3,0} + \mu)} + \frac{(\mu_{1,0}(\sigma\xi + \nu_p + \mu_{1,1} + \mu) + \mu_{1,1}\nu_p)(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \left(\frac{\mu_{2,0}(\mu_{2,1} + \mu) + \mu_{2,1}\nu_t}{(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)}\right)$$

$$\times \left[\frac{I_{2,0}}{(\nu_t + \mu_{2,0} + \mu)}\right.$$

$$+ \left.\frac{\sigma\xi(\nu_p + \sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}\right]$$

$$+ \left[\frac{\sigma\xi\big(\mu_{2,0}(\mu_{2,1} + \mu) + \mu_{2,1}\nu_t\big)\big(\nu_p(\omega + \sigma\xi + \mu_{1,0}) - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)\big)}{(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}\right.$$

$$+ \left.\frac{\mu_{3,0}\big(\mu_{1,0}(\omega\nu_p - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)) + \mu_{1,1}\nu_p(\sigma\xi + \mu_{1,0})\big)}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}\right] Y_{0,0}^{\star}(t)$$

$$+ \left[\frac{\sigma\xi\big(\mu_{2,0}(\mu_{2,1} + \mu) + \mu_{2,1}\nu_t\big)\big(\omega(\nu_p + \sigma\xi + \mu_{1,1}) - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)\big)}{(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}\right.$$

$$+ \left.\frac{\mu_{1,0}\omega(\sigma\xi + \mu_{1,1}) + \mu_{1,1}(\omega\nu_p - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu))}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}\right] Y_{0,1}^{\star}(t) \tag{4.58}$$

$$Y_{4,0}^{\star}(t) = \left(\frac{\mu_{3,0}}{(\mu_{4,0} + \mu)} \right)$$

$$\times \left[\frac{I_{3,0}}{(\mu_{3,0} + \mu)} + \frac{(\mu_{1,0}(\sigma\xi + \nu_p + \mu_{1,1} + \mu) + \mu_{1,1}\nu_p)(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)} \right.$$

$$+ \left(\frac{\mu_{2,0}(\mu_{2,1} + \mu) + \mu_{2,1}\nu_t}{(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)} \right) \left[\frac{I_{2,0}}{(\nu_t + \mu_{2,0} + \mu)} \right.$$

$$\left. + \frac{\sigma\xi(\nu_p + \sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)} \right]$$

$$+ \left[\frac{\sigma\xi\big(\mu_{2,0}(\mu_{2,1} + \mu) + \mu_{2,1}\nu_t\big)\big(\nu_p(\omega + \sigma\xi + \mu_{1,0}) - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)\big)}{(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)} \right.$$

$$\left. + \frac{\mu_{3,0}\big(\mu_{1,0}(\omega\nu_p - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)) + \mu_{1,1}\nu_p(\sigma\xi + \mu_{1,0})\big)}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)} \right] Y_{0,0}^{\star}(t)$$

$$+ \left[\frac{\sigma\xi\big(\mu_{2,0}(\mu_{2,1} + \mu) + \mu_{2,1}\nu_t\big)\big(\omega(\nu_p + \sigma\xi + \mu_{1,1}) - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)\big)}{(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)} \right.$$

$$\left. + \frac{\mu_{1,0}\omega(\sigma\xi + \mu_{1,1}) + \mu_{1,1}(\omega\nu_p - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu))}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)} \right] Y_{0,1}^{\star}(t) \right].$$

$$(4.59)$$

Based on equations (4.54) - (4.59) we now have the following vector notation that will be used for each of the original rate of infection functions

$$P := \begin{bmatrix} p_0 \\ p_0 \\ p_1 \\ p_1 \\ p_2 \\ p_2 \\ p_3 \\ p_4 \end{bmatrix}, \quad B := \begin{bmatrix} 0 \\ 0 \\ p_1\beta_{1,0}\eta_{00,10} \\ p_1\beta_{1,1}\eta_{00,11} \\ p_2\beta_{2,0}\eta_{00,20} \\ p_2\beta_{2,1}\eta_{00,21} \\ p_3\beta_{3,0}\eta_{00,30} \\ p_4\beta_{4,0}\eta_{00,40} \end{bmatrix} \quad B_\nu := \begin{bmatrix} 0 \\ 0 \\ p_1\beta_{1,0}\eta_{01,10} \\ p_1\beta_{1,1}\eta_{01,11} \\ p_2\beta_{2,0}\eta_{01,20} \\ p_2\beta_{2,1}\eta_{01,21} \\ p_3\beta_{3,0}\eta_{01,30} \\ p_4\beta_{4,0}\eta_{01,40} \end{bmatrix} \quad \Phi := \begin{bmatrix} \phi_{0,0} \\ \phi_{0,1} \\ \phi_{1,0} \\ \phi_{1,1} \\ \phi_{2,0} \\ \phi_{2,1} \\ \phi_{3,0} \\ \phi_{4,0} \end{bmatrix}$$

$$M := \begin{bmatrix} m_{0,0} \\ m_{0,1} \\ m_{1,0} \\ m_{1,1} \\ m_{2,0} \\ m_{2,1} \\ m_{3,0} \\ m_{4,0} \end{bmatrix} \quad M_\nu := \begin{bmatrix} m_{0,0}^\nu \\ m_{0,1}^\nu \\ m_{1,0}^\nu \\ m_{1,1}^\nu \\ m_{2,0}^\nu \\ m_{2,1}^\nu \\ m_{3,0}^\nu \\ m_{4,0}^\nu \end{bmatrix} \text{, such that}$$

$\phi_{0,0} := 0$

$\phi_{0,1} := 0$

$$\phi_{1,0} := \frac{(\sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}$$

$$\phi_{1,1} := \frac{\nu_p(I_{1,0} + I_{0,0})}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}$$

$$\phi_{2,0} := \frac{I_{2,0}}{(\nu_t + \mu_{2,0} + \mu)} + \frac{\sigma\xi(\nu_p + \sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$\phi_{2,1} := \frac{\nu_t I_{2,0}}{(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)}$$

$$+ \frac{\nu_t\sigma\xi(\nu_p + \sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$\phi_{3,0} := \frac{I_{3,0}}{(\mu_{3,0} + \mu)} + \frac{(\mu_{1,0}(\sigma\xi + \nu_p + \mu_{1,1} + \mu) + \mu_{1,1}\nu_p)(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \left(\frac{\mu_{2,0}(\mu_{2,1} + \mu) + \mu_{2,1}\nu_t}{(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)}\right)\left(\frac{I_{2,0}}{(\nu_t + \mu_{2,0} + \mu)}\right.$$

$$+ \left.\frac{\sigma\xi(\nu_p + \sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}\right)$$

$$+ \frac{(\mu_{1,0}(\sigma\xi + \omega + \mu_{1,1} + \mu) + \mu_{1,1}\nu_p)(I_{1,0} + I_{0,0})}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$\phi_{4,0} := \frac{\mu_{3,0} I_{3,0}}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)}$$

$$+ \frac{\mu_{3,0}(\mu_{1,0}(\sigma\xi + \nu_p + \mu_{1,1} + \mu) + \mu_{1,1}\nu_p)(I_{1,0} + I_{0,0})}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \Big(\frac{\mu_{3,0}\mu_{2,0}(\mu_{2,1} + \mu) + \mu_{2,1}\nu_t}{(\mu_{4,0} + \mu)(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)}\Big)\Big(\frac{I_{2,0}}{(\nu_t + \mu_{2,0} + \mu)}$$

$$+ \frac{\sigma\xi(\nu_p + \sigma\xi + \omega + \mu_{1,1} + \mu)(I_{1,0} + I_{0,0})}{(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}\Big)$$

$$m_{0,0} := 1$$

$$m_{0,1} := 0$$

$$m_{1,0} := \frac{\omega\nu_p - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}$$

$$m_{1,1} := \frac{\nu_p(\sigma\xi + \mu_{1,0})}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}$$

$$m_{2,0} := \frac{\sigma\xi\big(\nu_p(\omega + \sigma\xi + \mu_{1,0}) - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)\big)}{(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$m_{2,1} := \frac{\nu_t\sigma\xi\big(\nu_p(\omega + \sigma\xi + \mu_{1,0}) - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)\big)}{(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$m_{3,0} := \frac{\sigma\xi\big(\mu_{2,0}(\mu_{2,1} + \mu) + \mu_{2,1}\nu_t\big)\big(\nu_p(\omega + \sigma\xi + \mu_{1,0}) - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)\big)}{(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \frac{\mu_{3,0}\big(\mu_{1,0}(\omega\nu_p - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)) + \mu_{1,1}\nu_p(\sigma\xi + \mu_{1,0})\big)}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$m_{4,0} := \frac{\sigma\xi\big(\mu_{2,0}(\mu_{2,1} + \mu) + \mu_{2,1}\nu_t\big)\big(\nu_p(\omega + \sigma\xi + \mu_{1,0}) - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)\big)}{(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$+ \frac{\mu_{3,0}\big(\mu_{1,0}(\omega\nu_p - (\nu_p + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu)) + \mu_{1,1}\nu_p(\sigma\xi + \mu_{1,0})\big)}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$m^\nu_{0,0} := 0$$

$$m^\nu_{0,0} := 1$$

$$m^\nu_{1,0} := \frac{\omega(\sigma\xi + \mu_{1,1})}{(\sigma\xi + \nu_p + \mu_{1,0})(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}$$

$$m^\nu_{1,1} := \frac{\omega\nu_p - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)}{(\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p}$$

$$m^\nu_{2,0} := \frac{\sigma\xi\big(\omega(\nu_p + \sigma\xi + \mu_{1,1}) - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)\big)}{(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$m^\nu_{2,1} := \frac{\nu_t\sigma\xi\big(\omega(\nu_p + \sigma\xi + \mu_{1,1}) - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)\big)}{(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$m^\nu_{3,0} := \frac{\sigma\xi\big(\mu_{2,0}(\mu_{2,1} + \mu) + \mu_{2,1}\nu_t\big)\big(\omega(\nu_p + \sigma\xi + \mu_{1,1}) - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)\big)}{(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$
$$+ \frac{\mu_{1,0}\omega(\sigma\xi + \mu_{1,1}) + \mu_{1,1}(\omega\nu_p - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu))}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$

$$m^\nu_{4,0} := \frac{\sigma\xi\big(\mu_{2,0}(\mu_{2,1} + \mu) + \mu_{2,1}\nu_t\big)\big(\omega(\nu_p + \sigma\xi + \mu_{1,1}) - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu)\big)}{(\mu_{3,0} + \mu)(\mu_{2,1} + \mu)(\nu_t + \mu_{2,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}$$
$$+ \frac{\mu_{1,0}\omega(\sigma\xi + \mu_{1,1}) + \mu_{1,1}(\omega\nu_p - (\omega + \mu)(\sigma\xi + \nu_p + \mu_{1,0} + \mu))}{(\mu_{3,0} + \mu)\big((\sigma\xi + \nu_p + \mu_{1,0} + \mu)(\sigma\xi + \omega + \mu_{1,1} + \mu) - \omega\nu_p\big)}.$$

Again we have the following two expressions for the infection rate functions, defined using the vector notation given above,

$$\lambda(t) = \frac{B'\Phi + B'MY^\star_{0,0}(t) + B'M_\nu Y^\star_{0,1}(t)}{P'\Phi + P'MY^\star_{0,0}(t) + P'M_\nu Y^\star_{0,1}(t)} \tag{4.60}$$

$$\lambda_\nu(t) = \frac{B'_\nu\Phi + B'_\nu MY^\star_{0,0}(t) + B'_\nu M_\nu Y^\star_{0,1}(t)}{P'\Phi + P'MY^\star_{0,0}(t) + P'M_\nu Y^\star_{0,1}(t)}. \tag{4.61}$$

Then as we had in section 4.2.3, setting equations (4.60) and (4.61) equal to (4.52) and (4.53) respectively, will result with two equations for $Y^\star_{0,0}(t)$ and $Y^\star_{0,1}(t)$. To recall the solution and parameters we introduced in the last section we will give a brief description here,

$$0 = a_{00,2}(Y_{0,0}(t))^2 + (b_{00,1}Y_{0,1}(t) + b_{00,2})Y_{0,0}(t) + c_{00,0}(Y_{0,1}(t))^2 + c_{00,1}Y_{0,1}(t) + c_{00,2} \tag{4.62a}$$
$$0 = a_{01,2}(Y_{0,1}(t))^2 + (b_{01,1}Y_{0,0}(t) + b_{01,2})Y_{0,1}(t) + c_{01,0}(Y_{0,0}(t))^2 + c_{01,1}Y_{0,0}(t)) \tag{4.62b}$$

where

$$a_{00,2} = (P'M)(\nu_p + \mu) + (B'M)p_0$$

$$b_{00,1} = (B'M_\nu)p_0 + (P'M_\nu)(\nu_p + \mu) - (P'M)\omega$$

$$b_{00,2} = (B'\Phi)p_0 + (P'\Phi)(\nu_p + \mu) - (P'M)I_{0,0}$$

$$c_{00,0} = -(P'M_\nu)\omega$$

$$c_{00,1} = -(P'\Phi)\omega - (P'M_\nu)I_{0,0}$$

$$c_{00,2} = -(P'\Phi)I_{0,0}$$

$$a_{01,2} = (P'M_\nu)(\omega + \mu) + (B'_\nu M_\nu)p_0(1 - \varepsilon)$$

$$b_{01,1} = (P'M)(\omega + \mu) - (P'M_\nu)\nu_p + (B'_\nu M)p_0(1 - \varepsilon)$$

$$b_{01,2} = (P'\Phi)(\omega + \mu) + (B'_\nu \Phi)p_0(1 - \varepsilon)$$

$$c_{01,0} = -(P'M)\nu_p$$

$$c_{01,1} = -(P'\Phi)\nu_p.$$

Then from equation (4.62b) we get

$$Y^\star_{0,1}(t) = \frac{-b_{01,1}Y^\star_{0,0}(t) - b_{01,2} \pm \sqrt{\alpha_{01,0}(Y^\star_{0,0}(t))^2 + \alpha_{01,1}Y^\star_{0,0}(t) + \alpha_{01,2}}}{2a_{01,2}} \tag{4.63}$$

when $\alpha_{01,0}$, $\alpha_{01,1}$ and $\alpha_{01,2}$ are defined as the following

$$\alpha_{01,0} = (b_{01,1})^2 - 4a_{01,2}c_{01,0}$$

$$\alpha_{01,1} = 2b_{01,1}b_{01,2} - 4a_{01,2}c_{01,1}$$

$$\alpha_{01,2} = (b_{01,2})^2.$$

Plugging (4.63) into equation (4.62a) and introducing the final set of parameters

$$\phi_1 = 2a_{01,2}b_{00,1} - 2c_{00,0}b_{01,1}$$

$$\phi_2 = 2a_{01,2}c_{00,1} - 2c_{00,0}b_{01,2}$$

$$\gamma_0 = 4(a_{01,2})^2 a_{00,2} + c_{00,0}(b_{01,1})^2 + c_{00,0}\alpha_{01,0} - 2a_{01,2}b_{00,1}b_{01,1}$$

$$\gamma_1 = 4(a_{01,2})^2 b_{00,2} + 2c_{00,0}b_{01,1}b_{01,2} + c_{00,0}\alpha_{01,1} - 2a_{01,2}b_{00,1}b_{01,2} - 2a_{01,2}c_{00,1}b_{01,1}$$

$$\gamma_2 = 4(a_{01,2})^2 c_{00,2} + c_{00,0}(b_{01,2})^2 + c_{00,0}\alpha_{01,2} - 2a_{01,2}c_{00,1}b_{01,2},$$

we derived the quartic expression for $Y_{0,0}(t)$,

$$0 = \left[\gamma_0^2 - \phi_1^2\alpha_{01,0}\right](Y_{0,0}^\star(t))^4 + \left[2\gamma_0\gamma_1 - \phi_1^2\alpha_{01,1} - 2\phi_1\phi_2\alpha_{01,0}\right](Y_{0,0}^\star(t))^3$$
$$+ \left[\gamma_1^2 + 2\gamma_0\gamma_2 - 2\gamma_1\gamma_2\alpha_{01,1} - \phi_1^2\alpha_{01,2} - \phi_2^2\alpha_{01,0}\right](Y_{0,0}^\star)^2$$
$$+ \left[2\gamma_1\gamma_2 - 2\phi_1\phi_2\alpha_{01,2} - \phi_2^2\alpha_{01,1}\right]Y_{0,0}^\star(t) + \left[\gamma_2^2 - \phi_2^2\alpha_{01,2}\right].$$

Next, inputing the parameter assumptions and vector notation as they are defined for the combined strategy analysis the solutions for each of the roots to the quartic expression are given,

$$Y_{0,0}^\star(t) \approx 212,405$$
$$Y_{0,0}^\star(t) \approx 6,871$$
$$Y_{0,0}^\star(t) \approx 5,113$$
$$Y_{0,0}^\star(t) \approx -1,807.$$

For each solution to $Y_{0,0}^\star(t)$ we get two solutions for $Y_{0,1}^\star(t)$. In table 4.3 we let $b(Y_{0,0}^\star(t)) = -b_{01,1}Y_{0,0}^\star(t) - b_{01,2}$ and $\alpha(Y_{0,0}^\star(t)) = \alpha_{01,0}(Y_{0,0}^\star(t))^2 + \alpha_{01,1}Y_{0,0}^\star(t) + \alpha_{01,2}$.

Table 4.3: Solutions to $Y_{0,1}^\star(t)$ from the quadratic expression for each solution to $Y_{0,0}^\star(t)$ for the combined strategy model.

$Y_{0,0}^\star(t)$	$Y_{0,1}^\star(t) = \dfrac{b(Y_{0,0}^\star(t)) + \sqrt{\alpha(Y_{0,0}^\star(t))}}{2a_{01,2}}$	$Y_{0,1}^\star(t) = \dfrac{b(Y_{0,0}^\star(t)) - \sqrt{\alpha(Y_{0,0}^\star(t))}}{2a_{01,2}}$
212,405	1,352,947	-230,538
6,871	42,021	-24,665
5,113	30,957	-23,053
-1,807	-8,125	-21,177

We will again check the solutions to $Y_{0,0}^\star(t)$ and $Y_{0,1}^\star(t)$ to confirm that the solutions satisfy the reduced system of equations (4.46a) - (4.46b). The results of our verification are given in table 4.4. Thus, using the verified solutions for $Y_{0,0}^\star(t)$ and $Y_{0,1}^\star(t)$, along with the expressions for each of the infectious states defined by equations (4.54) - (4.59) we get the following four solutions for the equilibrium points to the dynamical system used to defined the infectious disease

model when a the combined, preventative and therapeutic, vaccine strategy is introduced,

Table 4.4: Verified solutions to $Y_{0,1}^\star(t)$ for each solution of $Y_{0,0}^\star(t)$ for the combined strategy model.

$Y_{0,0}^\star(t)$	$Y_{0,1}^\star(t) = \dfrac{b(Y_{0,0}^\star(t)) + \sqrt{\alpha(Y_{0,0}^\star(t))}}{2a_{01,2}}$	$Y_{0,1}^\star(t) = \dfrac{b(Y_{0,0}^\star(t)) - \sqrt{\alpha(Y_{0,0}^\star(t))}}{2a_{01,2}}$
212,405	1,352,947	**-230,538**
6,871	**42,021**	-24,665
5,113	30,957	**-23,053**
-1,807	-8,125	**-21,177**

$$E_1^\dagger \approx \begin{bmatrix} 212,405 \\ -230,538 \\ -159,824 \\ 164,870 \\ 885 \\ 6,736 \\ 3,465 \\ 2,575 \end{bmatrix} \quad E^\star \approx \begin{bmatrix} 6,871 \\ 42,021 \\ 74 \\ 181 \\ 97 \\ 741 \\ 330 \\ 245 \end{bmatrix} \quad E_2^\dagger \approx \begin{bmatrix} 5,113 \\ -23,053 \\ -3,952 \\ 8,994 \\ 883 \\ 6,719 \\ 3,456 \\ 2,568 \end{bmatrix} \quad E_3^\dagger \approx \begin{bmatrix} -1,807 \\ -21,177 \\ 847 \\ 4,555 \\ 942 \\ 7,170 \\ 3,692 \\ 2,744 \end{bmatrix}.$$

Just as we have seen in the analysis of the previous models, we again have only one physically relevant equilibrium point. Therefore, to continue our analysis of the dynamical system when the combined vaccination strategy is present we will only need to evaluate the stability of the one endemic equilibrium point,

$$E_c^\star = \begin{bmatrix} 6,871 \\ 42,021 \\ 74 \\ 181 \\ 97 \\ 741 \\ 330 \\ 245 \end{bmatrix}.$$

Equilibrium Stability

In referencing appendix A where the full symbolic representation for the Jacobian matrix is presented we will again evaluate the eigenvalues of the system and determine the stability of the equilibrium $E_c^\star$. Given the size of the system the calculations required to derive the characteristic polynomial in symbolic form will not be evaluated. Instead the numerical approximation to the coefficients of the characteristic polynomial was derived using the 'poly' function in MatLab,

$$c(x) = c_0 x^8 + c_1 x^7 + c_2 x^6 + c_3 x^5 + c_4 x^4 + c_5 x^3 + c_6 x^2 + c_7 x + c_8 \tag{4.64}$$

with the coefficients

$c_0 = 1$

$c_1 \approx 4.196533446473763$

$c_2 \approx 7.116144689040367$

$c_3 \approx 6.325660802484393$

$c_4 \approx 3.235613786491986$

$c_5 \approx 1.000397183370066$

$c_6 \approx 1.894899658645659\text{e-}01$

$c_7 \approx 1.906773638444585\text{e-}02$

$c_8 \approx 3.405782269716043\text{e-}04.$

For the fixed parameter values of the model we can verify that the endemic equilibrium is stable if all of the solutions to (4.64) have negative real parts. Solving for the roots numerically we get the following,

$x \approx -1.159924292995883$

$x \approx -9.871685753240487\text{e-}01$

$x \approx -8.561350492855480\text{e-}01$

$x \approx -4.884164960525558\text{e-}01$

$x \approx -4.103824189504522\text{e-}01$

$x \approx -1.361337159979307\text{e-}01 + (2.437350577832072\text{e-}01)i$

$x \approx -1.361337159979307\text{e-}01 - (2.437350577832072\text{e-}01)i$

$x \approx -2.223918186941349\text{e-}02.$

Given all eigenvalues have negative real parts we can conclude that the equilibrium is asymptotically stable. To verify the stability we will also confirm the results by checking the conditions for Routh-Hurwitz criterion 4.1.3. For an 8th degree polynomial the Hurwitz determinants are defined by the following[6]

$$\Delta_1(c) = c_1$$
$$\Delta_2(c) = c_2\Delta_1 - c_0 c_3$$
$$\Delta_3(c) = c_3\Delta_2 - c_4 c_1^2 + c_5 c_1 c_0$$
$$\Delta_4(c) = c_4\Delta_3 - c_5 c_2\Delta_2 + c_5 c_4 c_1 c_0 - c_5^2 c_0^2 + c_6 c_2 c_1^2 - c_6 c_3 c_1 c_0 - c_7 c_2 c_1 c_0 + c_7 c_3 c_0^2$$
$$\Delta_5(c) = c_5\Delta_4 - c_6 c_3\Delta_3 + (c_6 c_5 c_1 + c_7 c_3 c_2 - c_7 c_4 c_1)\Delta_2 - c_6^2 c_1^3 + c_6 c_7 c_1^2 c_0 - c_7 c_3 c_4 c_1 c_0$$
$$+ c_7 c_3 c_5 c_0^2 + c_7 c_6 c_1^2 c_0 - c_7^2 c_1 c_0^2 - c_8 c_3 c_2 c_1^2 + c_8 c_3^2 c_0 c_1 + c_8 c_4 c_1^3 - c_8 c_5 c_1^2 c_0$$
$$\Delta_6(c) = c_6\Delta_5 - c_7 c_4\Delta_4 + (c_7 c_6 c_2 + c_8 c_4 c_3 - c_8 c_5 c_2)\Delta_3$$
$$+ (c_7^2 c_4 c_0 - c_7 c_6 c_5 c_0 - c_7^2 c_2^2 - c_8 c_4 c_5 c_1 + c_8 c_5^2 c_0 + c_8 c_7 c_2 c_1 - c_8 c_7 c_3 c_0)\Delta_2$$
$$+ c_7 c_6^2 c_1^2 c_0 - c_7^2 c_6 c_1 c_0^2 + c_7^2 c_2 c_4 c_0 c_1 - c_7^2 c_2 c_5 c_0^2 - c_7^2 c_6 c_1 c_0^2 + c_7^3 c_0^3$$
$$+ c_7 c_8 c_2^2 c_1^2 - c_7 c_8 c_2 c_3 c_0 c_1 - c_7 c_8 c_4 c_1^2 c_0 + c_7 c_8 c_5 c_1 c_0^2$$
$$+ c_8 c_4 c_6 c_1^3 + c_8 c_4 c_7 c_1^2 c_0 - c_8 c_5 c_6 c_1^2 c_0 + c_8 c_5 c_7 c_1 c_0^2 - c_8^2 c_2 c_1^3 + c_8^2 c_3 c_1^2 c_0$$
$$\Delta_7(c) = c_7\Delta_6 - c_8 c_5\Delta_5 + c_8 c_7 c_3\Delta_4$$
$$+ (c_8^2 c_5 c_1 - c_8 c_7 c_6 c_1 - c_8^2 c_3^2)\Delta_3 + (c_8 c_7^2 c_1 c_2 + c_8^2 c_3 c_5 c_1 - c_8^2 c_7 c_1^2)\Delta_2$$
$$- c_8 c_7^2 c_1^2 c_4 c_0 + c_8 c_7^2 c_1 c_5 c_0^2 - c_8^2 c_7 c_1^3 c_2 + c_8^2 c_7 c_1^2 c_3 c_0 - c_8^2 c_3 c_6 c_1^3$$
$$+ c_8^2 c_3 c_7 c_1^2 c_0 + c_8^3 c_1^4$$
$$\Delta_8(c) = c_8\Delta_7.$$

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[6]The derivation for each of the Hurwitz determinants can be found in appendix B.

Evaluating the numerical approximation to each of the Hurwitz determinants for the characteristic polynomial at the endemic equilibrium for the combined strategy model we get,

$\Delta_1(c) \approx 4.196533446473763$

$\Delta_2(c) \approx 23.53747839502015$

$\Delta_3(c) \approx 210.0703527901395$

$\Delta_4(c) \approx 542.9950805724345$

$\Delta_5(c) \approx 319.9971836041562$

$\Delta_6(c) \approx 32.95073190264795$

$\Delta_7(c) \approx 5.397579299874337\text{e-}01$

$\Delta_8(c) \approx 1.838297987889835\text{e-}04.$

Now, given the approximations for the Hurwitz determinants, as well as $c_0 = 1$, we can verify that the equilibrium point $E_{p_1}^\star$ just nearly satisfies the Criterion of Routh-Hurwitz for stability,

$c_0\Delta_1(c) \approx 4.196533446473763 > 0$

$\Delta_2(c) \approx 23.53747839502015 > 0$

$c_0\Delta_3(c) \approx 210.0703527901395 > 0$

$\Delta_4(c) \approx 542.9950805724345 > 0$

$c_0\Delta_5(c) \approx 319.9971836041562 > 0$

$\Delta_6(c) \approx 32.95073190264795 > 0$

$c_0\Delta_7(c) \approx 5.397579299874337\text{e-}01 > 0$

$\Delta_8(c) \approx 1.838297987889835\text{e-}04 > 0.$

Therefore, by the Routh-Hurwitz Criterion for Stability the endemic equilibrium, $E_c^\star$, for the combined strategy model is locally asymptotically stable. Just as we mentioned with the equilibria for the other three variations of our infectious disease model, consideration can be made regarding the sensitivity for the stability of the equilibria based on any variation in the parameters. For the purposes of optimizing an intervention strategy knowing that each variation of the state space has exactly one physically relevant equilibrium that is locally asymptotically stable is sufficient.

4.3 Consideration for a Disease-Free Equilibrium

So far we have shown that each variation of the state space has exactly one feasible equilibrium and each is locally asymptotically stable. As we proceed with the control analysis, in later chapters, this will be the only expectation for the system when no intervention is present. Alternatively, to give a full epidemiological analysis of the infectious disease model we consider the behavior for a disease-free equilibrium when we assume constant immigration can only occur into the susceptible class.

To evaluate the system for a disease-free equilibrium we must first consider altering the dynamics so that constant immigration into the infective classes is no longer present. Recall from table 3.2 that overall immigration into the population is defined by the product between the non-AIDS related annual death rate (μ) and the initial size of the total population (Y_0) with the assumption that 90% of immigration belongs to the susceptible population, 8% are considered asymptomatic [7], while the last 2% of the incoming population are assumed to be symptomatic. Assuming that immigration into the infected population has ceased, we will assume that 100% of immigration belongs to the susceptible class, resulting with $I_{0,0} = \mu Y_0$. Thus, considering the dynamics for the system when no intervention is present (4.1) and assume that immigration will only occur in the susceptible class results with the following system of ordinary differential equations:

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\mu + p_0\lambda(t))Y_{0,0}(t) \tag{4.65a}$$

$$\frac{dY_{1,0}(t)}{dt} = p_0\lambda(t)Y_{0,0}(t) - (\sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) \tag{4.65b}$$

$$\frac{dY_{2,0}(t)}{dt} = \sigma\xi Y_{1,0}(t) - (\mu_{2,0} + \mu)Y_{2,0}(t) \tag{4.65c}$$

$$\frac{dY_{3,0}(t)}{dt} = \sum_{i=1}^{i=2} \mu_{i,0}Y_{i,0}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t) \tag{4.65d}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - \mu_{4,0}Y_{4,0}(t) - \mu Y_{4,0}(t) \tag{4.65e}$$

with only the primary infection rate function,

$$\lambda(t) = \frac{\sum_{j=0}^{j=1}\sum_{i=1}^{i=4} p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)}{\sum_{j=0}^{j=1}\sum_{i=1}^{i=4} p_iY_{i,j}(t)}. \tag{4.66}$$

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[7]The additional assumption is that half of the asymptomatic population entering the system is aware of their infection and half are note. Implying that 4% of immigration belong to the asymptomatic-unaware population and 4% belong to the asymptomatic-aware population.

Equilibrium Calculations

To determine the symbolic representation for the disease-free equilibrium point we set the five differential terms and four infectious states to zero and solve for the susceptible population. In doing so the system of equations (4.65) reduces to the following single equation in terms of $Y_{0,0}^{\star}(t)$; keeping in mind that $\lambda(t) = 0$ when the infected populations are equal to zero,

$$0 = I_{0,0} - \mu Y_{0,0}^{\star}(t).$$

Thus, the disease-free equilibrium point exists and is defined when all of the infective classes are zero,

$$E_{b_0}^{\star} = [I_{0,0}/\mu, 0, 0, 0, 0]^{\mathsf{T}},$$

where we use $E_{b_0}^{\star}$ to denote the base model disease-free equilibrium (when immigration only occurs in the susceptible population).

Recall, we initially assumed that all immigration will flow into the susceptible population only, which resulted with $I_{0,0} = \mu Y_0$. This implies that the disease-free equilibrium simplifies to

$$E_{b_0}^{\star} = [Y_0, 0, 0, 0, 0]^{\mathsf{T}}.$$

Since the initial population for the model described in section 3.1 is assumed to be 55,816 the disease-free equilibrium is,

$$E_{b_0}^{\star} = \begin{bmatrix} 55,816 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}.$$

Equilibrium Stability

To evaluate the stability of the disease-free equilibrium we will again consider whether the Criterion from Routh-Hurwitz for stability is satisfied. To begin, note that the solution to the characteristic polynomial when we remove the terms for constant immigration into the infective classes will be the same as the solution for the characteristic polynomial we derived for the base model without an intervention. Therefore, referring to appendix A we can evaluate the coefficients for the characteristic polynomial at $E_{b_0}^{\star} = [Y_0, 0, 0, 0, 0]$.

Recalling $\lambda(t)$ is dependent on the state variables we will begin by evaluating $\lambda(t)$ as well as all corresponding partial derivatives with respect to each of the state variables,

$$\lambda(t)|_{E_{b_0}^\star} = \left.\frac{\sum_{i=1}^{i=4} p_i \beta_{i,0} \eta_{00,i0} Y_{i,0}(t)}{\sum_{i=0}^{i=4} p_i Y_{i,0}(t)}\right|_{E_{b_0}^\star} = \frac{0}{p_0 Y_0} = 0.$$

The derivative of $\lambda(t)$ with respect to $Y_{0,0}(t)$, the susceptible class, at the disease-free equilibrium is also zero,

$$\lambda_{[0,0]}(t)|_{E_{b_0}^\star} = \left.\frac{-p_0 \sum_{i=1}^{i=4} p_i \beta_{i,0} \eta_{00,i0} Y_{i,0}(t)}{\left(\sum_{i=0}^{i=4} p_i Y_{i,0}(t)\right)^2}\right|_{E_{b_0}^\star} = \frac{0}{(p_0 Y_0)^2} = 0.$$

For each of the infective classes, $Y_{k,0}(t)$ for $k = 1, 2, \ldots, 4$, the respective partial derivatives of $\lambda(t)$ at the disease-free equilibrium are defined as the following,

$$\begin{aligned}
\lambda_{[k,0]}(t)|_{E_{b_0}^\star} &= \left.\frac{p_k \beta_{k,0} \eta_{00,k0} \sum_{i=0}^{i=4} p_i Y_{i,0}(t) - p_k \sum_{i=1}^{i=4} p_i \beta_{i,0} \eta_{00,i0} Y_{i,0}(t)}{\left(\sum_{i=0}^{i=4} p_i Y_{i,0}(t)\right)^2}\right|_{E_{b_0}^\star} \\
&= \frac{p_k \beta_{k,0} \eta_{00,k0} (p_0 Y_0)}{(p_0 Y_0)^2} \\
&= \frac{p_k \beta_{k,0} \eta_{00,k0}}{p_0 Y_0}.
\end{aligned}$$

Therefore, the coefficients of the characteristic polynomial defined by the parameters at the disease-free equilibrium are

$$c_0 = 1$$
$$c_1 = (\sigma\xi + \mu_{1,0} + \mu_{2,0} + \mu_{3,0} + \mu_{4,0} + 5\mu) - (p_1 \beta_{1,0} \eta_{00,10})$$
$$\begin{aligned}
c_2 = {}&(\sigma\xi + \mu_{1,0} + 2\mu)(\mu_{2,0} + \mu_{3,0} + \mu_{4,0} + 3\mu) \\
&+ \mu(\sigma\xi + \mu_{1,0} + \mu) + \left((\mu_{2,0} + \mu)(\mu_{3,0} + \mu) + (\mu_{2,0} + \mu_{3,0} + 2\mu)(\mu_{4,0} + \mu)\right) \\
&- (\mu_{2,0} + \mu_{3,0} + \mu_{4,0} + 4\mu)(p_1 \beta_{1,0} \eta_{00,10}) - \sigma\xi(p_2 \beta_{2,0} \eta_{00,20}) - \mu_{1,0}(p_3 \beta_{3,0} \eta_{00,30})
\end{aligned}$$

$$c_3 = (\sigma\xi + \mu_{1,0} + \mu)\big((\mu_{2,0} + \mu)(\mu_{3,0} + \mu) + (\mu_{2,0} + \mu_{3,0} + 2\mu)(\mu_{4,0} + \mu)\big)$$
$$+ \mu(\sigma\xi + \mu_{1,0} + \mu)(\mu_{2,0} + \mu_{3,0} + \mu_{4,0} + 3\mu) + (\mu_{2,0} + \mu)(\mu_{3,0} + \mu)(\mu_{4,0} + \mu)$$
$$- \Big((\mu_{2,0} + \mu)(\mu_{3,0} + \mu) + (\mu_{2,0} + \mu_{3,0} + 2\mu)(\mu_{4,0} + \mu)$$
$$+ \mu(\mu_{2,0} + \mu_{3,0} + \mu_{4,0} + 3\mu)\Big)(p_1\beta_{1,0}\eta_{00,10})$$
$$- \sigma\xi(\mu_{3,0} + \mu_{4,0+3\mu})(p_2\beta_{2,0}\eta_{00,20}) - (\sigma\xi\mu_{2,0} + \mu_{1,0}(\mu_{2,0} + \mu_{4,0} + 3\mu))(p_3\beta_{3,0}\eta_{00,30})$$
$$+ \mu_{1,0}\mu_{3,0}(p_4\beta_{4,0}\eta_{00,40})$$

$$c_4 = (\sigma\xi + \mu_{1,0} + \mu)(\mu_{2,0} + \mu)(\mu_{3,0} + \mu)(\mu_{4,0} + \mu)$$
$$+ \mu(\sigma\xi + \mu_{1,0} + \mu)\big((\mu_{2,0} + \mu)(\mu_{3,0} + \mu) + (\mu_{2,0} + \mu_{3,0} + 2\mu)(\mu_{4,0} + \mu)\big)$$
$$- \Big((\mu_{2,0} + \mu)(\mu_{3,0} + \mu)(\mu_{4,0} + \mu) + \mu\big((\mu_{2,0} + \mu)(\mu_{3,0} + \mu)$$
$$+ (\mu_{2,0} + \mu_{3,0} + 2\mu)(\mu_{4,0} + \mu)\big)\Big)(p_1\beta_{1,0}\eta_{00,10})$$
$$- \sigma\xi\big((\mu_{3,0} + \mu)(\mu_{4,0} + \mu)\mu(\mu_{3,0} + \mu_{4,0} + 2\mu)\big)(p_2\beta_{2,0}\eta_{00,20})$$
$$- \Big(\sigma\xi\mu_{2,0}(\mu_{4,0} + \mu) + \mu_{1,0}\big((\mu_{2,0} + \mu)(\mu_{4,0} + \mu)$$
$$+ \mu(\mu_{2,0} + \mu_{4,0} + 2\mu)\big)\Big)(p_3\beta_{3,0}\eta_{00,30})$$
$$- \big(\sigma\xi\mu_{2,0}\mu_{3,0} + \mu_{1,0}\mu_{3,0}(\mu_{2,0} + 2\mu)\big)(p_4\beta_{4,0}\eta_{00,40})$$

$$c_5 = \mu(\sigma\xi + \mu_{1,0} + \mu)(\mu_{2,0} + \mu)(\mu_{3,0} + \mu)(\mu_{4,0} + \mu)$$
$$- \mu(\mu_{2,0} + \mu)(\mu_{3,0} + \mu)(\mu_{4,0} + \mu)(p_1\beta_{1,0}\eta_{00,10})$$
$$- \mu\sigma\xi(\mu_{3,0} + \mu)(\mu_{4,0} + \mu)(p_2\beta_{2,0}\eta_{00,20})$$
$$- \mu\big(\sigma\xi\mu_{2,0}(\mu_{4,0} + \mu) + \mu_{1,0}(\mu_{2,0} + \mu)(\mu_{4,0} + \mu)\big)(p_3\beta_{3,0}\eta_{00,30})$$
$$- \mu\big(\sigma\xi\mu_{2,0}\mu_{30} + \mu_{1,0}\mu_{3,0}(\mu_{2,0} + \mu)\big)(p_4\beta_{4,0}\eta_{4,0}),$$

Evaluating the numerical approximation to each of the coefficients defined above we get the following

$c_0 = 1$

$c_1 \approx 1.36886151283$

$c_2 \approx 6.06507587946\text{e-}01$

$c_3 \approx 1.43754416252\text{e-}01$

$c_4 \approx 1.17082196757\text{e-}02$

$c_5 \approx 1.96151498574\text{e-}04.$

Again, we will consider the Routh-Hurwitz Criterion for stability to determine whether the

disease-free equilibrium is stable, just as we have already done for the endemic equilibrium. Recall the Hurwitz determinants for the characteristic polynomial, $c(x) = c_0 x^5 + c_1 x^4 + c_2 x^3 + c_3 x^2 + c_4 x + c5$, are defined as;

$$\Delta_1(c) = c_1$$
$$\Delta_2(c) = c_2\Delta_1 - c_0 c_3$$
$$\Delta_3(c) = c_3\Delta_2 - c_4 c_1^2 + c_5 c_1 c_0$$
$$\Delta_4(c) = c_4\Delta_3 - c_5 c_2 \Delta_2 + c_5 c_4 c_1 c_0 - c_5^2 c_0^2$$
$$\Delta_5(c) = c_5\Delta_4.$$

Evaluating each of the Hurwitz determinants for the coefficients of the characteristic polynomial at the disease free equilibrium when immigration is restricted to the susceptible population only, we get the next approximations

$$\Delta_1(c) \approx 1.368861512825629$$

$$\Delta_2(c) \approx 6.864704781242760\text{e-}01$$

$$\Delta_3(c) \approx 7.701301767157777\text{e-}02$$

$$\Delta_4(c) \approx 8.231229710455165\text{e-}04$$

$$\Delta_5(c) \approx 1.614568042810366\text{e-}07,$$

Therefore, by the Routh-Hurwitz Criterion for Stability, given

$$c_0\Delta_1(c) \approx 1.368861512825629 > 0$$
$$\Delta_2(c) \approx 6.864704781242760\text{e-}01 > 0$$
$$c_0\Delta_3(c) \approx 7.701301767157777\text{e-}02 > 0$$
$$\Delta_4(c) \approx 8.231229710455165\text{e-}04 > 0$$
$$c_0\Delta_5(c) \approx 1.614568042810366\text{e-}07 > 0,$$

implies we have an asymptotically stable equilibrium point at $E_{b_0}^\star$. As we continue with the consideration of optimizing an intervention strategy for controlling the spread of HIV we will remind the reader that the state space for the model without an intervention strategy has only one physically relevant equilibrium point; the endemic equilibrium $E_b^\star$. Therefore, in the rest of our analysis regarding the HIV-transmission model with vaccine intervention the consideration for the disease-free equilibrium will not be addressed.

Chapter 5

Optimizing an Intervention Strategy

Taking into consideration our earlier analysis regarding the three direct approaches for intervention (the therapeutic vaccine only, the preventative vaccine only and the combined strategy) we note that for each one of these strategies we made the assumption that the available vaccine(s) would be offered for the full 20 year time horizon. Alternatively, allowing the timing for each vaccine to vary could result with a more cost-effective strategy. Therefore, we will need to structure the statement of a problem that will allow us to derive such a solution.

To begin our analysis we will introduce the standard definitions and terminology for a general nonlinear optimal control problem. From there we will be able to introduce Pontryagin's maximum principle, which states the necessary conditions required to satisfy optimality [30]. For a particular class of problems we will find that further investigation will allow us to get more information regarding the structure of the optimal solution. The class of problems we will consider satisfy the assumptions made regarding the "bang-bang" principle, which we will also introduce in full detail. One of the limitations of optimal control theory is the assumption of one objective functional. Therefore, we will also define a multiobjective optimization problem along with the definitions for Pareto optimality and introduce the weighted-sums method for evaluating Pareto optimal solutions.

The goal in the first couple of sections will be to lay the ground work to structure a multiobjective control problem for the purpose of optimizing an intervention strategy to mitigate the impact the spread of the HIV virus has on a society. This leads to methods for solving the optimization problem numerically, taking into consideration an approach that offers an efficient algorithm for evaluating "bang-bang" controls. Thus, we will give a description for the method of control parameterization and present the solution for the optimal intervention strategy. Noting that the method we have chosen for its efficiency will only guarantee an approximation to the optimal solution, we will also check that the solution satisfies the conditions from the "bang-bang" principle.

5.1 Introduction to Optimal Control Theory

5.1.1 Formulation of an Optimal Control Problem

In the first section of this chapter we will introduce the terminology, notation and necessary definitions from optimal control theory as they appear in *Nonlinear Optimal Control Theory* by Leonard D. Berkovitz and Negash G. Medhin [9]. Noting that not every notation will be exactly as Berkovitz and Medhin define them in their book, instead we introduce notation that will be consistent with the notation already presented by Edwards *et al.*, while keeping the definitions the same.

We will begin with introducing the basic notation and some terminology as they relate to the formulation of an optimal control problem. Let t denote a non-negative real value, $t \in \mathbb{R}^+ \cup \{0\}$, representing time. Let the variable y denote a vector in the real Euclidean space $\mathbb{R}^n$, where $n \in \mathbb{N}$ and $y = (y_1, \ldots, y_n)$ is referred to as the *state variable*. Let the variable ν denote a vector in the real Euclidean space $\mathbb{R}^m$, where $m \in \mathbb{N}$ and $\nu = (\nu_1, \ldots, \nu_m)$ is referred to as the *control variable*. We consider the regions $\mathcal{R}$ and $\mathcal{U}$, each defined by an open connected set, where R is a region of the (t, y)-space and $\mathcal{U}$ is a region of the ν-space. The cartesian product of the two regions, $\mathcal{R}$ and $\mathcal{U}$, defines the region $\mathcal{F} = \mathcal{R} \times \mathcal{U}$. Then we let $f_0, f_1, \ldots, f_n$ define real valued continuous functions of the variables (t, y, ν) on the region $\mathcal{F}$.

We will emphasize before moving on that the standard notation for vector component indexing will be used. This results with y_i denoting the ith component of the vector y. Therefore, we will use the superscript to distinguish between the vectors from the same space, such that $y^{(i)}$ and $y^{(j)}$ are two vectors in $\mathcal{R}$.

In many situations an objective control problem may require that either the initial state $y^{(0)}$ comes from a pre-assigned set $\mathcal{T}^{(0)}$ in $\mathcal{R}$ as well as reach a second state $y^{(1)}$ from a second pre-assigned set $\mathcal{T}^{(1)}$ in $\mathcal{R}$. Therefore, we will also define the set $\mathcal{B}$ for the points $(t^{(0)}, y^{(0)}, t^{(1)}, y^{(1)}) = (t^{(0)}, y_1^{(0)}, \ldots, y_n^{(0)}, t^{(1)}, y_1^{(1)}, \ldots, y_n^{(1)})$ such that $(t^{(i)}, y^{(i)})$ for $i = 0, 1$ are in $\mathcal{R}$ and $t^{(1)} \geq t^{(0)} + \delta$ for some fixed $\delta > 0$. Then $\mathcal{B}$ is said to define the *end conditions* for the problem.

As a fundamental aspect to many optimal control problems, typically the state of the system at time t is described by a point or vector

$$y(t) = (y_1(t), \ldots, y_n(t))$$

such that $(t, y(t))$ is in $\mathcal{R}$ and initially, at time $t^{(0)}$,

$$y(t^{(0)}) = y^{(0)} = (y_1^{(0)}, \ldots, y_n^{(0)})$$

is such that $(t^{(0)}, y^{(0)})$ is also in $\mathcal{R}$. Then a measurable function ν defined on $[t^{(0)}, t^{(1)}]$ with a range in $\mathcal{U}$ is chosen such that the system is said to vary with time according to the system of differential equations

$$y_i'(t) = \frac{dy_i}{dt} = f_i(t, y(t), \nu(t)), \quad y_i(t^{(0)}) = y_i^{(0)}, \quad \text{for } i = 1, \ldots, n. \tag{5.1}$$

At points of discontinuity of ν, equation (5.1) holds for the one-sided limits. As a function of time, y describes the evolution of the system and will be referred to as a *trajectory*. As we continue we will use the standard vector notation for systems of differential equations

$$y'(t) = \frac{dy}{dt} = f(t, y(t), \nu(t)), \quad y(t^{(0)}) = y^{(0)}, \tag{5.2}$$

where $y = (y_1, \ldots, y_n)$ and $f = (f_1, \ldots, f_n)$, such that (5.2) defines the relationships between column vectors. The system of differential equations $y'(t) = f(t, y(t), \nu(t))$ will be called the *state equations*.

It is often further required that the control ν and corresponding state trajectory y satisfy a pre-defined system of inequality constraints

$$R_i(t, y(t), \nu(t)) \geq 0, \quad \text{for } i = 1, 2, \ldots, r \tag{5.3}$$

for all $t^{(0)} \leq t \leq t^{(1)}$, where the functions $R_1, \ldots, R_r$ are given functions of (t, y, ν). These constraints are referred to as the *control constraints* and can be defined by a mapping $\mathcal{V}$ from $\mathcal{R}$ to a subset $\mathcal{V}(t, x)$ of $\mathcal{U}$ such that

$$\mathcal{V}(t, y) = \{\nu : R_i(t, y, \nu) \geq 0, i = 1, \ldots, r\}.$$

Thus the requirement that a function ν and a corresponding trajectory y satisfy the constraints (5.3) can be written as

$$\nu(t) \in \mathcal{V}(t, y(t)) \quad \text{for } t^{(0)} \leq t \leq t^{(1)}.$$

Definition 5.1.1. A control ν is said to be an *admissible control* if there exists a trajectory y corresponding to ν such that

(i) $t \to f_0(t, y(t), \nu(t))$ is in $L_1[t^{(0)}, t^{(1)}]$.

(ii) $\nu(t) \in \mathcal{V}(t, y(t))$ a.e. on $[t^{(0)}, t^{(1)}]$.

(iii) $(t^{(0)}, y(t^{(0)}), t^{(1)}, y(t^{(1)})) \in \mathcal{B}$.

Definition 5.1.2. A trajectory corresponding to an admissible control is called an *admissible trajectory*.

Definition 5.1.3. A pair of functions (y, ν) such that ν is an admissible control and y is an admissible trajectory corresponding to ν will be called an *admissible pair*.

Problem 5.1.4. Let $\mathcal{A}$ denote the set of all admissible pairs (y, ν) and let $\mathcal{A}$ be non-empty. Let

$$J(y, \nu) = g(t^{(0)}, y(t^{(0)}), t^{(1)}, y(t^{(1)})) + \int_{t^{(0)}}^{t^{(1)}} f_0(t, y(t), \nu(t)) dt, \tag{5.4}$$

where (y, ν) is an admissible pair and g is a given real valued function defined on $\mathcal{B}$. Find a pair $(y^\star, \nu^\star)$ in $\mathcal{A}$ that minimizes (5.4) in the class $\mathcal{A}$. That is, find an element $(y^\star, \nu^\star)$ in $\mathcal{A}$ such that

$$J(y^\star, \nu^\star) \leq J(y, \nu) \text{ for all } (y, \nu) \text{ in } \mathcal{A}$$

Definition 5.1.5. The objective functional $J(y, \nu)$ defined by equation (5.4) is called a *cost* or *payoff* or *performance index*.[1]

The statement for the optimal control problem 5.1.4 is sometimes referred to as the Bolza problem. Alternatively, when we consider special cases of the Bolza problem where $f_0 = 0$ or $g = 0$ these problems are referred to as the Mayer problem and Lagrange problem, respectively. As we continue onto the subsequent sections, we will assume that we are always dealing with the Lagrange problem.

Problem 5.1.6 (The Lagrange Problem)**.** Let $\mathcal{A}$ denote the set of all admissible pairs (y, ν) and let $\mathcal{A}$ be non-empty. Let

$$J(y, \nu) = \int_{t^{(0)}}^{t^{(1)}} f_0(t, y(t), \nu(t)) dt, \tag{5.5}$$

where (y, ν) is an admissible pair. Find a pair $(y^\star, \nu^\star)$ in $\mathcal{A}$ that minimizes (5.5) in the class $\mathcal{A}$. That is, find an element $(y^\star, \nu^\star)$ in $\mathcal{A}$ such that

$$J(y^\star, \nu^\star) \leq J(y, \nu) \text{ for all } (y, \nu) \text{ in } \mathcal{A}$$

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[1]For the objective optimization problem that we will address in our research, we will refer to the objective functional as the payoff.

5.1.2 Pontryagin's Maximum Principle

In this section we will introduce Pontryagin's maximum principle which states the necessary conditions required to satisfy optimality for the control problem 5.1.6 [30]. We will point out that in problem 5.1.6 the statement addresses a minimization problem and in this section we will be introducing the maximum principle. Since every minimization problem can be solved by taking the negation of the objective and approaching the problem as a maximization problem, it will suffice to present the maximum principle as a means to addressing both maximization and minimization problems. To begin, we start by introducing the *Hamiltonian*, $H : \mathbb{R}^1 \times \mathbb{R}^n \times \mathbb{R}^m \times \mathbb{R}^1 \times \mathbb{R}^n$ defined by

$$H(t, y, \nu, z, z_0) := \langle z, f(t, y, \nu) \rangle + z_0 f_0(t, y, \nu)$$

where $\langle \cdot, \cdot \rangle$ is the inner product on $\mathbb{R}^n$, z is a vector valued function defined on $[t^{(0)}, t^{(1)}]$ with a range in $\mathbb{R}^n$ and z_0 is a nonzero constant value. The vector valued function z will be referred to as the *costate variable*.

Although we use the 1962 English translation of original publication from Pontryagin *et al.*, we will state the theorem for the maximum principle in integral form along with the corollary for the pointwise maximum principle as it was introduced by Berkovitz in 1974 [7, 44].

Theorem 5.1.7 (Maximum Principle in Integral Form)**.** Let $(y^\star, \nu^\star)$ be an optimal pair defined on the interval $[t^{(0)}, t^{(1)}]$. Then there exists a constant $z_0 \leq 0$ and an absolutely continuous vector function $z^\star : [t^{(0)}, t^{(1)}] \to \mathbb{R}^n$ such that the following hold:

(i) $(z_0, z^\star)$ is never zero on $[t^{(0)}, t^{(1)}]$.

(ii) For a.e. t in $[t^{(0)}, t^{(1)}]$

$$\frac{dy^\star(t)}{dt} = H_z(t, y^\star(t), \nu^\star(t), z^\star(t), z_0)$$
$$\frac{dz^\star(t)}{dt} = -H_y(t, y^\star(t), \nu^\star(t), z^\star(t), z_0).$$

(iii) For any admissible control ν defined on the interval $[t^{(0)}, t^{(1)}]$

$$\int_{t^{(0)}}^{t^{(1)}} H(t, y^\star(t), \nu^\star(t), z^\star(t), z_0) dt \geq \int_{t^{(0)}}^{t^{(1)}} H(t, y^\star(t), \nu(t), z^\star(t), z_0) dt.$$

(iv) If the mapping $t \to \hat{f}(t, y(t), \nu(t))$, for $\hat{f} := (f_0, f_1, \ldots, f_n)$, is continuous at $t = t^{(i)}$, $i = 0, 1$, then the $(2n + 2)$-vector

$$\left(H(\pi(t^{(0)})), -z^\star(t^{(0)}), -H(\pi(t^{(1)})), z^\star(t^{(1)}) \right)$$

is orthogonal to $\mathcal{B}$ at the point $(t^{(0)}, y^\star(t^{(0)}), t^{(1)}, y^\star(t^{(1)}))$, where

$$\pi(t^{(i)}) = (t^{(i)}, y^\star(t^{(i)}), \nu^\star(t^{(i)}), z^\star(t^{(i)}), z_0) \quad \text{for } i = 0, 1.$$

The system of differential equations defining $z'(t) = -H_y(t, y(t), \nu(t), z(t), z_0)$ will be called the *costate equations*.

Corollary 5.1.8 (Pointwise Maximum Principle)**.** If for all t, $\mathcal{V}(t) = \mathcal{V}$, where $\mathcal{V}$ is a fixed set, and $\hat{f}$ is continuous on $\mathcal{F}$, then

$$H(t, y^\star(t), \nu^\star(t), z^\star(t), z_0) \geq H(t, y^\star(t), \nu(t), z^\star(t), z_0)$$

for almost all t in $[t^{(0)}, t^{(1)}]$ and all ν in $\mathcal{V}$.

From theorem 5.1.7 and the corollary 5.1.8 we obtain a set of *necessary conditions for optimality* that become the focus for evaluating an optimal solution to any control problem in the form of 5.1.6. Setting $z_0 = -1$ the Hamiltonian is defined as

$$H(t, y, \nu, z) := \langle z, f(t, y, \nu) \rangle - f_0(t, y, \nu).$$

For the Lagrange problem, with $g = 0$, the assumption for the terminal condition for the costate equations is $z^\star(t^{(1)}) = 0$. This results with the following conditions that must hold true for the optimal control $\nu^\star$ along with the corresponding state and costate trajectories, $y^\star$ and $z^\star$.

1. $\dfrac{dy^\star(t)}{dt} = H_z(y^\star(t), \nu^\star(t), z^\star(t)), \quad y^\star(t^{(0)}) = y^{(0)}$

2. $\dfrac{dz^\star(t)}{dt} = -H_y(y^\star(t), \nu^\star(t), z^\star(t)), \quad z^\star(t^{(1)}) = 0$

3. $H(t, y^\star(t), \nu^\star(t), z^\star(t)) \geq H(t, y^\star(t), \nu(t), z^\star(t))$ for all $\nu \in \mathcal{V}$

5.1.3 The "Bang-Bang" Principle

Next we consider a particular class of optimal control problems, where the control is bounded and appears linearly in both the dynamics and payoff. These types of optimal control problem

require special consideration since the necessary conditions are insufficient for solving the control problem analytically. To give a general description to an optimal control problem whose solution fits the "bang-bang" principle we will start with a couple of assumptions.

Assumption 5.1.9. The state equations are defined by an autonomous system of differential equations,

$$\frac{dy(t)}{dt} = f(y(t), \nu(t)).$$

Assumption 5.1.10. The control variable is bounded both above and below

$$M_i^- \leq \nu_i(t) \leq M_i^+, \qquad i = 1, \ldots, m,$$

where M_i^- and M_i^+ define the lower and upper bounds of the ith control component.

Assumption 5.1.11. The state equations of the system are of the form

$$\frac{dy(t)}{dt} = a(y(t)) + B(y(t))\nu(t),$$

where a is a continuous vector-valued function whose range is defined in $\mathbb{R}^n$, and B is an $n \times m$ matrix of continuous functions.

Assumption 5.1.12. The cost functional (payoff) is in the form

$$J(y, \nu) = \int_{t^{(0)}}^{t^{(1)}} \left[a_0(y(t)) + B_0(y(t))\nu(t) \right] dt,$$

where a_0 is a continuous scalar valued function and B_0 is an $1 \times m$ vector of continuous functions.

Making the same assumptions that were made in section 5.1.2, the maximum principle can be used to develop a generalized solution for this particular class of optimal control problems. According to assumptions 5.1.9 - 5.1.12 and $z_0 = -1$, the Hamiltonian is defined as

$$H(y(t), \nu(t), z(t)) = \langle z(t), a(y(t)) + B(y(t))\nu(t) \rangle - a_0(y(t)) - B_0(y(t))\nu(t)$$
$$= \left[\langle z(t), B(y(t)) \rangle - B_0(y(t)) \right] \nu(t) + \langle z(t), a(y(t)) \rangle - a_0(y(t)).$$

From the pointwise maximum principle 5.1.8, an optimal pair $(y^\star, \nu^\star)$ must satisfy the following inequality for a.e. t in $[t^{(0)}, t^{(1)}]$ and each admissible control $\nu \in \mathcal{V}$,

$$\left[\langle z^\star(t), B(y^\star(t))\rangle - B_0(y^\star(t))\right]\nu^\star(t) + \langle z^\star(t), a(y^\star(t))\rangle - a_0(y^\star(t))$$

$$\geq \left[\langle z^\star(t), B(y^\star(t))\rangle - B_0(y^\star(t))\right]\nu(t) + \langle z^\star(t), a(y^\star(t))\rangle - a_0(y^\star(t)). \quad (5.6)$$

Simplifying the inequality (5.6) results with the following necessary condition for the class of maximization problems with bounded linear control functions,

$$\left[\langle z^\star(t), B(y^\star(t))\rangle - B_0(y^\star(t))\right]\nu^\star(t) \geq \left[\langle z^\star(t), B(y^\star(t))\rangle - B_0(y^\star(t))\right]\nu(t). \quad (5.7)$$

Let $G(y^\star(t), z^\star(t)) = \langle z^\star(t), B(y^\star(t))\rangle - B_0(y^\star(t))$ define the $1 \times m$ matrix of continuous functions representing the coefficient to the control function in (5.7). If we take $G = (g_1, g_2, \ldots, g_m)$, then we can write (5.7) as a system of inequalities

$$g_i(y^\star(t), z^\star(t))\nu_i^\star(t) \geq g_i(y^\star(t), z^\star(t))\nu_i(t), \quad i = 1, 2, \ldots, m. \quad (5.8)$$

Then the solution to the maximization problem with assumptions 5.1.9 - 5.1.12 can be given in the general form

$$\nu_i^\star(t) = \begin{cases} M_i^+, & g_i(y(t), z(t)) > 0 \\ M_i^-, & g_i(y(t), z(t)) < 0 \\ \text{Undetermined}, & g_i(y(t), z(t)) = 0 \end{cases} \quad i = 1, 2, \ldots, m. \quad (5.9)$$

For the case when $g_i(y(t), z(t)) = 0$ the results for the optimal control are considered undetermined because it depends on whether this case is valid for only a set of unique points with measure zero on the interval $[t^{(0)}, t^{(1)}]$ or if it holds true on a set of subintervals on $[t^{(0)}, t^{(1)}]$. When it holds true for only a finite set of points, this set of points are referred to as the *switching times*. Alternatively, when $g_i(y(t), z(t)) = 0$ on any subinterval the control is referred to as *singular* on that interval and since the necessary conditions do not give us sufficient information for this case the solution would require further investigation. The consideration for whether a control is singular on any subinterval is handled by case by case scenario and depends directly on the specifics for a particular optimal control problem. Therefore, we will leave the investigation to the case when the switching function, $G(y(t), z(t))) = 0$, for later consideration when we approach a solution to the objective control problem we will consider for optimizing an intervention strategy.

We will note, that the core principles of optimal control theory consider a single objective cost functional. Alternatively and as it is in our case, there are many control problems where there are an array of objectives, that may or may not be directly competing. Therefore in the

next section we will outline the fundamental concepts of a multiobjective optimization.

5.2   Multiobjective Optimization

Multiobjective optimization problems have been studied since the late 1800's, originating with Edgeworth in 1881 [35]. The concepts and definitions for multiobjective optimization and Pareto optimality are presented here as stated from Miettinin's book *Nonlinear Multiobjective Optimization* [35]. As it is presented in a majority of the literature, we will present the multiobjective optimization problem as a minimization problem with the understanding that any maximization problem can be made a minimization problem by negating the objective.

Problem 5.2.1 (Multiobjective Optimization). To minimize a set of 2 or more objective functions over a constrained space,

$$\min_{u \in \mathcal{U}} \{J_1(u), J_2(u), \ldots, J_k(u)\},$$

where we have $k \in \mathbb{N}$, such that $k \geq 2$, objective functions $J_i : \mathbb{R}^m \to \mathbb{R}$. We denote the objective functions by $J(u) = (J_1(u), \ldots, J_k(u))$. The *decision variable* $u = (u_1, \ldots, u_m)$ belong to a feasible region U a subset of $\mathbb{R}^m$. To 'minimize' the set of objective functions means we want to minimize all the objective functions simultaneously.

In the scalar case optimization can be straight forward, in the sense that a maximum or minimum is clearly understood to be the value that exceeds all others. Alternatively, with the multiobjective optimization problem it is rarely the case that you would ever find a unique decision variable $u^\star$ that satisfies each and every one of the objectives simultaneously. This leads us to the discussion of optimizing trade-offs, when it is not possible to satisfy one objective without sacrificing an alternative objective.

5.2.1   Pareto Optimality

Since Vilfredo Pareto's developments in 1896, furthering the work done by Edgeworth in 1881, the concept known as Pareto optimality that has been widely used to describe the solutions for a multiobjective optimization problem. Introducing the definitions for Pareto optimality will lay the foundation for interpreting methods for solving a multiobjective problem.

Definition 5.2.2. If $\mathbb{R}^k$ is *partially ordered* in a natural way, then given $v^{(1)}, v^{(2)} \in \mathbb{R}^k$ with $v^{(1)} = (v_1^{(1)}, \ldots, v_k^{(1)})$ and $v^{(2)} = (v_1^{(2)}, \ldots, v_k^{(2)})$, we have $v^{(1)} \leq v^{(2)}$ if and only if $v_i^{(1)} \leq v_i^{(2)}$ for all $i = 1, \ldots, k$.

Assuming that $\mathcal{U}$ is a nonempty subset of $\mathbb{R}^m$ and $J : \mathcal{U} \to \mathbb{R}^k$ is a vector function whose range is defined on a partially ordered space, we have the following definitions required for evaluating Pareto optimality for a multiobjective optimization problem.

Definition 5.2.3. If there exists $u^{(1)}, u^{(2)} \in \mathcal{U}$ such that $J(u^{(1)}) \leq J(u^{(2)})$ and $J_i(u^{(1)}) < J_i(u^{(2)})$ for any $i = 1, \ldots, k$, then $u^{(1)}$ is considered a *Pareto improvement* to $u^{(2)}$.

Definition 5.2.4. *Pareto optimality* is obtained when no more Pareto improvements can be made to a solution $u^\star \in \mathcal{U}$ where $J(u^\star) \leq J(u)$ for all $u \in \mathcal{U}$. That is to say, it is not possible to move from that point $u^\star$ and improve any one objective function without detriment to any other objective function.

Definition 5.2.5. A vector $v' = (v'_1, \ldots, v'_k) \in \mathbb{R}^k$ is said to *dominate* $v = (v_1, \ldots, v_k) \in \mathbb{R}^k$ if and only if $v' \leq v$ and there exists j such that $v'_j < v_j$. Then the *Pareto dominance* is denoted by $v' \preceq v$.

Definition 5.2.6. For a given multiobjective optimization problem, the *Pareto optimal set* is defined as,

$$PS(\mathcal{U}) = \{u \in \mathcal{U} | \text{ there does not exist } u' \in \mathcal{U} \text{ such that } J(u') \preceq J(u)\}.$$

Definition 5.2.7. For a given multiobjective optimization problem with a Pareto optimal set $PS(\mathcal{U})$, the *Pareto front* is defined as,

$$PF^\star = \{w = J(u) = (J_1(u), \ldots, J_k(u)) \in \mathbb{R}^k \mid u \in PS(\mathcal{U})\}.$$

Definition 5.2.8. A decision vector $u^\star \in \mathcal{U}$ is *locally Pareto optimal* if there exists a $\delta > 0$ ball centered at $u^\star$ such that $u^\star$ is Pareto optimal in $\mathcal{U} \cap B_\delta(u^\star)$.

We will emphasize the importance of locally Pareto optimal when numerical methods are used to solve a multiobjective optimization problem. As it will be in our case, the solution to many optimization problems can be too complex to solve analytically. Therefore, when considering the techniques and methods for solving a problem by numerical methods will at most be locally optimal.

5.2.2 Weighted-Sums Method

The weighted-sums method is the most commonly used approach for evaluating a multiobjective optimization problem. Given the vector-valued function $J(u) = (J_1(u), \ldots, J_k(u))$ a selection of weights is chosen $(\alpha_1, \ldots, \alpha_k)$, relating to each objective functions respectively, such that $\alpha_i > 0$ for $i = 1, \ldots, k$ and $\sum_{i=1}^{k} \alpha_i = 1$. Then a single objective function is defined as,

$$L(u) = \sum_{i=1}^{k} \alpha_i J_i(u). \tag{5.10}$$

Where the Pareto optimal solution to (5.10) defines a Pareto optimal solution to the multiobjective optimization problem 5.2.1.

As with any approach for solving a multiobjective optimization problem the weighted-sum method require some preference relationship between the objective functions. Without one, it would be impossible to consider a ranking of the solutions from the Pareto optimal set. Depending on which one of the following approaches is taken, the technique for defining this precedence relationship can be done at various stages of implementing an optimization algorithm.

1. *a priori* - The selection for the weights are assigned before the optimization routine is implemented, based on the expertise of the decision maker.

2. *progressive* - The weights are updated during the optimization process using feedback from the solutions as they evolve.

3. *a posteriori* - At the end of the end of the optimization routine, a decision maker selects a solution from the Pareto optimal set, $PS(\mathcal{U})$, thus selecting its corresponding weights.

For the purpose of deriving an optimal intervention strategy we will consider the opposing objectives to minimize cost and maximize QALYs. In chapter 3, when we introduced the model, we ran a cost-effective analysis for the three intervention strategies (therapeutic vaccine only, preventative vaccine only, and the combined strategy). We will use this information and select the weights for the objective functionals *a priori*.

5.3 Optimizing an Intervention Strategy as a Multiobjective Control Problem

Referring back the cost-effective analysis applied in chapter 3 we learned that the best strategy, for a 20 year time horizon, is to offer both vaccines for the full duration. This conclusion was made with regards to the comparison between the three direct cases, where we only considered the options of offering either one of the vaccines or both for the entire time, to the alternative of not offering either vaccine. To quantify the effectiveness of each of the intervention strategies the comparison to each of the alternatives is done by evaluating the resulting cumulative monetary cost (both direct and indirect costs) as well as the total combined QALYs for the population as a whole. The objective, as we mentioned before, is to minimize the monetary cost while maximizing QALYs,

$$\min C(T) = \int_0^T \left[\kappa_p \nu_p(t)(Y_{0,0}(t) + Y_{1,0}(t)) + \kappa_t \nu_t(t)Y_{2,0}(t) \right] e^{-rt} dt + \int_0^T \sum_{j=0}^{j=1} \sum_{i=0}^{i=4} c_i Y_{i,j}(t) e^{-rt} dt$$

$$\max Q(T) = \int_0^T \sum_{j=0}^{j=1} \sum_{i=0}^{i=4} q_i Y_{i,j}(t) e^{-rt} dt,$$

dependent on the time horizon and the solution to the dynamical system,

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - \nu_p(t)Y_{0,0}(t) - \mu Y_{0,0}(t) - p_0 \lambda(t)Y_{0,0}(t) + \omega Y_{0,1}(t) \tag{5.11a}$$

$$\frac{dY_{0,1}(t)}{dt} = \nu_p(t)Y_{0,0}(t) - \mu Y_{0,1}(t) - \omega Y_{0,1}(t) - p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}(t) \tag{5.11b}$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0 \lambda(t)Y_{0,0}(t) - \sigma \xi Y_{1,0}(t) - \nu_p(t)Y_{1,0}(t) + \omega Y_{1,1}(t) - \mu_{1,0}Y_{1,0}(t) - \mu Y_{1,0}(t) \tag{5.11c}$$

$$\frac{dY_{1,1}(t)}{dt} = p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}(t) + \nu_p(t)Y_{1,0}(t) - \omega Y_{1,1}(t) - \sigma \xi Y_{1,1}(t) - \mu_{1,1}Y_{1,1}(t) - \mu Y_{1,1}(t) \tag{5.11d}$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma \xi (Y_{1,0}(t) + Y_{1,1}(t)) - \nu_t(t)Y_{2,0}(t) - \mu_{2,0}Y_{2,0}(t) - \mu Y_{2,0}(t) \tag{5.11e}$$

$$\frac{dY_{2,1}(t)}{dt} = \nu_t(t)Y_{2,0}(t) - \mu_{2,1}Y_{2,1}(t) - \mu Y_{2,1}(t) \tag{5.11f}$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{j=0}^{j=1} \sum_{i=1}^{i=2} \mu_{i,j} Y_{i,j}(t) - \mu_{3,0}Y_{3,0}(t) - \mu Y_{3,0}(t) \tag{5.11g}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - \mu_{4,0}Y_{4,0}(t) - \mu Y_{4,0}(t) \tag{5.11h}$$

with,

$$\lambda(t) = \frac{\sum_{j=0}^{j=1} \sum_{i=1}^{i=4} p_i \beta_{i,j} \eta_{00,ij} Y_{i,j}(t)}{\sum_{j=0}^{j=1} \sum_{i=0}^{i=4} p_i Y_{i,j}(t)} \qquad \lambda_\nu(t) = \frac{\sum_{j=0}^{j=1} \sum_{i=1}^{i=4} p_i \beta_{i,j} \eta_{01,ij} Y_{i,j}(t)}{\sum_{j=0}^{j=1} \sum_{i=0}^{i=4} p_i Y_{i,j}(t)}$$

and initial condition,

$$Y_{0,0}(0) = (1 - \phi_0)Y_0$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_j 1/\mu_{j,0}} \phi_0 \cdot Y_0, \text{ for } i = 1,2,3,4$$

$$Y_{i,1}(0) = 0, \text{ for } i = 0,1,2,3,4.$$

For the assumptions we made regarding the vaccines resulted with dominant options for

each. For every alternative that saved more money, we also had an increase in QALYs (As a reminder we included table 5.1[2] as a reference.).

Table 5.1: Projected accumulated cost and QALYs, as well as the cost/QALY, for each of the four variations of the model on a 20 year time horizon; no intervention, therapeutic only, preventative only, and the combined vaccination strategy.

	Accumulated Cost	Accumulated QALYs	Cost/QALY
No Intervention	$3,778,541,557	495,630	$7623/QALY
Therapeutic Vaccine	$3,747,402,695	506,808	$7394/QALY
Preventative Vaccine	$3,711,111,604	508,220	$7302/QALY
Combination Both Vaccines	$3,674,411,239	519,572	$7072/QALY

To determine whether or not there is a strategy that will further optimize the trade-off between minimizing monetary cost and maximizing QALYs we will set up a multiobjective optimization problem. Then utilizing the weighted-sums method, with weights assigned a priori, we can implement numerical methods from optimal control theory. To begin, we will first introduce the following vector notation for the variables and functions of the model. Let,

$Y(t) = (Y_{0,0}(t), Y_{0,1}(t), Y_{1,0}(t), Y_{1,1}(t), Y_{2,0}(t), Y_{2,1}(t), Y_{3,0}(t), Y_{4,0}(t))$

$Y(0) = Y^{(0)}$

$\nu(t) = (\nu_p(t), \nu_t(t))$

$F(Y(t), \nu(t)) = (F_1(Y(t), \nu(t)), F_2(Y(t), \nu(t)), \ldots, F_8(Y(t), \nu(t)))$

be used to define the right hand side of equations (5.11a) - (5.11h). Continuing with the consideratin for an optimal intervention strategy we will refer to $Y(t)$ as the *state variable* and $\nu(t)$

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[2]Table 5.1 is a duplicate of the table 3.11 found in section 3.2 where the initial cost effective analysis was presented.

as the *control variable*. Recall, given the physical limitations for the interpretation of the model we assume the range of $Y(t)$ is restricted to $\mathbb{R}_+^8$. In addition, given the control variables define a proportion of a population that receives a vaccine we will require an upper bound of 1, but according to the assumptions of Edwards *et al.* and our earlier analysis we will restrict the space of feasible controls to $\mathcal{V} = [0, 0.75] \times [0, 0.75]$. To determine the *payoff*, as it would relate to the two objective functions $C(T)$ and $Q(T)$, we need to chose a single optimization objective and make a reasonable selection for the weights used to combine the two objectives. Considering we have opposing objectives, $\min C(T)$ and $\max Q(T)$, we will instead require that the solution for our multiobjective optimization problem minimizes both, $C(T)$ and $-Q(T)$. Although the objective functions were originally defined in terms of the final time T, we are also assuming for the purposes of the cost-effective analysis a fixed 20 year time horizon, $T = 20$. Therefore, with the vaccine parameters defining the control variables we will now assume the cost functionals to also be dependent on the choice of $\nu(t)$ and consequently $Y(t)$. Let

$$J(Y(t), \nu(t)) = (C(Y(t), \nu(t)), -Q(Y(t), \nu(t)))$$

then the multiobjective optimization problem for intervention strategies of the HIV virus is defined by:

$$\min_{\nu(t) \in \mathcal{V}} J(Y(t), \nu(t))$$

subject to

$$\frac{dY(t)}{dt} = F(Y(t), \nu(t)), \quad Y(t_0) = Y_{t_0}.$$

With the statement of the multiobjective optimization problem, we can now consider the weighted-sums method to derive one objective functional. With only two objective functions we can simply consider one parameter α, resulting with the second weight simply defined by $(1-\alpha)$. For the purpose of defining the problem statement for optimizing an intervention strategy, the parameter definitions will be sufficient. We will get into defining the weights when we discuss numerical methods for solving the Pareto optimal solution.

$$L(Y(t), \nu(t)) = \alpha C(Y(t), \nu(t)) - (1-\alpha)Q(Y(t), \nu(t))$$

$$= \alpha \Bigg[\int_0^{20} [\kappa_p \nu_p(t)(Y_{0,0}(t) + Y_{1,0}(t)) + \kappa_t \nu_t(t) Y_{2,0}(t)] e^{-rt} dt$$

$$+ \int_0^{20} \sum_{j=0}^{j=1} \sum_{i=0}^{i=4} c_i Y_{i,j} e^{-rt} dt \Bigg]$$

$$-(1-\alpha)\left[\int_0^{20}\sum_{j=0}^{j=1}\sum_{i=0}^{i=4}q_iY_{i,j}(t)e^{-rt}dt\right]$$

$$=\int_0^{20}\left[\alpha\left[\kappa_p\nu_p(t)(Y_{0,0}(t)+Y_{1,0}(t))+\kappa_t\nu_t(t)Y_{2,0}(t)\sum_{j=0}^{j=1}\sum_{i=0}^{i=4}c_iY_{i,j}\right]\right.$$

$$\left.-(1-\alpha)\left[\sum_{j=0}^{j=1}\sum_{i=0}^{i=4}q_iY_{i,j}(t)\right]\right]e^{-rt}dt$$

Therefore, we can now make the following statement for an optimal control problem.

Problem 5.3.1 (Optimizing Intervention Strategies for the HIV Virus; as a minimization problem). Find an admissible control $\nu^\star(t)\in\mathcal{V}$ along with its corresponding admissible trajectory $Y^\star(t)$ defined by the system

$$\frac{dY(t)}{dt}=F(Y(t),\nu(t)),\quad Y(t_0)=Y_{t_0}$$

that will minimize the payoff

$$L(Y(t),\nu(t))=\int_0^{20}\left[\alpha\left[\kappa_p\nu_p(t)(Y_{0,0}(t)+Y_{1,0}(t))+\kappa_t\nu_t(t)Y_{2,0}(t)\sum_{j=0}^{j=1}\sum_{i=0}^{i=4}c_iY_{i,j}\right]\right.$$

$$\left.-(1-\alpha)\left[\sum_{j=0}^{j=1}\sum_{i=0}^{i=4}q_iY_{i,j}(t)\right]\right]e^{-rt}dt.$$

5.3.1 Necessary Conditions

Now that we have defined our optimal intervention strategy problem as a fundamental optimal control problem we will use the pointwise maximum principle 5.1.8 to derive the necessary conditions to get an analytical interpretation of the optimal control. Then we will follow up in the next chapter implementing numerical methods for solving "bang-bang" controls.

Noting that we will use the maximum principle to define the necessary conditions we will have to make the translation from the minimization problem stated in 5.3.1 to the following maximization problem, by negating the payoff functional.

Problem 5.3.2 (Optimizing Intervention Strategies for the HIV Virus; as a maximization problem). Find an admissible control $\nu^\star(t)\in\mathcal{V}$ along with its corresponding admissible trajectory $Y^\star(t)$ defined by the system

$$\frac{dY(t)}{dt}=F(Y(t),\nu(t)),\quad Y(t_0)=Y_{t_0}$$

that will maximize the payoff

$$-L(Y(t), \nu(t)) = \int_0^{20} \Big[(1 - \alpha) \Big[\sum_{j=0}^{j=1} \sum_{i=0}^{i=4} q_i Y_{i,j}(t) \Big]$$

$$- \alpha \Big[\kappa_p \nu_p(t)(Y_{0,0}(t) + Y_{1,0}(t)) + \kappa_t \nu_t(t) Y_{2,0}(t) \sum_{j=0}^{j=1} \sum_{i=0}^{i=4} c_i Y_{i,j} \Big] \Big] e^{-rt} dt.$$

Given the statement of a maximization problem 5.3.2 for the objective of optimizing an intervention strategy we will introduce the Hamiltonian

$$H(Y(t), \nu(t), Z(t)) = \langle Z(t), F(Y(t), \nu(t)) \rangle - f^0(Y(t), \nu(t))$$

where the costate variable will be denoted by

$$Z(t) = (Z_{0,0}(t), Z_{0,1}(t), Z_{1,0}(t), Z_{1,1}(t), Z_{2,0}(t), Z_{2,1}(t), Z_{3,0}(t), Z_{4,0}(t)).$$

Then the necessary conditions for the optimal solution $\nu^\star$ along with the corresponding state and costate trajectories $Y^\star$ and $Z^\star$ are the following. For a.e. t in $[0, 20]$,

1. $\dfrac{dY^\star(t)}{dt} = H_Z(Y^\star(t), \nu^\star(t), Z^\star(t)), \quad Y^\star(0) = Y^{(0)}$

2. $\dfrac{dZ^\star(t)}{dt} = -H_Y(Y^\star(t), \nu^\star(t), Z^\star(t)), \quad Z^\star(20) = 0$

3. $H(t, Y^\star(t), \nu^\star(t), Z^\star(t)) \geq H(t, Y^\star(t), \nu(t), Z^\star(t))$ for all $\nu(t) \in \mathcal{V}$.

Thus, defining the Hamiltonian we get:

$$H(Y(t), \nu(t), Z(t))$$
$$= \Big[I_{0,0} - (\nu_p(t) + \mu + p_0 \lambda(t)) Y_{0,0}(t) + \omega Y_{0,1}(t) \Big] Z_{0,0}(t)$$
$$+ \Big[\nu_p(t) Y_{0,0}(t) - (\mu + \omega + p_0(1 - \varepsilon) \lambda_\nu(t)) Y_{0,1}(t) \Big] Z_{0,1}(t)$$
$$+ \Big[I_{1,0} + p_0 \lambda(t) Y_{0,0}(t) - (\sigma \xi + \nu_p(t) + \mu_{1,0} + \mu) Y_{1,0}(t) + \omega Y_{1,1}(t) \Big] Z_{1,0}(t)$$
$$+ \Big[p_0(1 - \varepsilon) \lambda_\nu(t) Y_{0,1}(t) + \nu_p(t) Y_{1,0}(t) - (\omega + \sigma \xi + \mu_{1,1} + \mu) Y_{1,1}(t) \Big] Z_{1,1}(t)$$
$$+ \Big[I_{2,0} + \sigma \xi (Y_{1,0}(t) + Y_{1,1}(t)) - \nu_t(t) + \mu_{2,0} + \mu) Y_{2,0}(t) \Big] Z_{2,0}(t)$$
$$+ \Big[\nu_t(t) Y_{2,0}(t) - (\mu_{2,1} + \mu) Y_{2,1}(t) \Big] Z_{2,1}(t)$$
$$+ \Big[I_{3,0} + \sum_{j=0}^{j=1} \sum_{i=1}^{i=2} \mu_{i,j} Y_{i,j}(t) - (\mu_{3,0} + \mu) Y_{3,0}(t) \Big] Z_{3,0}(t)$$

$$+ \Big[\mu_{3,0} Y_{3,0}(t) - (\mu_{4,0} + \mu) Y_{4,0}(t) \Big] Z_{4,0}(t)$$

$$+ \Big[\alpha \big[\kappa_p \nu_p(t)(Y_{0,0}(t) + Y_{1,0}(t)) + \kappa_t \nu_t(t) Y_{2,0}(t) + \sum_{j=0}^{j=1} \sum_{i=0}^{i=4} c_i Y_{i,j} \big]$$

$$- (1 - \alpha) \Big[\sum_{j=0}^{j=1} \sum_{i=0}^{i=4} q_i Y_{i,j}(t) \big] \Big] e^{-rt}. \tag{5.12}$$

Next, deriving the necessary conditions, we will note that the first condition is a statement for the state equations (5.11). Then second condition gives us the costate equations as the following system of ordinary differential equations,

$$\frac{dZ_{0,0}(t)}{dt} = \Big[\nu_p(t) + p_0 \Big(\frac{\partial \lambda(t)}{\partial Y_{0,0}} Y_{0,0}(t) + \lambda(t) \Big) + \mu \Big] Z_{0,0}(t)$$

$$+ \Big[p_0(1 - \varepsilon) \Big(\frac{\partial \lambda_\nu(t)}{\partial Y_{0,0}} Y_{0,1}(t) \Big) - \nu_p(t) \Big] Z_{0,1}(t)$$

$$- p_0 \Big(\frac{\partial \lambda(t)}{\partial Y_{0,0}} Y_{0,0}(t) + \lambda(t) \Big) Z_{1,0}(t) - p_0(1 - \varepsilon) \Big(\frac{\partial \lambda_\nu(t)}{\partial Y_{0,0}} Y_{0,1}(t) \Big) Z_{1,1}(t)$$

$$- (\alpha(\kappa_p \nu_p(t) + c_0 + q_0) - q_0) e^{-rt} \tag{5.13a}$$

$$\frac{dZ_{0,1}(t)}{dt} = \Big[p_0 \Big(\frac{\partial \lambda(t)}{\partial Y_{0,1}} Y_{0,0}(t) \Big) + \omega \Big] Z_{0,0}(t)$$

$$+ \Big[p_0(1 - \varepsilon) \Big(\frac{\partial \lambda_\nu(t)}{\partial Y_{0,1}} Y_{0,1}(t) + \lambda_\nu(t) \Big) + \mu + \omega \Big] Z_{0,1}(t)$$

$$- p_0 \Big(\frac{\partial \lambda(t)}{\partial Y_{0,1}} Y_{0,0}(t) \Big) Z_{1,0}(t) - p_0(1 - \varepsilon) \Big(\frac{\partial \lambda_\nu(t)}{\partial Y_{0,1}} Y_{0,1}(t) + \lambda_\nu(t) \Big) Z_{1,1}(t)$$

$$- (\alpha(c_0 + q_0) - q_0) e^{-rt} \tag{5.13b}$$

$$\frac{dZ_{1,0}(t)}{dt} = p_0 \Big(\frac{\partial \lambda(t)}{\partial Y_{1,0}} Y_{0,0}(t) \Big) Z_{0,0}(t) + p_0(1 - \varepsilon) \Big(\frac{\partial \lambda_\nu(t)}{\partial Y_{1,0}} Y_{0,1}(t) \Big) Z_{0,1}(t)$$

$$+ \Big[\nu_p(t) - p_0 \Big(\frac{\partial \lambda(t)}{\partial Y_{1,0}} Y_{0,0}(t) \Big) + \sigma \xi + \mu_{1,0} + \mu \Big] Z_{1,0}(t)$$

$$- \Big[\nu_p(t) + p_0(1 - \varepsilon) \Big(\frac{\partial \lambda_\nu(t)}{\partial Y_{1,0}} Y_{0,1}(t) \Big) \Big] Z_{1,1}(t)$$

$$- \sigma \xi Z_{2,0}(t) - \mu_{1,0} Z_{3,0}(t) - (\alpha(\kappa_p \nu_p(t) + c_1 + q_1) - q_1) e^{-rt} \tag{5.13c}$$

$$\frac{dZ_{1,1}(t)}{dt} = p_0\Big(\frac{\partial\lambda(t)}{\partial Y_{1,1}}Y_{0,0}(t)\Big)Z_{0,0}(t) + p_0(1-\varepsilon)\Big(\frac{\partial\lambda_\nu(t)}{\partial Y_{1,1}}Y_{0,1}(t)\Big)Z_{0,1}(t)$$

$$- \Big[p_0\Big(\frac{\partial\lambda(t)}{\partial Y_{1,1}}Y_{0,0}(t)\Big) + \omega\Big]Z_{1,0}(t)$$

$$+ \Big[\omega + \sigma\xi + \mu_{1,1} + \mu - p_0(1-\varepsilon)\Big(\frac{\partial\lambda_\nu(t)}{\partial Y_{1,1}}Y_{0,1}(t)\Big)\Big]Z_{1,1}(t)$$

$$- \sigma\xi Z_{2,0}(t) - \mu_{1,1}Z_{3,0}(t) - (\alpha(c_1+q_1)-q_1)e^{-rt} \tag{5.13d}$$

$$\frac{dZ_{2,0}(t)}{dt} = p_0\Big(\frac{\partial\lambda(t)}{\partial Y_{2,0}}Y_{0,0}(t)\Big)Z_{0,0}(t) + p_0(1-\varepsilon)\Big(\frac{\partial\lambda_\nu(t)}{\partial Y_{2,0}}Y_{0,1}(t)\Big)Z_{0,1}(t)$$

$$- p_0\Big(\frac{\partial\lambda(t)}{\partial Y_{2,0}}Y_{0,0}(t)\Big)Z_{1,0}(t) - p_0(1-\varepsilon)\Big(\frac{\partial\lambda_\nu(t)}{\partial Y_{2,0}}Y_{0,1}(t)\Big)Z_{1,1}(t)$$

$$+ \Big[\nu_t(t) + \mu_{2,0} + \mu\Big]Z_{2,0}(t) - \nu_t(t)Z_{2,1}(t) - \mu_{2,0}Z_{3,0}(t)$$

$$- (\alpha(\kappa_t\nu_t(t) + c_2 + q_2) - q_2)e^{-rt} \tag{5.13e}$$

$$\frac{dZ_{2,1}(t)}{dt} = p_0\Big(\frac{\partial\lambda(t)}{\partial Y_{2,1}}Y_{0,0}(t)\Big)Z_{0,0}(t) + p_0(1-\varepsilon)\Big(\frac{\partial\lambda_\nu(t)}{\partial Y_{2,1}}Y_{0,1}(t)\Big)Z_{0,1}(t)$$

$$- p_0\Big(\frac{\partial\lambda(t)}{\partial Y_{2,1}}Y_{0,0}(t)\Big)Z_{1,0}(t) - p_0(1-\varepsilon)\Big(\frac{\partial\lambda_\nu(t)}{\partial Y_{2,1}}Y_{0,1}(t)\Big)Z_{1,1}(t)$$

$$+ (\mu_{2,1} + \mu)Z_{2,1}(t) - \mu_{2,1}Z_{3,0}(t) - (\alpha(c_2+q_2)-q_2)e^{-rt} \tag{5.13f}$$

$$\frac{dZ_{3,0}(t)}{dt} = p_0\Big(\frac{\partial\lambda(t)}{\partial Y_{3,0}}Y_{0,0}(t)\Big)Z_{0,0}(t) + p_0(1-\varepsilon)\Big(\frac{\partial\lambda_\nu(t)}{\partial Y_{3,0}}Y_{0,1}(t)\Big)Z_{0,1}(t)$$

$$- p_0\Big(\frac{\partial\lambda(t)}{\partial Y_{3,0}}Y_{0,0}(t)\Big)Z_{1,0}(t) - p_0(1-\varepsilon)\Big(\frac{\partial\lambda_\nu(t)}{\partial Y_{3,0}}Y_{0,1}(t)\Big)Z_{1,1}(t)$$

$$+ (\mu_{3,0} + \mu)Z_{3,0}(t) - \mu_{3,0}Z_{4,0}(t) - (\alpha(c_3+q_3)-q_3)e^{-rt} \tag{5.13g}$$

$$\frac{dZ_{4,0}(t)}{dt} = p_0\Big(\frac{\partial\lambda(t)}{\partial Y_{4,0}}Y_{0,0}(t)\Big)Z_{0,0}(t) + p_0(1-\varepsilon)\Big(\frac{\partial\lambda_\nu(t)}{\partial Y_{4,0}}Y_{0,1}(t)\Big)Z_{0,1}(t)$$

$$- p_0\Big(\frac{\partial\lambda(t)}{\partial Y_{4,0}}Y_{0,0}(t)\Big)Z_{1,0}(t) - p_0(1-\varepsilon)\Big(\frac{\partial\lambda_\nu(t)}{\partial Y_{4,0}}Y_{0,1}(t)\Big)Z_{1,1}(t)$$

$$+ (\mu_{4,0} + \mu)Z_{4,0}(t) - (\alpha(c_4+q_4)-q_4)e^{-rt} \tag{5.13h}$$

with $Z(20) = 0$.

Then the final necessary condition,

$$H(t, Y^\star(t), \nu^\star(t), Z^\star(t)) \geq H(t, Y^\star(t), \nu(t), Z^\star(t))$$

for a.e. t in $[0, 20]$ and every $\nu(t) \in \mathcal{V}$, gives us the optimality condition for which the optimal solution must satisfy. Emphasizing that the control variable $\nu(t)$ appears linearly in

the Hamiltonian (5.12) and $\mathcal{V} = [0, 0.75] \times [0, 0.75]$ implies that the "bang-bang" principle can be applied to derive an interpretation for the solution of the optimal control based on its switching functions. Combining like terms and evaluating the Hamiltonian in the form $H(Y(t), \nu(t), Z(t)) = g_p(Y(t), Z(t))\nu_p(t) + g_t(Y(t), Z(t))\nu_t(t) + h(Y(t), Z(t))$, we get

$$
\begin{aligned}
&H(Y(t), \nu(t), Z(t)) \\
=& \Big[(Z_{0,1}(t) - Z_{0,0}(t))Y_{0,0}(t) + (Z_{1,1}(t) - Z_{0,1}(t))Y_{1,0}(t) + \alpha\kappa_p(Y_{0,0}(t) + Y_{1,0}(t))e^{-rt}\Big]\nu_p(t) \\
&+ \Big[(Z_{2,1}(t) - Z_{2,0}(t))Y_{2,0}(t) + \alpha\kappa_t Y_{2,0}(t)e^{-rt}\Big]\nu_t(t) \\
&\quad + \Big[I_{0,0} - \mu Y_{0,0}(t) - p_0\lambda(t)Y_{0,0}(t) + \omega Y_{0,1}(t)\Big]Z_{0,0}(t) \\
&\quad - \Big[\mu Y_{0,1}(t) + \omega Y_{0,1}(t) + p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}(t)\Big]Z_{0,1}(t) \\
&\quad + \Big[I_{1,0} + p_0\lambda(t)Y_{0,0}(t) - \sigma\xi Y_{1,0}(t) + \omega Y_{1,1}(t) - \mu_{1,0}Y_{1,0}(t) - \mu Y_{1,0}(t)\Big]Z_{1,0}(t) \\
&\quad + \Big[p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}(t) - \omega Y_{1,1}(t) - \sigma\xi Y_{1,1}(t) - \mu_{1,1}Y_{1,1}(t) - \mu Y_{1,1}(t)\Big]Z_{1,1}(t) \\
&\quad + \Big[I_{2,0} + \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) - \mu_{2,0}Y_{2,0}(t) - \mu Y_{2,0}(t)\Big]Z_{2,0}(t) \\
&\quad - \Big[\mu_{2,1}Y_{2,1}(t) + \mu Y_{2,1}(t)\Big]Z_{2,1}(t) \\
&\quad + \Big[I_{3,0} + \sum_{j=0}^{j=1}\sum_{i=1}^{i=2}\mu_{i,j}Y_{i,j}(t) - \mu_{3,0}Y_{3,0}(t) - \mu Y_{3,0}(t)\Big]Z_{3,0}(t) \\
&\quad + \Big[\mu_{3,0}Y_{3,0}(t) - \mu_{4,0}Y_{4,0}(t) - \mu Y_{4,0}(t)\Big]Z_{4,0}(t) \\
&\quad + \Big[\alpha\Big[\sum_{j=0}^{j=1}\sum_{i=0}^{i=4}c_i Y_{i,j}\Big] - (1-\alpha)\Big[\sum_{j=0}^{j=1}\sum_{i=0}^{i=4}q_i Y_{i,j}(t)\Big]\Big]e^{-rt}.
\end{aligned}
$$

By the "bang-bang" principle the solution to the optimal control for

$$
\begin{aligned}
g_p(t) =& (Z_{0,1}^\star(t) - Z_{0,0}^\star(t))Y_{0,0}^\star(t) + (Z_{1,1}^\star(t) - Z_{0,1}^\star(t))Y_{1,0}^\star(t) + \alpha\kappa_p(Y_{0,0}^\star(t) + Y_{1,0}^\star(t))e^{-rt} \\
g_t(t) =& (Z_{2,1}^\star(t) - Z_{2,0}^\star(t))Y_{2,0}^\star(t) + \alpha\kappa_t Y_{2,0}^\star(t)e^{-rt}
\end{aligned}
$$

is defined by the following step functions

$$
\nu_p^\star(t) = \begin{cases} 3/4, & g_p(t) < 0 \\ 0, & g_p(t) > 0 \\ ?, & g_p(t) = 0 \end{cases} \tag{5.14}
$$

$$\nu_t^\star(t) = \begin{cases} 3/4, & g_t(t) < 0 \\ 0, & g_t(t) > 0 \\ ?, & g_t(t) = 0 \end{cases} \quad . \tag{5.15}$$

5.4 Numerical Solution

As we have already discussed, the solution to the Pareto optimal intervention strategy can not be solved by analytical means. Therefore, we will now direct our attention to numerical methods. Solving optimal control problems numerically can be done in one of two ways. The first option is to take a direct approach, where the control and state space is discretized and then methods from nonlinear programming can be implemented. The alternative approach is known as the indirect approach and these methods take into consideration Pontryagin's maximum principle and solves for the admissible control that satisfies the necessary conditions. To derive a solution that optimizes on intervention strategies for the HIV virus we will begin with a direct numerical approach.

5.4.1 Control Parameterization

The direct numerical method we have chosen to implement is referred to as *control parameterization*, where the continuous optimal control problem is approximated by a discrete optimization problem that we can then solve by using methods from nonlinear programming [6]. Referencing "Nonlinear Programming: Theory and Applications" we will set up the statement for a nonlinear programming problem as the discrete approximation to the fundamental control problem 5.3.2. Recall, the objective problem statement is given by

$$\max_{\nu(t) \in \mathcal{V}} L(Y(t), \nu(t))$$

subject to

$$\frac{dY(t)}{dt} = F(Y(t), \nu(t)), \quad Y(0) = Y^{(0)}$$

on the interval $[0, 20]$. By choosing a discrete set of points $\{t^{[1]}, t^{[2]}, \dots, t^{[\ell]}\}$ such that $0 = t^{[1]} < t^{[2]} < \cdots < t^{[\ell]} = 20$, we define a piecewise constant function, that is right continuous, for the control variables such that

$$\nu(t) = \nu^{[k]} \text{ for } t \in [t^{[k]}, t^{[k+1]}) \text{ and } k = 1, \dots, \ell.$$

Assuming a uniform distribution of the discrete points, such that $h = t_{i+1} - t_i$ for $1 \leq i \leq (\ell-1)$, the discrete state variables can then be defined at each node $t^{[k]} \in \{t^{[1]}, t^{[2]}, \ldots, t^{[\ell]}\}$ by,

$$Y^{[k]} = Y^{[k-1]} + hF^{[k]}(Y^{[k-1]}, \nu^{[k]}) \text{ for } k = 1, \ldots, \ell,$$

with $Y^{[1]} = Y^{(0)}$. Such a solution that satisfies all of the requirements of the inequality as well as the equality constraints of the model is referred to as an *admissible solution*. For interpretation of the infectious disease model the set of admissible solutions to the discrete model is easily defined by,

$$D = \{(Y^{[1]}, Y^{[2]}, \ldots, Y^{[\ell]}, \nu^{[1]}, \nu^{[2]} \ldots, \nu^{[\ell]}) | 0 \leq Y^{[k]}, 0 \leq \nu_p^{[k]} \leq 0.75$$
$$\text{and } 0 \leq \nu_t^{[k]} \leq 0.75 \text{ for all } k = 1, \ldots, \ell\}.$$

Thus, making the translation from the continuous optimal control problem to the discrete nonlinear programming problem we get the following.

Problem 5.4.1 (Optimizing Intervention Strategies for the HIV Virus; as a nonlinear programming problem)**.**

$$\max \sum_{k=1}^{k=\ell} L(Y^{[k]}, \nu^{[k]})$$

subject to

$$Y^{[k]} = Y^{[k-1]} + hF^{[k]}(Y^{[k-1]}, \nu^{[k]}) \quad \text{for } k = 1, \ldots, \ell$$

such that $(Y^{[1]}, Y^{[2]}, \ldots, Y^{[\ell]}, \nu^{[1]}, \nu^{[2]}, \ldots, \nu^{[\ell]}) \in D$.

One of the benefits of taking a direct approach is the number of readily available algorithms, that already exist, for solving nonlinear programming problems. In our case, since we are using MatLab for all of our numerical analysis, we will be able to utilize the built-in function 'fmincon.m' to find a numerical approximation to the solution for 5.4.1. Keeping in mind that the nonlinear programming problem is already an approximation to the continuous optimal control problem, we will also validate the solution we get by verifying that it satisfies the necessary conditions from the "bang-bang" principle.

In addition to the ease for which solutions to nonlinear programming problems are found, by converting our optimal control problem, we have also removed the concerns for singularity that were introduced in section 5.3.1

5.4.2 Pareto Optimal Intervention Strategy

Before implementing control parameterization to optimize on the intervention strategy we need to assign a numerical value to α as an *a priori* selection for the weights associated to the two objective functions. Considering the fact that parameters associated to monetary cost are on an order of magnitude 10^4 larger than the quality index parameters, we found it reasonable to assign $\alpha = 10^{-4}$. By doing so, this results with weighting the objectives in such a way that one is not favored significantly more than the other.

Thus, setting up problem 5.4.1 in MatLab with a 20 year time horizon we chose 101 nodes, resulting with intervals of length 0.2. The nonlinear programming solver, 'fmincon', returned the solution given in figure 5.1. Based on the solution we found we have two switching times, one for each decision variable. Noting that the switching times will be defined by the choice made for discretizing the problem, we found that the switching time for the preventative vaccine is at $t_p^{[\star]} = 12.4$ and for the therapeutic vaccine $t_t^{[\star]} = 18.2$. Therefore,

$$\nu_p^{[\star]}(t) = \begin{cases} 3/4, & 0 \le t < 12.4 \\ 0, & 12.4 \le t \end{cases} \tag{5.16}$$

$$\nu_t^{[\star]}(t) = \begin{cases} 3/4, & 0 \le t < 18.2 \\ 0, & 18.2 \le t \end{cases}, \tag{5.17}$$

where the superscript $[\star]$ will be used to denote any solution that relates to the approximation for the optimal control.
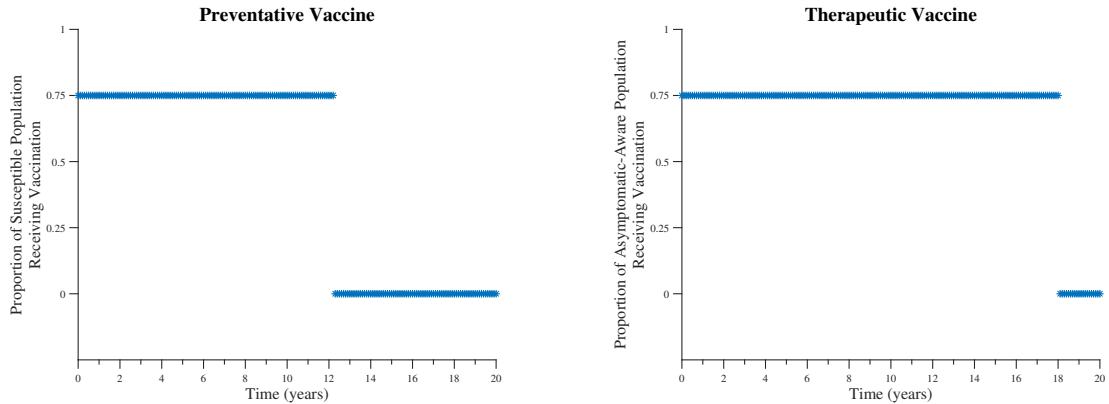
Figure 5.1: Pareto optimal intervention strategy derived by the direct numerical method, control parameterization.

To verify our solution we will first consider the cost-effective analysis and compare the results to the earlier direct strategies we evaluated, which will give us some satisfaction that we have found a 'better' strategy. Noting that the problem was approximated twice by converting the continuous control problem into a discrete nonlinear programming problem then using numerical methods to solve for the optimal solution we will also evaluate the corresponding switching functions and verify that the sign of each of the functions changes at approximately the same time as the switch occurs for each of the control variables.

5.4.3 Cost-Effective Analysis

To begin with the cost-effective analysis we evaluated the objective functionals for the monetary cost as well as the accumulated QALYs for the optimal control $\nu^{[\star]}$ and the corresponding state trajectory $Y^{[\star]}$. The results are present in table 5.2, along with the solutions for the four direct strategies that we evaluated in chapter 3.

Table 5.2: Projected accumulated cost and QALYs for each of the four variations of the model and how they compare to the Pareto optimal strategy.

	Accumulated Cost	Accumulated QALYs	Cost/QALY
No Intervention	$3,778,541,557	495,630	$7623/QALY
Therapeutic Vaccine	$3,747,402,695	506,808	$7394/QALY
Preventative Vaccine	$3,711,111,604	508,220	$7302/QALY
Combination Both Vaccines	$3,674,411,239	519,572	$7072/QALY
Pareto Optimal Strategy	$3,664,516,772	519,454	**$7055/QALY**

When the preventative vaccine is only offered to 75% of the susceptible population for the first 12.4 years and the therapeutic vaccine is offered to 75% of the asymptomatic-aware

population for the first 18.2 years we find that the solution offers the lowest cost per QALY compared to the other four strategies. In comparison to the direct combined, preventative and therapeutic, vaccine strategy the Pareto optimal solution decreased cost as well as QALYs. To understand how this can be considered a 'better' alternative to offering the vaccines for the full duration of time, we considered the ratio of cost relative to QALYs. This gives us a number that defines the relative cost for each QALY gained, resulting with a clear index for ranking the strategies[3]. Therefore, based on the cost ratio we have satisfied the objective for finding an alternative strategy that optimized the trade-off between minimizing monetary cost while maximizing the QALYs, resulting with a locally optimal intervention strategy.

5.4.4 Necessary Conditions for Pareto Optimal Solution

Considering the necessary conditions from the "bang-bang" principle for the Pareto optimal solution we found, we will derive the corresponding state and costate trajectories for $\nu_p^{[\star]}(t)$ and $\nu_t^{[\star]}(t)$ and evaluate the switching functions we derived in sections 5.3.1. If we can show that the switching times correspond to the point in time for which the sign of each of the switching functions changes, then we will have satisfied the necessary conditions for the "bang-bang" principle. Recall for the Hamiltonian,

$$H(Y(t), \nu(t), Z(t)) = \langle Z(t), F(Y(t), \nu(t)) \rangle + (Y(t), \nu(t)),$$

we have the following:

1. $\dfrac{dY(t)}{dt} = H_Z(Y^\star(t), \nu^\star(t), Z^\star(t)), \quad Y^\star(t^{(0)}) = Y^{(0)}$

2. $\dfrac{dZ(t)}{dt} = -H_Y(Y^\star(t), \nu^\star(t), Z^\star(t)), \quad Z^\star(t^{(1)}) = 0$

3.
$$\nu_p^\star(t) = \begin{cases} 3/4, & g_p(Y^\star(t), Z^\star(t)) < 0 \\ 0, & g_p(Y^\star(t), Z^\star(t)) > 0 \\ ?, & g_p(Y^\star(t), Z^\star(t)) = 0 \end{cases}$$

$$\nu_t^\star(t) = \begin{cases} 3/4, & g_t(Y^\star(t), Z^\star(t)) > 0 \\ 0, & g_t(Y^\star(t), Z^\star(t)) < 0 \\ ?, & g_t(Y^\star(t), Z^\star(t)) = 0 \end{cases}$$

---

[3]When cost-effective analysis is typically applied analyst will compare the discounted cost ratio. When this is done, it tends to be the case that the alternatives will both increase cost as well as the quality index. For the model we have been analyzing we have two dominant vaccine options. Thus considering the discounted cost ratio does not give us a clear understanding, so we consider the direct cost ratio instead.

with

$$g_p(Y^\star(t), Z^\star(t)) = (Z_{0,1}^\star(t) - Z_{0,0}^\star(t))Y_{0,0}^\star(t) + (Z_{1,1}^\star(t) - Z_{0,1}^\star(t))Y_{1,0}^\star(t)$$
$$+ \alpha\kappa_p(Y_{0,0}^\star(t) + Y_{1,0}^\star(t))e^{-rt}$$
$$g_t(Y^\star(t), Z^\star(t)) = (Z_{2,1}^\star(t) - Z_{2,0}^\star(t))Y_{2,0}^\star(t) + \alpha\kappa_t Y_{2,0}^\star(t)e^{-rt}.$$

Based on the solution to the numerical approximation we derived there is no need to be concerned with either of the switching functions vanishing for a period of time and resulting with a singular control. Instead there is exactly one switching time for each control. Thus, after deriving the corresponding state and costate trajectories for the Pareto optimal control $\nu^{[\star]}(t)$, using the initial value problems (1) and (2) from the necessary conditions, we will be able to evaluate the switching functions and determine if the numerical approximation to the local solution is in fact an approximation to the optimal solution. The results of the switching functions are presented along side of their control solution in figure 5.2. With the corresponding state and costate trajectories found in figures 5.4 and 5.5 respectively. Noting that the switching function for the therapeutic vaccine has such a significantly small slope around the switching time we also plotted a graph of the function on the interval $[10, 20]$, allowing us to zoom into the function values.

From the graphs of the switching functions it appears as though the Pareto optimal solution, derived by solving the corresponding nonlinear programming problem, is a valid approximation to the optimal control solution. Evaluating the switching functions at the corresponding switching times,

$$g_p(Y^{[\star]}(12.4), Z^{[\star]}(12.4)) \approx 2.189527297370716 \text{ and}$$
$$g_t(Y^{[\star]}(18.2), Z^{[\star]}(18.2)) \approx 0.6413617052318576,$$

reveals that the optimal solution was not obtained. Instead, by evaluating the switching functions at the time node just before $t_p^{[\star]}$ and $t_t^{[\star]}$, we get,

$$g_p(Y^{[\star]}(12.2), Z^{[\star]}(12.2)) \approx -1.260841910117648 \text{ and}$$
$$g_t(Y^{[\star]}(18), Z^{[\star]}(18)) \approx -0.9450336606823555.$$

Then, assuming a small change to the switching time would result with minimal variation to the switching functions, implies $12.2 \leq t_p^\star < 12.4$ and $18 \leq t_t^\star < 18.2$.

With this information we could further refine the approximation to the optimal control by focusing our nonlinear programming problem to optimize over the switching times. Note that we could not initially focus our problem statement around a single switching time because prior
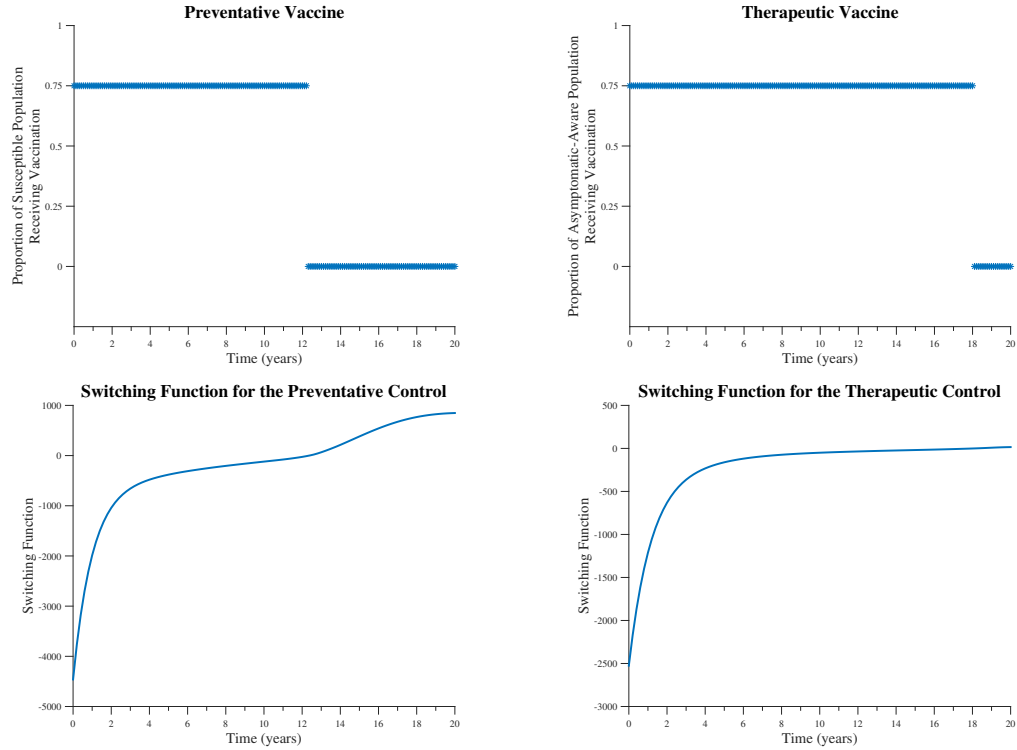
Figure 5.2: Numerical solutions to the Pareto optimal controls as they relate to their corresponding switching functions.

to deriving the solution we did not have a priori knowledge regarding the number of switches, or even whether or not there would be an issue with singularity.
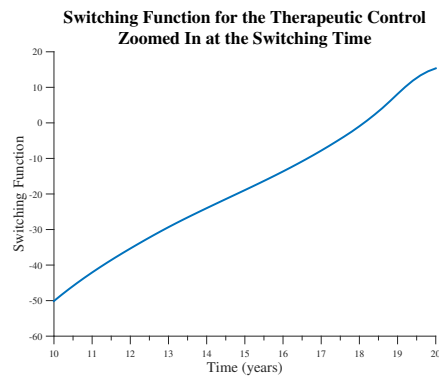
Figure 5.3: Zoomed-in window for the solution to the switching function for the therapeutic vaccine.
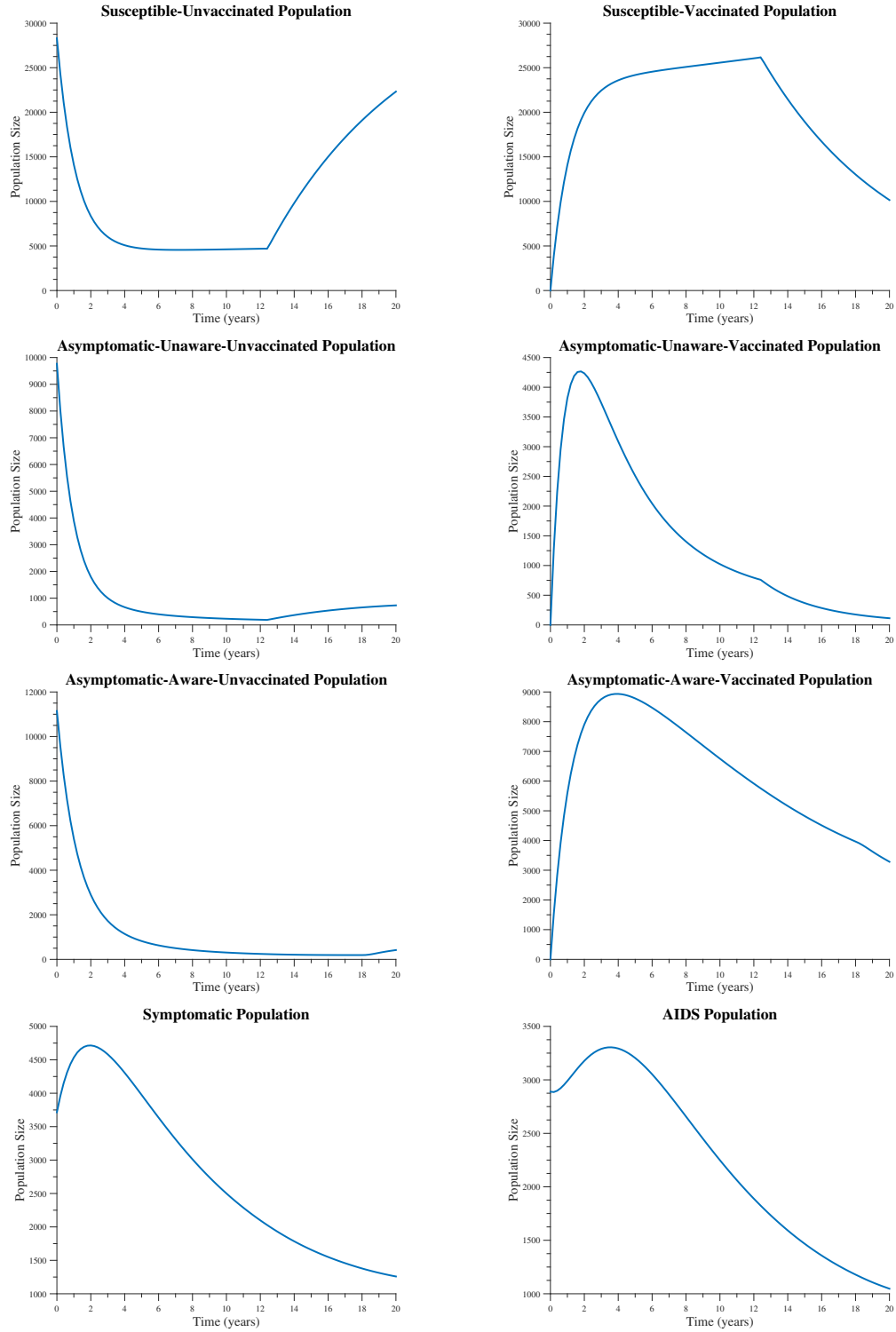
Figure 5.4: Projections for each class of the model over a 20 year time horizon with the Pareto optimal intervention strategy administered.
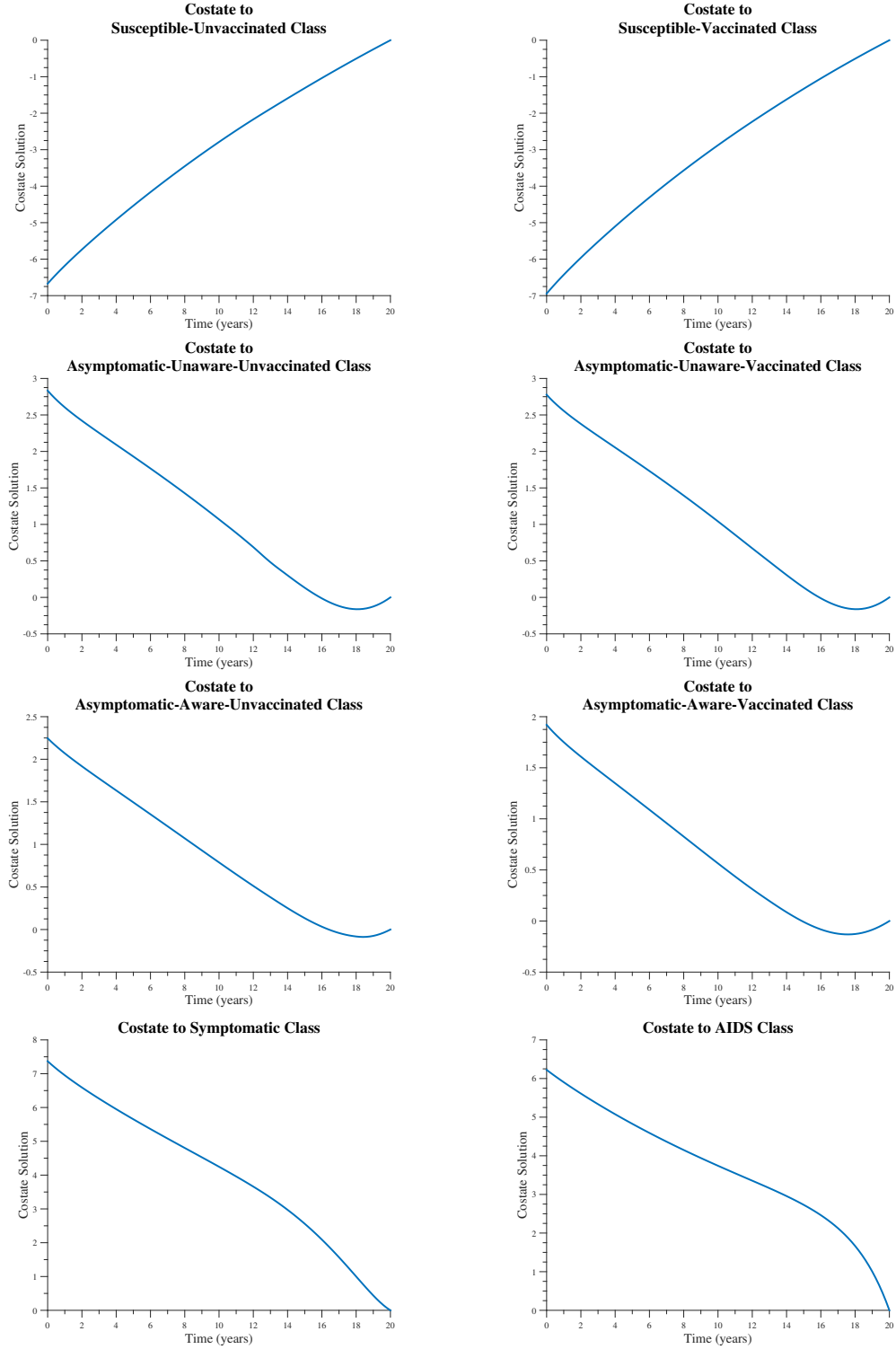
Figure 5.5: Projections for the costate variables as they relate to the classes of the model over a 20 year time horizon with the Pareto optimal intervention strategy administered.

5.4.5 The Pareto Front

As we have already mentioned in setting up the multiobjective problem statement for optimizing an intervention strategy the selection for the weights was made *a priori*. Noting that we only have two objectives the choice for weighting each of the opposing objectives is as simple as introducing a single parameter α, as the first weight, then $(1 - \alpha)$ defines the weight for the second objective. The decision to set $\alpha = 10^{-4}$ was done by considering the values that were driving the cost for the monetary objective compared to the proportional values that are used to assess the quality indexes for the various stages of infection.

In this section we will offer more insight into the choice for α and how it compares to alternative weighting options by means of analyzing the Pareto front. Recall the combined objective function we defined using the weighting method in section 5.3,

$$L(Y(t), \nu(t)) = \alpha C(Y(t), \nu(t)) - (1 - \alpha)Q(Y(t), \nu(t)).$$

Allowing α to vary between 0 and 1 then solving for the Pareto optimal solutions for each fixed α using the same numerical methods we applied in section 5.4 we derived the Pareto front shown in figure 5.6. We will note that the point on the Pareto front that agrees with the greatest cost and the greatest value for accumulated QALYs, defines the corresponding cost and QALYs for the optimal solution when the only objective is to increase QALYs ($\alpha = 0$). Alternatively, the other extreme with the lowest cost and QALYs agrees with the optimal solution when the only objective is decreasing cost ($\alpha = 1$). We will also note that, for all $\alpha \geq 10^{-3}$ the solution to the Pareto optimal control will all agree with the solution to the optimization problem when the only objective is to minimize cost. This can be explained by the wide range of discrepancy between the values associated to monetary cost relative to the values associated to QALYs. Originally, we used this distinction between the range of values for the opposing objectives to define α so that neither objective would be considered a higher priority than the other. We chose to emphasize this solution on the Pareto front, where $\hat{\alpha} = 10^{-4}$ is denoted with a red star. Comparing the results along the Pareto front we can see that the *a priori* selection we made for weighting the objective functions was a reasonable choice. If we chose to move along the Pareto front, away from the *a priori* selection for the weighted distribution of the objectives, will result with a trade-off between the objectives. Any choice for $\alpha > \hat{\alpha}$, corresponds to moving along the Pareto front in the direct that decreases cost and QALYs, which is a result to optimizes one objective while sacrificing the other. Alternatively, if a selection for $\alpha < \hat{\alpha}$ is made, the results indicate an optimal strategy with an increase in QALYs, but the increase to monetary cost is too substantial to ignore.

Whether or not the selection for $\hat{\alpha} = 10^{-4}$ is the ideal choice is something that will likely

be disputed between policy makers when consideration for implementing an optimal strategy is made. At that time, with the knowledge of the Pareto front, a *posteriori* selection for the weights can be made where the consideration for the rate of change for each objective has been made along the Pareto front. Answering the question, at what point does the gains for one objective become insignificant enough that it is not worth the loss to the opposing objective?
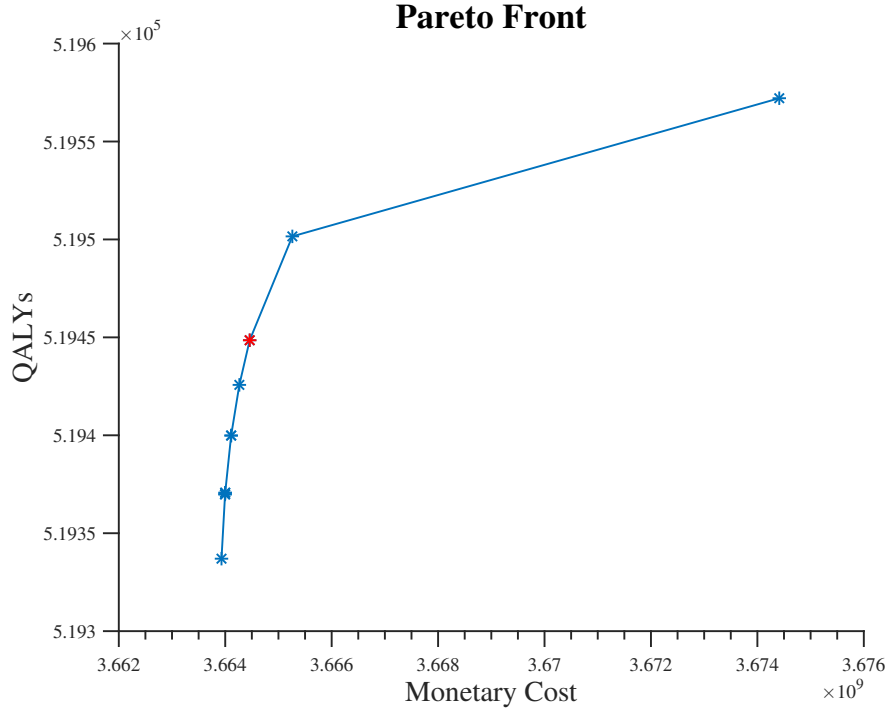
Figure 5.6: Pareto front for the multiobjective optimization problem to minimize monetary cost and increase QALYs.

Even though we can suggest that the selection for $\hat{\alpha} = 10^{-4}$ is a reasonable choice, either as an *a priori* or an *a posteriori* selection by analyzing the system, we are still limited to the assumptions made and data collected to understand the infectious disease model for the purpose of interpreting the spread and control of an infection. There may be, and usually are, additional outside factors that govern policy decisions. This highlights the importance for evaluating the full Pareto front whenever a multiobjective problem is addressed.

Chapter 6

Sensitivity Analysis

Sensitivity analysis is the study for understanding how variation in parameter values impact the results of a model [5, 51, 11, 52]. Many researchers are typically interested in running sensitivity analysis after implementing uncertainty analysis, a related field where the uncertainty for the model results is quantified based on the known uncertainty of the model parameters [52]. We will emphasize the distinction between uncertainty and sensitivity analysis by clarifying the difference between between the two. Uncertainty analysis gives researchers a means to quantify how uncertainty in the model inputs propagate through the model and define the uncertainty in the conclusion. For sensitivity analysis the result is a ranking that determines which parameters will contribute the most variation to the model if they were to change.

For the HIV-transmission model with vaccine intervention the uncertainty of the parameters is unknown. Therefore, we will forgo uncertainty analysis and focus on a means to rank the sensitivity of the parameters. Following the same approach from chapters 3 and 4 when we analyzed the dynamics for each variation of the model, we will again consider each case independently then compare the results of the sensitivities to get an interpretation for the model as a whole at the end.

6.1   Introduction to Sensitivity Analysis

Here we will present the necessary definitions and description for sensitivity analysis, as it is presented by Rosenwasser and Yusupov in *Sensitivity of Automatic Control Systems* [49]. This will introduce a general understanding of sensitivity before we continue on to presenting the method for which we will use to analyze the model parameters for the impact variations will have on the solution to the multiobjective optimal control problem we solved for in the last chapter.

First we will consider a system of ordinary differential equations:

$$\frac{dy(t)}{dt} = f(t, y) \quad y(t^{(0)}) = y^{(0)} \tag{6.1}$$

where $y = (y_1, y_2, \ldots, y_n)$ is a vector in the real Euclidean space $\mathbb{R}^n$ and $f = (f_1, f_2, \ldots, f_n)$ is a vector-valued function such that each f_i for $i = 1, \ldots, n$ are $C^{(1)}$ functions of the variables (t, y).

The solution and properties of the system (6.1) can further be described by its dependency on the selection of parameter values we will denote by $\Theta = [\theta_1, \theta_2, \ldots, \theta_k]$, where Θ is a vector in the real Euclidean space $\mathbb{R}^k$ we will refer to as the *parameter space*. Therefore, the finite-dimensional continuous system (6.1) can be written in expanded form as:

$$\frac{dy(t, \Theta)}{dt} = f(y(t, \Theta), \Theta), \quad y(t^{(0)}(\Theta), \Theta) = y^{(0)}(\Theta). \tag{6.2}$$

Assuming that each function f_i for $i = 1, \ldots, n$ are also $C^{(1)}$ functions of the variable Θ, we will have continuity and differentiability with respect to each one of the parameters θ_i for $i = 1, \ldots, k$. Thus, to determine the impact that variations in the parameters will have on the resulting solutions for the state trajectories means we are interested in evaluating,

$$\frac{\partial y(t)}{\partial \theta_i} \tag{6.3}$$

for each $\theta_i \in \Theta$.

Definition 6.1.1. The *first-order sensitivity functions* of the state trajectories y_j with respect to the corresponding parameters θ_i in the parameter space Θ are each defined by,

$$\frac{\partial y_j(t, \Theta)}{\partial \theta_i}, \quad \text{for } i = 1, 2, \ldots, k \text{ and } j = 1, 2, \ldots, n.$$

Therefore the objective is to derive the first-order sensitivity functions from the system of equations defined by (6.2). To do so, we will start with considering the fundamental theorem of calculus, such that (6.2) gives us

$$y(t, \Theta) = \int_{t^{(0)}(\Theta)}^{t} f(y(t, \Theta), \Theta) dt + y(t^{(0)}(\Theta), \Theta). \tag{6.4}$$

Differentiating with respect to $\theta_i \in \Theta$,

$$\frac{\partial}{\partial \theta_i}(y(t, \Theta)) = \frac{\partial}{\partial \theta_i}\left(\int_{t^{(0)}(\Theta)}^{t} f(y(t, \Theta), \Theta) dt + y(t^{(0)}(\Theta), \Theta)\right), \tag{6.5}$$

and applying Leibnitz's integration rule we can evaluate the right hand side the equation (6.5),

$$\frac{\partial}{\partial \theta_i} \left(\int_{t^{(0)}(\Theta)}^{t} f(y(t,\Theta),\Theta)dt + y(t^{(0)}(\Theta),\Theta) \right)$$

$$= \int_{t^{(0)}(\Theta)}^{t} \left[\frac{\partial}{\partial \theta_i} f(y(t,\Theta),\Theta) \right] dt - f(t^{(0)}(\Theta),\Theta)\frac{dt^{(0)}(\Theta)}{d\theta_i} + \frac{dy^{(0)}(\Theta)}{d\theta_i}$$

$$= \int_{t^{(0)}(\Theta)}^{t} \left[\left(\frac{\partial f(y(t,\Theta))}{\partial y} \frac{\partial y(t,\Theta)}{\partial \theta_i} \right) + \frac{\partial f}{\partial \theta_i} \right] dt - f(t^{(0)}(\Theta),\Theta)\frac{dt^{(0)}(\Theta)}{d\theta_i} + \frac{dy^{(0)}(\Theta)}{d\theta_i} \qquad (6.6)$$

Therefore,

$$\frac{\partial y(t,\Theta)}{\partial \theta_i} = \int_{t^{(0)}(\Theta)}^{t} \left[\left(\frac{\partial f(y(t,\Theta))}{\partial y} \frac{\partial y(t,\Theta)}{\partial \theta_i} \right) + \frac{\partial f}{\partial \theta_i} \right] dt - f(t^{(0)}(\Theta),\Theta)\frac{dt^{(0)}(\Theta)}{d\theta_i} + \frac{dy^{(0)}(\Theta)}{d\theta_i}$$

$$(6.7)$$

implies the solution to the first-order sensitivity functions can be found by solving for their corresponding initial value problem,

$$\frac{d}{dt} \left(\frac{\partial y(t,\Theta)}{\partial \theta_i} \right) = \left(\frac{\partial f(y(t,\Theta))}{\partial y} \frac{\partial y(t,\Theta)}{\partial \theta_i} \right) + \frac{\partial f}{\partial \theta_i}, \qquad (6.8)$$

with

$$\frac{\partial y(t^{(0)}(\Theta),\Theta)}{\partial \theta_i} = \frac{dy^{(0)}(\Theta)}{d\theta_i} - f(t^{(0)}(\Theta),\Theta)\frac{dt^{(0)}(\Theta)}{d\theta_i}. \qquad (6.9)$$

As a brief introduction to sensitivity analysis we have presented the motivation for understanding the impact that variations in the parameter values can have on the solutions for the state trajectories. For the purposes of understanding the impact that variations on the parameters can have on the payoff function for the multiobjective optimization problem we considered in chapter 5 we will introduce the adjoint variable method in the following section, were Lagrange multipliers are introduced to defined an augmented objective function that considers both the dynamics and payoff in tandem.

6.2 Adjoint Variable Method

The adjoint variable method is a differential approach to analyzing the first order sensitivity functions for the parameters as they relate to the objective payoff from an optimal control problem [5, 11]. To introduce the method we will consider the following generalize optimization problem, for which we use the notation from the objective control problem we addressed in

chapter 5.

Problem 6.2.1. For $Y \in \mathbb{R}^n$ minimize the payoff functional

$$L(Y, \nu) = \int_{t^{(0)}}^{t^{(1)}} \ell(Y(t), \nu(t)) dt$$

over the set of admissible controls $\nu \in \mathcal{V}$, subject to

$$\frac{dY(t)}{dt} = F(Y(t), \nu(t)), \quad Y(t^{(0)}) = Y^{(0)}.$$

Noting that we will be analyzing each variation of the state space independently we assume the fixed parameters for each of the control variables, $\nu_p(t) = \nu_p$ and $\nu_t(t) = \nu_t$, that will be defined as part of the parameter space we will continue to denote by $\Theta = [\theta_1, \theta_2, \ldots, \theta_k]$. Taking a differential approach to understanding the impact that the variations in the parameters have on the outcome of the payoff functional implies that the current objective is to evaluate $\partial L / \partial \theta_i$ for each parameter $\theta_i \in \Theta$. To do so we will implement the adjoint variable method that utilizes Lagrange multipliers to define an augmented objective function for which the variation of the parameters are calculated and results with the solution $\partial L / \partial \theta_i$ for each parameter $\theta_i \in \Theta$.

To begin we will start by introducing the following notation for the dynamical system,

$$\Psi(\dot{Y}(t), Y(t), \Theta) := \frac{dY(t)}{dt} - F(Y(t))$$
$$G(Y(t^{(0)}), \Theta) := Y(t^{(0)}) - Y^{(0)},$$

such that

$$\Psi(\dot{Y}(t), Y(t), \Theta) = 0 \tag{6.10a}$$
$$G(Y(t^{(0)}), \Theta) = 0. \tag{6.10b}$$

Introducing the Lagrange multipliers, Λ and Γ, we get the following augmented objective function

$$S(Y, \Theta) = L(Y, \Theta) + \int_{t^{(0)}}^{t^{(1)}} \langle \Lambda, \Psi(\dot{Y}(t), Y(t), \Theta) \rangle dt + \langle \Gamma, G(Y(t^{(0)}), \Theta) \rangle,$$

where $\langle \cdot, \cdot \rangle$ denotes the inner product. This implies, $L(Y, \Theta) = S(Y, \Theta)$ and

$$\frac{\partial L(Y, \Theta)}{\partial \theta_i} = \frac{\partial S(Y, \Theta)}{\partial \theta_i}$$

$$= \int_{t^{(0)}}^{t^{(1)}} (\ell_{\theta_i} + \ell_Y Y_{\theta_i}) dt$$

$$+ \int_{t^{(0)}}^{t^{(1)}} \langle \Lambda, (\Psi_{\theta_i} + \Psi_Y Y_{\theta_i} + \Psi_{\dot Y} \dot Y_{\theta_i}) \rangle dt + \langle \Gamma, (G_{Y(t^{(0)})} Y_{\theta_i}(t^{(0)}) + G_{\theta_i}) \rangle.$$

$$(6.11)$$

Applying integration by parts

$$\int_{t^{(0)}}^{t^{(1)}} \langle \Lambda, \Psi_{\dot Y} \dot Y_{\theta_i} \rangle dt = \langle \Lambda, \Psi_{\dot Y} Y_{\theta_i} \rangle \Big|_{t^{(0)}}^{t^{(1)}} - \int_{t^{(0)}}^{t^{(1)}} (\langle \dot\Lambda, \Psi_{\dot Y} Y_{\theta_i} \rangle + \langle \Lambda, \dot\Psi_{\dot Y} Y_{\theta_i} \rangle) dt$$

results with

$$\frac{\partial L(Y, \Theta)}{\partial \theta_i} = \int_{t^{(0)}}^{t^{(1)}} \left[\ell_{\theta_i} + \ell_Y Y_{\theta_i} + \langle \Lambda, (\Psi_{\theta_i} + \Psi_Y Y_{\theta_i} - \dot\Psi_{\dot Y} Y_{\theta_i}) \rangle - \langle \dot\Lambda, \Psi_{\dot Y} Y_{\theta_i} \rangle \right] dt$$

$$+ \langle \Lambda, \Psi_{\dot Y} Y_{\theta_i} \rangle \Big|_{t^{(1)}} + \left(\langle \Gamma, G_{Y(t^{(0)})} \rangle - \langle \dot\Lambda, \Psi_{\dot Y} \rangle \Big|_{t^{(0)}} \right) Y_{\theta_i} + \langle \Gamma, G_{\theta_i} \rangle. \qquad (6.12)$$

Assuming $\Gamma = \langle \Lambda, \Psi_{\dot Y} \rangle \Big|_{t^{(0)}} G_{Y(t^{(0)})}^{-1}$ and $\Lambda(t^{(1)}) = 0$ then

$$\frac{\partial L(Y, \Theta)}{\partial \theta_i} = \int_{t^{(0)}}^{t^{(1)}} (\ell_{\theta_i} + \langle \Lambda, \Psi_{\theta_i} \rangle) dt + \int_{t^{(0)}}^{t^{(1)}} (\ell_Y + \langle \Lambda, (\Psi_Y - \dot\Psi Y) \rangle - \langle \dot\Lambda, \Psi_{\dot Y} \rangle) Y_{\theta_i} dt$$

$$+ \langle \Lambda, \Psi_{\dot Y} \rangle \Big|_{t^{(0)}} G_{Y(t^{(0)})}^{-1} G_{\theta_i}. \qquad (6.13)$$

Noting that $\Psi(\dot Y(t), Y(t), \Theta) = \dot Y(t) - F(Y(t))$ and $G(Y(t^{(0)}), \Theta) = Y(t^{(0)}) - Y^{(0)}$ implies $\Psi_{\dot Y} = 1_{n \times 1}$, $\dot\Psi_{\dot Y} = 0_{n \times 1}$, and $G_{Y(t^{(0)})}^{-1} = I_{n \times n}$, then the sensitivity functions simplify to

$$\frac{\partial L(Y, \Theta)}{\partial \theta_i} = \int_{t^{(0)}}^{t^{(1)}} (\ell_{\theta_i} + \langle \Lambda, \Psi_{\theta_i} \rangle) dt + \int_{t^{(0)}}^{t^{(1)}} (\ell_Y + \langle \Lambda, \Psi_Y \rangle - \dot\Lambda) Y_{\theta_i} dt + \langle \Lambda \Big|_{t^{(0)}}, G_{\theta_i} \rangle. \qquad (6.14)$$

Therefore, if we let $\dot\Lambda = \langle \Lambda, \Psi_Y \rangle + \ell_Y$ then

$$\frac{\partial L(Y, \Theta)}{\partial \theta_i} = \int_{t^{(0)}}^{t^{(1)}} (\ell_{\theta_i} + \langle \Lambda, \Psi_{\theta_i} \rangle) dt + \langle \Lambda \Big|_{t^{(0)}}, G_{\theta_i} \rangle. \qquad (6.15)$$

By introducing the Lagrange multipliers results with a boundary value problem whose solution can be used to solve for each of the sensitivity functions.

Noting that $\Psi(\dot Y, Y, \Theta) = \dot Y(t) - F(Y(t))$, then $\Psi_Y = -F_Y$ and

$$\frac{\partial L(Y, \Theta)}{\partial \theta_i} = \int_{t^{(0)}}^{t^{(1)}} \left(\ell_{\theta_i} + \langle \Lambda, \Psi_{\theta_i} \rangle \right) dt + \langle \Lambda \big|_{t^{(0)}}, G_{\theta_i} \rangle$$

subject to

$$\frac{dY(t)}{dt} = F(Y(t)), \qquad Y(t^{(0)}) = Y^{(0)}$$
$$\frac{d\Lambda(t)}{dt} = -\langle \Lambda, F_Y \rangle + \ell_Y, \qquad \Lambda(t^{(1)}) = 0.$$

To solve the state and adjoint equations as well as the sensitivity functions for each parameter will require numerical values for the parameter assumptions that were made by Edwards *et al.* and presented in chapter 3. As we continue with the sensitivity analysis the point in the parameter space, Θ, defined by numerical values we have already considered during our simulations and solution to the optimization problem, will be denoted by $\hat{\Theta}$. This implies that the solution for each of the sensitivity functions will define the instantaneous rate of change for the payoff with respect to corresponding parameter evaluated at the point $\hat{\Theta}$,

$$\frac{\partial L(Y, \Theta)}{\partial \theta_i} = \frac{\partial L(Y, \Theta)}{\partial \theta_i} \bigg|_{\hat{\Theta}}.$$

In the following sections we will set up the equations as they are defined for each variation of the model then numerical solvers will be implemented to derive the solution to state trajectories (solving forward in time), as well as the adjoint equations (solved in reverse time). The solutions to the state and adjoint equations will then be used to evaluate the integral for the sensitivity functions for each parameter of the model[1].

6.2.1 HIV-Transmission Dynamics without Intervention

To evaluate the sensitivity for each of the parameters of the model when no intervention is present we present the system of differential equations with the introduction of three more parameters that were not defined in section 3.1. The three parameters we are introducing define the distribution of the immigration population as it relates to an individuals infection status. Originally each of the immigration terms were defined as the following,

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[1]Given the volume of parameters for each variation of the model the sensitivity functions are derived and presented in appendix C.

$$I_{0,0} = 0.9\mu Y_0 \tag{6.16a}$$

$$I_{1,0} = 0.04\mu Y_0 \tag{6.16b}$$

$$I_{2,0} = 0.04\mu Y_0 \tag{6.16c}$$

$$I_{3,0} = 0.02\mu Y_0. \tag{6.16d}$$

To evaluate the sensitivity for the outcome of the model to the distribution of the immigrating population we introduce the parameters ρ_1, ρ_2, and ρ_3 such that $0 \leq \rho_i \leq 1$ for $i = 1, 2, 3$ and $\sum_{i=1}^{i=3} \rho_i \leq 1$. Then the immigration parameters are defined by

$$I_{0,0} = (1 - \sum_{i=1}^{i=3})\mu Y_0 \tag{6.17a}$$

$$I_{1,0} = \rho_1 \mu Y_0 \tag{6.17b}$$

$$I_{2,0} = \rho_2 \mu Y_0 \tag{6.17c}$$

$$I_{3,0} = \rho_3 \mu Y_0, \tag{6.17d}$$

and the dynamics are defined as the following:

$$\frac{dY_{0,0}(t)}{dt} = (1 - \sum_{i=1}^{i=3} \rho_i)\mu Y_0 - (\mu + p_0\lambda(t))Y_{0,0}(t) \tag{6.18a}$$

$$\frac{dY_{1,0}(t)}{dt} = \rho_1 \mu Y_0 + p_0\lambda(t)Y_{0,0}(t) - (\sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) \tag{6.18b}$$

$$\frac{dY_{2,0}(t)}{dt} = \rho_2 \mu Y_0 + \sigma\xi Y_{1,0}(t) - (\mu_{2,0} + \mu)Y_{2,0}(t) \tag{6.18c}$$

$$\frac{dY_{3,0}(t)}{dt} = \rho_3 \mu Y_0 + \sum_{i=1}^{i=2} \mu_{i,0}Y_{i,0}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t) \tag{6.18d}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t), \tag{6.18e}$$

were $\lambda(t) = \dfrac{\sum_{i=1}^{i=4} p_i\beta_{i,0}\eta_{00,i0}Y_{i,0}(t)}{\sum_{i=0}^{i=4} p_iY_{i,0}(t)}$, along with the initial state

$$Y_{0,0}(0) = (1 - \phi_0)Y_0 \tag{6.19a}$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}}\phi_0 Y_0, \text{ for } i = 1, 2, 3, 4 \tag{6.19b}$$

$$\tag{6.19c}$$

and the corresponding payoff functional

$$L(T) = \int_0^T \left[\alpha \left(\sum_{i=0}^{i=4} c_i Y_{i,0}(t) \right) - (1 - \alpha) \left(\sum_{i=0}^{i=4} q_i Y_{i,0}(t) \right) \right] e^{-rt} dt. \tag{6.20}$$

For the base case, without an intervention, we have the following set of parameters governing the outcome

$$\Theta = [\mu, \mu_{1,0}, \mu_{2,0}, \mu_{3,0}, \mu_{4,0}, p_0, p_1, p_2, p_3, p_4, \beta_{1,0}, \beta_{2,0}, \beta_{3,0}, \beta_{4,0}, \eta_{00,10}, \eta_{00,20} \eta_{00,30}, \eta_{00,40}, \ldots$$
$$\ldots, \sigma, \xi, Y_0, \phi_0, \rho_1, \rho_2, \rho_3, c_0, c_1, c_2, c_3, c_4, q_0, q_1, q_2, q_3, q_4, r, \alpha],$$

where particular values at the point that the variations are analyzed are shown in the second column of table 6.1.

To evaluate the sensitivity analysis for each of the 37 parameters, we will start by setting up the system of differential equations that define the adjoint variables. Presenting the model using the notation introduced in the previous section we begin by defining $\Psi(\dot{Y}, Y, \Theta)$, $G(Y(0), \Theta)$ and $\ell(Y, \Theta)$,

$$\Psi(\dot{Y}, Y, \Theta) = \begin{bmatrix} \dot{Y}_{0,0}(t) + (\mu + p_0 \lambda(t)) Y_{0,0}(t) - (1 - \sum_{i=1}^{i=3} \rho_i) \mu Y_0 \\ \dot{Y}_{1,0}(t) - p_0 \lambda(t) Y_{0,0}(t) + (\sigma \xi + \mu_{1,0} + \mu) Y_{1,0}(t) - \rho_1 \mu Y_0 \\ \dot{Y}_{2,0}(t) - \sigma \xi Y_{1,0}(t) + (\mu_{2,0} + \mu) Y_{2,0}(t) - \rho_2 \mu Y_0 \\ \dot{Y}_{3,0}(t) - \mu_{1,0} Y_{1,0}(t) - \mu_{2,0} Y_{2,0}(t) + (\mu_{3,0} + \mu) Y_{3,0}(t) - \rho_3 \mu Y_0 \\ \dot{Y}_{4,0}(t) - \mu_{3,0} Y_{3,0}(t) + (\mu_{4,0} + \mu) Y_{4,0}(t) \end{bmatrix}$$

$$G(Y(0), \Theta) = \begin{bmatrix} Y_{0,0}(0) - (1 - \phi_0) Y_0 \\ Y_{1,0}(0) - \phi_0 \left(\dfrac{1/\mu_{1,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \right) Y_0 \\ Y_{2,0}(0) - \phi_0 \left(\dfrac{1/\mu_{2,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \right) Y_0 \\ Y_{3,0}(0) - \phi_0 \left(\dfrac{1/\mu_{3,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \right) Y_0 \\ Y_{4,0}(0) - \phi_0 \left(\dfrac{1/\mu_{4,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \right) Y_0 \end{bmatrix}$$

$$\ell(Y, \Theta) = \left[\alpha \left(\sum_{i=0}^{i=4} c_i Y_{i,0}(t) \right) - (1 - \alpha) \left(\sum_{i=0}^{i=4} q_i Y_{i,0}(t) \right) \right] e^{-rt}.$$

Then the initial value problem for the adjoint variables is defined by

$$\frac{d\Lambda(t)}{dt} = -\langle \Lambda, F_Y \rangle + \ell_Y, \quad \Lambda(t^{(1)}) = 0$$

with

$$\ell_Y = \begin{bmatrix} (\alpha(c_0 + q_0) - q_0)e^{-rt} \\ (\alpha(c_1 + q_1) - q_1)e^{-rt} \\ (\alpha(c_2 + q_2) - q_2)e^{-rt} \\ (\alpha(c_3 + q_3) - q_3)e^{-rt} \\ (\alpha(c_4 + q_4) - q_4)e^{-rt} \end{bmatrix},$$

and F_Y is the Jacobian matrix for the system (6.18), which can be referenced in appendix A. The resulting system of ordinary differential equations is given as the following:

$$\frac{d\Lambda_{0,0}(t)}{dt} = \left(\mu + p_0\left(\frac{\partial \lambda}{\partial Y_{0,0}}Y_{0,0}(t) + \lambda(t)\right)\right)\Lambda_{0,0}(t) - p_0\left(\frac{\partial \lambda}{\partial Y_{0,0}}Y_{0,0}(t)\right)\Lambda_{1,0}(t)$$
$$+ (\alpha(c_0 + q_0) - q_0)e^{-rt} \tag{6.21a}$$

$$\frac{d\Lambda_{1,0}(t)}{dt} = p_0\left(\frac{\partial \lambda}{\partial Y_{1,0}}Y_{0,0}(t)\right)\Lambda_{0,0}(t) + \left((\sigma\xi + \mu_{1,0} + \mu) - p_0\frac{\partial \lambda}{\partial Y_{1,0}}Y_{0,0}(t)\right)\Lambda_{0,0}(t)$$
$$- \sigma\xi\Lambda_{2,0}(t) - \mu_{1,0}\Lambda_{3,0}(t) + (\alpha(c_1 + q_1) - q_1)e^{-rt} \tag{6.21b}$$

$$\frac{d\Lambda_{2,0}(t)}{dt} = p_0\left(\frac{\partial \lambda}{\partial Y_{2,0}}Y_{0,0}(t)\right)\Lambda_{0,0}(t) - p_0\left(\frac{\partial \lambda}{\partial Y_{2,0}}Y_{0,0}(t)\right)\Lambda_{0,0}(t) + (\mu_{2,0} + \mu)\Lambda_{2,0}(t)$$
$$- \mu_{2,0}\Lambda_{3,0}(t) + (\alpha(c_2 + q_2) - q_2)e^{-rt} \tag{6.21c}$$

$$\frac{d\Lambda_{3,0}(t)}{dt} = p_0\left(\frac{\partial \lambda}{\partial Y_{3,0}}Y_{0,0}(t)\right)\Lambda_{0,0}(t) - p_0\left(\frac{\partial \lambda}{\partial Y_{3,0}}Y_{0,0}(t)\right)\Lambda_{0,0}(t) + (\mu_{3,0} + \mu)\Lambda_{3,0}(t)$$
$$- \mu_{3,0}\Lambda_{4,0}(t) + (\alpha(c_3 + q_3) - q_3)e^{-rt} \tag{6.21d}$$

$$\frac{d\Lambda_{4,0}(t)}{dt} = p_0\left(\frac{\partial \lambda}{\partial Y_{4,0}}Y_{0,0}(t)\right)\Lambda_{0,0}(t) - p_0\left(\frac{\partial \lambda}{\partial Y_{4,0}}Y_{0,0}(t)\right)\Lambda_{0,0}(t) + (\mu_{4,0} + \mu)\Lambda_{4,0}(t)$$
$$+ (\alpha(c_4 + q_4) - q_4)e^{-rt}. \tag{6.21e}$$

The solutions for both systems (6.18) and (6.21) were derived by numerical methods and are presented in figures 6.1 and 6.2 respectively. The solutions for both the state trajectories and adjoint variables are then used evaluate each of the sensitivity functions for all 37 parameters[2]. The results for each are presented in table 6.1 where they have been ranked in order by the most sensitive to the least. We will notice from the results that the range of sensitivities is on an order of magnitude equal to 10^9. This implies, any small change in the parameter in the size of the total initial population Y_0 will have the least significant impact on the payoff functional.

---

[2]All 37 sensitivity functions are derived and presented in appendix C.

Alternatively, any variation in the weighting parameter we introduced when we defined Pareto optimality, α, will have the most significant impact on the payoff function. The payoff functional is at least 100 times more sensitive to α than any other parameter.
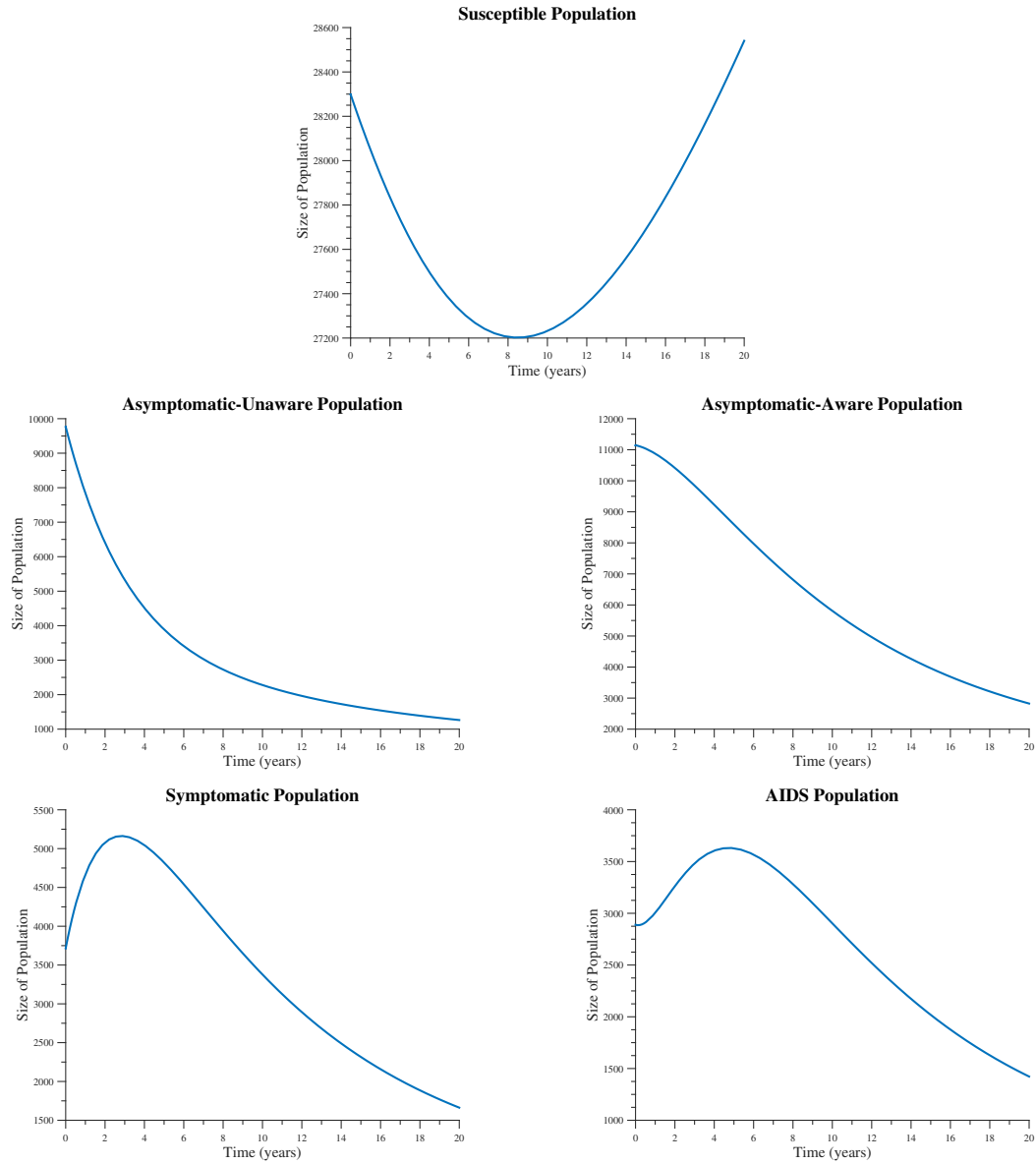
Figure 6.1: Model without an intervention: state trajectories for evaluating parameter sensitivity to the objective function.

Figure 6.2: Model without an intervention: adjoint variables for evaluating parameter sensitivity to the objective function.

Table 6.1: Adjoint variable method: parameter sensitivity to the objective function for the dynamics when no intervention is present. Solutions to the instantaneous rate of change for the payoff with respect to the corresponding parameter evaluated at $\hat{\Theta}$.

Parameters	Parameter Values (Assumptions, $\hat{\Theta}$)	Sensitivity of the Payoff Relative to each Parameter $\left(\left.\dfrac{\partial L(Y,\Theta)}{\partial \theta_i}\right\vert_{\hat{\Theta}}\right)$
α	1/10000	3.77893288584679e+09
μ	0.022	-2.05766844091403e+06
r	0.05	1.06877275341801e+06
ϕ_0	0.493	6.08681045598163e+05
$\mu_{2,0}$	1/8.1	4.71856179135082e+05
q_0	1	-3.49011143301420e+05
$\beta_{2,0}$	0.066	2.65391025219291e+05
$\mu_{1,0}$	1/7.1	2.48321336019011e+05
$\mu_{4,0}$	1/2.1	-2.31110989786677e+05
$\beta_{1,0}$	0.066	2.30344329463931e+05
ρ_3	0.02	1.77804374121074e+05
ρ_1	0.04	1.10034511112133e+05
ρ_2	0.04	1.09573991827064e+05
$\beta_{3,0}$	0.147	1.06171506498069e+05
q_2	0.83	-8.95411159820186e+04
$\mu_{3,0}$	1/2.7	-8.09226150773032e+04
$\eta_{00,30}$	0.235	6.64136657668773e+04
$\eta_{00,20}$	0.307	5.70547480927466e+04
q_3	0.42	-4.73824609258732e+04
q_1	1	-4.61969135242662e+04
q_4	0.17	-3.63181330680740e+04
$\eta_{00,10}$	0.505	3.01044074150881e+04
$\beta_{4,0}$	0.147	2.66508811130811e+04
$\eta_{00,40}$	0.235	1.66709766962677e+04
p_0	2	1.04141606044455e+04
p_3	2	5.35647554957312e+03
p_1	2	5.00036726417670e+03
p_4	0.667	4.06351423557415e+03
p_2	2	3.99552727984316e+03
σ	0.15	-3.61336579054310e+03
ξ	0.98	-5.53066192430067e+02
c_0	3307	3.49046047906211e+01
c_2	5467	8.95500709891175e+00
c_3	12586	4.73871996458378e+00
c_1	5467	4.62015336776339e+00
c_4	35394	3.63217652445984e+00
Y_0	55816	-2.10922602687988e+00

6.2.2 Therapeutic Vaccine Program

We will again emphasize the notation for immigration defined as we introduced it in section 6.2.1,

$$I_{0,0} = (1 - \sum_{i=1}^{i=3})\mu Y_0 \tag{6.22a}$$

$$I_{1,0} = \rho_1 \mu Y_0 \tag{6.22b}$$

$$I_{2,0} = \rho_2 \mu Y_0 \tag{6.22c}$$

$$I_{3,0} = \rho_3 \mu Y_0. \tag{6.22d}$$

This results with the following system of differential equations for the dynamics for the therapeutic vaccine program:

$$\frac{dY_{0,0}(t)}{dt} = (1 - \sum_{i=1}^{3} \rho_i)\mu Y_0 - (\mu + p_0\lambda(t))Y_{0,0}(t) \tag{6.23a}$$

$$\frac{dY_{1,0}(t)}{dt} = \rho_1 \mu Y_0 + p_0\lambda(t)Y_{0,0}(t) - (\sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) \tag{6.23b}$$

$$\frac{dY_{2,0}(t)}{dt} = \rho_2 \mu Y_0 + \sigma\xi Y_{1,0}(t) - (\nu_t + \mu_{2,0} + \mu)Y_{2,0}(t) \tag{6.23c}$$

$$\frac{dY_{2,1}(t)}{dt} = \nu_t Y_{2,0}(t) - (\mu_{2,1} + \mu)Y_{2,1}(t) \tag{6.23d}$$

$$\frac{dY_{3,0}(t)}{dt} = \rho_3 \mu Y_0 + \sum_{i=1}^{i=2}\sum_{j=0}^{j=1} \mu_{i,j}Y_{i,j}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t) \tag{6.23e}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t) \tag{6.23f}$$

were $\lambda(t) = \dfrac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i \beta_{i,j} \eta_{00,ij} Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,j}(t)}$ along with the initial state

$$Y_{0,0}(0) = (1 - \phi_0)Y_0 \tag{6.24a}$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}}\phi_0 Y_0, \text{ for } i = 1, 2, 3, 4 \tag{6.24b}$$

$$Y_{2,1}(0) = 0. \tag{6.24c}$$

and the corresponding payoff functional

$$L(T) = \int_0^T \left[\alpha \left(\kappa_t \nu_t Y_{2,0}(t) + \sum_{i=0}^{i=4} \sum_{j=0}^{j=1} c_i Y_{i,j}(t) \right) - (1-\alpha) \left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} q_i Y_{i,j}(t) \right) \right] e^{-rt} dt. \qquad (6.25)$$

For the model with only the therapeutic vaccine we have the following set of parameters governing the outcome,

$$\Theta = [\mu, \mu_{1,0}, \mu_{2,0}, \mu_{2,1}, \mu_{3,0}, \mu_{4,0}, p_0, p_1, p_2, p_3, p_4, \beta_{1,0}, \beta_{2,0}, \beta_{2,1}, \beta_{3,0}, \beta_{4,0}, \dots$$
$$\dots, \eta_{00,10}, \eta_{00,20}, \eta_{00,21} \eta_{00,30}, \eta_{00,40}, \nu_t, \sigma, \xi, Y_0, \phi_0, \rho_1, \rho_2, \rho_3, \dots$$
$$\dots, c_0, c_1, c_2, c_3, c_4, q_0, q_1, q_2, q_3, q_4, \kappa_t, r, \alpha]$$

where particular values at the point that the variations are analyzed are shown in the second column of table 6.2.

To evaluate the sensitivity analysis for each of the 42 parameters, we will start by setting up the system of differential equations that define the adjoint variable. Introducing the notation from section 6.2 we get the following for the therapeutic vaccine program,

$$\Phi(\dot{Y}, Y, \Theta) = \begin{bmatrix} \dot{Y}_{0,0}(t) + (\mu + p_0 \lambda(t)) Y_{0,0}(t) - (1 - \sum_{i=1}^{i=3} \rho_i) \mu Y_0 \\ \dot{Y}_{1,0}(t) - p_0 \lambda(t) Y_{0,0}(t) + (\sigma\xi + \mu_{1,0} + \mu) Y_{1,0}(t) - \rho_1 \mu Y_0 \\ \dot{Y}_{2,0}(t) - \sigma\xi Y_{1,0}(t) + (\mu_{2,0} + \mu + \nu_t) Y_{2,0}(t) - \rho_2 \mu Y_0 \\ \dot{Y}_{2,1}(t) - \nu_t Y_{2,0}(t) - (\mu_{2,1} + \mu) Y_{2,1}(t) \\ \dot{Y}_{3,0}(t) - \mu_{1,0} Y_{1,0}(t) - \mu_{2,0} Y_{2,0}(t) - \mu_{2,1} Y_{2,1}(t) + (\mu_{3,0} + \mu) Y_{3,0}(t) - \rho_3 \mu Y_0 \\ \dot{Y}_{4,0}(t) - \mu_{3,0} Y_{3,0}(t) + (\mu_{4,0} + \mu) Y_{4,0}(t) \end{bmatrix}$$

$$
G(Y(0), \Theta) = \begin{bmatrix}
Y_{0,0}(0) - (1 - \phi_0)Y_0 \\[2ex]
Y_{1,0}(0) - \phi_0 \left(\dfrac{1/\mu_{1,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \right) Y_0 \\[2ex]
Y_{2,0}(0) - \phi_0 \left(\dfrac{1/\mu_{2,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \right) Y_0 \\[2ex]
Y_{2,1}(0) \\[2ex]
Y_{3,0}(0) - \phi_0 \left(\dfrac{1/\mu_{3,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \right) Y_0 \\[2ex]
Y_{4,0}(0) - \phi_0 \left(\dfrac{1/\mu_{4,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \right) Y_0
\end{bmatrix}
$$

$$
\ell(Y, \Theta) = \left[\alpha \left(\kappa_t \nu_t Y_{2,0}(t) + \sum_{i=0}^{i=4} \sum_{j=0}^{j=1} c_i Y_{i,j}(t) \right) - (1 - \alpha) \left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} q_i Y_{i,j}(t) \right) \right] e^{-rt}.
$$

Then the initial value problem for the adjoint variables is defined by

$$
\frac{d\Lambda(t)}{dt} = -\langle \Lambda, F_Y \rangle + \ell_Y, \quad \Lambda(t^{(1)}) = 0
$$

with

$$
\ell_Y = \begin{bmatrix}
(\alpha(c_0 + q_0) - q_0)e^{-rt} \\[1ex]
(\alpha(c_1 + q_1) - q_1)e^{-rt} \\[1ex]
(\alpha(k_t + c_2 + q_2) - q_2)e^{-rt} \\[1ex]
(\alpha(c_2 + q_2) - q_2)e^{-rt} \\[1ex]
(\alpha(c_3 + q_3) - q_3)e^{-rt} \\[1ex]
(\alpha(c_4 + q_4) - q_4)e^{-rt}
\end{bmatrix},
$$

and F_Y is the Jacobian matrix for the system (6.23), which can be referenced in appendix A. The resulting system of ordinary differential equations is given as the following:

$$\frac{d\Lambda_{0,0}(t)}{dt} = \left(\mu + p_0\left(\frac{\partial\lambda}{\partial Y_{0,0}}Y_{0,0}(t) + \lambda(t)\right)\right)\Lambda_{0,0}(t) - p_0\left(\frac{\partial\lambda}{\partial Y_{0,0}}Y_{0,0}(t)\right)\Lambda_{1,0}(t)$$
$$+ (\alpha(c_0 + q_0) - q_0)e^{-rt} \tag{6.26a}$$

$$\frac{d\Lambda_{1,0}(t)}{dt} = p_0\left(\frac{\partial\lambda}{\partial Y_{1,0}}Y_{0,0}(t)\right)\Lambda_{0,0}(t) + \left((\sigma\xi + \mu_{1,0} + \mu) - p_0\frac{\partial\lambda}{\partial Y_{1,0}}Y_{0,0}(t)\right)\Lambda_{0,0}(t)$$
$$- \sigma\xi\Lambda_{2,0}(t) - \mu_{1,0}\Lambda_{3,0}(t) + (\alpha(c_1 + q_1) - q_1)e^{-rt} \tag{6.26b}$$

$$\frac{d\Lambda_{2,0}(t)}{dt} = p_0\left(\frac{\partial\lambda}{\partial Y_{2,0}}Y_{0,0}(t)\right)\Lambda_{0,0}(t) - p_0\left(\frac{\partial\lambda}{\partial Y_{2,0}}Y_{0,0}(t)\right)\Lambda_{0,0}(t) + (\nu_t + \mu_{2,0} + \mu)\Lambda_{2,0}(t)$$
$$- \nu_t\Lambda_{2,1}(t) - \mu_{2,0}\Lambda_{3,0}(t) + (\alpha(\kappa_t + c_2 + q_2) - q_2)e^{-rt} \tag{6.26c}$$

$$\frac{d\Lambda_{2,1}(t)}{dt} = p_0\left(\frac{\partial\lambda}{\partial Y_{2,1}}Y_{0,0}(t)\right)\Lambda_{0,0}(t) - p_0\left(\frac{\partial\lambda}{\partial Y_{2,1}}Y_{0,0}(t)\right)\Lambda_{0,0}(t) + (\mu_{2,1} + \mu)\Lambda_{2,1}(t)$$
$$- \mu_{2,1}\Lambda_{3,0}(t) + (\alpha(c_2 + q_2) - q_2)e^{-rt} \tag{6.26d}$$

$$\frac{d\Lambda_{3,0}(t)}{dt} = p_0\left(\frac{\partial\lambda}{\partial Y_{3,0}}Y_{0,0}(t)\right)\Lambda_{0,0}(t) - p_0\left(\frac{\partial\lambda}{\partial Y_{3,0}}Y_{0,0}(t)\right)\Lambda_{0,0}(t) + (\mu_{3,0} + \mu)\Lambda_{3,0}(t)$$
$$- \mu_{3,0}\Lambda_{4,0}(t) + (\alpha(c_3 + q_3) - q_3)e^{-rt} \tag{6.26e}$$

$$\frac{d\Lambda_{4,0}(t)}{dt} = p_0\left(\frac{\partial\lambda}{\partial Y_{4,0}}Y_{0,0}(t)\right)\Lambda_{0,0}(t) - p_0\left(\frac{\partial\lambda}{\partial Y_{4,0}}Y_{0,0}(t)\right)\Lambda_{0,0}(t) + (\mu_{4,0} + \mu)\Lambda_{4,0}(t)$$
$$+ (\alpha(c_4 + q_4) - q_4)e^{-rt}. \tag{6.26f}$$

Setting $T = 20$ and the parameters values as they are defined in section 3.1 the solutions for both systems (6.23) and (6.26) were derived by numerical methods and are presented in figures 6.3 and 6.4 respectively. These solutions for both the state trajectories and adjoint variables are then used evaluate each of the sensitivity functions for all 42 parameters[3]. The results for each are presented in table 6.2 where they have been ranked in order by the most sensitive to the least. We will notice the results for the therapeutic vaccine program are similar to the results for they dynamics when no intervention is present. Any variation in the weighting parameter we introduced when we defined Pareto optimality, α, will have the most significant impact on the payoff function. The payoff functional is at least 100 times more sensitive to α than any other parameter. Alternatively, in the case for the therapeutic vaccine we find that the least influential parameter is the direct cost for the therapeutic vaccine κ_t.

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[3]All 42 sensitivity functions are derived and presented in appendix C.
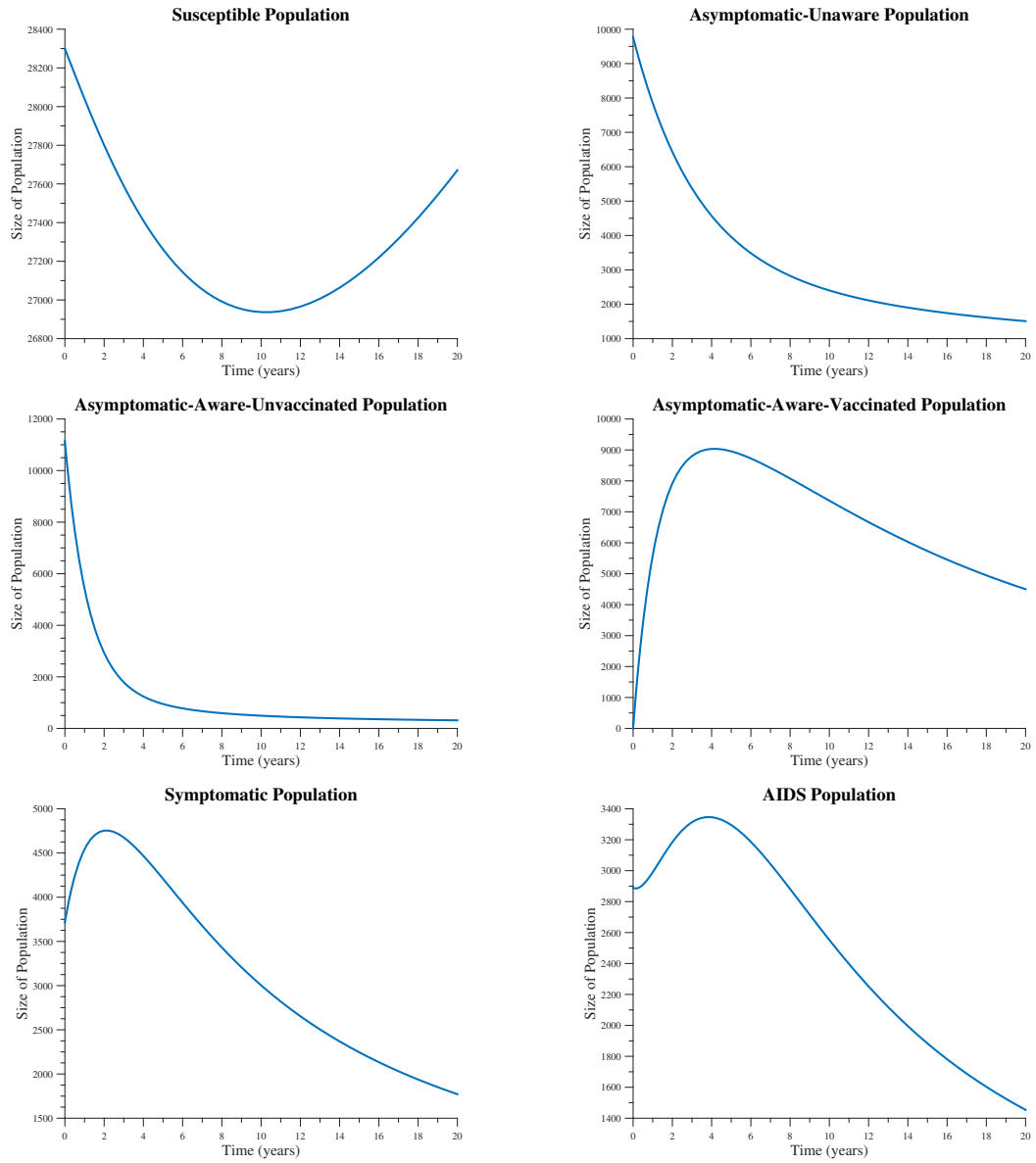
Figure 6.3:   Therapeutic vaccine program: state trajectories for evaluating parameter sensitivity to the objective function.
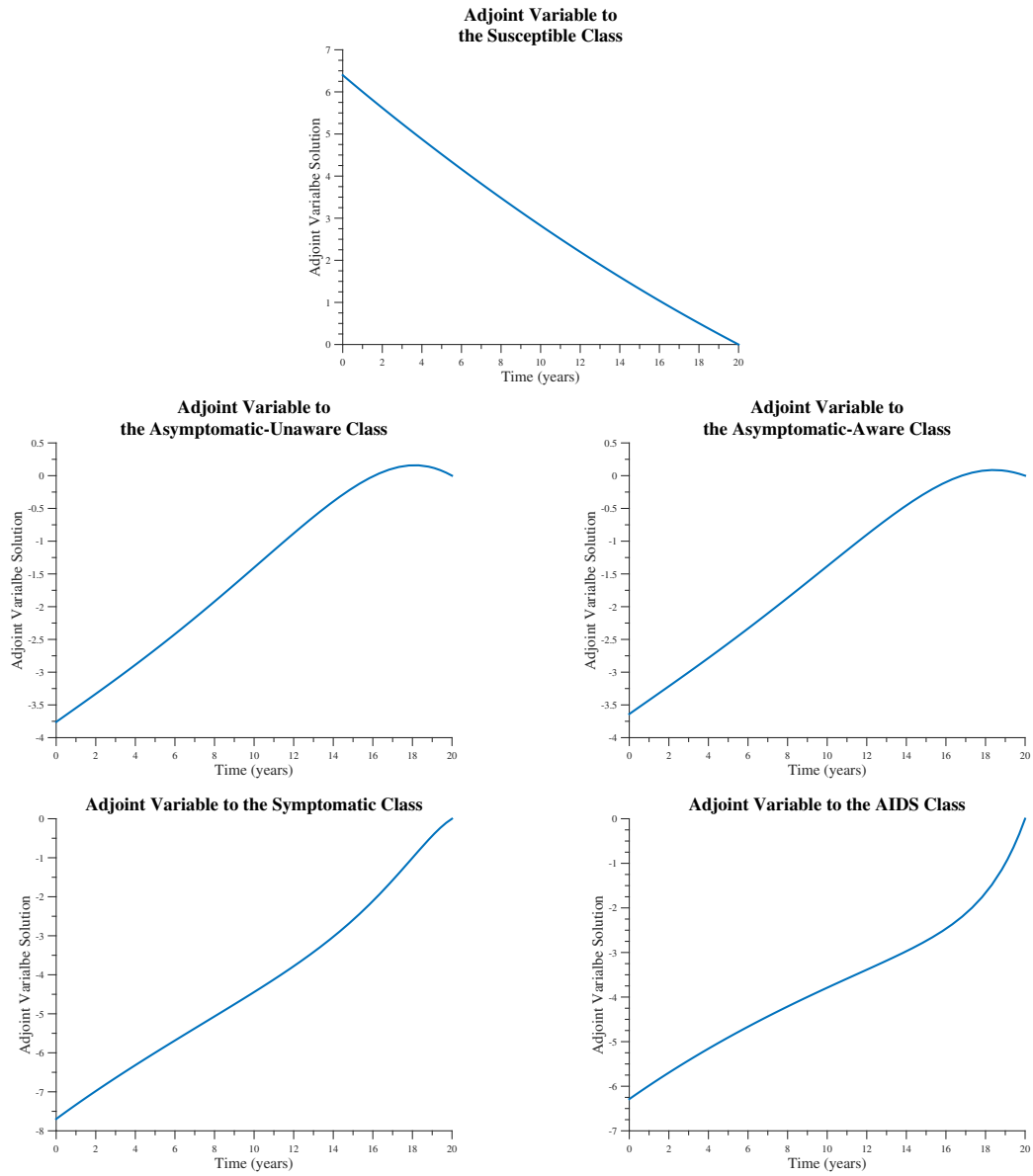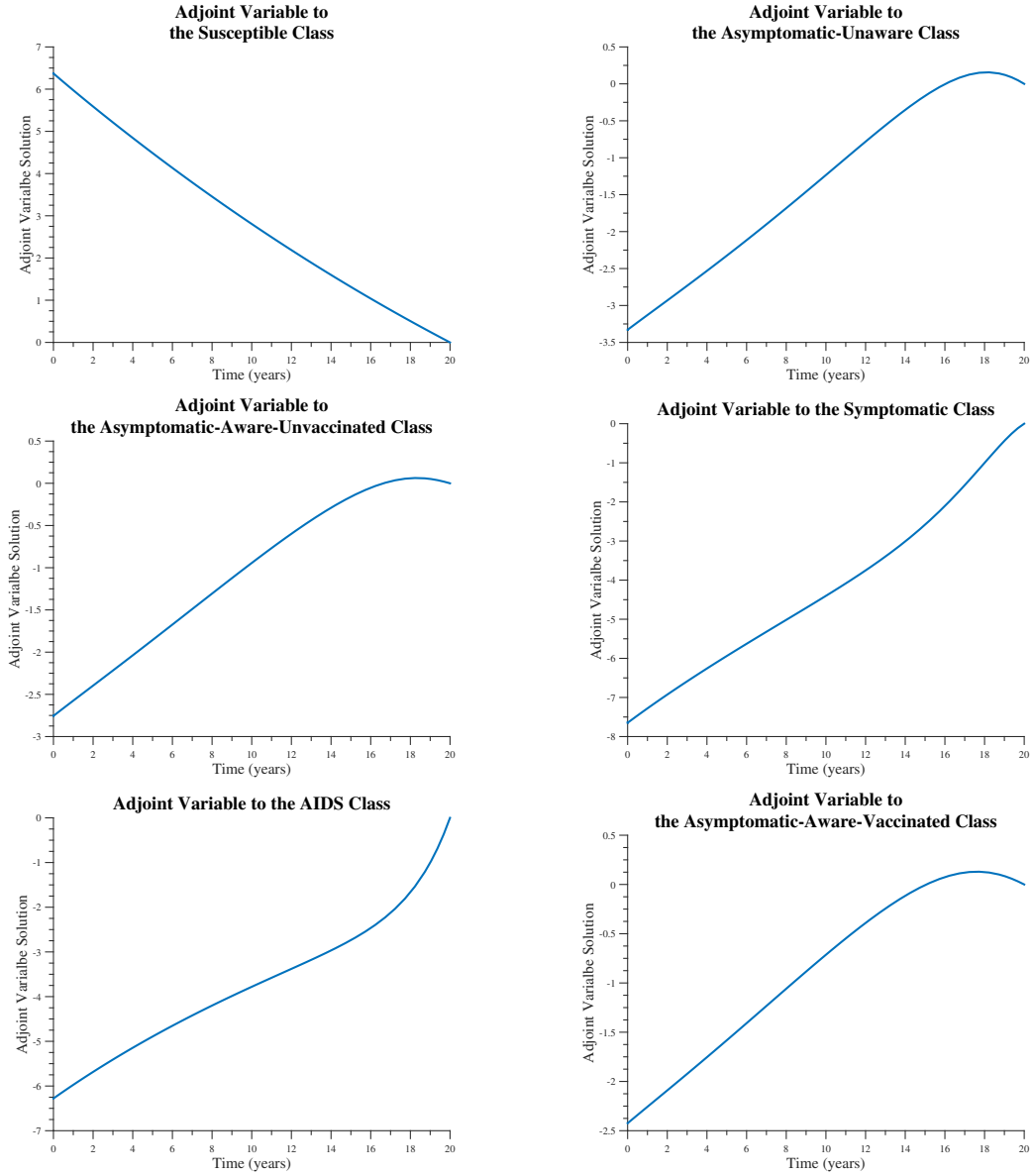
Figure 6.4: Therapeutic vaccine program: adjoint variables for evaluating parameter sensitivity to the objective function.

Table 6.2: Adjoint variable method: parameter sensitivity to the objective function for the dynamics when the therapeutic vaccine only is presented. Solutions to the instantaneous rate of change for the payoff with respect to the corresponding parameter evaluated at $\hat{\Theta}$.

Parameters	Parameter Values (Assumptions, $\hat{\Theta}$)	Sensitivity of the Payoff Relative to each Parameter $\left(\frac{\partial L(Y,\Theta)}{\partial \theta_i}\Big|_{\hat{\Theta}}\right)$
α	1/10000	3.73314584954996e+09
μ	0.022	-1.94939407662373e+06
r	0.05	1.18799979973974e+06
ϕ_0	0.493	5.78343566609914e+05
$\mu_{2,1}$	1/13.1	4.78803206121683e+05
$\beta_{2,1}$	0.0495	3.59942749007504e+05
q_0	1	-3.45551131516594e+05
$\mu_{1,0}$	1/7.1	2.62253208226607e+05
$\beta_{1,0}$	0.066	2.20468392709959e+05
$\mu_{4,0}$	1/2.1	-2.17234957728128e+05
$\mu_{2,0}$	1/8.1	2.10118559397876e+05
ρ_3	0.02	1.76531461143370e+05
q_2	0.83	-1.08086045851810e+05
ρ_1	0.04	1.05080291191557e+05
ρ_2	0.04	9.88698381721251e+04
$\beta_{3,0}$	0.147	9.02350940130041e+04
$\mu_{3,0}$	1/2.7	-7.86021537406759e+04
$\beta_{2,0}$	0.066	5.88664420442731e+04
$\eta_{00,30}$	0.235	5.64449311485600e+04
q_1	1	-4.75196118101732e+04
q_3	0.42	-4.34867302848632e+04
$\eta_{00,21}$	0.4803	3.70997731928610e+04
q_4	0.17	-3.36641304573673e+04
$\eta_{00,10}$	0.505	2.88136909284303e+04
σ	0.15	-2.31321596659052e+04
$\beta_{4,0}$	0.147	2.29900302273869e+04
$\eta_{00,40}$	0.235	1.43809976315994e+04
$\eta_{00,20}$	0.307	1.26553263026776e+04
p_0	2	1.08068363895652e+04
p_2	2	5.43799855927527e+03
p_1	2	4.66141533551225e+03
p_3	2	4.41207224324328e+03
ξ	0.98	-3.54063668355693e+03
p_4	0.667	3.38937335621676e+03
c_0	3307	3.45585690085603e+01
c_2	5467	1.08096855537364e+01
c_1	5467	4.75243642465978e+00
c_3	12586	4.34910793928024e+00
c_4	35394	3.36674972070880e+00
Y_0	55816	-2.35642199643805e+00
κ_t	1000	1.97349738175286e+00

6.2.3 Preventative Vaccine Program

We again start the section for parameter sensitivity for the preventative vaccine program by emphasize the notation for immigration defined as we introduced it in section 6.2.1,

$$I_{0,0} = (1 - \sum_{i=1}^{i=3})\mu Y_0 \tag{6.27a}$$

$$I_{1,0} = \rho_1 \mu Y_0 \tag{6.27b}$$

$$I_{2,0} = \rho_2 \mu Y_0 \tag{6.27c}$$

$$I_{3,0} = \rho_3 \mu Y_0. \tag{6.27d}$$

This results with the following system of ordinary differential equations:

$$\frac{dY_{0,0}(t)}{dt} = (1 - \sum_{i=1}^{3} \rho_i)\mu Y_0 - (\nu_p + \mu + p_0\lambda(t))Y_{0,0}(t) + \omega Y_{0,1}(t) \tag{6.28a}$$

$$\frac{dY_{0,1}(t)}{dt} = \nu_p Y_{0,0}(t) - (\mu + \omega + p_0(1-\varepsilon)\lambda_\nu(t))Y_{0,1}(t) \tag{6.28b}$$

$$\frac{dY_{1,0}(t)}{dt} = \rho_1 \mu Y_0 + p_0\lambda(t)Y_{0,0}(t) - (\nu_p + \sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) + \omega Y_{1,1}(t) \tag{6.28c}$$

$$\frac{dY_{1,1}(t)}{dt} = \nu_p Y_{1,0}(t) + p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}(t) - (\omega + \sigma\xi + \mu_{1,1} + \mu)Y_{1,1}(t) \tag{6.28d}$$

$$\frac{dY_{2,0}(t)}{dt} = \rho_2 \mu Y_0 + \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) - (\mu_{2,0} + \mu)Y_{2,0}(t) \tag{6.28e}$$

$$\frac{dY_{3,0}(t)}{dt} = \rho_3 \mu Y_0 + \sum_{i=1}^{i=2}\sum_{j=0}^{j=1} \mu_{i,j}Y_{i,j}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t) \tag{6.28f}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t) \tag{6.28g}$$

were $\lambda(t) = \dfrac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,j}(t)}$ and $\lambda_\nu(t) = \dfrac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{01,ij}Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,j}(t)}$, along with the initial state

$$Y_{0,0}(0) = (1 - \phi_0)Y_0 \tag{6.29a}$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}}\phi_0 Y_0, \text{ for } i = 1, 2, 3, 4 \tag{6.29b}$$

$$Y_{i,1}(0) = 0 \text{ for } i = 0, 1 \tag{6.29c}$$

and the corresponding payoff functional,

$$L(T) = \int_0^T \left[\alpha\big(\kappa_p \nu_p (Y_{0,0}(t) + Y_{1,0}(t)) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} c_i Y_{i,j}(t)\big) - (1-\alpha)\big(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} q_i Y_{i,j}(t)\big) \right] e^{-rt} dt.$$

(6.30)

From the dynamics, initial state, and the payoff functional, for the model with only the preventative vaccine we have the following set of parameters

$$\Theta = [\mu, \mu_{1,0}, \mu_{1,1}, \mu_{2,0}, \mu_{3,0}, \mu_{4,0}, p_0, p_1, p_2, p_3, p_4, \beta_{1,0}, \beta_{1,1}, \beta_{2,0}, \beta_{3,0}, \beta_{4,0}, \dots$$

$$\dots, \eta_{00,10}, \eta_{00,11}, \eta_{00,20}, \eta_{00,30}, \eta_{00,40}, \eta_{01,10}, \eta_{01,11}, \eta_{01,20}, \eta_{01,30}, \eta_{01,40}, \dots$$

$$\dots, \varepsilon, \nu_p, \omega, \sigma, \xi, Y_0, \phi_0, \rho_1, \rho_2, \rho_3, c_0, c_1, c_2, c_3, c_4, q_0, q_1, q_2, q_3, q_4, r, \alpha, \kappa_p]$$

where particular values at the point that the variations are analyzed are shown in the second column of tables 6.3 and 6.4.

To evaluate the sensitivity analysis for each of the 49 parameters, we will start by setting up the system of differential equations for the adjoint variable. Presenting the model in terms of the notation used in section 6.2 we get,

$$\Phi(\dot{Y}, Y, \Theta) =$$

$$\begin{bmatrix} \dot{Y}_{0,0}(t) + (\nu_p + \mu + p_0 \lambda(t))Y_{0,0}(t) - \omega Y_{0,1}(t) - (1 - \sum_{i=1}^{i=3} \rho_i)\mu Y_0 \\ \dot{Y}_{0,1}(t) - \nu_p Y_{0,0}(t) + (\mu + \omega + p_0(1 - \varepsilon)\lambda_\nu(t))Y_{0,1}(t) \\ \dot{Y}_{1,0}(t) - p_0 \lambda(t)Y_{0,0}(t) + (\nu_p + \sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) - \omega Y_{1,1}(t) - \rho_1 \mu Y_0 \\ \dot{Y}_{1,1}(t) - p_0(1 - \varepsilon)\lambda_\nu(t)Y_{0,1}(t) - \nu_p Y_{1,0}(t) + (\sigma\xi + \omega + \mu_{1,1} + \mu)Y_{1,1}(t) \\ \dot{Y}_{2,0}(t) - \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) + (\mu_{2,0} + \mu)Y_{2,0}(t) - \rho_2 \mu Y_0 \\ \dot{Y}_{3,0}(t) - \mu_{1,0} Y_{1,0}(t) - \mu_{1,1} Y_{1,1}(t) - \mu_{2,0} Y_{2,0}(t) + (\mu_{3,0} + \mu)Y_{3,0}(t) - \rho_3 \mu Y_0 \\ \dot{Y}_{4,0}(t) - \mu_{3,0} Y_{3,0}(t) + (\mu_{4,0} + \mu)Y_{4,0}(t) \end{bmatrix}$$

$$
G(Y(0), \Theta) = \begin{bmatrix}
Y_{0,0}(0) - (1 - \phi_0)Y_0 \\
Y_{0,1}(0) \\
Y_{1,0}(0) - \phi_0 \left(\dfrac{1/\mu_{1,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \right) Y_0 \\
Y_{1,1}(0) \\
Y_{2,0}(0) - \phi_0 \left(\dfrac{1/\mu_{2,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \right) Y_0 \\
Y_{3,0}(0) - \phi_0 \left(\dfrac{1/\mu_{3,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \right) Y_0 \\
Y_{4,0}(0) - \phi_0 \left(\dfrac{1/\mu_{4,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \right) Y_0
\end{bmatrix}
$$

$$
\ell(Y, \Theta) = \left[\alpha \left(\kappa_p \nu_p (Y_{0,0}(t) + Y_{1,0}(t)) + \sum_{i=0}^{i=4} \sum_{j=0}^{j=1} c_i Y_{i,j}(t) \right) - (1 - \alpha) \left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} q_i Y_{i,j}(t) \right) \right] e^{-rt}.
$$

Then the initial value problem for the adjoint variables is defined by

$$
\frac{d\Lambda(t)}{dt} = -\langle \Lambda, F_Y \rangle + \ell_Y, \quad \Lambda(t^{(1)}) = 0
$$

with

$$
\ell_Y = \begin{bmatrix}
(\alpha(\kappa_p + c_0 + q_0) - q_0)e^{-rt} \\
(\alpha(c_0 + q_0) - q_0)e^{-rt} \\
(\alpha(\kappa_p + c_1 + q_1) - q_1)e^{-rt} \\
(\alpha(c_1 + q_1) - q_1)e^{-rt} \\
(\alpha(c_2 + q_2) - q_2)e^{-rt} \\
(\alpha(c_3 + q_3) - q_3)e^{-rt} \\
(\alpha(c_4 + q_4) - q_4)e^{-rt}
\end{bmatrix}
$$

and F_Y is the Jacobian matrix for the system (6.23), which can be referenced in appendix A. The resulting system of ordinary differential equations is given as the following:

$$\frac{d\Lambda_{0,0}(t)}{dt} = \left(\mu + \nu_p + p_0\left(\frac{\partial\lambda}{\partial Y_{0,0}}Y_{0,0} + \lambda(t)\right)\right)\Lambda_{0,0}(t) + \left(p_0(1-\varepsilon)\frac{\partial\lambda_\nu}{\partial Y_{0,0}}Y_{0,1} - \nu_p\right)\Lambda_{0,1}(t)$$
$$- p_0\left(\frac{\partial\lambda}{\partial Y_{0,0}}Y_{0,0} + \lambda(t)\right)\Lambda_{1,0}(t) - \left(p_0(1-\varepsilon)\frac{\partial\lambda_\nu}{\partial Y_{0,0}}Y_{0,1}\right)\Lambda_{1,1}(t)$$
$$+ (\alpha(\kappa_p + c_0 + q_0) - q_0)e^{-rt} \tag{6.31a}$$

$$\frac{d\Lambda_{0,1}(t)}{dt} = \left(p_0\frac{\partial\lambda}{\partial Y_{0,1}}Y_{0,0} - \omega\right)\Lambda_{0,0}(t) + \left(\omega + \mu + p_0(1-\varepsilon)\left(\frac{\partial\lambda_\nu}{\partial Y_{0,1}}Y_{0,1} + \lambda_\nu(t)\right)\right)\Lambda_{0,1}(t)$$
$$- p_0\frac{\partial\lambda}{\partial Y_{0,1}}Y_{0,0}\Lambda_{1,0}(t) - p_0(1-\varepsilon)\left(\frac{\partial\lambda_\nu}{\partial Y_{0,1}}Y_{0,1} + \lambda_\nu(t)\right)\Lambda_{0,1}(t)$$
$$+ (\alpha(c_0 + q_0) - q_0)e^{-rt} \tag{6.31b}$$

$$\frac{d\Lambda_{1,0}(t)}{dt} = p_0\frac{\partial\lambda}{\partial Y_{1,0}}Y_{0,0}\Lambda_{0,0}(t) + p_0(1-\varepsilon)\frac{\partial\lambda_\nu}{\partial Y_{1,0}}Y_{0,1}\Lambda_{0,1}(t)$$
$$+ \left(\sigma\xi + \nu_p + \mu_{1,0} + \mu - p_0\frac{\partial\lambda}{\partial Y_{1,0}}Y_{0,0}\right)\Lambda_{1,0}(t) - \left(p_0(1-\varepsilon)\frac{\partial\lambda_\nu}{\partial Y_{1,0}}Y_{0,1} + \nu_p\right)\Lambda_{1,1}(t)$$
$$- \sigma\xi\Lambda_{2,0}(t) - \mu_{1,0}\Lambda_{3,0}(t) + (\alpha(\kappa_p + c_1 + q_1) - q_1)e^{-rt} \tag{6.31c}$$

$$\frac{d\Lambda_{1,1}(t)}{dt} = p_0\frac{\partial\lambda}{\partial Y_{1,1}}Y_{0,0}\Lambda_{0,0}(t) + p_0(1-\varepsilon)\frac{\partial\lambda_\nu}{\partial Y_{1,1}}Y_{0,1}\Lambda_{0,1}(t)$$
$$- \left(p_0\frac{\partial\lambda}{\partial Y_{1,1}}Y_{0,0} + \omega\right)\Lambda_{1,0}(t) + \left(\sigma\xi + \omega + \mu_{1,1} + \mu - p_0(1-\varepsilon)\frac{\partial\lambda_\nu}{\partial Y_{1,1}}Y_{0,1}\right)\Lambda_{1,1}(t)$$
$$- \sigma\xi\Lambda_{2,0}(t) - \mu_{1,1}\Lambda_{3,0}(t) + (\alpha(c_1 + q_1) - q_1)e^{-rt} \tag{6.31d}$$

$$\frac{d\Lambda_{2,0}(t)}{dt} = p_0\frac{\partial\lambda}{\partial Y_{2,0}}Y_{0,0}\Lambda_{0,0}(t) + p_0(1-\varepsilon)\frac{\partial\lambda_\nu}{\partial Y_{2,0}}Y_{0,1}\Lambda_{0,1}(t) - p_0\frac{\partial\lambda}{\partial Y_{2,0}}Y_{0,0}\Lambda_{1,0}(t)$$
$$- p_0(1-\varepsilon)\frac{\partial\lambda_\nu}{\partial Y_{2,0}}Y_{0,1}\Lambda_{1,1}(t) + (\mu_{2,0} + \mu)\Lambda_{2,0}(t) - \mu_{2,0}\Lambda_{3,0}(t)$$
$$+ (\alpha(c_2 + q_2) - q_2)e^{-rt} \tag{6.31e}$$

$$\frac{d\Lambda_{3,0}(t)}{dt} = p_0\frac{\partial\lambda}{\partial Y_{3,0}}Y_{0,0}\Lambda_{0,0}(t) + p_0(1-\varepsilon)\frac{\partial\lambda_\nu}{\partial Y_{3,0}}Y_{0,1}\Lambda_{0,1}(t) - p_0\frac{\partial\lambda}{\partial Y_{3,0}}Y_{0,0}\Lambda_{1,0}(t)$$
$$- p_0(1-\varepsilon)\frac{\partial\lambda_\nu}{\partial Y_{3,0}}Y_{0,1}\Lambda_{1,1}(t) + (\mu_{3,0} + \mu)\Lambda_{3,0}(t) - \mu_{3,0}\Lambda_{4,0}(t)$$
$$+ (\alpha(c_3 + q_3) - q_3)e^{-rt} \tag{6.31f}$$

$$\frac{d\Lambda_{4,0}(t)}{dt} \ p_0\frac{\partial\lambda}{\partial Y_{4,0}}Y_{0,0}\Lambda_{0,0}(t) + p_0(1-\varepsilon)\frac{\partial\lambda_\nu}{\partial Y_{4,0}}Y_{0,1}\Lambda_{0,1}(t) - p_0\frac{\partial\lambda}{\partial Y_{4,0}}Y_{0,0}\Lambda_{1,0}(t)$$
$$- p_0(1-\varepsilon)\frac{\partial\lambda_\nu}{\partial Y_{4,0}}Y_{0,1}\Lambda_{1,1}(t) + (\mu_{4,0} + \mu)\Lambda_{4,0}(t)$$
$$+ (\alpha(c_4 + q_4) - q_4)e^{-rt}. \tag{6.31g}$$

Setting $T = 20$ and the parameters values as they are defined in section 3.1 the solutions for both systems (6.28) and (6.31) were derived by numerical methods and are presented in figures 6.5 and 6.6 respectively. These solutions for both the state trajectories and adjoint variables are then used evaluate each of the sensitivity functions for all 49 parameters[4]. The results for each are presented in tables 6.3 and 6.4 where they have been ranked in order by the most sensitive to the least. Again we find some similar results compared to the analysis for the therapeutic vaccine program and the dynamics without an intervention. Any variation in the weighting parameter we introduced when we defined Pareto optimality, α, will have the most significant impact on the payoff function, again the payoff functional is at least 100 times more sensitive to α than any other parameter. Regarding the least sensitive parameter we find that the total initial population size Y_0 has the smallest impact, just like the case when no intervention was presented. This is an interesting alternative considering in the case for the therapeutic vaccine we find that the least influential parameter is the direct cost of the vaccine κ_t. Alternatively, for the preventative vaccine program, the direct cost of the vaccine κ_p ranks higher in sensitivity than the average medical expenses for all the infectious states, as well as the total initial population.

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[4]All 49 sensitivity functions are derived and presented in appendix C.
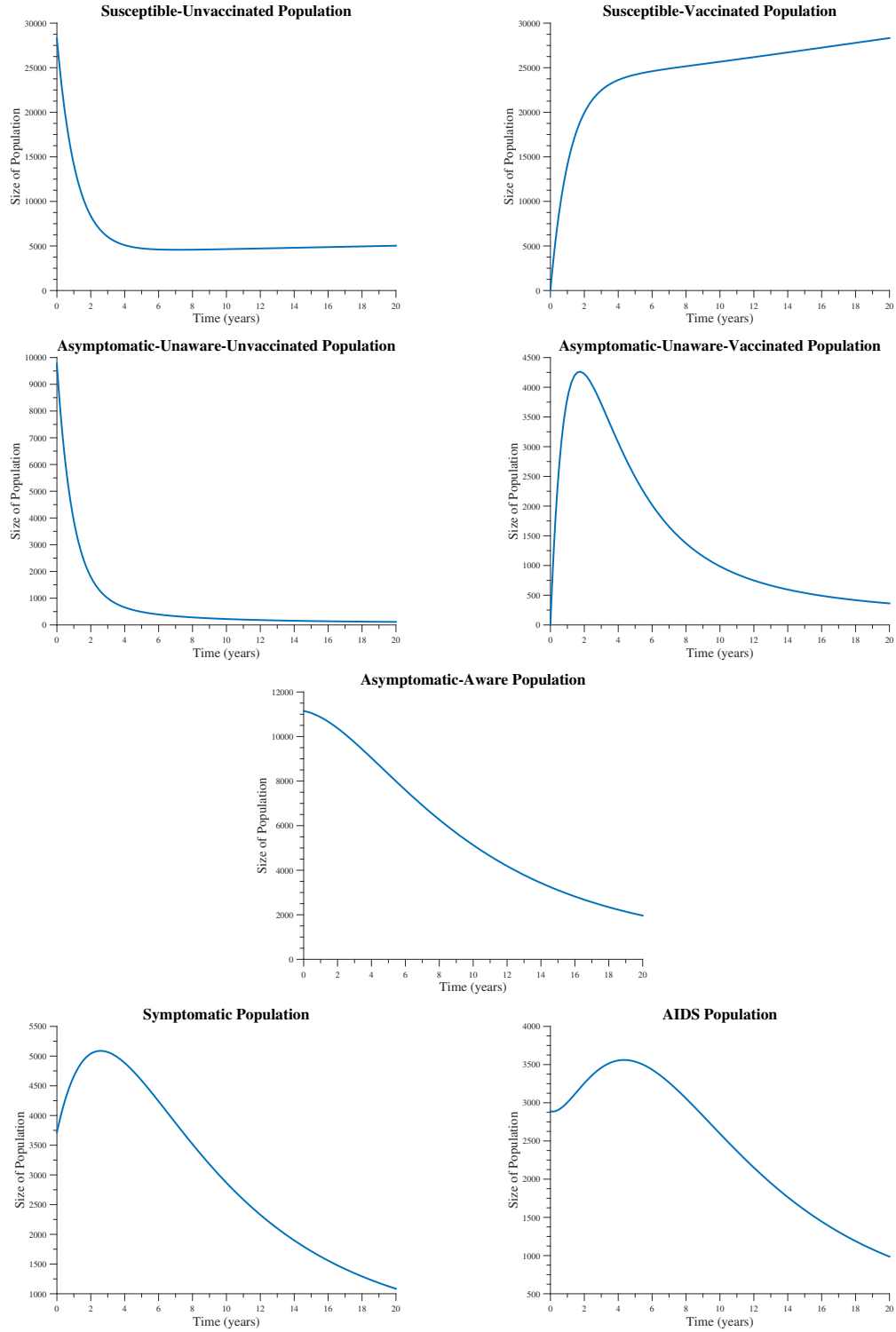
Figure 6.5: Preventative vaccine program: state trajectories for evaluating parameter sensitivity to the objective function.
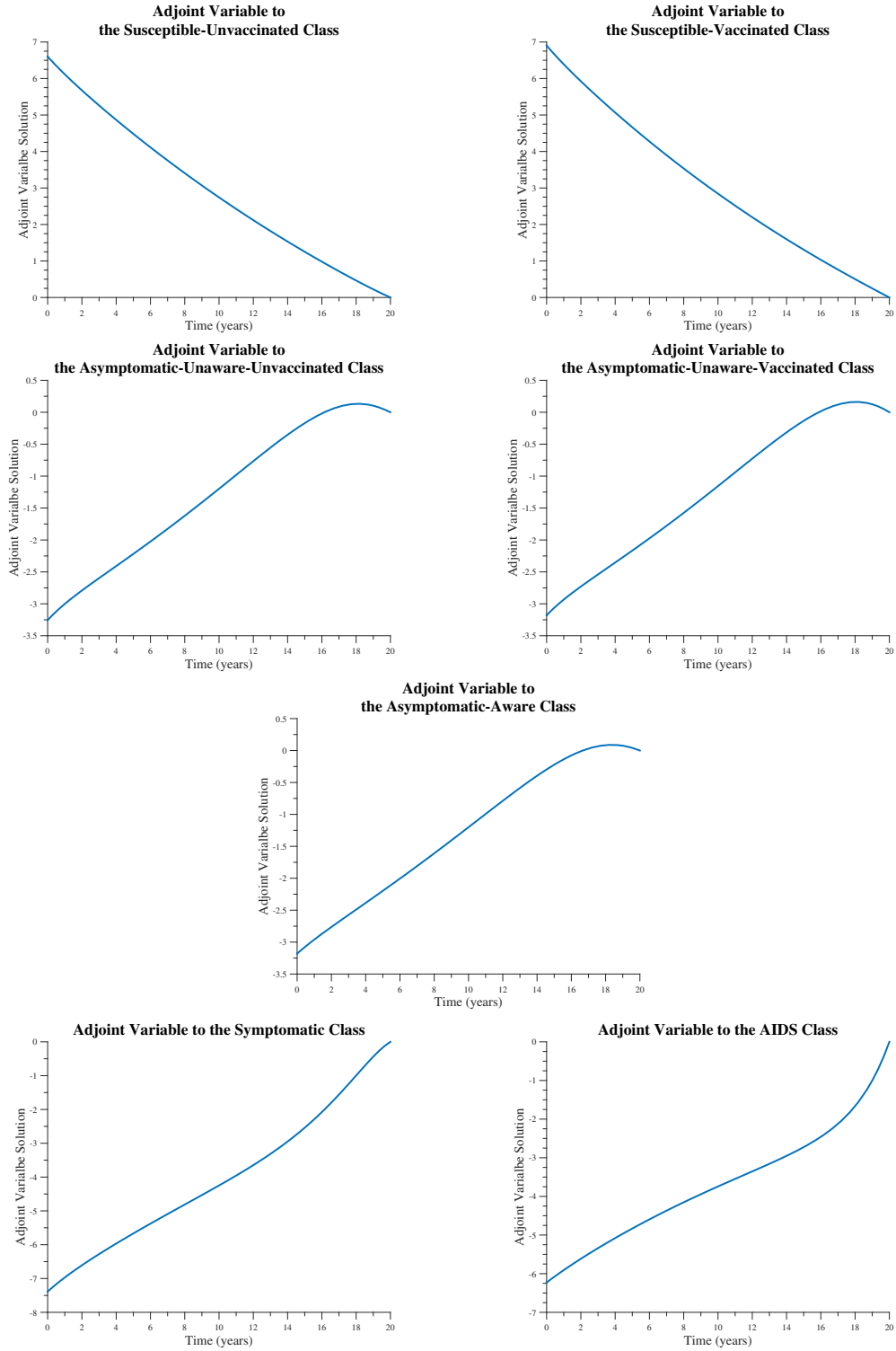
Figure 6.6: Preventative vaccine program: adjoint variables for evaluating parameter sensitivity to the objective function.

Table 6.3: Adjoint variable method: parameter sensitivity $(> 10^4)$ to the objective function for the dynamics when the preventative vaccine only is presented. Solutions to the instantaneous rate of change for the payoff with respect to the corresponding parameter evaluated at $\hat{\Theta}$.

Parameters	Parameter Values (Assumptions, $\hat{\Theta}$)	Sensitivity of the Payoff Relative to each Parameter $\left(\frac{\partial L(Y,\Theta)}{\partial \theta_i}\Big|_{\hat{\Theta}}\right)$
α	1/10000	3.73577120279128e+09
μ	0.022	-1.76168388644912e+06
r	0.05	1.34465379582781e+06
ϕ_0	0.493	5.97118442945960e+05
$\mu_{2,0}$	1/8.1	4.53729931437988e+05
q_0	1	-3.79004949678658e+05
$\mu_{4,0}$	1/2.1	-2.15889377099890e+05
ρ_3	0.02	1.72259283001503e+05
$\beta_{2,0}$	0.066	1.14763063446554e+05
$\mu_{1,0}$	1/7.1	1.12787189077008e+05
ρ_2	0.04	1.03661505443833e+05
ρ_1	0.04	1.03496963430559e+05
$\mu_{1,1}$	1/7.1	1.03423908147592e+05
q_2	0.83	-8.35525825274645e+04
$\mu_{3,0}$	1/2.7	-6.86797430405222e+04
$\beta_{1,1}$	0.066	5.85545377394499e+04
ω	1/10	5.54577780498569e+04
$\beta_{3,0}$	0.147	4.32513231685160e+04
q_3	0.42	-4.29781414034382e+04
$\beta_{1,0}$	0.066	4.17796011305228e+04
q_1	1	-3.60599100168914e+04
ε	0.75	-3.52289334651797e+04
q_4	0.17	-3.36339039156473e+04
$\eta_{00,30}$	0.235	1.54627687922365e+04
$\eta_{00,20}$	0.307	1.48186305384655e+04
$\eta_{01,30}$	0.235	1.15923150991761e+04
$\beta_{4,0}$	0.147	1.08853602008431e+04

Table 6.4: Adjoint variable method: parameter sensitivity ($< 10^4$) to the objective function for the dynamics when the preventative vaccine only is presented. Solutions to the instantaneous rate of change for the payoff with respect to the corresponding parameter evaluated at $\hat{\Theta}$.

Parameters	Parameter Values (Assumptions, $\hat{\Theta}$)	Sensitivity of the Payoff Relative to each Parameter $\left(\left.\frac{\partial L(Y,\Theta)}{\partial \theta_i}\right\|_{\hat{\Theta}}\right)$
$\eta_{01,20}$	0.307	9.85355746768976e+03
$\eta_{00,10}$	0.505	4.37950333783591e+03
p_0	2	4.34725531234807e+03
$\eta_{00,11}$	0.505	4.08371644541146e+03
$\eta_{00,40}$	0.235	3.78844405501942e+03
$\eta_{01,40}$	0.235	3.02071847369263e+03
$\eta_{01,11}$	0.6287	2.86651634174733e+03
p_3	2	2.20483204969525e+03
p_1	2	2.20478521185174e+03
p_2	2	1.75841785106467e+03
p_4	0.667	1.68504904280168e+03
$\eta_{01,10}$	0.505	1.08080096244802e+03
σ	0.15	6.64914913458124e+02
ξ	0.98	1.01772690835427e+02
c_0	3307	3.79042853964055e+01
κ_p	1000	9.62510195285204e+00
c_2	5467	8.35609386213267e+00
c_3	12586	4.29824396474029e+00
c_1	5467	3.60635163685282e+00
c_4	35394	3.36372676424115e+00
Y_0	55816	-2.41248231562490e+00

6.2.4 Combined, Preventative and Therapeutic, Vaccine Program

We again start the section for parameter sensitivity for the preventative vaccine program by emphasize the notation for immigration defined as we introduced it in section 6.2.1,

$$I_{0,0} = (1 - \sum_{i=1}^{i=3})\mu Y_0 \tag{6.32a}$$

$$I_{1,0} = \rho_1 \mu Y_0 \tag{6.32b}$$

$$I_{2,0} = \rho_2 \mu Y_0 \tag{6.32c}$$

$$I_{3,0} = \rho_3 \mu Y_0. \tag{6.32d}$$

For the full model with both vaccinations, the preventative and therapeutic, we have the following system of ordinary differential equations:

$$\frac{dY_{0,0}(t)}{dt} = (1 - \sum_{i=1}^{3} \rho_i)\mu Y_0 - (\nu_p + \mu + p_0\lambda(t))Y_{0,0}(t) + \omega Y_{0,1}(t) \tag{6.33a}$$

$$\frac{dY_{0,1}(t)}{dt} = \nu_p Y_{0,0}(t) - (\mu + \omega + p_0(1 - \varepsilon)\lambda_\nu(t))Y_{0,1}(t) \tag{6.33b}$$

$$\frac{dY_{1,0}(t)}{dt} = \rho_1 \mu Y_0 + p_0\lambda(t)Y_{0,0}(t) - (\nu_p + \sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) + \omega Y_{1,1}(t) \tag{6.33c}$$

$$\frac{dY_{1,1}(t)}{dt} = \nu_p Y_{1,0}(t) + p_0(1 - \varepsilon)\lambda_\nu(t)Y_{0,1}(t) - (\omega + \sigma\xi + \mu_{1,1} + \mu)Y_{1,1}(t) \tag{6.33d}$$

$$\frac{dY_{2,0}(t)}{dt} = \rho_2 \mu Y_0 + \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) - (\nu_t + \mu_{2,0} + \mu)Y_{2,0}(t) \tag{6.33e}$$

$$\frac{dY_{2,1}(t)}{dt} = \nu_t Y_{2,0}(t) - (\mu_{2,1} + \mu)Y_{2,1}(t) \tag{6.33f}$$

$$\frac{dY_{3,0}(t)}{dt} = \rho_3 \mu Y_0 + \sum_{i=1}^{i=2}\sum_{j=0}^{j=1} \mu_{i,j}Y_{i,j}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t) \tag{6.33g}$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t) \tag{6.33h}$$

were $\lambda(t) = \dfrac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_iY_{i,j}(t)}$ and $\lambda_\nu(t) = \dfrac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{01,ij}Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_iY_{i,j}(t)}$, along with the initial state

$$Y_{0,0}(0) = (1 - \phi_0)Y_0 \tag{6.34a}$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \phi_0 Y_0, \text{ for } i = 1, 2, 3, 4 \tag{6.34b}$$

$$Y_{i,1}(0) = 0 \text{ for } i = 0, 1, 2 \tag{6.34c}$$

$$\tag{6.34d}$$

and the corresponding payoff functional

$$L(T) = \int_0^T \left[\alpha \left(\kappa_p \nu_p (Y_{0,0}(t) + Y_{1,0}(t)) + \kappa_t \nu_t Y_{2,0}(t) + \sum_{i=0}^{i=4} \sum_{j=0}^{j=1} c_i Y_{i,j}(t) \right) \right.$$
$$\left. - (1 - \alpha) \left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} q_i Y_{i,j}(t) \right) \right] e^{-rt} dt. \tag{6.35}$$

From the dynamics, initial state, and the payoff functional, for the combined strategy model we have the following set of parameters

$$\Theta = [\mu, \mu_{1,0}, \mu_{1,1}, \mu_{2,0}, \mu_{2,1}, \mu_{3,0}, \mu_{4,0}, p_0, p_1, p_2, p_3, p_4, \beta_{1,0}, \beta_{1,1}, \beta_{2,0}, \beta_{2,1}, \beta_{3,0}, \beta_{4,0}, \dots$$
$$\dots, \eta_{00,10}, \eta_{00,11}, \eta_{00,20}, \eta_{00,21}, \eta_{00,30}, \eta_{00,40}, \eta_{01,10}, \eta_{01,11}, \eta_{01,20}, \eta_{01,21}, \eta_{01,30}, \eta_{01,40}, \dots$$
$$\dots, \varepsilon, \nu_p, \nu_t, \omega, \sigma, \xi, Y_0, \phi_0, \rho_1, \rho_2, \rho_3, c_0, c_1, c_2, c_3, c_4, q_0, q_1, q_2, q_3, q_4, r, \alpha, \kappa_p, \kappa_t]$$

where particular values at the point that the variations are analyzed are shown in the second column of tables 6.5 and 6.6.

To evaluate the sensitivity analysis for each of the 55 parameters, we will start by setting up the system of differential equations for the adjoint variable. Presenting the model in terms of the notation used in section 6.2 we get,

$$\Phi(\dot{Y}, Y, \Theta) =$$

$$
\begin{bmatrix}
\dot{Y}_{0,0}(t) + (\nu_p + \mu + p_0\lambda(t))Y_{0,0}(t) - \omega Y_{0,1}(t) - (1 - \sum_{i=1}^{i=3}\rho_i)\mu Y_0 \\
\dot{Y}_{0,1}(t) - \nu_p Y_{0,0}(t) + (\mu + \omega + p_0(1-\varepsilon)\lambda_\nu(t))Y_{0,1}(t) \\
\dot{Y}_{1,0}(t) - p_0\lambda(t)Y_{0,0}(t) + (\nu_p + \sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) - \omega Y_{1,1}(t) - \rho_1\mu Y_0 \\
\dot{Y}_{1,1}(t) - p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}(t) - \nu_p Y_{1,0}(t) + (\sigma\xi + \omega + \mu_{1,1} + \mu)Y_{1,1}(t) \\
\dot{Y}_{2,0}(t) - \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) + (\mu_{2,0} + \mu + \nu_t)Y_{2,0}(t) - \rho_2\mu Y_0 \\
\dot{Y}_{2,1}(t) - \nu_t Y_{2,0}(t) + (\mu_{2,1} + \mu)Y_{2,1}(t) \\
\dot{Y}_{3,0}(t) - \mu_{1,0}Y_{1,0}(t) - \mu_{1,1}Y_{1,1}(t) - \mu_{2,0}Y_{2,0}(t) - \mu_{2,1}Y_{2,1}(t) + (\mu_{3,0} + \mu)Y_{3,0}(t) - \rho_3\mu Y_0 \\
\dot{Y}_{4,0}(t) - \mu_{3,0}Y_{3,0}(t) + (\mu_{4,0} + \mu)Y_{4,0}(t)
\end{bmatrix}
$$

$$
G(Y(0), \Theta) =
\begin{bmatrix}
Y_{0,0}(0) - (1 - \phi_0)Y_0 \\
Y_{0,1}(0) \\
Y_{1,0}(0) - \phi_0\left(\dfrac{1/\mu_{1,0}}{\sum_{j=1}^{j=4}1/\mu_{j,0}}\right)Y_0 \\
Y_{1,1}(0) \\
Y_{2,0}(0) - \phi_0\left(\dfrac{1/\mu_{2,0}}{\sum_{j=1}^{j=4}1/\mu_{j,0}}\right)Y_0 \\
Y_{2,1}(0) \\
Y_{3,0}(0) - \phi_0\left(\dfrac{1/\mu_{3,0}}{\sum_{j=1}^{j=4}1/\mu_{j,0}}\right)Y_0 \\
Y_{4,0}(0) - \phi_0\left(\dfrac{1/\mu_{4,0}}{\sum_{j=1}^{j=4}1/\mu_{j,0}}\right)Y_0
\end{bmatrix}
$$

$$
\ell(Y, \Theta) = \left[\alpha\left(\kappa_p\nu_p(Y_{0,0}(t) + Y_{1,0}(t)) + \kappa_t\nu_t Y_{2,0}(t) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1}c_i Y_{i,j}(t)\right)\right.
$$
$$
\left. - (1-\alpha)\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}q_i Y_{i,j}(t)\right)\right]e^{-rt}.
$$

Then the initial value problem for the adjoint variables is defined by

$$\frac{d\Lambda(t)}{dt} = -\langle \Lambda, F_Y \rangle + \ell_Y, \quad \Lambda(t^{(1)}) = 0$$

with

$$\ell_Y = \begin{bmatrix} (\alpha(\kappa_p + c_0 + q_0) - q_0)e^{-rt} \\ (\alpha(c_0 + q_0) - q_0)e^{-rt} \\ (\alpha(\kappa_p + c_1 + q_1) - q_1)e^{-rt} \\ (\alpha(c_1 + q_1) - q_1)e^{-rt} \\ (\alpha(c_2 + q_2) - q_2)e^{-rt} \\ (\alpha(\kappa_t + c_2 + q_2) - q_2)e^{-rt} \\ (\alpha(c_3 + q_3) - q_3)e^{-rt} \\ (\alpha(c_4 + q_4) - q_4)e^{-rt} \end{bmatrix},$$

and F_Y is the Jacobian matrix for the system (6.23), which can be referenced in appendix A. The resulting system of ordinary differential equations is given as the following:

$$\frac{d\Lambda_{0,0}(t)}{dt} = \left(\mu + \nu_p + p_0\left(\frac{\partial \lambda}{\partial Y_{0,0}}Y_{0,0} + \lambda(t)\right)\right)\Lambda_{0,0}(t) + \left(p_0(1-\varepsilon)\frac{\partial \lambda_\nu}{\partial Y_{0,0}}Y_{0,1} - \nu_p\right)\Lambda_{0,1}(t)$$
$$- p_0\left(\frac{\partial \lambda}{\partial Y_{0,0}}Y_{0,0} + \lambda(t)\right)\Lambda_{1,0}(t) - \left(p_0(1-\varepsilon)\frac{\partial \lambda_\nu}{\partial Y_{0,0}}Y_{0,1}\right)\Lambda_{1,1}(t)$$
$$+ (\alpha(\kappa_p + c_0 + q_0) - q_0)e^{-rt} \tag{6.36a}$$

$$\frac{d\Lambda_{0,1}(t)}{dt} = \left(p_0\frac{\partial \lambda}{\partial Y_{0,1}}Y_{0,0} - \omega\right)\Lambda_{0,0}(t) + \left(\omega + \mu + p_0(1-\varepsilon)\left(\frac{\partial \lambda_\nu}{\partial Y_{0,1}}Y_{0,1} + \lambda_\nu(t)\right)\right)\Lambda_{0,1}(t)$$
$$- p_0\frac{\partial \lambda}{\partial Y_{0,1}}Y_{0,0}\Lambda_{1,0}(t) - p_0(1-\varepsilon)\left(\frac{\partial \lambda_\nu}{\partial Y_{0,1}}Y_{0,1} + \lambda_\nu(t)\right)\Lambda_{0,1}(t)$$
$$+ (\alpha(c_0 + q_0) - q_0)e^{-rt} \tag{6.36b}$$

$$\frac{d\Lambda_{1,0}(t)}{dt} = p_0\frac{\partial \lambda}{\partial Y_{1,0}}Y_{0,0}\Lambda_{0,0}(t) + p_0(1-\varepsilon)\frac{\partial \lambda_\nu}{\partial Y_{1,0}}Y_{0,1}\Lambda_{0,1}(t)$$
$$+ (\sigma\xi + \nu_p + \mu_{1,0} + \mu - p_0\frac{\partial \lambda}{\partial Y_{1,0}}Y_{0,0})\Lambda_{1,0}(t) - \left(p_0(1-\varepsilon)\frac{\partial \lambda_\nu}{\partial Y_{1,0}}Y_{0,1} + \nu_p\right)\Lambda_{1,1}(t)$$
$$- \sigma\xi\Lambda_{2,0}(t) - \mu_{1,0}\Lambda_{3,0}(t) + (\alpha(\kappa_p + c_1 + q_1) - q_1)e^{-rt} \tag{6.36c}$$

$$\frac{d\Lambda_{1,1}(t)}{dt} = p_0\frac{\partial \lambda}{\partial Y_{1,1}}Y_{0,0}\Lambda_{0,0}(t) + p_0(1-\varepsilon)\frac{\partial \lambda_\nu}{\partial Y_{1,1}}Y_{0,1}\Lambda_{0,1}(t)$$
$$- \left(p_0\frac{\partial \lambda}{\partial Y_{1,1}}Y_{0,0} + \omega\right)\Lambda_{1,0}(t) + \left(\sigma\xi + \omega + \mu_{1,1} + \mu - p_0(1-\varepsilon)\frac{\partial \lambda_\nu}{\partial Y_{1,1}}Y_{0,1}\right)\Lambda_{1,1}(t)$$
$$- \sigma\xi\Lambda_{2,0}(t) - \mu_{1,1}\Lambda_{3,0}(t) + (\alpha(c_1 + q_1) - q_1)e^{-rt} \tag{6.36d}$$

$$\frac{d\Lambda_{2,0}(t)}{dt} = p_0 \frac{\partial \lambda}{\partial Y_{2,0}} Y_{0,0} \Lambda_{0,0}(t) + p_0(1-\varepsilon)\frac{\partial \lambda_\nu}{\partial Y_{2,0}} Y_{0,1}\Lambda_{0,1}(t) - p_0 \frac{\partial \lambda}{\partial Y_{2,0}} Y_{0,0}\Lambda_{1,0}(t)$$

$$- p_0(1-\varepsilon)\frac{\partial \lambda_\nu}{\partial Y_{2,0}} Y_{0,1}\Lambda_{1,1}(t) + (\nu_t + \mu_{2,0} + \mu)\Lambda_{2,0}(t) - \nu_t \Lambda_{2,1}(t) - \mu_{2,1}\Lambda_{3,0}(t)$$

$$+ (\alpha(c_2 + q_2) - q_2)e^{-rt} \tag{6.36e}$$

$$\frac{d\Lambda_{2,1}(t)}{dt} = p_0 \frac{\partial \lambda}{\partial Y_{2,1}} Y_{0,0}(t) \Lambda_{0,0}(t) + p_0(1-\varepsilon)\frac{\partial \lambda_\nu}{\partial Y_{2,1}} Y_{0,1}(t)\Lambda_{0,1}(t) - p_0 \frac{\partial \lambda}{\partial Y_{2,1}} Y_{0,0}(t)\Lambda_{1,0}(t)$$

$$- p_0(1-\varepsilon)\frac{\partial \lambda_\nu}{\partial Y_{2,1}} Y_{0,1}(t)\Lambda_{1,1}(t) + (\mu_{2,1} + \mu)\Lambda_{2,1}(t) - \mu_{2,1}\Lambda_{3,0}(t)$$

$$+ (\alpha(c_2 + q_2) - q_2)e^{-rt} \tag{6.36f}$$

$$\frac{d\Lambda_{3,0}(t)}{dt} = p_0 \frac{\partial \lambda}{\partial Y_{3,0}} Y_{0,0}\Lambda_{0,0}(t) + p_0(1-\varepsilon)\frac{\partial \lambda_\nu}{\partial Y_{3,0}} Y_{0,1}\Lambda_{0,1}(t) - p_0 \frac{\partial \lambda}{\partial Y_{3,0}} Y_{0,0}\Lambda_{1,0}(t)$$

$$- p_0(1-\varepsilon)\frac{\partial \lambda_\nu}{\partial Y_{3,0}} Y_{0,1}\Lambda_{1,1}(t) + (\mu_{3,0} + \mu)\Lambda_{3,0}(t) - \mu_{3,0}\Lambda_{4,0}(t)$$

$$+ (\alpha(c_3 + q_3) - q_3)e^{-rt} \tag{6.36g}$$

$$\frac{d\Lambda_{4,0}(t)}{dt} = p_0 \frac{\partial \lambda}{\partial Y_{4,0}} Y_{0,0}\Lambda_{0,0}(t) + p_0(1-\varepsilon)\frac{\partial \lambda_\nu}{\partial Y_{4,0}} Y_{0,1}\Lambda_{0,1}(t) - p_0 \frac{\partial \lambda}{\partial Y_{4,0}} Y_{0,0}\Lambda_{1,0}(t)$$

$$- p_0(1-\varepsilon)\frac{\partial \lambda_\nu}{\partial Y_{4,0}} Y_{0,1}\Lambda_{1,1}(t) + (\mu_{4,0} + \mu)\Lambda_{4,0}(t)$$

$$+ (\alpha(c_4 + q_4) - q_4)e^{-rt}. \tag{6.36h}$$

Setting $T = 20$ and the parameters values as they are defined in section 3.1 the solutions for both systems (6.33) and (6.36) were derived by numerical methods and are presented in figures 6.7 and 6.8 respectively. These solutions for both the state trajectories and adjoint variables are then used evaluate each of the sensitivity functions for all 49 parameters[5]. The results for each are presented in tables 6.5 and 6.6 where they have been ranked in order by the most sensitive to the least. Again we find some similar results compared to the analysis for the preventative vaccine program, the therapeutic vaccine program and the dynamics without an intervention. Instead of getting into too much detail here we will address the parameter sensitivity comparison for each variation of the model in the following section.

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[5]All 49 sensitivity functions are derived and presented in appendix C.
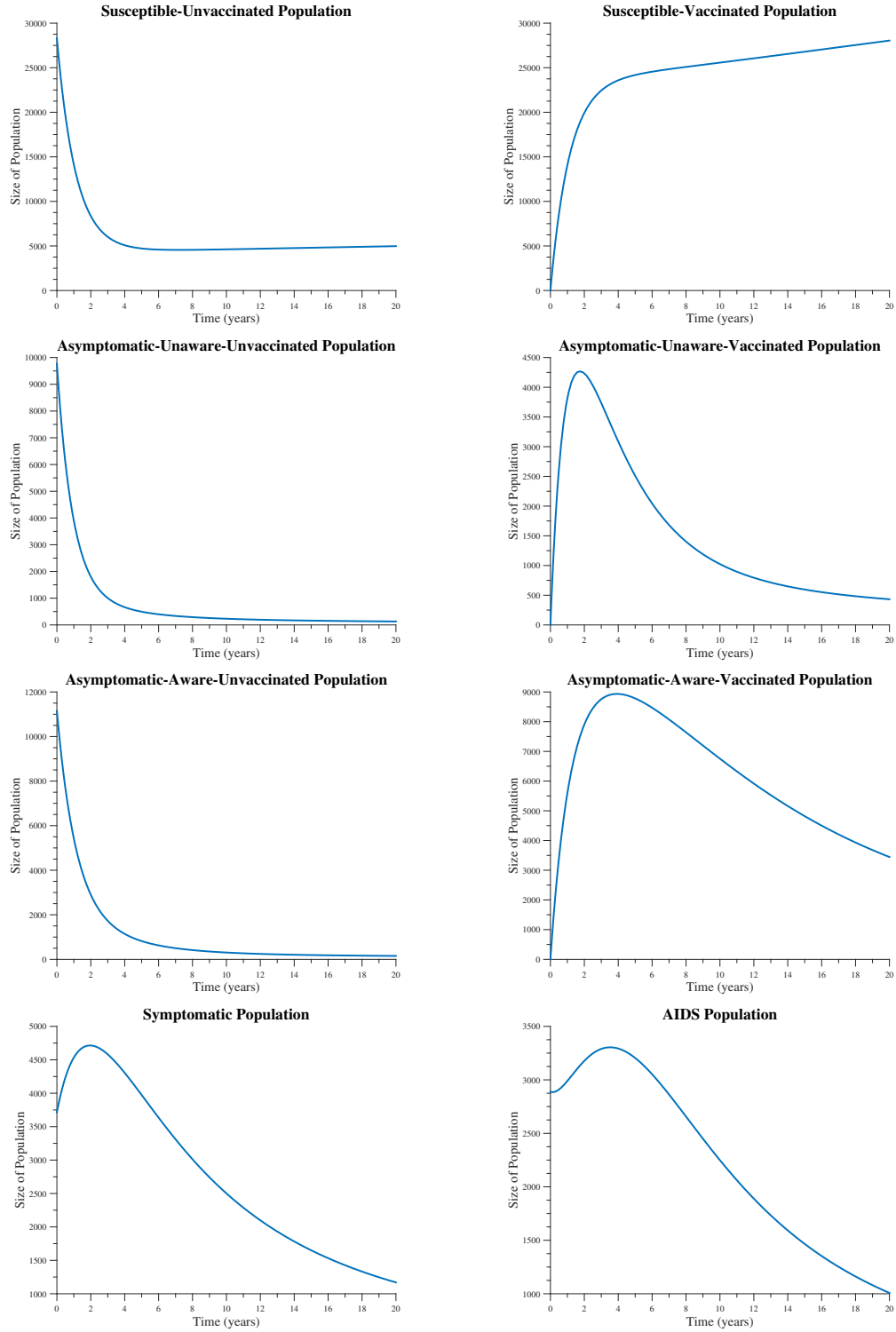
Figure 6.7: Combined, preventative and therapeutic, vaccine program: state trajectories for evaluating parameter sensitivity to the objective function.
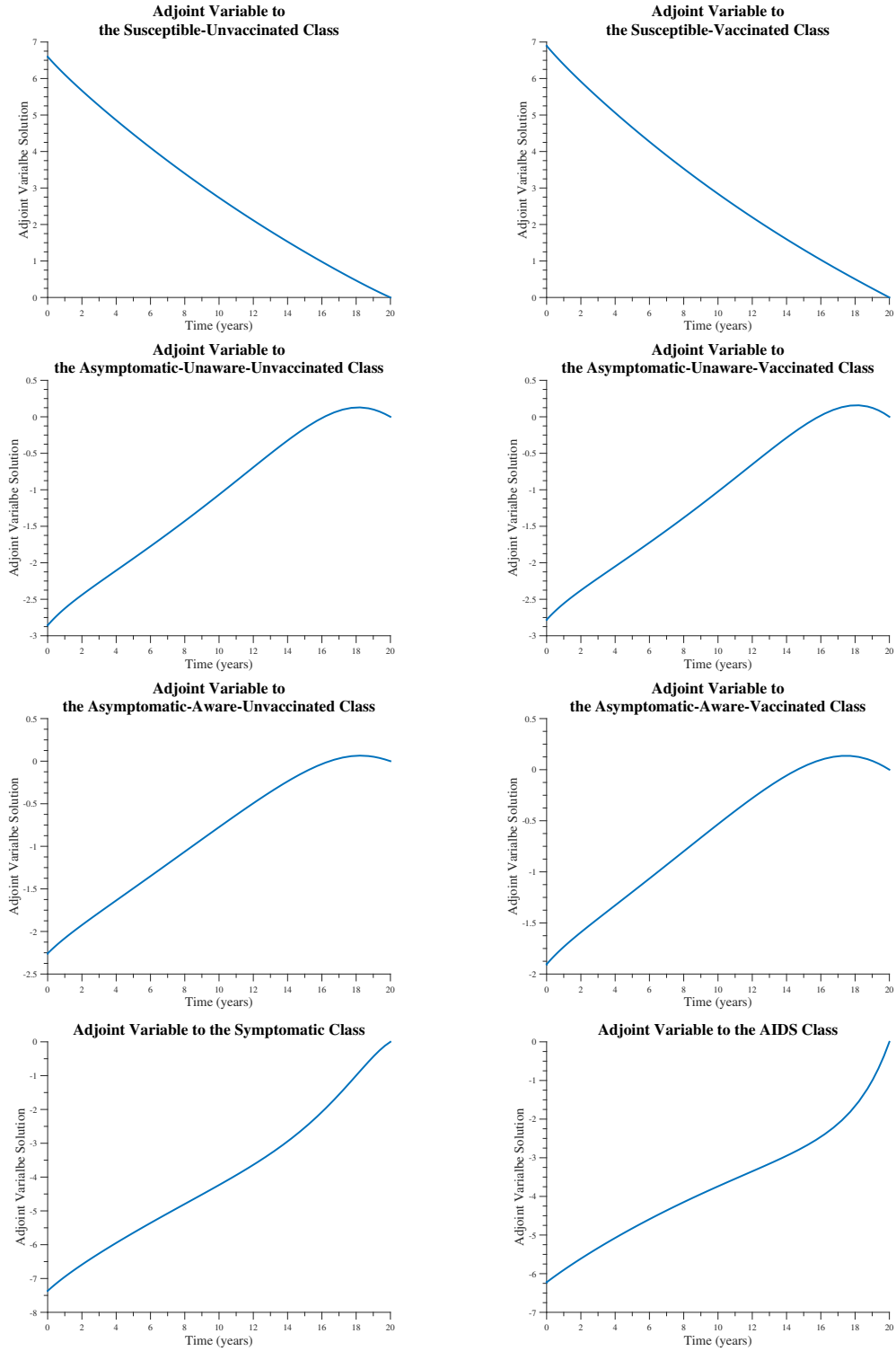
Figure 6.8: Combined, preventative and therapeutic, vaccine program: adjoint variables for evaluating parameter sensitivity to the objective function.

Table 6.5: Adjoint variable method: parameter sensitivity ($> 10^4$) to the objective function for the dynamics when the combined, preventative and therapeutic, vaccine program is presented. Solutions to the instantaneous rate of change for the payoff with respect to the corresponding parameter evaluated at $\hat{\Theta}$.

Parameters	Parameter Values (Assumptions, $\hat{\Theta}$)	Sensitivity of the Payoff Relative to each Parameter $\left(\left.\dfrac{\partial L(Y,\Theta)}{\partial\theta_i}\right|_{\hat{\Theta}}\right)$
α	1/10000	3.70359321468862e+09
μ	0.022	-1.65413747648665e+06
r	0.05	1.47423642072584e+06
ϕ_0	0.493	5.67929917275335e+05
$\mu_{2,1}$	1/13.1	4.58133123581753e+05
q_0	1	-3.77589250197162e+05
$\mu_{2,0}$	1/8.1	2.12287966514073e+05
$\mu_{4,0}$	1/2.1	-2.02620150508584e+05
ρ_3	0.02	1.71836349519474e+05
$\beta_{2,1}$	0.0495	1.42276656025451e+05
$\mu_{1,1}$	1/7.1	1.12418452861067e+05
$\mu_{1,0}$	1/7.1	1.09508599874891e+05
q_2	0.83	-1.00803348982309e+05
ρ_1	0.04	9.95780374055173e+04
ρ_2	0.04	9.32597404241762e+04
$\mu_{3,0}$	1/2.7	-6.91744147989177e+04
ω	1/10	5.63999070301863e+04
$\beta_{1,1}$	0.066	5.61725900047318e+04
$\beta_{1,0}$	0.066	4.01102140197220e+04
q_3	0.42	-3.90816504103753e+04
$\beta_{3,0}$	0.147	3.74429473139820e+04
q_1	1	-3.65924209679311e+04
ε	0.75	-3.63580959136667e+04
$\beta_{2,0}$	0.066	3.28956012966058e+04
q_4	0.17	-3.09878773947230e+04
σ	0.15	-1.74062671055518e+04
$\eta_{00,30}$	0.235	1.36332256515006e+04

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Table 6.6: Adjoint variable method: parameter sensitivity ($< 10^4$) to the objective function for the dynamics when the combined, preventative and therapeutic, vaccine program is presented. Solutions to the instantaneous rate of change for the payoff with respect to the corresponding parameter evaluated at $\hat{\Theta}$.

Parameters	Parameter Values (Assumptions, $\hat{\Theta}$)	Sensitivity of the Payoff Relative to each Parameter $\left(\frac{\partial L(Y,\Theta)}{\partial \theta_i}\big|_{\hat{\Theta}}\right)$
$\eta_{01,30}$	0.235	9.78853100843731e+03
$\beta_{4,0}$	0.147	9.58275137238856e+03
$\eta_{00,21}$	0.4803	7.48895689258012e+03
$\eta_{01,21}$	0.4803	7.17568283257671e+03
$\eta_{00,20}$	0.307	5.52278688504569e+03
p_0	2	4.45860644393792e+03
$\eta_{00,10}$	0.505	4.20137022351679e+03
$\eta_{00,11}$	0.505	3.91341510897369e+03
$\eta_{00,40}$	0.235	3.39523630244231e+03
$\eta_{01,11}$	0.6287	2.75326526208321e+03
ξ	0.98	-2.66422455697222e+03
$\eta_{01,40}$	0.235	2.59908019055416e+03
p_2	2	2.36667122992879e+03
p_1	2	2.07851716566375e+03
p_3	2	1.85674451113226e+03
$\eta_{01,20}$	0.307	1.54923150010401e+03
p_4	0.667	1.43952897262286e+03
$\eta_{01,10}$	0.505	1.04075606832242e+03
c_0	3307	3.77627012898452e+01
c_2	5467	1.00813430325342e+01
κ_p	1000	9.61289664215710e+00
c_3	12586	3.90855589662719e+00
c_1	5467	3.65960805759887e+00
c_4	35394	3.09909764923722e+00
Y_0	55816	-2.67356071108355e+00
κ_t	1000	1.80908668817771e+00

6.3 Parameter Sensitivity Comparison

In the previous sections we applied the adjoint variable method to derive the sensitivity of the parameters for each of the four variation of the state space of the HIV-transmission model with vaccine intervention. The results independently give us a ranking of the most sensitive parameters to the least sensitive, for the set of distinct parameters for each variation of the state space. Some of the parameters are consistent throughout all four variations of the model, specifically the parameters associated to the model when no intervention is present. As we analyze the impact that each vaccine program has on the population dynamics there are vaccine specific parameters added to the model, resulting with an impact to the sensitivity of the base parameters. Therefore we were interested in comparing the results of the individual state space sensitivity analysis, which is presented in tables 6.7 - 6.9.

From the results we find that the most sensitive parameter is the weighting parameter α that we introduced during the discussion of Pareto optimality. To consider the impact the variations of α will have on the solution for optimizing an intervention strategy, we allowed α to vary between 10^{-3} to 10^{-5}. The results indicated that the timing of the intervention strategy is highly dependent with the choice of α, which is consistent with the concept of the Pareto Front (PF) defined in section 5.2.1 and analyzed in section 5.4.5. If $\alpha = 10^{-3}$, the assumption would indicate that minimizing cost was more important than the original analysis. This results with an optimal strategy with both vaccines being offered immediately, then removing the preventative vaccine around $t = 10.8$ and the therapeutic vaccine around $t = 17.6$. Both of which is earlier than the original analysis, but the change is more prevalent in the preventative vaccine than the therapeutic. Alternatively, when we evaluated the results for $\alpha = 10^{-5}$ we found an alternative optimal strategy to administer both vaccines right away, then remove the preventative vaccine around $t = 15.2$ and the therapeutic around $t = 19$. Since $\alpha = 10^{-5}$ indicates a greater importance for maximizing QALYs over minimizing cost the results support offering both vaccines for a longer period of time.

Alternatively, we want to emphasize how much variation we find in the sensitivity for the portion of the population that is screened for the infection (σ) between the variations of the state spaces. It is the least sensitive for the case when only the preventative vaccine is present, with a sensitivity of 6.6492e+02. On an order of magnitude, the sensitivity for σ is 100 times less sensitive then it is in all of the other three state spaces. To determine the impact this variation would have on the optimal control solution we allowed σ to vary between 1% to 50% and found that there was no change to results for the optimal intervention strategy presented in sections 5.4.2.

The comparison of the sensitivity analysis for the impact that variation in the parameters has on the payoff functional allows us to interpret the impact that variations will have on the

solution to the optimal intervention strategy. The results indicate that when a parameter is highly sensitivity in all variations of the state space then we can expect to find variation in the solution to the optimal control. Alternatively, even when the sensitivity changes between variations of the state space but is low enough then the impact on the solution to the optimal control is negligible.

Table 6.7: Parameter sensitivity comparison for the four variations of the model with sensitivities greater than 9e+05.

Combined Vaccination Strategy		Preventative Vaccine Program		Therapeutic Vaccine Program		No Intervention	
α	3.7036e+09	α	3.7358e+09	α	3.7331e+09	α	3.7789e+09
μ	-1.6541e+06	μ	-1.7617e+06	μ	-1.9494e+06	μ	-2.0577e+069
r	1.4742e+06	r	1.3447e+06	r	1.1880e+06	r	1.0688e+06
ϕ_0	5.6793e+05	ϕ_0	5.9712e+05	ϕ_0	5.7834e+05	ϕ_0	6.0868e+05
$\mu_{2,1}$	4.5813e+05	$\mu_{2,0}$	4.5373e+05	$\mu_{2,1}$	4.7880e+05	$\mu_{2,0}$	4.7186e+05
q_0	-3.7759e+05	q_0	-3.7901e+05	$\beta_{2,1}$	3.5994e+05	q_0	-3.4901e+05
$\mu_{2,0}$	2.1229e+05	$\mu_{4,0}$	-2.1589e+05	q_0	-3.4555e+05	$\beta_{2,0}$	2.6539e+05
$\mu_{4,0}$	-2.0262e+05	ρ_3	1.7226e+05	$\mu_{1,0}$	2.6225e+05	$\mu_{1,0}$	2.4832e+05
ρ_3	1.7184e+05	$\beta_{2,0}$	1.1476e+05	$\beta_{1,0}$	2.2047e+05	$\mu_{4,0}$	-2.3111e+05
$\beta_{2,1}$	1.4228e+05	$\mu_{1,0}$	1.1279e+05	$\mu_{4,0}$	-2.1723e+05	$\beta_{1,0}$	2.3034e+05
$\mu_{1,1}$	1.1242e+05	ρ_2	1.0366e+05	$\mu_{2,0}$	2.1012e+05	ρ_3	1.7780e+05
$\mu_{1,0}$	1.0951e+05	ρ_1	1.0350e+05	ρ_3	1.7653e+05	ρ_1	1.1003e+05
q_2	-1.0080e+05	$\mu_{1,1}$	1.0342e+05	q_2	-1.0809e+05	ρ_2	1.0957e+05
ρ_1	9.9578e+04			ρ_1	1.0508e+05	$\beta_{3,0}$	1.0617e+05
ρ_2	9.3260e+04			ρ_2	9.8870e+04		
				$\beta_{3,0}$	9.0235e+04		

Table 6.8: Parameter sensitivity comparison for the four variations of the model with sensitivities between 1e+03 and 9e+05.

Combined Vaccination Strategy		Preventative Vaccine Program		Therapeutic Vaccine Program		No Intervention	
$\mu_{3,0}$	-6.9174e+04	q_2	-8.3553e+04	$\mu_{3,0}$	-7.8602e+04	q_2	-8.9541e+04
ω	5.6400e+04	$\mu_{3,0}$	-6.8680e+04	$\beta_{2,0}$	5.8866e+04	$\mu_{3,0}$	-8.0923e+04
$\beta_{1,1}$	5.6173e+04	$\beta_{1,1}$	5.8555e+04	$\eta_{00,30}$	5.6445e+04	$\eta_{00,30}$	6.6414e+04
$\beta_{1,0}$	4.0110e+04	ω	5.5458e+04	q_1	-4.7520e+04	$\eta_{00,20}$	5.7055e+04
q_3	-3.9082e+04	$\beta_{3,0}$	4.3251e+04	q_3	-4.3487e+04	q_3	-4.7382e+04
$\beta_{3,0}$	3.7443e+04	q_3	-4.2978e+04	$\eta_{00,21}$	3.7100e+04	q_1	-4.6197e+04
q_1	-3.6592e+04	$\beta_{1,0}$	4.1780e+04	q_4	-3.3664e+04	q_4	-3.6318e+04
ε	-3.6358e+04	q_1	-3.6060e+04	$\eta_{00,10}$	2.8814e+04	$\eta_{00,10}$	3.0104e+04
$\beta_{2,0}$	3.2896e+04	ε	-3.5229e+04	σ	-2.3132e+04	$\beta_{4,0}$	2.6651e+04
q_4	-3.0988e+04	q_4	-3.3634e+04	$\beta_{4,0}$	2.2990e+04	$\eta_{00,40}$	1.6671e+04
ν_p	-1.9426e+04	ν_p	-1.9303e+04	$\eta_{00,40}$	1.4381e+04	p_0	1.0414e+04
σ	-1.7406e+04	$\eta_{00.30}$	1.5463e+04	$\eta_{00,20}$	1.2655e+04		
$\eta_{00,30}$	1.3633e+04	$\eta_{00.20}$	1.4819e+04	p_0	1.0807e+04		
$\eta_{01,30}$	9.7885e+03	$\eta_{01,30}$	1.1592e+04				
$\beta_{4,0}$	9.5828e+03	$\beta_{4,0}$	1.0885e+04				
		$\eta_{01,20}$	9.8536e+03				
$\eta_{00,21}$	7.4890e+03	$\eta_{00,10}$	4.3795e+03	ν_t	-6.6398e+03	p_3	5.3565e+03
$\eta_{01,21}$	7.1757e+03	p_0	4.3473e+03	p_2	5.4380e+03	p_1	5.0004e+03
ν_t	-6.5796e+03	$\eta_{00,11}$	4.0837e+03	p_1	4.6614e+03	p_4	4.0635e+03
$\eta_{00,20}$	5.5228e+03	$\eta_{00,40}$	3.7884e+03	p_3	4.4121e+03	p_2	3.9955e+03
p_0	4.4586e+03	$\eta_{01,40}$	3.0207e+03	ξ	-3.5406e+03	σ	-3.6134e+03
$\eta_{00,10}$	4.2014e+03	$\eta_{01,11}$	2.8665e+03	p_4	3.3894e+03		
$\eta_{00,11}$	3.9134e+03	p_3	2.2048e+03				
$\eta_{00,40}$	3.3952e+03	p_1	2.2048e+03				
$\eta_{01,11}$	2.7533e+03	p_2	1.7584e+03				
ξ	-2.6642e+03	p_4	1.6851e+03				
$\eta_{01,40}$	2.5991e+03	$\eta_{01,10}$	1.0808e+03				
p_2	2.3667e+03						
p_1	2.0785e+03						
p_3	1.8567e+03						
$\eta_{01,20}$	1.5492e+03						
p_4	1.4395e+03						
$\eta_{01,10}$	1.0408e+03						

Table 6.9: Parameter sensitivity comparison for the four variations of the model with sensitivities less than 1e+03.

Combined Vaccination Strategy		Preventative Vaccine Program		Therapeutic Vaccine Program		No Intervention	
		σ	6.6492e+02			ξ	-5.5307e+02
		ξ	1.0177e+02				
c_0	3.7763e+01	c_0	3.7904e+01	c_0	3.4559e+01	c_0	3.4905e+01
c_2	1.0081e+01	κ_p	9.6251e+00	c_2	1.0810e+01		
κ_p	9.6129e+00						
c_3	3.9086e+00	c_2	8.3561e+00	c_1	4.7524e+00	c_2	8.9550e+00
c_1	3.6596e+00	c_3	4.2982e+00	c_3	4.3491e+00	c_3	4.7387e+00
c_4	3.0991e+00	c_1	3.6064e+00	c_4	3.3667e+00	c_1	4.6202e+00
Y_0	-2.6736e+00	c_4	3.3637e+00	Y_0	-2.3564e+00	c_4	3.6322e+00
κ_t	1.8091e+00	Y_0	-2.4125e+00	κ_t	1.9735e+00	Y_0	-2.1092e+00

Chapter 7

Conclusion

7.1 Summary

This concludes the research for the HIV-transmission model with vaccine intervention for the purpose of deriving an optimal intervention strategy. In offering a full analysis of the system we started with the cost-effective analysis for the base case HIV-transmission model without an intervention, as well as each of the vaccine programs independently, followed by the analysis of the combined, preventative and therapeutic, vaccine strategy for a time horizon of 20 years. Both of the vaccine programs we chose are considered dominant programs with the expectation that they will reduce cost and increase QALYs. Although, we found in the case for the therapeutic vaccine, even though the dominant therapeutic vaccine saved money and increased QALYs the adverse effects of vaccinating resulted with the vaccinated population having a higher risk in transmitting the disease than the unvaccinated population. This implied that the results generated more infections when the therapeutic vaccine was offered.

This led us to analyzing the dynamical system in consideration for the R_0 threshold, in an attempt to characterize the secondary infection number. From our review of the literature it is standard practice to derive the R_0 threshold by evaluating the conditions for which the disease free equilibrium will be stable or unstable. By assuming that immigration into the infected population is defined by constant parameters in the dynamics a disease-free equilibrium will not exist without altering the original assumptions of the model. This implies that the characterization for the R_0 threshold was not possible in our case. Instead we found with each variation of the state space there is exactly one physically relevant, locally asymptotically stable, equilibrium point; described as an endemic equilibrium. This implies that regardless of the strategy implemented the disease will continue to persist. We did find though, that some outcomes, specifically when the preventative vaccine is introduced, will have a more desirable outcome.

After understanding the expected outcomes for each variation of the model we proceeded to the analysis for optimizing an intervention strategy. In consideration of opposing objectives, to minimize cost and maximize QALYs, an introduction to multiobjective optimization and Pareto optimality was made so that we could structure a problem statement that fit the objective for optimizing an intervention strategy for which methods from optimal control theory could be applied. Upon structuring the problem statement we implemented a direct numerical method (control parameterization) for solving the optimal intervention strategy. The results of a direct numerical optimization method only guarantee a locally optimal solution, so to verify whether or not the solution was a globally optimal intervention strategy we checked the necessary conditions from Pontryagin's maximum principle. We found, with two dominant vaccine programs, the globally optimal strategy on a 20 year time horizon is to offer both vaccines immediately then stop offering the preventative vaccine after 12 years and the therapeutic vaccine after 18 years. Although, we do not attempt to get into an ethical discussion regarding offering a vaccine then taking it away, what we do get out of the analysis is that even with a dominant program further research can provide insight into even more cost-effective savings.

To understand the expectations for the model results, relative to the assumptions regarding the parameters that govern the outcomes, we concluded with sensitivity analysis for each of the variations of the state space as well as the implications this has on the outcome for the optimal intervention strategy. We did find, as we would have expected after the discussion of Pareto optimality, that the results of the analysis is highly dependent on the choice for the weighting parameter α. In the consideration for sensitivity analysis we only offer a ranking for the sensitivity of the payoff function relative to the parameter changes and how it impact the results for optimizing an intervention strategy. Although uncertainty analysis is typically offered in tandem to sensitivity analysis, without knowledge for the uncertainty in the parameters we didn't quantify the uncertainty in the conclusion.

7.2   Model Development

The research we have presented for the HIV-transmission model with vaccine intervention has resulted with an understanding for the underlying dynamics, a consideration for an optimal strategy, and insight into the sensitivity of the model to the parameter assumptions. All of which gives us a well rounded analysis for the projections made regarding controlling the spread of HIV. In addition, the research also highlighted a couple of concerns regarding the epidemiological and cost-effective analysis. This leads us to the consideration regarding model development for the purpose of characterizing the secondary infection rate threshold, R_0. The lack of an R_0 threshold for HIV-transmission models with constant immigration into the infected population requires further consideration for adding a dependency on the prevalence of the infection within

a population. As a simple and yet extreme example, we would not expect susceptible individuals to migrate to a region where everyone in the population is infected. Keeping this in mind and along with careful consideration, a population dependent immigration function will result with a model whose dynamics have two equilibria, a disease-free equilibrium and an endemic equilibrium, then the epidemiological analysis can be applied for the secondary infection rate. This will also allow the researcher to consider two benefits of vaccinating, minimizing R_0 and increasing QALYs. The importance of adding the second benefit of vaccinating has already been apparent from the analysis we presented on the dominant therapeutic vaccine in chapter 3. The vaccine in this case increased QALYs, which is considered a beneficial outcome, but it was apparent by the trajectory for the susceptible population that the number of secondary infections also appeared to increase, which is an undesirable outcome. A symbolic representation for R_0 would allow for a direct comparison between intervention programs to determine which one will be expected to decrease R_0 to a value below 1 in a reasonable amount of time.

In addition to the concern regarding the R_0 threshold there are a number of areas of development that have been considered for the mathematical modeling of infectious disease [27]. To begin, we will emphasize the assumptions that are made regarding the HIV-transmission model that was the subject of our analysis in the earlier chapters. The model presented by Edwards *et al.* was originally designed to interpret the spread of HIV infections amongst the homosexual population of San Francisco, CA during the mid to late 1990's. Clearly a very restrictive model regarding the population and region, which allowed the researchers to make generalized assumptions regarding the target population that were considered reasonably accurate. As a deterministic compartmental model the assumptions are made that the whole population behaves with the same risk factors. This refers to a homogenous model because the consideration for variation in behavioral patterns are not included. For models attempting to simulate a social system, heterogenous models would describe a better fit for interpreting the impact that human behavior can have on the projections. A heterogenous model will take into account that various factors, such as social/economic status, age, education, and religious beliefs (to name a few) of the individuals in the population will have an impact on how the disease spreads. As an example we will consider a simple age distinction between two men in the population. Something as simple as distinguishing the behavioral differences between a millennial and a baby boomer would better characterize the dynamics for the population. In adding heterogeneity to the model a significant number of compartments will be added to the dynamics and then the additional consideration for mixing between groups would also need to be addressed. This leads us to environmental factors that are associated to where the population is located. These factors can include ethnicity, whether the total population belongs to the same ethnic group or if there is mix of ethnic backgrounds. Another possibility is whether the population is from a major city, the suburbs, or a small rural town. All of which have a unique way of influence behav-

ioral patterns within the population. Evaluating the environmental factors will allow the model development to go further and incorporate the heterogeneity with the possibility of migration between regions. We will make the distinction between migration and mixing by clarifying that when individuals from one region migrate to another region they will be influenced by environmental factors and the possibility for behavioral changes are excepted. Alternatively, when we refer to mixing there is no assumption that the individuals acquire the behavioral patterns of the population they are mingling with.

Thus far we have named a few examples for developing the model and it is already apparent that the level of complexity for analysis will grow with each consideration. We will emphasize that with all the examples for development of the homogenous model to a heterogenous model, we have yet to address the consideration of sexual orientation, gender, or methods for which individuals can acquire the infection. With the model restricted to the interpretation for the homosexual male population the assumption was also made that the disease will only transfer by means of homosexual partnerships. Although there are additional means of transmission including heterosexual partnerships, needle sharing, as well as the infection passing from mother to child. Adding any one of additional means for transmission would require careful consideration for additional infection functions. Further more, with the addition of heterosexual partnerships the model would need to include a gender classification as well as sexual orientation. Then if vertical transmission, from mother to child, is taken into consideration there would need to be an additional consideration for the likelihood of becoming pregnant as well as the probability that the women in the population use contraceptives. Again, just to name a couple of additional key factors that we know to be true in real life but the mathematical model we have already analyzed does not take into consideration.

We can see how quickly the considerations for model development can grow in number. Everything that has been discussed thus far has all been in consideration to a deterministic compartmental model governed by a system of ordinary differential equations. This time we will place the emphasize on deterministic modeling, where the assumption for the system is that the solution to the state trajectories is known at each time, t. The alternative to deterministic modeling is stochastic modeling, where the exact position of the system at time t is unknown, instead a distribution of possible positions is the interpretation. Converting a deterministic model to a stochastic model can be done by replacing the infection rate function with a random variable so that the likelihood for the disease spreading will be more accurately interpreted by simulating the true randomness of human behavior. This will result with dynamics driven by chance where the basic entities of the model are defined by discrete individuals [27, 46].

7.3 Current Efforts in the Fight Against HIV and AIDS

To better understand the path that we will pursue for future research we need to understand what is currently being done to control the HIV/AIDS epidemic and align our efforts with those who have already started paving the way.

The motivation presented at the beginning of our research was done to give an introduction to the importance of analyzing an HIV-transmission model with vaccine intervention as well as present the advancements by researchers in the development of a preventative vaccine for HIV infections in addition to presenting the prospects of a therapeutic vaccine. Although there has been significant progress in both regards, the reality of offering either vaccine to an infected population is not expected, and definitely not guaranteed, any time in the near future. Therefore, knowing the alternative efforts currently being implemented for controlling the spread of infections as well as managing the symptoms for those already infected, the model can be converted to consider the cost-effective analysis of current intervention programs.

We will continue our focus on San Francisco, CA where the San Francisco AIDS foundation leads the efforts for managing the HIV/AIDS epidemic for their city. The foundation's mission to reduce the number of new HIV infections and help people live longer, healthier lives by 2019 is guided by three goals: ① build healthier communities by fostering personal resilience and social support, increasing community engagement, and reducing harms associated with alcohol and other drugs; ② reduce new HIV diagnoses in San Francisco to fewer than 100 per year; and ③ improve the health and lifespan of San Franciscans living with HIV [18]. These three goals align directly with the three goals outlined by the National HIV/AIDS Strategy by the White House Office of National AIDS Policy: ① decrease HIV-associated health disparities; ② reduce new HIV infections; and ③ improve access to high-quality care and optimize health outcomes for people living with HIV. With the initiative for controlling the spread of HIV reaching the focus of the White House we will soon find that more of the local and state initiatives will start to follow the same guidelines.

As a means for controlling the spread of infections the efforts have been focused on awareness and education about the disease to help the population understand better the risks they may be taking based on various behaviors they portray. Quantifying the benefits of these educational intervention programs will introduce a new challenge, but once that hurdle is crossed the cost-effective analysis for competing program can easily be assessed.

7.4   Future Research

In addition to some of the comments we have already made regarding model development there is one area of the current model that would be important to explore a little further than we already have. The purpose of our research was to give a well rounded analysis for strategizing vaccine programs when one would become available. To do this required assumptions regarding the vaccine specific parameters. At the beginning of our research we chose to assume that both vaccines would be considered dominant vaccines, meaning they would reduce cost and increase QALYs, then the parameters were defined that supported this conclusion based on the research from the original authors of the model. For the purpose of optimizing an intervention strategy for the model we also fixed the time horizon to 20 years. A couple of additional questions that could use more exploration are the following.

- What if one or both of the vaccines are not considered dominant vaccines? How could this impact the results for optimizing the intervention strategy?

- What would happen to the solution for the optimal intervention strategy if we considered longer time horizons? Could this result with more switching times? Would it be possible to have a scenario that results with an optimal strategy where there is a delay in providing either one of the vaccines?

Some preliminary analysis was run prior to making the decision to fixed the model with dominant vaccines on a 20 years times horizon. It will be expected that alternative choices for the vaccine related parameter assumptions will result with some significant variation in the solution for the optimal intervention strategy. This would be analyzed best by considering the sensitivity analysis for the model when we allow multiple parameters to vary. The sensitivity analysis that we have already presented only considered single parameter variation. To consider the impact to the solution for alternative vaccine program we can focus on varying all of the parameters associated to each of the vaccines and analyze the impact to the cost and optimization problem. This will result with an efficient means to considering the largest variety of variations, then we can target particular vaccine programs for further analysis of the state trajectories and optimal solution. This can then be followed with consideration for longer time horizons and the impact this can have on the variations to the solution. We will point out that when the time horizon was extended to 50 or 100 years in our preliminary analysis the results for the optimal strategy did not show any new interesting behavior worth exploring for the case when both vaccines are dominant.

Next, taking into consideration the areas for which we can develop the model and the current efforts being made in the fight against HIV and AIDS the goals as we move forward with our

research will be to develop a model that offers beneficial analysis for the intervention strategies that are available today. To begin, the first objective in the model development will be to address the concerns of having constant immigration parameters. Instead, taking into consideration that immigration will depend not only on the infectivity level of the individuals migrating but also on the prevalence of infection within the population that they are migrating to. This will allow us to have a component to the dynamics that is defined by the ratio of the total infected population relative to the population as a whole, which will result with dynamics that have an appropriate disease-free equilibrium. With careful consideration for defining the immigration function, a selection can be made that results with an interpretation for an endemic equilibrium as well. This will result with the application of stability analysis to consider a characterization of the R_0 threshold in symbolic form.

Once a characterization for the R_0 threshold has been evaluated, the next consideration that needs to be made relates to the fact that the original model we analyzed was defined and presented by Edwards *et al.* in the late 1990's and it is reasonable to assume that the parameter assumptions have changed in the last 20 years. Therefore, the next objective would be to determine what the assumptions are regarding the parameters of the model and evaluating how well the model will fit to the data for spread of HIV infections within the San Francisco homosexual population today. This information will lead us to more insights that will help determine the most appropriate areas for which the model needs to be further developed.

Next, the consideration for development will focus on adding heterogeneity to the model. Considering an age structured model will result with the most diversity in behavioral differences, risk factors and the ideal approach for to introducing mixing between cohorts. At this time additional consideration can be made to determine other distinguishing characteristics for introducing significant behavioral difference between members of the population based on additional demographic/environmental factors.

With developed deterministic compartment model for HIV-transmission that accurately fits the data for the homosexual male population in San Francisco the next objective will be to research the specifics regarding the educational programs implemented for the purposes of controlling the spread of HIV infections in San Francisco and determine an appropriate means to quantify their benefits. This will then allow us to further update the model to interpret current active intervention programs that will allow us to run comparative analysis between various programs. We have already discussed the therapies currently available to the infected population at the beginning of the research. Although highly active antiretroviral therapies (HAART) don't classify as a therapeutic vaccine, they mitigate the symptoms of the disease as well as reduce an individuals infectivity. Therefore, the implications for modeling HAART programs will be very similar to that of the therapeutic vaccine the parameters will need to be evaluated to accurately simulate the current programs offered to the infected population.

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APPENDICES

Appendix A

The Jacobian Matrices and Characteristic Polynomials

To reduce the amount of calculations presented in chapter 4 we will provide all of the calculations necessary for deriving the symbolic representation for the characteristic polynomials for each of the four variations for the state space of the model.

As an approach to deriving the characteristic polynomial, which is defined as $c(x) = \det{(xI - J)}$ where J is the Jacobian matrix for the system of differential equations and I is the appropriate corresponding identity matrix, we will instead approach the calculations by solving

$$\det{((xI - J)^{\mathsf{T}})} = \det{(xI - J^{\mathsf{T}})}.$$

Since the determinant of the transpose of any non-singular square matrix is equal to the determinant of that matrix, the solution to $\det{(xI - J^{\mathsf{T}})}$ is equivalent to $\det{(xI - J)}$ [34].

In addition to using the transpose of the Jacobian to derive the characteristic polynomial, we will also find that the following notation regarding the partial derivatives for the rate of infection functions will be useful

$$Q_{i,j} := p_0 \frac{\partial \lambda}{\partial Y_{i,j}} Y_{0,0}(t)$$

$$Q^{\nu}_{i,j} := p_0(1 - \varepsilon) \frac{\partial \lambda_{\nu}}{\partial Y_{i,j}} Y_{0,1}(t)$$

A.1   HIV-Transmission Dynamics without Intervention

For the model without an intervention we have following system of ordinary differential equations

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\mu + p_0\lambda(t))Y_{0,0}(t)$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0\lambda(t)Y_{0,0}(t) - (\sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t)$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi Y_{1,0}(t) - (\mu_{2,0} + \mu)Y_{2,0}(t)$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{i=1}^{i=2} \mu_{i,0}Y_{i,0}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t)$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t)$$

were

$$\lambda(t) = \frac{\sum_{i=1}^{i=4} p_i\beta_{i,0}\eta_{00,i0}Y_{i,0}(t)}{\sum_{i=0}^{i=4} p_iY_{i,0}(t)}.$$

A.1.1   The Jacobian Matrix

$$\begin{bmatrix}
-Q_{0,0} - (\mu + p_0\lambda(t)) & -Q_{1,0} & -Q_{2,0} & -Q_{3,0} & -Q_{4,0} \\
Q_{0,0} + p_0\lambda(t) & Q_{1,0} - (\sigma\xi + \mu_{1,0} + \mu) & Q_{2,0} & Q_{3,0} & Q_{4,0} \\
0 & \sigma\xi & -(\mu_{2,0} + \mu) & 0 & 0 \\
0 & \mu_{1,0} & \mu_{2,0} & -(\mu_{3,0} + \mu) & 0 \\
0 & 0 & 0 & \mu_{3,0} & -(\mu_{4,0} + \mu)
\end{bmatrix}$$

A.1.2   Characteristic Polynomial

We note the additional notation will also help in reducing the calculation by introducing a single term for the combined rate at which a population leaves each compartment of the model.

$$d_{0,0} := \mu + p_0\lambda(t)$$

$$d_{1,0} := \sigma\xi + \mu_{1,0} + \mu$$

$$d_{2,0} := \mu_{2,0} + \mu$$

$$d_{3,0} := \mu_{3,0} + \mu$$

$$d_{4,0} := \mu_{4,0} + \mu$$

Thus, the calculations for deriving the characteristic polynomial are given as the following.

$$c(x) = \det\left(xI - J^\mathsf{T}\right)$$

$$= \begin{vmatrix} x + Q_{0,0} + d_{0,0} & -Q_{0,0} - p_0\lambda(t) & 0 & 0 & 0 \\ Q_{1,0} & x - Q_{1,0} + d_{1,0} & -\sigma\xi & -\mu_{1,0} & 0 \\ Q_{2,0} & -Q_{2,0} & x + d_{2,0} & -\mu_{2,0} & 0 \\ Q_{3,0} & -Q_{3,0} & 0 & x + d_{3,0} & -\mu_{3,0} \\ Q_{4,0} & -Q_{4,0} & 0 & 0 & x + d_{4,0} \end{vmatrix}$$

$$= (x + Q_{0,0} + d_{0,0}) \begin{vmatrix} x - Q_{1,0} + d_{1,0} & -\sigma\xi & -\mu_{1,0} & 0 \\ -Q_{2,0} & x + d_{2,0} & -\mu_{2,0} & 0 \\ -Q_{3,0} & 0 & x + d_{3,0} & -\mu_{3,0} \\ -Q_{4,0} & 0 & 0 & x + d_{4,0} \end{vmatrix}$$

$$+ (Q_{0,0} + p_0\lambda(t)) \begin{vmatrix} Q_{1,0} & -\sigma\xi & -\mu_{1,0} & 0 \\ Q_{2,0} & x + d_{2,0} & -\mu_{2,0} & 0 \\ Q_{3,0} & 0 & x + d_{3,0} & -\mu_{3,0} \\ Q_{4,0} & 0 & 0 & x + d_{4,0} \end{vmatrix}$$

$$= (x + Q_{0,0} + d_{0,0})(x - Q_{1,0} + d_{1,0}) \begin{vmatrix} x + d_{2,0} & -\mu_{2,0} & 0 \\ 0 & x + d_{3,0} & -\mu_{3,0} \\ 0 & 0 & x + d_{4,0} \end{vmatrix}$$

$$+ (x + Q_{0,0} + d_{0,0})(\sigma\xi) \begin{vmatrix} -Q_{2,0} & -\mu_{2,0} & 0 \\ -Q_{3,0} & x + d_{3,0} & -\mu_{3,0} \\ -Q_{4,0} & 0 & x + d_{4,0} \end{vmatrix}$$

$$- (x + Q_{0,0} + d_{0,0})(\mu_{1,0}) \begin{vmatrix} -Q_{2,0} & x + d_{2,0} & 0 \\ -Q_{3,0} & 0 & -\mu_{3,0} \\ -Q_{4,0} & 0 & x + d_{4,0} \end{vmatrix}$$

$$+ (Q_{0,0} + p_0\lambda(t))(Q_{1,0}) \begin{vmatrix} x + d_{2,0} & -\mu_{2,0} & 0 \\ 0 & x + d_{3,0} & -\mu_{3,0} \\ 0 & 0 & x + d_{4,0} \end{vmatrix}$$

$$+ (Q_{0,0} + p_0\lambda(t))(\sigma\xi) \begin{vmatrix} Q_{2,0} & -\mu_{2,0} & 0 \\ Q_{3,0} & x + d_{3,0} & -\mu_{3,0} \\ Q_{4,0} & 0 & x + d_{4,0} \end{vmatrix}$$

$$- (Q_{0,0} + p_0\lambda(t))(\mu_{1,0}) \begin{vmatrix} Q_{2,0} & x + d_{2,0} & 0 \\ Q_{3,0} & 0 & -\mu_{3,0} \\ Q_{4,0} & 0 & x + d_{4,0} \end{vmatrix}$$

$$= (x + Q_{0,0} + d_{0,0})(x - Q_{1,0} + d_{1,0})(x + d_{2,0})(x + d_{3,0})(x + d_{4,0})$$

$$- (x + Q_{0,0} + d_{0,0})(\sigma\xi)(Q_{2,0})(x + d_{3,0})(x + d_{4,0})$$

$$- (x + Q_{0,0} + d_{0,0})(\sigma\xi)(\mu_{2,0})(Q_{3,0}(x + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$- (x + Q_{0,0} + d_{0,0})(\mu_{1,0})(x + d_{2,0})(Q_{3,0}(x + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$+ (Q_{0,0} + p_0\lambda(t))(Q_{1,0})(x + d_{2,0})(x + d_{3,0})(x + d_{4,0})$$

$$+ (Q_{0,0} + p_0\lambda(t))(\sigma\xi)(Q_{2,0})(x + d_{3,0})(x + d_{4,0})$$

$$+ (Q_{0,0} + p_0\lambda(t))(\sigma\xi)(\mu_{2,0})(Q_{3,0}(x + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$+ (Q_{0,0} + p_0\lambda(t))(\mu_{1,0})(x + d_{2,0})(Q_{3,0}(x + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$= \big[(x^2 + (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})x - (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0}))$$

$$\cdot (x^3 + (d_{2,0} + d_{3,0} + d_{4,0})x^2 + (d_{2,0}d_{3,0} + d_{2,0}d_{4,0} + d_{3,0}d_{4,0})x + d_{2,0}d_{3,0}d_{4,0}) \big]$$

$$-\sigma\xi Q_{2,0}(x + Q_{0,0} + d_{0,0})(x^2 + (d_{3,0} + d_{4,0})x + d_{3,0}d_{4,0})$$

$$-\sigma\xi\mu_{2,0}(x + Q_{0,0} + d_{0,0})(Q_{3,0}x + Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$-\big[\mu_{1,0}(x^2 + (Q_{0,0} + d_{0,0} + d_{2,0})x + d_{2,0}(Q_{0,0} + d_{0,0}))$$

$$\cdot (Q_{3,0}x + Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})\big]$$

$$+ \big[Q_{1,0}(Q_{0,0} + p_0\lambda(t))$$

$$\cdot (x^3 + (d_{2,0} + d_{3,0} + d_{4,0})x^2 + (d_{2,0}d_{3,0} + d_{2,0}d_{4,0} + d_{3,0}d_{4,0})x + d_{2,0}d_{3,0}d_{4,0})\big]$$

$$+ \sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))(x^2 + (d_{3,0} + d_{4,0})x + d_{3,0}d_{4,0})$$

$$+ \sigma\xi\mu_{2,0}(Q_{0,0} + p_0\lambda(t))(Q_{3,0}x + Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$+ \mu_{1,0}(Q_{0,0} + p_0\lambda(t))(x + d_{2,0})(Q_{3,0}x + Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$= \Big[x^5 + (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0} + d_{2,0} + d_{3,0} + d_{4,0})x^4$$

$$+ \big[d_{2,0}d_{3,0} + d_{2,0}d_{4,0} + d_{3,0}d_{4,0} + (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})(d_{2,0} + d_{3,0} + d_{4,0})$$

$$- (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})\big]x^3$$

$$+ \big[d_{2,0}d_{3,0}d_{4,0} + (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})(d_{2,0}d_{3,0} + d_{2,0}d_{4,0} + d_{3,0}d_{4,0})$$

$$- (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})(d_{2,0} + d_{3,0} + d_{4,0})\big]x^2$$

$$+ \big[d_{2,0}d_{3,0}d_{4,0}(Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})$$

$$- (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})(d_{2,0}d_{3,0} + d_{2,0}d_{4,0} + d_{3,0}d_{4,0})\big]x$$

$$- d_{2,0}d_{3,0}d_{4,0}(Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})\Big]$$

$$- \Big[\sigma\xi Q_{2,0}\big(x^3 + (Q_{0,0} + d_{0,0} + d_{3,0} + d_{4,0})x^2 + (d_{3,0}d_{4,0} + (d_{3,0} + d_{4,0})(Q_{0,0} + d_{0,0}))x$$

$$+ d_{3,0}d_{4,0}(Q_{0,0} + d_{0,0}))\Big]$$

$$- \Big[\sigma\xi\mu_{2,0}\big(Q_{3,0}x^2 + (Q_{3,0}(Q_{0,0} + d_{0,0} + d_{4,0}) + Q_{4,0}\mu_{3,0})x$$

$$+ (Q_{0,0} + d_{0,0})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0}))\Big]$$

$$- \Big[\mu_{1,0}\big(Q_{3,0}x^3 + (Q_{3,0}(Q_{0,0} + d_{0,0} + d_{2,0} + d_{4,0}) + Q_{4,0}\mu_{3,0})x^2$$

$$+ ((Q_{0,0} + d_{0,0} + d_{2,0})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0}) + d_{2,0}Q_{3,0}(Q_{0,0} + d_{0,0}))x$$

$$+ d_{2,0}(Q_{0,0} + d_{0,0})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0}))\Big]$$

$$+ \Big[Q_{1,0}(Q_{0,0} + p_0\lambda(t))$$

$$\cdot (x^3 + (d_{2,0} + d_{3,0} + d_{4,0})x^2 + (d_{2,0}d_{3,0} + d_{2,0}d_{4,0} + d_{3,0}d_{4,0})x + d_{2,0}d_{3,0}d_{4,0})\Big]$$

$$+ \sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))(x^2 + (d_{3,0} + d_{4,0})x + d_{3,0}d_{4,0})$$

$$+ \sigma\xi\mu_{2,0}(Q_{0,0} + p_0\lambda(t))(Q_{3,0}x + Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$+ \Big[\mu_{1,0}(Q_{0,0} + p_0\lambda(t))\big(Q_{3,0}x^2 + (Q_{3,0}(d_{2,0} + d_{4,0}) + Q_{4,0}\mu_{3,0})x$$

$$+ d_{2,0}(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0}))\Big]$$

$$= x^5 + (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0} + d_{2,0} + d_{3,0} + d_{4,0})x^4$$

$$+ \Big[d_{2,0}d_{3,0} + d_{2,0}d_{4,0} + d_{3,0}d_{4,0} + (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})(d_{2,0} + d_{3,0} + d_{4,0})$$

$$- (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0}) - \sigma\xi Q_{2,0} - \mu_{1,0}Q_{3,0} + Q_{1,0}(Q_{0,0} + p_0\lambda(t))\Big]x^3$$

$$+ \left[d_{2,0}d_{3,0}d_{4,0} - (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})(d_{2,0}d_{3,0} + d_{2,0}d_{4,0} + d_{3,0}d_{4,0}) \right.$$

$$- (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})(d_{2,0} + d_{3,0} + d_{4,0}) - \sigma\xi Q_{2,0}(Q_{0,0} + d_{0,0} + d_{3,0} + d_{4,0})$$

$$- \sigma\xi\mu_{2,0}Q_{3,0} - \mu_{1,0}(Q_{3,0}(Q_{0,0} + d_{0,0} + d_{2,0} + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$+ Q_{1,0}(Q_{0,0} + p_0\lambda(t))(d_{2,0} + d_{3,0} + d_{4,0}) + \sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))$$

$$\left. + \mu_{1,0}Q_{3,0}(Q_{0,0} + p_0\lambda(t)) \right] x^2$$

$$+ \left[d_{2,0}d_{3,0}d_{4,0}(Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0}) \right.$$

$$- (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})(d_{2,0}d_{3,0} + d_{2,0}d_{4,0} + d_{3,0}d_{4,0})$$

$$- \sigma\xi Q_{2,0}(d_{3,0}d_{4,0} + (d_{3,0} + d_{4,0})(Q_{0,0} + d_{0,0}))$$

$$- \sigma\xi\mu_{2,0}(Q_{3,0}(Q_{0,0} + d_{0,0} + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$- \mu_{1,0}((Q_{0,0} + d_{0,0} + d_{2,0})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0}) + d_{2,0}Q_{3,0}(Q_{0,0} + d_{0,0}))$$

$$+ Q_{1,0}(Q_{0,0} + p_0\lambda(t))(d_{2,0}d_{3,0} + d_{2,0}d_{4,0} + d_{3,0}d_{4,0})$$

$$+ \sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))(d_{3,0} + d_{4,0})$$

$$+ \sigma\xi\mu_{2,0}Q_{3,0}(Q_{0,0} + p_0\lambda(t))$$

$$\left. + \mu_{1,0}(Q_{0,0} + p_0\lambda(t))(Q_{3,0}(d_{2,0} + d_{4,0}) + Q_{4,0}\mu_{3,0}) \right] x$$

$$- \left[d_{2,0}d_{3,0}d_{4,0}(Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0}) + \sigma\xi Q_{2,0}d_{3,0}d_{4,0}(Q_{0,0} + d_{0,0}) \right.$$

$$+ \sigma\xi\mu_{2,0}(Q_{0,0} + d_{0,0})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$+ \mu_{1,0}d_{2,0}(Q_{0,0} + d_{0,0})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$- d_{2,0}d_{3,0}d_{4,0}Q_{1,0}(Q_{0,0} + p_0\lambda(t)) - \sigma\xi d_{3,0}d_{4,0}Q_{2,0}(Q_{0,0} + p_0\lambda(t))$$

$$- \sigma\xi\mu_{2,0}(Q_{0,0} + p_0\lambda(t))(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$\left. - \mu_{1,0}d_{2,0}(Q_{0,0} + p_0\lambda(t))(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0}) \right]$$

Therefore, the characteristic polynomial $c(x) = c_0 x^5 + c_1 x^4 + c_2 x^3 + c_3 x^2 + c_4 x + c_5$ for the system without an intervention is defined with the following coefficients.

$c_0 = 1$

$c_1 = Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0} + d_{2,0} + d_{3,0} + d_{4,0}$

$c_2 = d_{2,0} d_{3,0} + d_{2,0} d_{4,0} + d_{3,0} d_{4,0} + (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})(d_{2,0} + d_{3,0} + d_{4,0})$

$\qquad - (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0}) - \sigma\xi Q_{2,0} - \mu_{1,0} Q_{3,0} + Q_{1,0}(Q_{0,0} + p_0\lambda(t))$

$c_3 = d_{2,0} d_{3,0} d_{4,0} - (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})(d_{2,0} d_{3,0} + d_{2,0} d_{4,0} + d_{3,0} d_{4,0})$

$\qquad - (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})(d_{2,0} + d_{3,0} + d_{4,0}) - \sigma\xi Q_{2,0}(Q_{0,0} + d_{0,0} + d_{3,0} + d_{4,0})$

$\qquad - \sigma\xi \mu_{2,0} Q_{3,0} - \mu_{1,0}(Q_{3,0}(Q_{0,0} + d_{0,0} + d_{2,0} + d_{4,0}) + Q_{4,0}\mu_{3,0})$

$\qquad + Q_{1,0}(Q_{0,0} + p_0\lambda(t))(d_{2,0} + d_{3,0} + d_{4,0}) + \sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))$

$\qquad + \mu_{1,0} Q_{3,0}(Q_{0,0} + p_0\lambda(t))$

$c_4 = d_{2,0} d_{3,0} d_{4,0}(Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})$

$\qquad - (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})(d_{2,0} d_{3,0} + d_{2,0} d_{4,0} + d_{3,0} d_{4,0})$

$\qquad - \sigma\xi Q_{2,0}(d_{3,0} d_{4,0} + (d_{3,0} + d_{4,0})(Q_{0,0} + d_{0,0}))$

$\qquad - \sigma\xi \mu_{2,0}(Q_{3,0}(Q_{0,0} + d_{0,0} + d_{4,0}) + Q_{4,0}\mu_{3,0})$

$\qquad - \mu_{1,0}((Q_{0,0} + d_{0,0} + d_{2,0})(Q_{3,0} d_{4,0} + Q_{4,0}\mu_{3,0}) + d_{2,0} Q_{3,0}(Q_{0,0} + d_{0,0}))$

$\qquad + Q_{1,0}(Q_{0,0} + p_0\lambda(t))(d_{2,0} d_{3,0} + d_{2,0} d_{4,0} + d_{3,0} d_{4,0})$

$\qquad + \sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))(d_{3,0} + d_{4,0})$

$\qquad + \sigma\xi \mu_{2,0} Q_{3,0}(Q_{0,0} + p_0\lambda(t)) + \mu_{1,0}(Q_{0,0} + p_0\lambda(t))(Q_{3,0}(d_{2,0} + d_{4,0}) + Q_{4,0}\mu_{3,0})$

$c_5 = d_{2,0} d_{3,0} d_{4,0}(Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0}) + \sigma\xi Q_{2,0} d_{3,0} d_{4,0}(Q_{0,0} + d_{0,0})$

$\qquad + \sigma\xi \mu_{2,0}(Q_{0,0} + d_{0,0})(Q_{3,0} d_{4,0} + Q_{4,0}\mu_{3,0}) + \mu_{1,0} d_{2,0}(Q_{0,0} + d_{0,0})(Q_{3,0} d_{4,0} + Q_{4,0}\mu_{3,0})$

$\qquad - d_{2,0} d_{3,0} d_{4,0} Q_{1,0}(Q_{0,0} + p_0\lambda(t)) - \sigma\xi d_{3,0} d_{4,0} Q_{2,0}(Q_{0,0} + p_0\lambda(t))$

$\qquad - \sigma\xi \mu_{2,0}(Q_{0,0} + p_0\lambda(t))(Q_{3,0} d_{4,0} + Q_{4,0}\mu_{3,0})$

$\qquad - \mu_{1,0} d_{2,0}(Q_{0,0} + p_0\lambda(t))(Q_{3,0} d_{4,0} + Q_{4,0}\mu_{3,0})$

A.2 Therapeutic Vaccine Program

For the model with only the therapeutic vaccine we have following system of ordinary differential equations

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\mu + p_0\lambda(t))Y_{0,0}(t)$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0\lambda(t)Y_{0,0}(t) - (\sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t)$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi Y_{1,0}(t) - (\nu_t + \mu_{2,0} + \mu)Y_{2,0}(t)$$

$$\frac{dY_{2,1}(t)}{dt} = \nu_t Y_{2,0}(t) - (\mu_{2,1} + \mu)Y_{2,1}(t)$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{i=1}^{i=2}\sum_{j=0}^{j=1}\mu_{i,j}Y_{i,j}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t)$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t)$$

were $\lambda(t) = \dfrac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,j}(t)}$, along with the initial state

A.2.1 The Jacobian Matrix

$$
\begin{bmatrix}
-Q_{0,0} - (\mu + p_0\lambda(t)) & -Q_{1,0} & -Q_{2,0} & -Q_{2,1} & -Q_{3,0} & -Q_{4,0} \\
Q_{0,0} + p_0\lambda(t) & Q_{1,0} - (\sigma\xi + \mu_{1,0} + \mu) & Q_{2,0} & Q_{2,1} & Q_{3,0} & Q_{4,0} \\
0 & \sigma\xi & -(\nu_t + \mu_{2,0} + \mu) & 0 & 0 & 0 \\
0 & 0 & \nu_t & -(\mu_{2,1} + \mu) & 0 & 0 \\
0 & \mu_{1,0} & \mu_{2,0} & \mu_{2,1} & -(\mu_{3,0} + \mu) & 0 \\
0 & 0 & 0 & 0 & \mu_{3,0} & -(\mu_{4,0} + \mu)
\end{bmatrix}
$$

A.2.2 Characteristic Polynomial

We note the additional notation will also help in reducing the calculation by introducing a single term for the combined rate at which a population leaves each compartment of the model.

$$d_{0,0} := \mu + p_0\lambda(t)$$

$$d_{1,0} := \sigma\xi + \mu_{1,0} + \mu$$

$$d_{2,0} := \nu_t + \mu_{2,0} + \mu$$

$$d_{2,1} := \mu_{2,1} + \mu$$

$$d_{3,0} := \mu_{3,0} + \mu$$

$$d_{4,0} := \mu_{4,0} + \mu$$

Thus, the calculations for deriving the characteristic polynomial are given as the following. and something else to find the line width

$$c(x) = \det\left(xI - J^{\mathsf{T}}\right)$$

$$= \begin{vmatrix} x + Q_{0,0} + d_{0,0} & -Q_{0,0} - p_0\lambda(t) & 0 & 0 & 0 & 0 \\ Q_{1,0} & x - Q_{1,0} + d_{1,0} & -\sigma\xi & 0 & -\mu_{1,0} & 0 \\ Q_{2,0} & -Q_{2,0} & x + d_{2,0} & -\nu_t & -\mu_{2,0} & 0 \\ Q_{2,1} & -Q_{2,1} & 0 & x + d_{2,1} & -\mu_{2,1} & 0 \\ Q_{3,0} & -Q_{3,0} & 0 & 0 & x + d_{3,0} & -\mu_{3,0} \\ Q_{4,0} & -Q_{4,0} & 0 & 0 & 0 & x + d_{4,0} \end{vmatrix}$$

$$= (x + Q_{0,0} + d_{0,0}) \begin{vmatrix} x - Q_{1,0} + d_{1,0} & -\sigma\xi & 0 & -\mu_{1,0} & 0 \\ -Q_{2,0} & x + d_{2,0} & -\nu_t & -\mu_{2,0} & 0 \\ -Q_{2,1} & 0 & x + d_{2,1} & -\mu_{2,1} & 0 \\ -Q_{3,0} & 0 & 0 & x + d_{3,0} & -\mu_{3,0} \\ -Q_{4,0} & 0 & 0 & 0 & x + d_{4,0} \end{vmatrix}$$

$$+ (Q_{0,0} + p_0\lambda(t)) \begin{vmatrix} Q_{1,0} & -\sigma\xi & 0 & -\mu_{1,0} & 0 \\ Q_{2,0} & x + d_{2,0} & -\nu_t & -\mu_{2,0} & 0 \\ Q_{2,1} & 0 & x + d_{2,1} & -\mu_{2,1} & 0 \\ Q_{3,0} & 0 & 0 & x + d_{3,0} & -\mu_{3,0} \\ Q_{4,0} & 0 & 0 & 0 & x + d_{4,0} \end{vmatrix}$$

$$= (x + Q_{0,0} + d_{0,0})(x - Q_{1,0} + d_{1,0}) \begin{vmatrix} x + d_{2,0} & -\nu_t & -\mu_{2,0} & 0 \\ 0 & x + d_{2,1} & -\mu_{2,1} & 0 \\ 0 & 0 & x + d_{3,0} & -\mu_{3,0} \\ 0 & 0 & 0 & x + d_{4,0} \end{vmatrix}$$

$$+ (x + Q_{0,0} + d_{0,0})(\sigma\xi) \begin{vmatrix} -Q_{2,0} & -\nu_t & -\mu_{2,0} & 0 \\ -Q_{2,1} & x + d_{2,1} & -\mu_{2,1} & 0 \\ -Q_{3,0} & 0 & x + d_{3,0} & -\mu_{3,0} \\ -Q_{4,0} & 0 & 0 & x + d_{4,0} \end{vmatrix}$$

$$+ (x + Q_{0,0} + d_{0,0})(\mu_{1,0}) \begin{vmatrix} -Q_{2,0} & x + d_{2,0} & -\nu_t & 0 \\ -Q_{2,1} & 0 & x + d_{2,1} & 0 \\ -Q_{3,0} & 0 & 0 & -\mu_{3,0} \\ -Q_{4,0} & 0 & 0 & x + d_{4,0} \end{vmatrix}$$

$$+ (Q_{0,0} + p_0\lambda(t))(Q_{1,0}) \begin{vmatrix} x + d_{2,0} & -\nu_t & -\mu_{2,0} & 0 \\ 0 & x + d_{2,1} & -\mu_{2,1} & 0 \\ 0 & 0 & x + d_{3,0} & -\mu_{3,0} \\ 0 & 0 & 0 & x + d_{4,0} \end{vmatrix}$$

$$+ (Q_{0,0} + p_0\lambda(t))(\sigma\xi) \begin{vmatrix} Q_{2,0} & \nu_t & -\mu_{2,0} & 0 \\ Q_{2,1} & x + d_{2,1} & -\mu_{2,1} & 0 \\ Q_{3,0} & 0 & x + d_{3,0} & -\mu_{3,0} \\ Q_{4,0} & 0 & 0 & x + d_{4,0} \end{vmatrix}$$

$$+ (Q_{0,0} + p_0\lambda(t))(\mu_{1,0}) \begin{vmatrix} Q_{2,0} & x + d_{2,0} & -\nu_t & 0 \\ Q_{2,1} & 0 & x + d_{2,1} & 0 \\ Q_{3,0} & 0 & 0 & -\mu_{3,0} \\ Q_{4,0} & 0 & 0 & x + d_{4,0} \end{vmatrix}$$

$$= (x + Q_{0,0} + d_{0,0})(x - Q_{1,0} + d_{1,0})(x + d_{2,0})(x + d_{2,1})(x + d_{3,0})(x + d_{4,0})$$

$$- (x + Q_{0,0} + d_{0,0})(\sigma\xi)(Q_{2,0})(x + d_{2,1})(x + d_{3,0})(x + d_{4,0})$$

$$+ (x + Q_{0,0} + d_{0,0})(\sigma\xi)(\nu_t) \begin{vmatrix} -Q_{2,1} & \mu_{2,1} & 0 \\ -Q_{3,0} & x + d_{3,0} & -\mu_{3,0} \\ -Q_{4,0} & 0 & x + d_{4,0} \end{vmatrix}$$

$$- (x + Q_{0,0} + d_{0,0})(\sigma\xi)(\mu_{2,0}) \begin{vmatrix} -Q_{2,1} & x + d_{2,1} & 0 \\ -Q_{3,0} & 0 & -\mu_{3,0} \\ -Q_{4,0} & 0 & x + d_{4,0} \end{vmatrix}$$

$$- (x + Q_{0,0} + d_{0,0})(\mu_{1,0})(x + d_{2,0}) \begin{vmatrix} -Q_{2,1} & x + d_{2,1} & 0 \\ -Q_{3,0} & 0 & -\mu_{3,0} \\ -Q_{4,0} & 0 & x + d_{4,0} \end{vmatrix}$$

$$+ (Q_{0,0} + p_0\lambda(t))(Q_{1,0})(x + d_{2,0})(x + d_{2,1})(x + d_{3,0})(x + d_{4,0})$$

$$+ (Q_{0,0} + p_0\lambda(t))(\sigma\xi)(Q_{2,0}) \begin{vmatrix} x + d_{2,1} & -\mu_{2,1} & 0 \\ 0 & x + d_{3,0} & -\mu_{3,0} \\ 0 & 0 & x + d_{4,0} \end{vmatrix}$$

$$+ (Q_{0,0} + p_0\lambda(t))(\sigma\xi)(\nu_t) \begin{vmatrix} Q_{2,1} & -\mu_{2,1} & 0 \\ Q_{3,0} & x + d_{3,0} & -\mu_{3,0} \\ Q_{4,0} & 0 & x + d_{4,0} \end{vmatrix}$$

$$- (Q_{0,0} + p_0\lambda(t))(\mu_{1,0})(x + d_{2,0}) \begin{vmatrix} Q_{2,1} & x + d_{2,1} & 0 \\ Q_{3,0} & 0 & -\mu_{3,0} \\ Q_{4,0} & 0 & x + d_{4,0} \end{vmatrix}$$

$$= (x + Q_{0,0} + d_{0,0})(x - Q_{1,0} + d_{1,0})(x + d_{2,0})(x + d_{2,1})(x + d_{3,0})(x + d_{4,0})$$

$$- (x + Q_{0,0} + d_{0,0})(\sigma\xi)(Q_{2,0})(x + d_{2,1})(x + d_{3,0})(x + d_{4,0})$$

$$- (x + Q_{0,0} + d_{0,0})(\sigma\xi)(\nu_t)(Q_{2,1})(x + d_{3,0})(x + d_{4,0})$$

$$+ (x + Q_{0,0} + d_{0,0})(\sigma\xi)(\nu_t)(\mu_{2,1})(Q_{3,0}(x + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$- (x + Q_{0,0} + d_{0,0})(\sigma\xi)(\mu_{2,0})(x + d_{2,1})(Q_{3,0}(x + d_{4,0}) + Q_{4,0}\mu_{4,0})$$

$$- (x + Q_{0,0} + d_{0,0})(\mu_{1,0})(x + d_{2,0})(x + d_{2,1})(Q_{3,0}(x + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$+ (Q_{0,0} + p_0\lambda(t))(Q_{1,0})(x + d_{2,0})(x + d_{2,1})(x + d_{3,0})(x + d_{4,0})$$

$$+ (Q_{0,0} + p_0\lambda(t))(\sigma\xi)(Q_{2,0})(x + d_{2,1})(x + d_{3,0})(x + d_{4,0})$$

$$+ (Q_{0,0} + p_0\lambda(t))(\sigma\xi)(\nu_t)(Q_{2,1})(x + d_{3,0})(x + d_{4,0})$$

$$+ (Q_{0,0} + p_0\lambda(t))(\sigma\xi)(\nu_t)(\mu_{2,1})(Q_{3,0}(x + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$+ (Q_{0,0} + p_0\lambda(t))(\mu_{1,0})(x + d_{2,0})(x + d_{2,1})(Q_{3,0}(x + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$= \left[(x^2 + (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})x - (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0}))\right.$$

$$\left. \cdot (x^2 + (d_{2,0} + d_{2,1})x + d_{2,0}d_{2,1})(x^2 + (d_{3,0} + d_{4,0})x + d_{3,0}d_{4,0})\right]$$

$$- \left[\sigma\xi Q_{2,0}(x^2 + (Q_{0,0} + d_{0,0} + d_{2,1})x + d_{2,1}(Q_{0,0} + d_{0,0}))\right.$$

$$\left. \cdot (x^2 + (d_{3,0} + d_{4,0})x + d_{3,0}d_{4,0})\right]$$

$$- \sigma\xi\nu_t Q_{2,1}(x + Q_{0,0} + d_{0,0})(x^2 + (d_{3,0} + d_{4,0})x + d_{3,0}d_{4,0})$$

$$+ \left[\sigma\xi\nu_t\mu_{2,1}(Q_{3,0}x^2 + (Q_{3,0}(Q_{0,0} + d_{0,0} + d_{4,0}) + Q_{4,0}\mu_{3,0})x\right.$$

$$\left. + (Q_{0,0} + d_{0,0})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})\right]$$

$$- \big[\sigma\xi\mu_{2,0}(x^2 + (Q_{0,0} + d_{0,0} + d_{2,1})x + d_{2,1}(Q_{0,0} + d_{0,0}))$$

$$\cdot (Q_{3,0}x + Q_{3,0}d_{4,0} + Q_{4,0}\mu_{4,0})\big]$$

$$- \big[\mu_{1,0}(x^2 + (Q_{0,0} + d_{0,0} + d_{2,0})x + d_{2,0}(Q_{0,0} + d_{0,0}))$$

$$\cdot (Q_{3,0}x^2 + (Q_{3,0}(d_{2,1} + d_{4,0}) + Q_{4,0}\mu_{3,0})x + d_{2,1}(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0}))\big]$$

$$+ Q_{1,0}(Q_{0,0} + p_0\lambda(t))(x^2 + (d_{2,0} + d_{2,1})x + d_{2,0}d_{2,1})(x^2 + (d_{3,0} + d_{4,0})x + d_{3,0}d_{4,0})$$

$$+ \big[\sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))(x^3 + (d_{2,1} + d_{3,0} + d_{4,0})x^2$$

$$+ (d_{2,1}d_{3,0} + d_{2,1}d_{4,0} + d_{3,0}d_{4,0})x + d_{2,1}d_{3,0}d_{4,0})\big]$$

$$+ \sigma\xi\nu_t Q_{2,1}(Q_{0,0} + p_0\lambda(t))(x^2 + (d_{3,0} + d_{4,0})x + d_{3,0}d_{4,0})$$

$$+ \sigma\xi\nu_t\mu_{2,1}(Q_{0,0} + p_0\lambda(t))(Q_{3,0}x + Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$+ \big[\mu_{1,0}(Q_{0,0} + p_0\lambda(t))(x^2 + (d_{2,0} + d_{2,1})x + d_{2,0}d_{2,1})$$

$$\cdot (Q_{3,0}x + Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})\big]$$

$$= \big[x^6 + (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0} + d_{2,0} + d_{2,1} + d_{3,0} + d_{4,0})x^5$$

$$+ \big[d_{2,0}d_{2,1} + d_{3,0}d_{4,0} + (d_{2,0} + d_{2,1})(d_{3,0} + d_{4,0})$$

$$+ (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})(d_{2,0} + d_{2,1} + d_{3,0} + d_{4,0})$$

$$- (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})\big]x^4$$

$$+ \big[d_{2,0}d_{2,1}(d_{3,0} + d_{4,0}) + d_{3,0}d_{4,0}(d_{2,0} + d_{2,1})$$

$$+ (Q_{0,0} - Q_{1.0} + d_{0,0} + d_{1,0})(d_{2,0}d_{2,1} + d_{3,0}d_{4,0} + (d_{2,0} + d_{2,1})(d_{3,0} + d_{4,0}))$$

$$- (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})(d_{2,0} + d_{2,1} + d_{3,0} + d_{4,0})\big]x^3$$

$$- \big[(Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})(d_{2,0}d_{2,1} + d_{3,0}d_{4,0} + (d_{2,0} + d_{2,1})(d_{3,0} + d_{4,0}))$$

$$- (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})(d_{2,0}d_{2,1}(d_{3,0} + d_{4,0}) + d_{3,0}d_{4,0}(d_{2,0} + d_{2,1}))$$

$$- d_{2,0}d_{2,1}d_{3,0}d_{4,0}\big]x^2$$

$$+ \big[d_{2,0}d_{2,1}d_{3,0}d_{4,0}(Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})$$

$$- (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})$$

$$\cdot (d_{2,0}d_{2,1}(d_{3,0} + d_{4,0}) + d_{3,0}d_{4,0}(d_{2,0} + d_{2,1}))\big]x$$

$$- d_{2,0}d_{2,1}d_{3,0}d_{4,0}(Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})\big]$$

$$- \big[\sigma\xi\nu_t Q_{2,1}(x^3 + (Q_{0,0} + d_{0,0} + d_{3,0} + d_{4,0})x^2$$

$$+ (d_{3,0}d_{4,0} + (Q_{0,0} + d_{0,0})(d_{3,0} + d_{4,0}))x + d_{3,0}d_{4,0}(Q_{0,0} + d_{0,0}))\big]$$

$$+ \big[\sigma\xi\nu_t\mu_{2,1}(Q_{3,0}x^2 + (Q_{3,0}(Q_{0,0} + d_{0,0} + d_{4,0}) + Q_{4,0}\mu_{3,0})x$$

$$+ (Q_{0,0} + d_{0,0})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})\big]$$

$$- \big[\sigma\xi Q_{2,0}\big(x^4 + (Q_{0,0} + d_{0,0} + d_{2,1} + d_{3,0} + d_{4,0})x^3$$

$$+ (d_{2,1}(Q_{0,0} + d_{0,0}) + d_{3,0}d_{4,0} + (Q_{0,0} + d_{0,0} + d_{2,1})(d_{3,0} + d_{4,0}))x^2$$

$$+ (d_{2,1}(Q_{0,0} + d_{0,0})(d_{3,0} + d_{4,0}) + d_{3,0}d_{4,0}(Q_{0,0} + d_{0,0} + d_{2,1}))x$$

$$+ d_{2,1}d_{3,0}d_{4,0}(Q_{0,0} + d_{0,0})\big)\big]$$

$$- \big[\sigma\xi\mu_{2,0}\big(Q_{3,0}x^3 + (Q_{3,0}(Q_{0,0} + d_{0,0} + d_{2,1} + d_{4,0}) + Q_{4,0}\mu_{3,0})x^2$$

$$+ ((Q_{0,0} + d_{0,0} + d_{2,1})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0}) + d_{2,1}Q_{3,0}(Q_{0,0} + d_{0,0}))x$$

$$+ d_{2,1}(Q_{3,0}d_{3,0} + Q_{4,0}\mu_{3,0})(Q_{0,0} + d_{0,0})\big)\big]$$

$$- \Big[\mu_{1,0} \big(Q_{3,0} x^4 + (Q_{3,0}(Q_{0,0} + d_{0,0} + d_{2,0} + d_{2,1} + d_{4,0}) + Q_{4,0}\mu_{3,0}) x^3$$

$$+ \big[(d_{2,0} Q_{3,0}(Q_{0,0} + d_{0,0}) + d_{2,1}(Q_{3,0} d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$+ (Q_{0,0} + d_{0,0} + d_{2,0})(Q_{3,0}(d_{2,1} + d_{4,0}) + Q_{4,0}\mu_{3,0})) \big] x^2$$

$$+ (d_{2,1}(Q_{0,0} + d_{0,0} + d_{2,0})(Q_{3,0} d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$+ d_{2,0}(Q_{0,0} + d_{0,0})(Q_{3,0}(d_{2,1} + d_{4,0}) + Q_{4,0}\mu_{3,0})) x$$

$$+ d_{2,0} d_{2,1}(Q_{0,0} + d_{0,0})(Q_{3,0} d_{4,0} + Q_{4,0}\mu_{3,0})) \Big]$$

$$+ \Big[Q_{1,0}(Q_{0,0} + p_0\lambda(t))\big(x^4 + (d_{2,0} + d_{2,1} + d_{3,0} + d_{4,0}) x^3$$

$$+ (d_{2,0} d_{2,1} + d_{3,0} d_{4,0} + (d_{2,0} + d_{2,1})(d_{3,0} + d_{4,0})) x^2$$

$$+ (d_{2,0} d_{2,1}(d_{3,0} + d_{4,0}) + d_{3,0} d_{4,0}(d_{2,0} + d_{2,1})) x$$

$$+ d_{2,0} d_{2,1} d_{3,0} d_{4,0} \big) \Big]$$

$$+ \big[\sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))(x^3 + (d_{2,1} + d_{3,0} + d_{4,0}) x^2$$

$$+ (d_{2,1} d_{3,0} + d_{2,1} d_{4,0} + d_{3,0} d_{4,0}) x + d_{2,1} d_{3,0} d_{4,0}) \big]$$

$$+ \sigma\xi\nu_t Q_{2,1}(Q_{0,0} + p_0\lambda(t))(x^2 + (d_{3,0} + d_{4,0}) x + d_{3,0} d_{4,0})$$

$$+ \sigma\xi\nu_t \mu_{2,1}(Q_{0,0} + p_0\lambda(t))(Q_{3,0} x + Q_{3,0} d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$+ \Big[\mu_{1,0}(Q_{0,0} + p_0\lambda(t))\big(Q_{3,0} x^3 + (Q_{3,0}(d_{2,0} + d_{2,1} + d_{4,0}) + Q_{4,0}\mu_{3,0}) x^2$$

$$+ (Q_{3,0} d_{2,0} d_{2,1} + (d_{2,0} + d_{2,1})(Q_{3,0} d_{4,0} + Q_{4,0}\mu_{3,0})) x$$

$$+ d_{2,0} d_{2,1}(Q_{3,0} d_{4,0} + Q_{4,0}\mu_{3,0})) \Big]$$

$$= x^6 + ((Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0} + d_{2,0} + d_{2,1} + d_{3,0} + d_{4,0}))x^5$$

$$+ \big[d_{2,0}d_{2,1} + d_{3,0}d_{4,0} + (d_{2,0} + d_{2,1})(d_{3,0} + d_{4,0})$$

$$+ (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})(d_{2,0} + d_{2,1} + d_{3,0} + d_{4,0})$$

$$- (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0}) - \sigma\xi Q_{2,0} - \mu_{1,0}Q_{3,0} + Q_{1,0}(Q_{0,0} + p_0\lambda(t)) \big] x^4$$

$$+ \big[d_{2,0}d_{2,1}(d_{3,0} + d_{4,0}) + d_{3,0}d_{4,0}(d_{2,0} + d_{2,1})$$

$$+ (Q_{0,0} - Q_{1.0} + d_{0,0} + d_{1,0})(d_{2,0}d_{2,1} + d_{3,0}d_{4,0} + (d_{2,0} + d_{2,1})(d_{3,0} + d_{4,0}))$$

$$- (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})(d_{2,0} + d_{2,1} + d_{3,0} + d_{4,0}) - \sigma\xi\nu_t Q_{2,1}$$

$$- \sigma\xi Q_{2,0}(Q_{0,0} + d_{0,0} + d_{2,1} + d_{3,0} + d_{4,0}) - \sigma\xi\mu_{2,0}Q_{3,0}$$

$$+ \mu_{1,0}(Q_{3,0}(Q_{0,0} + d_{0,0} + d_{2,0} + d_{2,1} + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$+ Q_{1,0}(Q_{0,0} + p_0\lambda(t))(d_{2,0} + d_{2,1} + d_{3,0} + d_{4,0}) + \sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))$$

$$+ \mu_{1,0}Q_{3,0}(Q_{0,0} + p_0\lambda(t)) \big] x^3$$

$$+ \big[(Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})(d_{2,0}d_{2,1} + d_{3,0}d_{4,0} + (d_{2,0} + d_{2,1})(d_{3,0} + d_{4,0}))$$

$$- (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})(d_{2,0}d_{2,1}(d_{3,0} + d_{4,0}) + d_{3,0}d_{4,0}(d_{2,0} + d_{2,1}))$$

$$- d_{2,0}d_{2,1}d_{3,0}d_{4,0} - \sigma\xi\nu_t Q_{2,1}(Q_{0,0} + d_{0,0} + d_{3,0} + d_{4,0}) + \sigma\xi\nu_t\mu_{2,1}Q_{3,0}$$

$$d_{2,1}(Q_{0,0} + d_{0,0}) + d_{3,0}d_{4,0} + (Q_{0,0} + d_{0,0} + d_{2,1})(d_{3,0} + d_{4,0})$$

$$- \sigma\xi\mu_{2,0}(Q_{3,0}(Q_{0,0} + d_{0,0} + d_{2,1} + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$- \mu_{1,0}\big(d_{2,0}Q_{3,0}(Q_{0,0} + d_{0,0}) + d_{2,1}(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$+ (Q_{0,0} + d_{0,0} + d_{2,0})(Q_{3,0}(d_{2,1} + d_{4,0}) + Q_{4,0}\mu_{3,0}) \big)$$

$$+ Q_{1,0}(Q_{0,0} + p_0\lambda(t))(d_{2,0}d_{2,1} + d_{3,0}d_{4,0} + (d_{2,0} + d_{2,1})(d_{3,0} + d_{4,0}))$$

$$+ \sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))(d_{2,1} + d_{3,0} + d_{4,0}) + \sigma\xi\nu_t Q_{2,1}(Q_{0,0} + p_0\lambda(t))$$

$$+ \mu_{1,0}(Q_{0,0} + p_0\lambda(t))(Q_{3,0}(d_{2,0} + d_{2,1} + d_{4,0}) + Q_{4,0}\mu_{3,0})\big]x^2$$

$$+ \big[d_{2,0}d_{2,1}d_{3,0}d_{4,0}(Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})$$

$$- (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})(d_{2,0}d_{2,1}(d_{3,0} + d_{4,0}) + d_{3,0}d_{4,0}(d_{2,0} + d_{2,1}))$$

$$- \sigma\xi\nu_t Q_{2,1}(d_{3,0}d_{4,0} + (Q_{0,0} + d_{0,0})(d_{3,0} + d_{4,0}))$$

$$+ \sigma\xi\nu_t\mu_{2,1}(Q_{3,0}(Q_{0,0} + d_{0,0} + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$- \sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))(d_{2,1}d_{3,0} + d_{2,1}d_{4,0} + d_{3,0}d_{4,0})$$

$$- \sigma\xi\mu_{2,0}((Q_{0,0} + d_{0,0} + d_{2,1})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0}) + d_{2,1}Q_{3,0}(Q_{0,0} + d_{0,0}))$$

$$- \mu_{1,0}(d_{2,1}(Q_{0,0} + d_{0,0} + d_{2,0})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$+ d_{2,0}(Q_{0,0} + d_{0,0})(Q_{3,0}(d_{2,1} + d_{4,0}) + Q_{4,0}\mu_{3,0}))$$

$$+ Q_{1,0}(Q_{0,0} + p_0\lambda(t))(d_{2,0}d_{2,1}(d_{3,0} + d_{4,0}) + d_{3,0}d_{4,0}(d_{2,0} + d_{2,1}))$$

$$+ \sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))(d_{2,1}d_{3,0} + d_{2,1}d_{4,0} + d_{3,0}d_{4,0})$$

$$+ \sigma\xi\nu_t Q_{2,1}(Q_{0,0} + p_0\lambda(t))(d_{3,0} + d_{4,0}) + \sigma\xi\nu_t\mu_{2,1}(Q_{0,0} + p_0\lambda(t))Q_{3,0}$$

$$+ \mu_{1,0}(Q_{0,0} + p_0\lambda(t))(Q_{3,0}d_{2,0}d_{2,1} + (d_{2,0} + d_{2,1})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0}))\big]x$$

$$+ \big[\sigma\xi\nu_t\mu_{2,1}(Q_{0,0} + d_{0,0})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$- d_{2,0}d_{2,1}d_{3,0}d_{4,0}(Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0}) - \sigma\xi\nu_t Q_{2,1}d_{3,0}d_{4,0}(Q_{0,0} + d_{0,0})$$

$$- \sigma\xi Q_{2,0}d_{2,1}d_{3,0}d_{4,0}(Q_{0,0} + d_{0,0})$$

$$- \sigma\xi\mu_{2,0}d_{2,1}(Q_{3,0}d_{3,0} + Q_{4,0}\mu_{3,0})(Q_{0,0} + d_{0,0})$$

$$- \mu_{1,0}d_{2,0}d_{2,1}(Q_{0,0} + d_{0,0})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$+ Q_{1,0}(Q_{0,0} + p_0\lambda(t))d_{2,0}d_{2,1}d_{3,0}d_{4,0} + \sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))d_{2,1}d_{3,0}d_{4,0}$$

$$+ \sigma\xi\nu_t Q_{2,1}(Q_{0,0} + p_0\lambda(t))d_{3,0}d_{4,0}$$

$$+ \sigma\xi\nu_t\mu_{2,1}(Q_{0,0} + p_0\lambda(t))(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$+ \mu_{1,0}(Q_{0,0} + p_0\lambda(t))d_{2,0}d_{2,1}(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})\big]$$

Therefore, the characteristic polynomial $c(x) = c_0 x^6 + c_1 x^5 + c_2 x^4 + c_3 x^3 + c_4 x^2 + c_5 x + c_6$ for the system without an intervention is defined with the following coefficients.

$c_0 = 1$

$c_1 = (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0} + d_{2,0} + d_{2,1} + d_{3,0} + d_{4,0})$

$c_2 = d_{2,0}d_{2,1} + d_{3,0}d_{4,0} + (d_{2,0} + d_{2,1})(d_{3,0} + d_{4,0})$

$$+ (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})(d_{2,0} + d_{2,1} + d_{3,0} + d_{4,0})$$

$$- (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0}) - \sigma\xi Q_{2,0} - \mu_{1,0}Q_{3,0} + Q_{1,0}(Q_{0,0} + p_0\lambda(t))$$

$c_3 = d_{2,0}d_{2,1}(d_{3,0} + d_{4,0}) + d_{3,0}d_{4,0}(d_{2,0} + d_{2,1})$

$$+ (Q_{0,0} - Q_{1.0} + d_{0,0} + d_{1,0})(d_{2,0}d_{2,1} + d_{3,0}d_{4,0} + (d_{2,0} + d_{2,1})(d_{3,0} + d_{4,0}))$$

$$- (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})(d_{2,0} + d_{2,1} + d_{3,0} + d_{4,0}) - \sigma\xi\nu_t Q_{2,1}$$

$$- \sigma\xi Q_{2,0}(Q_{0,0} + d_{0,0} + d_{2,1} + d_{3,0} + d_{4,0}) - \sigma\xi\mu_{2,0}Q_{3,0}$$

$$+ \mu_{1,0}(Q_{3,0}(Q_{0,0} + d_{0,0} + d_{2,0} + d_{2,1} + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$+ Q_{1,0}(Q_{0,0} + p_0\lambda(t))(d_{2,0} + d_{2,1} + d_{3,0} + d_{4,0}) + \sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))$$

$$+ \mu_{1,0}Q_{3,0}(Q_{0,0} + p_0\lambda(t))$$

$c_4 = (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})(d_{2,0}d_{2,1} + d_{3,0}d_{4,0} + (d_{2,0} + d_{2,1})(d_{3,0} + d_{4,0}))$

$$- (Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})(d_{2,0}d_{2,1}(d_{3,0} + d_{4,0}) + d_{3,0}d_{4,0}(d_{2,0} + d_{2,1}))$$

$$- d_{2,0}d_{2,1}d_{3,0}d_{4,0} - \sigma\xi\nu_t Q_{2,1}(Q_{0,0} + d_{0,0} + d_{3,0} + d_{4,0}) + \sigma\xi\nu_t\mu_{2,1}Q_{3,0}$$

$$+ d_{2,1}(Q_{0,0} + d_{0,0}) + d_{3,0}d_{4,0} + (Q_{0,0} + d_{0,0} + d_{2,1})(d_{3,0} + d_{4,0})$$

$$- \sigma\xi\mu_{2,0}(Q_{3,0}(Q_{0,0} + d_{0,0} + d_{2,1} + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$- \mu_{1,0}\big(d_{2,0}Q_{3,0}(Q_{0,0} + d_{0,0}) + d_{2,1}(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$+ (Q_{0,0} + d_{0,0} + d_{2,0})(Q_{3,0}(d_{2,1} + d_{4,0}) + Q_{4,0}\mu_{3,0})\big)$$

$$+ Q_{1,0}(Q_{0,0} + p_0\lambda(t))(d_{2,0}d_{2,1} + d_{3,0}d_{4,0} + (d_{2,0} + d_{2,1})(d_{3,0} + d_{4,0}))$$

$$+ \sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))(d_{2,1} + d_{3,0} + d_{4,0}) + \sigma\xi\nu_t Q_{2,1}(Q_{0,0} + p_0\lambda(t))$$

$$+ \mu_{1,0}(Q_{0,0} + p_0\lambda(t))(Q_{3,0}(d_{2,0} + d_{2,1} + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$c_5 = d_{2,0}d_{2,1}d_{3,0}d_{4,0}(Q_{0,0} - Q_{1,0} + d_{0,0} + d_{1,0})$$

$$- (Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0})(d_{2,0}d_{2,1}(d_{3,0} + d_{4,0}) + d_{3,0}d_{4,0}(d_{2,0} + d_{2,1}))$$

$$- \sigma\xi\nu_t Q_{2,1}(d_{3,0}d_{4,0} + (Q_{0,0} + d_{0,0})(d_{3,0} + d_{4,0}))$$

$$+ \sigma\xi\nu_t\mu_{2,1}(Q_{3,0}(Q_{0,0} + d_{0,0} + d_{4,0}) + Q_{4,0}\mu_{3,0})$$

$$- \sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))(d_{2,1}d_{3,0} + d_{2,1}d_{4,0} + d_{3,0}d_{4,0})$$

$$- \sigma\xi\mu_{2,0}((Q_{0,0} + d_{0,0} + d_{2,1})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0}) + d_{2,1}Q_{3,0}(Q_{0,0} + d_{0,0}))$$

$$- \mu_{1,0}(d_{2,1}(Q_{0,0} + d_{0,0} + d_{2,0})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$+ d_{2,0}(Q_{0,0} + d_{0,0})(Q_{3,0}(d_{2,1} + d_{4,0}) + Q_{4,0}\mu_{3,0}))$$

$$+ Q_{1,0}(Q_{0,0} + p_0\lambda(t))(d_{2,0}d_{2,1}(d_{3,0} + d_{4,0}) + d_{3,0}d_{4,0}(d_{2,0} + d_{2,1}))$$

$$+ \sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))(d_{2,1}d_{3,0} + d_{2,1}d_{4,0} + d_{3,0}d_{4,0})$$

$$+ \sigma\xi\nu_t Q_{2,1}(Q_{0,0} + p_0\lambda(t))(d_{3,0} + d_{4,0}) + \sigma\xi\nu_t\mu_{2,1}(Q_{0,0} + p_0\lambda(t))Q_{3,0}$$

$$+ \mu_{1,0}(Q_{0,0} + p_0\lambda(t))(Q_{3,0}d_{2,0}d_{2,1} + (d_{2,0} + d_{2,1})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0}))$$

$$c_6 = \sigma\xi\nu_t\mu_{2,1}(Q_{0,0} + d_{0,0})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$- d_{2,0}d_{2,1}d_{3,0}d_{4,0}(Q_{0,0} + d_{0,0})(Q_{1,0} - d_{1,0}) - \sigma\xi\nu_t Q_{2,1}d_{3,0}d_{4,0}(Q_{0,0} + d_{0,0})$$

$$- \sigma\xi Q_{2,0}d_{2,1}d_{3,0}d_{4,0}(Q_{0,0} + d_{0,0})$$

$$- \sigma\xi\mu_{2,0}d_{2,1}(Q_{3,0}d_{3,0} + Q_{4,0}\mu_{3,0})(Q_{0,0} + d_{0,0})$$

$$- \mu_{1,0}d_{2,0}d_{2,1}(Q_{0,0} + d_{0,0})(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$+ Q_{1,0}(Q_{0,0} + p_0\lambda(t))d_{2,0}d_{2,1}d_{3,0}d_{4,0} + \sigma\xi Q_{2,0}(Q_{0,0} + p_0\lambda(t))d_{2,1}d_{3,0}d_{4,0}$$

$$+ \sigma\xi\nu_t Q_{2,1}(Q_{0,0} + p_0\lambda(t))d_{3,0}d_{4,0}$$

$$+ \sigma\xi\nu_t\mu_{2,1}(Q_{0,0} + p_0\lambda(t))(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

$$+ \mu_{1,0}(Q_{0,0} + p_0\lambda(t))d_{2,0}d_{2,1}(Q_{3,0}d_{4,0} + Q_{4,0}\mu_{3,0})$$

A.3   Preventative Vaccine Program

For the model with the preventative vaccine only we have the following system of ordinary differential equations

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\nu_p + \mu + p_0\lambda(t))Y_{0,0}(t) + \omega Y_{0,1}(t)$$

$$\frac{dY_{0,1}(t)}{dt} = \nu_p Y_{0,0}(t) - (\mu + \omega + p_0(1-\varepsilon)\lambda_\nu(t))Y_{0,1}(t)$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0\lambda(t)Y_{0,0}(t) - (\nu_p + \sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) + \omega Y_{1,1}(t)$$

$$\frac{dY_{1,1}(t)}{dt} = \nu_p Y_{1,0}(t) + p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}(t) - (\omega + \sigma\xi + \mu_{1,1} + \mu)Y_{1,1}(t)$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) - (\mu_{2,0} + \mu)Y_{2,0}(t)$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{i=1}^{i=2}\sum_{j=0}^{j=1}\mu_{i,j}Y_{i,j}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t)$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t)$$

were $\lambda(t) = \dfrac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1}p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)}$ and $\lambda_\nu(t) = \dfrac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1}p_i\beta_{i,j}\eta_{01,ij}Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)}.$

We will find that the Jacobian is a non-sparse matrix which implies directly calculating the characteristic polynomial for the preventative vaccine program dynamics and the combined vaccine strategy dynamics is not as reasonable as it is for the dynamics without an intervention and the therapeutic vaccine program dynamics. Therefore, we will only present the Jacobian matrix for the preventative vaccine program dynamics.

A.3.1 The Jacobian Matrix

$$
\begin{bmatrix}
-Q_{0,0} - (\nu_p + \mu + p_0\lambda(t)) & -Q_{0,1} + \omega & -Q_{1,0} & -Q_{1,1} & -Q_{2,0} & -Q_{3,0} & -Q_{4,0} \\[2ex]
-Q_{0,0}^{\nu} + \nu_p & -Q_{0,1}^{\nu} - (\mu + \omega + p_0(1-\varepsilon)\lambda_\nu(t)) & -Q_{1,0}^{\nu} & -Q_{1,1}^{\nu} & -Q_{2,0}^{\nu} & -Q_{3,0}^{\nu} & -Q_{4,0}^{\nu} \\[2ex]
Q_{0,0} + p_0\lambda(t) & Q_{0,1} & Q_{1,0} - (\nu_p + \sigma\xi + \mu_{1,0} + \mu) & Q_{1,1} + \omega & Q_{2,0} & Q_{3,0} & Q_{4,0} \\[2ex]
Q_{0,0}^{\nu} & Q_{0,1}^{\nu} + p_0(1-\varepsilon)\lambda_\nu(t) & Q_{1,0}^{\nu} + \nu_p & Q_{1,1}^{\nu} - (\sigma\xi + \omega + \mu_{1,1} + \mu) & Q_{2,0}^{\nu} & Q_{3,0}^{\nu} & Q_{4,0}^{\nu} \\[2ex]
0 & 0 & \sigma\xi & \sigma\xi & -(\mu_{2,0} + \mu) & 0 & 0 \\[2ex]
0 & 0 & \mu_{1,0} & \mu_{1,1} & \mu_{2,0} & -(\mu_{3,0} + \mu) & 0 \\[2ex]
0 & 0 & 0 & 0 & 0 & \mu_{3,0} & -(\mu_{4,0} + \mu)
\end{bmatrix}
$$

A.4 Combined, Preventative and Therapeutic, Vaccine Strategy

For the full model with both vaccinations, the preventative and therapeutic, we have the following system of ordinary differential equations

$$\frac{dY_{0,0}(t)}{dt} = I_{0,0} - (\nu_p + \mu + p_0\lambda(t))Y_{0,0}(t) + \omega Y_{0,1}(t)$$

$$\frac{dY_{0,1}(t)}{dt} = \nu_p Y_{0,0}(t) - (\mu + \omega + p_0(1-\varepsilon)\lambda_\nu(t))Y_{0,1}(t)$$

$$\frac{dY_{1,0}(t)}{dt} = I_{1,0} + p_0\lambda(t)Y_{0,0}(t) - (\nu_p + \sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) + \omega Y_{1,1}(t)$$

$$\frac{dY_{1,1}(t)}{dt} = \nu_p Y_{1,0}(t) + p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}(t) - (\omega + \sigma\xi + \mu_{1,1} + \mu)Y_{1,1}(t)$$

$$\frac{dY_{2,0}(t)}{dt} = I_{2,0} + \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) - (\nu_t + \mu_{2,0} + \mu)Y_{2,0}(t)$$

$$\frac{dY_{2,1}(t)}{dt} = \nu_t Y_{2,0}(t) - (\mu_{2,1} + \mu)Y_{2,1}(t)$$

$$\frac{dY_{3,0}(t)}{dt} = I_{3,0} + \sum_{i=1}^{i=2}\sum_{j=0}^{j=1}\mu_{i,j}Y_{i,j}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t)$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t)$$

were $\lambda(t) = \dfrac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1}p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)}$ and $\lambda_\nu(t) = \dfrac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1}p_i\beta_{i,j}\eta_{01,ij}Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)}$.

We will find that the Jacobian is a non-sparse matrix which implies directly calculating the characteristic polynomial for the preventative vaccine program dynamics and the combined vaccine strategy dynamics is not as reasonable as it is for the dynamics without an intervention and the therapeutic vaccine program dynamics. Therefore, we will only present the Jacobian matrix for the combined vaccine strategy dynamics.

A.4.1 The Jacobian Matrix

$$
\begin{bmatrix}
-Q_{0,0} - (\nu_p + \mu + p_0\lambda(t)) & -Q_{0,1} + \omega & -Q_{1,0} & -Q_{1,1} & -Q_{2,0} & -Q_{2,1} & -Q_{3,0} & -Q_{4,0} \\[2mm]
-Q_{0,0}^{\nu} + \nu_p & -Q_{0,1}^{\nu} - (\mu + \omega + p_0(1-\varepsilon)\lambda_\nu(t)) & -Q_{1,0}^{\nu} & -Q_{1,1}^{\nu} & -Q_{2,0}^{\nu} & -Q_{2,1}^{\nu} & -Q_{3,0}^{\nu} & -Q_{4,0}^{\nu} \\[2mm]
Q_{0,0} + p_0\lambda(t) & Q_{0,1} & Q_{1,0} - (\nu_p + \sigma\xi + \mu_{1,0} + \mu) & Q_{1,1} + \omega & Q_{2,0} & Q_{2,1} & Q_{3,0} & Q_{4,0} \\[2mm]
Q_{0,0}^{\nu} & Q_{0,1}^{\nu} + p_0(1-\varepsilon)\lambda_\nu(t) & Q_{1,0}^{\nu} + \nu_p & Q_{1,1}^{\nu} - (\sigma\xi + \omega + \mu_{1,1} + \mu) & Q_{2,0}^{\nu} & Q_{2,1}^{\nu} & Q_{3,0}^{\nu} & Q_{4,0}^{\nu} \\[2mm]
0 & 0 & \sigma\xi & \sigma\xi & -(\nu_t + \mu_{2,0} + \mu) & 0 & 0 & 0 \\[2mm]
0 & 0 & 0 & 0 & \nu_t & -(\mu_{2,1} + \mu) & 0 & 0 \\[2mm]
0 & 0 & \mu_{1,0} & \mu_{1,1} & \mu_{2,0} & \mu_{2,1} & -(\mu_{3,0} + \mu) & 0 \\[2mm]
0 & 0 & 0 & 0 & 0 & 0 & \mu_{3,0} & -(\mu_{4,0} + \mu)
\end{bmatrix}
$$

Appendix B

Hurwitz Determinants

In chapter 4 the stability for each equilibrium for the four variations of the state space of the HIV-transmission model with vaccine intervention is determined using the Routh-Hurwitz Criterion for stability. Since the dimensions for the state space varies depending whether or not each vaccine program is present we need to calculate each of the Hurwitz determines for the corresponding characteristic polynomials of order 5, 6, 7 and 8.

As a quick reference to all necessary definitions from section 4.1 we present them again here as they were originally stated by Gantmakher in 1959 [?].

Definition B.0.1 (Hurwitz matrix). *Is a square matrix of order n defined by the coefficients of the polynomial $c(x) = c_0 x^n + c_1 x^{(n-1)} + \cdots + c_{n-1}x + c_n$ as the following.*

$$
H = \begin{bmatrix}
c_1 & c_3 & c_5 & \cdots & \cdots & \cdots & 0 & 0 & 0 \\
c_0 & c_2 & c_4 & & & & \vdots & \vdots & \vdots \\
0 & c_1 & c_3 & & & & \vdots & \vdots & \vdots \\
\vdots & c_0 & c_2 & \ddots & & 0 & & \vdots & \vdots \\
\vdots & 0 & c_1 & & \ddots & & c_n & \vdots & \vdots \\
\vdots & \vdots & c_0 & & & \ddots & c_{n-1} & 0 & \vdots \\
\vdots & \vdots & 0 & & & & c_{n-2} & c_n & \vdots \\
\vdots & \vdots & \vdots & & & & c_{n-3} & c_{n-1} & 0 \\
0 & 0 & 0 & \cdots & \cdots & \cdots & c_{n-4} & c_{n-2} & c_n
\end{bmatrix}
$$

For even n: $c_k = 0$ when $k > \dfrac{n}{2}$.

For odd n: $c_k = 0$ when $k > \dfrac{n-1}{2}$.

Definition B.0.2 (Hurwitz determinants). *The principle minors of the Hurwitz matrix.*

$$\Delta_1(c) = c_1, \Delta_2(c) = \begin{vmatrix} c_1 & c_3 \\ c_0 & c_2 \end{vmatrix}, \Delta_3(c) = \begin{vmatrix} c_1 & c_3 & c_5 \\ c_0 & c_2 & c_4 \\ 0 & c_1 & c_3 \end{vmatrix}, \dots, \Delta_n(c) = \det(H)$$

To simplify calculations for the Hurwitz determinants for large n we make the following proposition.

Proposition B.0.3. *Given two square matrices A and B, of order n, such that B is the off diagonal reflection of A then $\det(A) = \det(B)$.*

Proof. Let A be defined by

$$A = \begin{bmatrix} a_{11} & a_{12} & \cdots & a_{1[n-1]} & a_{1n} \\ a_{21} & a_{22} & \cdots & a_{2[n-1]} & a_{2n} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ a_{[n-1]1} & a_{[n-1]2} & \cdots & a_{[n-1][n-1]} & a_{[n-1]n} \\ a_{n1} & a_{n2} & \cdots & a_{n[n-1]} & a_{nn} \end{bmatrix}$$

then B is defined as the off diagonal reflection of A,

$$B = \begin{bmatrix} a_{nn} & a_{[n-1]n} & \cdots & a_{2n} & a_{1n} \\ a_{n[n-1]} & a_{[n-1][n-1]} & \cdots & a_{2[n-1]} & a_{1[n-1]} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ a_{n2} & a_{[n-1]2} & \cdots & a_{22} & a_{12} \\ a_{n1} & a_{[n-1]1} & \cdots & a_{21} & a_{11} \end{bmatrix}.$$

If D defines the square matrix of order n with ones on the off diagonal and zeros everywhere else,

$$D = \begin{bmatrix} 0 & 0 & \cdots & 0 & 1 \\ 0 & & & 1 & 0 \\ \vdots & & \cdot^{\cdot^{\cdot}} & & \vdots \\ 0 & 1 & & & 0 \\ 1 & 0 & \cdots & 0 & 0 \end{bmatrix},$$

then the series of matrix multiplication steps can be followed to derive B from A.

$$DA^\mathsf{T} = \begin{bmatrix} 0 & 0 & \cdots & 0 & 1 \\ 0 & & & 1 & 0 \\ \vdots & & \cdot^{\cdot^{\cdot}} & & \vdots \\ 0 & 1 & & & 0 \\ 1 & 0 & \cdots & 0 & 0 \end{bmatrix} \begin{bmatrix} a_{11} & a_{21} & \cdots & a_{[n-1]1} & a_{n1} \\ a_{12} & a_{22} & \cdots & a_{[n-1]2} & a_{n2} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ a_{1[n-1]} & a_{2[n-1]} & \cdots & a_{[n-1][n-1]} & a_{n[n-1]} \\ a_{1n} & a_{2n} & \cdots & a_{[n-1]n} & a_{nn} \end{bmatrix}$$

$$= \begin{bmatrix} a_{1n} & a_{2n} & \cdots & a_{[n-1]n} & a_{nn} \\ a_{1[n-1]} & a_{2[n-1]} & \cdots & a_{[n-1][n-1]} & a_{n[n-1]} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ a_{12} & a_{22} & \cdots & a_{[n-1]2} & a_{n2} \\ a_{11} & a_{21} & \cdots & a_{[n-1]1} & a_{n1} \end{bmatrix}$$

$$D\left(DA^\mathsf{T}\right)^\mathsf{T} = \begin{bmatrix} 0 & 0 & \cdots & 0 & 1 \\ 0 & & & 1 & 0 \\ \vdots & & \cdot^{\cdot^{\cdot}} & & \vdots \\ 0 & 1 & & & 0 \\ 1 & 0 & \cdots & 0 & 0 \end{bmatrix} \begin{bmatrix} a_{1n} & a_{1[n-1]} & \cdots & a_{12} & a_{11} \\ a_{2n} & a_{2[n-1]} & \cdots & a_{22} & a_{21} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ a_{[n-1]n} & a_{[n-1][n-1]} & \cdots & a_{[n-1]2} & a_{[n-1]1} \\ a_{nn} & a_{n[n-1]} & \cdots & a_{[n-1]2} & a_{n1} \end{bmatrix}$$

$$= \begin{bmatrix} a_{nn} & a_{2[n-1]} & \cdots & a_{n2} & a_{n1} \\ a_{[n-1]n} & a_{[n-1][n-1]} & \cdots & a_{[n-1]2} & a_{[n-1]1} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ a_{2n} & a_{2[n-1]} & \cdots & a_{22} & a_{21} \\ a_{1n} & a_{2[n-1]} & \cdots & a_{12} & a_{11} \end{bmatrix}$$

$$\left(D\left(DA^\mathsf{T}\right)^\mathsf{T}\right)^\mathsf{T} = \begin{bmatrix} a_{nn} & a_{[n-1]n} & \cdots & a_{2n} & a_{1n} \\ a_{n[n-1]} & a_{[n-1][n-1]} & \cdots & a_{2[n-1]} & a_{1[n-1]} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ a_{n2} & a_{[n-1]2} & \cdots & a_{22} & a_{12} \\ a_{n1} & a_{[n-1]1} & \cdots & a_{21} & a_{11} \end{bmatrix} = B$$

Therefore,

$$\det(B) = \det\left(\left(D(DA^\mathsf{T})^\mathsf{T}\right)^\mathsf{T}\right)$$

$$= \det\left(D(DA^\mathsf{T})^\mathsf{T}\right)$$

$$= \det(D)\det\left((DA^\mathsf{T})^\mathsf{T}\right)$$

$$= -\det\left(DA^\mathsf{T}\right)$$

$$= -\left(\det(D)\det(A^\mathsf{T})\right)$$

$$= -\left(-\det(A)\right)$$

$$= \det(A)$$

□

The results of proposition B.0.3 will consolidate the calculations for the Hurwitz determinants in each case, by allowing the use of earlier Hurwitz determinants to be used in the calculations of later ones.

B.1   5th Degree Polynomial

Let $c(x) = c_0 x^5 + c_1 x^4 + c_2 x^3 + c_3 x^2 + c_4 x + c_5$, then the corresponding Hurwitz matrix is

$$H = \begin{bmatrix} c_1 & c_3 & c_5 & 0 & 0 \\ c_0 & c_2 & c_4 & 0 & 0 \\ 0 & c_1 & c_3 & c_5 & 0 \\ 0 & c_0 & c_2 & c_4 & 0 \\ 0 & 0 & c_1 & c_3 & c_5 \end{bmatrix}$$

with the following Hurwitz determinants.

$$\Delta_1(c) = c_1$$

$$\Delta_2(c) = \begin{vmatrix} c_1 & c_3 \\ c_0 & c_2 \end{vmatrix} = \begin{vmatrix} c_2 & c_3 \\ c_0 & c_1 \end{vmatrix} = c_2\Delta_1 - c_0 c_3$$

$$\Delta_3(c) = \begin{vmatrix} c_1 & c_3 & c_5 \\ c_0 & c_2 & c_4 \\ 0 & c_1 & c_3 \end{vmatrix} = \begin{vmatrix} c_3 & c_4 & c_5 \\ c_1 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} = c_3\Delta_2 - c_4 c_1^2 + c_5 c_1 c_0$$

$$\Delta_4(c) = \begin{vmatrix} c_1 & c_3 & c_5 & 0 \\ c_0 & c_2 & c_4 & 0 \\ 0 & c_1 & c_3 & c_5 \\ 0 & c_0 & c_2 & c_4 \end{vmatrix} = \begin{vmatrix} c_4 & c_5 & 0 & 0 \\ c_2 & c_3 & c_4 & c_5 \\ c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$= c_4\Delta_3 - c_5 \begin{vmatrix} c_2 & c_4 & c_5 \\ c_0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} = c_4\Delta_3 - c_5 c_2 \Delta_2 + c_5 c_4 c_1 c_0 - c_5^2 c_0^2$$

$$\Delta_5(c) = \begin{vmatrix} c_1 & c_3 & c_5 & 0 & 0 \\ c_0 & c_2 & c_4 & 0 & 0 \\ 0 & c_1 & c_3 & c_5 & 0 \\ 0 & c_0 & c_3 & c_4 & 0 \\ 0 & 0 & c_1 & c_3 & c_5 \end{vmatrix} = \begin{vmatrix} c_5 & 0 & 0 & 0 & 0 \\ c_3 & c_4 & c_5 & 0 & 0 \\ c_1 & c_2 & c_3 & c_4 & c_5 \\ 0 & c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & 0 & c_0 & c_1 \end{vmatrix} = c_5\Delta_4$$

B.2   6th Degree Polynomial

Let $c(x) = c_0 x^6 + c_1 x^5 + c_2 x^4 + c_3 x^3 + c_4 x^2 + c_5 x + c_6$, then the corresponding Hurwitz matrix is

$$H = \begin{bmatrix} c_1 & c_3 & c_5 & 0 & 0 & 0 \\ c_0 & c_2 & c_4 & c_6 & 0 & 0 \\ 0 & c_1 & c_3 & c_5 & 0 & 0 \\ 0 & c_0 & c_2 & c_4 & c_6 & 0 \\ 0 & 0 & c_1 & c_3 & c_5 & 0 \\ 0 & 0 & c_0 & c_2 & c_4 & c_6 \end{bmatrix}$$

with the following Hurwitz determinants.

$$\Delta_1(c) = c_1$$

$$\Delta_2(c) = \begin{vmatrix} c_1 & c_3 \\ c_0 & c_2 \end{vmatrix} = \begin{vmatrix} c_2 & c_3 \\ c_0 & c_1 \end{vmatrix} = c_2\Delta_1 - c_0 c_3$$

$$\Delta_3(c) = \begin{vmatrix} c_1 & c_3 & c_5 \\ c_0 & c_2 & c_4 \\ 0 & c_1 & c_3 \end{vmatrix} = \begin{vmatrix} c_3 & c_4 & c_5 \\ c_1 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} = c_3\Delta_2 - c_4 c_1^2 + c_5 c_1 c_0$$

$$\Delta_4(c) = \begin{vmatrix} c_1 & c_3 & c_5 & 0 \\ c_0 & c_2 & c_4 & c_6 \\ 0 & c_1 & c_3 & c_5 \\ 0 & c_0 & c_2 & c_4 \end{vmatrix} = \begin{vmatrix} c_4 & c_5 & c_6 & 0 \\ c_2 & c_3 & c_4 & c_5 \\ c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix} = c_4\Delta_3 - c_5 \begin{vmatrix} c_2 & c_4 & c_5 \\ c_0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} + c_6 \begin{vmatrix} c_2 & c_3 & c_5 \\ c_0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix}$$

$$= c_4\Delta_3 - c_5 c_2 \Delta_2 + c_5 c_4 c_1 c_0 - c_5^2 c_0^2 + c_6 c_2 c_1^2 - c_6 c_3 c_1 c_0$$

$$\Delta_5(c) = \begin{vmatrix} c_1 & c_3 & c_5 & 0 & 0 \\ c_0 & c_2 & c_4 & c_6 & 0 \\ 0 & c_1 & c_3 & c_5 & 0 \\ 0 & c_0 & c_2 & c_4 & c_6 \\ 0 & 0 & c_1 & c_3 & c_5 \end{vmatrix} = \begin{vmatrix} c_5 & c_6 & 0 & 0 & 0 \\ c_3 & c_4 & c_5 & c_6 & 0 \\ c_1 & c_2 & c_3 & c_4 & c_5 \\ 0 & c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & 0 & c_0 & c_1 \end{vmatrix} = c_5\Delta_4 - c_6 \begin{vmatrix} c_3 & c_5 & c_6 & 0 \\ c_1 & c_3 & c_4 & c_5 \\ 0 & c_1 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$= c_5\Delta_4 - c_6 c_3 \Delta_3 + c_6 c_5 \begin{vmatrix} c_1 & c_4 & c_5 \\ 0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} - c_6^2 \begin{vmatrix} c_1 & c_3 & c_5 \\ 0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix}$$

$$= c_5\Delta_4 - c_6 c_3 \Delta_3 + c_6 c_5 c_1 \Delta_2 - c_6^2 c_1^3$$

$$\Delta_6(c) = \begin{vmatrix} c_1 & c_3 & c_5 & 0 & 0 & 0 \\ c_0 & c_2 & c_4 & c_6 & 0 & 0 \\ 0 & c_1 & c_3 & c_5 & 0 & 0 \\ 0 & c_0 & c_2 & c_4 & c_6 & 0 \\ 0 & 0 & c_1 & c_3 & c_5 & 0 \\ 0 & 0 & c_0 & c_2 & c_4 & c_6 \end{vmatrix} = \begin{vmatrix} c_6 & 0 & 0 & 0 & 0 & 0 \\ c_4 & c_5 & c_6 & 0 & 0 & 0 \\ c_2 & c_3 & c_4 & c_5 & c_6 & 0 \\ c_0 & c_1 & c_2 & c_3 & c_4 & c_5 \\ 0 & 0 & c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & 0 & 0 & c_0 & c_1 \end{vmatrix} = c_6\Delta_5$$

B.3 7th Degree Polynomial

Let $c(x) = c_0 x^7 + c_1 x^6 + c_2 x^5 + c_3 x^4 + c_4 x^3 + c_5 x^2 + c_6 x + c_7$, then the corresponding Hurwitz matrix is

$$H = \begin{bmatrix} c_1 & c_3 & c_5 & c_7 & 0 & 0 & 0 \\ c_0 & c_2 & c_4 & c_6 & 0 & 0 & 0 \\ 0 & c_1 & c_3 & c_5 & c_7 & 0 & 0 \\ 0 & c_0 & c_2 & c_4 & c_6 & 0 & 0 \\ 0 & 0 & c_1 & c_3 & c_5 & c_7 & 0 \\ 0 & 0 & c_0 & c_2 & c_4 & c_6 & 0 \\ 0 & 0 & 0 & c_1 & c_3 & c_5 & c_7 \end{bmatrix}$$

with the following Hurwitz determinants.

$$\Delta_1(c) = c_1$$

$$\Delta_2(c) = \begin{vmatrix} c_1 & c_3 \\ c_0 & c_2 \end{vmatrix} = \begin{vmatrix} c_2 & c_3 \\ c_0 & c_1 \end{vmatrix} = c_2\Delta_1 - c_0 c_3$$

$$\Delta_3(c) = \begin{vmatrix} c_1 & c_3 & c_5 \\ c_0 & c_2 & c_4 \\ 0 & c_1 & c_3 \end{vmatrix} = \begin{vmatrix} c_3 & c_4 & c_5 \\ c_1 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} = c_3\Delta_2 - c_4 \begin{vmatrix} c_1 & c_3 \\ 0 & c_1 \end{vmatrix} + c_5 \begin{vmatrix} c_1 & c_2 \\ 0 & c_0 \end{vmatrix}$$

$$= c_3\Delta_2 - c_4 c_1^2 + c_5 c_1 c_0$$

$$\Delta_4(c) = \begin{vmatrix} c_1 & c_3 & c_5 & c_7 \\ c_0 & c_2 & c_4 & c_6 \\ 0 & c_1 & c_3 & c_5 \\ 0 & c_0 & c_2 & c_4 \end{vmatrix} = \begin{vmatrix} c_4 & c_5 & c_6 & c_7 \\ c_2 & c_3 & c_4 & c_5 \\ c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$= c_4\Delta_3 - c_5 \begin{vmatrix} c_2 & c_4 & c_5 \\ c_0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} + c_6 \begin{vmatrix} c_2 & c_3 & c_5 \\ c_0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} - c_7 \begin{vmatrix} c_2 & c_3 & c_4 \\ c_0 & c_1 & c_2 \\ 0 & 0 & c_0 \end{vmatrix}$$

$$= c_4\Delta_3 - c_5 c_2\Delta_2 + c_5 c_4 c_1 c_0 - c_5^2 c_0^2 + c_6 c_2 c_1^2 - c_6 c_3 c_1 c_0 - c_7 c_2 c_1 c_0 + c_7 c_3 c_0^2$$

$$\Delta_5(c) = \begin{vmatrix} c_1 & c_3 & c_5 & c_7 & 0 \\ c_0 & c_2 & c_4 & c_6 & 0 \\ 0 & c_1 & c_3 & c_5 & c_7 \\ 0 & c_0 & c_2 & c_4 & c_6 \\ 0 & 0 & c_1 & c_3 & c_5 \end{vmatrix} = \begin{vmatrix} c_5 & c_6 & c_7 & 0 & 0 \\ c_3 & c_4 & c_5 & c_6 & c_7 \\ c_1 & c_2 & c_3 & c_4 & c_5 \\ 0 & c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$= c_5\Delta_4 - c_6 \begin{vmatrix} c_3 & c_5 & c_6 & c_7 \\ c_1 & c_3 & c_4 & c_5 \\ 0 & c_1 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix} + c_7 \begin{vmatrix} c_3 & c_4 & c_6 & c_7 \\ c_1 & c_2 & c_4 & c_5 \\ 0 & c_0 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$= c_5\Delta_4 - c_6 c_3 \Delta_3 + c_6 c_5 \begin{vmatrix} c_1 & c_4 & c_5 \\ 0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} - c_6^2 \begin{vmatrix} c_1 & c_3 & c_5 \\ 0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} + c_6 c_7 \begin{vmatrix} c_1 & c_3 & c_4 \\ 0 & c_1 & c_2 \\ 0 & 0 & c_0 \end{vmatrix}$$

$$+ c_7 c_3 \begin{vmatrix} c_2 & c_4 & c_5 \\ c_0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} - c_7 c_4 \begin{vmatrix} c_1 & c_4 & c_5 \\ 0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} + c_7 c_6 \begin{vmatrix} c_1 & c_2 & c_5 \\ 0 & c_0 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} - c_7^2 \begin{vmatrix} c_1 & c_2 & c_4 \\ 0 & c_0 & c_2 \\ 0 & 0 & c_0 \end{vmatrix}$$

$$= c_5\Delta_4 - c_6 c_3 \Delta_3 + c_6 c_5 c_1 \Delta_2 - c_6^2 c_1^3 + c_6 c_7 c_1^2 c_0$$

$$+ c_7 c_3 c_2 \Delta_2 - c_7 c_3 c_4 c_1 c_0 + c_7 c_3 c_5 c_0^2 - c_7 c_4 c_1 \Delta_2 + c_7 c_6 c_1^2 c_0 - c_7^2 c_1 c_0^2$$

$$= c_5\Delta_4 - c_6 c_3 \Delta_3 + (c_6 c_5 c_1 + c_7 c_3 c_2 - c_7 c_4 c_1)\Delta_2 - c_6^2 c_1^3 + c_6 c_7 c_1^2 c_0$$

$$- c_7 c_3 c_4 c_1 c_0 + c_7 c_3 c_5 c_0^2 + c_7 c_6 c_1^2 c_0 - c_7^2 c_1 c_0^2$$

$$\Delta_6(c) = \begin{vmatrix} c_1 & c_3 & c_5 & c_7 & 0 & 0 \\ c_0 & c_2 & c_4 & c_6 & 0 & 0 \\ 0 & c_1 & c_3 & c_5 & c_7 & 0 \\ 0 & c_0 & c_2 & c_4 & c_6 & 0 \\ 0 & 0 & c_1 & c_3 & c_5 & c_7 \\ 0 & 0 & c_0 & c_2 & c_4 & c_6 \end{vmatrix} = \begin{vmatrix} c_6 & c_7 & 0 & 0 & 0 & 0 \\ c_4 & c_5 & c_6 & c_7 & 0 & 0 \\ c_2 & c_3 & c_4 & c_5 & c_6 & c_7 \\ c_0 & c_1 & c_2 & c_3 & c_4 & c_5 \\ 0 & 0 & c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$= c_6\Delta_5 - c_7 \begin{vmatrix} c_4 & c_6 & c_7 & 0 & 0 \\ c_2 & c_4 & c_5 & c_6 & c_7 \\ c_0 & c_2 & c_3 & c_4 & c_5 \\ 0 & c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$= c_6\Delta_5 - c_7c_4\Delta_4 + c_7c_6 \begin{vmatrix} c_2 & c_5 & c_6 & c_7 \\ c_0 & c_3 & c_4 & c_5 \\ 0 & c_1 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix} - c_7^2 \begin{vmatrix} c_2 & c_4 & c_6 & c_7 \\ c_0 & c_2 & c_4 & c_5 \\ 0 & c_0 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$= c_6\Delta_5 - c_7c_4\Delta_4 + c_7c_6c_2\Delta_3$$

$$- c_7c_6c_5 \begin{vmatrix} c_0 & c_4 & c_5 \\ 0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} + c_7c_6^2 \begin{vmatrix} c_0 & c_3 & c_5 \\ 0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} - c_7^2c_6 \begin{vmatrix} c_0 & c_3 & c_4 \\ 0 & c_1 & c_2 \\ 0 & 0 & c_0 \end{vmatrix}$$

$$- c_7^2c_2 \begin{vmatrix} c_2 & c_4 & c_5 \\ c_0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} + c_7^2c_4 \begin{vmatrix} c_0 & c_4 & c_5 \\ 0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix}$$

$$- c_7^2c_6 \begin{vmatrix} c_0 & c_2 & c_5 \\ 0 & c_0 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} + c_7^3 \begin{vmatrix} c_0 & c_2 & c_4 \\ 0 & c_0 & c_2 \\ 0 & 0 & c_0 \end{vmatrix}$$

$$= c_6\Delta_5 - c_7c_4\Delta_4 + c_7c_6c_2\Delta_3 - c_7c_6c_5c_0\Delta_2 + c_7c_6^2c_1^2c_0 - c_7^2c_6c_1c_0^2 - c_7^2c_2^2\Delta_2$$

$$+ c_7^2c_2c_4c_1c_0 - c_7^2c_2c_5c_0^2 + c_7^2c_4c_0\Delta_2 - c_7^2c_6c_1c_0^2 + c_7^3c_0^3$$

$$= c_6\Delta_5 - c_7c_4\Delta_4 + c_7c_6c_2\Delta_3 + (c_7^2c_4c_0 - c_7^2c_2^2 - c_7c_6c_5c_0)\Delta_2$$

$$+ c_7c_6^2c_1^2c_0 - c_7^2c_6c_1c_0^2 + c_7^2c_2c_4c_1c_0 - c_7^2c_2c_5c_0^2 - c_7^2c_6c_1c_0^2 + c_7^3c_0^3$$

$$\Delta_7(c) = \begin{vmatrix} c_1 & c_3 & c_5 & c_7 & 0 & 0 & 0 \\ c_0 & c_2 & c_4 & c_6 & 0 & 0 & 0 \\ 0 & c_1 & c_3 & c_5 & c_7 & 0 & 0 \\ 0 & c_0 & c_2 & c_4 & c_6 & 0 & 0 \\ 0 & 0 & c_1 & c_3 & c_5 & c_7 & 0 \\ 0 & 0 & c_0 & c_2 & c_4 & c_6 & 0 \\ 0 & 0 & 0 & c_1 & c_3 & c_5 & c_7 \end{vmatrix} = \begin{vmatrix} c_7 & 0 & 0 & 0 & 0 & 0 & 0 \\ c_5 & c_6 & c_7 & 0 & 0 & 0 & 0 \\ c_3 & c_4 & c_5 & c_6 & c_7 & 0 & 0 \\ c_1 & c_2 & c_3 & c_4 & c_5 & c_6 & c_7 \\ 0 & c_0 & c_1 & c_2 & c_3 & c_4 & c_5 \\ 0 & 0 & 0 & c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & 0 & 0 & 0 & c_0 & c_1 \end{vmatrix} = c_7\Delta_6$$

B.4   8th Degree Polynomial

Let $c(x) = c_0x^8 + c_1x^7 + c_2x^6 + c_3x^5 + c_4x^4 + c_5x^3 + c_6x^2 + c_7x + c_8$, then the corresponding Hurwitz matrix is

$$H = \begin{bmatrix} c_1 & c_3 & c_5 & c_7 & 0 & 0 & 0 \\ c_0 & c_2 & c_4 & c_6 & c_8 & 0 & 0 \\ 0 & c_1 & c_3 & c_5 & c_7 & 0 & 0 \\ 0 & c_0 & c_2 & c_4 & c_6 & c_8 & 0 \\ 0 & 0 & c_1 & c_3 & c_5 & c_7 & 0 \\ 0 & 0 & c_0 & c_2 & c_4 & c_6 & c_8 \\ 0 & 0 & 0 & c_1 & c_3 & c_5 & c_7 \end{bmatrix}$$

with the following Hurwitz determinants.

$$\Delta_1(c) = c_1$$

$$\Delta_2(c) = \begin{vmatrix} c_1 & c_3 \\ c_0 & c_2 \end{vmatrix} = \begin{vmatrix} c_2 & c_3 \\ c_0 & c_1 \end{vmatrix} = c_2 \Delta_1 - c_0 c_3$$

$$\Delta_3(c) = \begin{vmatrix} c_1 & c_3 & c_5 \\ c_0 & c_2 & c_4 \\ 0 & c_1 & c_3 \end{vmatrix} = \begin{vmatrix} c_3 & c_4 & c_5 \\ c_1 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} = c_3 \Delta_2 - c_4 \begin{vmatrix} c_1 & c_3 \\ 0 & c_1 \end{vmatrix} + c_5 \begin{vmatrix} c_1 & c_2 \\ 0 & c_0 \end{vmatrix}$$

$$= c_3 \Delta_2 - c_4 c_1^2 + c_5 c_1 c_0$$

$$\Delta_4(c) = \begin{vmatrix} c_1 & c_3 & c_5 & c_7 \\ c_0 & c_2 & c_4 & c_6 \\ 0 & c_1 & c_3 & c_5 \\ 0 & c_0 & c_2 & c_4 \end{vmatrix} = \begin{vmatrix} c_4 & c_5 & c_6 & c_7 \\ c_2 & c_3 & c_4 & c_5 \\ c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$= c_4 \Delta_3 - c_5 \begin{vmatrix} c_2 & c_4 & c_5 \\ c_0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} + c_6 \begin{vmatrix} c_2 & c_3 & c_5 \\ c_0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} - c_7 \begin{vmatrix} c_2 & c_3 & c_4 \\ c_0 & c_1 & c_2 \\ 0 & 0 & c_0 \end{vmatrix}$$

$$= c_4 \Delta_3 - c_5 c_2 \Delta_2 + c_5 c_4 c_1 c_0 - c_5^2 c_0^2 + c_6 c_2 c_1^2 - c_6 c_3 c_1 c_0 - c_7 c_2 c_1 c_0 + c_7 c_3 c_0^2$$

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$$\Delta_5(c) = \begin{vmatrix} c_1 & c_3 & c_5 & c_7 & 0 \\ c_0 & c_2 & c_4 & c_6 & c_8 \\ 0 & c_1 & c_3 & c_5 & c_7 \\ 0 & c_0 & c_2 & c_4 & c_6 \\ 0 & 0 & c_1 & c_3 & c_5 \end{vmatrix} = \begin{vmatrix} c_5 & c_6 & c_7 & c_8 & 0 \\ c_3 & c_4 & c_5 & c_6 & c_7 \\ c_1 & c_2 & c_3 & c_4 & c_5 \\ 0 & c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$= c_5 \Delta_4 - c_6 \begin{vmatrix} c_3 & c_5 & c_6 & c_7 \\ c_1 & c_3 & c_4 & c_5 \\ 0 & c_1 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix} + c_7 \begin{vmatrix} c_3 & c_4 & c_6 & c_7 \\ c_1 & c_2 & c_4 & c_5 \\ 0 & c_0 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix} - c_8 \begin{vmatrix} c_3 & c_4 & c_5 & c_7 \\ c_1 & c_2 & c_3 & c_5 \\ 0 & c_0 & c_1 & c_3 \\ 0 & 0 & 0 & c_1 \end{vmatrix}$$

$$= c_5 \Delta_4 - c_6 c_3 \Delta_3 + c_6 c_5 \begin{vmatrix} c_1 & c_4 & c_5 \\ 0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} - c_6^2 \begin{vmatrix} c_1 & c_3 & c_5 \\ 0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} + c_6 c_7 \begin{vmatrix} c_1 & c_3 & c_4 \\ 0 & c_1 & c_2 \\ 0 & 0 & c_0 \end{vmatrix}$$

$$+ c_7 c_3 \begin{vmatrix} c_2 & c_4 & c_5 \\ c_0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} - c_7 c_4 \begin{vmatrix} c_1 & c_4 & c_5 \\ 0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} + c_7 c_6 \begin{vmatrix} c_1 & c_2 & c_5 \\ 0 & c_0 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} - c_7^2 \begin{vmatrix} c_1 & c_2 & c_4 \\ 0 & c_0 & c_2 \\ 0 & 0 & c_0 \end{vmatrix}$$

$$- c_8 c_3 \begin{vmatrix} c_2 & c_3 & c_5 \\ c_0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} + c_8 c_4 \begin{vmatrix} c_1 & c_3 & c_5 \\ 0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} - c_8 c_5 \begin{vmatrix} c_1 & c_2 & c_5 \\ 0 & c_0 & c_3 \\ 0 & 0 & c_1 \end{vmatrix}$$

$$= c_5 \Delta_4 - c_6 c_3 \Delta_3 + c_6 c_5 c_1 \Delta_2 - c_6^2 c_1^3 + c_6 c_7 c_1^2 c_0 + c_7 c_3 c_2 \Delta_2 - c_7 c_3 c_4 c_1 c_0 + c_7 c_3 c_5 c_0^2$$

$$- c_7 c_4 c_1 \Delta_2 + c_7 c_6 c_1^2 c_0 - c_7^2 c_1 c_0^2 - c_8 c_3 c_2 c_1^2 + c_8 c_3^2 c_0 c_1 + c_8 c_4 c_1^3 - c_8 c_5 c_1^2 c_0$$

$$= c_5 \Delta_4 - c_6 c_3 \Delta_3 + (c_6 c_5 c_1 + c_7 c_3 c_2 - c_7 c_4 c_1) \Delta_2 - c_6^2 c_1^3 + c_6 c_7 c_1^2 c_0 - c_7 c_3 c_4 c_1 c_0$$

$$+ c_7 c_3 c_5 c_0^2 + c_7 c_6 c_1^2 c_0 - c_7^2 c_1 c_0^2 - c_8 c_3 c_2 c_1^2 + c_8 c_3^2 c_0 c_1 + c_8 c_4 c_1^3 - c_8 c_5 c_1^2 c_0$$

$$\Delta_6(c) = \begin{vmatrix} c_1 & c_3 & c_5 & c_7 & 0 & 0 \\ c_0 & c_2 & c_4 & c_6 & c_8 & 0 \\ 0 & c_1 & c_3 & c_5 & c_7 & 0 \\ 0 & c_0 & c_2 & c_4 & c_6 & c_8 \\ 0 & 0 & c_1 & c_3 & c_5 & c_7 \\ 0 & 0 & c_0 & c_2 & c_4 & c_6 \end{vmatrix} = \begin{vmatrix} c_6 & c_7 & c_8 & 0 & 0 & 0 \\ c_4 & c_5 & c_6 & c_7 & c_8 & 0 \\ c_2 & c_3 & c_4 & c_5 & c_6 & c_7 \\ c_0 & c_1 & c_2 & c_3 & c_4 & c_5 \\ 0 & 0 & c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$= c_6\Delta_5 - c_7 \begin{vmatrix} c_4 & c_6 & c_7 & c_8 & 0 \\ c_2 & c_4 & c_5 & c_6 & c_7 \\ c_0 & c_2 & c_3 & c_4 & c_5 \\ 0 & c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & 0 & c_0 & c_1 \end{vmatrix} + c_8 \begin{vmatrix} c_4 & c_5 & c_7 & c_8 & 0 \\ c_2 & c_3 & c_5 & c_6 & c_7 \\ c_0 & c_1 & c_3 & c_4 & c_5 \\ 0 & 0 & c_1 & c_2 & c_3 \\ 0 & 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$= c_6\Delta_5 - c_7 c_4 \Delta_4 + c_7 c_6 \begin{vmatrix} c_2 & c_5 & c_6 & c_7 \\ c_0 & c_3 & c_4 & c_5 \\ 0 & c_1 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix} - c_7^2 \begin{vmatrix} c_2 & c_4 & c_6 & c_7 \\ c_0 & c_2 & c_4 & c_5 \\ 0 & c_0 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$+ c_7 c_8 \begin{vmatrix} c_2 & c_4 & c_5 & c_7 \\ c_0 & c_2 & c_3 & c_5 \\ 0 & c_0 & c_1 & c_3 \\ 0 & 0 & 0 & c_1 \end{vmatrix} + c_8 c_4 \begin{vmatrix} c_3 & c_5 & c_6 & c_7 \\ c_1 & c_3 & c_4 & c_5 \\ 0 & c_1 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix} - c_8 c_5 \begin{vmatrix} c_2 & c_5 & c_6 & c_7 \\ c_0 & c_3 & c_4 & c_5 \\ 0 & c_1 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$+ c_8 c_7 \begin{vmatrix} c_2 & c_3 & c_6 & c_7 \\ c_0 & c_1 & c_4 & c_5 \\ 0 & 0 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix} - c_8^2 \begin{vmatrix} c_2 & c_3 & c_5 & c_7 \\ c_0 & c_1 & c_3 & c_5 \\ 0 & 0 & c_1 & c_3 \\ 0 & 0 & 0 & c_1 \end{vmatrix}$$

$$= c_6\Delta_5 - c_7 c_4 \Delta_4 + c_7 c_6 c_2 \Delta_3$$

$$- c_7 c_6 c_5 \begin{vmatrix} c_0 & c_4 & c_5 \\ 0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} + c_7 c_6^2 \begin{vmatrix} c_0 & c_3 & c_5 \\ 0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} - c_7^2 c_6 \begin{vmatrix} c_0 & c_3 & c_4 \\ 0 & c_1 & c_2 \\ 0 & 0 & c_0 \end{vmatrix}$$

$$- c_7^2 c_2 \begin{vmatrix} c_2 & c_4 & c_5 \\ c_0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} + c_7^2 c_4 \begin{vmatrix} c_0 & c_4 & c_5 \\ 0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} - c_7^2 c_6 \begin{vmatrix} c_0 & c_2 & c_5 \\ 0 & c_0 & c_3 \\ 0 & 0 & c_1 \end{vmatrix}$$

$$+ c_7^3 \begin{vmatrix} c_0 & c_2 & c_4 \\ 0 & c_0 & c_2 \\ 0 & 0 & c_0 \end{vmatrix} + c_7 c_8 c_2 \begin{vmatrix} c_2 & c_3 & c_5 \\ c_0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} - c_7 c_8 c_4 \begin{vmatrix} c_0 & c_3 & c_5 \\ 0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix}$$

$$+ c_7 c_8 c_5 \begin{vmatrix} c_0 & c_2 & c_5 \\ 0 & c_0 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} + c_8 c_4 c_3 \Delta_3 - c_8 c_4 c_5 \begin{vmatrix} c_1 & c_4 & c_5 \\ 0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix}$$

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$$+ c_8 c_4 c_6 \begin{vmatrix} c_1 & c_3 & c_5 \\ 0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} + c_8 c_4 c_7 \begin{vmatrix} c_1 & c_3 & c_4 \\ 0 & c_1 & c_2 \\ 0 & 0 & c_0 \end{vmatrix} - c_8 c_5 c_2 \Delta_3$$

$$+ c_8 c_5^2 \begin{vmatrix} c_0 & c_4 & c_5 \\ 0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} - c_8 c_5 c_6 \begin{vmatrix} c_0 & c_3 & c_5 \\ 0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} + c_8 c_5 c_7 \begin{vmatrix} c_0 & c_3 & c_4 \\ 0 & c_1 & c_2 \\ 0 & 0 & c_0 \end{vmatrix}$$

$$+ c_8 c_7 c_2 \begin{vmatrix} c_1 & c_4 & c_5 \\ 0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} - c_8 c_7 c_3 \begin{vmatrix} c_0 & c_4 & c_5 \\ 0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix}$$

$$- c_8^2 c_2 \begin{vmatrix} c_1 & c_3 & c_5 \\ 0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} + c_8^2 c_3 \begin{vmatrix} c_0 & c_3 & c_5 \\ 0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix}$$

$$= c_6 \Delta_5 - c_7 c_4 \Delta_4 + c_7 c_6 c_2 \Delta_3 - c_7 c_6 c_5 c_0 \Delta_2 + c_7 c_6^2 c_1^2 c_0 - c_7^2 c_6 c_1 c_0^2 - c_7^2 c_2^2 \Delta_2$$

$$+ c_7^2 c_2 c_4 c_0 c_1 - c_7^2 c_2 c_5 c_0^2 + c_7^2 c_4 c_0 \Delta_2 - c_7^2 c_6 c_1 c_0^2 + c_7^3 c_0^3 + c_7 c_8 c_2^2 c_1^2 - c_7 c_8 c_2 c_3 c_0 c_1$$

$$- c_7 c_8 c_4 c_1^2 c_0 + c_7 c_8 c_5 c_1 c_0^2 + c_8 c_4 c_3 \Delta_3 - c_8 c_4 c_5 c_1 \Delta_2 + c_8 c_4 c_6 c_1^3$$

$$+ c_8 c_5^2 c_0 \Delta_2 - c_8 c_5 c_6 c_1^2 c_0 + c_8 c_5 c_7 c_1 c_0^2 + c_8 c_4 c_7 c_1^2 c_0$$

$$+ c_8 c_7 c_2 c_1 \Delta_2 - c_8 c_7 c_3 c_0 \Delta_2 - c_8^2 c_2 c_1^3 + c_8^2 c_3 c_1^2 c_0 - c_8 c_5 c_2 \Delta_3$$

$$= c_6 \Delta_5 - c_7 c_4 \Delta_4 + (c_7 c_6 c_2 + c_8 c_4 c_3 - c_8 c_5 c_2) \Delta_3$$

$$+ (c_7^2 c_4 c_0 - c_7 c_6 c_5 c_0 - c_7^2 c_2^2 - c_8 c_4 c_5 c_1 + c_8 c_5^2 c_0 + c_8 c_7 c_2 c_1 - c_8 c_7 c_3 c_0) \Delta_2$$

$$+ c_7 c_6^2 c_1^2 c_0 - c_7^2 c_6 c_1 c_0^2 + c_7^2 c_2 c_4 c_0 c_1 - c_7^2 c_2 c_5 c_0^2 - c_7^2 c_6 c_1 c_0^2 + c_7^3 c_0^3$$

$$+ c_7 c_8 c_2^2 c_1^2 - c_7 c_8 c_2 c_3 c_0 c_1 - c_7 c_8 c_4 c_1^2 c_0 + c_7 c_8 c_5 c_1 c_0^2$$

$$+ c_8 c_4 c_6 c_1^3 + c_8 c_4 c_7 c_1^2 c_0 - c_8 c_5 c_6 c_1^2 c_0 + c_8 c_5 c_7 c_1 c_0^2 - c_8^2 c_2 c_1^3 + c_8^2 c_3 c_1^2 c_0$$

$$\Delta_7(c) = \begin{vmatrix} c_1 & c_3 & c_5 & c_7 & 0 & 0 & 0 \\ c_0 & c_2 & c_4 & c_6 & c_8 & 0 & 0 \\ 0 & c_1 & c_3 & c_5 & c_7 & 0 & 0 \\ 0 & c_0 & c_2 & c_4 & c_6 & c_8 & 0 \\ 0 & 0 & c_1 & c_3 & c_5 & c_7 & 0 \\ 0 & 0 & c_0 & c_2 & c_4 & c_6 & c_8 \\ 0 & 0 & 0 & c_1 & c_3 & c_5 & c_7 \end{vmatrix} = \begin{vmatrix} c_7 & c_8 & 0 & 0 & 0 & 0 & 0 \\ c_5 & c_6 & c_7 & c_8 & 0 & 0 & 0 \\ c_3 & c_4 & c_5 & c_6 & c_7 & c_8 & 0 \\ c_1 & c_2 & c_3 & c_4 & c_5 & c_6 & c_7 \\ 0 & c_0 & c_1 & c_2 & c_3 & c_4 & c_5 \\ 0 & 0 & 0 & c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & 0 & 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$= c_7 \Delta_6 - c_8 \begin{vmatrix} c_5 & c_7 & c_8 & 0 & 0 & 0 \\ c_3 & c_5 & c_6 & c_7 & c_8 & 0 \\ c_1 & c_3 & c_4 & c_5 & c_6 & c_7 \\ 0 & c_1 & c_2 & c_3 & c_4 & c_5 \\ 0 & 0 & c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$= c_7 \Delta_6 - c_8 c_5 \Delta_5 + c_8 c_7 \begin{vmatrix} c_3 & c_6 & c_7 & c_8 & 0 \\ c_1 & c_4 & c_5 & c_6 & c_7 \\ 0 & c_2 & c_3 & c_4 & c_5 \\ 0 & c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & 0 & c_0 & c_1 \end{vmatrix} - c_8^2 \begin{vmatrix} c_3 & c_5 & c_7 & c_8 & 0 \\ c_1 & c_3 & c_5 & c_6 & c_7 \\ 0 & c_1 & c_3 & c_4 & c_5 \\ 0 & 0 & c_1 & c_2 & c_3 \\ 0 & 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$= c_7 \Delta_6 - c_8 c_5 \Delta_5 + c_8 c_7 c_3 \Delta_4$$

$$- c_8 c_7 c_6 \begin{vmatrix} c_1 & c_5 & c_6 & c_7 \\ 0 & c_3 & c_4 & c_5 \\ 0 & c_1 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix} + c_8 c_7^2 \begin{vmatrix} c_1 & c_4 & c_6 & c_7 \\ 0 & c_2 & c_4 & c_5 \\ 0 & c_0 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix} - c_8^2 c_7 \begin{vmatrix} c_1 & c_4 & c_5 & c_7 \\ 0 & c_2 & c_3 & c_5 \\ 0 & c_0 & c_1 & c_3 \\ 0 & 0 & 0 & c_1 \end{vmatrix}$$

$$- c_8^2 c_3 \begin{vmatrix} c_3 & c_5 & c_6 & c_7 \\ c_1 & c_3 & c_4 & c_5 \\ 0 & c_1 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix} + c_8^2 c_5 \begin{vmatrix} c_1 & c_5 & c_6 & c_7 \\ 0 & c_3 & c_4 & c_5 \\ 0 & c_1 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix}$$

$$- c_8^2 c_7 \begin{vmatrix} c_1 & c_3 & c_6 & c_7 \\ 0 & c_1 & c_4 & c_5 \\ 0 & 0 & c_2 & c_3 \\ 0 & 0 & c_0 & c_1 \end{vmatrix} + c_8^3 \begin{vmatrix} c_1 & c_3 & c_5 & c_7 \\ 0 & c_1 & c_3 & c_5 \\ 0 & 0 & c_1 & c_3 \\ 0 & 0 & 0 & c_1 \end{vmatrix}$$

$$= c_7\Delta_6 - c_8c_5\Delta_5 + c_8c_7c_3\Delta_4 - c_8c_7c_6c_1\Delta_3$$

$$+ c_8c_7^2c_1 \begin{vmatrix} c_2 & c_4 & c_5 \\ c_0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} - c_8^2c_7c_1 \begin{vmatrix} c_2 & c_3 & c_5 \\ c_0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} - c_8^2c_3^2\Delta_3 + c_8^2c_3c_5 \begin{vmatrix} c_1 & c_4 & c_5 \\ 0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix}$$

$$- c_8^2c_3c_6 \begin{vmatrix} c_1 & c_3 & c_5 \\ 0 & c_1 & c_3 \\ 0 & 0 & c_1 \end{vmatrix} + c_8^2c_3c_7 \begin{vmatrix} c_1 & c_3 & c_4 \\ 0 & c_1 & c_2 \\ 0 & 0 & c_0 \end{vmatrix} + c_8^2c_5c_1\Delta_3$$

$$- c_8^2c_7c_1 \begin{vmatrix} c_1 & c_4 & c_5 \\ 0 & c_2 & c_3 \\ 0 & c_0 & c_1 \end{vmatrix} + c_8^3c_1^4$$

$$= c_7\Delta_6 - c_8c_5\Delta_5 + c_8c_7c_3\Delta_4 - c_8c_7c_6c_1\Delta_3 + c_8c_7^2c_1c_2\Delta_2 - c_8c_7^2c_1^2c_4c_0 + c_8c_7^2c_1c_5c_0^2$$

$$- c_8^2c_7c_1^3c_2 + c_8^2c_7c_1^2c_3c_0 - c_8^2c_3^2\Delta_3 + c_8^2c_3c_5c_1\Delta_2 - c_8^2c_3c_6c_1^3 + c_8^2c_3c_7c_1^2c_0$$

$$+ c_8^2c_5c_1\Delta_3 - c_8^2c_7c_1^2\Delta_2 + c_8^3c_1^4$$

$$= c_7\Delta_6 - c_8c_5\Delta_5 + c_8c_7c_3\Delta_4$$

$$+ (c_8^2c_5c_1 - c_8c_7c_6c_1 - c_8^2c_3^2)\Delta_3 + (c_8c_7^2c_1c_2 + c_8^2c_3c_5c_1 - c_8^2c_7c_1^2)\Delta_2$$

$$- c_8c_7^2c_1^2c_4c_0 + c_8c_7^2c_1c_5c_0^2 - c_8^2c_7c_1^3c_2 + c_8^2c_7c_1^2c_3c_0 - c_8^2c_3c_6c_1^3$$

$$+ c_8^2c_3c_7c_1^2c_0 + c_8^3c_1^4$$

$$\Delta_8(c) = \begin{vmatrix} c_1 & c_3 & c_5 & c_7 & 0 & 0 & 0 & 0 \\ c_0 & c_2 & c_4 & c_6 & c_8 & 0 & 0 & 0 \\ 0 & c_1 & c_3 & c_5 & c_7 & 0 & 0 & 0 \\ 0 & c_0 & c_2 & c_4 & c_6 & c_8 & 0 & 0 \\ 0 & 0 & c_1 & c_3 & c_5 & c_7 & 0 & 0 \\ 0 & 0 & c_0 & c_2 & c_4 & c_6 & c_8 & 0 \\ 0 & 0 & 0 & c_1 & c_3 & c_5 & c_7 & 0 \\ 0 & 0 & 0 & c_0 & c_2 & c_4 & c_6 & c_8 \end{vmatrix} = \begin{vmatrix} c_8 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & c_7 & c_8 & 0 & 0 & 0 & 0 & 0 \\ 0 & c_5 & c_6 & c_7 & c_8 & 0 & 0 & 0 \\ 0 & c_3 & c_4 & c_5 & c_6 & c_7 & c_8 & 0 \\ 0 & c_1 & c_2 & c_3 & c_4 & c_5 & c_6 & c_7 \\ 0 & 0 & c_0 & c_1 & c_2 & c_3 & c_4 & c_5 \\ 0 & 0 & 0 & 0 & c_0 & c_1 & c_2 & c_3 \\ 0 & 0 & 0 & 0 & 0 & 0 & c_0 & c_1 \end{vmatrix} = c_8\Delta_7$$

Appendix C

Sensitivity Equations

By deriving the sensitivity of the payoff functional to the parameters of the model by the adjoint variable method requires that the integral equation is evaluated for each of the parameters in the model.

C.1   HIV-Transmission Dynamics without Intervention

For the model without an intervention we have following system of ordinary differential equations

$$\frac{dY_{0,0}(t)}{dt} = (1 - \sum_{i=1}^{i=3} \rho_i)\mu Y_0 - (\mu + p_0\lambda(t))Y_{0,0}(t)$$

$$\frac{dY_{1,0}(t)}{dt} = \rho_1\mu Y_0 + p_0\lambda(t)Y_{0,0}(t) - (\sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t)$$

$$\frac{dY_{2,0}(t)}{dt} = \rho_2\mu Y_0 + \sigma\xi Y_{1,0}(t) - (\mu_{2,0} + \mu)Y_{2,0}(t)$$

$$\frac{dY_{3,0}(t)}{dt} = \rho_3\mu Y_0 + \sum_{i=1}^{i=2} \mu_{i,0}Y_{i,0}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t)$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t)$$

were $\lambda(t) = \dfrac{\sum_{i=1}^{i=4} p_i\beta_{i,0}\eta_{00,i0}Y_{i,0}(t)}{\sum_{i=0}^{i=4} p_iY_{i,0}(t)}$, along with the initial state

$$Y_{0,0}(0) = (1 - \phi_0)Y_0$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \phi_0 Y_0, \text{ for } i = 1, 2, 3, 4$$

and the corresponding payoff functional

$$L(T) = \int_0^T \left[\alpha \Big(\sum_{i=0}^{i=4} c_i Y_{i,0}(t) \Big) - (1 - \alpha) \Big(\sum_{i=0}^{i=4} q_i Y_{i,0}(t) \Big) \right] e^{-rt} dt.$$

In all, we are considering 37 parameters for the model without an intervention.

$$\Theta = \{ \mu, \mu_{1,0}, \mu_{2,0}, \mu_{3,0}, \mu_{4,0}, p_0, p_1, p_2, p_3, p_4, \beta_{1,0}, \beta_{2,0}, \beta_{3,0}, \beta_{4,0}, \eta_{00,10}, \eta_{00,20} \eta_{00,30}, \eta_{00,40}, \ldots$$
$$\ldots, \sigma, \xi, Y_0, \phi_0, \rho_1, \rho_2, \rho_3, c_0, c_1, c_2, c_3, c_4, q_0, q_1, q_2, q_3, q_4, r, \alpha \}$$

To set up the sensitivity equations for each of the 37 parameters, we'll first present the vectors using the notation we introduced in the chapter 6.

$$F(\dot{Y}, Y, \Theta) = \begin{bmatrix} \dot{Y}_{0,0}(t) + (\mu + p_0 \lambda(t))Y_{0,0}(t) - (1 - \sum_{i=1}^{i=3} \rho_i)\mu Y_0 \\ \dot{Y}_{1,0}(t) - p_0 \lambda(t) Y_{0,0}(t) + (\sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) - \rho_1 \mu Y_0 \\ \dot{Y}_{2,0}(t) - \sigma\xi Y_{1,0}(t) + (\mu_{2,0} + \mu)Y_{2,0}(t) - \rho_2 \mu Y_0 \\ \dot{Y}_{3,0}(t) - \mu_{1,0}Y_{1,0}(t) - \mu_{2,0}Y_{2,0}(t) + (\mu_{3,0} + \mu)Y_{3,0}(t) - \rho_3 \mu Y_0 \\ \dot{Y}_{4,0}(t) - \mu_{3,0}Y_{3,0}(t) + (\mu_{4,0} + \mu)Y_{4,0}(t) \end{bmatrix}$$

$$G(Y(0), \Theta) = \begin{bmatrix} Y_{0,0}(0) - (1 - \phi_0)Y_0 \\ Y_{1,0}(0) - \phi_0 \left(\frac{1/\mu_{1,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \right) Y_0 \\ Y_{2,0}(0) - \phi_0 \left(\frac{1/\mu_{2,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \right) Y_0 \\ Y_{3,0}(0) - \phi_0 \left(\frac{1/\mu_{3,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \right) Y_0 \\ Y_{4,0}(0) - \phi_0 \left(\frac{1/\mu_{4,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}} \right) Y_0 \end{bmatrix}$$

$$\ell(Y, \Theta) = \left[\alpha \Big(\sum_{i=0}^{i=4} c_i Y_{i,0}(t) \Big) - (1 - \alpha) \Big(\sum_{i=0}^{i=4} q_i Y_{i,0}(t) \Big) \right] e^{-rt}$$

Then, by the adjoint variable method, the sensitivity equations are defined by,

$$\frac{\partial L}{\partial \vartheta_i} = \int_0^T \left(\ell_{\vartheta_i} + \Lambda^\intercal F_{\vartheta_i} \right) dt + \Lambda^\intercal \Big|_{t=0} G_{\vartheta_i}$$

where $\Lambda^\intercal = [\Lambda_{0,0}, \Lambda_{1,0}, \Lambda_{2,0}, \Lambda_{3,0}, \Lambda_{4,0}]$. Thus, in defining the sensitivity equations for each of the parameters in Θ we will have to evaluate F_{ϑ_i}, G_{ϑ_i} and ℓ_{ϑ_i}.

Average non-disease related death rate, μ

For the HIV infectious disease model, without an intervention, the sensitivity equation for the non-disease related death rate is defined by the following.

With
$$F_\mu = \begin{bmatrix} Y_{0,0}(t) - (1 - \sum_{i=1}^{i=3} \rho_i) Y_0 \\ Y_{1,0}(t) - \rho_1 Y_0 \\ Y_{2,0}(t) - \rho_2 Y_0 \\ Y_{3,0}(t) - \rho_3 Y_0 \\ Y_{4,0}(t) \end{bmatrix}, \quad G_\mu = 0, \quad \text{and} \quad \ell_\mu = 0,$$

implies,

$$\frac{\partial L}{\partial \mu} = \int_0^T \Big[\Lambda_{0,0}(t)(Y_{0,0}(t) - (1 - \sum_{i=1}^{i=3} \rho_i) Y_0) + \Lambda_{1,0}(t)(Y_{1,0}(t) - \rho_1 Y_0)$$
$$+ \Lambda_{2,0}(t)(Y_{2,0}(t) - \rho_2 Y_0) + \Lambda_{3,0}(t)(Y_{3,0}(t) - \rho_3 Y_0) + \Lambda_{4,0}(t) Y_{4,0}(t)) \Big] dt.$$

Disease related transition rates, $\mu_{i,0}$

For the HIV infectious disease model, without an intervention, the sensitivity equation for the rate at which an infected individual transitions out of each of the disease classes are each evaluated.

For $\mu_{1,0}$, we get,

$$F_{\mu_{1,0}} = \begin{bmatrix} 0 \\ Y_{1,0}(t) \\ 0 \\ -Y_{1,0}(t) \\ 0 \end{bmatrix},$$

$$G_{\mu_{1,0}} = \frac{\phi_0 Y_0 (1/\mu_{1,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \begin{bmatrix} 0 \\ 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0} \\ -1/\mu_{2,0} \\ -1/\mu_{3,0} \\ -1/\mu_{4,0} \end{bmatrix}, \quad \text{and}$$

$\ell_{\mu_{1,0}} = 0$,

implies,

$$\frac{\partial L}{\partial \mu_{1,0}} = \int_0^T Y_{1,0}(t)(\Lambda_{1,0}(t) - \Lambda_{3,0}(t))dt$$

$$+ \frac{\phi_0 Y_0 (1/\mu_{1,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \Big((1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0})\Lambda_{1,0}(0)$$

$$- (1/\mu_{2,0})\Lambda_{2,0}(0) - (1/\mu_{3,0})\Lambda_{3,0}(0) - (1/\mu_{4,0})\Lambda_{4,0}(0) \Big).$$

For $\mu_{2,0}$ we get,

$$F_{\mu_{2,0}} = \begin{bmatrix} 0 \\ 0 \\ Y_{2,0}(t) \\ -Y_{2,0}(t) \\ 0 \end{bmatrix},$$

$$G_{\mu_{2,0}} = \frac{\phi_0 Y_0 (1/\mu_{2,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \begin{bmatrix} 0 \\ -1/\mu_{1,0} \\ 1/\mu_{1,0} + 1/\mu_{3,0} + 1/\mu_{4,0} \\ -1/\mu_{3,0} \\ -1/\mu_{4,0} \end{bmatrix}, \quad \text{and}$$

$\ell_{\mu_{2,0}} = 0$,

implies,

$$\frac{\partial L}{\partial \mu_{2,0}} = \int_0^T Y_{2,0}(t)(\Lambda_{2,0}(t) - \Lambda_{3,0}(t))dt$$

$$+ \frac{\phi_0 Y_0 (1/\mu_{2,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \Big((1/\mu_{1,0} + 1/\mu_{3,0} + 1/\mu_{4,0})\Lambda_{2,0}(0)$$

$$- (1/\mu_{1,0})\Lambda_{1,0}(0) - (1/\mu_{3,0})\Lambda_{3,0}(0) - (1/\mu_{4,0})\Lambda_{4,0}(0) \Big).$$

For $\mu_{3,0}$ we get,

$$
F_{\mu_{3,0}} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ Y_{3,0}(t) \\ -Y_{3,0}(t) \end{bmatrix},
$$

$$
G_{\mu_{3,0}} = \frac{\phi_0 Y_0 (1/\mu_{3,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \begin{bmatrix} 0 \\ -1/\mu_{1,0} \\ -1/\mu_{2,0} \\ 1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{4,0} \\ -1/\mu_{4,0} \end{bmatrix} \quad \text{and}
$$

$\ell_{\mu_{3,0}} = 0$,

implies,

$$
\frac{\partial L}{\partial \mu_{3,0}} = \int_0^T Y_{3,0}(t)(\Lambda_{3,0}(t) - \Lambda_{4,0}(t))dt
$$
$$
+ \frac{\phi_0 Y_0 (1/\mu_{3,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \Big((1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{4,0})\Lambda_{3,0}(0)
$$
$$
- (1/\mu_{1,0})\Lambda_{1,0}(0) - (1/\mu_{2,0})\Lambda_{2,0}(0) - (1/\mu_{4,0})\Lambda_{4,0}(0) \Big).
$$

For $\mu_{4,0}$ we get,

$$
F_{\mu_{4,0}} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ Y_{4,0}(t) \end{bmatrix},
$$

$$
G_{\mu_{4,0}} = \frac{\phi_0 Y_0 (1/\mu_{4,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \begin{bmatrix} 0 \\ -1/\mu_{1,0} \\ -1/\mu_{2,0} \\ -1/\mu_{3,0} \\ 1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} \end{bmatrix}, \quad \text{and}
$$

$\ell_{\mu_{4,0}} = 0$,

implies,

$$\frac{\partial L}{\partial \mu_{4,0}} = \int_0^T Y_{4,0}(t)\Lambda_{4,0}(t)dt$$

$$+ \frac{\phi_0 Y_0 (1/\mu_{4,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \Big((1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0})\Lambda_{4,0}(0)$$

$$- (1/\mu_{1,0})\Lambda_{1,0}(0) - (1/\mu_{2,0})\Lambda_{2,0}(0) - (1/\mu_{3,0})\Lambda_{3,0}(0) \Big).$$

Average number of partners an individual will have in a year, for each population class, p_i

For the HIV infectious disease model, without an intervention, the sensitivity equation for the average number of partners an individual, with disease status i, will have within a year are evaluated for each population classes.

For p_0 we get,

$$F_{p_0} = \begin{bmatrix} Y_{0,0}(t)\left(\lambda(t) + p_0 \left[\frac{\partial \lambda}{\partial p_0}\right]\right) \\ -Y_{0,0}(t)\left(\lambda(t) + p_0 \left[\frac{\partial \lambda}{\partial p_0}\right]\right) \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{with} \quad \frac{\partial \lambda}{\partial p_0} = \frac{-Y_{0,0}(t)\sum_{i=1}^{i=4} p_i \beta_{i,0}\eta_{00,i0}Y_{i,0}(t)}{\left(\sum_{i=0}^{i=4} p_i Y_{i,0}(t)\right)^2},$$

$G_{p_0} = 0$, and $\ell_{p_0} = 0$, implies

$$\frac{\partial L}{\partial p_0} = \int_0^T Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))\left(\lambda(t) + p_0 \left[\frac{\partial \lambda}{\partial p_0}\right]\right)dt.$$

For p_1 we get,

$$
F_{p_1} = \begin{bmatrix} p_0\left(\dfrac{\partial\lambda}{\partial p_1}\right)Y_{0,0}(t) \\[2mm] -p_0\left(\dfrac{\partial\lambda}{\partial p_1}\right)Y_{0,0}(t) \\[2mm] 0 \\[1mm] 0 \\[1mm] 0 \end{bmatrix}
$$

$$
\text{with } \frac{\partial\lambda}{\partial p_1} = \frac{\beta_{1,0}\eta_{00,10}Y_{1,0}(t)\left(\sum_{i=0}^{i=4}p_iY_{i,0}(t)\right) - Y_{1,0}(t)\left(\sum_{i=1}^{i=4}p_i\beta_{i,0}\eta_{00,i0}Y_{i,0}(t)\right)}{\left(\sum_{i=0}^{i=4}p_iY_{i,0}(t)\right)^2},
$$

$G_{p_1} = 0$, and $\ell_{p_1} = 0$, implies

$$
\frac{\partial L}{\partial p_1} = \int_0^T p_0\left(\frac{\partial\lambda}{\partial p_1}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.
$$

For p_2 we get,

$$
F_{p_2} = \begin{bmatrix} p_0\left(\dfrac{\partial\lambda}{\partial p_2}\right)Y_{0,0}(t) \\[2mm] -p_0\left(\dfrac{\partial\lambda}{\partial p_2}\right)Y_{0,0}(t) \\[2mm] 0 \\[1mm] 0 \\[1mm] 0 \end{bmatrix}
$$

$$
\text{with } \frac{\partial\lambda}{\partial p_2} = \frac{\beta_{2,0}\eta_{00,20}Y_{2,0}(t)\left(\sum_{i=0}^{i=4}p_iY_{i,0}(t)\right) - Y_{2,0}(t)\left(\sum_{i=1}^{i=4}p_i\beta_{i,0}\eta_{00,i0}Y_{i,0}(t)\right)}{\left(\sum_{i=0}^{i=4}p_iY_{i,0}(t)\right)^2},
$$

$G_{p_2} = 0$, and $\ell_{p_2} = 0$, implies

$$
\frac{\partial L}{\partial p_2} = \int_0^T p_0\left(\frac{\partial\lambda}{\partial p_2}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.
$$

For p_3 we get,

$$
F_{p3} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial p_3} \right) Y_{0,0}(t) \\[2ex] - p_0 \left(\dfrac{\partial \lambda}{\partial p_3} \right) Y_{0,0}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix}
$$

$$
\text{with } \frac{\partial \lambda}{\partial p_3} = \frac{\beta_{3,0}\eta_{00,30}Y_{3,0}(t)\left(\sum_{i=0}^{i=4} p_i Y_{i,0}(t) \right) - Y_{3,0}(t)\left(\sum_{i=1}^{i=4} p_i \beta_{i,0}\eta_{00,i0}Y_{i,0}(t) \right)}{\left(\sum_{i=0}^{i=4} p_i Y_{i,0}(t) \right)^2},
$$

$G_{p3} = 0$, and $\ell_{p3} = 0$, implies

$$
\frac{\partial L}{\partial p_3} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial p_3} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.
$$

For p_4 we get,

$$
F_{p4} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial p_4} \right) Y_{0,0}(t) \\[2ex] - p_0 \left(\dfrac{\partial \lambda}{\partial p_4} \right) Y_{0,0}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix}
$$

$$
\text{with } \frac{\partial \lambda}{\partial p_4} = \frac{\beta_{4,0}\eta_{00,40}Y_{4,0}(t)\left(\sum_{i=0}^{i=4} p_i Y_{i,0}(t) \right) - Y_{4,0}(t)\left(\sum_{i=1}^{i=4} p_i \beta_{i,0}\eta_{00,i0}Y_{i,0}(t) \right)}{\left(\sum_{i=0}^{i=4} p_i Y_{i,0}(t) \right)^2},
$$

$G_{p4} = 0$, and $\ell_{p4} = 0$, implies

$$
\frac{\partial L}{\partial p_4} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial p_4} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.
$$

Infectivity rate for each of the infectious classes, $\beta_{i,0}$

For the HIV infectious disease model, without an intervention, the sensitivity equation for the infectivity rates are evaluated for each of the infectious classes.

For $\beta_{1,0}$ we get,

$$
F_{\beta_{1,0}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{1,0}} \right) Y_{0,0}(t) \\[2ex] -p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{1,0}} \right) Y_{0,0}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix} \qquad \text{with} \quad \frac{\partial \lambda}{\partial \beta_{1,0}} = \frac{p_1 \eta_{00,10} Y_{1,0}(t)}{\sum_{i=0}^{i=4} p_i Y_{i,0}(t)},
$$

$G_{\beta_{1,0}} = 0$, and $\ell_{\beta_{1,0}} = 0$, implies

$$
\frac{\partial L}{\partial \beta_{1,0}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \beta_{1,0}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.
$$

For $\beta_{2,0}$ we get,

$$
F_{\beta_{2,0}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{2,0}} \right) Y_{0,0}(t) \\[2ex] -p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{2,0}} \right) Y_{0,0}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix}, \qquad \text{with} \quad \frac{\partial \lambda}{\partial \beta_{2,0}} = \frac{p_2 \eta_{00,20} Y_{2,0}(t)}{\sum_{i=0}^{i=4} p_i Y_{i,0}(t)}
$$

$G_{\beta_{2,0}} = 0$, and $\ell_{\beta_{2,0}} = 0$, implies

$$
\frac{\partial L}{\partial \beta_{2,0}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \beta_{2,0}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.
$$

For $\beta_{3,0}$ we get,

$$
F_{\beta_{3,0}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{3,0}} \right) Y_{0,0}(t) \\[2ex] -p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{3,0}} \right) Y_{0,0}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix}, \quad \text{with} \quad \frac{\partial \lambda}{\partial \beta_{3,0}} = \frac{p_3 \eta_{00,30} Y_{3,0}(t)}{\sum_{i=0}^{i=4} p_i Y_{i,0}(t)}
$$

$G_{\beta_{3,0}} = 0$, and $\ell_{\beta_{3,0}} = 0$, implies

$$
\frac{\partial L}{\partial \beta_{3,0}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \beta_{3,0}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.
$$

For $\beta_{4,0}$ we get,

$$
F_{\beta_{4,0}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{4,0}} \right) Y_{0,0}(t) \\[2ex] -p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{4,0}} \right) Y_{0,0}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix}, \quad \text{with} \quad \frac{\partial \lambda}{\partial \beta_{4,0}} = \frac{p_4 \eta_{00,40} Y_{4,0}(t)}{\sum_{i=0}^{i=4} p_i Y_{i,0}(t)}
$$

$G_{\beta_{4,0}} = 0$, and $\ell_{\beta_{4,0}} = 0$, implies

$$
\frac{\partial L}{\partial \beta_{4,0}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \beta_{4,0}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.
$$

Probability that a partnership between a susceptible individual and an infected individual is not protected by a condom, $\eta_{00,i0}$

For the HIV infectious disease model, without an intervention, the sensitivity equations for the probability that a partnership between a susceptible individual with an infected individual is not protected by a condom are evaluated for each of the infectious classes.

For $\eta_{00,10}$ we get,

$$F_{\eta_{00,10}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,10}} \right) Y_{0,0}(t) \\[2ex] -p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,10}} \right) Y_{0,0}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix} \quad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,10}} = \frac{p_1 \beta_{1,0} Y_{1,0}(t)}{\sum_{i=0}^{i=4} p_i Y_{i,0}(t)},$$

$G_{\eta_{00,10}} = 0$, and $\ell_{\eta_{00,10}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,10}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,10}} \right) Y_{0,0}(t) (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For $\eta_{00,20}$ we get,

$$F_{\eta_{00,20}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,20}} \right) Y_{0,0}(t) \\[2ex] -p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,20}} \right) Y_{0,0}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix} \quad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,20}} = \frac{p_2 \beta_{2,0} Y_{2,0}(t)}{\sum_{i=0}^{i=4} p_i Y_{i,0}(t)},$$

$G_{\eta_{00,20}} = 0$, and $\ell_{\eta_{00,20}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,20}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,20}} \right) Y_{0,0}(t) (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For $\eta_{00,30}$ we get,

$$
F_{\eta_{00,30}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,30}} \right) Y_{0,0}(t) \\[2ex] -p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,30}} \right) Y_{0,0}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix} \qquad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,30}} = \frac{p_3 \beta_{3,0} Y_{3,0}(t)}{\sum_{i=0}^{i=4} p_i Y_{i,0}(t)}
$$

$G_{\eta_{00,30}} = 0$, and $\ell_{\eta_{00,30}} = 0$, implies

$$
\frac{\partial L}{\partial \eta_{00,30}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,30}} \right) Y_{0,0}(t) (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.
$$

For $\eta_{00,40}$ we get,

$$
F_{\eta_{00,40}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,40}} \right) Y_{0,0}(t) \\[2ex] -p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,40}} \right) Y_{0,0}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix} \qquad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,40}} = \frac{p_4 \beta_{4,0} Y_{4,0}(t)}{\sum_{i=0}^{i=4} p_i Y_{i,0}(t)}
$$

$G_{\eta_{00,40}} = 0$, and $\ell_{\eta_{00,40}} = 0$, implies

$$
\frac{\partial L}{\partial \eta_{00,40}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,40}} \right) Y_{0,0}(t) (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.
$$

Parameters related to the rate at which asymptomatic-unaware individuals become aware, σ and ξ

For the HIV infectious disease model, without an intervention, the sensitivity equations for the rate at which an asymptomatic-unaware individual becomes aware are evaluated for both the screening rate, σ, along with the true-positive rate of screening, ξ.

For σ we get,

$$
F_\sigma = \begin{bmatrix} 0 \\ \xi Y_{1,0}(t) \\ -\xi Y_{1,0}(t) \\ 0 \\ 0 \end{bmatrix}, \quad G_\sigma = 0, \text{ and } \ell_\sigma = 0,
$$

implies,

$$
\frac{\partial L}{\partial \sigma} = \int_0^T \xi Y_{1,0}(t)(\Lambda_{1,0}(t) - \Lambda_{2,0}(t))dt.
$$

For ξ we get,

$$
F_\xi = \begin{bmatrix} 0 \\ \sigma Y_{1,0}(t) \\ -\sigma Y_{1,0}(t) \\ 0 \\ 0 \end{bmatrix}, \quad G_\xi = 0, \text{ and } \ell_\xi = 0,
$$

implies,

$$
\frac{\partial L}{\partial \xi} = \int_0^T \sigma Y_{1,0}(t)(\Lambda_{1,0}(t) - \Lambda_{2,0}(t))dt.
$$

Total initial population, Y_0

For the HIV infectious disease model, without an intervention, the sensitivity equation for the total initial population is defined by the following.

$$
F_{Y_0} = \begin{bmatrix} -\left(1 - \sum_{i=1}^{i=3} \rho_i\right)\mu \\ -\rho_1 \mu \\ -\rho_2 \mu \\ -\rho_3 \mu \\ 0 \end{bmatrix},
$$

$$
G_{Y_0} = \begin{bmatrix} -(1-\phi_0) \\ -\left(\dfrac{1/\mu_{1,0}}{1/\mu_{1,0}+1/\mu_{2,0}+1/\mu_{3,0}+1/\mu_{4,0}}\right)\phi_0 \\ -\left(\dfrac{1/\mu_{2,0}}{1/\mu_{1,0}+1/\mu_{2,0}+1/\mu_{3,0}+1/\mu_{4,0}}\right)\phi_0 \\ -\left(\dfrac{1/\mu_{3,0}}{1/\mu_{1,0}+1/\mu_{2,0}+1/\mu_{3,0}+1/\mu_{4,0}}\right)\phi_0 \\ -\left(\dfrac{1/\mu_{4,0}}{1/\mu_{1,0}+1/\mu_{2,0}+1/\mu_{3,0}+1/\mu_{4,0}}\right)\phi_0 \end{bmatrix}, \quad \text{and } \ell_{Y_0} = 0,
$$

implies,

$$
\frac{\partial L}{\partial Y_0} = \int_0^T -\mu\left(\left(1-\sum_{i=1}^{1=3}\rho_i\right)\Lambda_{0,0}(t)+\rho_1\Lambda_{1,0}(t)+\rho_2\Lambda_{2,0}(t)+\rho_3\Lambda_{3,0}(t)\right)dt - (1-\phi_0)\Lambda_{0,0}(0)
$$
$$
- \frac{\phi_0}{1/\mu_{1,0}+1/\mu_{2,0}+1/\mu_{3,0}+1/\mu_{4,0}}\Big((1/\mu_{1,0})\Lambda_{1,0}(0)+(1/\mu_{2,0})\Lambda_{2,0}(0)
$$
$$
+ (1/\mu_{3,0})\Lambda_{3,0}(0)+(1/\mu_{4,0})\Lambda_{4,0}(0)\Big).
$$

Seroprevalence of the infected population, ϕ_0

For the HIV infectious disease model, without an intervention, the sensitivity equation for the seroprevalence of the infected population is defined by the following.

$$
F_{\phi_0}=0, \quad G_{\phi_0} = \begin{bmatrix} Y_0 \\ -\left(\dfrac{1/\mu_{1,0}}{1/\mu_{1,0}+1/\mu_{2,0}+1/\mu_{3,0}+1/\mu_{4,0}}\right)Y_0 \\ -\left(\dfrac{1/\mu_{2,0}}{1/\mu_{1,0}+1/\mu_{2,0}+1/\mu_{3,0}+1/\mu_{4,0}}\right)Y_0 \\ -\left(\dfrac{1/\mu_{3,0}}{1/\mu_{1,0}+1/\mu_{2,0}+1/\mu_{3,0}+1/\mu_{4,0}}\right)Y_0 \\ -\left(\dfrac{1/\mu_{4,0}}{1/\mu_{1,0}+1/\mu_{2,0}+1/\mu_{3,0}+1/\mu_{4,0}}\right)Y_0 \end{bmatrix}, \quad \text{and } \ell_{\phi_0} = 0,
$$

implies,

$$
\frac{\partial L}{\partial \phi_0} = Y_0\Lambda_{0,0}(0) - \frac{Y_0}{1/\mu_{1,0}+1/\mu_{2,0}+1/\mu_{3,0}+1/\mu_{4,0}}\Big((1/\mu_{1,0})\Lambda_{1,0}(0)+(1/\mu_{2,0})\Lambda_{2,0}(0)
$$
$$
+ (1/\mu_{3,0})\Lambda_{3,0}(0)+(1/\mu_{4,0})\Lambda_{4,0}(0)\Big).
$$

Distribution of disease-related immigration, ρ_i

For the HIV infectious disease model, without an intervention, the sensitivity equations for the parameters associated with the distribution of disease-related immigration is evaluated for each

of the respective classes.

For ρ_1 we get,

$$F_{\rho_1} = \begin{bmatrix} \mu Y_0 \\ -\mu Y_0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad G_{\rho_1} = 0, \quad \text{and} \quad \ell_{\rho_1} = 0,$$

implies,

$$\frac{\partial L}{\partial \rho_1} = \int_0^{20} \mu Y_0 (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For ρ_2 we get,

$$F_{\rho_2} = \begin{bmatrix} \mu Y_0 \\ 0 \\ -\mu Y_0 \\ 0 \\ 0 \end{bmatrix}, \quad G_{\rho_2} = 0, \quad \text{and} \quad \ell_{\rho_2} = 0,$$

implies,

$$\frac{\partial L}{\partial \rho_2} = \int_0^{T} \mu Y_0 (\Lambda_{0,0}(t) - \Lambda_{2,0}(t)) dt.$$

For ρ_3 we get,

$$F_{\rho_3} = \begin{bmatrix} \mu Y_0 \\ 0 \\ 0 \\ -\mu Y_0 \\ 0 \end{bmatrix}, \quad G_{\rho_3} = 0, \quad \text{and} \quad \ell_{\rho_3} = 0,$$

implies,

$$\frac{\partial L}{\partial \rho_3} = \int_0^{20} \mu Y_0 (\Lambda_{0,0}(t) - \Lambda_{3,0}(t)) dt.$$

Average yearly medical expenses for each class, c_i

For the HIV infectious disease model, without an intervention, the sensitivity equations for the average yearly medical expenses is evaluated for each of the population classes.

For c_0 we get,

$$F_{c_0} = 0, \quad G_{c_0} = 0, \quad \text{and} \quad \ell_{c_0} = \alpha Y_{0,0}(t) e^{-rt},$$
implies,

$$\frac{\partial L}{\partial c_0} = \int_0^T \alpha Y_{0,0}(t) e^{-rt} dt.$$

For c_1 we get,

$$F_{c_1} = 0, \quad G_{c_1} = 0, \quad \text{and} \quad \ell_{c_1} = \alpha Y_{1,0}(t) e^{-rt},$$
implies,

$$\frac{\partial L}{\partial c_1} = \int_0^T \alpha Y_{1,0}(t) e^{-rt} dt.$$

For c_2 we get,

$$F_{c_2} = 0, \quad G_{c_2} = 0, \quad \text{and} \quad \ell_{c_2} = \alpha Y_{2,0}(t) e^{-rt},$$
implies,

$$\frac{\partial L}{\partial c_2} = \int_0^T \alpha Y_{2,0}(t) e^{-rt} dt.$$

For c_3 we get,

$$F_{c_3} = 0, \quad G_{c_3} = 0, \quad \text{and} \quad \ell_{c_3} = \alpha Y_{3,0}(t)e^{-rt},$$
implies

$$\frac{\partial L}{\partial c_3} = \int_0^T \alpha Y_{3,0}(t)e^{-rt} dt.$$

For c_4 we get,

$$F_{c_4} = 0, \quad G_{c_4} = 0, \quad \text{and} \quad \ell_{c_4} = \alpha Y_{4,0}(t)e^{-rt},$$
implies,

$$\frac{\partial L}{\partial c_4} = \int_0^T \alpha Y_{4,0}(t)e^{-rt} dt.$$

QALYs, q_i

For the HIV infectious disease model, without an intervention, the sensitivity equations for QALYs is evaluated for each of the population classes.

For q_0 we get,

$$F_{q_0} = 0, \quad G_{q_0} = 0, \quad \text{and} \quad \ell_{q_0} = (\alpha - 1)Y_{0,0}(t)e^{-rt},$$
implies,

$$\frac{\partial L}{\partial q_0} = \int_0^T (\alpha - 1)Y_{0,0}(t)e^{-rt} dt.$$

For q_1 we get,

$$F_{q_1} = 0, \quad G_{q_1} = 0, \quad \text{and} \quad \ell_{q_1} = (\alpha - 1)Y_{1,0}(t)e^{-rt},$$
implies,

$$\frac{\partial L}{\partial q_1} = \int_0^T (\alpha - 1) Y_{1,0}(t) e^{-rt} dt.$$

For q_2 we get,

$$F_{q_2} = 0, \quad G_{q_2} = 0, \quad \text{and} \quad \ell_{q_2} = (\alpha - 1) Y_{2,0}(t) e^{-rt},$$
implies,

$$\frac{\partial L}{\partial q_2} = \int_0^T (\alpha - 1) Y_{2,0}(t) e^{-rt} dt.$$

For q_3 we get,

$$F_{q_3} = 0, \quad G_{q_3} = 0, \quad \text{and} \quad \ell_{q_3} = (\alpha - 1) Y_{3,0}(t) e^{-rt},$$
implies,

$$\frac{\partial L}{\partial q_3} = \int_0^T (\alpha - 1) Y_{3,0}(t) e^{-rt} dt.$$

For q_4 we get,

$$F_{q_4} = 0, \quad G_{q_4} = 0, \quad \text{and} \quad \ell_{q_4} = (\alpha - 1) Y_{4,0}(t) e^{-rt},$$
implies,

$$\frac{\partial L}{\partial q_4} = \int_0^T (\alpha - 1) Y_{4,0}(t) e^{-rt} dt.$$

Annual discount rate, r

For the HIV infectious disease model, without an intervention, the sensitivity equation for the annual discount rate is defined by the following.

$$F_r = 0, \quad G_r = 0, \quad \text{and}$$

$$\ell_r = -t\Big(\alpha \sum_{i=0}^{i=4} c_i Y_{i,0}(t) - (1-\alpha) \sum_{i=0}^{i=4} q_i Y_{i,0}(t)\Big)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial r} = \int_0^T -t\Big(\alpha \sum_{i=0}^{i=4} c_i Y_{i,0}(t) - (1-\alpha) \sum_{i=0}^{i=4} q_i Y_{i,0}(t)\Big)e^{-rt} dt.$$

Weight for combining objectives for optimization, α

For the HIV infectious disease model, without an intervention, the sensitivity equation for the weight introduced to evaluate the multi-objective optimization is defined by the following.

$$F_\alpha = 0, \quad G_\alpha = 0, \quad \text{and}$$

$$\ell_\alpha = \Big(\sum_{i=0}^{i=4} c_i Y_{i,0}(t) + \sum_{i=0}^{i=4} q_i Y_{i,0}(t)\Big)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial \alpha} = \int_0^T \Big(\sum_{i=0}^{i=4} c_i Y_{i,0}(t) + \sum_{i=0}^{i=4} q_i Y_{i,0}(t)\Big)e^{-rt} dt.$$

C.2 Therapeutic Vaccine Program

For the model with only the therapeutic vaccine we have following system of ordinary differential equations

$$\frac{dY_{0,0}(t)}{dt} = (1 - \sum_{i=1}^{3} \rho_i)\mu Y_0 - (\mu + p_0\lambda(t))Y_{0,0}(t)$$

$$\frac{dY_{1,0}(t)}{dt} = \rho_1\mu Y_0 + p_0\lambda(t)Y_{0,0}(t) - (\sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t)$$

$$\frac{dY_{2,0}(t)}{dt} = \rho_2\mu Y_0 + \sigma\xi Y_{1,0}(t) - (\nu_t + \mu_{2,0} + \mu)Y_{2,0}(t)$$

$$\frac{dY_{2,1}(t)}{dt} = \nu_t Y_{2,0}(t) - (\mu_{2,1} + \mu)Y_{2,1}(t)$$

$$\frac{dY_{3,0}(t)}{dt} = \rho_3\mu Y_0 + \sum_{i=1}^{i=2}\sum_{j=0}^{j=1} \mu_{i,j}Y_{i,j}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t)$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t)$$

were $\lambda(t) = \dfrac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,j}(t)}$, along with the initial state

$$Y_{0,0}(0) = (1 - \phi_0)Y_0$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}}\phi_0 Y_0, \text{ for } i = 1,2,3,4$$

$$Y_{2,1}(0) = 0$$

and the corresponding payoff functional

$$L(T) = \int_0^T \left[\alpha\left(\kappa_t\nu_t Y_{2,0}(t) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} c_i Y_{i,j}(t)\right) - (1-\alpha)\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} q_i Y_{i,j}(t)\right) \right] e^{-rt} dt.$$

In all, we are considering 42 parameters for the model with the therapeutic vaccine only.
$$\Theta = \{\mu, \mu_{1,0}, \mu_{2,0}, \mu_{2,1}, \mu_{3,0}, \mu_{4,0}, p_0, p_1, p_2, p_3, p_4, \beta_{1,0}, \beta_{2,0}, \beta_{2,1}, \beta_{3,0}, \beta_{4,0}, \dots$$
$$\dots, \eta_{00,10}, \eta_{00,20}, \eta_{00,21}\eta_{00,30}, \eta_{00,40}, \nu_t, \sigma, \xi, Y_0, \phi_0, \rho_1, \rho_2, \rho_3, \dots$$
$$\dots, c_0, c_1, c_2, c_3, c_4, q_0, q_1, q_2, q_3, q_4, \kappa_t, r, \alpha\}$$

To set up the sensitivity equations for each of the 42 parameters, we'll first present the vectors

using the notation we introduced in the chapter 6.

$$F(\dot{Y}, Y, \Theta) = \begin{bmatrix} \dot{Y}_{0,0}(t) + (\mu + p_0\lambda(t))Y_{0,0}(t) - (1 - \sum_{i=1}^{i=3}\rho_i)\mu Y_0 \\ \dot{Y}_{1,0}(t) - p_0\lambda(t)Y_{0,0}(t) + (\sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) - \rho_1\mu Y_0 \\ \dot{Y}_{2,0}(t) - \sigma\xi Y_{1,0}(t) + (\mu_{2,0} + \mu + \nu_t)Y_{2,0}(t) - \rho_2\mu Y_0 \\ \dot{Y}_{2,1}(t) - \nu_t Y_{2,0}(t) - (\mu_{2,1} + \mu)Y_{2,1}(t) \\ \dot{Y}_{3,0}(t) - \mu_{1,0}Y_{1,0}(t) - \mu_{2,0}Y_{2,0}(t) - \mu_{2,1}Y_{2,1}(t) + (\mu_{3,0} + \mu)Y_{3,0}(t) - \rho_3\mu Y_0 \\ \dot{Y}_{4,0}(t) - \mu_{3,0}Y_{3,0}(t) + (\mu_{4,0} + \mu)Y_{4,0}(t) \end{bmatrix}$$

$$G(Y(0), \Theta) = \begin{bmatrix} Y_{0,0}(0) - (1 - \phi_0)Y_0 \\ Y_{1,0}(0) - \phi_0\left(\dfrac{1/\mu_{1,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}}\right)Y_0 \\ Y_{2,0}(0) - \phi_0\left(\dfrac{1/\mu_{2,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}}\right)Y_0 \\ Y_{2,1}(0) \\ Y_{3,0}(0) - \phi_0\left(\dfrac{1/\mu_{3,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}}\right)Y_0 \\ Y_{4,0}(0) - \phi_0\left(\dfrac{1/\mu_{4,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}}\right)Y_0 \end{bmatrix}$$

$$\ell(Y, \Theta) = \left[\alpha\left(\kappa_t\nu_t Y_{2,0}(t) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} c_i Y_{i,j}(t)\right) - (1 - \alpha)\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} q_i Y_{i,j}(t)\right)\right]e^{-rt}$$

Then, by the adjoint variable method, the sensitivity equations are defined by,

$$\frac{\partial L}{\partial \vartheta_i} = \int_0^T \left(\ell_{\vartheta_i} + \Lambda^\intercal F_{\vartheta_i}\right)dt + \Lambda^\intercal\Big|_{t=0} G_{\vartheta_i}$$

where $\Lambda^\intercal = [\Lambda_{0,0}, \Lambda_{1,0}, \Lambda_{2,0}, \Lambda_{2,1}, \Lambda_{3,0}, \Lambda_{4,0}]$. Thus, in defining the sensitivity equations for each of the parameters in Θ we will have to evaluate F_{ϑ_i}, G_{ϑ_i} and ℓ_{ϑ_i}.

Average non-disease related death rate, μ

For the HIV infectious disease model, with the therapeutic vaccine only, the sensitivity equation for the non-disease related death rate is defined by the following.

$$F_\mu = \begin{bmatrix} Y_{0,0}(t) - (1 - \sum_{i=1}^{i=3} \rho_i)Y_0 \\ Y_{1,0}(t) - \rho_1 Y_0 \\ Y_{2,0}(t) - \rho_2 Y_0 \\ Y_{2,1}(t) \\ Y_{3,0}(t) - \rho_3 Y_0 \\ Y_{4,0}(t) \end{bmatrix}, \qquad G_\mu = 0, \qquad \text{and} \qquad \ell_\mu = 0,$$

implies,

$$\frac{\partial L}{\partial \mu} = \int_0^T \Big[\Lambda_{0,0}(t)(Y_{0,0}(t) - (1 - \sum_{i=1}^{i=3} \rho_i)Y_0) + \Lambda_{1,0}(t)(Y_{1,0}(t) - \rho_1 Y_0)$$
$$+ \Lambda_{2,0}(t)(Y_{2,0}(t) - \rho_2 Y_0) + \Lambda_{2,1}(t)Y_{2,1}(t) + \Lambda_{3,0}(t)(Y_{3,0}(t) - \rho_3 Y_0)$$
$$+ \Lambda_{4,0}(t)Y_{4,0}(t)) \Big] dt.$$

Disease related transition rates, $\mu_{i,0}$

For the HIV infectious disease model, with the therapeutic vaccine only, the sensitivity equation for the rate at which an infected individual transitions out of each of the disease classes are each evaluated.

For $\mu_{1,0}$, we get,

$$F_{\mu_{1,0}} = \begin{bmatrix} 0 \\ Y_{1,0}(t) \\ 0 \\ 0 \\ -Y_{1,0}(t) \\ 0 \end{bmatrix},$$

$$G_{\mu_{1,0}} = \frac{\phi_0 Y_0 (1/\mu_{1,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \begin{bmatrix} 0 \\ 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0} \\ -1/\mu_{2,0} \\ 0 \\ -1/\mu_{3,0} \\ -1/\mu_{4,0} \end{bmatrix}, \qquad \text{and}$$

$$\ell_{\mu_{1,0}} = 0,$$

implies,

$$\frac{\partial L}{\partial \mu_{1,0}} = \int_0^T Y_{1,0}(t)(\Lambda_{1,0}(t) - \Lambda_{3,0}(t))dt$$
$$+ \frac{\phi_0 Y_0 (1/\mu_{1,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2}\Big((1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0})\Lambda_{1,0}(0)$$
$$- (1/\mu_{2,0})\Lambda_{2,0}(0) - (1/\mu_{3,0})\Lambda_{3,0}(0) - (1/\mu_{4,0})\Lambda_{4,0}(0)\Big).$$

For $\mu_{2,0}$ we get,

$$F_{\mu_{2,0}} = \begin{bmatrix} 0 \\ 0 \\ Y_{2,0}(t) \\ 0 \\ -Y_{2,0}(t) \\ 0 \end{bmatrix},$$

$$G_{\mu_{2,0}} = \frac{\phi_0 Y_0 (1/\mu_{2,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \begin{bmatrix} 0 \\ -1/\mu_{1,0} \\ 1/\mu_{1,0} + 1/\mu_{3,0} + 1/\mu_{4,0} \\ 0 \\ -1/\mu_{3,0} \\ -1/\mu_{4,0} \end{bmatrix}, \quad \text{and}$$

$\ell_{\mu_{2,0}} = 0,$

implies,

$$\frac{\partial L}{\partial \mu_{2,0}} = \int_0^T Y_{2,0}(t)(\Lambda_{2,0}(t) - \Lambda_{3,0}(t))dt$$
$$+ \frac{\phi_0 Y_0 (1/\mu_{2,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2}\Big((1/\mu_{1,0} + 1/\mu_{3,0} + 1/\mu_{4,0})\Lambda_{2,0}(0)$$
$$- (1/\mu_{1,0})\Lambda_{1,0}(0) - (1/\mu_{3,0})\Lambda_{3,0}(0) - (1/\mu_{4,0})\Lambda_{4,0}(0)\Big).$$

For $\mu_{2,1}$ we get,

$$
F_{\mu_{2,1}} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ Y_{2,1}(t) \\ -Y_{2,1}(t) \\ 0 \end{bmatrix}, \quad G_{\mu_{2,1}} = 0, \quad \text{and} \quad \ell_{\mu_{2,1}} = 0,
$$

implies,

$$
\frac{\partial L}{\partial \mu_{2,1}} = \int_0^T Y_{2,1}(t)(\Lambda_{2,1}(t) - \Lambda_{3,0}(t))dt.
$$

For $\mu_{3,0}$ we get,

$$
F_{\mu_{3,0}} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ Y_{3,0}(t) \\ -Y_{3,0}(t) \end{bmatrix},
$$

$$
G_{\mu_{3,0}} = \frac{\phi_0 Y_0 (1/\mu_{3,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \begin{bmatrix} 0 \\ -1/\mu_{1,0} \\ -1/\mu_{2,0} \\ 0 \\ 1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{4,0} \\ -1/\mu_{4,0} \end{bmatrix} \quad \text{and}
$$

$\ell_{\mu_{3,0}} = 0$,

implies,

$$
\frac{\partial L}{\partial \mu_{3,0}} = \int_0^T Y_{3,0}(t)(\Lambda_{3,0}(t) - \Lambda_{4,0}(t))dt
$$
$$
+ \frac{\phi_0 Y_0 (1/\mu_{3,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \Big((1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{4,0})\Lambda_{3,0}(0)
$$
$$
- (1/\mu_{1,0})\Lambda_{1,0}(0) - (1/\mu_{2,0})\Lambda_{2,0}(0) - (1/\mu_{4,0})\Lambda_{4,0}(0) \Big).
$$

For $\mu_{4,0}$ we get,

$$F_{\mu_{4,0}} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ Y_{4,0}(t) \end{bmatrix},$$

$$G_{\mu_{4,0}} = \frac{\phi_0 Y_0 (1/\mu_{4,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \begin{bmatrix} 0 \\ -1/\mu_{1,0} \\ -1/\mu_{2,0} \\ 0 \\ -1/\mu_{3,0} \\ 1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} \end{bmatrix}, \quad \text{and}$$

$$\ell_{\mu_{4,0}} = 0,$$

implies,

$$\frac{\partial L}{\partial \mu_{4,0}} = \int_0^T Y_{4,0}(t) \Lambda_{4,0}(t) dt$$

$$+ \frac{\phi_0 Y_0 (1/\mu_{4,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \Big((1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0}) \Lambda_{4,0}(0)$$

$$- (1/\mu_{1,0}) \Lambda_{1,0}(0) - (1/\mu_{2,0}) \Lambda_{2,0}(0) - (1/\mu_{3,0}) \Lambda_{3,0}(0) \Big).$$

Average number of partners an individual will have in a year, for each population class, p_i

For the HIV infectious disease model, with the therapeutic vaccine only, the sensitivity equation for the average number of partners an individual, with disease status i, will have within a year are evaluated for each population classes.

For p_0 we get,

$$F_{p_0} = \begin{bmatrix} Y_{0,0}(t)\left(\lambda(t) + p_0\left[\dfrac{\partial \lambda}{\partial p_0}\right]\right) \\[2mm] -Y_{0,0}(t)\left(\lambda(t) + p_0\left[\dfrac{\partial \lambda}{\partial p_0}\right]\right) \\[2mm] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{with} \quad \frac{\partial \lambda}{\partial p_0} = \frac{-Y_{0,0}(t)\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_iY_{i,0}(t)\right)^2},$$

$G_{p_0} = 0$, and $\ell_{p_0} = 0$, implies

$$\frac{\partial L}{\partial p_0} = \int_0^T Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))\left(\lambda(t) + p_0\left[\frac{\partial \lambda}{\partial p_0}\right]\right)dt.$$

For p_1 we get,

$$F_{p_1} = \begin{bmatrix} p_0\left(\dfrac{\partial \lambda}{\partial p_1}\right)Y_{0,0}(t) \\[2mm] -p_0\left(\dfrac{\partial \lambda}{\partial p_1}\right)Y_{0,0}(t) \\[2mm] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

$$\text{with} \quad \frac{\partial \lambda}{\partial p_1} = \frac{\beta_{1,0}\eta_{00,10}Y_{1,0}(t)\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_iY_{i,j}(t)\right) - Y_{1,0}(t)\left(\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)\right)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_iY_{i,j}(t)\right)^2},$$

$G_{p_1} = 0$, and $\ell_{p_1} = 0$, implies

$$\frac{\partial L}{\partial p_1} = \int_0^T p_0\left(\frac{\partial \lambda}{\partial p_1}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.$$

For p_2 we get,

$$F_{p_2} = \begin{bmatrix} p_0\left(\dfrac{\partial\lambda}{\partial p_2}\right)Y_{0,0}(t) \\[2mm] -p_0\left(\dfrac{\partial\lambda}{\partial p_2}\right)Y_{0,0}(t) \\[2mm] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

with $\dfrac{\partial\lambda}{\partial p_2} = \dfrac{(\beta_{2,0}\eta_{00,20}Y_{2,0}(t) + \beta_{2,1}\eta_{00,21}Y_{2,1}(t))\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,j}(t)\right)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,j}(t)\right)^2}$

$$-\dfrac{(Y_{2,0}(t) + Y_{2,1}(t))\left(\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)\right)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,j}(t)\right)^2},$$

$G_{p_2} = 0$, and $\ell_{p_2} = 0$, implies

$$\frac{\partial L}{\partial p_2} = \int_0^T p_0\left(\frac{\partial\lambda}{\partial p_2}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.$$

For p_3 we get,

$$F_{p_3} = \begin{bmatrix} p_0\left(\dfrac{\partial\lambda}{\partial p_3}\right)Y_{0,0}(t) \\[2mm] -p_0\left(\dfrac{\partial\lambda}{\partial p_3}\right)Y_{0,0}(t) \\[2mm] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

with $\dfrac{\partial\lambda}{\partial p_3} = \dfrac{\beta_{3,0}\eta_{00,30}Y_{3,0}(t)\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,j}(t)\right) - Y_{3,0}(t)\left(\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)\right)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,j}(t)\right)^2},$

$G_{p_3} = 0$, and $\ell_{p_3} = 0$, implies

$$\frac{\partial L}{\partial p_3} = \int_0^T p_0\left(\frac{\partial \lambda}{\partial p_3}\right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.$$

For p_4 we get,

$$F_{p_4} = \begin{bmatrix} p_0\left(\dfrac{\partial \lambda}{\partial p_4}\right) Y_{0,0}(t) \\[2mm] -p_0\left(\dfrac{\partial \lambda}{\partial p_4}\right) Y_{0,0}(t) \\[2mm] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

with $\dfrac{\partial \lambda}{\partial p_4} = \dfrac{\beta_{4,0}\eta_{00,40}Y_{4,0}(t)\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)\right) - Y_{4,0}(t)\left(\sum_{i=1}^{i=4}\sum_{j=0}^{j=1}p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)\right)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j1}p_iY_{i,0}(t)\right)^2},$

$G_{p_4} = 0$, and $\ell_{p_4} = 0$, implies

$$\frac{\partial L}{\partial p_4} = \int_0^T p_0\left(\frac{\partial \lambda}{\partial p_4}\right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.$$

Infectivity rate for each of the infectious classes, $\beta_{i,0}$

For the HIV infectious disease model, with the therapeutic vaccine only, the sensitivity equation for the infectivity rates are evaluated for each of the infectious classes.

For $\beta_{1,0}$ we get,

$$
F_{\beta_{1,0}} = \begin{bmatrix} p_0\left(\dfrac{\partial\lambda}{\partial\beta_{1,0}}\right)Y_{0,0}(t) \\[2mm] -p_0\left(\dfrac{\partial\lambda}{\partial\beta_{1,0}}\right)Y_{0,0}(t) \\[2mm] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{with} \quad \dfrac{\partial\lambda}{\partial\beta_{1,0}} = \dfrac{p_1\eta_{00,10}Y_{1,0}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)},
$$

$G_{\beta_{1,0}} = 0$, and $\ell_{\beta_{1,0}} = 0$, implies

$$
\dfrac{\partial L}{\partial\beta_{1,0}} = \int_0^T p_0\left(\dfrac{\partial\lambda}{\partial\beta_{1,0}}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.
$$

For $\beta_{2,0}$ we get,

$$
F_{\beta_{2,0}} = \begin{bmatrix} p_0\left(\dfrac{\partial\lambda}{\partial\beta_{2,0}}\right)Y_{0,0}(t) \\[2mm] -p_0\left(\dfrac{\partial\lambda}{\partial\beta_{2,0}}\right)Y_{0,0}(t) \\[2mm] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad \text{with} \quad \dfrac{\partial\lambda}{\partial\beta_{2,0}} = \dfrac{p_2\eta_{00,20}Y_{2,0}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)}
$$

$G_{\beta_{2,0}} = 0$, and $\ell_{\beta_{2,0}} = 0$, implies

$$
\dfrac{\partial L}{\partial\beta_{2,0}} = \int_0^T p_0\left(\dfrac{\partial\lambda}{\partial\beta_{2,0}}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.
$$

For $\beta_{2,1}$ we get,

$$F_{\beta_{2,1}} = \begin{bmatrix} p_0\left(\dfrac{\partial\lambda}{\partial\beta_{2,1}}\right)Y_{0,0}(t) \\[2ex] -p_0\left(\dfrac{\partial\lambda}{\partial\beta_{2,1}}\right)Y_{0,0}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix}, \quad \text{with} \quad \frac{\partial\lambda}{\partial\beta_{2,1}} = \frac{p_2\eta_{00,21}Y_{2,1}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)}$$

$G_{\beta_{2,1}} = 0$, and $\ell_{\beta_{2,1}} = 0$, implies

$$\frac{\partial L}{\partial\beta_{2,1}} = \int_0^T p_0\left(\frac{\partial\lambda}{\partial\beta_{2,1}}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.$$

For $\beta_{3,0}$ we get,

$$F_{\beta_{3,0}} = \begin{bmatrix} p_0\left(\dfrac{\partial\lambda}{\partial\beta_{3,0}}\right)Y_{0,0}(t) \\[2ex] -p_0\left(\dfrac{\partial\lambda}{\partial\beta_{3,0}}\right)Y_{0,0}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix}, \quad \text{with} \quad \frac{\partial\lambda}{\partial\beta_{3,0}} = \frac{p_3\eta_{00,30}Y_{3,0}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)}$$

$G_{\beta_{3,0}} = 0$, and $\ell_{\beta_{3,0}} = 0$, implies

$$\frac{\partial L}{\partial\beta_{3,0}} = \int_0^T p_0\left(\frac{\partial\lambda}{\partial\beta_{3,0}}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.$$

For $\beta_{4,0}$ we get,

$$
F_{\beta_{4,0}} = \begin{bmatrix} p_0\left(\dfrac{\partial\lambda}{\partial\beta_{4,0}}\right)Y_{0,0}(t) \\[2ex] -p_0\left(\dfrac{\partial\lambda}{\partial\beta_{4,0}}\right)Y_{0,0}(t) \\[2ex] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad \text{with} \quad \frac{\partial\lambda}{\partial\beta_{4,0}} = \frac{p_4\eta_{00,40}Y_{4,0}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)}
$$

$G_{\beta_{4,0}} = 0$, and $\ell_{\beta_{4,0}} = 0$, implies

$$
\frac{\partial L}{\partial\beta_{4,0}} = \int_0^T p_0\left(\frac{\partial\lambda}{\partial\beta_{4,0}}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.
$$

Probability that a partnership between a susceptible individual and an infected individual is not protected by a condom, $\eta_{00,i0}$

For the HIV infectious disease model, with the therapeutic vaccine only, the sensitivity equations for the probability that a partnership between a susceptible individual with an infected individual is not protected by a condom are evaluated for each of the infectious classes.

For $\eta_{00,10}$ we get,

$$
F_{\eta_{00,10}} = \begin{bmatrix} p_0\left(\dfrac{\partial\lambda}{\partial\eta_{00,10}}\right)Y_{0,0}(t) \\[2ex] -p_0\left(\dfrac{\partial\lambda}{\partial\eta_{00,10}}\right)Y_{0,0}(t) \\[2ex] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{with} \quad \frac{\partial\lambda}{\partial\eta_{00,10}} = \frac{p_1\beta_{1,0}Y_{1,0}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)},
$$

$G_{\eta_{00,10}} = 0$, and $\ell_{\eta_{00,10}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,10}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,10}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.$$

For $\eta_{00,20}$ we get,

$$F_{\eta_{00,20}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,20}} \right) Y_{0,0}(t) \\[2ex] - p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,20}} \right) Y_{0,0}(t) \\[2ex] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,20}} = \frac{p_2 \beta_{2,0} Y_{2,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$$

$G_{\eta_{00,20}} = 0$, and $\ell_{\eta_{00,20}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,20}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,20}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.$$

For $\eta_{00,21}$ we get,

$$F_{\eta_{00,21}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,21}} \right) Y_{0,0}(t) \\[2ex] - p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,21}} \right) Y_{0,0}(t) \\[2ex] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,21}} = \frac{p_2 \beta_{2,1} Y_{2,1}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$$

$G_{\eta_{00,21}} = 0$, and $\ell_{\eta_{00,21}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,21}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,21}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For $\eta_{00,30}$ we get,

$$F_{\eta_{00,30}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,30}} \right) Y_{0,0}(t) \\[2ex] - p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,30}} \right) Y_{0,0}(t) \\[2ex] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,30}} = \frac{p_3 \beta_{3,0} Y_{3,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,0}(t)}$$

$G_{\eta_{00,30}} = 0$, and $\ell_{\eta_{00,30}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,30}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,30}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For $\eta_{00,40}$ we get,

$$F_{\eta_{00,40}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,40}} \right) Y_{0,0}(t) \\[2ex] - p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,40}} \right) Y_{0,0}(t) \\[2ex] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,40}} = \frac{p_4 \beta_{4,0} Y_{4,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,0}(t)}$$

$G_{\eta_{00,40}} = 0$, and $\ell_{\eta_{00,40}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,40}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,40}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.$$

Proportion of the asymptomatic-aware population that receives the therapeutic vaccine, ν_t

For the HIV infectious disease model, with the therapeutic vaccine only, the sensitivity equation for the parameter defining the proportion of the asymptomatic-aware population that receives the therapeutic vaccine is defined by the following.

$$F_{\nu_t} = \begin{bmatrix} 0 \\ 0 \\ Y_{2,0}(t) \\ -Y_{2,0}(t) \\ 0 \\ 0 \end{bmatrix}, \quad G_{\nu_t} = 0, \text{ and } \ell_{\nu_t} = 0,$$

implies,

$$\frac{\partial L}{\partial \nu_t} = \int_0^T Y_{2,0}(t)(\Lambda_{2,0}(t) - \Lambda_{2,1}(t))dt.$$

Parameters related to the rate at which asymptomatic-unaware individuals become aware, σ and ξ

For the HIV infectious disease model, with the therapeutic vaccine only, the sensitivity equations for the rate at which an asymptomatic-unaware individual becomes aware are evaluated for both the screening rate, σ, along with the true-positive rate of screening, ξ.

For σ we get,

$$F_\sigma = \begin{bmatrix} 0 \\ \xi Y_{1,0}(t) \\ -\xi Y_{1,0}(t) \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad G_\sigma = 0, \text{ and } \ell_\sigma = 0,$$

implies,

$$\frac{\partial L}{\partial \sigma} = \int_0^T \xi Y_{1,0}(t)(\Lambda_{1,0}(t) - \Lambda_{2,0}(t))dt.$$

For ξ we get,

$$F_\xi = \begin{bmatrix} 0 \\ \sigma Y_{1,0}(t) \\ -\sigma Y_{1,0}(t) \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad G_\xi = 0, \text{ and } \ell_\xi = 0,$$

implies,

$$\frac{\partial L}{\partial \xi} = \int_0^T \sigma Y_{1,0}(t)(\Lambda_{1,0}(t) - \Lambda_{2,0}(t))dt.$$

Total initial population, Y_0

For the HIV infectious disease model, with the therapeutic vaccine only, the sensitivity equation for the total initial population is defined by the following.

$$
F_{Y_0} = \begin{bmatrix} -\left(1 - \sum_{i=1}^{i=3} \rho_i\right)\mu \\ -\rho_1\mu \\ -\rho_2\mu \\ 0 \\ -\rho_3\mu \\ 0 \end{bmatrix},
$$

$$
G_{Y_0} = \begin{bmatrix} -(1 - \phi_0) \\ -\left(\dfrac{1/\mu_{1,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)\phi_0 \\ -\left(\dfrac{1/\mu_{2,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)\phi_0 \\ 0 \\ -\left(\dfrac{1/\mu_{3,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)\phi_0 \\ -\left(\dfrac{1/\mu_{4,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)\phi_0 \end{bmatrix}, \quad \text{and } \ell_{Y_0} = 0,
$$

implies,

$$
\frac{\partial L}{\partial Y_0} = \int_0^T -\mu\left(\left(1 - \sum_{i=1}^{1=3} \rho_i\right)\Lambda_{0,0}(t) + \rho_1\Lambda_{1,0}(t) + \rho_2\Lambda_{2,0}(t) + \rho_3\Lambda_{3,0}(t)\right)dt - (1 - \phi_0)\Lambda_{0,0}(0)
$$
$$
- \frac{\phi_0}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\Big((1/\mu_{1,0})\Lambda_{1,0}(0) + (1/\mu_{2,0})\Lambda_{2,0}(0)
$$
$$
+ (1/\mu_{3,0})\Lambda_{3,0}(0) + (1/\mu_{4,0})\Lambda_{4,0}(0)\Big).
$$

Seroprevalence of the infected population, ϕ_0

For the HIV infectious disease model, with the therapeutic vaccine only, the sensitivity equation for the seroprevalence of the infected population is defined by the following.

$$
F_{\phi_0} = 0, \quad G_{\phi_0} = \begin{bmatrix} Y_0 \\ -\left(\dfrac{1/\mu_{1,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)Y_0 \\ -\left(\dfrac{1/\mu_{2,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)Y_0 \\ 0 \\ -\left(\dfrac{1/\mu_{3,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)Y_0 \\ -\left(\dfrac{1/\mu_{4,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)Y_0 \end{bmatrix}, \quad \text{and } \ell_{\phi_0} = 0,
$$

implies,

$$\frac{\partial L}{\partial \phi_0} = Y_0 \Lambda_{0,0}(0) - \frac{Y_0}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}} \Big((1/\mu_{1,0})\Lambda_{1,0}(0) + (1/\mu_{2,0})\Lambda_{2,0}(0)$$
$$+ (1/\mu_{3,0})\Lambda_{3,0}(0) + (1/\mu_{4,0})\Lambda_{4,0}(0) \Big).$$

Distribution of disease-related immigration, ρ_i

For the HIV infectious disease model, with the therapeutic vaccine only, the sensitivity equations for the parameters associated with the distribution of disease-related immigration is evaluated for each of the respective classes.

For ρ_1 we get,

$$F_{\rho_1} = \begin{bmatrix} \mu Y_0 \\ -\mu Y_0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad G_{\rho_1} = 0, \quad \text{and} \quad \ell_{\rho_1} = 0,$$

implies,

$$\frac{\partial L}{\partial \rho_1} = \int_0^{20} \mu Y_0 (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For ρ_2 we get,

$$F_{\rho_2} = \begin{bmatrix} \mu Y_0 \\ 0 \\ -\mu Y_0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad G_{\rho_2} = 0, \quad \text{and} \quad \ell_{\rho_2} = 0,$$

implies,

$$\frac{\partial L}{\partial \rho_2} = \int_0^T \mu Y_0 (\Lambda_{0,0}(t) - \Lambda_{2,0}(t)) dt.$$

For ρ_3 we get,

$$F_{\rho_3} = \begin{bmatrix} \mu Y_0 \\ 0 \\ 0 \\ 0 \\ -\mu Y_0 \\ 0 \end{bmatrix}, \quad G_{\rho_3} = 0, \quad \text{and} \quad \ell_{\rho_3} = 0,$$

implies,

$$\frac{\partial L}{\partial \rho_3} = \int_0^{20} \mu Y_0 (\Lambda_{0,0}(t) - \Lambda_{3,0}(t)) dt.$$

Average yearly medical expenses for each class, c_i

For the HIV infectious disease model, with the therapeutic vaccine only, the sensitivity equations for the average yearly medical expenses is evaluated for each of the population classes.

For c_0 we get,

$$F_{c_0} = 0, \quad G_{c_0} = 0, \quad \text{and} \quad \ell_{c_0} = \alpha Y_{0,0}(t) e^{-rt},$$

implies,

$$\frac{\partial L}{\partial c_0} = \int_0^T \alpha Y_{0,0}(t) e^{-rt} dt.$$

For c_1 we get,

$$F_{c_1} = 0, \quad G_{c_1} = 0, \quad \text{and} \quad \ell_{c_1} = \alpha Y_{1,0}(t) e^{-rt},$$

implies,

$$\frac{\partial L}{\partial c_1} = \int_0^T \alpha Y_{1,0}(t)e^{-rt}dt.$$

For c_2 we get,

$$F_{c_2} = 0, \quad G_{c_2} = 0, \quad \text{and} \quad \ell_{c_2} = \alpha(Y_{2,0}(t) + Y_{2,1}(t))e^{-rt},$$

implies,

$$\frac{\partial L}{\partial c_2} = \int_0^T \alpha(Y_{2,0}(t) + Y_{2,1}(t))e^{-rt}dt.$$

For c_3 we get,

$$F_{c_3} = 0, \quad G_{c_3} = 0, \quad \text{and} \quad \ell_{c_3} = \alpha Y_{3,0}(t)e^{-rt},$$

implies

$$\frac{\partial L}{\partial c_3} = \int_0^T \alpha Y_{3,0}(t)e^{-rt}dt.$$

For c_4 we get,

$$F_{c_4} = 0, \quad G_{c_4} = 0, \quad \text{and} \quad \ell_{c_4} = \alpha Y_{4,0}(t)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial c_4} = \int_0^T \alpha Y_{4,0}(t)e^{-rt}dt.$$

QALYs, q_i

For the HIV infectious disease model, with the therapeutic vaccine only, the sensitivity equations for QALYs is evaluated for each of the population classes.

For q_0 we get,

$$F_{q_0} = 0, \quad G_{q_0} = 0, \quad \text{and} \quad \ell_{q_0} = (\alpha - 1)Y_{0,0}(t)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial q_0} = \int_0^T (\alpha - 1)Y_{0,0}(t)e^{-rt}dt.$$

For q_1 we get,

$$F_{q_1} = 0, \quad G_{q_1} = 0, \quad \text{and} \quad \ell_{q_1} = (\alpha - 1)Y_{1,0}(t)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial q_1} = \int_0^T (\alpha - 1)Y_{1,0}(t)e^{-rt}dt.$$

For q_2 we get,

$$F_{q_2} = 0, \quad G_{q_2} = 0, \quad \text{and} \quad \ell_{q_2} = (\alpha - 1)(Y_{2,0}(t) + Y_{2,1}(t))e^{-rt},$$

implies,

$$\frac{\partial L}{\partial q_2} = \int_0^T (\alpha - 1)(Y_{2,0}(t) + Y_{2,1}(t))e^{-rt}dt.$$

For q_3 we get,

$$F_{q_3} = 0, \quad G_{q_3} = 0, \quad \text{and} \quad \ell_{q_3} = (\alpha - 1)Y_{3,0}(t)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial q_3} = \int_0^T (\alpha - 1)Y_{3,0}(t)e^{-rt}dt.$$

For q_4 we get,

$$F_{q_4} = 0, \quad G_{q_4} = 0, \quad \text{and} \quad \ell_{q_4} = (\alpha - 1)Y_{4,0}(t)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial q_4} = \int_0^T (\alpha - 1)Y_{4,0}(t)e^{-rt}dt.$$

Direct cost for the therapeutic vaccine, κ_t

For the HIV infectious disease model, with the therapeutic vaccine only, the sensitivity equation for the direct cost for the therapeutic vaccine is defined by the following.

$$F_\alpha = 0, \quad G_\alpha = 0, \quad \text{and}$$

$$\ell_\alpha = \alpha \nu_t Y_{2,0}(t)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial \alpha} = \int_0^T \alpha \nu_t Y_{2,0}(t)e^{-rt}dt.$$

Annual discount rate, r

For the HIV infectious disease model, with the therapeutic vaccine only, the sensitivity equation for the annual discount rate is defined by the following.

$$F_r = 0, \quad G_r = 0, \quad \text{and}$$

$$\ell_r = -t\left(\alpha\left(\kappa_t\nu_t Y_{2,0}(t) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1}c_iY_{i,j}(t)\right) - (1-\alpha)\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}q_iY_{i,j}(t)\right)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial r} = \int_0^T -t\Big(\alpha\big(\kappa_t\nu_t Y_{2,0}(t) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} c_i Y_{i,j}(t)\big) - (1-\alpha)\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} q_i Y_{i,j}(t)\Big)e^{-rt}dt.$$

Weight for combining objectives for optimization, α

For the HIV infectious disease model, with the therapeutic vaccine only, the sensitivity equation for the weight introduced to evaluate the multi-objective optimization is defined by the following.

$$F_\alpha = 0, \quad G_\alpha = 0, \quad \text{and}$$

$$\ell_\alpha = \Big(\kappa_t\nu_t Y_{2,0}(t) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} c_i Y_{i,j}(t) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} q_i Y_{i,j}(t)\Big)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial \alpha} = \int_0^T \Big(\kappa_t\nu_t Y_{2,0}(t) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} c_i Y_{i,j}(t) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} q_i Y_{i,j}(t)\Big)e^{-rt}dt.$$

C.3   Preventative Vaccine Program

For the model with the preventative vaccine only we have the following system of ordinary differential equations

$$\frac{dY_{0,0}(t)}{dt} = \left(1 - \sum_{i=1}^{3} \rho_i\right)\mu Y_0 - (\nu_p + \mu + p_0\lambda(t))Y_{0,0}(t) + \omega Y_{0,1}(t)$$

$$\frac{dY_{0,1}(t)}{dt} = \nu_p Y_{0,0}(t) - (\mu + \omega + p_0(1 - \varepsilon)\lambda_\nu(t))Y_{0,1}(t)$$

$$\frac{dY_{1,0}(t)}{dt} = \rho_1\mu Y_0 + p_0\lambda(t)Y_{0,0}(t) - (\nu_p + \sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) + \omega Y_{1,1}(t)$$

$$\frac{dY_{1,1}(t)}{dt} = \nu_p Y_{1,0}(t) + p_0(1 - \varepsilon)\lambda_\nu(t)Y_{0,1}(t) - (\omega + \sigma\xi + \mu_{1,1} + \mu)Y_{1,1}(t)$$

$$\frac{dY_{2,0}(t)}{dt} = \rho_2\mu Y_0 + \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) - (\mu_{2,0} + \mu)Y_{2,0}(t)$$

$$\frac{dY_{3,0}(t)}{dt} = \rho_3\mu Y_0 + \sum_{i=1}^{i=2}\sum_{j=0}^{j=1}\mu_{i,j}Y_{i,j}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t)$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t)$$

were $\lambda(t) = \dfrac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_iY_{i,j}(t)}$ and $\lambda_\nu(t) = \dfrac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{01,ij}Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_iY_{i,j}(t)}$, along with the initial state

$$Y_{0,0}(0) = (1 - \phi_0)Y_0$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}}\phi_0 Y_0, \text{ for } i = 1, 2, 3, 4$$

$$Y_{i,1}(0) = 0 \text{ for } i = 0, 1$$

and the corresponding payoff functional

$$L(T) = \int_0^T \left[\alpha\left(\kappa_p\nu_p(Y_{0,0}(t) + Y_{1,0}(t)) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} c_iY_{i,j}(t)\right)\right.$$

$$\left. - (1 - \alpha)\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} q_iY_{i,j}(t)\right)\right]e^{-rt}dt.$$

In all, we are considering 49 parameters for the model without an intervention.

$\Theta = \{\mu, \mu_{1,0}, \mu_{1,1}, \mu_{2,0}, \mu_{3,0}, \mu_{4,0}, p_0, p_1, p_2, p_3, p_4, \beta_{1,0}, \beta_{1,1}, \beta_{2,0}, \beta_{3,0}, \beta_{4,0}, \ldots$

$\ldots, \eta_{00,10}, \eta_{00,11}, \eta_{00,20}, \eta_{00,30}, \eta_{00,40}, \eta_{01,10}, \eta_{01,11}, \eta_{01,20}, \eta_{01,30}, \eta_{01,40}, \ldots$

$\ldots, \varepsilon, \nu_p, \omega, \sigma, \xi, Y_0, \phi_0, \rho_1, \rho_2, \rho_3, c_0, c_1, c_2, c_3, c_4, q_0, q_1, q_2, q_3, q_4, r, \alpha, \kappa_p\}$

To set up the sensitivity equations for each of the 49 parameters, we'll first present the vectors

using the notation we introduced in the chapter 6.

$$F(\dot{Y}, Y, \Theta) =$$

$$
\begin{bmatrix}
\dot{Y}_{0,0}(t) + (\nu_p + \mu + p_0\lambda(t))Y_{0,0}(t) - \omega Y_{0,1}(t) - (1 - \sum_{i=1}^{i=3}\rho_i)\mu Y_0 \\
\dot{Y}_{0,1}(t) - \nu_p Y_{0,0}(t) + (\mu + \omega + p_0(1-\varepsilon)\lambda_\nu(t))Y_{0,1}(t) \\
\dot{Y}_{1,0}(t) - p_0\lambda(t)Y_{0,0}(t) + (\nu_p + \sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) - \omega Y_{1,1}(t) - \rho_1\mu Y_0 \\
\dot{Y}_{1,1}(t) - p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}(t) - \nu_p Y_{1,0}(t) + (\sigma\xi + \omega + \mu_{1,1} + \mu)Y_{1,1}(t) \\
\dot{Y}_{2,0}(t) - \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) + (\mu_{2,0} + \mu)Y_{2,0}(t) - \rho_2\mu Y_0 \\
\dot{Y}_{3,0}(t) - \mu_{1,0}Y_{1,0}(t) - \mu_{1,1}Y_{1,1}(t) - \mu_{2,0}Y_{2,0}(t) + (\mu_{3,0} + \mu)Y_{3,0}(t) - \rho_3\mu Y_0 \\
\dot{Y}_{4,0}(t) - \mu_{3,0}Y_{3,0}(t) + (\mu_{4,0} + \mu)Y_{4,0}(t)
\end{bmatrix}
$$

$$
G(Y(0), \Theta) =
\begin{bmatrix}
Y_{0,0}(0) - (1 - \phi_0)Y_0 \\
Y_{0,1}(0) \\
Y_{1,0}(0) - \phi_0\left(\dfrac{1/\mu_{1,0}}{\sum_{j=1}^{j=4}1/\mu_{j,0}}\right)Y_0 \\
Y_{1,1}(0) \\
Y_{2,0}(0) - \phi_0\left(\dfrac{1/\mu_{2,0}}{\sum_{j=1}^{j=4}1/\mu_{j,0}}\right)Y_0 \\
Y_{3,0}(0) - \phi_0\left(\dfrac{1/\mu_{3,0}}{\sum_{j=1}^{j=4}1/\mu_{j,0}}\right)Y_0 \\
Y_{4,0}(0) - \phi_0\left(\dfrac{1/\mu_{4,0}}{\sum_{j=1}^{j=4}1/\mu_{j,0}}\right)Y_0
\end{bmatrix}
$$

$$\ell(Y, \Theta) = \left[\alpha\left(\kappa_p\nu_p(Y_{0,0}(t) + Y_{1,0}(t)) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1}c_iY_{i,j}(t)\right) - (1-\alpha)\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}q_iY_{i,j}(t)\right)\right]e^{-rt}$$

Then, by the adjoint variable method, the sensitivity equations are defined by,

$$\frac{\partial L}{\partial \vartheta_i} = \int_0^{20}\left(\ell_{\vartheta_i} + \Lambda^{\mathsf{T}}F_{\vartheta_i}\right)dt + \Lambda^{\mathsf{T}}\Big|_{t=0}G_{\vartheta_i}$$

where $\Lambda^{\mathsf{T}} = [\Lambda_{0,0}, \Lambda_{0,1}, \Lambda_{1,0}, \Lambda_{1,1}, \Lambda_{2,0}, \Lambda_{3,0}, \Lambda_{4,0}]$. Thus, in defining the sensitivity equations for each of the parameters in Θ we will have to evaluate F_{ϑ_i}, G_{ϑ_i} and ℓ_{ϑ_i}.

Average non-disease related death rate, μ

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equation for the non-disease related death rate is defined by the following.

$$
F_\mu = \begin{bmatrix} Y_{0,0}(t) - (1 - \sum_{i=1}^{i=3} \rho_i)Y_0 \\ Y_{0,1}(t) \\ Y_{1,0}(t) - \rho_1 Y_0 \\ Y_{1,1}(t) \\ Y_{2,0}(t) - \rho_2 Y_0 \\ Y_{3,0}(t) - \rho_3 Y_0 \\ Y_{4,0}(t) \end{bmatrix}, \quad G_\mu = 0, \quad \text{and} \quad \ell_\mu = 0,
$$

implies,

$$
\frac{\partial L}{\partial \mu} = \int_0^T \Big[\Lambda_{0,0}(t)(Y_{0,0}(t) - (1 - \sum_{i=1}^{i=3} \rho_i)Y_0) + \Lambda_{0,1}(t)Y_{0,1}(t)
$$

$$
+ \Lambda_{1,0}(t)(Y_{1,0}(t) - \rho_1 Y_0) + \Lambda_{1,1}(t)Y_{1,1}(t) + \Lambda_{2,0}(t)(Y_{2,0}(t) - \rho_2 Y_0)
$$

$$
+ \Lambda_{3,0}(t)(Y_{3,0}(t) - \rho_3 Y_0) + \Lambda_{4,0}(t)Y_{4,0}(t)) \Big] dt.
$$

Disease related transition rates, $\mu_{i,0}$

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equation for the rate at which an infected individual transitions out of each of the disease classes are each evaluated.

For $\mu_{1,0}$, we get,

$$
F_{\mu_{1,0}} = \begin{bmatrix} 0 \\ 0 \\ Y_{1,0}(t) \\ 0 \\ 0 \\ -Y_{1,0}(t) \\ 0 \end{bmatrix},
$$

$$G_{\mu_{1,0}} = \frac{\phi_0 Y_0 (1/\mu_{1,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \begin{bmatrix} 0 \\ 0 \\ 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0} \\ 0 \\ -1/\mu_{2,0} \\ -1/\mu_{3,0} \\ -1/\mu_{4,0} \end{bmatrix}, \qquad \text{and}$$

$$\ell_{\mu_{1,0}} = 0,$$

implies,

$$\frac{\partial L}{\partial \mu_{1,0}} = \int_0^T Y_{1,0}(t)(\Lambda_{1,0}(t) - \Lambda_{3,0}(t))dt$$

$$+ \frac{\phi_0 Y_0 (1/\mu_{1,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \Big((1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0})\Lambda_{1,0}(0)$$

$$- (1/\mu_{2,0})\Lambda_{2,0}(0) - (1/\mu_{3,0})\Lambda_{3,0}(0) - (1/\mu_{4,0})\Lambda_{4,0}(0) \Big).$$

For $\mu_{1,1}$ we get,

$$F_{\mu_{1,1}} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ Y_{1,1}(t) \\ 0 \\ -Y_{1,1}(t) \\ 0 \end{bmatrix}, \qquad G_{\mu_{1,1}} = 0, \quad \text{and} \quad \ell_{\mu_{1,1}} = 0,$$

implies,

$$\frac{\partial L}{\partial \mu_{1,1}} = \int_0^T Y_{1,1}(t)(\Lambda_{1,1}(t) - \Lambda_{3,0}(t))dt.$$

For $\mu_{2,0}$ we get,

$$
F_{\mu_{2,0}} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ Y_{2,0}(t) \\ -Y_{2,0}(t) \\ 0 \end{bmatrix},
$$

$$
G_{\mu_{2,0}} = \frac{\phi_0 Y_0 (1/\mu_{2,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \begin{bmatrix} 0 \\ 0 \\ -1/\mu_{1,0} \\ 0 \\ 1/\mu_{1,0} + 1/\mu_{3,0} + 1/\mu_{4,0} \\ -1/\mu_{3,0} \\ -1/\mu_{4,0} \end{bmatrix}, \qquad \text{and}
$$

$\ell_{\mu_{2,0}} = 0$,

implies,

$$
\begin{aligned}
\frac{\partial L}{\partial \mu_{2,0}} = \int_0^T & Y_{2,0}(t)(\Lambda_{2,0}(t) - \Lambda_{3,0}(t))dt \\
& + \frac{\phi_0 Y_0 (1/\mu_{2,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \Big((1/\mu_{1,0} + 1/\mu_{3,0} + 1/\mu_{4,0})\Lambda_{2,0}(0) \\
& \qquad\qquad\qquad - (1/\mu_{1,0})\Lambda_{1,0}(0) - (1/\mu_{3,0})\Lambda_{3,0}(0) - (1/\mu_{4,0})\Lambda_{4,0}(0) \Big).
\end{aligned}
$$

For $\mu_{3,0}$ we get,

$$
F_{\mu_{3,0}} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ Y_{3,0}(t) \\ -Y_{3,0}(t) \end{bmatrix},
$$

$$G_{\mu_{3,0}} = \frac{\phi_0 Y_0 (1/\mu_{3,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \begin{bmatrix} 0 \\ 0 \\ -1/\mu_{1,0} \\ 0 \\ -1/\mu_{2,0} \\ 1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{4,0} \\ -1/\mu_{4,0} \end{bmatrix} \quad \text{and}$$

$$\ell_{\mu_{3,0}} = 0,$$

implies,

$$\frac{\partial L}{\partial \mu_{3,0}} = \int_0^T Y_{3,0}(t)(\Lambda_{3,0}(t) - \Lambda_{4,0}(t))dt$$
$$+ \frac{\phi_0 Y_0 (1/\mu_{3,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \Big((1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{4,0})\Lambda_{3,0}(0)$$
$$- (1/\mu_{1,0})\Lambda_{1,0}(0) - (1/\mu_{2,0})\Lambda_{2,0}(0) - (1/\mu_{4,0})\Lambda_{4,0}(0) \Big).$$

For $\mu_{4,0}$ we get,

$$F_{\mu_{4,0}} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ Y_{4,0}(t) \end{bmatrix},$$

$$G_{\mu_{4,0}} = \frac{\phi_0 Y_0 (1/\mu_{4,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \begin{bmatrix} 0 \\ 0 \\ -1/\mu_{1,0} \\ 0 \\ -1/\mu_{2,0} \\ -1/\mu_{3,0} \\ 1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} \end{bmatrix}, \quad \text{and}$$

$$\ell_{\mu_{4,0}} = 0,$$

implies,

$$\frac{\partial L}{\partial \mu_{4,0}} = \int_0^T Y_{4,0}(t)\Lambda_{4,0}(t)dt$$

$$+ \frac{\phi_0 Y_0 (1/\mu_{4,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2}\Big((1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0})\Lambda_{4,0}(0)$$

$$- (1/\mu_{1,0})\Lambda_{1,0}(0) - (1/\mu_{2,0})\Lambda_{2,0}(0) - (1/\mu_{3,0})\Lambda_{3,0}(0)\Big).$$

Average number of partners an individual will have in a year, for each population class, p_i

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equation for the average number of partners an individual, with disease status i, will have within a year are evaluated for each population classes.

For p_0 we get,

$$F_{p_0} = \begin{bmatrix} Y_{0,0}(t)\left(\lambda(t) + p_0\left[\frac{\partial\lambda}{\partial p_0}\right]\right) \\ (1-\varepsilon)Y_{0,0}(t)\left(\lambda_\nu(t) + p_0\left[\frac{\partial\lambda_\nu}{\partial p_0}\right]\right) \\ -Y_{0,0}(t)\left(\lambda(t) + p_0\left[\frac{\partial\lambda}{\partial p_0}\right]\right) \\ -(1-\varepsilon)Y_{0,0}(t)\left(\lambda_\nu(t) + p_0\left[\frac{\partial\lambda_\nu}{\partial p_0}\right]\right) \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

$$\text{with } \frac{\partial\lambda}{\partial p_0} = \frac{-(Y_{0,0}(t) + Y_{0,1}(t))\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,0}(t)\right)^2}$$

$$\text{and } \frac{\partial\lambda_\nu}{\partial p_0} = \frac{-(Y_{0,0}(t) + Y_{0,1}(t))\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{01,ij}Y_{i,j}(t)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,0}(t)\right)^2},$$

$G_{p_0} = 0$, and $\ell_{p_0} = 0$, implies

$$\frac{\partial L}{\partial p_0} = \int_0^T Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))\left(\lambda(t) + p_0\left[\frac{\partial\lambda}{\partial p_0}\right]\right)$$

$$+ (1-\varepsilon)Y_{0,1}(t)(\Lambda_{0,1}(t) - \Lambda_{1,1}(t))\left(\lambda_\nu(t) + p_0\left[\frac{\partial\lambda_\nu}{\partial p_0}\right]\right)dt.$$

For p_1 we get,

$$F_{p_1} = \begin{bmatrix} p_0\left(\frac{\partial\lambda}{\partial p_1}\right)Y_{0,0}(t) \\[2mm] p_0(1-\varepsilon)\left(\frac{\partial\lambda\nu}{\partial p_1}\right)Y_{0,1}(t) \\[2mm] -p_0\left(\frac{\partial\lambda}{\partial p_1}\right)Y_{0,0}(t) \\[2mm] -p_0(1-\varepsilon)\left(\frac{\partial\lambda\nu}{\partial p_1}\right)Y_{0,1}(t) \\[2mm] 0 \\[2mm] 0 \\[2mm] 0 \end{bmatrix}$$

with $\frac{\partial\lambda}{\partial p_1} = \dfrac{(\beta_{1,0}\eta_{00,10}Y_{1,0}(t) + \beta_{1,1}\eta_{00,11}Y_{1,1}(t))\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)\right)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)\right)^2}$

$$- \frac{(Y_{1,0}(t) + Y_{1,1}(t))\left(\sum_{i=1}^{i=4}\sum_{j=0}^{j=1}p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)\right)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)\right)^2}$$

and $\frac{\partial\lambda_\nu}{\partial p_1} = \dfrac{(\beta_{1,0}\eta_{01,10}Y_{1,0}(t) + \beta_{1,1}\eta_{01,11}Y_{1,1}(t))\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)\right)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)\right)^2}$

$$- \frac{(Y_{1,0}(t) + Y_{1,1}(t))\left(\sum_{i=1}^{i=4}\sum_{j=0}^{j=1}p_i\beta_{i,j}\eta_{01,ij}Y_{i,j}(t)\right)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)\right)^2}$$

$G_{p_1} = 0$, and $\ell_{p_1} = 0$, implies

$$\frac{\partial L}{\partial p_1} = \int_0^T p_0\left[\left(\frac{\partial\lambda}{\partial p_1}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1-\varepsilon)\left(\frac{\partial\lambda_\nu}{\partial p_1}\right)Y_{0,1}(t)(\Lambda_{0,1}(t) - \Lambda_{1,1}(t))\right]dt.$$

For p_2 we get,

$$F_{p_2} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial p_2} \right) Y_{0,0}(t) \\[2ex] p_0(1 - \varepsilon) \left(\dfrac{\partial \lambda \nu}{\partial p_2} \right) Y_{0,1}(t) \\[2ex] - p_0 \left(\dfrac{\partial \lambda}{\partial p_2} \right) Y_{0,0}(t) \\[2ex] - p_0(1 - \varepsilon) \left(\dfrac{\partial \lambda \nu}{\partial p_2} \right) Y_{0,1}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix}$$

with $\dfrac{\partial \lambda}{\partial p_2} = \dfrac{\beta_{2,0}\eta_{00,20}Y_{2,0}(t)\left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right) - Y_{2,0}(t)\left(\sum_{i=1}^{i=4} \sum_{j=0}^{j=1} p_i \beta_{i,j}\eta_{00,ij}Y_{i,j}(t) \right)}{\left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right)^2}$

and $\dfrac{\partial \lambda_\nu}{\partial p_2} = \dfrac{\beta_{2,0}\eta_{01,20}Y_{2,0}(t)\left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right) - Y_{2,0}(t)\left(\sum_{i=1}^{i=4} \sum_{j=0}^{j=1} p_i \beta_{i,j}\eta_{01,ij}Y_{i,j}(t) \right)}{\left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right)^2}$

$G_{p_2} = 0$, and $\ell_{p_2} = 0$, implies

$$\frac{\partial L}{\partial p_2} = \int_0^T p_0 \left[\left(\frac{\partial \lambda}{\partial p_2} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1 - \varepsilon)\left(\frac{\partial \lambda_\nu}{\partial p_2} \right) Y_{0,1}(t)(\Lambda_{0,1}(t) - \Lambda_{1,1}(t)) \right] dt.$$

For p_3 we get,

$$
F_{p_3} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial p_3} \right) Y_{0,0}(t) \\[2ex] p_0(1-\varepsilon) \left(\dfrac{\partial \lambda \nu}{\partial p_3} \right) Y_{0,1}(t) \\[2ex] -p_0 \left(\dfrac{\partial \lambda}{\partial p_3} \right) Y_{0,0}(t) \\[2ex] -p_0(1-\varepsilon) \left(\dfrac{\partial \lambda \nu}{\partial p_3} \right) Y_{0,1}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix}
$$

with $\dfrac{\partial \lambda}{\partial p_3} = \dfrac{\beta_{3,0}\eta_{00,30}Y_{3,0}(t)\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right) - Y_{3,0}(t)\left(\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i \beta_{i,j}\eta_{00,ij}Y_{i,j}(t) \right)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right)^2}$

and $\dfrac{\partial \lambda_\nu}{\partial p_3} = \dfrac{\beta_{3,0}\eta_{01,30}Y_{3,0}(t)\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right) - Y_{3,0}(t)\left(\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i \beta_{i,j}\eta_{01,ij}Y_{i,j}(t) \right)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right)^2}$

$G_{p_3} = 0$, and $\ell_{p_3} = 0$, implies

$$
\frac{\partial L}{\partial p_3} = \int_0^T p_0 \left[\left(\frac{\partial \lambda}{\partial p_3} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1-\varepsilon)\left(\frac{\partial \lambda_\nu}{\partial p_3} \right) Y_{0,1}(t)(\Lambda_{0,1}(t) - \Lambda_{1,1}(t)) \right] dt.
$$

For p_4 we get,

$$F_{p_4} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial p_4} \right) Y_{0,0}(t) \\[2ex] p_0 (1 - \varepsilon) \left(\dfrac{\partial \lambda \nu}{\partial p_4} \right) Y_{0,1}(t) \\[2ex] - p_0 \left(\dfrac{\partial \lambda}{\partial p_4} \right) Y_{0,0}(t) \\[2ex] - p_0 (1 - \varepsilon) \left(\dfrac{\partial \lambda \nu}{\partial p_4} \right) Y_{0,1}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix}$$

with $\dfrac{\partial \lambda}{\partial p_4} = \dfrac{\beta_{4,0} \eta_{00,40} Y_{4,0}(t) \left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right) - Y_{4,0}(t) \left(\sum_{i=1}^{i=4} \sum_{j=0}^{j=1} p_i \beta_{i,j} \eta_{00,ij} Y_{i,j}(t) \right)}{\left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right)^2}$

and $\dfrac{\partial \lambda_\nu}{\partial p_4} = \dfrac{\beta_{4,0} \eta_{01,40} Y_{4,0}(t) \left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right) - Y_{4,0}(t) \left(\sum_{i=1}^{i=4} \sum_{j=0}^{j=1} p_i \beta_{i,j} \eta_{01,ij} Y_{i,j}(t) \right)}{\left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right)^2}$

$G_{p_4} = 0$, and $\ell_{p_4} = 0$, implies

$$\frac{\partial L}{\partial p_4} = \int_0^T p_0 \left[\left(\frac{\partial \lambda}{\partial p_4} \right) Y_{0,0}(t) (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1 - \varepsilon) \left(\frac{\partial \lambda_\nu}{\partial p_4} \right) Y_{0,1}(t) (\Lambda_{0,1}(t) - \Lambda_{1,1}(t)) \right] dt.$$

Infectivity rate for each of the infectious classes, $\beta_{i,0}$

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equation for the infectivity rates are evaluated for each of the infectious classes.

For $\beta_{1,0}$ we get,

$$F_{\beta_{1,0}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{1,0}} \right) Y_{0,0}(t) \\[2ex] p_0 (1 - \varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{1,0}} \right) Y_{0,1}(t) \\[2ex] - p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{1,0}} \right) Y_{0,0}(t) \\[2ex] - p_0 (1 - \varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{1,0}} \right) Y_{0,1}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix}$$

with $\quad \dfrac{\partial \lambda}{\partial \beta_{1,0}} = \dfrac{p_1 \eta_{00,10} Y_{1,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)} \quad$ and $\quad \dfrac{\partial \lambda_\nu}{\partial \beta_{1,0}} = \dfrac{p_1 \eta_{01,10} Y_{1,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$

$G_{\beta_{1,0}} = 0$, and $\ell_{\beta_{1,0}} = 0$, implies

$$\frac{\partial L}{\partial \beta_{1,0}} = \int_0^T p_0 \left[\left(\frac{\partial \lambda}{\partial \beta_{1,0}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1 - \varepsilon) \left(\frac{\partial \lambda_\nu}{\partial \beta_{1,0}} \right) Y_{0,1}(t)(\Lambda_{0,1}(t) - \Lambda_{1,1}(t)) \right] dt.$$

For $\beta_{1,1}$ we get,

$$F_{\beta_{1,1}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{1,1}} \right) Y_{0,0}(t) \\[2ex] p_0 (1 - \varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{1,1}} \right) Y_{0,1}(t) \\[2ex] - p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{1,1}} \right) Y_{0,0}(t) \\[2ex] - p_0 (1 - \varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{1,1}} \right) Y_{0,1}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix}$$

with $\quad \dfrac{\partial \lambda}{\partial \beta_{1,1}} = \dfrac{p_1 \eta_{00,11} Y_{1,1}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)} \quad$ and $\quad \dfrac{\partial \lambda_\nu}{\partial \beta_{1,1}} = \dfrac{p_1 \eta_{01,11} Y_{1,1}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$

$G_{\beta_{1,1}} = 0$, and $\ell_{\beta_{1,1}} = 0$, implies

$$\frac{\partial L}{\partial \beta_{1,1}} = \int_0^T p_0 \left[\left(\frac{\partial \lambda}{\partial \beta_{1,1}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1-\varepsilon) \left(\frac{\partial \lambda_\nu}{\partial \beta_{1,1}} \right) Y_{0,1}(t)(\Lambda_{0,1}(t) - \Lambda_{1,1}(t)) \right] dt.$$

For $\beta_{2,0}$ we get,

$$F_{\beta_{2,0}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{2,0}} \right) Y_{0,0}(t) \\[2ex] p_0(1-\varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{2,0}} \right) Y_{0,1}(t) \\[2ex] - p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{2,0}} \right) Y_{0,0}(t) \\[2ex] - p_0(1-\varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{2,0}} \right) Y_{0,1}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix}$$

with $\quad \dfrac{\partial \lambda}{\partial \beta_{2,0}} = \dfrac{p_2 \eta_{00,20} Y_{2,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)} \quad$ and $\quad \dfrac{\partial \lambda_\nu}{\partial \beta_{2,0}} = \dfrac{p_2 \eta_{01,20} Y_{2,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$

$G_{\beta_{2,0}} = 0$, and $\ell_{\beta_{2,0}} = 0$, implies

$$\frac{\partial L}{\partial \beta_{2,0}} = \int_0^T p_0 \left[\left(\frac{\partial \lambda}{\partial \beta_{2,0}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1-\varepsilon) \left(\frac{\partial \lambda_\nu}{\partial \beta_{2,0}} \right) Y_{0,1}(t)(\Lambda_{0,1}(t) - \Lambda_{1,1}(t)) \right] dt.$$

For $\beta_{3,0}$ we get,

$$F_{\beta_{3,0}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{3,0}} \right) Y_{0,0}(t) \\[2ex] p_0(1-\varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{3,0}} \right) Y_{0,1}(t) \\[2ex] -p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{3,0}} \right) Y_{0,0}(t) \\[2ex] -p_0(1-\varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{3,0}} \right) Y_{0,1}(t) \\[2ex] 0 \\[1ex] 0 \\[1ex] 0 \end{bmatrix}$$

with $\quad \dfrac{\partial \lambda}{\partial \beta_{3,0}} = \dfrac{p_3 \eta_{00,30} Y_{3,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)} \quad$ and $\quad \dfrac{\partial \lambda_\nu}{\partial \beta_{3,0}} = \dfrac{p_3 \eta_{01,30} Y_{3,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$

$G_{\beta_{3,0}} = 0,$ and $\ell_{\beta_{3,0}} = 0,$ implies

$$\frac{\partial L}{\partial \beta_{3,0}} = \int_0^T p_0 \left[\left(\frac{\partial \lambda}{\partial \beta_{3,0}} \right) Y_{0,0}(t) (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1-\varepsilon) \left(\frac{\partial \lambda_\nu}{\partial \beta_{3,0}} \right) Y_{0,1}(t) (\Lambda_{0,1}(t) - \Lambda_{1,1}(t)) \right] dt.$$

For $\beta_{4,0}$ we get,

$$
F_{\beta_{4,0}} = \begin{bmatrix}
p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{4,0}} \right) Y_{0,0}(t) \\[2.5ex]
p_0(1-\varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{4,0}} \right) Y_{0,1}(t) \\[2.5ex]
- p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{4,0}} \right) Y_{0,0}(t) \\[2.5ex]
- p_0(1-\varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{4,0}} \right) Y_{0,1}(t) \\[2.5ex]
0 \\[1ex]
0 \\[1ex]
0
\end{bmatrix}
$$

with $\quad \dfrac{\partial \lambda}{\partial \beta_{4,0}} = \dfrac{p_4 \eta_{00,40} Y_{4,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)} \quad$ and $\quad \dfrac{\partial \lambda_\nu}{\partial \beta_{4,0}} = \dfrac{p_4 \eta_{01,40} Y_{4,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$

$G_{\beta_{4,0}} = 0,$ and $\ell_{\beta_{4,0}} = 0,$ implies

$$
\frac{\partial L}{\partial \beta_{4,0}} = \int_0^T p_0 \left[\left(\frac{\partial \lambda}{\partial \beta_{4,0}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1-\varepsilon) \left(\frac{\partial \lambda_\nu}{\partial \beta_{4,0}} \right) Y_{0,1}(t)(\Lambda_{0,1}(t) - \Lambda_{1,1}(t)) \right] dt.
$$

Probability that a partnership between a susceptible-unvaccinated individual and an infected individual is not protected by a condom, $\eta_{00,i0}$

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equations for the probability that a partnership between a susceptible-unvaccinated individual with an infected individual is not protected by a condom are evaluated for each of the infectious classes.

For $\eta_{00,10}$ we get,

$$F_{\eta_{00,10}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,10}} \right) Y_{0,0}(t) \\ 0 \\ -p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,10}} \right) Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,10}} = \frac{p_1 \beta_{1,0} Y_{1,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$$

$G_{\eta_{00,10}} = 0$, and $\ell_{\eta_{00,10}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,10}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,10}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For $\eta_{00,11}$ we get,

$$F_{\eta_{00,11}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,11}} \right) Y_{0,0}(t) \\ 0 \\ -p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,11}} \right) Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,11}} = \frac{p_1 \beta_{1,1} Y_{1,1}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$$

$G_{\eta_{00,11}} = 0$, and $\ell_{\eta_{00,11}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,11}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,11}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For $\eta_{00,20}$ we get,

$$F_{\eta_{00,20}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,20}} \right) Y_{0,0}(t) \\ 0 \\ -p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,20}} \right) Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,20}} = \frac{p_2 \beta_{2,0} Y_{2,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$$

$G_{\eta_{00,20}} = 0$, and $\ell_{\eta_{00,20}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,20}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,20}} \right) Y_{0,0}(t) (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For $\eta_{00,30}$ we get,

$$F_{\eta_{00,30}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,30}} \right) Y_{0,0}(t) \\ 0 \\ -p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,30}} \right) Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,30}} = \frac{p_3 \beta_{3,0} Y_{3,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,0}(t)}$$

$G_{\eta_{00,30}} = 0$, and $\ell_{\eta_{00,30}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,30}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,30}} \right) Y_{0,0}(t) (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For $\eta_{00,40}$ we get,

$$
F_{\eta_{00,40}} = \begin{bmatrix} p_0\left(\dfrac{\partial\lambda}{\partial\eta_{00,40}}\right)Y_{0,0}(t) \\ 0 \\ -p_0\left(\dfrac{\partial\lambda}{\partial\eta_{00,40}}\right)Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \text{with} \quad \dfrac{\partial\lambda}{\partial\eta_{00,40}} = \dfrac{p_4\beta_{4,0}Y_{4,0}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,0}(t)}
$$

$G_{\eta_{00,40}} = 0$, and $\ell_{\eta_{00,40}} = 0$, implies

$$
\dfrac{\partial L}{\partial\eta_{00,40}} = \int_0^T p_0\left(\dfrac{\partial\lambda}{\partial\eta_{00,40}}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.
$$

Probability that a partnership between a susceptible-vaccinated individual and an infected individual is not protected by a condom, $\eta_{01,i0}$

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equations for the probability that a partnership between a susceptible-vaccinated individual with an infected individual is not protected by a condom are evaluated for each of the infectious classes.

For $\eta_{01,10}$ we get,

$$
F_{\eta_{01,10}} = \begin{bmatrix} 0 \\ p_0(1-\varepsilon)\left(\dfrac{\partial\lambda_\nu}{\partial\eta_{01,10}}\right)Y_{0,0}(t) \\ 0 \\ -p_0(1-\varepsilon)\left(\dfrac{\partial\lambda_\nu}{\partial\eta_{01,10}}\right)Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \text{with} \quad \dfrac{\partial\lambda}{\partial\eta_{01,10}} = \dfrac{p_1\beta_{1,0}Y_{1,0}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)},
$$

$G_{\eta_{01,10}} = 0$, and $\ell_{\eta_{01,10}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{01,10}} = \int_0^T p_0(1-\varepsilon)\left(\frac{\partial \lambda}{\partial \eta_{01,10}}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.$$

For $\eta_{01,11}$ we get,

$$F_{\eta_{01,11}} = \begin{bmatrix} 0 \\ p_0(1-\varepsilon)\left(\dfrac{\partial \lambda_\nu}{\partial \eta_{01,11}}\right)Y_{0,0}(t) \\ 0 \\ -p_0(1-\varepsilon)\left(\dfrac{\partial \lambda_\nu}{\partial \eta_{01,11}}\right)Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{01,11}} = \frac{p_1\beta_{1,1}Y_{1,1}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)},$$

$G_{\eta_{01,11}} = 0$, and $\ell_{\eta_{01,11}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{01,11}} = \int_0^T p_0\left(\frac{\partial \lambda}{\partial \eta_{01,11}}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.$$

For $\eta_{01,20}$ we get,

$$F_{\eta_{01,20}} = \begin{bmatrix} 0 \\ p_0(1-\varepsilon)\left(\dfrac{\partial \lambda_\nu}{\partial \eta_{01,20}}\right)Y_{0,0}(t) \\ 0 \\ -p_0(1-\varepsilon)\left(\dfrac{\partial \lambda_\nu}{\partial \eta_{01,20}}\right)Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{01,20}} = \frac{p_2\beta_{2,0}Y_{2,0}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)},$$

$G_{\eta_{01,20}} = 0$, and $\ell_{\eta_{01,20}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{01,20}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{01,20}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For $\eta_{01,30}$ we get,

$$F_{\eta_{01,30}} = \begin{bmatrix} 0 \\ p_0(1-\varepsilon)\left(\dfrac{\partial \lambda_\nu}{\partial \eta_{01,30}}\right) Y_{0,0}(t) \\ 0 \\ -p_0(1-\varepsilon)\left(\dfrac{\partial \lambda_\nu}{\partial \eta_{01,30}}\right) Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \text{with} \qquad \frac{\partial \lambda}{\partial \eta_{01,30}} = \frac{p_3 \beta_{3,0} Y_{3,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,0}(t)}$$

$G_{\eta_{01,30}} = 0$, and $\ell_{\eta_{01,30}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{01,30}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{01,30}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For $\eta_{01,40}$ we get,

$$F_{\eta_{01,40}} = \begin{bmatrix} 0 \\ p_0(1-\varepsilon)\left(\dfrac{\partial \lambda_\nu}{\partial \eta_{01,40}}\right) Y_{0,0}(t) \\ 0 \\ -p_0(1-\varepsilon)\left(\dfrac{\partial \lambda_\nu}{\partial \eta_{01,40}}\right) Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \text{with} \qquad \frac{\partial \lambda}{\partial \eta_{01,40}} = \frac{p_4 \beta_{4,0} Y_{4,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,0}(t)}$$

$G_{\eta_{01,40}} = 0$, and $\ell_{\eta_{01,40}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{01,40}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{01,40}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.$$

Efficacy of preventative vaccine, ε

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equation for the efficacy of the preventative vaccine is defined by the following.

$$F_\varepsilon = \begin{bmatrix} 0 \\ -p_0\lambda_\nu(t)Y_{0,1}(t) \\ 0 \\ p_0\lambda_\nu(t)Y_{0,1}(t) \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad G_\varepsilon = 0, \text{ and } \ell_\varepsilon = 0,$$

implies,

$$\frac{\partial L}{\partial \varepsilon} = \int_0^T p_0\lambda_\nu(t)Y_{0,1}(t)(\Lambda_{1,1}(t) - \Lambda_{0,1}(t))dt.$$

Proportion of the susceptible and asymptomatic-unaware populations that receives the preventative vaccine, ν_p

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equation for the parameter defining the proportion of the susceptible and asymptomatic-unaware population that receives the preventative vaccine is defined by the following.

$$F_{\nu_p} = \begin{bmatrix} Y_{0,0}(t) \\ -Y_{0,0}(t) \\ Y_{1,0}(t) \\ -Y_{1,0}(t) \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad G_{\nu_p} = 0, \text{ and } \ell_{\nu_p} = 0,$$

implies,

$$\frac{\partial L}{\partial \nu_p} = \int_0^T Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{0,1}(t)) + Y_{1,0}(t)(\Lambda_{1,0}(t) - \Lambda_{1,1}(t))dt.$$

Waning rate of the preventative vaccine, ω

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equation for the waning rate of the preventative vaccine is defined by the following.

$$F_{\omega} = \begin{bmatrix} -Y_{0,1}(t) \\ Y_{0,1}(t) \\ -Y_{1,1}(t) \\ Y_{1,1}(t) \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad G_{\omega} = 0, \text{ and } \ell_{\omega} = 0,$$

implies,

$$\frac{\partial L}{\partial \omega} = \int_0^T Y_{0,1}(t)(\Lambda_{0,1}(t) - \Lambda_{0,0}(t))Y_{1,1}(t)(\Lambda_{1,1}(t) - \Lambda_{1,0}(t))dt.$$

Parameters related to the rate at which asymptomatic-unaware individuals become aware, σ and ξ

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equations for the rate at which an asymptomatic-unaware individual becomes aware are evaluated

for both the screening rate, σ, along with the true-positive rate of screening, ξ.

For σ we get,

$$F_\sigma = \begin{bmatrix} 0 \\ 0 \\ \xi Y_{1,0}(t) \\ \xi Y_{1,1}(t) \\ -\xi(Y_{1,0}(t) + Y_{1,1}(t)) \\ 0 \\ 0 \end{bmatrix}, \quad G_\sigma = 0, \text{ and } \ell_\sigma = 0,$$

implies,

$$\frac{\partial L}{\partial \sigma} = \int_0^T \xi \Big[Y_{1,0}(t)\Lambda_{1,0}(t) + Y_{1,1}(t)\Lambda_{1,1}(t) - (Y_{1,0}(t) + Y_{1,1}(t))\Lambda_{2,0}(t)) \Big] dt.$$

For ξ we get,

$$F_\xi = \begin{bmatrix} 0 \\ 0 \\ \sigma Y_{1,0}(t) \\ \sigma Y_{1,1}(t) \\ -\sigma(Y_{1,0}(t) + Y_{1,1}(t)) \\ 0 \\ 0 \end{bmatrix}, \quad G_\xi = 0, \text{ and } \ell_\xi = 0,$$

implies,

$$\frac{\partial L}{\partial \xi} = \int_0^T \sigma \Big[Y_{1,0}(t)\Lambda_{1,0}(t) + Y_{1,1}(t)\Lambda_{1,1}(t) - (Y_{1,0}(t) + Y_{1,1}(t))\Lambda_{2,0}(t)) \Big] dt.$$

Total initial population, Y_0

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equation for the total initial population is defined by the following.

$$F_{Y_0} = \begin{bmatrix} -\left(1 - \sum_{i=1}^{i=3} \rho_i\right)\mu \\ 0 \\ -\rho_1\mu \\ 0 \\ -\rho_2\mu \\ -\rho_3\mu \\ 0 \end{bmatrix},$$

$$G_{Y_0} = \begin{bmatrix} -(1 - \phi_0) \\ 0 \\ -\left(\dfrac{1/\mu_{1,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)\phi_0 \\ 0 \\ -\left(\dfrac{1/\mu_{2,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)\phi_0 \\ -\left(\dfrac{1/\mu_{3,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)\phi_0 \\ -\left(\dfrac{1/\mu_{4,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)\phi_0 \end{bmatrix}, \quad \text{and } \ell_{Y_0} = 0,$$

implies,

$$\frac{\partial L}{\partial Y_0} = \int_0^T -\mu\left(\left(1 - \sum_{i=1}^{1=3} \rho_i\right)\Lambda_{0,0}(t) + \rho_1\Lambda_{1,0}(t) + \rho_2\Lambda_{2,0}(t) + \rho_3\Lambda_{3,0}(t)\right)dt - (1 - \phi_0)\Lambda_{0,0}(0)$$

$$- \frac{\phi_0}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\Big((1/\mu_{1,0})\Lambda_{1,0}(0) + (1/\mu_{2,0})\Lambda_{2,0}(0)$$

$$+ (1/\mu_{3,0})\Lambda_{3,0}(0) + (1/\mu_{4,0})\Lambda_{4,0}(0)\Big).$$

Seroprevalence of the infected population, ϕ_0

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equation for the seroprevalence of the infected population is defined by the following.

$$
F_{\phi_0} = 0, \quad
G_{\phi_0} =
\begin{bmatrix}
Y_0 \\
0 \\
-\left(\dfrac{1/\mu_{1,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)Y_0 \\
0 \\
-\left(\dfrac{1/\mu_{2,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)Y_0 \\
-\left(\dfrac{1/\mu_{3,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)Y_0 \\
-\left(\dfrac{1/\mu_{4,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)Y_0
\end{bmatrix},
\quad \text{and } \ell_{\phi_0} = 0,
$$

implies,

$$
\frac{\partial L}{\partial \phi_0} = Y_0 \Lambda_{0,0}(0) - \frac{Y_0}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\Big((1/\mu_{1,0})\Lambda_{1,0}(0) + (1/\mu_{2,0})\Lambda_{2,0}(0)
$$
$$
+ (1/\mu_{3,0})\Lambda_{3,0}(0) + (1/\mu_{4,0})\Lambda_{4,0}(0)\Big).
$$

Distribution of disease-related immigration, ρ_i

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equations for the parameters associated with the distribution of disease-related immigration is evaluated for each of the respective classes.

For ρ_1 we get,

$$
F_{\rho_1} =
\begin{bmatrix}
\mu Y_0 \\
0 \\
-\mu Y_0 \\
0 \\
0 \\
0 \\
0
\end{bmatrix},
\quad G_{\rho_1} = 0, \quad \text{and} \quad \ell_{\rho_1} = 0,
$$

implies,

$$
\frac{\partial L}{\partial \rho_1} = \int_0^{20} \mu Y_0 (\Lambda_{0,0}(t) - \Lambda_{1,0}(t))\,dt.
$$

For ρ_2 we get,

$$F_{\rho_2} = \begin{bmatrix} \mu Y_0 \\ 0 \\ 0 \\ 0 \\ -\mu Y_0 \\ 0 \\ 0 \end{bmatrix}, \quad G_{\rho_2} = 0, \quad \text{and} \quad \ell_{\rho_2} = 0,$$

implies,

$$\frac{\partial L}{\partial \rho_2} = \int_0^T \mu Y_0 (\Lambda_{0,0}(t) - \Lambda_{2,0}(t)) dt.$$

For ρ_3 we get,

$$F_{\rho_3} = \begin{bmatrix} \mu Y_0 \\ 0 \\ 0 \\ 0 \\ 0 \\ -\mu Y_0 \\ 0 \end{bmatrix}, \quad G_{\rho_3} = 0, \quad \text{and} \quad \ell_{\rho_3} = 0,$$

implies,

$$\frac{\partial L}{\partial \rho_3} = \int_0^{20} \mu Y_0 (\Lambda_{0,0}(t) - \Lambda_{3,0}(t)) dt.$$

Average yearly medical expenses for each class, c_i

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equations for the average yearly medical expenses is evaluated for each of the population classes.

For c_0 we get,

$$F_{c_0} = 0, \quad G_{c_0} = 0, \quad \text{and} \quad \ell_{c_0} = \alpha(Y_{0,0}(t) + Y_{0,1}(t))e^{-rt},$$

implies,

$$\frac{\partial L}{\partial c_0} = \int_0^T \alpha(Y_{0,0}(t) + Y_{0,1}(t))e^{-rt}dt.$$

For c_1 we get,

$$F_{c_1} = 0, \quad G_{c_1} = 0, \quad \text{and} \quad \ell_{c_1} = \alpha(Y_{1,0}(t) + Y_{1,1}(t))e^{-rt},$$

implies,

$$\frac{\partial L}{\partial c_1} = \int_0^T \alpha(Y_{1,0}(t) + Y_{1,1}(t))e^{-rt}dt.$$

For c_2 we get,

$$F_{c_2} = 0, \quad G_{c_2} = 0, \quad \text{and} \quad \ell_{c_2} = \alpha Y_{2,0}(t)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial c_2} = \int_0^T \alpha Y_{2,0}(t)e^{-rt}dt.$$

For c_3 we get,

$$F_{c_3} = 0, \quad G_{c_3} = 0, \quad \text{and} \quad \ell_{c_3} = \alpha Y_{3,0}(t)e^{-rt},$$

implies

$$\frac{\partial L}{\partial c_3} = \int_0^T \alpha Y_{3,0}(t)e^{-rt}dt.$$

For c_4 we get,

$$F_{c_4} = 0, \qquad G_{c_4} = 0, \qquad \text{and} \qquad \ell_{c_4} = \alpha Y_{4,0}(t)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial c_4} = \int_0^T \alpha Y_{4,0}(t)e^{-rt}dt.$$

QALYs, q_i

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equations for QALYs is evaluated for each of the population classes.

For q_0 we get,

$$F_{q_0} = 0, \qquad G_{q_0} = 0, \qquad \text{and} \qquad \ell_{q_0} = (\alpha - 1)(Y_{0,0}(t) + Y_{0,1}(t))e^{-rt},$$

implies,

$$\frac{\partial L}{\partial q_0} = \int_0^T (\alpha - 1)(Y_{0,0}(t) + Y_{0,1}(t))e^{-rt}dt.$$

For q_1 we get,

$$F_{q_1} = 0, \qquad G_{q_1} = 0, \qquad \text{and} \qquad \ell_{q_1} = (\alpha - 1)(Y_{1,0}(t) + Y_{1,1}(t))e^{-rt},$$

implies,

$$\frac{\partial L}{\partial q_1} = \int_0^T (\alpha - 1)(Y_{1,0}(t) + Y_{1,1}(t))e^{-rt}dt.$$

For q_2 we get,

$$F_{q_2} = 0, \qquad G_{q_2} = 0, \qquad \text{and} \qquad \ell_{q_2} = (\alpha - 1)Y_{2,0}(t)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial q_2} = \int_0^T (\alpha - 1) Y_{2,0}(t) e^{-rt} dt.$$

For q_3 we get,

$$F_{q_3} = 0, \quad G_{q_3} = 0, \quad \text{and} \quad \ell_{q_3} = (\alpha - 1) Y_{3,0}(t) e^{-rt},$$

implies,

$$\frac{\partial L}{\partial q_3} = \int_0^T (\alpha - 1) Y_{3,0}(t) e^{-rt} dt.$$

For q_4 we get,

$$F_{q_4} = 0, \quad G_{q_4} = 0, \quad \text{and} \quad \ell_{q_4} = (\alpha - 1) Y_{4,0}(t) e^{-rt},$$

implies,

$$\frac{\partial L}{\partial q_4} = \int_0^T (\alpha - 1) Y_{4,0}(t) e^{-rt} dt.$$

Direct cost for the preventative vaccine, κ_p

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equation for the direct cost for the preventative vaccine is defined by the following.

$$F_\alpha = 0, \quad G_\alpha = 0, \quad \text{and}$$

$$\ell_\alpha = \alpha \nu_p (Y_{0,0}(t) + Y_{1,0}(t)) e^{-rt},$$

implies,

$$\frac{\partial L}{\partial \alpha} = \int_0^T \alpha \nu_p (Y_{0,0}(t) + Y_{1,0}(t)) e^{-rt} dt.$$

Annual discount rate, r

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equation for the annual discount rate is defined by the following.

$$F_r = 0, \quad G_r = 0, \quad \text{and}$$

$$\ell_r = -t\Big[\alpha\big(\kappa_p\nu_p(Y_{0,0}(t) + Y_{1,0}(t)) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} c_i Y_{i,j}(t)\big) - (1-\alpha)\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} q_i Y_{i,j}(t)\Big]e^{-rt},$$

implies,

$$\frac{\partial L}{\partial r} = \int_0^T -t\Big[\alpha\big(\kappa_p\nu_p(Y_{0,0}(t) + Y_{1,0}(t)) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} c_i Y_{i,j}(t)\big) - (1-\alpha)\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} q_i Y_{i,j}(t)\Big]e^{-rt}dt.$$

Weight for combining objectives for optimization, α

For the HIV infectious disease model, with the preventative vaccine only, the sensitivity equation for the weight introduced to evaluate the multi-objective optimization is defined by the following.

$$F_\alpha = 0, \quad G_\alpha = 0, \quad \text{and}$$

$$\ell_\alpha = \Big(\kappa_p\nu_p(Y_{0,0}(t) + Y_{1,0}(t)) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} c_i Y_{i,j}(t) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} q_i Y_{i,j}(t)\Big)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial \alpha} = \int_0^T \Big(\kappa_p\nu_p(Y_{0,0}(t) + Y_{1,0}(t)) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} c_i Y_{i,j}(t) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} q_i Y_{i,j}(t)\Big)e^{-rt}dt.$$

C.4 Combined, Preventative and Therapeutic, Vaccine Strategy

For the full model with both vaccinations, the preventative and therapeutic, we have the following system of ordinary differential equations

$$\frac{dY_{0,0}(t)}{dt} = (1 - \sum_{i=1}^{3} \rho_i)\mu Y_0 - (\nu_p + \mu + p_0\lambda(t))Y_{0,0}(t) + \omega Y_{0,1}(t)$$

$$\frac{dY_{0,1}(t)}{dt} = \nu_p Y_{0,0}(t) - (\mu + \omega + p_0(1-\varepsilon)\lambda_\nu(t))Y_{0,1}(t)$$

$$\frac{dY_{1,0}(t)}{dt} = \rho_1\mu Y_0 + p_0\lambda(t)Y_{0,0}(t) - (\nu_p + \sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) + \omega Y_{1,1}(t)$$

$$\frac{dY_{1,1}(t)}{dt} = \nu_p Y_{1,0}(t) + p_0(1-\varepsilon)\lambda_\nu(t)Y_{0,1}(t) - (\omega + \sigma\xi + \mu_{1,1} + \mu)Y_{1,1}(t)$$

$$\frac{dY_{2,0}(t)}{dt} = \rho_2\mu Y_0 + \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) - (\nu_t + \mu_{2,0} + \mu)Y_{2,0}(t)$$

$$\frac{dY_{2,1}(t)}{dt} = \nu_t Y_{2,0}(t) - (\mu_{2,1} + \mu)Y_{2,1}(t)$$

$$\frac{dY_{3,0}(t)}{dt} = \rho_3\mu Y_0 + \sum_{i=1}^{i=2}\sum_{j=0}^{j=1} \mu_{i,j}Y_{i,j}(t) - (\mu_{3,0} + \mu)Y_{3,0}(t)$$

$$\frac{dY_{4,0}(t)}{dt} = \mu_{3,0}Y_{3,0}(t) - (\mu_{4,0} + \mu)Y_{4,0}(t)$$

were $\lambda(t) = \dfrac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,j}(t)}$ and $\lambda_\nu(t) = \dfrac{\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{01,ij}Y_{i,j}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_i Y_{i,j}(t)}$, along with the initial state

$$Y_{0,0}(0) = (1 - \phi_0)Y_0$$

$$Y_{i,0}(0) = \frac{1/\mu_{i,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}}\phi_0 Y_0, \text{ for } i = 1,2,3,4$$

$$Y_{i,1}(0) = 0 \text{ for } i = 0,1,2$$

and the corresponding payoff functional

$$L(T) = \int_0^T \left[\alpha\left(\kappa_p\nu_p(Y_{0,0}(t) + Y_{1,0}(t)) + \kappa_t\nu_t Y_{2,0}(t) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} c_i Y_{i,j}(t)\right)\right.$$
$$\left. - (1-\alpha)\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} q_i Y_{i,j}(t)\right)\right]e^{-rt}dt.$$

In all, we are considering 55 parameters for the model without an intervention.
$$\Theta = \{\mu, \mu_{1,0}, \mu_{1,1}, \mu_{2,0}, \mu_{2,1}, \mu_{3,0}, \mu_{4,0}, p_0, p_1, p_2, p_3, p_4, \beta_{1,0}, \beta_{1,1}, \beta_{2,0}, \beta_{2,1}, \beta_{3,0}, \beta_{4,0}, \dots$$
$$\dots, \eta_{00,10}, \eta_{00,11}, \eta_{00,20}, \eta_{00,21}, \eta_{00,30}, \eta_{00,40}, \eta_{01,10}, \eta_{01,11}, \eta_{01,20}, \eta_{01,21}, \eta_{01,30}, \eta_{01,40}, \dots$$

$$\ldots, \varepsilon, \nu_p, \nu_t, \omega, \sigma, \xi, Y_0, \phi_0, \rho_1, \rho_2, \rho_3, c_0, c_1, c_2, c_3, c_4, q_0, q_1, q_2, q_3, q_4, r, \alpha, \kappa_p, \kappa_t\}$$

To set up the sensitivity equations for each of the 55 parameters, we'll first present the vectors using the notation we introduced in the chapter 6.

$F(\dot{Y}, Y, \Theta) =$

$$\begin{bmatrix}
\dot{Y}_{0,0}(t) + (\nu_p + \mu + p_0\lambda(t))Y_{0,0}(t) - \omega Y_{0,1}(t) - (1 - \sum_{i=1}^{i=3} \rho_i)\mu Y_0 \\
\dot{Y}_{0,1}(t) - \nu_p Y_{0,0}(t) + (\mu + \omega + p_0(1 - \varepsilon)\lambda_\nu(t))Y_{0,1}(t) \\
\dot{Y}_{1,0}(t) - p_0\lambda(t)Y_{0,0}(t) + (\nu_p + \sigma\xi + \mu_{1,0} + \mu)Y_{1,0}(t) - \omega Y_{1,1}(t) - \rho_1\mu Y_0 \\
\dot{Y}_{1,1}(t) - p_0(1 - \varepsilon)\lambda_\nu(t)Y_{0,1}(t) - \nu_p Y_{1,0}(t) + (\sigma\xi + \omega + \mu_{1,1} + \mu)Y_{1,1}(t) \\
\dot{Y}_{2,0}(t) - \sigma\xi(Y_{1,0}(t) + Y_{1,1}(t)) + (\mu_{2,0} + \mu + \nu_t)Y_{2,0}(t) - \rho_2\mu Y_0 \\
\dot{Y}_{2,1}(t) - \nu_t Y_{2,0}(t) + (\mu_{2,1} + \mu)Y_{2,1}(t) \\
\dot{Y}_{3,0}(t) - \mu_{1,0}Y_{1,0}(t) - \mu_{1,1}Y_{1,1}(t) - \mu_{2,0}Y_{2,0}(t) - \mu_{2,1}Y_{2,1}(t) + (\mu_{3,0} + \mu)Y_{3,0}(t) - \rho_3\mu Y_0 \\
\dot{Y}_{4,0}(t) - \mu_{3,0}Y_{3,0}(t) + (\mu_{4,0} + \mu)Y_{4,0}(t)
\end{bmatrix}$$

$$G(Y(0), \Theta) = \begin{bmatrix}
Y_{0,0}(0) - (1 - \phi_0)Y_0 \\
Y_{0,1}(0) \\
Y_{1,0}(0) - \phi_0\left(\dfrac{1/\mu_{1,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}}\right)Y_0 \\
Y_{1,1}(0) \\
Y_{2,0}(0) - \phi_0\left(\dfrac{1/\mu_{2,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}}\right)Y_0 \\
Y_{2,1}(0) \\
Y_{3,0}(0) - \phi_0\left(\dfrac{1/\mu_{3,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}}\right)Y_0 \\
Y_{4,0}(0) - \phi_0\left(\dfrac{1/\mu_{4,0}}{\sum_{j=1}^{j=4} 1/\mu_{j,0}}\right)Y_0
\end{bmatrix}$$

$$\ell(Y, \Theta) = \left[\alpha\left(\kappa_p\nu_p(Y_{0,0}(t) + Y_{1,0}(t)) + \kappa_t\nu_t Y_{2,0}(t) + \sum_{i=0}^{i=4}\sum_{j=0}^{j=1} c_i Y_{i,j}(t)\right)\right.$$
$$\left. - (1 - \alpha)\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} q_i Y_{i,j}(t)\right)\right]e^{-rt}$$

Then, by the adjoint variable method, the sensitivity equations are defined by,

$$\frac{\partial L}{\partial \vartheta_i} = \int_0^{20}\left(\ell_{\vartheta_i} + \Lambda^{\mathsf{T}} F_{\vartheta_i}\right)dt + \Lambda^{\mathsf{T}}\Big|_{t=0} G_{\vartheta_i}$$

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where $\Lambda^\intercal = [\Lambda_{0,0}, \Lambda_{0,1}, \Lambda_{1,0}, \Lambda_{1,1}, \Lambda_{2,0}, \Lambda_{2,1}, \Lambda_{3,0}, \Lambda_{4,0}]$. Thus, in defining the sensitivity equations for each of the parameters in Θ we will have to evaluate F_{ϑ_i}, G_{ϑ_i} and ℓ_{ϑ_i}.

Average non-disease related death rate, μ

For the HIV infectious disease model, with the combined strategy, the sensitivity equation for the non-disease related death rate is defined by the following.

$$
F_\mu = \begin{bmatrix} Y_{0,0}(t) - (1 - \sum_{i=1}^{i=3} \rho_i)Y_0 \\ Y_{0,1}(t) \\ Y_{1,0}(t) - \rho_1 Y_0 \\ Y_{1,1}(t) \\ Y_{2,0}(t) - \rho_2 Y_0 \\ Y_{2,1}(t) \\ Y_{3,0}(t) - \rho_3 Y_0 \\ Y_{4,0}(t) \end{bmatrix}, \quad G_\mu = 0, \quad \text{and} \quad \ell_\mu = 0,
$$

implies,

$$
\begin{aligned}
\frac{\partial L}{\partial \mu} = \int_0^T &\Big[\Lambda_{0,0}(t)(Y_{0,0}(t) - (1 - \sum_{i=1}^{i=3} \rho_i)Y_0) + \Lambda_{0,1}(t)Y_{0,1}(t) \\
&+ \Lambda_{1,0}(t)(Y_{1,0}(t) - \rho_1 Y_0) + \Lambda_{1,1}(t)Y_{1,1}(t) + \Lambda_{2,0}(t)(Y_{2,0}(t) - \rho_2 Y_0) \\
&+ \Lambda_{2,1}(t)Y_{2,1}(t) + \Lambda_{3,0}(t)(Y_{3,0}(t) - \rho_3 Y_0) + \Lambda_{4,0}(t)Y_{4,0}(t)) \Big] dt.
\end{aligned}
$$

Disease related transition rates, $\mu_{i,0}$

For the HIV infectious disease model, with the combined strategy, the sensitivity equation for the rate at which an infected individual transitions out of each of the disease classes are each evaluated.

For $\mu_{1,0}$, we get,

$$F_{\mu_{1,0}} = \begin{bmatrix} 0 \\ 0 \\ Y_{1,0}(t) \\ 0 \\ 0 \\ 0 \\ -Y_{1,0}(t) \\ 0 \end{bmatrix},$$

$$G_{\mu_{1,0}} = \frac{\phi_0 Y_0 (1/\mu_{1,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \begin{bmatrix} 0 \\ 0 \\ 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0} \\ 0 \\ -1/\mu_{2,0} \\ 0 \\ -1/\mu_{3,0} \\ -1/\mu_{4,0} \end{bmatrix}, \qquad \text{and}$$

$\ell_{\mu_{1,0}} = 0,$

implies,

$$\frac{\partial L}{\partial \mu_{1,0}} = \int_0^T Y_{1,0}(t)(\Lambda_{1,0}(t) - \Lambda_{3,0}(t))dt$$

$$+ \frac{\phi_0 Y_0 (1/\mu_{1,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \Big((1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0})\Lambda_{1,0}(0)$$

$$- (1/\mu_{2,0})\Lambda_{2,0}(0) - (1/\mu_{3,0})\Lambda_{3,0}(0) - (1/\mu_{4,0})\Lambda_{4,0}(0)\Big).$$

For $\mu_{1,1}$ we get,

$$F_{\mu_{1,1}} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ Y_{1,1}(t) \\ 0 \\ 0 \\ -Y_{1,1}(t) \\ 0 \end{bmatrix}, \quad G_{\mu_{1,1}} = 0, \quad \text{and} \quad \ell_{\mu_{1,1}} = 0,$$

implies,

$$\frac{\partial L}{\partial \mu_{1,1}} = \int_0^T Y_{1,1}(t)(\Lambda_{1,1}(t) - \Lambda_{3,0}(t))dt.$$

For $\mu_{2,0}$ we get,

$$F_{\mu_{2,0}} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ Y_{2,0}(t) \\ 0 \\ -Y_{2,0}(t) \\ 0 \end{bmatrix},$$

$$G_{\mu_{2,0}} = \frac{\phi_0 Y_0 (1/\mu_{2,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \begin{bmatrix} 0 \\ 0 \\ -1/\mu_{1,0} \\ 0 \\ 1/\mu_{1,0} + 1/\mu_{3,0} + 1/\mu_{4,0} \\ 0 \\ -1/\mu_{3,0} \\ -1/\mu_{4,0} \end{bmatrix}, \quad \text{and}$$

$$\ell_{\mu_{2,0}} = 0,$$

implies,

$$\frac{\partial L}{\partial \mu_{2,0}} = \int_0^T Y_{2,0}(t)(\Lambda_{2,0}(t) - \Lambda_{3,0}(t))dt$$

$$+ \frac{\phi_0 Y_0 (1/\mu_{2,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \Big((1/\mu_{1,0} + 1/\mu_{3,0} + 1/\mu_{4,0})\Lambda_{2,0}(0)$$

$$- (1/\mu_{1,0})\Lambda_{1,0}(0) - (1/\mu_{3,0})\Lambda_{3,0}(0) - (1/\mu_{4,0})\Lambda_{4,0}(0) \Big).$$

For $\mu_{2,1}$ we get,

$$F_{\mu_{2,1}} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ Y_{2,1}(t) \\ -Y_{2,1}(t) \\ 0 \end{bmatrix}, \quad G_{\mu_{2,1}} = 0, \quad \text{and} \quad \ell_{\mu_{2,1}} = 0,$$

implies,

$$\frac{\partial L}{\partial \mu_{2,1}} = \int_0^T Y_{2,1}(t)(\Lambda_{2,1}(t) - \Lambda_{3,0}(t))dt.$$

For $\mu_{3,0}$ we get,

$$F_{\mu_{3,0}} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ Y_{3,0}(t) \\ -Y_{3,0}(t) \end{bmatrix},$$

$$G_{\mu_{3,0}} = \frac{\phi_0 Y_0 (1/\mu_{3,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \begin{bmatrix} 0 \\ 0 \\ -1/\mu_{1,0} \\ 0 \\ -1/\mu_{2,0} \\ 0 \\ 1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{4,0} \\ -1/\mu_{4,0} \end{bmatrix} \quad \text{and}$$

$\ell_{\mu_{3,0}} = 0,$

implies,

$$\frac{\partial L}{\partial \mu_{3,0}} = \int_0^T Y_{3,0}(t)(\Lambda_{3,0}(t) - \Lambda_{4,0}(t))dt$$

$$+ \frac{\phi_0 Y_0 (1/\mu_{3,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \Big((1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{4,0})\Lambda_{3,0}(0)$$

$$- (1/\mu_{1,0})\Lambda_{1,0}(0) - (1/\mu_{2,0})\Lambda_{2,0}(0) - (1/\mu_{4,0})\Lambda_{4,0}(0) \Big).$$

For $\mu_{4,0}$ we get,

$$F_{\mu_{4,0}} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ Y_{4,0}(t) \end{bmatrix},$$

$$G_{\mu_{4,0}} = \frac{\phi_0 Y_0 (1/\mu_{4,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \begin{bmatrix} 0 \\ 0 \\ -1/\mu_{1,0} \\ 0 \\ -1/\mu_{2,0} \\ 0 \\ -1/\mu_{3,0} \\ 1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} \end{bmatrix}, \quad \text{and}$$

$$\ell_{\mu_{4,0}} = 0,$$

implies,

$$\frac{\partial L}{\partial \mu_{4,0}} = \int_0^T Y_{4,0}(t) \Lambda_{4,0}(t) dt$$

$$+ \frac{\phi_0 Y_0 (1/\mu_{4,0})^2}{\left(1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}\right)^2} \Big((1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0}) \Lambda_{4,0}(0)$$

$$- (1/\mu_{1,0}) \Lambda_{1,0}(0) - (1/\mu_{2,0}) \Lambda_{2,0}(0) - (1/\mu_{3,0}) \Lambda_{3,0}(0) \Big).$$

Average number of partners an individual will have in a year, for each population class, p_i

For the HIV infectious disease model, with the combined strategy, the sensitivity equation for the average number of partners an individual, with disease status i, will have within a year are evaluated for each population classes.

For p_0 we get,

$$F_{p_0} = \begin{bmatrix} Y_{0,0}(t)\left(\lambda(t) + p_0\left[\dfrac{\partial\lambda}{\partial p_0}\right]\right) \\[2mm] (1-\varepsilon)Y_{0,0}(t)\left(\lambda_\nu(t) + p_0\left[\dfrac{\partial\lambda_\nu}{\partial p_0}\right]\right) \\[2mm] -Y_{0,0}(t)\left(\lambda(t) + p_0\left[\dfrac{\partial\lambda}{\partial p_0}\right]\right) \\[2mm] -(1-\varepsilon)Y_{0,0}(t)\left(\lambda_\nu(t) + p_0\left[\dfrac{\partial\lambda_\nu}{\partial p_0}\right]\right) \\[2mm] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

with $\dfrac{\partial\lambda}{\partial p_0} = \dfrac{-(Y_{0,0}(t) + Y_{0,1}(t))\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_iY_{i,0}(t)\right)^2}$

and $\dfrac{\partial\lambda_\nu}{\partial p_0} = \dfrac{-(Y_{0,0}(t) + Y_{0,1}(t))\sum_{i=1}^{i=4}\sum_{j=0}^{j=1} p_i\beta_{i,j}\eta_{01,ij}Y_{i,j}(t)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1} p_iY_{i,0}(t)\right)^2}$,

$G_{p_0} = 0$, and $\ell_{p_0} = 0$, implies

$$\frac{\partial L}{\partial p_0} = \int_0^T Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))\left(\lambda(t) + p_0\left[\frac{\partial\lambda}{\partial p_0}\right]\right)$$
$$+ (1-\varepsilon)Y_{0,1}(t)(\Lambda_{0,1}(t) - \Lambda_{1,1}(t))\left(\lambda_\nu(t) + p_0\left[\frac{\partial\lambda_\nu}{\partial p_0}\right]\right)dt.$$

For p_1 we get,

$$F_{p_1} = \begin{bmatrix} p_0\left(\dfrac{\partial\lambda}{\partial p_1}\right)Y_{0,0}(t) \\[2mm] p_0(1-\varepsilon)\left(\dfrac{\partial\lambda\nu}{\partial p_1}\right)Y_{0,1}(t) \\[2mm] -p_0\left(\dfrac{\partial\lambda}{\partial p_1}\right)Y_{0,0}(t) \\[2mm] -p_0(1-\varepsilon)\left(\dfrac{\partial\lambda\nu}{\partial p_1}\right)Y_{0,1}(t) \\[2mm] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

with $\dfrac{\partial\lambda}{\partial p_1} = \dfrac{\left(\beta_{1,0}\eta_{00,10}Y_{1,0}(t) + \beta_{1,1}\eta_{00,11}Y_{1,1}(t)\right)\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)\right)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)\right)^2}$

$$-\dfrac{\left(Y_{1,0}(t) + Y_{1,1}(t)\right)\left(\sum_{i=1}^{i=4}\sum_{j=0}^{j=1}p_i\beta_{i,j}\eta_{00,ij}Y_{i,j}(t)\right)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)\right)^2}$$

and $\dfrac{\partial\lambda_\nu}{\partial p_1} = \dfrac{\left(\beta_{1,0}\eta_{01,10}Y_{1,0}(t) + \beta_{1,1}\eta_{01,11}Y_{1,1}(t)\right)\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)\right)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)\right)^2}$

$$-\dfrac{\left(Y_{1,0}(t) + Y_{1,1}(t)\right)\left(\sum_{i=1}^{i=4}\sum_{j=0}^{j=1}p_i\beta_{i,j}\eta_{01,ij}Y_{i,j}(t)\right)}{\left(\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)\right)^2}$$

$G_{p_1} = 0$, and $\ell_{p_1} = 0$, implies

$$\frac{\partial L}{\partial p_1} = \int_0^T p_0\left[\left(\frac{\partial\lambda}{\partial p_1}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1-\varepsilon)\left(\frac{\partial\lambda_\nu}{\partial p_1}\right)Y_{0,1}(t)(\Lambda_{0,1}(t) - \Lambda_{1,1}(t))\right]dt.$$

For p_2 we get,

$$
F_{p_2} = \begin{bmatrix}
p_0 \left(\dfrac{\partial \lambda}{\partial p_2} \right) Y_{0,0}(t) \\[2ex]
p_0(1-\varepsilon) \left(\dfrac{\partial \lambda \nu}{\partial p_2} \right) Y_{0,1}(t) \\[2ex]
- p_0 \left(\dfrac{\partial \lambda}{\partial p_2} \right) Y_{0,0}(t) \\[2ex]
- p_0(1-\varepsilon) \left(\dfrac{\partial \lambda \nu}{\partial p_2} \right) Y_{0,1}(t) \\[2ex]
0 \\[1ex]
0 \\[1ex]
0 \\[1ex]
0
\end{bmatrix}
$$

with $\dfrac{\partial \lambda}{\partial p_2} = \dfrac{(\beta_{2,0}\eta_{00,20}Y_{2,0}(t) + \beta_{2,1}\eta_{00,21}Y_{2,1}(t)) \left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right)}{\left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right)^2}$

$$
- \dfrac{(Y_{2,0}(t) + Y_{2,1}(t)) \left(\sum_{i=1}^{i=4} \sum_{j=0}^{j=1} p_i \beta_{i,j}\eta_{00,ij}Y_{i,j}(t) \right)}{\left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right)^2}
$$

and $\dfrac{\partial \lambda_\nu}{\partial p_2} = \dfrac{(\beta_{2,0}\eta_{01,20}Y_{2,0}(t) + \beta_{2,1}\eta_{01,21}Y_{2,1}(t)) \left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right)}{\left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right)^2}$

$$
- \dfrac{(Y_{2,0}(t) + Y_{2,1}(t)) \left(\sum_{i=1}^{i=4} \sum_{j=0}^{j=1} p_i \beta_{i,j}\eta_{01,ij}Y_{i,j}(t) \right)}{\left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right)^2}
$$

$G_{p_2} = 0$, and $\ell_{p_2} = 0$, implies

$$
\frac{\partial L}{\partial p_2} = \int_0^T p_0 \left[\left(\frac{\partial \lambda}{\partial p_2} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1-\varepsilon) \left(\frac{\partial \lambda_\nu}{\partial p_2} \right) Y_{0,1}(t)(\Lambda_{0,1}(t) - \Lambda_{1,1}(t)) \right] dt.
$$

For p_3 we get,

$$
F_{p_3} = \begin{bmatrix}
p_0 \left(\dfrac{\partial \lambda}{\partial p_3} \right) Y_{0,0}(t) \\[2ex]
p_0(1-\varepsilon) \left(\dfrac{\partial \lambda \nu}{\partial p_3} \right) Y_{0,1}(t) \\[2ex]
- p_0 \left(\dfrac{\partial \lambda}{\partial p_3} \right) Y_{0,0}(t) \\[2ex]
- p_0(1-\varepsilon) \left(\dfrac{\partial \lambda \nu}{\partial p_3} \right) Y_{0,1}(t) \\[2ex]
0 \\[1ex]
0 \\[1ex]
0 \\[1ex]
0
\end{bmatrix}
$$

with $\dfrac{\partial \lambda}{\partial p_3} = \dfrac{\beta_{3,0}\eta_{00,30}Y_{3,0}(t)\left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right) - Y_{3,0}(t)\left(\sum_{i=1}^{i=4} \sum_{j=0}^{j=1} p_i \beta_{i,j}\eta_{00,ij}Y_{i,j}(t) \right)}{\left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right)^2}$

and $\dfrac{\partial \lambda_\nu}{\partial p_3} = \dfrac{\beta_{3,0}\eta_{01,30}Y_{3,0}(t)\left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right) - Y_{3,0}(t)\left(\sum_{i=1}^{i=4} \sum_{j=0}^{j=1} p_i \beta_{i,j}\eta_{01,ij}Y_{i,j}(t) \right)}{\left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right)^2}$

$G_{p_3} = 0$, and $\ell_{p_3} = 0$, implies

$$
\frac{\partial L}{\partial p_3} = \int_0^T p_0 \left[\left(\frac{\partial \lambda}{\partial p_3} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1-\varepsilon)\left(\frac{\partial \lambda_\nu}{\partial p_3} \right) Y_{0,1}(t)(\Lambda_{0,1}(t) - \Lambda_{1,1}(t)) \right] dt.
$$

For p_4 we get,

$$
F_{p_4} = \begin{bmatrix}
p_0 \left(\dfrac{\partial \lambda}{\partial p_4} \right) Y_{0,0}(t) \\[2ex]
p_0 (1 - \varepsilon) \left(\dfrac{\partial \lambda \nu}{\partial p_4} \right) Y_{0,1}(t) \\[2ex]
- p_0 \left(\dfrac{\partial \lambda}{\partial p_4} \right) Y_{0,0}(t) \\[2ex]
- p_0 (1 - \varepsilon) \left(\dfrac{\partial \lambda \nu}{\partial p_4} \right) Y_{0,1}(t) \\[2ex]
0 \\
0 \\
0 \\
0
\end{bmatrix}
$$

with $\dfrac{\partial \lambda}{\partial p_4} = \dfrac{\beta_{4,0} \eta_{00,40} Y_{4,0}(t) \left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right) - Y_{4,0}(t) \left(\sum_{i=1}^{i=4} \sum_{j=0}^{j=1} p_i \beta_{i,j} \eta_{00,ij} Y_{i,j}(t) \right)}{\left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right)^2}$

and $\dfrac{\partial \lambda_\nu}{\partial p_4} = \dfrac{\beta_{4,0} \eta_{01,40} Y_{4,0}(t) \left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right) - Y_{4,0}(t) \left(\sum_{i=1}^{i=4} \sum_{j=0}^{j=1} p_i \beta_{i,j} \eta_{01,ij} Y_{i,j}(t) \right)}{\left(\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t) \right)^2}$

$G_{p_4} = 0$, and $\ell_{p_4} = 0$, implies

$$
\frac{\partial L}{\partial p_4} = \int_0^T p_0 \left[\left(\frac{\partial \lambda}{\partial p_4} \right) Y_{0,0}(t) (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1 - \varepsilon) \left(\frac{\partial \lambda_\nu}{\partial p_4} \right) Y_{0,1}(t) (\Lambda_{0,1}(t) - \Lambda_{1,1}(t)) \right] dt.
$$

Infectivity rate for each of the infectious classes, $\beta_{i,0}$

For the HIV infectious disease model, with the combined strategy, the sensitivity equation for the infectivity rates are evaluated for each of the infectious classes.

For $\beta_{1,0}$ we get,

$$
F_{\beta_{1,0}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{1,0}} \right) Y_{0,0}(t) \\[2ex] p_0(1-\varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{1,0}} \right) Y_{0,1}(t) \\[2ex] - p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{1,0}} \right) Y_{0,0}(t) \\[2ex] - p_0(1-\varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{1,0}} \right) Y_{0,1}(t) \\[2ex] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}
$$

with $\quad \dfrac{\partial \lambda}{\partial \beta_{1,0}} = \dfrac{p_1 \eta_{00,10} Y_{1,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)} \quad$ and $\quad \dfrac{\partial \lambda_\nu}{\partial \beta_{1,0}} = \dfrac{p_1 \eta_{01,10} Y_{1,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$

$G_{\beta_{1,0}} = 0$, and $\ell_{\beta_{1,0}} = 0$, implies

$$
\frac{\partial L}{\partial \beta_{1,0}} = \int_0^T p_0 \left[\left(\frac{\partial \lambda}{\partial \beta_{1,0}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1-\varepsilon) \left(\frac{\partial \lambda_\nu}{\partial \beta_{1,0}} \right) Y_{0,1}(t)(\Lambda_{0,1}(t) - \Lambda_{1,1}(t)) \right] dt.
$$

For $\beta_{1,1}$ we get,

$$
F_{\beta_{1,1}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{1,1}} \right) Y_{0,0}(t) \\[2ex] p_0 (1 - \varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{1,1}} \right) Y_{0,1}(t) \\[2ex] - p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{1,1}} \right) Y_{0,0}(t) \\[2ex] - p_0 (1 - \varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{1,1}} \right) Y_{0,1}(t) \\[2ex] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}
$$

with $\quad \dfrac{\partial \lambda}{\partial \beta_{1,1}} = \dfrac{p_1 \eta_{00,11} Y_{1,1}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)} \quad$ and $\quad \dfrac{\partial \lambda_\nu}{\partial \beta_{1,1}} = \dfrac{p_1 \eta_{01,11} Y_{1,1}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$

$G_{\beta_{1,1}} = 0$, and $\ell_{\beta_{1,1}} = 0$, implies

$$
\frac{\partial L}{\partial \beta_{1,1}} = \int_0^T p_0 \left[\left(\frac{\partial \lambda}{\partial \beta_{1,1}} \right) Y_{0,0}(t) (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1 - \varepsilon) \left(\frac{\partial \lambda_\nu}{\partial \beta_{1,1}} \right) Y_{0,1}(t) (\Lambda_{0,1}(t) - \Lambda_{1,1}(t)) \right] dt.
$$

For $\beta_{2,0}$ we get,

$$F_{\beta_{2,0}} = \begin{bmatrix} p_0\left(\dfrac{\partial\lambda}{\partial\beta_{2,0}}\right)Y_{0,0}(t) \\[2ex] p_0(1-\varepsilon)\left(\dfrac{\partial\lambda_\nu}{\partial\beta_{2,0}}\right)Y_{0,1}(t) \\[2ex] -p_0\left(\dfrac{\partial\lambda}{\partial\beta_{2,0}}\right)Y_{0,0}(t) \\[2ex] -p_0(1-\varepsilon)\left(\dfrac{\partial\lambda_\nu}{\partial\beta_{2,0}}\right)Y_{0,1}(t) \\[2ex] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

with $\quad \dfrac{\partial\lambda}{\partial\beta_{2,0}} = \dfrac{p_2\eta_{00,20}Y_{2,0}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)} \quad$ and $\quad \dfrac{\partial\lambda_\nu}{\partial\beta_{2,0}} = \dfrac{p_2\eta_{01,20}Y_{2,0}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)},$

$G_{\beta_{2,0}} = 0,$ and $\ell_{\beta_{2,0}} = 0,$ implies

$$\frac{\partial L}{\partial\beta_{2,0}} = \int_0^T p_0\left[\left(\frac{\partial\lambda}{\partial\beta_{2,0}}\right)Y_{0,0}(t)(\Lambda_{0,0}(t)-\Lambda_{1,0}(t))+(1-\varepsilon)\left(\frac{\partial\lambda_\nu}{\partial\beta_{2,0}}\right)Y_{0,1}(t)(\Lambda_{0,1}(t)-\Lambda_{1,1}(t))\right]dt.$$

For $\beta_{2,1}$ we get,

$$
F_{\beta_{2,1}} =
\begin{bmatrix}
p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{2,1}} \right) Y_{0,0}(t) \\[2ex]
p_0 (1-\varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{2,1}} \right) Y_{0,1}(t) \\[2ex]
- p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{2,1}} \right) Y_{0,0}(t) \\[2ex]
- p_0 (1-\varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{2,1}} \right) Y_{0,1}(t) \\[2ex]
0 \\
0 \\
0 \\
0
\end{bmatrix}
$$

with $\quad \dfrac{\partial \lambda}{\partial \beta_{2,1}} = \dfrac{p_2 \eta_{00,21} Y_{2,1}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)} \quad$ and $\quad \dfrac{\partial \lambda_\nu}{\partial \beta_{2,1}} = \dfrac{p_2 \eta_{01,21} Y_{2,1}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$

$G_{\beta_{2,1}} = 0,$ and $\ell_{\beta_{2,1}} = 0,$ implies

$$
\frac{\partial L}{\partial \beta_{2,1}} = \int_0^T p_0 \left[\left(\frac{\partial \lambda}{\partial \beta_{2,1}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1-\varepsilon) \left(\frac{\partial \lambda_\nu}{\partial \beta_{2,1}} \right) Y_{0,1}(t)(\Lambda_{0,1}(t) - \Lambda_{1,1}(t)) \right] dt.
$$

For $\beta_{3,0}$ we get,

$$F_{\beta_{3,0}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{3,0}} \right) Y_{0,0}(t) \\[2ex] p_0 (1 - \varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{3,0}} \right) Y_{0,1}(t) \\[2ex] - p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{3,0}} \right) Y_{0,0}(t) \\[2ex] - p_0 (1 - \varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{3,0}} \right) Y_{0,1}(t) \\[2ex] 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

with $\quad \dfrac{\partial \lambda}{\partial \beta_{3,0}} = \dfrac{p_3 \eta_{00,30} Y_{3,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)} \quad$ and $\quad \dfrac{\partial \lambda_\nu}{\partial \beta_{3,0}} = \dfrac{p_3 \eta_{01,30} Y_{3,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$

$G_{\beta_{3,0}} = 0$, and $\ell_{\beta_{3,0}} = 0$, implies

$$\frac{\partial L}{\partial \beta_{3,0}} = \int_0^T p_0 \left[\left(\frac{\partial \lambda}{\partial \beta_{3,0}} \right) Y_{0,0}(t) (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1 - \varepsilon) \left(\frac{\partial \lambda_\nu}{\partial \beta_{3,0}} \right) Y_{0,1}(t) (\Lambda_{0,1}(t) - \Lambda_{1,1}(t)) \right] dt.$$

For $\beta_{4,0}$ we get,

$$
F_{\beta_{4,0}} = \begin{bmatrix}
p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{4,0}} \right) Y_{0,0}(t) \\[2ex]
p_0 (1 - \varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{4,0}} \right) Y_{0,1}(t) \\[2ex]
- p_0 \left(\dfrac{\partial \lambda}{\partial \beta_{4,0}} \right) Y_{0,0}(t) \\[2ex]
- p_0 (1 - \varepsilon) \left(\dfrac{\partial \lambda_\nu}{\partial \beta_{4,0}} \right) Y_{0,1}(t) \\[2ex]
0 \\
0 \\
0 \\
0
\end{bmatrix}
$$

with $\quad \dfrac{\partial \lambda}{\partial \beta_{4,0}} = \dfrac{p_4 \eta_{00,40} Y_{4,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)} \quad$ and $\quad \dfrac{\partial \lambda_\nu}{\partial \beta_{4,0}} = \dfrac{p_4 \eta_{01,40} Y_{4,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$

$G_{\beta_{4,0}} = 0$, and $\ell_{\beta_{4,0}} = 0$, implies

$$
\frac{\partial L}{\partial \beta_{4,0}} = \int_0^T p_0 \left[\left(\frac{\partial \lambda}{\partial \beta_{4,0}} \right) Y_{0,0}(t) (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) + (1 - \varepsilon) \left(\frac{\partial \lambda_\nu}{\partial \beta_{4,0}} \right) Y_{0,1}(t) (\Lambda_{0,1}(t) - \Lambda_{1,1}(t)) \right] dt.
$$

Probability that a partnership between a susceptible-unvaccinated individual and an infected individual is not protected by a condom, $\eta_{00,i0}$

For the HIV infectious disease model, with the combined strategy, the sensitivity equations for the probability that a partnership between a susceptible-unvaccinated individual with an infected individual is not protected by a condom are evaluated for each of the infectious classes.

For $\eta_{00,10}$ we get,

$$F_{\eta_{00,10}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,10}} \right) Y_{0,0}(t) \\ 0 \\ -p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,10}} \right) Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,10}} = \frac{p_1 \beta_{1,0} Y_{1,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$$

$G_{\eta_{00,10}} = 0$, and $\ell_{\eta_{00,10}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,10}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,10}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For $\eta_{00,11}$ we get,

$$F_{\eta_{00,11}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,11}} \right) Y_{0,0}(t) \\ 0 \\ -p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,11}} \right) Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,11}} = \frac{p_1 \beta_{1,1} Y_{1,1}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$$

$G_{\eta_{00,11}} = 0$, and $\ell_{\eta_{00,11}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,11}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,11}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For $\eta_{00,20}$ we get,

$$F_{\eta_{00,20}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,20}} \right) Y_{0,0}(t) \\ 0 \\ -p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,20}} \right) Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,20}} = \frac{p_2 \beta_{2,0} Y_{2,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$$

$G_{\eta_{00,20}} = 0$, and $\ell_{\eta_{00,20}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,20}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,20}} \right) Y_{0,0}(t) (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For $\eta_{00,21}$ we get,

$$F_{\eta_{00,21}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,21}} \right) Y_{0,0}(t) \\ 0 \\ -p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,21}} \right) Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,21}} = \frac{p_2 \beta_{2,1} Y_{2,1}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},$$

$G_{\eta_{00,21}} = 0$, and $\ell_{\eta_{00,21}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,21}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,21}} \right) Y_{0,0}(t) (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For $\eta_{00,30}$ we get,

$$F_{\eta_{00,30}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,30}} \right) Y_{0,0}(t) \\ 0 \\ -p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,30}} \right) Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,30}} = \frac{p_3 \beta_{3,0} Y_{3,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,0}(t)}$$

$G_{\eta_{00,30}} = 0$, and $\ell_{\eta_{00,30}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,30}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,30}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For $\eta_{00,40}$ we get,

$$F_{\eta_{00,40}} = \begin{bmatrix} p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,40}} \right) Y_{0,0}(t) \\ 0 \\ -p_0 \left(\dfrac{\partial \lambda}{\partial \eta_{00,40}} \right) Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{00,40}} = \frac{p_4 \beta_{4,0} Y_{4,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,0}(t)}$$

$G_{\eta_{00,40}} = 0$, and $\ell_{\eta_{00,40}} = 0$, implies

$$\frac{\partial L}{\partial \eta_{00,40}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{00,40}} \right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

Probability that a partnership between a susceptible-vaccinated individual and an infected individual is not protected by a condom, $\eta_{01,i0}$

For the HIV infectious disease model, with the combined strategy, the sensitivity equations for the probability that a partnership between a susceptible-vaccinated individual with an infected individual is not protected by a condom are evaluated for each of the infectious classes.

For $\eta_{01,10}$ we get,

$$
F_{\eta_{01,10}} = \begin{bmatrix} 0 \\ p_0(1-\varepsilon)\left(\dfrac{\partial\lambda_\nu}{\partial\eta_{01,10}}\right)Y_{0,0}(t) \\ 0 \\ -p_0(1-\varepsilon)\left(\dfrac{\partial\lambda_\nu}{\partial\eta_{01,10}}\right)Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{with} \quad \dfrac{\partial\lambda}{\partial\eta_{01,10}} = \dfrac{p_1\beta_{1,0}Y_{1,0}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)},
$$

$G_{\eta_{01,10}} = 0$, and $\ell_{\eta_{01,10}} = 0$, implies

$$
\frac{\partial L}{\partial\eta_{01,10}} = \int_0^T p_0(1-\varepsilon)\left(\frac{\partial\lambda}{\partial\eta_{01,10}}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.
$$

For $\eta_{01,11}$ we get,

$$
F_{\eta_{01,11}} = \begin{bmatrix} 0 \\ p_0(1-\varepsilon)\left(\dfrac{\partial \lambda_\nu}{\partial \eta_{01,11}}\right) Y_{0,0}(t) \\ 0 \\ -p_0(1-\varepsilon)\left(\dfrac{\partial \lambda_\nu}{\partial \eta_{01,11}}\right) Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{01,11}} = \frac{p_1 \beta_{1,1} Y_{1,1}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},
$$

$G_{\eta_{01,11}} = 0$, and $\ell_{\eta_{01,11}} = 0$, implies

$$
\frac{\partial L}{\partial \eta_{01,11}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{01,11}}\right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.
$$

For $\eta_{01,20}$ we get,

$$
F_{\eta_{01,20}} = \begin{bmatrix} 0 \\ p_0(1-\varepsilon)\left(\dfrac{\partial \lambda_\nu}{\partial \eta_{01,20}}\right) Y_{0,0}(t) \\ 0 \\ -p_0(1-\varepsilon)\left(\dfrac{\partial \lambda_\nu}{\partial \eta_{01,20}}\right) Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \text{with} \quad \frac{\partial \lambda}{\partial \eta_{01,20}} = \frac{p_2 \beta_{2,0} Y_{2,0}(t)}{\sum_{i=0}^{i=4} \sum_{j=0}^{j=1} p_i Y_{i,j}(t)},
$$

$G_{\eta_{01,20}} = 0$, and $\ell_{\eta_{01,20}} = 0$, implies

$$
\frac{\partial L}{\partial \eta_{01,20}} = \int_0^T p_0 \left(\frac{\partial \lambda}{\partial \eta_{01,20}}\right) Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.
$$

For $\eta_{01,21}$ we get,

$$
F_{\eta_{01,21}} = \begin{bmatrix} 0 \\ p_0(1-\varepsilon)\left(\dfrac{\partial\lambda_\nu}{\partial\eta_{01,21}}\right)Y_{0,0}(t) \\ 0 \\ -p_0(1-\varepsilon)\left(\dfrac{\partial\lambda_\nu}{\partial\eta_{01,21}}\right)Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \text{with} \quad \frac{\partial\lambda}{\partial\eta_{01,21}} = \frac{p_2\beta_{2,1}Y_{2,1}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,j}(t)},
$$

$G_{\eta_{01,21}} = 0$, and $\ell_{\eta_{01,21}} = 0$, implies

$$
\frac{\partial L}{\partial\eta_{01,21}} = \int_0^T p_0\left(\frac{\partial\lambda}{\partial\eta_{01,21}}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.
$$

For $\eta_{01,30}$ we get,

$$
F_{\eta_{01,30}} = \begin{bmatrix} 0 \\ p_0(1-\varepsilon)\left(\dfrac{\partial\lambda_\nu}{\partial\eta_{01,30}}\right)Y_{0,0}(t) \\ 0 \\ -p_0(1-\varepsilon)\left(\dfrac{\partial\lambda_\nu}{\partial\eta_{01,30}}\right)Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad \text{with} \quad \frac{\partial\lambda}{\partial\eta_{01,30}} = \frac{p_3\beta_{3,0}Y_{3,0}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,0}(t)}
$$

$G_{\eta_{01,30}} = 0$, and $\ell_{\eta_{01,30}} = 0$, implies

$$
\frac{\partial L}{\partial\eta_{01,30}} = \int_0^T p_0\left(\frac{\partial\lambda}{\partial\eta_{01,30}}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.
$$

For $\eta_{01,40}$ we get,

$$
F_{\eta_{01,40}} = \begin{bmatrix} 0 \\ p_0(1-\varepsilon)\left(\dfrac{\partial\lambda_\nu}{\partial\eta_{01,40}}\right)Y_{0,0}(t) \\ 0 \\ -p_0(1-\varepsilon)\left(\dfrac{\partial\lambda_\nu}{\partial\eta_{01,40}}\right)Y_{0,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{with} \quad \dfrac{\partial\lambda}{\partial\eta_{01,40}} = \dfrac{p_4\beta_{4,0}Y_{4,0}(t)}{\sum_{i=0}^{i=4}\sum_{j=0}^{j=1}p_iY_{i,0}(t)}
$$

$G_{\eta_{01,40}} = 0$, and $\ell_{\eta_{01,40}} = 0$, implies

$$
\frac{\partial L}{\partial\eta_{01,40}} = \int_0^T p_0\left(\frac{\partial\lambda}{\partial\eta_{01,40}}\right)Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{1,0}(t))dt.
$$

Efficacy of preventative vaccine, ε

For the HIV infectious disease model, with the combined strategy, the sensitivity equation for the efficacy of the preventative vaccine is defined by the following.

$$
F_\varepsilon = \begin{bmatrix} 0 \\ -p_0\lambda_\nu(t)Y_{0,1}(t) \\ 0 \\ p_0\lambda_\nu(t)Y_{0,1}(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad G_\varepsilon = 0, \text{ and } \ell_\varepsilon = 0,
$$

implies,

$$
\frac{\partial L}{\partial\varepsilon} = \int_0^T p_0\lambda_\nu(t)Y_{0,1}(t)(\Lambda_{1,1}(t) - \Lambda_{0,1}(t))dt.
$$

Proportion of the susceptible and asymptomatic-unaware populations that receives the preventative vaccine, ν_p

For the HIV infectious disease model, with the combined strategy, the sensitivity equation for the parameter defining the proportion of the susceptible and asymptomatic-unaware population that receives the preventative vaccine is defined by the following.

$$
F_{\nu_p} = \begin{bmatrix} Y_{0,0}(t) \\ -Y_{0,0}(t) \\ Y_{1,0}(t) \\ -Y_{1,0}(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad G_{\nu_p} = 0, \text{ and } \ell_{\nu_p} = 0,
$$

implies,

$$
\frac{\partial L}{\partial \nu_p} = \int_0^T Y_{0,0}(t)(\Lambda_{0,0}(t) - \Lambda_{0,1}(t)) + Y_{1,0}(t)(\Lambda_{1,0}(t) - \Lambda_{1,1}(t))dt.
$$

Waning rate of the preventative vaccine, ω

For the HIV infectious disease model, with the combined strategy, the sensitivity equation for the waning rate of the preventative vaccine is defined by the following.

$$
F_{\omega} = \begin{bmatrix} -Y_{0,1}(t) \\ Y_{0,1}(t) \\ -Y_{1,1}(t) \\ Y_{1,1}(t) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad G_{\omega} = 0, \text{ and } \ell_{\omega} = 0,
$$

implies,

$$\frac{\partial L}{\partial \omega} = \int_0^T Y_{0,1}(t)(\Lambda_{0,1}(t) - \Lambda_{0,0}(t))Y_{1,1}(t)(\Lambda_{1,1}(t) - \Lambda_{1,0}(t))dt.$$

Proportion of the asymptomatic-aware population that receives the therapeutic vaccine, ν_t

For the HIV infectious disease model, with the combined strategy, the sensitivity equation for the parameter defining the proportion of the asymptomatic-aware population that receives the therapeutic vaccine is defined by the following.

$$F_{\nu_t} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ Y_{2,0}(t) \\ -Y_{2,0}(t) \\ 0 \\ 0 \end{bmatrix}, \quad G_{\nu_t} = 0, \text{ and } \ell_{\nu_t} = 0,$$

implies,

$$\frac{\partial L}{\partial \nu_t} = \int_0^T Y_{2,0}(t)(\Lambda_{2,0}(t) - \Lambda_{2,1}(t))dt.$$

Parameters related to the rate at which asymptomatic-unaware individuals become aware, σ and ξ

For the HIV infectious disease model, with the combined strategy, the sensitivity equations for the rate at which an asymptomatic-unaware individual becomes aware are evaluated for both the screening rate, σ, along with the true-positive rate of screening, ξ.

For σ we get,

$$F_\sigma = \begin{bmatrix} 0 \\ 0 \\ \xi Y_{1,0}(t) \\ \xi Y_{1,1}(t) \\ -\xi(Y_{1,0}(t) + Y_{1,1}(t)) \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad G_\sigma = 0, \text{ and } \ell_\sigma = 0,$$

implies,

$$\frac{\partial L}{\partial \sigma} = \int_0^T \xi \left[Y_{1,0}(t)\Lambda_{1,0}(t) + Y_{1,1}(t)\Lambda_{1,1}(t) - (Y_{1,0}(t) + Y_{1,1}(t))\Lambda_{2,0}(t)) \right] dt.$$

For ξ we get,

$$F_\xi = \begin{bmatrix} 0 \\ 0 \\ \sigma Y_{1,0}(t) \\ \sigma Y_{1,1}(t) \\ -\sigma(Y_{1,0}(t) + Y_{1,1}(t)) \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad G_\xi = 0, \text{ and } \ell_\xi = 0,$$

implies,

$$\frac{\partial L}{\partial \xi} = \int_0^T \sigma \left[Y_{1,0}(t)\Lambda_{1,0}(t) + Y_{1,1}(t)\Lambda_{1,1}(t) - (Y_{1,0}(t) + Y_{1,1}(t))\Lambda_{2,0}(t)) \right] dt.$$

Total initial population, Y_0

For the HIV infectious disease model, with the combined strategy, the sensitivity equation for the total initial population is defined by the following.

$$F_{Y_0} = \begin{bmatrix} -\left(1 - \sum_{i=1}^{i=3} \rho_i\right)\mu \\ 0 \\ -\rho_1\mu \\ 0 \\ -\rho_2\mu \\ 0 \\ -\rho_3\mu \\ 0 \end{bmatrix},$$

$$G_{Y_0} = \begin{bmatrix} -(1 - \phi_0) \\ 0 \\ -\left(\dfrac{1/\mu_{1,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)\phi_0 \\ 0 \\ -\left(\dfrac{1/\mu_{2,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)\phi_0 \\ 0 \\ -\left(\dfrac{1/\mu_{3,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)\phi_0 \\ -\left(\dfrac{1/\mu_{4,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)\phi_0 \end{bmatrix}, \quad \text{and } \ell_{Y_0} = 0,$$

implies,

$$\frac{\partial L}{\partial Y_0} = \int_0^T -\mu\left(\left(1 - \sum_{i=1}^{1=3} \rho_i\right)\Lambda_{0,0}(t) + \rho_1\Lambda_{1,0}(t) + \rho_2\Lambda_{2,0}(t) + \rho_3\Lambda_{3,0}(t)\right)dt - (1 - \phi_0)\Lambda_{0,0}(0)$$

$$- \frac{\phi_0}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\left((1/\mu_{1,0})\Lambda_{1,0}(0) + (1/\mu_{2,0})\Lambda_{2,0}(0)\right.$$

$$\left. + (1/\mu_{3,0})\Lambda_{3,0}(0) + (1/\mu_{4,0})\Lambda_{4,0}(0)\right).$$

Seroprevalence of the infected population, ϕ_0

For the HIV infectious disease model, with the combined strategy, the sensitivity equation for the seroprevalence of the infected population is defined by the following.

$$F_{\phi_0} = 0, \quad G_{\phi_0} = \begin{bmatrix} Y_0 \\ 0 \\ -\left(\dfrac{1/\mu_{1,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)Y_0 \\ 0 \\ -\left(\dfrac{1/\mu_{2,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)Y_0 \\ 0 \\ -\left(\dfrac{1/\mu_{3,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)Y_0 \\ -\left(\dfrac{1/\mu_{4,0}}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}}\right)Y_0 \end{bmatrix}, \quad \text{and } \ell_{\phi_0} = 0,$$

implies,

$$\frac{\partial L}{\partial \phi_0} = Y_0 \Lambda_{0,0}(0) - \frac{Y_0}{1/\mu_{1,0} + 1/\mu_{2,0} + 1/\mu_{3,0} + 1/\mu_{4,0}} \Big((1/\mu_{1,0})\Lambda_{1,0}(0) + (1/\mu_{2,0})\Lambda_{2,0}(0)$$
$$+ (1/\mu_{3,0})\Lambda_{3,0}(0) + (1/\mu_{4,0})\Lambda_{4,0}(0) \Big).$$

Distribution of disease-related immigration, ρ_i

For the HIV infectious disease model, with the combined strategy, the sensitivity equations for the parameters associated with the distribution of disease-related immigration is evaluated for each of the respective classes.

For ρ_1 we get,

$$F_{\rho_1} = \begin{bmatrix} \mu Y_0 \\ 0 \\ -\mu Y_0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad G_{\rho_1} = 0, \quad \text{and} \quad \ell_{\rho_1} = 0,$$

implies,

$$\frac{\partial L}{\partial \rho_1} = \int_0^{20} \mu Y_0 (\Lambda_{0,0}(t) - \Lambda_{1,0}(t)) dt.$$

For ρ_2 we get,

$$F_{\rho_2} = \begin{bmatrix} \mu Y_0 \\ 0 \\ 0 \\ 0 \\ -\mu Y_0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad G_{\rho_2} = 0, \quad \text{and} \quad \ell_{\rho_2} = 0,$$

implies,

$$\frac{\partial L}{\partial \rho_2} = \int_0^T \mu Y_0 (\Lambda_{0,0}(t) - \Lambda_{2,0}(t)) dt.$$

For ρ_3 we get,

$$F_{\rho_3} = \begin{bmatrix} \mu Y_0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ -\mu Y_0 \\ 0 \end{bmatrix}, \quad G_{\rho_3} = 0, \quad \text{and} \quad \ell_{\rho_3} = 0,$$

implies,

$$\frac{\partial L}{\partial \rho_3} = \int_0^{20} \mu Y_0 (\Lambda_{0,0}(t) - \Lambda_{3,0}(t)) dt.$$

Average yearly medical expenses for each class, c_i

For the HIV infectious disease model, with the combined strategy, the sensitivity equations for the average yearly medical expenses is evaluated for each of the population classes.

For c_0 we get,

$$F_{c_0} = 0, \quad G_{c_0} = 0, \quad \text{and} \quad \ell_{c_0} = \alpha(Y_{0,0}(t) + Y_{0,1}(t))e^{-rt},$$

implies,

$$\frac{\partial L}{\partial c_0} = \int_0^T \alpha(Y_{0,0}(t) + Y_{0,1}(t))e^{-rt}dt.$$

For c_1 we get,

$$F_{c_1} = 0, \quad G_{c_1} = 0, \quad \text{and} \quad \ell_{c_1} = \alpha(Y_{1,0}(t) + Y_{1,1}(t))e^{-rt},$$

implies,

$$\frac{\partial L}{\partial c_1} = \int_0^T \alpha(Y_{1,0}(t) + Y_{1,1}(t))e^{-rt}dt.$$

For c_2 we get,

$$F_{c_2} = 0, \quad G_{c_2} = 0, \quad \text{and} \quad \ell_{c_2} = \alpha(Y_{2,0}(t) + Y_{2,1}(t))e^{-rt},$$

implies,

$$\frac{\partial L}{\partial c_2} = \int_0^T \alpha(Y_{2,0}(t) + Y_{2,1}(t))e^{-rt}dt.$$

For c_3 we get,

$$F_{c_3} = 0, \quad G_{c_3} = 0, \quad \text{and} \quad \ell_{c_3} = \alpha Y_{3,0}(t)e^{-rt},$$

implies

$$\frac{\partial L}{\partial c_3} = \int_0^T \alpha Y_{3,0}(t)e^{-rt}dt.$$

For c_4 we get,

$$F_{c_4} = 0, \quad G_{c_4} = 0, \quad \text{and} \quad \ell_{c_4} = \alpha Y_{4,0}(t)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial c_4} = \int_0^T \alpha Y_{4,0}(t)e^{-rt}dt.$$

QALYs, q_i

For the HIV infectious disease model, with the combined strategy, the sensitivity equations for QALYs is evaluated for each of the population classes.

For q_0 we get,

$$F_{q_0} = 0, \quad G_{q_0} = 0, \quad \text{and} \quad \ell_{q_0} = (\alpha - 1)(Y_{0,0}(t) + Y_{0,1}(t))e^{-rt},$$

implies,

$$\frac{\partial L}{\partial q_0} = \int_0^T (\alpha - 1)(Y_{0,0}(t) + Y_{0,1}(t))e^{-rt}dt.$$

For q_1 we get,

$$F_{q_1} = 0, \quad G_{q_1} = 0, \quad \text{and} \quad \ell_{q_1} = (\alpha - 1)(Y_{1,0}(t) + Y_{1,1}(t))e^{-rt},$$

implies,

$$\frac{\partial L}{\partial q_1} = \int_0^T (\alpha - 1)(Y_{1,0}(t) + Y_{1,1}(t))e^{-rt}dt.$$

For q_2 we get,

$$F_{q_2} = 0, \quad G_{q_2} = 0, \quad \text{and} \quad \ell_{q_2} = (\alpha - 1)(Y_{2,0}(t) + Y_{2,1}(t))e^{-rt},$$

implies,

$$\frac{\partial L}{\partial q_2} = \int_0^T (\alpha - 1)(Y_{2,0}(t) + Y_{2,1}(t))e^{-rt}dt.$$

For q_3 we get,

$$F_{q_3} = 0, \quad G_{q_3} = 0, \quad \text{and} \quad \ell_{q_3} = (\alpha - 1)Y_{3,0}(t)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial q_3} = \int_0^T (\alpha - 1)Y_{3,0}(t)e^{-rt}dt.$$

For q_4 we get,

$$F_{q_4} = 0, \quad G_{q_4} = 0, \quad \text{and} \quad \ell_{q_4} = (\alpha - 1)Y_{4,0}(t)e^{-rt},$$

implies,

$$\frac{\partial L}{\partial q_4} = \int_0^T (\alpha - 1)Y_{4,0}(t)e^{-rt}dt.$$

Direct cost for the preventative vaccine, κ_p

For the HIV infectious disease model, with the combined strategy, the sensitivity equation for the direct cost for the preventative vaccine is defined by the following.

$$F_\alpha = 0, \quad G_\alpha = 0, \quad \text{and}$$

$$\ell_\alpha = \alpha \nu_p(Y_{0,0}(t) + Y_{1,0}(t))e^{-rt},$$

implies,

$$\frac{\partial L}{\partial \alpha} = \int_0^T \alpha \nu_p (Y_{0,0}(t) + Y_{1,0}(t)) e^{-rt} dt.$$

Direct cost for the therapeutic vaccine, κ_t

For the HIV infectious disease model, with the combined strategy, the sensitivity equation for the direct cost for the therapeutic vaccine is defined by the following.

$$F_\alpha = 0, \quad G_\alpha = 0, \quad \text{and}$$

$$\ell_\alpha = \alpha \nu_t Y_{2,0}(t) e^{-rt},$$

implies,

$$\frac{\partial L}{\partial \alpha} = \int_0^T \alpha \nu_t Y_{2,0}(t) e^{-rt} dt.$$

Annual discount rate, r

For the HIV infectious disease model, with the combined strategy, the sensitivity equation for the annual discount rate is defined by the following.

$$F_r = 0, \quad G_r = 0, \quad \text{and}$$

$$\ell_r =$$
$$- t \left[\alpha \big(\kappa_p \nu_p (Y_{0,0}(t) + Y_{1,0}(t)) + \kappa_t \nu_t Y_{2,0}(t) + \sum_{i=0}^{i=4} \sum_{j=0}^{j=1} c_i Y_{i,j}(t) \big) - (1-\alpha) \sum_{i=0}^{i=4} \sum_{j=0}^{j=1} q_i Y_{i,j}(t) \right] e^{-rt},$$

implies,

$$\frac{\partial L}{\partial r} = \int_0^T -t \left[\alpha \big(\kappa_p \nu_p (Y_{0,0}(t) + Y_{1,0}(t)) + \kappa_t \nu_t Y_{2,0}(t) + \sum_{i=0}^{i=4} \sum_{j=0}^{j=1} c_i Y_{i,j}(t) \big) \right.$$
$$\left. - (1-\alpha) \sum_{i=0}^{i=4} \sum_{j=0}^{j=1} q_i Y_{i,j}(t) \right] e^{-rt} dt.$$

Weight for combining objectives for optimization, α

For the HIV infectious disease model, with the combined strategy, the sensitivity equation for the weight introduced to evaluate the multi-objective optimization is defined by the following.

$$F_\alpha = 0, \quad G_\alpha = 0, \quad \text{and}$$

$$\ell_\alpha = \left(\kappa_p \nu_p (Y_{0,0}(t) + Y_{1,0}(t)) + \kappa_t \nu_t Y_{2,0}(t) + \sum_{i=0}^{i=4} \sum_{j=0}^{j=1} c_i Y_{i,j}(t) + \sum_{i=0}^{i=4} \sum_{j=0}^{j=1} q_i Y_{i,j}(t) \right) e^{-rt},$$

implies,

$$\frac{\partial L}{\partial \alpha} = \int_0^T \left(\kappa_p \nu_p (Y_{0,0}(t) + Y_{1,0}(t)) + \kappa_t \nu_t Y_{2,0}(t) + \sum_{i=0}^{i=4} \sum_{j=0}^{j=1} c_i Y_{i,j}(t) + \sum_{i=0}^{i=4} \sum_{j=0}^{j=1} q_i Y_{i,j}(t) \right) e^{-rt} dt.$$