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The HIV Epidemic: What kind of vaccine are we looking for?

1 Problem Background

33.2 million people are living with HIV and AIDS worldwide [4]. Human Immunodeficiency Virus (HIV) is a virus that attacks the immune system and renders it weak to infection. HIV can progress to Acquired Immune Deficiency Syndrom (AIDS) once the number of T cells in the immune system have been significantly reduced [2]. People living with HIV are prone to infections and illnesses including pneumonia, Kaposi's sarcoma skin cancer, and yeast infections. Although treatments are available to prolong life for HIV infected people, such anti-retroviral therapies are extremely expensive and patients can acquire drug resistance if the medication is not taken everyday [2]. HIV is transmitted through unprotected sex, needle exchange, the birthing process, and breast feeding. In 2007, 2.1 million people died from HIV/AIDS related complications, while 2.5 million people were newly infected with HIV worldwide [4]. The extent to which the disease has spread and the devastation it leaves behind emphasizes the need for useful and effective preventative measures against the spread of the disease.

There are many prevention strategies used to minimize the spread of HIV and AIDS but none have been successful at eradicating the disease. Since the disease is primarily transmitted sexually, the effective prevention strategies currently in use to curb the spread of HIV are abstinence and condoms [2]. Even with these prevention methods in use, HIV is still spreading rapidly, especially in developing countries. Scientists and researchers therefore need to look towards more potent prevention strategies like vaccines.

A significant portion of HIV/AIDS research funding is being spent on vaccine research. Thirty clinical trials have been initiated on 30 vaccines since the early 1990s. None of these vaccines have graduated past the human testing (stage III), as their efficacy has been hard to prove [2]. Additionally it is extremely difficult to produce a vaccine that is able to adapt to the varying nature of the disease itself which mutates up to one million times each day. Drug resistance is common, and it is currently believed that any vaccine that is produced will be imperfect, and would wane in efficacy over time.

In order to predict what effect a vaccine will have on the current epidemic, we produce a mathematical model and study the dynamics of its solutions to make predictions for the number of infections and deaths that might be prevented by a vaccine. The first section of this paper will describe the equations and parameters of the differential equations model I chose to study. The second section outlines the ultimate goal of the study and the study's larger implications. This discussion is followed by a description of the steady state equilibrium and how it was characterized computationally. Section four outlines the sensitivity analyses I chose to employ and the results from these sensitivity analyses. The paper is concluded with a brief description of the conclusions and ideas for future work to extend the project.

1.1 The Model

Although there are many mathematical models in the literature that investigate the dynamics of the spread of HIV in the presence of a vaccine, I chose to focus on one such ordinary differential equation (ODE) compartment model. This model, developed by Elbasha, Gumel et al. in 2006, describes the spread of HIV through five distinct population groups (Figure 1). These subgroups are: unvaccinated susceptible individuals (X), vaccinated susceptible individuals (V), unvaccinated infected individuals (Y), vaccinated infected individuals (W), and individuals with AIDS (A). The model assumes that individuals are vaccinated before they enter the sexually active population, and that individuals cannot be infected by HIV at birth. The model takes into account recruitment into the sexually active population, deaths, waning immunity rate,

Table 1: A list of variable state descriptions.

Variables	Description
$X(t)$	Unvaccinated susceptible individuals
$V(t)$	Vaccinated susceptible individuals
$Y(t)$	Unvaccinated infected individuals
$W(t)$	Vaccinated infected individuals
$A(t)$	Individuals with AIDS

Table 2: A list of parameter descriptions and ranges.

Parameters	Description	Range	U.S. Estimate
Λ	Rate of recruitment (birth rate)	$(0, 1]$	0.01 (UNAIDS)
β	Transmission coefficient	$(0, 1]$	0.04 (UNAIDS)
p	Vaccination rate	$(0, 1]$	
$1 - q$	Degree of protection	$(0, 1]$	
s	Relative risk of infection	$(0, 1]$	0.5
θ	Modification parameter	$(0, 1]$	
μ	Removal rate (death rate)	$(0.02, 0.07]$	0.00826 (CIA)
γ	Rate of waning immunity	$(0, 0.5]$	
σ	Progression rate to AIDS	$(0, 1]$	0.03 (UNAIDS)
N_{pop}	Population size		298,213,000 (UNAIDS)

and the imperfection of the vaccine. The model can be represented by the five following ordinary differential equations:

$$\begin{aligned}
\frac{dX}{dt} &= (1-p)\Lambda - \mu X - \lambda X + \gamma V \\
\frac{dV}{dt} &= p\Lambda - \mu V - q\lambda V - \gamma V \\
\frac{dY}{dt} &= \lambda X - (\mu + \sigma) Y \\
\frac{dW}{dt} &= q\lambda V - (\mu + \theta\sigma) W \\
\frac{dA}{dt} &= \sigma Y + \theta\sigma W - (\mu + \alpha) A,
\end{aligned}$$

where the variable states and parameters are defined in Tables 1 and 2. Here λ is the infection rate at which susceptible individuals are infected with HIV and is represented by the following quantity:

$$\lambda = \frac{\beta Y + s\beta W}{N_{\text{pop}}}. \tag{1}$$

General ranges for each parameter are known. We can also estimate various parameters by referring to data banks like United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization

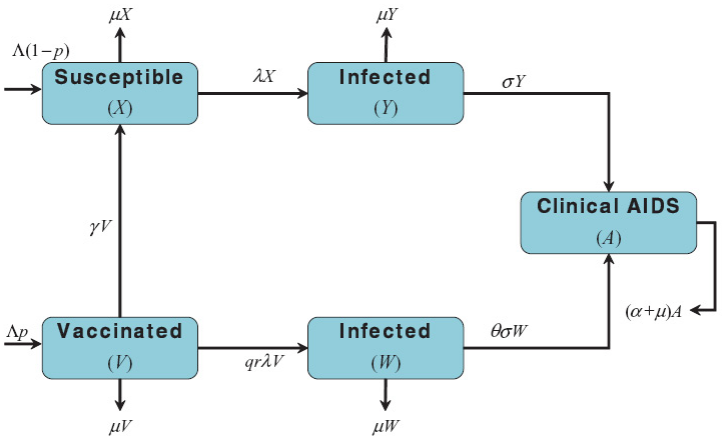

Figure 1: A pictoral depiction of the five compartment ODE model describing the spread of HIV through a population [3]. Individuals are expected to enter the sexually active population as either susceptible or vaccinated. Both of these groups can then become infected with HIV and progress to AIDS. Parameter descriptions can be found in Table 2.

(WHO) (U.S. estimates are presented in Table 2). The model is a non-linear set of five ODEs with a large number of parameters which makes working with the model computationally intensive.

In the paper that examines the model described above, the authors sought to characterize the bifurcations that took place when different incidence functions, λ, were used [6]. For the purposes of this paper, I will be considering the basic model with standard incidence (Equation 1). The stability and characterization of the disease free equilibrium state, when no one in the population is infected with HIV ($Y = W = 0$) is thoroughly described and examined by the authors. The authors also describe the basic reproductive number of the system. The basic reproductive number (R_p) describes the number of secondary infections that would result from one infected person entering the population. The existence of endemic equilibria, in which a proportion of the population is infected with HIV ($Y, W \geq 0$) is proven. The endemic equilibrium depends on whether R_p is greater than unity. The basic reproductive number for this model is given by:

$$R_p = \frac{\beta\left(\gamma(\mu+\theta\sigma)+\mu\left((pqs-p+1)\,\mu+(pqs-p\theta+\theta)\,\sigma\right)\right)}{(\gamma+\mu)(\mu+\sigma)(\mu+\theta\sigma)}. \tag{2}$$

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Elbasha and Gumel prove the following lemma in their analysis that gives conditions on the parameters such that an endemic equilibria exists [3].

Lemma: Given

$$\begin{aligned} B_1 &= q[\mu+\theta\mu+p(1-\theta)\sigma] \\ B_2 &= (\gamma+\mu+p\sigma)(\mu+\theta\sigma)-pqs(\mu+\sigma)^2\left(\frac{\beta}{\mu+\sigma}\right)+q(\mu+\sigma)[(\mu+\theta\sigma)(1-p)\left(1-\left(\frac{\beta}{\mu+\sigma}\right)\right)+\mu p] \\ B_3 &= (\gamma+\mu)(\mu+\sigma)(\mu+\theta\sigma)[1-R_p], \end{aligned}$$

the vaccination model has
(i) a unique endemic equilibrium if $B_3 < 0 \Leftrightarrow R_p > 1$;
(ii) a unique endemic equilibrium if $B_2 < 0$ and $B_3 = 0$ or $B_2^2 - 4B_1B_3 = 0$;
(iii) two endemic equilibria if $B_3 > 0$, $B_2 < 0$, and $B_2^2 - 4B_1B_3 > 0$;
(iv) no endemic equilibrium otherwise.

No analysis is done by the authors to determine the stability of the endemic equilibria or examine their properties.

2 Project Goals and Description

The general goal of this paper is to determine the range of vaccination parameters that will create a disease-free equilibrium. Ultimately, by perfoming a sensitivity analysis on the endemic equilibria, we enforce bounds on the vaccination parameters p, q, γ and θ such that a disease-free equilibrium is guaranteed. This information can then be used to understand better the conditions under which a vaccine will have a positive effect on the progression of HIV and AIDS in society.

The first step of the project is to verify the disease-free equilibrium results given by the authors. After the basic reproductive number and the Jacobian are produced for a general equilibrium point, I will then focus on finding the conditions under which the endemic equilibria exists, and the sensitivity of the endemic equilibrium points on the parameter values. The sensitivity of the endemic equilibrium to parameters will be determined using a Latin Hypercube Sampling method described in Section 4. Because of the computationally intensive nature of the problem, I will be performing all calculations and simulations using Wolfram's Mathematica.

3 Steady State Equilibria

The majority of the initial work on this project was spent verifying the results obtained in the paper regarding the disease-free equilibrium state:

$$(X_{\text{DFE}}, V_{\text{DFE}}, Y_{\text{DFE}}, W_{\text{DFE}}) = (\frac{[\gamma + (1-p)\mu]\Lambda}{\mu(\mu+\gamma)}, \frac{p\Lambda}{\mu+\gamma}, 0, 0), \tag{3}$$

as well as the Jacobian matrix for the disease-free equilibrium. This Jacobian determines the dominant eigenvalue, which verifies R_p (Equation 2). The general endemic equilibrium points (for $R_p \geq 1$) are defined to be

$$\begin{aligned} X^* &= \frac{(\gamma + (1-p)(q\lambda^* + \mu))\Lambda}{(\lambda^* + \mu)(\gamma + q\lambda^* + \mu)} \\ V^* &= \frac{p\Lambda}{\gamma + q\lambda^* + \mu} \\ Y^* &= \frac{(\gamma + (1-p)(q\lambda^* + \mu))\lambda^*\Lambda D_u}{(\lambda^* + \mu)(\gamma + q\lambda^* + \mu)} \\ W^* &= \frac{pq\lambda^*\Lambda D_v}{\gamma + q\lambda^* + \mu}, \end{aligned}$$

with $\lambda^* = \frac{(-B_2 + \sqrt{B_2^2 - 4B_1B_3})}{2B_1}$, $D_v = \frac{1}{\mu+\theta\sigma}$ and $D_u = \frac{1}{\mu+\sigma}$. We see that these endemic equilibria depend only on parameter values and can therefore be easily solved once parameter values are chosen.

4 Sensitivity Analysis

In order to determine the sensitivity of the endemic equilibria to changes in parameter values, a sensitivity analysis was performed on the model. Sensitivity analyses are usually done on one of three levels [5]. The first type is called screening and is usually performed by testing all possible combinations of parameters in the space and observing the effect on the model. This process is not only time-consuming but computationally taxing, since our model has ten parameters we would like to vary. Local sensitivity analysis is also used to

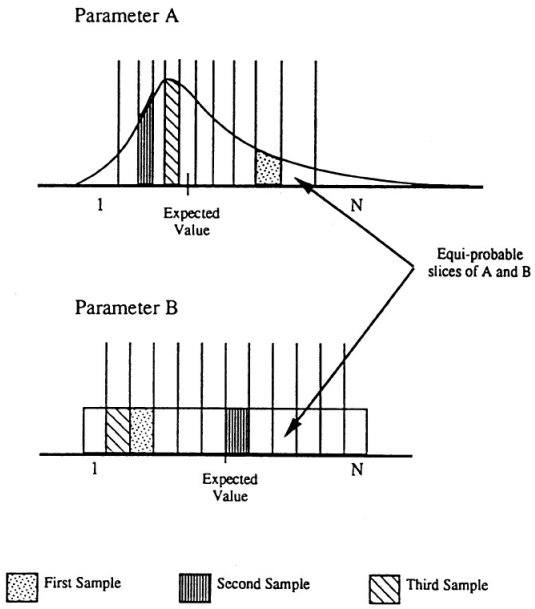

Figure 2: A pictoral example of the Latin Hypercube sampling method [1]. A mean and standard distribution are known for parameter A, then a distribution for it. A range of values is known for parameter B, so a uniform distribution is chosen. After splitting each distribution into N intervals, an interval is chosen at random and a random value from this interval is also chosen. The randomly chosen values for both parameters are used to calculate a solution and the process is repeated until all intervals have been sampled without replacement.

determine the sensitivity of the model on a local level and is usually done with a method called differential analysis. The last method is global sensitivity analysis, which once perfomed will describe the model's sensitivity to parameter values throughout parameter and variable space. The most common type of global sensitivity analysis is the Monte Carlo method. The method I chose to use in my analysis is described by Blower and Dowlatabadi [1]. This method, which is called Latin Hypercube Sampling (LHS), samples the parameter space efficiently while simulataneously allowing us to observe changes in the endemic equilibia.

4.1 Latin Hypercube Sampling

LHS is a type of stratified Monte Carlo method and allows the variation of all parameters simultaneously. It has been proven to be more efficient than random sampling since it estimates the mean value of the function in question more accurately [1]. The first step in LHS is to determine the probability distribution functions that describe the state parameters in the system. If we have an estimate for a specific parameter, we can produce a normal distribution about that estimate, or if we have no information about a specific parameter, we can use a uniform distribution. The next step outlined by Blower and Dowlatabadi is to calculate the number of simulations or calculations that need to be perfomed in order to sample the entire parameter space without replacement. We are then left to divide each of the parameter ranges into N equi-probable intervals, sample from these intervals without replacement and perform the N simulations or calculations. Once this is done, the resulting data can be plotted and analyzed using uncertainty analysis [1]. This process can also be visualized in Figure 2. We can use LHS to better understand what kind of vaccine parameters we would need in order to see a disease-free equilibrium in our system. These parameter values can then be used as guidelines for vaccine development in the context of this model.

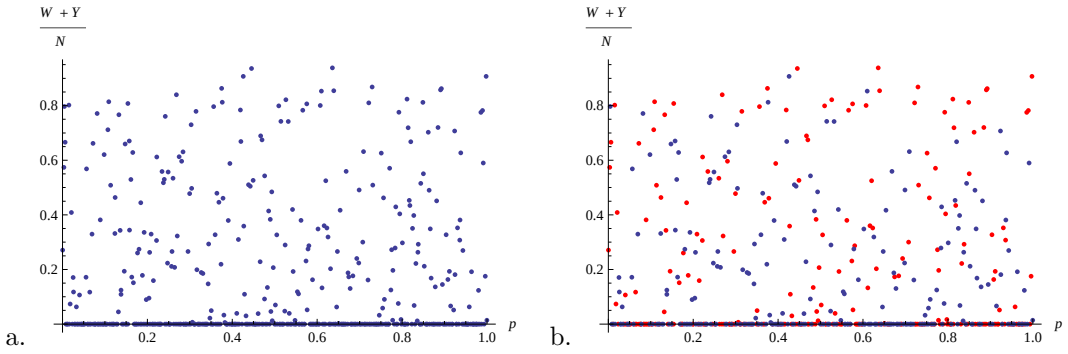

Figure 3: Infected population proportions for varying p values in LHS. (a) Displays the 500 interval results for the LHS implementation. As can be seen, there seems to be no relationship between infected equilibrium states and the proportion of the population that is vaccinated. (b) Simulation points with a q value of less than 0.5 are shown in red, while those with q values greater than or equal to 0.5 are shown in blue. As can be seen, there is no correlation between the parameter values and the proportion of the population that is infected with HIV at any one time.

4.1.1 Distributions Chosen

Although estimates were found for a majority of the parameters examined, I chose to define uniform distributions for all parameters when performing LHS. Sampling from uniform distributions across the entire range of possible values will give a better sense of the model's dynamics in parameter space. Uniform distributions also facilitate the division of distributions into N equi-probably intervals. Given more time I would like to see how the results of LHS differ when specific distributions are defined for parameters with known means and standard deviations. Uniform distributions were defined for all parameters within the ranges described in Table 2.

4.1.2 Difficulties

Implementing the LHS algorithm for general models proved to be relatively straightforward but I experienced difficulty performing the algorithm on the specific model described in Section 1. 1. The code, which was developed for a general model, runs through the LHS algorithm and produces plots to show how the infected proportion of the population varies with various parameter values. The plots (Figure 3) show no patterns or trends between the parameter values and the infected population proportions. Even when interactions between parameter values are taken into account, no clear trends were observed. The analysis of the LHS is therefore difficult to do. Blower and Dowlatabadi recommend using a partial rank correlation analysis to understand the results. Due to time constraints I was not able to perform this uncertainty analysis. Because this method did not illicit clear results, I chose to perform a simpler sensitivity analysis.

4.2 Screening

In order to get a clear picture about how vaccine parameters were affecting the endemic equilibria I chose to perform a screening analysis. This analysis was performed by varying one parameter and keeping all other parameters constant. This procedure was performed while varying p,q, γ, and θ individually. Four values (one low, two intermediate, one high) were chosen for each parameter. The dynamics of the population with the chosen parameters were then observed. After running a few simulations (Figure 4) I chose to focus on a population with initial conditions defined by $X(0) = 25$, $V(0) = 25$, $Y(0) = 25$, and $W(0) = 25$. Initial conditions that resembled current U.S. population proportions produced uninteresting endemic equilibria and will therefore not be analyzed.

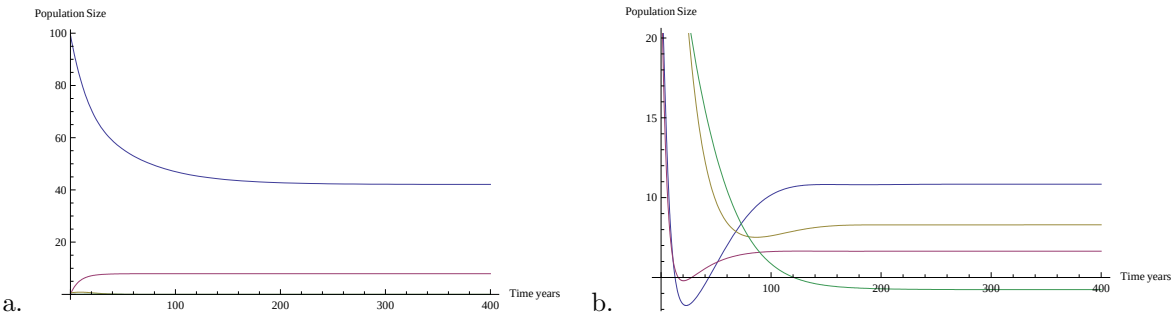

Figure 4: Both plots above show the dynamics of a 100 person population over 400 years with the following parameter values: $\Lambda = 1$, $\mu = 0.02$, $q = 0.5$, $p = 0.95$, $\theta = 0.4$, $s = 0.45$, $\sigma = 0.04$,$\beta = 0.45$, and $\gamma = 0.1$. The blue curve corresponds to X(t), purple to V(t), yellow to Y(t), and green to W(t). (a) Initial conditions are used that represent the HIV prevalence in the current U.S. population: $X(0) = 99.4$, $V(0) = 0$, $Y(0) = 0.6$, and $W(0) = 0$. The R_p value for these parameter choices and initial conditions is 1.09195. (b) Initial conditions are used that have even proportions of people in each subgroup: $X(0) = 25$, $V(0) = 25$, $Y(0) = 25$, and $W(0) = 25$. The R_p value for these parameter choices and initial conditions is 6.75781. Since more interesting results can be seen in endemic equilibria states for the evenly split population, the rest of the analyses will focus on these initial conditions.

4.2.1 Results

The plots in Figure 5 show how the proportion of the population of interest changes with varying parameter values. It should be kept in mind that this analysis is specific to the initial conditions chosen, and other initial conditions may produce different sensitivities. The vaccinated susceptible population, which would ideally be as high as possible, is most sensitive to changes in p and γ and least sensitive to changes in q and θ. We can maximize the vaccinated population by having low γ and q and high θ and p. This correponds to having low waning immunity, high effectiveness, little modification in behavior and high vaccination rates.

The general non-vaccinated infected population is again most sensitive to p and γ but we see that trends tend to be reversed. High vaccination rates result in small susceptible populations while high γ values result in high susceptible numbers. These trends make sense, since as waning immunity increases more vaccinated individuals enter the susceptible population. Also as vaccination rates increase more individuals are expected to enter the population as vaccinated and not susceptible individuals.

The vaccinated infected population has a lower prevalence rate in the population then the non-vaccinated infected population. We see that all parameters seem to have an effect on the prevalence of this group in the population. We observe that increasing p and q results in an increase in the population proportion of vaccinated susceptible individuals. Increasing γ and θ results in the decrease in the number of infected vaccinated individuals. Although none of these results are particularly surprising, it is interesting to note that q and θ have a larger effect on the vaccinated infected population then on the non-vaccinated infected population.

When we look at the total infected population we see that all parameters affect the endemic equilibria. We notice that to get a small endemic equilibria we want small γ and q and large p and θ. We notice also that the sensitivity to θ and γ seems to not be linear but looks exponential for both decay and increase.

5 Conclusions

The sensitivity analysis I have performed verified intuitive parameter choices that would produce low endemic equilibria values. We see that our screening sensitivity analysis allows us to conclude that in order to minimize the infected population we would want a vaccine to be developed with a low waning immunity rate ($\gamma \leq 0.5$) and a high effectiveness ($q \leq 0.5$). We would also like to see a large proportion of the population ($p \geq 0.5$)

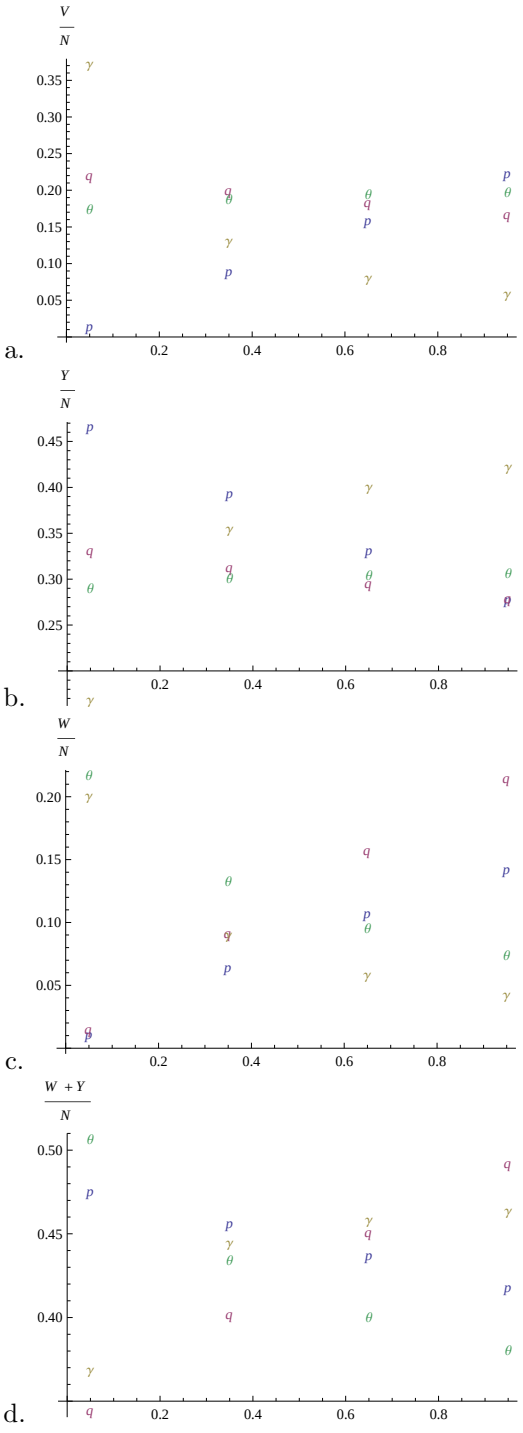

Figure 5: These plots describe how changing vaccine parameter values affects various populations of interest. (a) Vaccinated susceptible individuals are affected most by p and γ. (b) Non-vaccinated infected individuals are most sensitive to p and γ. (c) Vaccinated infected individuals are affected by changes in all parameters. (d) The total infected population proportion seems to be affected by all parameter choices.

vaccinated and no large difference in risky behavior between vaccinated and non-vaccinated individuals ($\theta \geq 0.5$). The screening sensitivity analysis therefore allowed us to make conclusions about the neccessary magnitudes of the vaccine parameters that produce a low endemic equilibrium. It should be emphasized that these results are only valid for the chosen initial conditions.

Throughout this process, I learned that it is often beneficial to begin with the simplest procedure possible and move on to more complex analyses once the dynamics of the model are better understood. Beginning with a general screening before implementing LHS may have narrowed down my focus to a specific subset of the parameter space. Although the general algorithm developed and implemented for LHS works on general models, including the model considered in this paper, the analysis of the results requires more complex and advanced methods than those I possess.

5.1 Future Work

Future attempts to finish this project should aim to better understand the results from LHS in the context of vaccine development. Efforts should be made to analyze the results using partial rank correlation analysis. The broad ranges found from the screening method could then be used as starting distributions for the LHS method, and this may narrow the scope of the LHS analysis. Work should also be done to better understand the dynamics of the model beginning with initial conditions that represent the United States population. Ultimately I would like to better understand how the introduction of a vaccine in the United States would affect the epidemic and the future of HIV in this country.

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