The Effects of a Potential National Campaign and a VEI Type Vaccine on an HIV-1 Infected Homosexually Active Population

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José Alvarado
University of Puerto Rico, Cayey Campus

Oscar Estrada
Universidad Autónoma de Ciudad Juárez

Emily Kajita
Harvey Mudd College

Nadia Monrose
University of the Virgin Islands

Carlos Hernández Suarez
Universidad de Colima, Mexico

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ABSTRACT

We build a stochastic model to analyze the dynamics of HIV in a homosexually active population. In our model, we introduce the effects of a hypothetical campaign that promotes HIV testing as well as the effect of a VEI (Vaccine Efficacy for Infectiousness) type vaccine. We analyze how the efficacy of the vaccine and campaign affect disease dynamics, particularly the probability of eventual extinction of the disease. The general conclusion is that increasing the efficacy of the vaccine results in a higher probability of extinction of the epidemic as expected. However, increasing the efficacy of the campaign above some optimum counter-intuitively decreases the probability of extinction. We find the minimum efficacy of the vaccine and the optimum efficacy of the campaign to drive the epidemic to extinction.

1 Introduction

Human Immunodeficiency Virus (HIV), the virus that causes Acquired Immune Deficiency Syndrome (AIDS), is the culprit of a worldwide growing epidemic. There are about 33.6 million people already infected with HIV/AIDS as of the end of 1999 and more than 16,000 new infections everyday [7,10]. Researchers have been struggling to understand the dynamics of this deadly virus in hope to find a cure. Vaccines may eventually be developed to effectively protect individuals from becoming infected or effectively slow progression of the virus in the infected. However, since a large proportion of the population would have to be vaccinated in order to halt the epidemic, it is expected that such drugs will be costly at both the individual and population level. A national campaign promoting HIV testing can be comparatively much less expensive and possibly just as effective at reducing the epidemic for the overall population. Such a campaign could also be put into effect sooner than a vaccine, which may take time to develop, test, approve, and distribute. Statistics show, however, that there is a higher risk of HIV infection among young gay men, largely due to the nature of the method of transmission [10]. Some researchers have discovered vaccines called Vaccine Efficacy for Infectiousness (VEI). These vaccines are atypical in that they prevent transmission of the virus from the vaccinated individual instead of protecting the individual from infection [5]. It may be possible to slow or halt the epidemic by lowering the transmission rate of the virus. Hence, we study the effects of the VEI vaccine and a national education campaign on an HIV epidemic within a homosexually-active male population.

The strain of HIV we use in our study is the HIV-1 virus. Studies suggest that there are four different levels of infectivity for this virus, the last stage being full-blown AIDS [6]. In the first stage, *initial innoculum*, the virus is introduced into the body and the individual becomes highly infectious because s/he has no immunity initially built up against the virus. In the second stage, *initial transient*, both the T-cell population that fights against foreign invaders of the body and the virus population fluctuate greatly. The cells of the body begin to create antibodies at this stage to fight the virus, and infectiousness decreases as a result. It is these antibodies that individuals test for when screened for HIV. It has been shown that 95% of newly infected individuals develop antibodies within three months, and nearly all individuals within six months [7]. In the third stage, *clinical latency*, there are extremely large numbers of virus and T cells which results in an appearance of a disease-steady state. Eventually, the virus overruns the immune

system so that the infected develops full-blown AIDS [9].

Recent studies have been conducted which show that up to 70% of people newly infected with HIV experience some flu-like symptoms which include fevers, chills, night sweat, and joint pain [7,8]. The hypothetical national campaign we introduce targets those who exhibit these early symptoms to test for HIV. We hope to educate some members of the population in the first stage of infection. We anticipate that when they are aware of these early symptoms of HIV, a fraction will go to the doctor, get tested, and change their behavior if tested positive. For the purposes of our study, we assume that those who test positive for the virus stop infecting other individuals. We examine the behavior of the epidemic by varying the efficacy of such a campaign on the population.

According to Koopman [6], a person is most infectious during the first two to three months of infection - up to 1,000 times more than those in the second or third stages of infection. The idea of the VEI type "nonvaccine-vaccine" as an epidemic immobilizer was conceived under this assumption [5]. Research is presently being conducted to develop and test these type of vaccines. The hypothetical vaccine we introduce in our model neither protects an individual from becoming infected with HIV nor keeps one from developing HIV and AIDS symptoms, nor stops or slows the progression of the infection to the AIDS stage. Its only function is to prevent an infected individual from passing the virus on to a susceptible. We show the potential of the vaccine to assuage the epidemic based on the fraction of the population vaccinated and the vaccine's efficacy.

Some researchers are skeptical, however, of the ability of prophylactic vaccines to perform as effective epidemic dampeners. Blower [4] believes that their effectiveness on the population level is hindered because people are unable to build immune systems strong enough to clear their infection, rendering traditional protective vaccines useless. It was also argued that the sexual behavior of the community has too much of an impact on the epidemic since HIV is mostly spread through sexual intercourse [4]. However, because of its non-traditional property of preventing transmission from vaccinated infectives rather than directly protecting susceptibles from infection, it is believed that the use of a VEI type vaccine can have a significant effect on the population [6].

In our study, we develop a model that is based on four stages of HIV infection. We use two compartments for each of the first three stages and the susceptibles class - one set of compartments representing the vaccinated, and the other, the non-vaccinated. We also include a compartment that represents the class of people who realize that they are infected through either

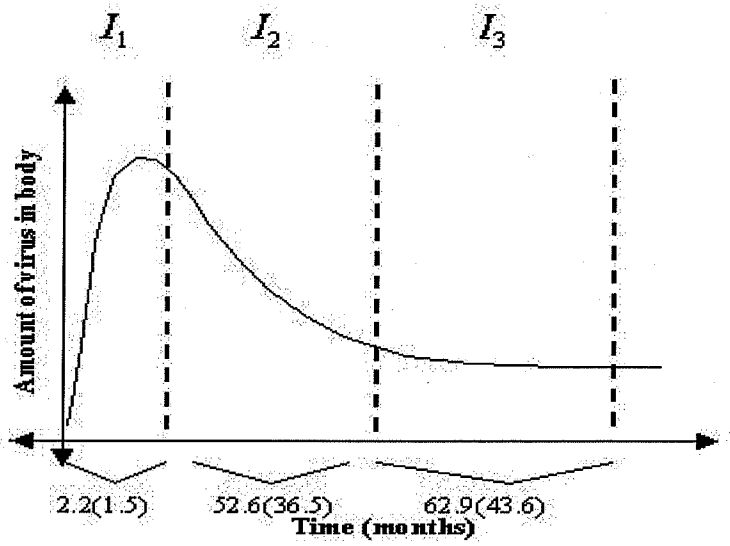


Figure 1: Stages of Infection (Time interval values obtained from [3]

developing full-blown AIDS or getting tested because of the campaign's influence and stop infecting others. We use our model to find an expression of the basic reproductive number using a modified Markov chain process, from which we obtain the probability of extinction of the epidemic. We then analyze the effects of the campaign and vaccine using 3-D plots and simulations.

1.1 The Model

Assumptions

- We assume a homogenous homosexual male population in which all members have the same immune system response. The vaccine has the same efficacy for everyone.
- We assume for our study that until the individual has been infected for six months, he will not test positive for the virus with the standard antibody test. If an individual tests negative, he will not test for HIV again.
- We assume three stages of infection I_1, I_2, I_3 before individuals develop full-blown AIDS. Every stage of infection has the same duration (i.e. an individual spends the same amount of time in I_1 as in I_2, as in I_3). We set each stage of infection to last for three years since it takes an individual

about nine years to develop full-blown AIDS.
I_1 is the most infectious state in which individuals are asymptomatic and test negative during the first six months, after which they test positive.
I_2 is the state in which individuals are asymptomatic and test positive.
I_3 is the state in which individuals are symptomatic and test positive.

- Since we are focusing on the effects of the campaign, we screen only those who exhibit early symptoms as dictated by the campaign - thus, only individuals in the first stage of infection can be screened. Since infected individuals do not test positive within the first six months of infection, only a fraction of people in the first stage of infection test positive.
- Individuals that have not developed AIDS are unaware of what stage of infection they are in except if confirmed by testing. Sexual behavior is therefore unaffected if individuals are not tested for their condition or if they develop full-blown AIDS.
- We assume that the virus does not mutate so that the efficacy of the vaccine does not change due to this factor.
- We focus on sexual contact as the method of transmission. We assume that contact between any non-vaccinated infected and a susceptible results in transmission of the virus to the susceptible. If the infected acquires the vaccine previous to the infection, then it transmits the infection with probability $1 - V_e$, V_e being the efficacy of the vaccine.
- We assume that any susceptible who becomes infected begins in the first stage of infection and follows the same progression of infection.
- We assume that those who develop full-blown AIDS do not infect others, as well as those who are confirmed to have HIV.
- The proportion of people who find out they have HIV by methods other than the campaign are assumed to be insignificantly small and are therefore disregarded. Also disregarded are those who enter the sexually active population already infected with HIV.
- Vaccination is random and is only effective on individuals who are not already infected with the HIV virus.
- Vaccination does not affect the transition rates from one stage of infection to the next.
- The rate at which the vaccine losses its efficacy is independent of the status of the vaccinated (S^V, I_1^V, I_2^V, I_3^V).

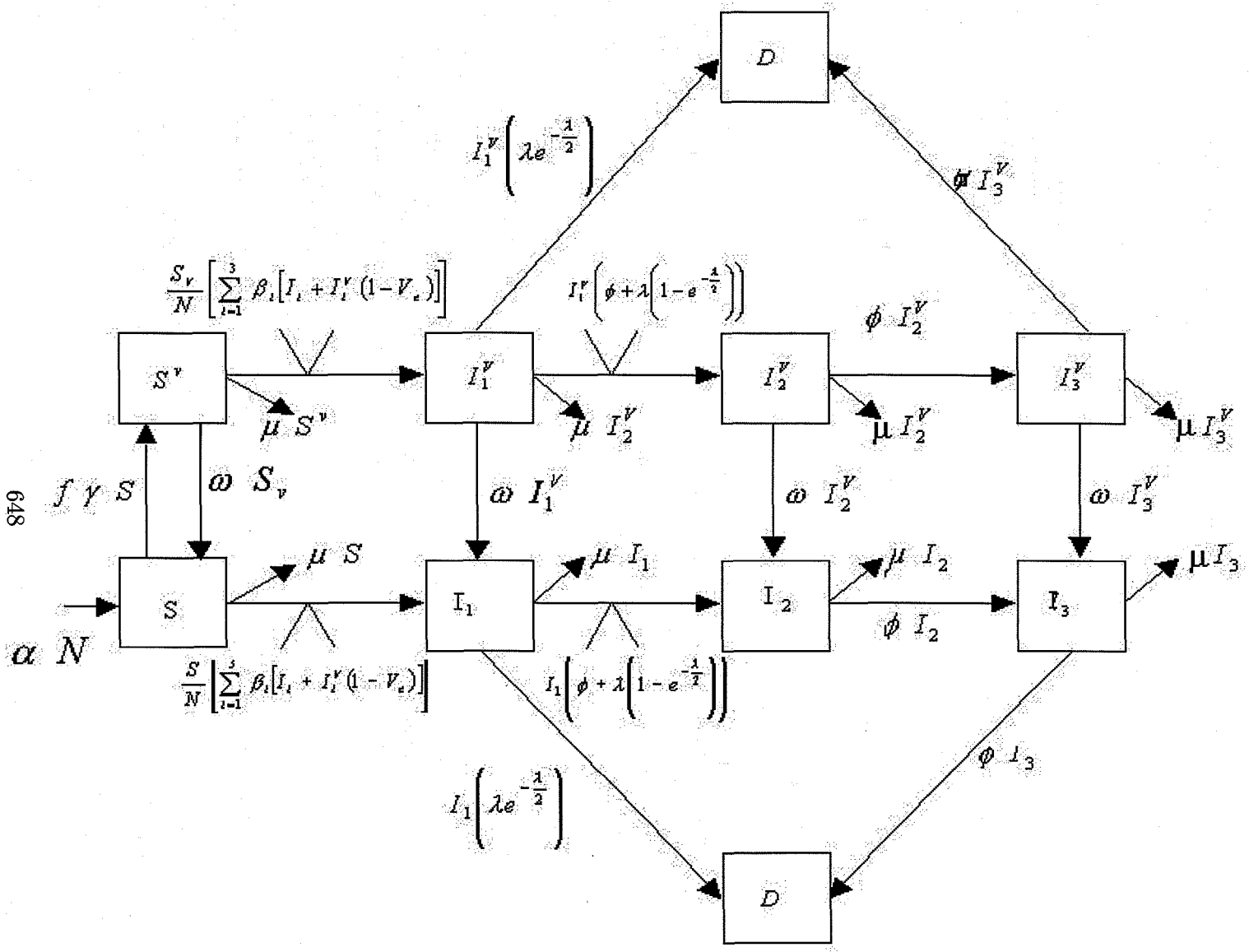


Figure 2: The Model

Rates Explanation

Parameters

- S = Susceptible population (sexually active)
- I_i = Population in infection stage i
- D = Population that becomes aware of their infection through campaign testing or developing full-blown AIDS
- v = Vaccinated (as superscript)
- $N = S + S^V + I_1 + I_1^V + I_2 + I_2^V + I_3 + I_3^V$ = Sexually active population
- $N + D$ = Total population
- α = Rate of sexually active susceptibles entering population ≈ 0.00125 since the growth rate of the population is 0.025 [12] and the fraction of the population that is homosexual is about 0.1 [13].
- d = Death rate by AIDS
- c = Contact rate
- θ_i = Probability that infected in state I_i will infect a susceptible $0 < \theta_i < 1$
- $\beta_i = c * \theta_i$ = Infectiousness at state i_i Note: $\beta_1 > \beta_2 > \beta_3$ We fix $\beta_1 = 2, \beta_2 = 1.5, \beta_3 = 1.1$
- f = Probability that an individual will be vaccinated $0 < f < 1$
- μ = Natural mortality rate $0 < \mu < 1$ We fix $\mu = 1/73 \approx 0.01355$ since the average life span is 73 years
- ϕ = Rate at which any of the infectious state is left; We fix $\phi = 1/3 \approx 0.333$ years
- γ = Vaccination rate; We fix $\gamma = 1$
- ω = Waning effect (rate at which vaccine loses its efficacy) We fix $\omega = 1/33 \approx 0.03$ (see Appendix D)

Parameters to Vary

- V_e = Probability that a vaccinated-infected will not infect a susceptible in every contact (independent of stage of infection)
- λ = Screening rate (rate at which individuals are screened for HIV due to campaign)

Since we assume that an individual cannot test positive for HIV within the first six months of infection, there is a probability $1 - e^{\frac{-\lambda}{2}}$ that an infected individual in the first stage of infection will test negative if λ is the screening rate.

We assume that the screening rate, λ is related to the campaign efficacy. We say that the campaign efficacy is the probability that an infected responds to the campaign by seeing the doctor and testing for HIV (at which point, he may be diagnosed positive). The campaign efficacy can be defined therefore as the probability that the infected individual is screened before passing to the next stage of infection, or

$$P = \frac{\lambda}{\lambda+\phi}$$

The screening rate corresponding to a campaign of efficacy P is

$$\lambda = \frac{P\phi}{1-P}$$

2 Methodology

We begin by computing the reproductive number R_0. Since our parameters are from exponential distributions, our model is a continuous-time Markov chain. Let δ_{ij} be the rate at which an individual passes from state i to stage j, then the probability of transition from i to j is:

$$k_{ij} = \frac{\delta_{ij}}{\sum_i^n \delta_{ij}}$$

In our epidemic model, there are states where individuals can produce new infected individuals through sexual contact or offspring. Following Hernandez [11] we label these states *active infectious states.* There are also non-infectious states that are considered part of the infectious state such as latent states, chronic states, etc. These will be called *passive infectious* if an individual in this state can visit one *infectious state* without the aid of external infection. We will divide the state space into two disjoint sets, ω and Δ, where ω has the active and passive infectious states and Δ contains

the rest of the states. Δ is called absorbing state. Thus, in our model $\omega = \{I_1, I_2, I_3, I_1^v, I_2^v, I_3^v\}$ and $\Delta = \{D, S, S^v\}$. If we define λ_r to be the contact rate of an individual when he is in $r \in \omega$, and also define $E[Z_r]$ as the expected time an individual spends in $r \in \omega$ before passing to a $k \in \Delta$, then R_0 can be written as

$$R_0 = \sum_{i \in \omega} \lambda_i E[Z_i]$$

where i is an *active infectious*. From here we can see that the problem of finding R_0 turns to the problem of finding the expected time an individual spends in evey *infectious state*. In order to calculate these expectations, we use a modified version of the Markov chain (Appendix A). Basically, it is known that the expected number of visits to stage r between two visits to Δ, $E[N_r]$, is given by

$$\mathrm{E}[N_r] = \frac{\pi_r}{\pi_\Delta}$$

where π_r is the element corresponding to state r, from the stationary distribution Π (see Appendix B), of the modified Markov chain we are using.

If we let δ_i be the rate at which an individual leaves state i, that is $\delta_i = \sum_{i \neq j} \delta_{ij}, i \in$ state space, then we can see that the expected time spent in state r between two visits to Δ, $E[Z_r]$ is given by

$$\mathrm{E}[Z_r] = \frac{\pi_r}{\pi_\Delta \delta_r}$$

It is very important to consider that when calculating R_0 the infected individual is introduced into a population already at the disease-free equilibrium with respect to the fraction of the population vaccinated and unvaccinated. This assumption is made in order to see the sole effects of the infected individual. We therefore introduce an infected into a population in which the rate from S to S^V equals the rate from S^V to S, or

$$f\gamma S = \omega S^V$$

thus, the fraction of vaccinated population at the disease-free equilibrium is equal to $\frac{f\gamma}{f\gamma+\omega}$.

We use this result to find probability of extinction of the epidemic, P_e (see Appendix C).

3 R_0 Results

In order to find the expression for the probability of extinction (P_e), we first find the expression for the reproductive number. Using the modified Markov Chain, we obtain R_0 (see Appendix A for a more in depth explanation of Markov Chains, Appendix B for calculations of R_0, and Appendix C for relationship between probability of P_e and R_0).

$$R_o^f = \frac{1}{f\gamma+\omega}\left(\frac{(e^{\frac{-\lambda}{2}}(e^{\frac{\lambda}{2}}C-\lambda)(A\omega B^2(\lambda+B)+f\gamma((1-V_e)C^2(\lambda+C)A-C(-\beta_3\phi(2\lambda+3C)+\beta_2C(\lambda(V_e-2)+C(V_e-3)))\omega+\omega^2(\lambda+3C)A+\omega^3A)))}{C^2(\lambda+C)B^2(\lambda+B)}+\right.$$
$$\left.\beta_1\left(\frac{\omega}{\lambda+C}+f\gamma\left(\frac{1}{\lambda+C}-\frac{V_e}{\lambda+B}\right)\right)\right)$$

where:

$A = \beta_3\phi + \beta_2(\mu+\phi)$

$B = \mu+\phi+\omega$

$C = \mu+\phi$

3.1 3-D Plots and analysis

We find that increasing V_e invariably results in increasing P_e for any value of the campaign efficacy until $P_e = 1$ for $V_e = 0.95$ or above (see figure 3).

One might think that increasing the efficacy of the campaign would invariably increase P_e as well. What we find from figure 3 tells otherwise - that there exists a threshold above which P_e decreases.

We can see how the probability of extinction depends on the waning effect and the efficacy of the vaccine in figure three. For large values of ω (when the vaccine is not effective for long periods of time), the probability of extinction is almost constant. For $0 < \omega < 0.04$ (if the vaccine is effective for 25 years or more), however, the probability of extinction is increased to one for some values of the efficacy of the vaccine. In order to make the epidemic die out, we fix ω equal to 0.03 - that is, the vaccine loses its efficacy at an average of 33.3 years.

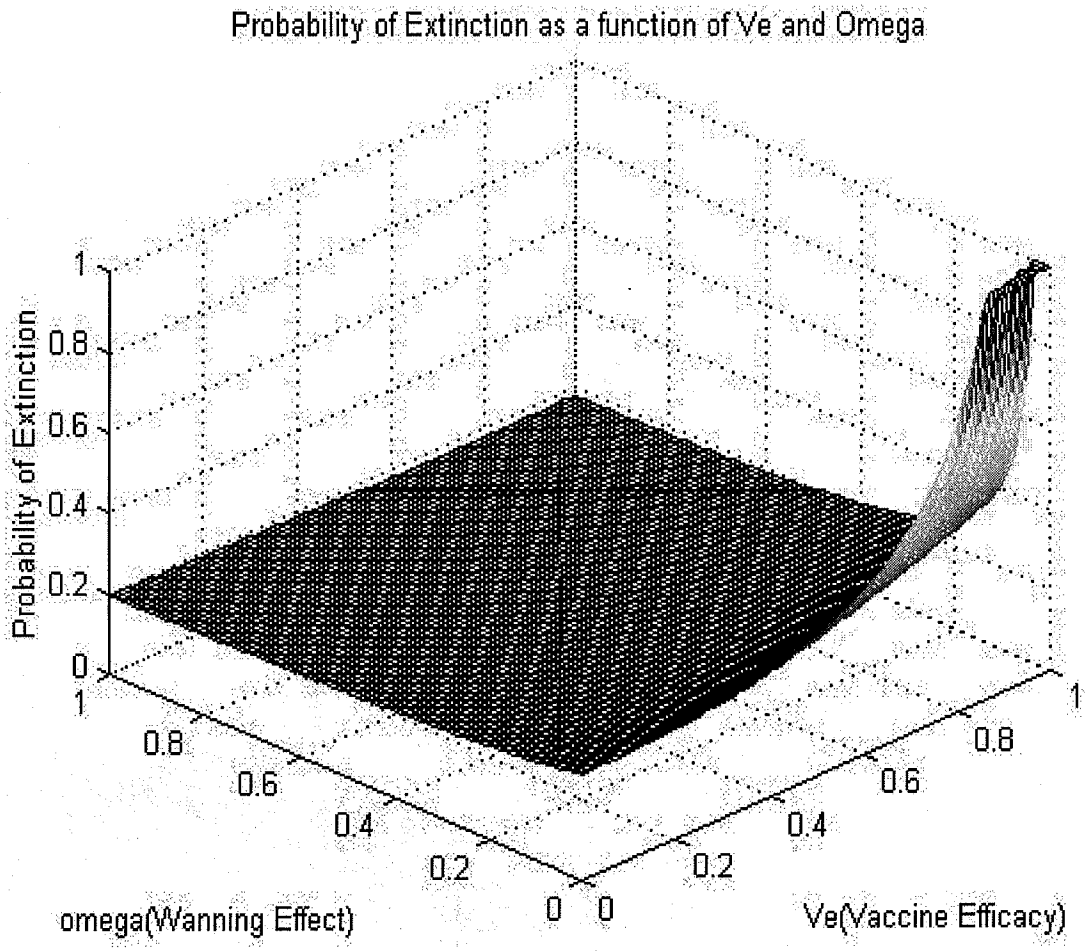


Figure 3: Probability of extintion Vs efficacy of the vaccine and wanning effect

Figure four shows how the probability of extinction depends on the efficacies of the campaign and vaccine. We see that there is an optimum value for the efficacy of the campaign at 66.3% - that is, for any vaccine efficacy, increasing the efficacy to this value increases the probability of extinction, but increasing the efficacy above this value decreases the probablity of extinction. This is counter-intuitive if one neglects to remember that the campaign provides a way in which infected individuals can move to the next stage of infection by testing falsely negative if tested during the

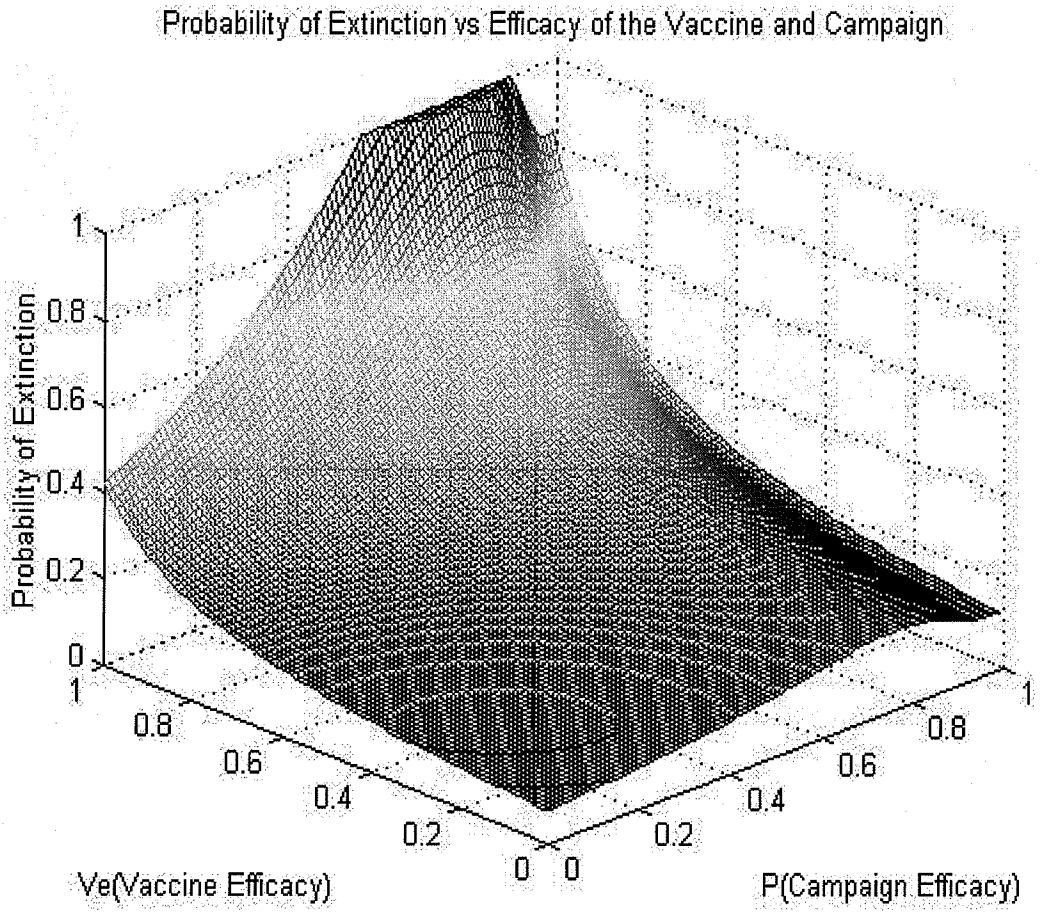


Figure 4: Probability of extintion Vs efficacy of the vaccine and campaign

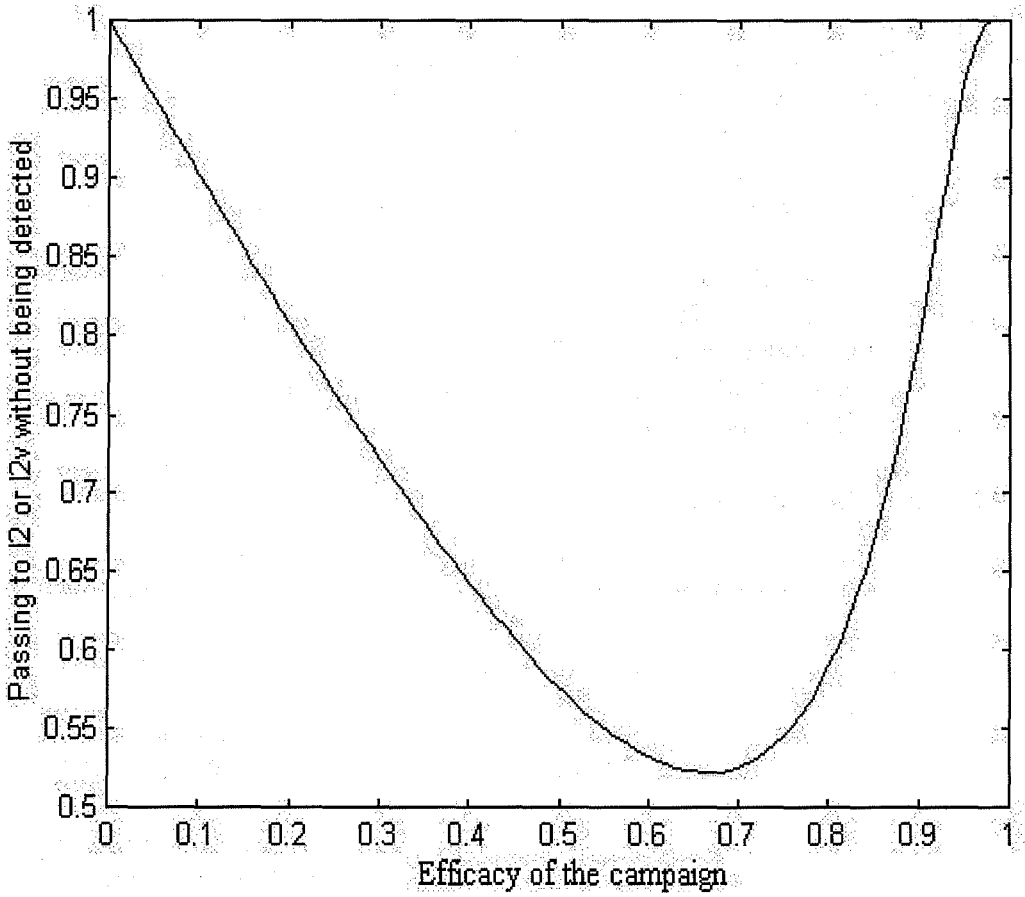


Figure 5: Probability of passing to I_2 or I_2^v without being detected Vs Efficacy of the Campaign

first six months of infection. We can explain this unexpected result using "real world" terms by remembering that individuals in I_1 and I_1^V can either be screened, tested positive, and moved to D (stage where they cannot infect others), or they can continue to the next stage of infection undetected. Again, they can escape detection by either missing the screening process entirely, or being screened during their first six months of infection and testing falsely negative. Increasing the efficacy of the campaign would result in individuals testing earlier, which would increase the proportion of those who test for HIV before they reach the six month mark. Because of this, overly increasing the efficacy of the campaign can actually help the epidemic to thrive since it would allow more infected individuals to pass through to the next stage of infection undetected (see Appendix D).

To calculate the threshold, we find the minimum of the expression for the probability that individuals move from the first stage of infection to the next, undetected (see Appendix C). We find that increasing P from 0 to about 0.663 increases P_e, but increasing P beyond 0.663 decreases P_e. If $V_e = 1$, we find that $P_e = 1$ for $0.565 \approx\leq P \approx\leq 0.887$. If V_e decreases, then the interval of P for which $P_e = 1$ shrinks until there is no value of P to make $P_e = 1$ (see Appendix E).

3.2 Simulations of R_0

In addition to making three-dimensional plots, we also ran stochastic simulation in order to investigate the effects of the vaccine and campaign on the epidemic. We ran computer simulations of a hypothetical population of 1000 people for a duration of 50 years. At $t = 0$, we start with 999 susceptibles and one infected individual. We fix all parameters at values that were assumed reasonable or obtained from data (see section 1.1 for parameter values), except for V_e and λ, where V_e is vaccine efficacy and λ is the screening rate, through which we investigate campaign efficacy. In order to fix a value for ω, we plotted it against V_e and P_e and found that ω needs to be between 0 and 0.04. We thus fix ω at 0.03 for the puposes of our simulations (see Appendix D). The general focus is not to gather numerical data but to observe general patterns in the effects of changing V_e and λ. The following are sample plots of our findings. It should be emphasized that these are representative of numerous simulations we ran throughout our study, and that because they are stochasic simulations, they do not represent all of the results we had obtained. No two runs of the same parameter values result in the same picture. We only use these simulations to show that such behavior is possible, and the only plots we choose to include

as figures in this paper reflect our results from the three-dimensional plots.

In our set of simulations, we show that solely changing V_e has a bigger effect on the population than solely changing λ by observing that the population dynamics does not change much when fixing V_e and changing λ (see figure 3). When fixing λ and changing V_e, however, there are noticeable changes in the dynamics of the population. In particular, we investigated changes in the population for a set of values within $0 \leq \lambda \leq 0.999$ where for each fixed value of λ, we varied V_e from 0.6 to 0.8. We observed a general pattern that the greater the λ, the less V_e had to be in order for the epidemic to die out.

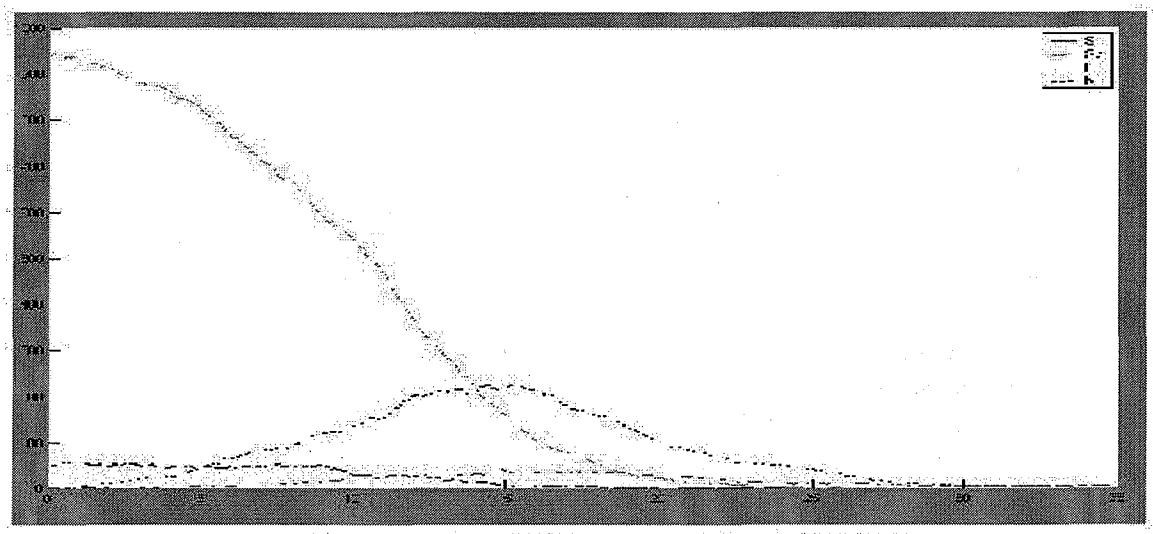
We also tried to simulate a population with a more realistic set of parameters where $V_e = 0.8$ and P $= 0.70$. This resulted in a endemic equilibrium, in which the epidemic was kept at minimum levels, that lasted for approximately 30 years before the infection took hold of the population. This result is promising in that although the epidemic did not die out completely, it is plausible that new vaccines or methods to combat the epidemic could be created during the thirty years that the equilibrium was maintained.

We show that increasing the value of V_e results in an increased P_e for fixed values of λ. We also show in the upper plot, the typical behavior of when conditions for disease-free equilibrium are not met - that is, there exists a period of time in which the epidemic is kept at a minimum, which gives way to an outbreak.

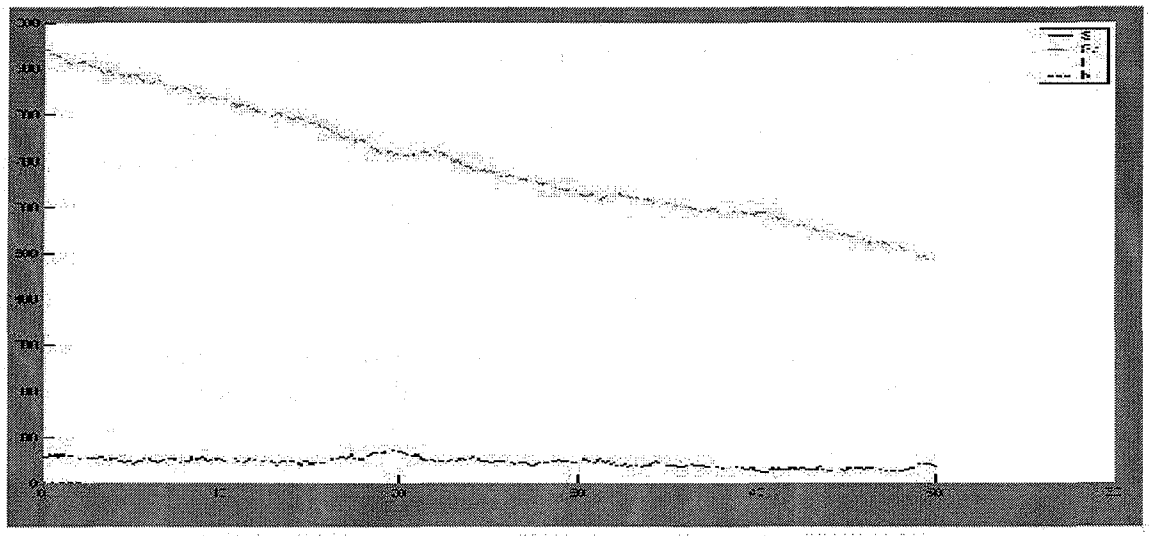
We show that increasing the value of P up to the optimum level of 66.3% results in an increased P_e (see figure 4). Increasing P above the optimum value decreases the P_e of the epidemic (lower plot).

4 Conclusions

In our study of how the efficacies of the VEI vaccine and campaign affect the behavior of an HIV epidemic, we conclude that in order for the epidemic to die out, the efficacies of the vaccine and campaign must be exceptional. We found from our graphical analyses that the efficacy of the vaccine has a greater impact on the epidemic than the efficacy of the campaign. The efficacy of the vaccine must be greater than or equal to approximately 95%, ω has to be less than 0.04 (i.e. the vaccine must be effective for 25 years or more), and the efficacy of the campaign must be between 56.5% and 86.5% if the vaccine were to be 100% effective. Anything less effective results in a period of controlled epidemic followed by the eventual infection of the entire susceptible population. A vaccine of an efficacy of 95% is unrealistic - it is

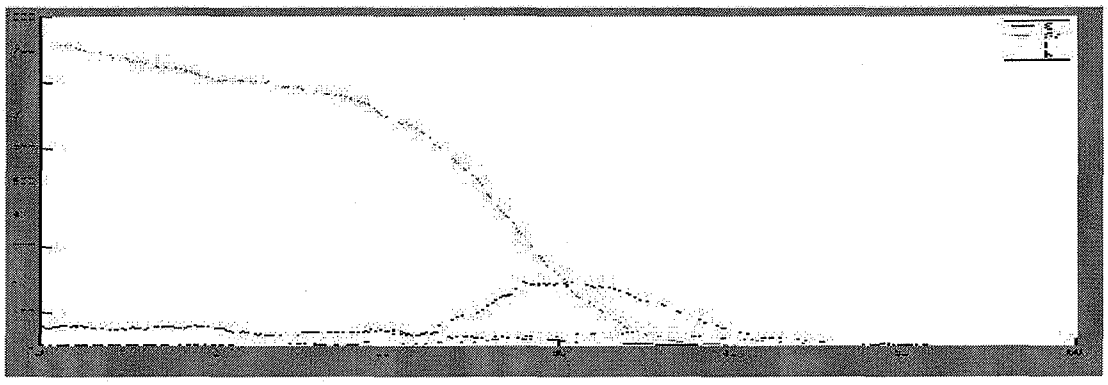


Efficacy of Vaccine = 70%,
Efficacy of Campaign = 66.3%

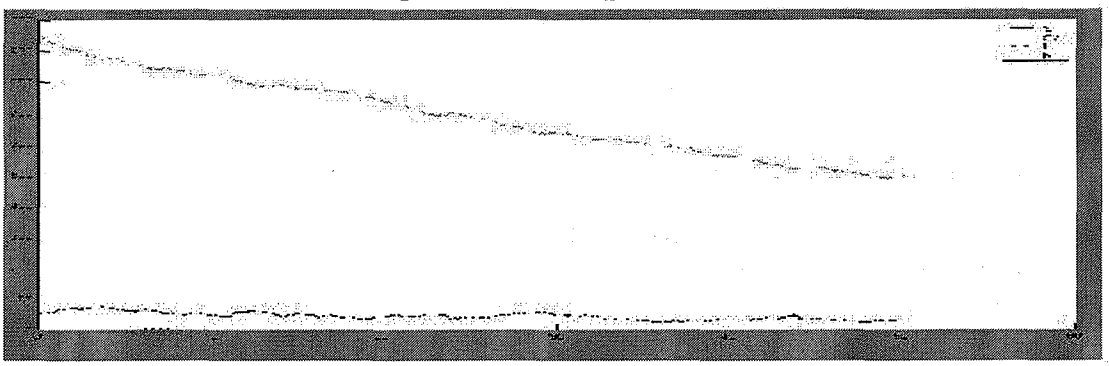


Efficacy of Vaccine = 95%,
Efficacy of Campaign = 66.3%

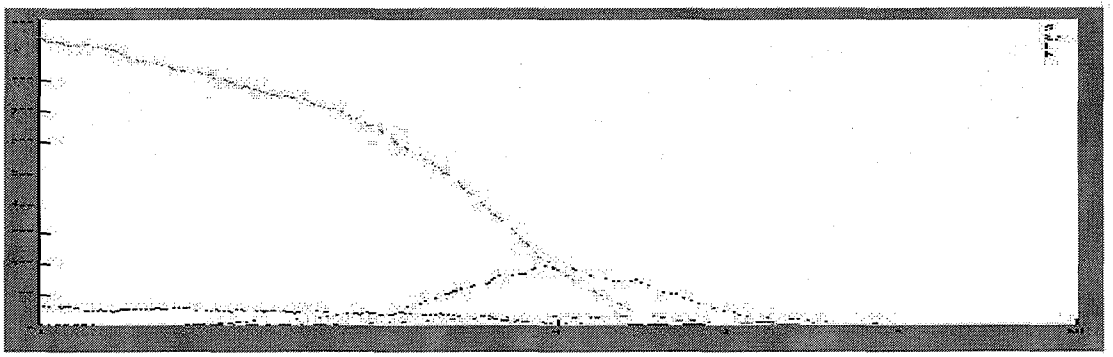
Figure 6:



Efficacy of Vaccine = 80%,
Efficacy of Campaign = 50%



Efficacy of Vaccine = 80%,
Efficacy of Campaign = 66.3%



Efficacy of Vaccine = 80%,
Efficacy of Campaign = 90%

Figure 7:

very difficult to create a vaccine with such a high efficacy. Our study shows, however, that although a vaccine with an efficacy of less than 95% is used, although it will not allow the epidemic to be completely eradicated, such an vaccine would still benefit the population in that it would reduce the prevalence of the disease for a prolonged period of time, especially if coupled with a national campaign. We can hope that if this period is long enough, this will give scientists and researchers enough time to develop new methods to combat the epidemic, to either prolong the control of the epidemic or cause the epidemic to die out completely.

Probably the most important conclusion from our study is that there is such a thing as a campaign that is too effective - that is, the campaign efficacy promotes a higher P_e only up to a threshold, above which it is becomes detrimental rather than helpful to the population in eradicating the epidemic. Due to time constraints, we did not investigate how the efficacy of vaccine depends on the infectiousness of the people in different stages of infection, nor the sexual activity of the population.

5 Future Studies

There are many ways in which the dynamics of our model can be further analyzed. Much more can be done to further explain how a campaign and a VEI type vaccine can or cannot help to eradicate and/or lower the HIV/AIDS epidemic. For example, the model can be modified by using a heterosexually active population instead of a homosexually active male population. We can vary more parameters and run more simulations over a longer time scale to more fully understand this model. For example, we saw that the waning effect had a strong impact on the value of R_o but an in depth analysis can be conducted using simulations to reveal more insights. We can also investigate the dependence of the population on the infection rates and fraction of population vaccinated. There are unlimited possibilities for modifications that can be made due to the fact that new developments are being made daily towards the advancement of assessing the virus.

Appendix A : Modified Markov Chains

A discrete-time Markov chain is a stochastic process $\{X_n, n = 0, 1, ...\}$ that takes on finite or countable number of possible values. The set of possible values in the process will be denoted by $\{0, 1, 2, ...\}$. If $X_n = i$, the process is said to be at state i at time n. We suppose that whenever the

process is in state i, there is a fixed probability δ_{ij} that it will be in state j in the next time unit. That is,

$$P\{X_{n+1} = j | X_n = i, X_{n-1} = i_{n-1}, \ldots, X_1 = i_1, X_0 = i_0\} = \delta_{ij}$$

for all states $i_0, i_1, i_2, \ldots, i_{n-1}, i_n, j$ and $\forall n \geq 0$

For our purposes, we use a continuous-time Markov chain - that is, a discrete-time Markov chain whose domain is an interval of the real line. We calculate $\Pi = \lim_{n\to\infty} P^n$, where P is the transition matrix of the Markov chain. Since

$$\Pi = \lim_{n\to\infty} P^n = \lim_{n\to\infty} P^{n-1}P = \Pi P$$

That is,

$$\underline{\Pi} = \underline{\Pi} P$$

From this property, we obtain:

$$\begin{aligned} \underline{\Pi} P + \underline{\Pi} J &= \underline{\Pi} + \underline{\Pi} J \\ \underline{\Pi} P + \underline{\Pi} J - \underline{\Pi} &= 1' \\ \underline{\Pi}(P + J - I) &= 1' \end{aligned}$$

That is,

$$\underline{\Pi} = 1'(P + J - I)^{-1} \tag{1}$$

where J is a matrix with all its entries equal to 1, I is the identity matrix, and 1' is the vector [1 1 1 1 1 1 1].

We tried to calculate $\underline{\Pi}$ directly using the Continuous-time Markov Chain process and our solution was

$$\underline{\Pi} = [\, 0\ 0\ 0\ 0\ 0\ 0\ 1]$$

which means that no matter which stage one begins at, we always finish in the absorbent state (with probability of one). This solution does not give the desired information. Therefore, in order to obtain the time an individual spends in each infectious stage, we used a modified version of a continuous-time Markov chain. This version allows an individual at a absorbing state, Δ, to come back to an infectious state, we called Δ the reflective state. Then we can form the *reflective matrix* by adding in the last row of the transition matrix the probability that once in stage Δ one begins in I_1^v or I_1 [11].

Appendix B : Computation of R_0

To begin our computation of R_0, we first compute a transition matrix, the entries of which contain the probabilities of moving from any examined state to another [11]. The transition matrix is given by:

$$\mathrm{B} = \begin{bmatrix} 0 & \frac{\phi+\lambda-\lambda e^{\frac{-\lambda}{2}}}{\phi+\mu+\lambda} & 0 & 0 & 0 & 0 & \frac{\mu+\lambda e^{\frac{-\lambda}{2}}}{\phi+\mu+\lambda} \\ 0 & 0 & \frac{\phi}{\phi+\mu} & 0 & 0 & 0 & \frac{\mu}{\phi+\mu} \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ \frac{\omega}{\omega+\phi+\mu+\lambda} & 0 & 0 & 0 & \frac{\phi+\lambda-\lambda e^{\frac{-\lambda}{2}}}{\omega+\phi+\mu+\lambda} & 0 & \frac{\mu+\lambda e^{\frac{-\lambda}{2}}}{\omega+\phi+\mu+\lambda} \\ 0 & \frac{\omega}{\omega+\phi+\mu} & 0 & 0 & 0 & \frac{\phi}{\phi+\mu+\omega} & \frac{\mu}{\phi+\mu+\omega} \\ 0 & 0 & \frac{\omega}{\omega+\phi+\mu} & 0 & 0 & 0 & \frac{\mu+\phi}{\omega+\phi+\mu} \\ 1-\frac{f\gamma}{f\gamma+\omega} & 0 & 0 & \frac{f\gamma}{f\gamma+\omega} & 0 & 0 & 0 \end{bmatrix}$$

To simplify calculations, we divide R_0 into two disjoint cases and take their weighted sum. R_0^1 will be the R_0 value when the probability of starting at stage I_1 is 1, and R_0^2 will be the value of R_0 when the probability of starting at stage I_1^v is 1. We weight R_0^1 with $\frac{f\gamma}{f\gamma+\omega}$ and R_0^2 with the term $1-\frac{f\gamma}{f\gamma+\omega}$. The sum of these two quantities gives the same result as R_0 for the matrix B.

$$\mathrm{P} = \begin{bmatrix} 0 & \frac{\phi+\lambda-\lambda e^{\frac{-\lambda}{2}}}{\phi+\mu+\lambda} & 0 & 0 & 0 & 0 & \frac{\mu+\lambda e^{\frac{-\lambda}{2}}}{\phi+\mu+\lambda} \\ 0 & 0 & \frac{\phi}{\phi+\mu} & 0 & 0 & 0 & \frac{\mu}{\phi+\mu} \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ \frac{\omega}{\omega+\phi+\mu+\lambda} & 0 & 0 & 0 & \frac{\phi+\lambda-\lambda e^{\frac{-\lambda}{2}}}{\omega+\phi+\mu+\lambda} & 0 & \frac{\mu+\lambda e^{\frac{-\lambda}{2}}}{\omega+\phi+\mu+\lambda} \\ 0 & \frac{\omega}{\omega+\phi+\mu} & 0 & 0 & 0 & \frac{\phi}{\phi+\mu+\omega} & \frac{\mu}{\phi+\mu+\omega} \\ 0 & 0 & \frac{\omega}{\omega+\phi+\mu} & 0 & 0 & 0 & \frac{\mu+\phi}{\omega+\phi+\mu} \\ 1 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$A = \begin{bmatrix} 0 & \frac{\phi+\lambda-\lambda e^{\frac{-\lambda}{2}}}{\phi+\mu+\lambda} & 0 & 0 & 0 & 0 & \frac{\mu+\lambda e^{\frac{-\lambda}{2}}}{\phi+\mu+\lambda} \\ 0 & 0 & \frac{\phi}{\phi+\mu} & 0 & 0 & 0 & \frac{\mu}{\phi+\mu} \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ \frac{\omega}{\omega+\phi+\mu+\lambda} & 0 & 0 & 0 & \frac{\phi+\lambda-\lambda e^{\frac{-\lambda}{2}}}{\omega+\phi+\mu+\lambda} & 0 & \frac{\mu+\lambda e^{\frac{-\lambda}{2}}}{\omega+\phi+\mu+\lambda} \\ 0 & \frac{\omega}{\omega+\phi+\mu} & 0 & 0 & 0 & \frac{\phi}{\phi+\mu+\omega} & \frac{\mu}{\phi+\mu+\omega} \\ 0 & 0 & \frac{\omega}{\omega+\phi+\mu} & 0 & 0 & 0 & \frac{\mu+\phi}{\omega+\phi+\mu} \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 \end{bmatrix}$$

The transition matrix P is for the case when we assume that the probability of starting at stage I_1 is 1, and transition matrix A is for the case when we assume that the probability of starting at stage I_1^v is 1. Note that the matrices are identical except for the last row of each, which represents the reflective distribution. We calculate R_o for each of the matrices above. We use (1) and obtain

$$\begin{aligned} E[Z_{I_1}] &= \frac{1}{\lambda+\phi+\mu} \\ E[Z_{I_2}] &= \frac{\lambda+\phi-\lambda e^{\frac{-\lambda}{2}}}{(\phi+\mu)(\lambda+\mu+\phi)} \\ E[Z_{I_3}] &= \frac{\phi(\lambda+\phi-\lambda e^{\frac{-\lambda}{2}}}{(\mu+\phi)^2(\lambda+\mu+\phi)} \end{aligned}$$

Solving for R_0^1, we obtain:

$$R_0^1 = \frac{\beta_1 + \frac{e^{\frac{-\lambda}{2}}(e^{\frac{\lambda}{2}}(\lambda+\phi)-\lambda)(\beta_3\phi+\beta_2(\mu+\phi))}{(\mu+\phi)^2}}{\lambda+\mu+\phi}$$

In the same way we calculate the time an individual spends in each stage for the matrix P,

$$
\begin{aligned}
E[Z_{I_1}] &= \frac{\omega}{(\lambda+\mu+\phi)(\lambda+\mu+\phi+\omega)} \\
E[Z_{I_2}] &= \frac{e^{\frac{-\lambda}{2}}\omega(e^{\frac{\lambda}{2}}(\lambda+\phi)-\lambda)(\lambda+2(\mu+\phi)+\omega)}{(\mu+\phi)(\lambda+\mu+\phi)(\mu+\phi+\omega)(\lambda+\mu+\phi+\omega)} \\
E[Z_{I_3}] &= \frac{e^{\frac{-\lambda}{2}}\omega\phi(e^{\frac{\lambda}{2}}(\lambda+\phi)-\lambda)(3(\mu+\phi)^2+3\omega(\mu+\phi)+\omega^2+\lambda(2(\mu+\phi)+\omega))}{(\mu+\phi)^2(\lambda+\mu+\phi)(\mu+\phi+\omega)^2(\lambda+\mu+\phi+\omega)} \\
E[Z_{I_1^v}] &= \frac{1}{\mu+\phi+\omega+\lambda} \\
E[Z_{I_2^v}] &= \frac{\lambda-e^{\frac{-\lambda}{2}}+\phi}{(\mu+\phi+\omega)(\lambda+\mu+\phi+\omega)} \\
E[Z_{I_3^v}] &= \frac{e^{\frac{-\lambda}{2}}\phi(e^{\frac{\lambda}{2}}(\lambda+\phi)-\lambda)}{(\mu+\phi+\omega)^2(\lambda+\mu+\phi+\omega)}
\end{aligned}
$$

We obtain:

$$R_o^2 = \frac{1}{\lambda+B}(\beta_1(1-V_e+\frac{\omega}{\lambda+C})+\frac{1}{C^2(\lambda+C)B^2}(e^{\frac{-\lambda}{2}}(e^{\frac{\lambda}{2}}(\lambda+\phi)-\lambda)(1-V_e)C^2(\lambda+C)A-\omega C(-\beta_3\phi(2\lambda+3C)+\beta_2 C(\lambda(V_e-2)+(V_e-3)C))+\omega^2(\lambda+3C)A+\omega^3 A)))$$

where:
A $= \beta_3\phi+\beta_2(\mu+\phi)$
B $= \mu+\phi+\omega$
C $= \mu+\phi$

Thus, the weighted R_0 is a combination of R_0^1 and R_0^2 obtained from both cases:

$$R_o^f = \frac{1}{f\gamma+\omega}(\frac{(e^{\frac{-\lambda}{2}}(e^{\frac{\lambda}{2}}C-\lambda)(A\omega B^2(\lambda+B)+f\gamma((1-V_e)C^2(\lambda+C)A-C(-\beta_3\phi(2\lambda+3C)+\beta_2 C(\lambda(V_e-2)+C(V_e-3)))\omega+\omega^2(\lambda+3C)A+\omega^3 A)))}{C^2(\lambda+C)B^2(\lambda+B)}+\beta_1(\frac{\omega}{\lambda+C}+f\gamma(\frac{1}{\lambda+C}-\frac{V_e}{\lambda+B})))$$

Appendix C : The Probability of Extinction

The probability of extinction of the epidemic (P_e) is inversely related to the reproductive number, or

$$PE = \frac{1}{R_0}$$

We calculate the probability of extinction using conditional probabilities. We assume that an infected individual can either infect one other person or infect no others before being removed from the system. Therefore

P_e = P[Epidemic goes extinct | Infected infects none]P[Infected infects none]+
P[Epidemic goes extinct | Infected infects another]P[Infected infects another]

where if P[Infected infects no one]=p,

$$P_e = p + P_e^2(1-p)$$

Solving for P_e, we obtain

$$P_e = min(\frac{p}{1-p}, 1)$$

But since R_0 is the number of people an individual infects, it is given by

$$R_0 = \frac{1-p}{p}$$

Therefore,

$$P_e = min(\frac{1}{R_0}, 1)$$

Appendix D : The Waning Effect

Since $\frac{d\omega}{dt} = -\omega S$, we have

$$S^V = S_0 e^{(-\omega t)}$$

We begin our investigation by plotting P_e as a function of V_e and ω. In figure 8, we see the small changes in ω results in great changes in P_e - the probability of extinction of the epidemic is therefore highly sensitive to the waning effect of the vaccine. In order to make P_e greater than one, ω has to be between 0 and 0.04. In other words, the vaccine must be effective for at least twenty five years. Since we are not interested in studying the impact of various degrees of the waning effect in our system for this study, we set the value of ω to 0.03 when investigating the effects of other parameters.

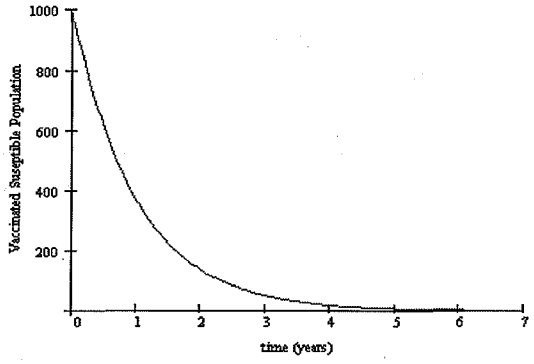


Figure 8: Waning effect of vaccine with $S_0 = 1000$

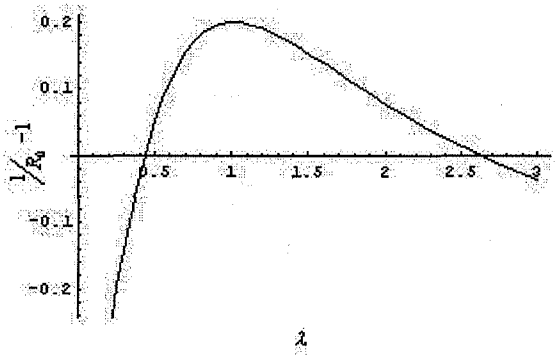


Figure 9: Interval for Lambda for which $P_e = 1$

Appendix E : Calculation of P Interval

In order to find the optimum interval for the efficacy of the campaign, we find where $\frac{1}{R_0} = 1$. We do this by fixing a value for V_e, and solving for the roots of where the expression for $\frac{1}{R_0} = 1$. Using figure 3, we see that the largest interval for P to drive $P_e = 1$ occurs where $V_e = 1$, under which the interval shrinks and eventually is non-existent. We then substitute $V_e = 1$ into the expression for $\frac{1}{R_0}$ and plot $\frac{1}{R_0} - 1$ (see figure 9). The roots for the graph are $\lambda \approx 0.4328, 2.62274$ which corresponds to $P \approx 0.5652, 0.887337$.

Appendix F : Command to make figure 3 in MatLab

```
function z=grafica_Ro2( LVe1,HVe1,inc1,LOmega2,HOmega2,inc2
,Mu,Phi,f,Beta1,Beta2,Beta3,p,Gamma);
%Lp1 = Lower bound for parameter 1
%Hp1 = Upper bound for parameter 1
%inc1= step increment for parameter1

%Lp2 = Lower bound for parameter 2
%Hp2 = Upper bound for parameter 2
%inc2= step increment for parameter2
% par1, par2, par3 = additional parameters your function may have

[X,Y]= meshgrid(LVe1:inc1:HVe1, LOmega2:inc2:HOmega2);



%this is the function you may want to plot


lambda=p.*Phi./(1-p);
R_o=(1./(f.*Gamma+Y)).*((exp(-lambda/2).*(-lambda+exp(lambda/2).*
(lambda+Phi)).*((Beta3*Phi+Beta2.*(Mu+Phi)).*Y.*...
   (Mu+Phi+Y).^2.*(lambda+Mu+Phi+Y)+f.*Gamma.*((1-X).*(Mu+Phi).^2.*
(lambda+Mu+Phi).*(Beta3*Phi+Beta2*...
   (Mu+Phi))-(Mu+Phi).*(-Beta3.*Phi.*(2.*lambda+3.*(Mu+Phi))+Beta2.*
(Mu+Phi).*((-2+X).*lambda+(X-3).*(Mu+Phi))).*Y+...
   (lambda+3.*(Mu+Phi)).*(Beta3.*Phi+Beta2.*(Mu+Phi)).*Y.^2+(Beta3.*
Phi+Beta2.*(Mu+Phi)).*Y.^3))./...
   ((Mu+Phi)^2.*(lambda+Mu+Phi).*(Mu+Phi+Y).^2.*
(lambda+Mu+Phi+Y))+...
   Beta1.*((Y./(lambda+Mu+Phi))+X.*Gamma.*
((1./(lambda+Mu+Phi))-(X./(lambda+Mu+Phi+Y)))));

z = min(1,1./R_o);



%this makes gets the plot
```

```
mesh(X,Y,z);

%you add title here

title('Probability of Extinction as a function of Ve and Omega');

%...and ploting for axes

xlabel('Ve(Vaccine Efficacy)');
ylabel('omega(Wanning Effect)');
zlabel('Probability of Extinction');
```

Appendix G : Command to make figure4 in MatLab

```
function z=grafica_Ro( Lp1,Hp1,inc1,LVe2,HVe2,inc2,Mu
,Phi,Omega,Beta1,Beta2,Beta3,f,Gamma);
%Lp1 = Lower bound for parameter 1
%Hp1 = Upper bound for parameter 1
%inc1= step increment for parameter1

%Lp2 = Lower bound for parameter 2
%Hp2 = Upper bound for parameter 2
%inc2= step increment for parameter2
% par1, par2, par3 = additional parameters your function may have

[X,Y]= meshgrid(Lp1:inc1:Hp1, LVe2:inc2:HVe2);
lambda=X*Phi./(1-X);
R_o=(1/(f*Gamma+Omega))*((exp(-lambda/2).*(-lambda+exp(lambda/2).*
(lambda+Phi)).*((Beta3*Phi+Beta2.*(Mu+Phi)).*Omega....
   *(Mu+Phi+Omega)^2.*(lambda+Mu+Phi+Omega)+f.*Gamma.
*((1-Y).*(Mu+Phi)^2.*(lambda+Mu+Phi).*(Beta3*Phi+Beta2*...
   (Mu+Phi))-(Mu+Phi).*(-Beta3.*Phi.*(2.*lambda+3.*
(Mu+Phi))+Beta2.*(Mu+Phi).*((-2+Y).*lambda+(Y-3).*
(Mu+Phi))).*Omega+...
   (lambda+3.*(Mu+Phi)).*(Beta3.*Phi+Beta2.*(Mu+Phi)).*
Omega^2+(Beta3.*Phi+Beta2.*(Mu+Phi)).*Omega^3))./...
   ((Mu+Phi)^2.*(lambda+Mu+Phi).*(Mu+Phi+Omega)^2.*
(lambda+Mu+Phi+Omega))+...
   Beta1.*((Omega./(lambda+Mu+Phi))+f.*Gamma.*
```

```
((1./(lambda+Mu+Phi))-(Y./(lambda+Mu+Phi+Omega)))));

z = min(1,1./R_o);
%this makes gets the plot

mesh(X,Y,z);

%you add title here

title('Probability of Extinction vs Efficacy of the Vaccine and Campaign');

%...and ploting for axes

xlabel('P(Campaign Efficacy)');
ylabel('Ve(Vaccine Efficacy)');
zlabel('Probability of Extinction');
```

Appendix H : Command to make figure 5 in MatLab

```
 function Z=grafica_P(inc1,Phi);
 p=0:inc1:.99;
 lam=p*Phi./(1-p);
y=(Phi+lam.*(1-exp(-lam/2))./((Phi+lam.*
(1-exp(-lam/2))+lam.*exp(-lam/2)));
plot(p,y)
xlabel('P(Efficacy of the campaing)');
ylabel('Passing to I2 or I2v with out being detected');
```

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