HIV VACCINE MODEL WITH APPLICATION TO KENYA

By

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ABSTRACT

Many models for HIV pandemic have come up as humankind grapples with the blight. Scientists and policy makers are struggling to contain the scourge. Mathematicians are not left behind. They are modeling the epidemic as to demystify the transmission dynamics.

This dissertation goes a step further than where the other modelers have reached. It envisages a situation where vaccine is found and administered to the Kenyan population. The weaknesses of vaccine are taken into account. Even though effective induction of immunological response may be engendered by HIV vaccine, the vaccine effect may wane with time or worse, the vaccine may protect only a fraction of the population in whom the effective immunological response was induced.

A model to take the waning and the degree of protection into account is developed and simulated using SAS® model procedure. The results show that any HIV vaccine with substantial efficacy will not only reduce the epidemic but may also stop it.

ACKNOWLEDGMENTS

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More importantly, the author wishes to show gratitude to God the almighty for safekeeping and showing the way in all difficult situations.

CHAPTER 1

HIV/AIDS KENYA'S SITUATION ANALYSIS

1. 0. INTRODUCTION

HIV/AIDS has flustered the whole world. It is estimated that more than 33 million people are infected with the HIV[1]. Many measures have been taken to control the epidemic. Antiretroviral chemotherapy can temporarily control HIV infection in an individual however, the cost and quandary of the antiretroviral regimens is very prohibitive[2]. Behavioral tweaking through education has had a limited impact on the worldwide spread of HIV infection except in much defined groups. The control of HIV epidemic is found only through development of HIV vaccines.

Kenya AIDS vaccine initiative[3] reports that the over 700 Kenyans are getting infected with HIV everyday. Already about 2.2 million Kenyans are infected with HIV. There are major intervention strategies put in place. Many of these strategies are facilitated by the National AIDS control Council (NACC). There

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[1] UN AIDS/WHO: *AIDS Epidemic Update,* December 2000. Geneva, Joint United Nations Program on HIV/AIDS, 2000

[2] Blower SM, Koelle K, Mills J. (2002) *Health policy modeling: Epidemic control, HIV vaccines, and Risk Behavior,* Eds Kaplan and Brookmeyer, Yale University press, pages 260-289

are three strategies put in place by the NACC. The first is increasing awareness and positive behavior change among priority groups in Kenya. The second is prevention of mother-to-child transmission (**PMCT**), and lastly, increasing accessibility to voluntary counseling and testing (**VCT**). These strategies have shown some success. It is clear now that the efforts put by the Kenyan government and the entire stake holders have born fruits. The sentinel surveillance in Kenya reveals that the Kenyans HIV epidemic prevalence rate has gone down from 13.5% (2000 figure) to 10.2% in the year 2002. It has also been reported that the Kenya's population growth rate has reduced to 2.9% per year[1]

In this thesis we present *mathematical models to predict the epidemiological dynamics of HIV epidemic in the presence of vaccine.* In the next chapter, we present a simple HIV vaccine epidemic model. In this model we present the epidemic as dividing the population into vaccinated and unvaccinated groups and follows through with their epidemic dynamics.

In chapter 3, we introduce the predominant stages in the progression of HIV infection. The three prime stages of disease progression are; 'window stage' otherwise known as primary stage, assymptomatic stage, and symptomatic stage [4]. Simwa and Pokhariyal first developed this kind of model in 2000. We adopt this

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[3] International AIDS Vaccine Initiative website; http://www.iavi.org

[4] Simwa R. O, Pokhariyal GP. (2002) *A dynamical model for stage-specific HIV incidences with application to sub-Saharan Africa, Applied mathematical computational,* Elsevier Science.

model to reflect the dynamics of HIV pandemic in a population that everybody is vaccinated against HIV infection.

Chapters 4 and 5 exploit the two models in an existing community. The scenario exploited here is the Kenyan scenario. The two chapters are different in the dynamics of the HIV infection. In Chapter 4 we play down the influence of waning, 'taking' and duration of HIV vaccine by assuming categorically that the vaccine does not wane. In another instance the whole population subscribe to immunity development against the HIV infection. Finally we also discard the possibility of degree of protection being less than unit. The two chapters gain similarity in the sense that they both have the same model structure. However, we introduce new recruits who survive to maturity after fifteen years. With assumption that age fifteen is the maturity age for one to be sexually active.

In chapter 5, we further deal with parameter estimation. We perform a review of results and perform a summary of them and further conclude and give recommendations and way forward for further research.

1. 1 RESEARCH EVIDENCE

Many papers have been written to take a crack at the dynamics of the HIV epidemic. Many of these have glimpsed at the influence of vaccine once made available. Simwa and Pokhariyal have discussed in their paper the stage specificity

of HIV/AIDS transmission dynamic[4]. Longini et al.[5] discussed the measurement of vaccine efficacy for prophylactic HIV-1 vaccines. McLean and Blower also modeled HIV vaccination[6].

By the end of the year 2001, UNAID reports that 2.5 million people were infected with HIV virus in Kenya. Meaning nearly 8% of Kenyans was infected[1].

1. 2. MOTIVATION

Transition of HIV infection is now known to be in stages. The stages can be broadly categorized into three strata: primary infection, asymptomatic stage, and symptomatic stage, depending on the level of viral load and the CD_4 cells count. Vaccine influence in the HIV transmission is such that some vaccines are expected to induce immune response for some individuals but not in others. Although vaccine induces immune response against HIV infection, this might only be effective for some strains of HIV. More to the point, for those who are successfully vaccinated against HIV, the immune response might wane with time due to lack of exposure. Models of stage specificity and of HIV vaccine have been designed. A fusion of the two is exigent because both are realities albeit for the future and to this end this paper is written.

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[5] Longini IM, Datta S, Holloran ME. *Measuring Vaccine Efficacy for both Susceptibility to Infection and reduction in infectiousness for prophylactic HIV-1 vaccines,* Journal of Acquired Immune deficiency syndromes and retrovirology (1996), 13: 440-447.

[6] McLean A. R. and Blower S. M., (1995) *Modeling HIV vaccination,* Elsevier Science

1. 3. OBJECTIVE

The thesis presented here has three objectives. The first is to develop a general simple mathematical model of HIV transmission for a structured population with vaccination process. The second is to develop a mathematical model of HIV transmission for a population that is partially vaccinated. The final goal is to develop a mixture of the above two models in a realistic society.

Chapter 2 of this report discusses the first model. Chapter 3 discusses another model where the whole population of infecteds undergo the confirmed stages of an infected individual undergoes. Chapter 4 combines the two models to give our model that defines the population with some individuals vaccinated and some not vaccinated. Chapter 5 not only gives a clear view of the HIV epidemiological dynamics in Kenya but also concludes with parameter estimation and situation analysis in Kenya with a summary. Recommendations and model implication are given at the end.

1. 4. DATA COLLECTION

Kenya's demographical censuses and scanty data already collected on HIV/AIDS incidences provide the needed data that we utilize to produce simulations for the epidemic[7]. Data is available from Central Bureau of Statistics branches countrywide. Volume 1 of 1999 population and housing Census for Kenya has

[7] National council for population and development, (1999), Kenya Demographic Health Survey, 1998

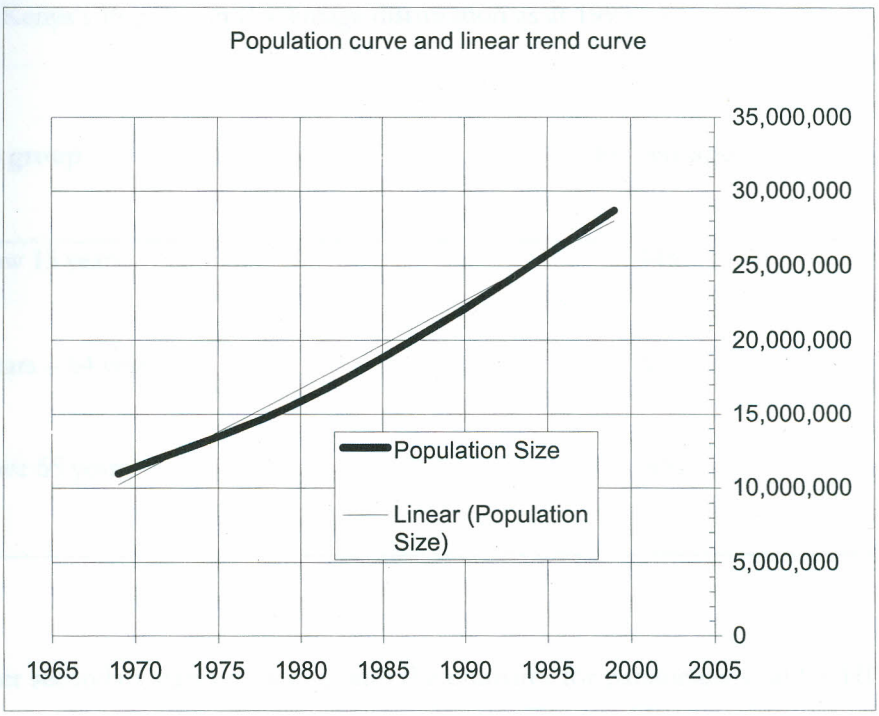
data on censuses from 1969 to 1999. Table 1 gives the Kenyan population trend since 1969.

This information is arraigned next page.

1.1: Kenya populations

Year	Population Size
1969	10,942,705
1979	15,327,061
1989	21,448,774
1999	28,686,607

Table 1.1 shows Kenya's population size for the past 4 censuses. Kenya gained independence in 1963, 6 years later the government counted people who were estimated to be at approximately 10.9 million. Since then census has been conducted after every decade. This gives a gradient of about 0.6million. Meaning, for every year the population increases by 600,000 individuals



1.2: Kenya's intercensal growth rate. The trend line shows how the population of Kenya is growing. This can be extrapolated to project the population in future.

Year	**Kenya's growth rate**
1969—1979	3.4
1979—1989	3.4
1989—1999	2.9

1.3: Kenya's Population Percentage distribution as at 1999

Age group	**Percentage**
Below 15 years	44%
15years – 64 years	52%
Above 65 years	4%

Other secondary data provide us with the estimates for parameters vital for HIV epidemic model simulation[8]. Kerenromp et al. provide us with such data in their published paper on HIV dynamics and behavioral change as determinants of the impact of sexually transmitted diseases on HIV transmission in the context of Rakai trial. Rakai is in Uganda a neighbor of Kenya. Without lose of generality this information suits the Kenyan scenario since Uganda and Kenya are geographically contiguous. Thus table 1.4.

1.4: Representation of natural history and transmission HIV in the simulation of the Uganda HIV epidemic.

[8] Kerenromp R., Eline L. *HIV dynamics and behavior change determinants of the impact of sexually transmitted disease treatment on HIV transmission in the context of the Rakai trial.ISSN 0269-9370* © *2002* Lippincott Williams & Wilkins

		Transmission Probabilities		
Infection Stage	**Mean Duration**	**M → F**	**F → M**	**Harmonic mean**
Primary	10 weeks	0.045	0.015	0.02598076
Assymptomatic	5 years	0.0025	0.00075	0.00136931
Symptomatic pre-AIDS	2 years	0.00225	0.00075	0.00129904
AIDS	40 weeks	0.01125	0.00375	0.00649519

Mean duration refers to the average amount of time needed for one to move from that stage to the next stage. For example it takes 10 weeks for one to move from primary stage to asymptomatic stage. The rate of transmission provided for by the reciprocal of the mean duration engenders the **v**'s. The duration for one HIV infected individual to transit from primary to AIDS infection stage is a total duration of 7.83 years, of which the average transmission for this stretch is the reciprocal of 7.83, which is approximately 0.128. The total transmission probability that generate the betas is approximately 0.029.

CHAPTER 2

SIMPLE HIV VACCINE MODEL

2. 0. INTRODUCTION

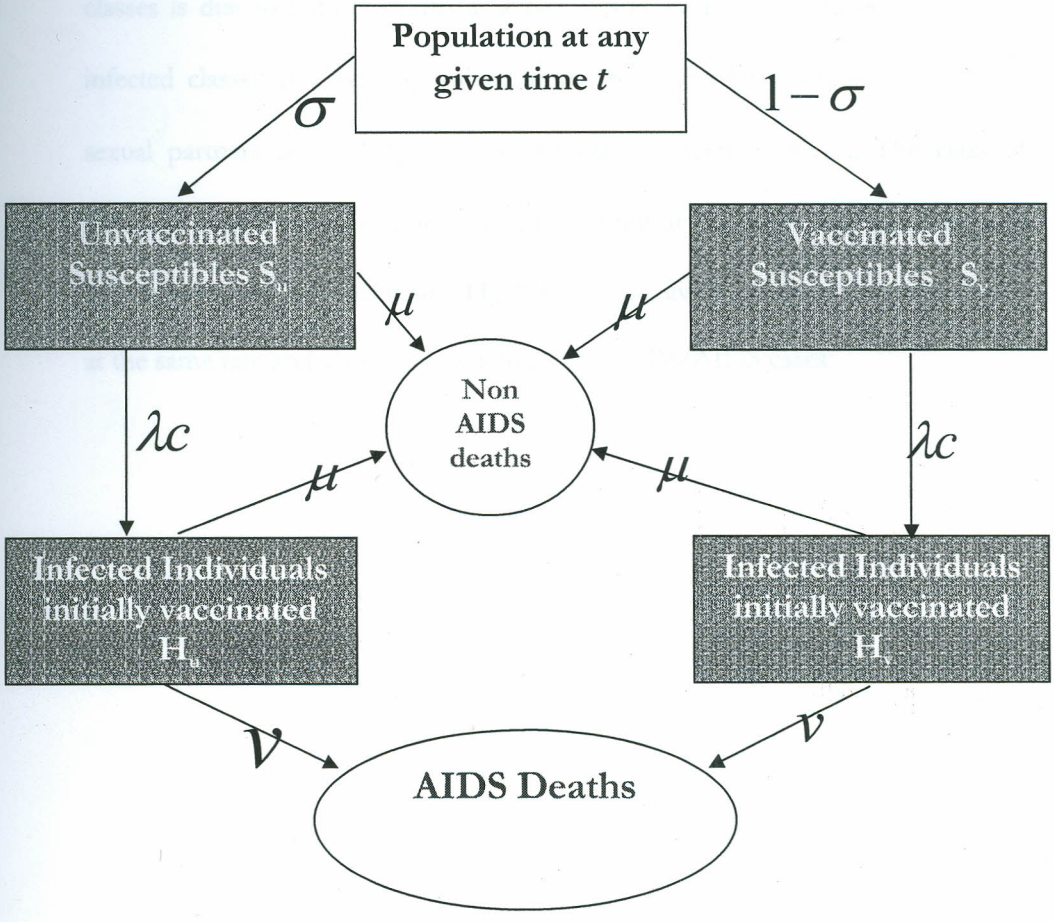
Envisage a population dividing itself into two groups of susceptibles at any particular time. The first group is susceptibles who are not vaccinated and the second group is susceptibles who are vaccinated against HIV infection. In this chapter we consider a population of adults only. The population is assumed to be transmitting the HIV infection through heterosexual transmission. In this paper we shall refer to those who have the HIV infection as infecteds and infectives and those who are liable to HIV infection as susceptibles.

2. 1. VACCINE MODEL FOR SIMPLE HIV EPIDEMIC

Let a proportion δ of the initial susceptible population be unvaccinated and $1-\delta$ be vaccinated. The value δ is simulated in steps of 0.0, 0.5 and 1.0 in this chapter. A δ of 1.0 would mean nobody got the HIV vaccine jab and 0.0 would mean the whole susceptible population got the jab. More simulations shall be required as more data stream in.

Population at any given time divides into susceptibles and infecteds. The initial population will be assumed to be as at 32 million. 52% of these are actively involved in the HIV epidemic transmission dynamics.

2.1: Simple HIV vaccine chart



At any given time the population involved in meaningful transmission of the epidemic divides itself into unvaccinated and vaccinated individuals. A proportion δ of susceptible population joins the unvaccinated susceptible class $\mathbf{S_u}$, and the remainder joins the vaccinated susceptible class $\mathbf{S_v}$. Reduction in both susceptible classes is due to natural deaths at a rate μ and by getting infected to join the infected classes at a rate equivalent to the product of the average number of sexual partners per year c and the per capita infection rate λ. The class of infecteds is also partitioned in to 2; infected but at one time vaccinated $\mathbf{H_v}$ and infected and was not vaccinated $\mathbf{H_u}$. These also leave by means of natural deaths at the same rate and also by a rate v to join the HIV/AIDS cases.

Let $\mathbf{S_U(t)}$, $\mathbf{S_V(t)}$, $\mathbf{H_U(t)}$ $\mathbf{H_V(t)}$ and $\mathbf{N(t)}$ be unvaccinated susceptibles, vaccinated susceptibles, unvaccinated Infecteds vaccinated Infecteds and the size of the total population at any given time t respectively. Then, we have four states where an individual can enter, stay or leave. $S_u(t), S_v(t), H_u(t), H_v(t)$.

$$S(t) = s_u(t) + s_v(t) \tag{2.1}$$

$$H(t) = H_u(t) + H_v(t) \tag{2.2}$$

$$N(t) = S(t) + H(t) \tag{2.3}$$

Let $N_u(t) = s_u(t) + H_u(t)$ and (2.4)

$$N_v(t) = s_v(t) + H_v(t) \tag{2.5}$$

The initial $\mathbf{H(0)}$ of infecteds are distributed between the two subpopulations of HIV infecteds at time $\mathbf{(t=0)}$. Assume homogeneous of sexual partners between

the two strata, a possible allocation of the **H(0)** to the two strata is achieved by establishing on a proportional allocation strategy[9].

$$\frac{N_v(0)}{N(0)} = \frac{H_v(0)}{H(0)} \text{ and } \frac{N_u(0)}{N(0)} = \frac{H_u(0)}{H(0)} \tag{2.6}$$

the proportion of vaccinated population is equivalent to the proportion of vaccinated infecteds among the infected population.

Let $\mathbf{q_U(t)}$ and $\mathbf{q_V(t)}$ denote the proportional of the population in the unvaccinated and vaccinated stratum respectively at any given time **t**,

Then $q_u(t) = \sigma$ and $q_v(t) = (1-\sigma)$ where

$$q_u(t) = \frac{N_u(t)}{N(t)} \text{ and } q_v(t) = \frac{N_v(t)}{N(t)} \tag{2.7}$$

Therefore assuming the epidemic dynamics is such that there is a proportional distribution of the infecteds between the two strata at any given time **t**, as before in equation (2.7)

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[9] Cochran William (1977), *Sampling Techniques,* 3-edition page 60-65.

For unvaccinated susceptibles, individuals enter this group through population's new recruits and vaccine did not 'take'. The term 'take' means the individual was vaccinated against HIV infection but did not develop proper immune system to guard against future HIV infection.

Let λ be the **probability of acquiring infection from a randomly chosen infected partner** or the per capita risk of acquiring infection.

If β_U and β_V are the **per partner transmission probabilities** of an infective who was initially unvaccinated and vaccinated respectively, $\mathbf{H_U(0)}$ and $\mathbf{H_V(0)}$ be the population of infectives who were initially unvaccinated and vaccinated respectively, and **N(t)** be the total population who are actively involved in the HIV epidemic dynamics at time **(t)** then,

$$\lambda(t) = \frac{\beta_u H_u(t) + \beta_v H_v(t)}{N(t)} \tag{2.8}$$

Let μ be the **natural death rate** and,

Let $\nu=\nu_U=\nu_V$ be the **rate of transmission from HIV infection to AIDS**.

Further, let **C** denote the average number of sexual partners per year.

These lead to a mathematical formulation of the epidemic during this period that is described by equations (2.9) to (2.12).

$$\frac{dS_u(t)}{dt} = \sigma[S(0)]e^{\rho t} - (\lambda(t)c + \mu)S_u(t) \tag{2.9}$$

$$\frac{dS_v(t)}{dt} = (1-\sigma)[S(0)]e^{\rho t} - (\lambda(t)c + \mu)S_v(t) \tag{2.10}$$

$$\frac{dH_u(t)}{dt} = \lambda(t)c\,S_u(t) - (\mu + \nu_u)H_u(t) \tag{2.11}$$

$$\frac{dH_v(t)}{dt} = \lambda(t)c\,S_v(t) - (\mu + \nu_v)H_v(t) \tag{2.12}$$

ρ is the average population growth rate.

For vaccinated and unvaccinated, the rates at which they join the AIDS class are different. It is assumed that even though the vaccine may be permeable, it still has the benefit of delaying the onset of HIV infection.

2. 2. MODEL SIMULATION

A review of the parameters already described above is as follows:

- ρ = the **average** population growth rate.
- λ = the **probability of acquiring infection from a randomly chosen infected partner** or the per capita risk of acquiring infection.
- β_U and β_V are the **per partner transmission probabilities** of an infective who was initially unvaccinated and vaccinated respectively.
- $\mathbf{H_U(0)}$ and $\mathbf{H_V(0)}$ be the population of infecteds who were initially unvaccinated and vaccinated respectively, and **N(t)** be the total population who are actively involved in the HIV epidemic dynamics at time **(t)** then,

$$\lambda(t)=\{\beta_U H_U(t)+\beta_V H_V(t)\}/N(t). \text{ Equation (2.8).}$$

- μ = the **natural death rate**
- ν_U and ν_V be the **rate of transmission from HIV infection to AIDS** for unvaccinated and vaccinated Infecteds respectively.

Numerical integration method is applied to solve the model equations for the given initial values and parameter estimates. The relevant SAS code is applied using the model procedure. We let the prevalence for the vaccinated and unvaccinated stages be defined as:

$$P_v(t) = \frac{H_v(t)}{N_v(t)} \quad \text{and} \quad P_u(t) = \frac{H_u(t)}{N_u(t)} \quad \text{respectively} \qquad (2.13)$$

Then

$$\frac{dP_v(t)}{dt} = \frac{d\left\{\frac{H_v(t)}{N_v(t)}\right\}}{dt} = \frac{N_v(t)\frac{dH_v(t)}{dt} - H_v(t)\frac{dN_v(t)}{dt}}{[N_v(t)]^2} \qquad (2.14a)$$

and

$$\frac{dP_u(t)}{dt} = \frac{d\left\{\frac{H_u(t)}{N_u(t)}\right\}}{dt} = \frac{N_u(t)\frac{dH_u(t)}{dt} - H_u(t)\frac{dN_u(t)}{dt}}{[N_u(t)]^2} \qquad (2.14b)$$

Equation (2.14a) is for vaccinated individuals and equation (2.14b). is for unvaccinated individuals

Epidemic curve for the vaccinated individuals is defined by

$$\frac{dH_v(t)}{dt} \approx \frac{\Delta H_v(t)}{\Delta t} \qquad (2.15)$$

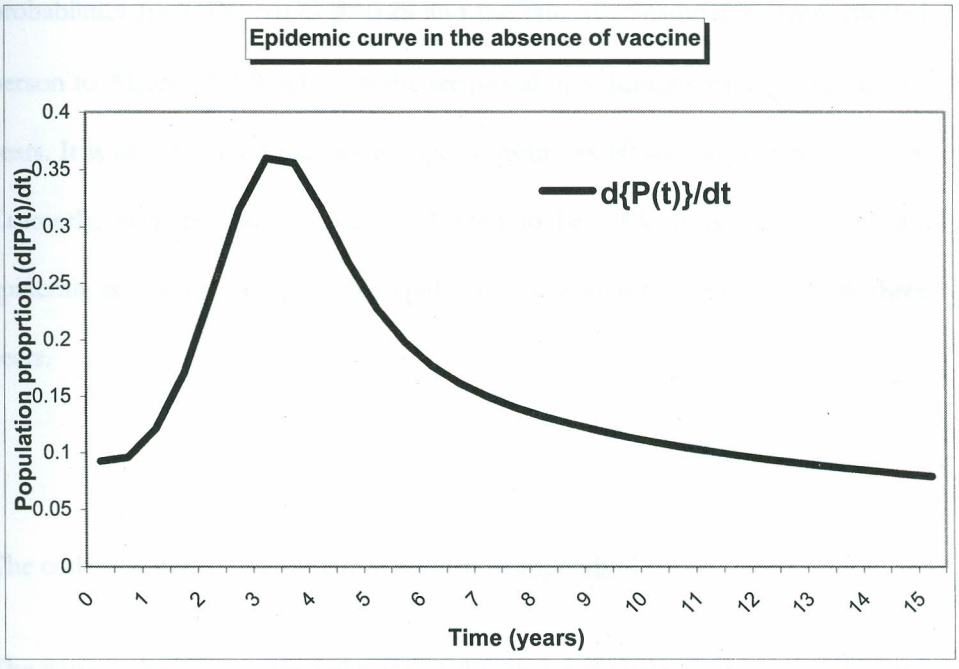
Where v is f or vaccinated individuals. The equation follows for the unvaccinated group.

Hence the curve $\frac{dP_v(t)}{dt}$ versus time t gives the epidemic curve scaled down by the factor $\frac{1}{N_v(t)}$ for v = vaccinated individuals.

SAS® software's PROC MODEL function is used to generate data for plotting the HIV vaccine epidemic curves.

Hence the curve:

2.2: Simple HIV-Epidemic vaccine model curve



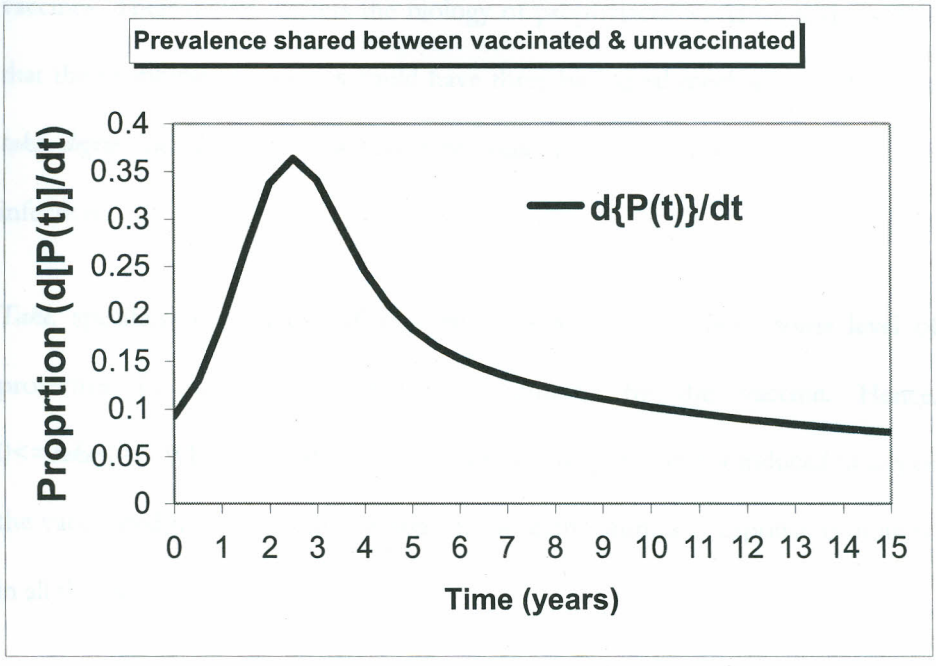
The rate of transmission from HIV infection to HIV/AIDS is assumed to be the same for the unvaccinated and the vaccinated individuals. The size of the Susceptible population, who are unvaccinated at time t=0 is 12,717,036. This is 52% of the total population at Kenya's census at 1999. We are taking 15 years from now. The years after 15th year becomes irrelevant, as there are additional recruits of children engendered by infected mothers and have not contracted HIV infection. Susceptibles and infecteds who are vaccinated are null. Vaccine against HIV infection has not yet been found. Therefore, the unvaccinated

infecteds still stands at 2.2 million. According to 2000 demography, the average population growth rate stands at 2.9%. The per partnership transmission probabilities for HIV/AIDS β=0.29 and the rate of transmission from infected person to AIDS is 0.128 which is the reciprocal of a duration of approximately 8 years. It is also assumed that an average Kenyan has 60 sexual partners per year. Currently, HIV prevalence rate is assumed to be 10%. It is evident that the epidemic is not subsiding in this epidemic scenario for at least the next three years.

The code that generated this curve is given in appendix 1.

The curve below shows the behavior of the epidemic curve in a population that a third is vaccinated at any given time t.

2.3: Simple HIV Epidemic model curve with population sharing vaccine



The epidemic curve is shared between the proportion of vaccinated and the unvaccinated individuals' curves. This model assumes that at any given time the population divides itself, such that a 1/3 is vaccinated and the rest is not. This curve has a similar trend to curve 2.2. It means delta is apparently not a vaccine variant. The epidemic trend does not depend on how many individuals are vaccinated so long as the transmission probabilities are not changing.

The syntax generating data for this curve is in appendix 2.

2. 3. VACCINE PARAMETERS

Blower and McLean[6] published the first epidemic control model for HIV vaccines. Their model reflects the biology of prophylactic vaccines and assumes that the prophylactic vaccines could have three biological mechanisms of action, *take, degree* and *duration*, by which they could fail to protect against the HIV-infection:

Take, specifies the fraction of vaccinated individuals in whom some level of protective immunological response is induced by the vaccine. Hence, $0<=take<=1$. When $take=0$, protective immune response is not induced in any of the vaccinated individuals. When $take=1$, protective immune response is induced in all the vaccinated individuals.

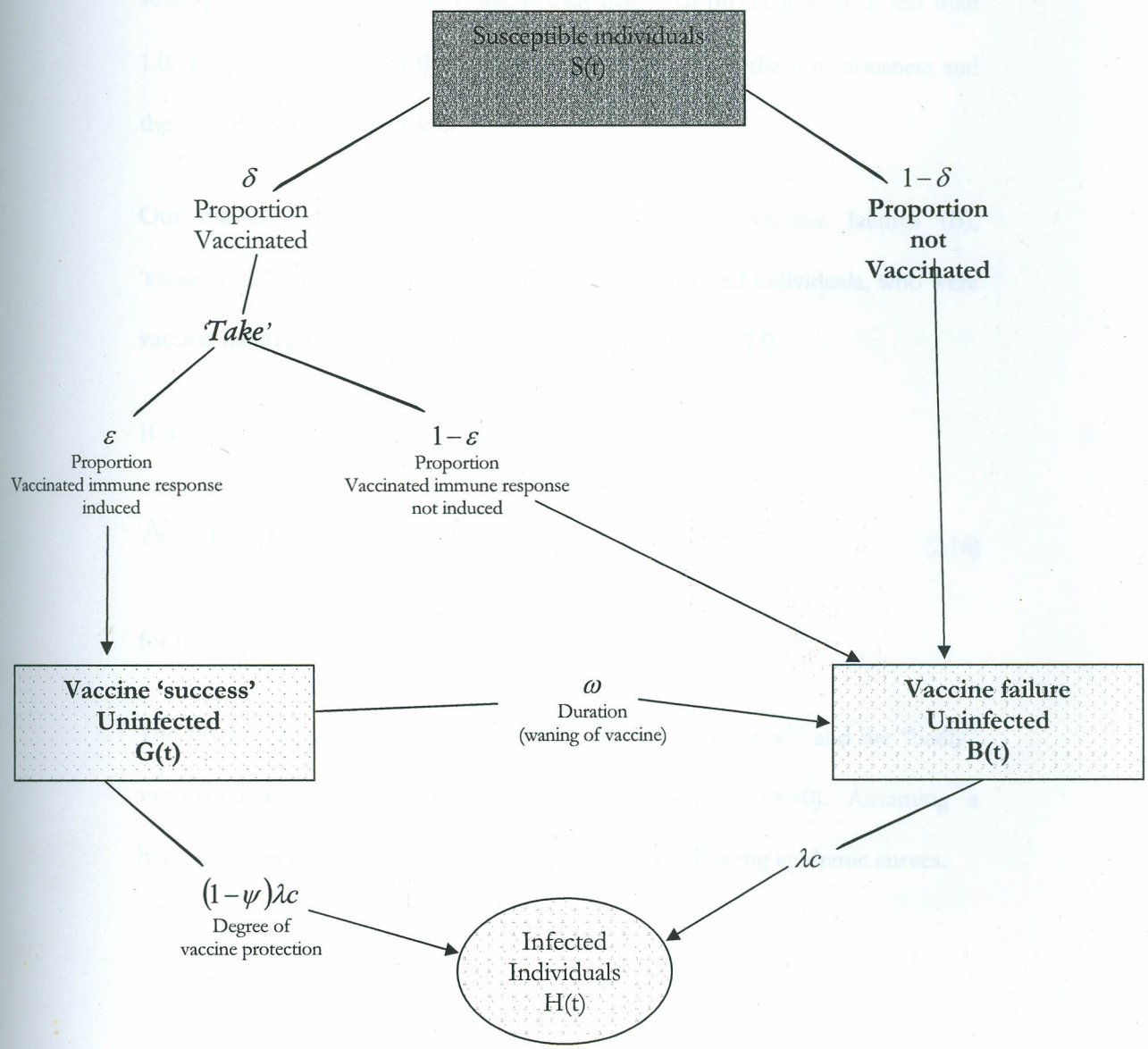
Degree specifies the degree of vaccine-induced protection against HIV-infection that is induced in those individuals in whom the vaccine *takes.* In other words it is the reduction in the probability of infection given exposure. Hence, $0<=degree<=1$. Where if $degree=0$, there is no protection and when $degree=1$, there is complete protection.

Duration specifies the duration of vaccine-induced immunity. *Duration* is assumed to decay exponentially.

So if we let *take,* be represented by the parameter ε; *duration* to be represented by parameter ω and degree of protection be given by the parameter ψ, for the

susceptibles in the model, a chart properly showing the transition in the model is as below.

2.4: Vaccine parameters model



The diagram shows that individuals are defined as 'successfully' vaccinated if they are vaccinated (δ), the vaccine takes (ε) them, and the vaccine-induced immunity (ω) does not wane. However, 'successfully' vaccinated individuals can subsequently become HIV-infected, if their degree of protection (ψ) is less than 1.0. There is a wide belief that vaccine can influence both the infectiousness and the rate of disease progression.

Our model thus consists of susceptibles who are vaccine failures (**B**), 'successfully' vaccinated individuals (**G**), and HIV-infected individuals, who were vaccine failures and vaccine 'success' but got the infection (**H**).

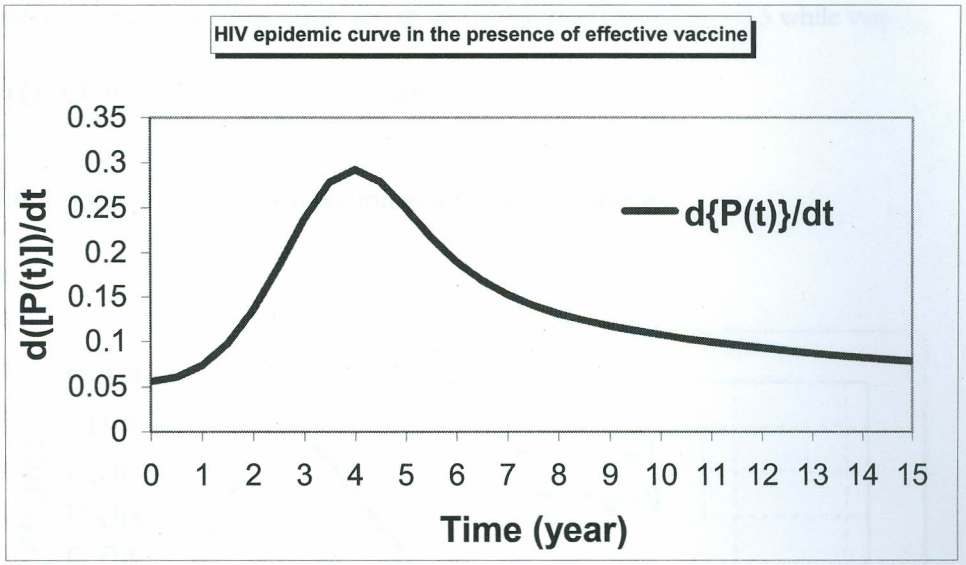
If we let

$$N(t) = G(t) + B(t) + H(t) \tag{2.16}$$

for the population involved in the HIV transmission.

The **H(t)** of infecteds infect susceptibles from both the "good" and the "badly" vaccinated susceptibles; **G(t)** and **B(t)** at any time (t>=0). Assuming a homogeneous mixing of sexual partners, we get the following epidemic curves.

2.5: Prevalence in the presence of effective vaccine

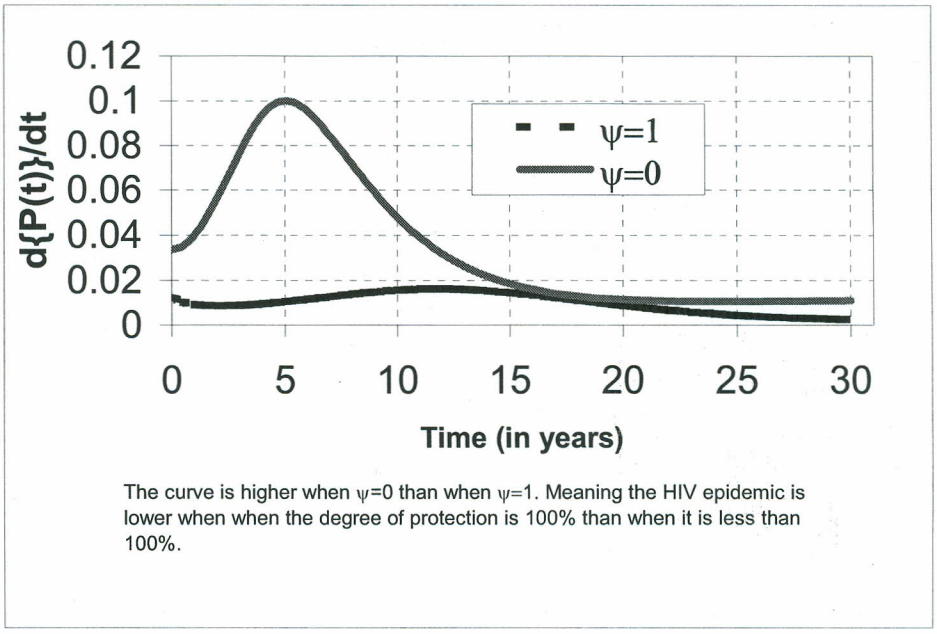


In this graph the epidemic curve is at a lower peak than in the previous curves. We assume that the vaccine reduces the per partnership transmission probabilities from 0.029 to 0.0145. Therefore betas are vaccine variants. If we vary the beta we get varied curves. If we reduce the probability of transmission from an infected to susceptible or reduce the probability of infection given exposure, we affect beta, hence interfering with the spread of infection. The epidemic curve peak is lower in reduced beta and the peak comes a year or two later than before.

2. 4. EFFECT VACCINE PARAMETER

If we let half of the population to be vaccinated at any given time, and hold two vaccine parameters constant ε and ω. Such that ε =0.5, and ω =0.5 while varying ψ **(1.0, 0.0)**. We get the following epidemic curves.

2.6: Effect of degree of protection as a vaccine parameter

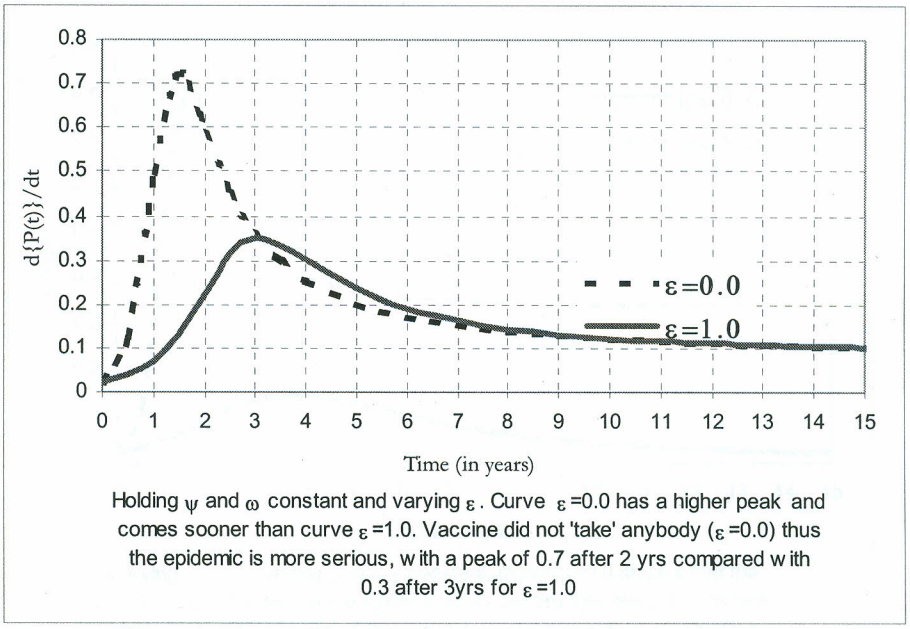


The curve is higher when ψ=0 than when ψ=1. Meaning the HIV epidemic is lower when when the degree of protection is 100% than when it is less than 100%.

When the vaccine accords complete protection to those susceptibles who were "successfully vaccinated" in other words ψ=1.0, the epidemic is not as high and picks up slower than when there is no protection ψ=0.0.

Now holding ψ and ω constant and varying ε, such that ψ =0.5, and ω =0.5 while varying ε **(1.0, 0.0)**. We get the following epidemic curves.

2.7: Effect of 'take' as a vaccine parameter

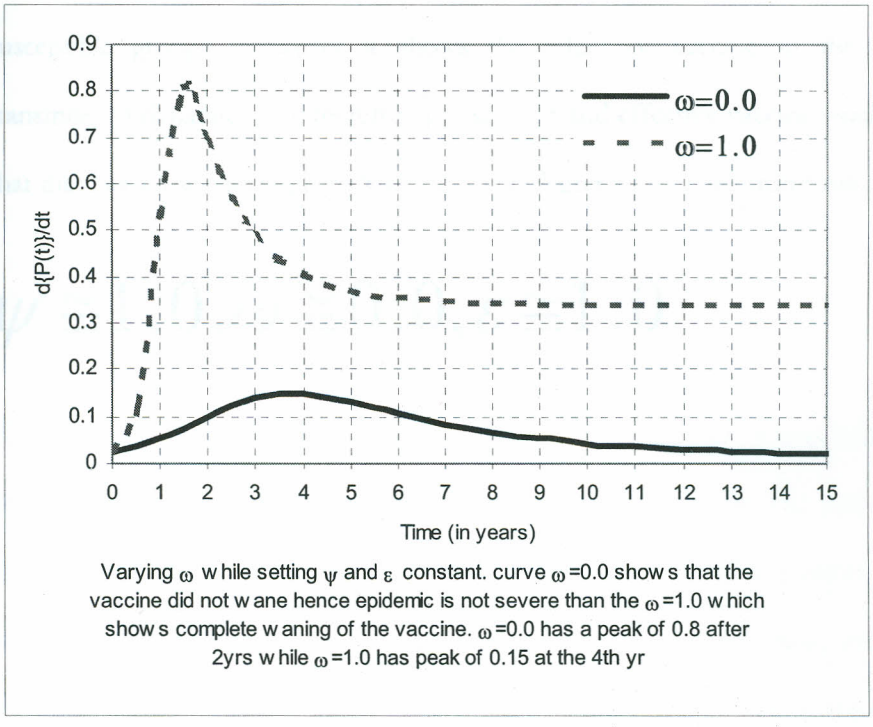


Holding ψ and ω constant and varying ε. Curve ε=0.0 has a higher peak and comes sooner than curve ε=1.0. Vaccine did not 'take' anybody (ε=0.0) thus the epidemic is more serious, with a peak of 0.7 after 2 yrs compared with 0.3 after 3yrs for ε=1.0

The epidemic is more serious in unvaccinated population than in vaccinated population. More precisely, for those susceptibles vaccinated, all had their immune response not induced for the case where $\varepsilon=0.0$ thus being as good as the unvaccinated susceptibles. On the other hand, all the vaccinated susceptibles had their immune response induced for $\varepsilon=1.0$, and subsequently giving a distinct path from those not vaccinated.

Similarly, holding ψ and ε constant and varying ω, such that $\psi=0.5$, and $\varepsilon=0.5$ while varying ω **(1.0, 0.0)**. We get the following epidemic curves.

2.8: Effect of duration of waning as a vaccine parameter



Varying ω while setting ψ and ε constant. curve ω=0.0 shows that the vaccine did not wane hence epidemic is not severe than the ω=1.0 which shows complete waning of the vaccine. ω=0.0 has a peak of 0.8 after 2yrs while ω=1.0 has peak of 0.15 at the 4th yr

Vaccine waned (ω=1.0) hence making susceptibles become infected once exposed to HIV infection. However, if there is no waning (ω=0.0), the HIV epidemic is not as severe.

2. 5. MODEL EVALUATION

The model is simplistic in its approach. It does not reflect the real situation in the Kenya's scenario. In the Kenyan scenario new recruits function is not linear. Apart from the population dividing itself into a linear proportion at any given

time, there are new recruits in terms of children born of infected mothers who did not get infected at birth and survive 15 years of the epidemic to join susceptible groups. However it shows the effect of vaccine in the HIV transmission dynamics. We therefore predict that and effective vaccine would be that that has a low waning, high 'take' and high degree of vaccine protection.

$$\psi \cong 1.0, \omega \cong 0.0, \varepsilon \cong 1.0$$

CHAPTER 3

STAGE SPECIFIC EPIDEMIC MODEL FOR UNVACCINATED POPULATION

3. 0. INTRODUCTION

HIV infection is known to develop in stages. Several years ago it was believed that there was window stage. Window stage was believed to be that period in HIV infection when an individual is infected but does not test HIV positive. Due to advancements in methods of testing for certainty of HIV infection, window stage has become blurry. However, 'window stage' can still be categorized depending on the number of CD_4 cells count.

For a healthy individual the CD_4 cells count ranges between 450 to 1,200 cells per cubic millimeter of blood. Somebody who has developed HIV related complications would have less than 200 CD_4 cells count per cubic millimeter of blood. With this cataloging, we can still categorize the progression in HIV infection in stages.

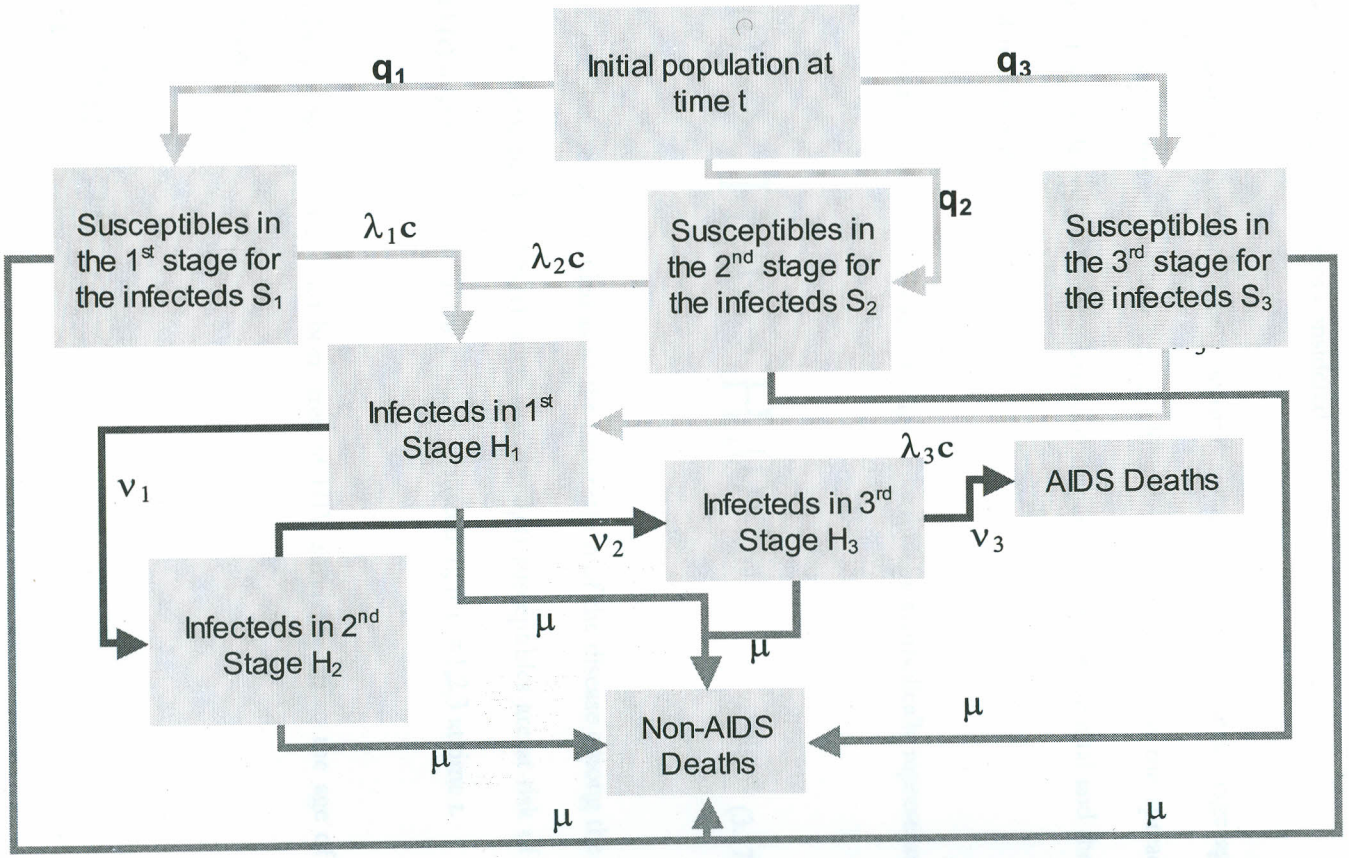
3. 1. STAGE SPECIFIC MODEL FOR UNVACCINATED INDIVIDUALS

In this model we assume HIV vaccine has not been found. That means the whole population is not vaccinated.

Assume that once infected the infection develops through stages. In this case we assume the three main stages are the 'window' stage, asymptomatic stage and symptomatic stage, based on the CD_4 cells count per cubic milliliter of blood[10].

[10] Longini, I. M. (1992). *Estimating the stage-specific numbers of HIV infection using backcalculation,* Statistics in Medicine, vol. 11 pg 831-843

3.1: The stage specific model for unvaccinated individuals chart



This stage specific simple epidemic model for unvaccinated population takes into account three stages of HIV infection. The 'window' stage, asymptomatic stage and the symptomatic stage are the stages considered.

The model assumes that individuals become sexually mature at the average age of 15 years. The population of sexually active adults only is considered in the spread of the infection. The modes of HIV transmission considered are the horizontal and the vertical modes of transmission.

The number of infecteds in the various stages may thus be symbolically represented as:

$$H_1(t) \rightarrow H_2(t) \rightarrow H_3(t) \qquad (3.17)$$

The susceptibles are also divided as to the progression of the disease among the infecteds at time t as $\mathbf{S_1(t)}$, $\mathbf{S_2(t)}$ and $\mathbf{S_3(t)}$, such that the $\mathbf{S_j(t)}$ susceptibles are at risk of infection from $\mathbf{H_j(t)}$ infecteds who are in the j^{th} stage of infection, for j=1,2,3 at time t.

Let P_2 be probability of a child born free of HIV surviving up to the age of 15 years, which is given by;

$$p_2 = e^{-15\mu_2 - 5(\mu_1 - \mu_2)} \qquad (3.2)$$

Where μ_1=average mortality rate between age 0 – 5 years and μ_2=average mortality rate between age 5 – 15 years.

As in the first model, let **N(t), S(t)** and **H(t)** be the size of the total population, susceptibles and infecteds at time t respectively, we have

$$S(t)=S_1(t)+S_2(t)+S_3(t) \quad (3.3)$$

$$H(t)=H_1(t)+H_2(t)+H_3(t) \quad (3.4)$$

$$N(t)=S(t)+H(t) \quad (3.5)$$

Let $n_j(t)=S_j(t)+H_j(t)$ for j=1,2,3 (3.6)

The initial H(0) of infecteds are distributed among the 3 strata. Assuming homogeneous mixing of sexual partners among the 3 strata, a possible allocation of the H(0) to the three strata is accomplished by basing on proportional allocation strategy. Hence

$$N_j(0)/N(0) = H_j(0)/H(0) \text{ for j=1,2,3,} \quad (3.7)$$

Let the proportion of the population in the j^{th} stratum at time t be denoted by $q_j(t)$, where j=1,2,3, Such that

$$q_j(t) = N_j(t) / N(t) \quad \text{for j=1,2,3} \tag{3.8}$$

Then the epidemic dynamics can be assumed to be proportionally distributed for the infecteds among the three strata at the instant time t, where $t \geq 0$, the proportion

$$q_j(t) = H_j(t) / H(t) \tag{3.9}$$

Children born free of HIV infection form new recruits later after the fifteenth year. This assumes sexual maturity of fifteen years. Due to time lag phenomenon, the epidemic may be considered in two phases. The first phase considers the first fifteen years and the second stage considers the period thereafter. However, in this model we consider only the first fifteen years since the beginning of the epidemic.

3. 2. THE FIRST FIFTEEN YEARS OF THE EPIDEMIC FOR THE STAGE SPECIFIC EPIDEMIC MODEL

Impaglazzo (1987)[11] in his bid to shed light on stable population growth theory stipulates that the population at time t is given by

$$N(t) = N(0)e^{\rho t} \tag{3.10}$$

[11] 11. Impaglazzo, J. (1987). *Stage population Theory,* Biomathematical computational modeling vol.18

Where the variables and the parameters are as explained before. The corresponding population of infecteds at time t is given by

$$H(t)=H(0)e^{\rho t} \tag{3.11}$$

Therefore we have,

$$S(t)=\{N(0)-H(0)\}e^{\rho t} \tag{3.12}$$

where this relationship is assumed to hold for each of the three strata. Susceptibles in any stratum may decrease through either death at the force of mortality μ or HIV infection by the $H_j(t)$ infecteds that is given by,

$$\beta_j c[\frac{H_j(t)}{n_j(t)}] \tag{3.13}$$

Where β_j is the probability of infection per contact with an infected individual in the j^{th} stratum, j=1, 2, 3. This leads to the mathematical formulation of the epidemic during this period described by

$$\frac{dS_1(t)}{dt} = q_1(0)[N(0)-H(0)]e^{\alpha t} - \beta_1 c[\frac{H_1(t)S_1(t)}{n_1(t)}] - \mu S_1(t) \quad (3.14)$$

$$\frac{dS_2(t)}{dt} = q_2(0)[N(0)-H(0)]e^{\alpha t} - \beta_2 c[\frac{H_2(t)S_2(t)}{n_2(t)}] - \mu S_2(t) \quad (3.15)$$

$$\frac{dS_3(t)}{dt} = q_3(0)[N(0)-H(0)]e^{\alpha t} - \beta_3 c[\frac{H_3(t)S_3(t)}{n_3(t)}] - \mu S_3(t) \quad (3.16)$$

If infected one proceeds to the first stage of the disease where exit is either by death at the rate of mortality μ, or if alive, to the next stage of the disease at the rate ν_j, depending on whether j=1,2,3. This leads to equation(3.17). The progressive stages are equivalently reached by those who survive and transit from the proceeding stages and in each case exit from the stage is either by death or, if alive, transiting to a higher stage, if any. This leads to equation (3.18) and equation (3.19) for the first fifteen years.

$$\frac{dH_1(t)}{dt} = \sum_{j=1}^{3} \frac{\beta_j c S_j(t) H_j(t)}{n_j(t)} - (\mu + \nu_1) H_1(t) \quad (3.17)$$

$$\frac{dH_2(t)}{dt} = \nu_1 H_1(t) - (\mu + \nu_2) H_2(t) \quad (3.18)$$

$$\frac{dH_3(t)}{dt} = \nu_2 H_2(t) - (\mu + \nu_3)\mathrm{H}_3(t) \qquad (3.19)$$

However, equation (3.17) to (3.19) are only true if we do not consider new recruits in terms of children born fifteen years ago surviving up to the fifteenth year.

3. 3. AFTER INITIAL 15 YEARS OF THE EPIDEMIC

After 15 years later, there will be additional recruits into the susceptible population of those children born of infected mothers at least 15 years earlier. Thus at a time *t*, for $t \geq 15$, there is contribution of the susceptible population which can be represented mathematically by,

$$\Lambda p_2 \sum_{j=1}^{3} (1-\xi_j) H_j(t-15), \text{ for } t \geq 15 \qquad (3.20)$$

where ξ_j = the probability of HIV transmission at birth by an infected mother in the j^{th} stage to her unborn child. Assuming a proportional allocation same as the one discussed earlier, this distribution is further divided among the three strata such that

$$q_j \Lambda p_2 \sum_{j=1}^{3} (1-\xi)_j H_j(t-15) \qquad (3.21)$$

is the number of susceptible contribution to the j^{th} stratum, j=1,2,3.

The final epidemic dynamics, incorporating the additional recruits into the susceptible class, thus take the form of a system of delayed first order differential equations given by:

$$\frac{dS_1(t)}{dt} = q_1(t)\Lambda\sum_{j=1}^{3}(1-\xi_j)H_j(t-15)p_2 + \left[q_1(0)N(0) - H_1(0)\right]e^{\mu t} - (\lambda c+\mu)S_1(t) \tag{3.22}$$

$$\frac{dS_2(t)}{dt} = q_2(t)\Lambda\sum_{j=1}^{3}(1-\xi_j)H_j(t-15)p_2 + \left[q_2(0)N(0) - H_2(0)\right]e^{\mu t} - (\lambda c+\mu)S_2(t) \tag{3.23}$$

$$\frac{dS_3(t)}{dt} = q_3(t)\Lambda\sum_{j=1}^{3}(1-\xi_j)H_j(t-15)p_2 + \left[q_3(0)N(0) - H_3(0)\right]e^{\mu t} - (\lambda c+\mu)S_3(t) \tag{3.24}$$

$$\frac{dH_1(t)}{dt} = \lambda c\sum_{j=1}^{3}S_j(t) - (\nu_1+\mu)H_1(t) \tag{3.25}$$

$$\frac{dH_2(t)}{dt} = \nu_1 H_1(t) - (\nu_2+\mu)H_2(t) \tag{3.26}$$

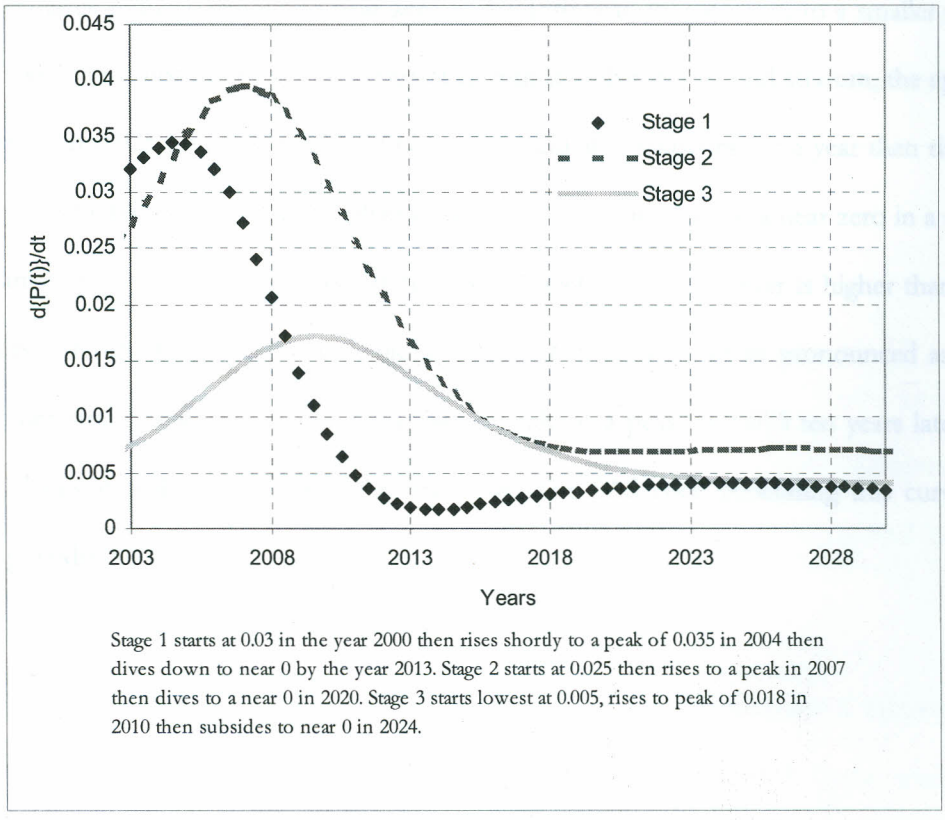
$$\frac{d H_3(t)}{dt} = \nu_2 H_2(t) - (\nu_3 + \mu) H_3(t) \qquad (3.27)$$

This system is coupled with that given before. These two systems are solved by SAS model system and then graphed explained in the next part.

3. 4. MODEL SIMULATIONS FOR KENYA'S HIV EPIDEMIC

The initial values and model parameters for Kenya epidemic, taken from published records, are used to generate simulated epidemic curves for the three stages. We then discuss the findings. The graphs obtained from these equations are given as below:

3.2: Stage specific epidemic curves



Stage 1 starts at 0.03 in the year 2000 then rises shortly to a peak of 0.035 in 2004 then dives down to near 0 by the year 2013. Stage 2 starts at 0.025 then rises to a peak in 2007 then dives to a near 0 in 2020. Stage 3 starts lowest at 0.005, rises to peak of 0.018 in 2010 then subsides to near 0 in 2024.

The patterns, for each stage are similar to those noted in Simwa et al4 However, there are differences. In Simwa's[12] curves the epidemic curves are drawn as from the beginning of the epidemic, whereas our curves reflect the HIV epidemic at an advanced stage (from 2000, fifteen years later). Bumps in Simwa's curves are more pronounced than in ours, but all the same the bumps are also experienced in ours. The epidemic in the 1st stratum

[12] Simwa R. O., Mathematical and statistical analysis of HIV/AIDS-epidemic with reference to East Africa. International Biometric conference (2000), USA, vol I, pg 144.

starts at 0.03 fifteen years since the onset of HIV epidemic, then stagnates for a year after which it rises to a peak of 0.035 after 5 years. After the 5th year from the year 2000, the epidemic reduces steadily to near zero at the 15th year, it again rises to a smaller peak of 0.005, then subsides to zero 35 years later. Similarly, for the second stratum, the epidemic starts at 0.025 lower than in the first stratum and also stagnates for a year then rises to a peak of 0.04, (this time higher than in stratum 1) then reduces to a near zero in a manner similar to epidemic in the first stratum. The 'smaller' peak however is higher than in the first stratum at 0.01. The epidemic in the third stratum is not as pronounced as in the other strata. It starts at 0.005 then rises steadily to a peak of 0.015 ten years later, then reduces steadily to zero after the 35th year. The SAS code generating this curve is in appendix 3.

CHAPTER 4

STAGE SPECIFIC MODEL FOR VACCINATED POPULATION WITH RECRUITMENT

4.0. INTRODUCTION

As with stage specificity model for unvaccinated population described above, we not only emulate the methodology to the vaccinated population but also incorporate the introduction of new recruits fifteen years later since start of the epidemic and introduce vaccine variants.

This section views the vaccine effects in terms of those vaccinated, and if vaccinated, did their effective immune response against the HIV infection induced? It further analyses the induced immune response as to whether it waned with time. Further, for those in whom the immune response was developed and did not wane we shall look at the degree of protection they acquired, whether a fraction of the said individuals still succeeded in getting infected from other strains of HIV.

Assume these new recruits are children born of mothers who were free of infection, or children who were born of infected mothers but did not get infected at birth. They will join in the active transmission dynamics of the HIV epidemic fifteen years later. This also

assumes that infected children die at birth and so are excluded from the transmission of HIV/AIDS.

We note here that an effective vaccine has so far not been found. Trials are still going on in different parts of the world[2], including Kenya. Assume an effective vaccine will be available and will be made available for all and sundry by the year 2005. Meaning newborns will be vaccinated against HIV infection at birth and everyone will be vaccinated 25 years later since the onset of HIV pandemic.

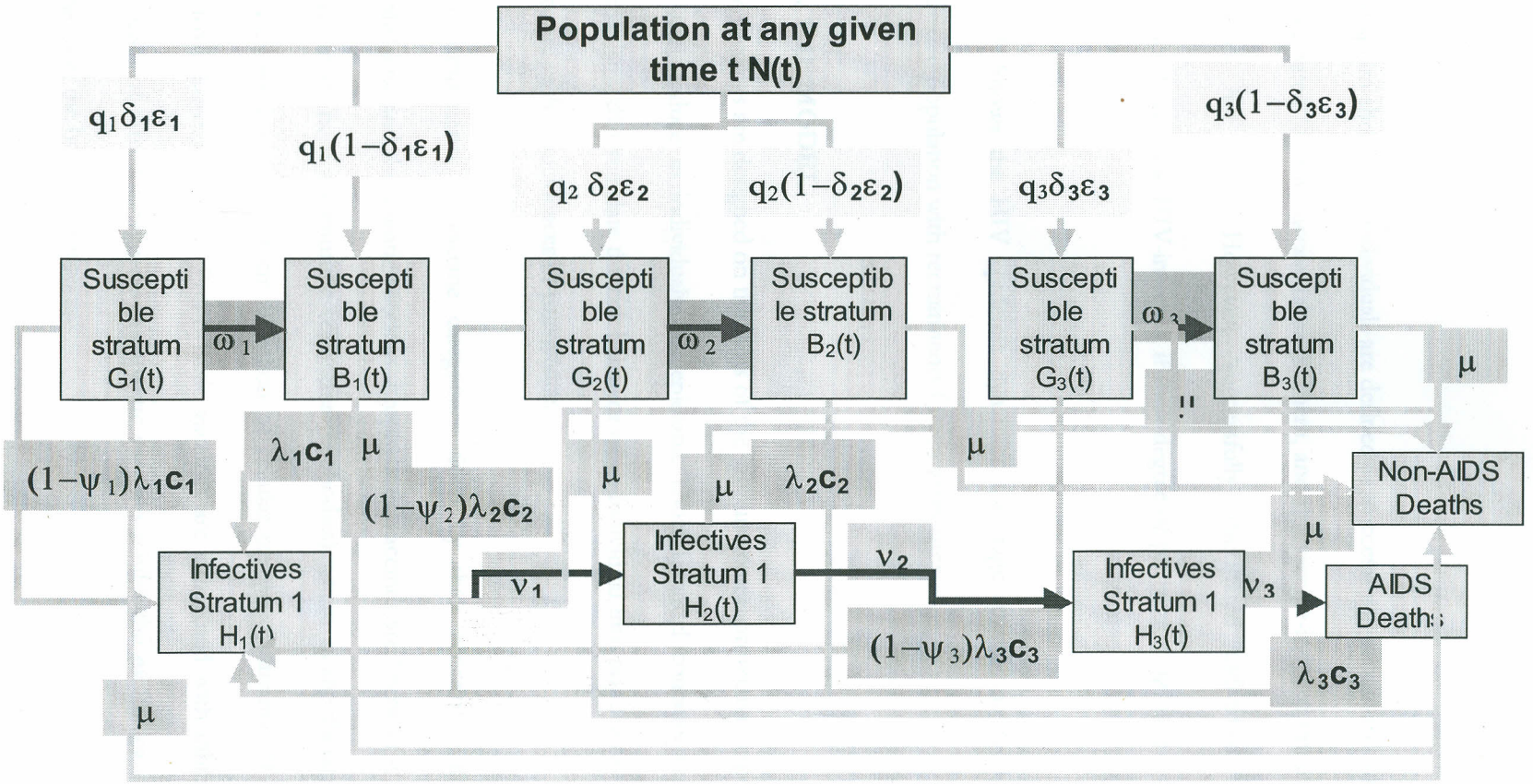
From these two foundations we build our third model.

4. 1. STAGE SPECIFIC MODEL FOR VACCINATED POPULATION WITH RECRUITMENT

The model assumes that an effective HIV vaccine has been found, such that the whole population is subjected to HIV vaccine.

However, the transmission dynamics change with the influence of vaccine. A chart to that effect is as follows.

4.1: stage specific model for vaccinated population with recruitments chart



The diagram shows that individuals are defined as 'successfully' vaccinated if they are vaccinated (δ), the vaccine takes (ε) them, and the vaccine-induced immunity (ω) does not wane. However, 'successfully' vaccinated individuals can subsequently become HIV-infected, if their degree of protection (ψ) is less than 1.0.

Chart 3. Shows the HIV epidemic dynamics for stage specific model for a vaccinated population with recruitments fifteen years later.

4. 2. THE MODEL

HIV vaccines are designed on the basis of the immunological protective response that they induce in individuals. An epidemic control model contains explicit mechanisms that translate the risk behavior of an individual into population-level outcome such as incidences or prevalence.

Two components of vaccine categorizes them by their functions; namely prophylactic and therapeutic vaccines. Prophylactic vaccines are known for their induction of humoral immune responses (antibodies) where as the therapeutic vaccines are known for their induction of cellular reposes (primarily CTLS—cytotoxic-T-lymphocytes). Prophylactic vaccines are concerned with inhibiting the onset of infection whereas therapeutic vaccines inhibit the multiplication of antigens in the body once infected.

Blower and McLean published the first epidemic control model for HIV vaccines. Their model reflects the biology of prophylactic vaccines and assumes that the prophylactic vaccines could have three biological mechanisms of action, *take, degree* and *duration*, by which they could fail to protect against the HIV-infection:

Take, specifies the fraction of vaccinated individuals in whom some level of protective immunological response is induced by the vaccine. Hence, 0<=*take*<=1. When *take*=0, protective immune response is not induced in any of the vaccinated individuals. When *take*=1, protective immune response is induced in all the vaccinated individuals.

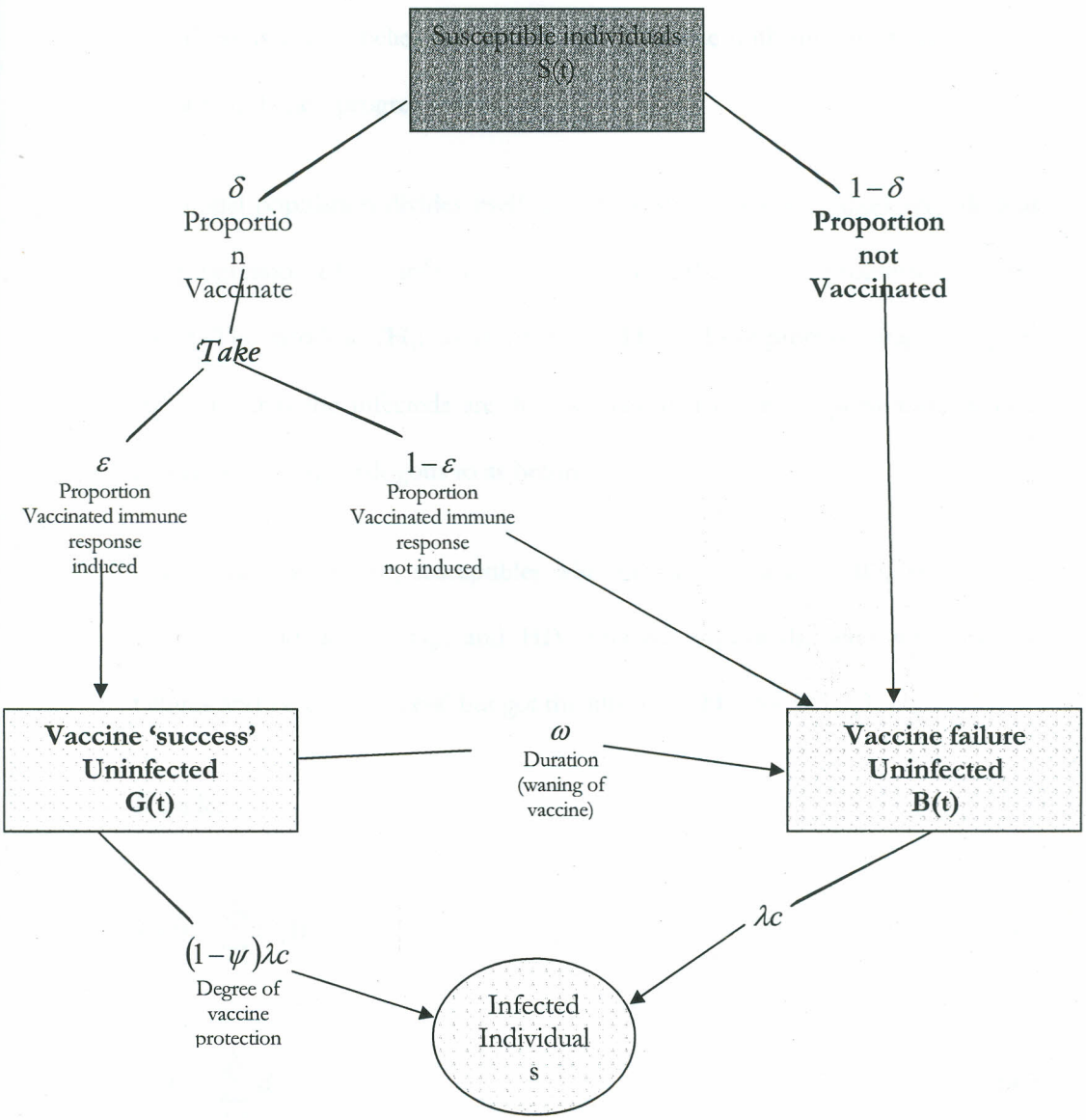
Degree specifies the degree of vaccine-induced protection against HIV-infection that is induced in those individuals in whom the vaccine *takes.* In other words it is the reduction in the probability of infection given exposure. Hence, 0<=*degree*<=1. Where if *degree*=0, there is no protection and when *degree*=1, there is complete protection.

Duration specifies the duration of vaccine-induced immunity. *Duration* is assumed to decay exponentially.

So if we let *take,* be represented by the parameter ε_j; *duration* to be represented by parameter ω_j and degree of protection be given by the parameter ψ_j j=1,2,3, for

the susceptibles in the three strata in the model, a chart properly showing the transition for this part of the model is as below.

4.2: A subsection of the model



The diagram shows that individuals are defined as 'successfully' vaccinated if they are vaccinated (δ), the vaccine takes (ε) them, and the vaccine-induced immunity (ω) does not wane. However, 'successfully' vaccinated individuals can subsequently become HIV-infected, if their degree of protection (ψ) is less than 1.0. There is a wide belief that vaccine can influence both the infectiousness and the rate of disease progression.

The initial population divides itself into three strata of susceptibles according as the progression of the infection. Infection as earlier stated, progresses in three stages. The 'window' ($\mathbf{H}_1$), assymptomatic ($\mathbf{H}_2$) and symptomatic stages ($\mathbf{H}_3$) are the strata that the infecteds are divided. The division is proportionally divided into $\mathbf{q}_1$, $\mathbf{q}_2$, and $\mathbf{q}_3$ analogous to as before.

Our model consists of; susceptibles who are vaccine failures ($\mathbf{B}_j$), 'successfully' vaccinated individuals ($\mathbf{G}_j$), and HIV-infected individuals, who were vaccine failures and vaccine 'success' but got the infection ($\mathbf{H}_j$), for j=1,2,3.

If we let

$$G(t) = \sum_{j=1}^{3} G_j(t) \tag{4.1}$$

$$B(t) = \sum_{j=1}^{3} B_j(t) \tag{4.2}$$

$$H(t) = \sum_{j=1}^{3} H_j(t) \tag{4.3}$$

$$N(t) = G(t) + B(t) + H(t) \tag{4.4}$$

And let

$$N_j(t) = B_j(t) + G_j(t) + H_j(t) \quad \text{for j=1,2,3} \tag{4.5}$$

The initial **H(0)** of infecteds are distributed among the three sub strata (the j^{th} stratum being made up of the $\mathbf{G_j(t)}$ and $\mathbf{B_j(t)}$ susceptibles and the $H_j(t)$ infecteds at time t for j=1,2,3 and t>=0). Assuming a homogeneous mixing of sexual partners among the three strata [independent of the stage of the infected individuals], a possible allocation of the **H(0)** to the three strata is achieved by basing on proportional allocation strategy, noted under proportional stratified sampling design, in which case

$$\frac{N_j(0)}{N(0)} = \frac{H_j(0)}{H(0)} \quad \text{for j=1,2,3} \tag{4.6}$$

Let $\mathbf{q_j(t)}$, for j=1,2,3 denote the proportion of the population in the j^{th} stratum at time t, $0 \leq t \leq \infty$, then

$$q_j(t) = \frac{N_j(t)}{N(t)} = \frac{H_j(t)}{H(0)} \quad \text{for j=1,2,3} \tag{4.7}$$

Therefore assuming the epidemics are such that there is proportional distribution of the infecteds among the three strata proportional to $q_j(t) = \frac{H_j(t)}{H(t)}$

Newborns of HIV-free-mothers form new recruits to the susceptibles if they survive to maturity. These recruits begin to appear after some years of the epidemic when they reach maturity age. If we assume sexual maturity age of about 15 years, it would mean we have contribution to the susceptible class by these children who are maturing.

Owing to the time lag phenomenon, we consider the epidemic in two phases namely the first 15 years and the period thereafter as was done in Simwa, (2000)[12].

4. 3. PHASE 1 OF THE EPIDEMIC

The stable population growth theory gives the population at time **t** by

$$N(t) = N(0)e^{\rho t} \tag{4.8}$$

And the corresponding population of infecteds at time t is given by

$$H(t) = H(0)e^{\rho t} \tag{4.9}$$

We have $S_j(t) = G_j(t) + B_j(t)$, for every j=1,2,3. Since **N(t)=S(t)+H(t)** we generalize that the susceptibles can also be categorized as

$$S(t) = \{N(0) - H(0)\}e^{\rho t} \tag{4.10}$$

This relationship is assumed to hold for each of the three strata.

The fraction of new susceptibles in whom the vaccine 'takes' enters the 'successfully' vaccinated states at rate $\varepsilon_j\delta_j$. They may leave these states for one of the three reasons: they may leave the community at average rate μ, their vaccine-induced immunity may wane at an average rate ω_j, or they may acquire HIV-infection. The degree of vaccine-induced protection against HIV infection is ψ_j:

thus, their probability of becoming HIV-infected is $\lambda_j c(1-\psi_j)$. Hence the rate of change in the number of 'successfully' vaccinated individuals ($\mathbf{G_j}$) per unit time is specified by:

$$\frac{dG_j(t)}{dt} = \varepsilon_j \delta_j S_j(0) e^{\alpha} - \left[\lambda_j c(1-\psi_j) G_j(t)\right] - (\mu + \omega_j) G_j(t) \quad (4.11)$$

Vaccine-induced immunity in the 'successfully' vaccinated wanes at a rate ω_j; thus the average duration of vaccinated-induced immunity is $1/\omega_j$ years, and the number of 'successfully' vaccinated individuals entering the susceptible pool per unit time is $\omega_j \mathbf{G_j}$. Hence the rate of change in the number of susceptible individuals who were not successfully vaccinated per unit time is specified by:

$$\frac{dB_j(t)}{dt} = (1-\varepsilon_j \delta_j) S_j(0) e^{\alpha} - \left[\lambda_j c B_j(t)\right] - \mu B_j(t) + \omega_j G_j(t) \quad (4.12)$$

"Successfully" vaccinated individuals who became HIV-infected and unvaccinated individuals plus vaccine failures who became HIV-infected enter the infectious class $\mathbf{H_j}$. Individuals leave this class if they leave the sexually active community (at an average rate μ) or if they progress to higher stages of the HIV-

infection at average rates ν_j, for j=1,2,3. Hence a mathematical representation of the transition in this infected class is tentatively specified by:

$$\frac{dH_1(t)}{dt} = \sum_{j-1}^{3}\left[\lambda_j c(1-\psi_j)G_j(t) + \lambda_j c B_j(t)\right] - (\nu_1 + \mu)H_1(t) \quad (4.13)$$

Generalizing for the three stages of the epidemic we have the following set of equations:

$$\frac{dG_1(t)}{dt} = \varepsilon_1\delta_1 S_1(0)e^{\alpha} - \lambda_1 c(1-\psi_1)G_1(t) - (\mu+\omega_1)G_1(t) \quad (4.14)$$

$$\frac{dG_2(t)}{dt} = \varepsilon_2\delta_2 S_2(0)e^{\alpha} - \lambda_2 c(1-\psi_2)G_2(t) - (\mu+\omega_2)G_2(t) \quad (4.15)$$

$$\frac{dG_3(t)}{dt} = \varepsilon_3\delta_3 S_3(0)e^{\alpha} - \lambda_3 c(1-\psi_3)G_3(t) - (\mu+\omega_3)G_3(t) \quad (4.16)$$

$$\frac{dB_1(t)}{dt} = (1-\varepsilon_1\delta_1)S_1(0)e^{\alpha} - \lambda_1 c B_1(t) - \mu B_1(t) + \omega_1 G_1(t) \quad (4.17)$$

$$\frac{dB_2(t)}{dt} = (1-\varepsilon_2\delta_2)S_2(0)e^{\rho t} - \lambda_2 cB_2(t) - \mu B_2(t) + \omega_2 G_2(t) \quad (4.18)$$

$$\frac{dB_3(t)}{dt} = q_3(1-\varepsilon_3\delta_3)S_3(0)e^{\rho t} - \lambda_3 cB_3(t) - \mu B_3(t) + \omega_3 G_3(t) \quad (4.19)$$

$$\frac{dH_1(t)}{dt} = \sum_{J=1}^{3}\left[\lambda_j c(1-\psi_j)G_j(t) + \lambda_j cB_j(t)\right] - (v_1+\mu)H_1(t) \quad (4.20)$$

$$\frac{dH_2(t)}{dt} = v_1 H_1(t) - (v_2+\mu)H_2(t) \quad (4.21)$$

$$\frac{dH_3(t)}{dt} = v_2 H_2(t) - (v_3+\mu)H_3(t) \quad (4.22)$$

The above nine differential equations define the epidemic in the presence of vaccine for the initial fifteen year period.

4. 4. EPIDEMIC AFTER THE INITIAL 15 YEARS SINCE THE INTRODUCTION HIV-VACCINE

As was explained in chapter 3, there will be additional recruits into the susceptible populations of those children born of infected mothers at least 15 years earlier

who become sexually active and hence become susceptible to HIV infection through heterosexual contact. The contribution is represented mathematically by equation (3.20).

Here again, we assume proportional distribution of infecteds among the three strata such that

$$\varepsilon_j \delta_j q_j(t) p_2 \Lambda \sum_{j=1}^{3} (1-\xi_j) H_j(t-15) \tag{4.23}$$

, is the number of susceptible contributed to the j^{th} stratum for the "vaccine success" and

$$(1-\varepsilon_j \delta_j) q_j(t) p_2 \Lambda \sum_{j=1}^{3} (1-\xi_j) H_j(t-15) \tag{4.24}$$

, is the number of susceptibles contributed to the j^{th} stratum for the "vaccine failure", j=1,2,3.

Thence we have an overall epidemic incorporating the additional recruits into the susceptible class taking the form of a system of delayed first order differential equations given by:

$$\frac{dG_1(t)}{dt} = q_1(t)\varepsilon_1\delta_1\Lambda p_2\sum_{j=1}^{3}(1-\xi_j)H_j(t-15) + \varepsilon_1\delta_1 S_1(0)e^{\rho t}$$
$$-\lambda_1 c(1-\psi_1)G_1(t) - (\mu+\omega_1)G_1(t) \tag{4.25}$$

$$\frac{dG_2(t)}{dt} = q_2(t)\varepsilon_2\delta_2\Lambda p_2\sum_{j=1}^{3}(1-\xi_j)H_j(t-15) + \varepsilon_2\delta_2 S_2(0)e^{\rho t}$$
$$-\lambda_2 c(1-\psi_2)G_2(t) - (\mu+\omega_2)G_2(t) \tag{4.26}$$

$$\frac{dG_3(t)}{dt} = q_3(t)\varepsilon_3\delta_3\Lambda p_2\sum_{j=1}^{3}(1-\xi_j)H_j(t-15) + \varepsilon_3\delta_3 S_3(0)e^{\rho t}$$
$$-\lambda_3 c(1-\psi_3)G_3(t) - (\mu+\omega_3)G_3(t) \tag{4.27}$$

$$\frac{dB_1(t)}{dt} = q_1(t)(1-\varepsilon_1\delta_1)\Lambda p_2\sum_{j=1}^{3}(1-\xi_j)H_j(t-15) + (1-\varepsilon_1\delta_1)S_1(0)e^{\rho t}$$
$$-\lambda_1 cB_1(t) - \mu B_1(t) + \omega_1 G_1(t) \tag{4.28}$$

$$\frac{dB_2(t)}{dt} = q_2(t)(1-\varepsilon_2\delta_2)\Lambda p_2\sum_{j=1}^{3}(1-\xi_j)H_j(t-15) + (1-\varepsilon_2\delta_2)S_2(0)e^{\rho t}$$
$$-\lambda_2 cB_2(t) - \mu B_2(t) + \omega_2 G_2(t) \tag{4.29}$$

$$\frac{dB_3(t)}{dt} = q_3(t)(1-\varepsilon_3\delta_3)\Lambda p_2\sum_{j=1}^{3}(1-\xi_j)H_j(t-15)+(1-\varepsilon_3\delta_3)S_3(0)e^{\alpha} - \lambda_3 cB_3(t)-\mu B_3(t)+\omega_3 G_3(t) \quad (4.30)$$

$$\frac{dH_1(t)}{dt} = \sum_{J=1}^{3}\left[\lambda_j c(1-\psi_j)G_j(t)+\lambda_j cB_j(t)\right]-(\nu_1+\mu)H_1(t) \quad (4.31)$$

$$\frac{dH_2(t)}{dt} = \nu_1 H_1(t)-(\nu_2+\mu)H_2(t) \quad (4.32)$$

$$\frac{dH_3(t)}{dt} = \nu_2 H_2(t)-(\nu_3+\mu)H_3(t) \quad (4.33)$$

This system of equations (4.25) to (4.33) is coupled with that given by equations (4.14) – (4.22) through the terms in expression (4.23) and expression (2.24). The two systems of equations are solved in chapter 5 using SAS proc model procedure given initial conditions and model parameter estimates.

CHAPTER 5

MODEL SIMULATIONS FOR THE KENYAN HIV/AIDS EPIDEMIC

5. 0. INTRODUCTION

The initial values and model parameters for the Kenyan epidemic, taken from published records, are used to generate the simulation epidemic curves. These records are as at the beginning of the year 2000. The simulations are then compared with the previous findings, especially the Simwa's[12], Longini's[10] and Blower et al[2].

5. 1. PARAMETER ESTIMATES AND INITIAL VALUES

The life expectancy at birth in Kenya as at the beginning of 2000 was 47.49 years, therefore the average mortality rate $\mu=1/47.49 = \mathbf{0.02}$. The value for the average force of mortality for the age group 0-5 years, $\mu_1=\mathbf{0.028571}$, and for age group 5-15 years, $\mu_2=\mathbf{0.0057143}$. Similarly in Kenya, on the average there are 28 births/1,000 population (2001 est.), per year and thus $\Lambda=28/1000= \mathbf{0.028}$.

$\lambda_j = \beta_j \frac{H_j(t)}{N_j(t)}$, for j=1,2,3 where β is the per partnership transition probability, thus λ is the probability of acquiring infection from a randomly chosen infected partner or the per capita risk of acquiring infection. Using values for parameter estimates given in Luboobi[13], 1994, May et al[14], 1995, and Longini, 1992, we have:

β_1=0.07, β_2=0.007, β_3=0.03, ν_1=2, ν_2=1/3, ν_3=1/4.5

ξ is the probability of HIV transmission at birth by an HIV-infected mother to her unborn child.

We assume that $\xi_1 = \xi_2 = \xi_3$=0.7 although, an average $\xi_1 \geq \xi_2 \geq \xi_3$. In the simulations we assume that the average number of sexual partners vary between 10 and 100 irrespective of stratum. Such that $10 \leq c_1, c_2, c_3 \leq 100$.

We shall do simulation for δ=0, δ=0.5 and for δ=1, that is for the first instant nobody in the population is vaccinated against the HIV-infection, half of the

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[13] Luboobi L. M. (1994). *A three-stage model for HIV/AIDS epidemic and effects of medical/social interventions,* Mathematical computational modeling, vol. 19 pg 91-105

[14] Anderson R. M. and May R. M. (1995), *Infectious Diseases of Humans, Dynamics and control,* Oxford Science Publications

population is vaccinated, and lastly, the whole population is vaccinated against HIV-infection. This approach may be improved to include time dependence of vaccination. Same treatment goes for 'taking' aspect. We shall simulate when the whole population, for the two possibilities of being vaccinated, the vaccine does not induce immune response in 100% fraction of the population vaccinated, thus $\varepsilon=0$, for no immune response induction in the vaccinated individuals, $\varepsilon=0.5$ for half of the population who is vaccinated immune response is induced. Then $\varepsilon=1$ for everyone who was vaccinated, immune response was induced. The same treatment goes for degree of vaccine protection, where $\psi=0$,$\psi=0.5$ and $\psi=1$. However, since duration of vaccine protection ω decays exponentially we may resort to simulate it at $\omega=0.9$

The initial conditions are chosen as at when the vaccines were purported to have started gained much impetus. This will be started and gained as from the year 2000. These conditions may be adjusted as data become available. In the meantime we let the initial values be:

$N(0)=12,717,036$ $q_1(0)=H_1(0)/H(0)=5/9$, $q_2(0)=H_2(0)/H(0)=3/9$, $q_3(0)=H_3(0)/H(0)=1/9$.

5. 2. VACCINE MODEL SIMULATIONS

Numerical integration method is applied to solve the model equations for the given initial values and parameter estimates. Procedure model syntax is written in SAS software to evaluate the differential equations.

The following curves were obtained:

5.1: Epidemic curve with initial vaccine parameters.

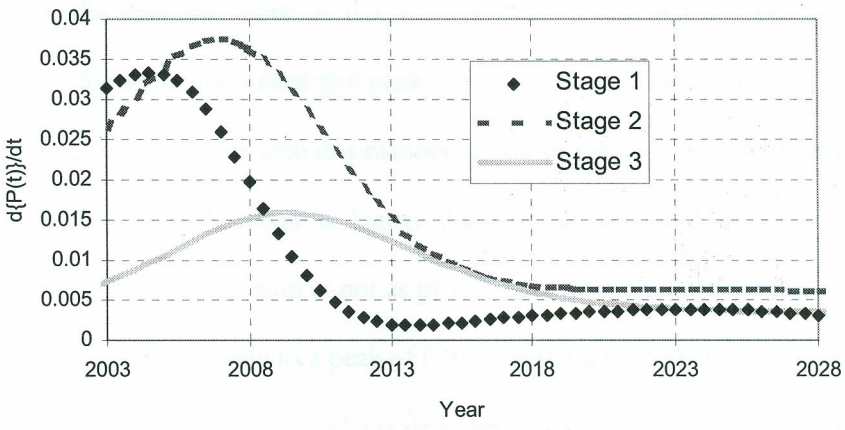

Fig. 5.1; the HIV epidemic in stage 1 dorminates epidemic in other stages for 2 years since 2003. It is overtaken by epidemic in stage 2, which dorminated thereafter. Epidemic in stage 3 trails for 10 years and is overtaken by epidemic in stage .

The curves give the epidemic trend in the next 40 years if we consider that individuals are not vaccinated ($\delta=0$), and therefore the vaccine does not take anybody ($\varepsilon=0$), and similarly the vaccine-induced immunity ($\omega=0$) becomes irrelevant. And therefore individuals can subsequently become HIV-infected, i.e. their degree of protection ($\psi=0$) is zero. The patterns, for each stage are similar to those noted curve IV. The epidemic in the 1st stratum starts at 0.03 fifteen years since the onset of HIV epidemic, then stagnates for a year after which it rises to a peak of 0.035 after 5 years. After the 5th year from the year 2000, the epidemic reduces steadily to near zero at the 15th year, it again rises to a smaller peak of 0.005, then subsides to zero 35 years later. Similarly, for the second stratum, the epidemic starts at 0.025 lower than in the first stratum and also stagnates for a year then rises to a peak of 0.04, (this time higher than in stratum 1) then reduces to a near zero in a manner similar to epidemic in the first stratum. The 'smaller' peak however is higher than in the first stratum at 0.01. The epidemic in the third stratum is not as pronounced as in the other strata. It starts at 0.005 then rises steadily to a peak of 0.015 ten years later, then reduces steadily to zero after the 35th year. The SAS code generating this curve is in Appendix 4.

5.2: Epidemic curve with half the population vaccinated with a defective vaccine type.

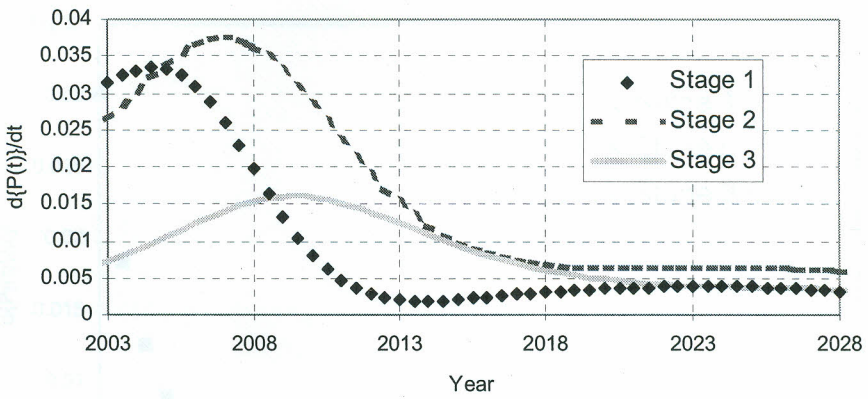

Fig. 5.2; the HIV epidemic is highest in stage 1 in 2003. This trend does not last for long as epidemic in stage 2 takes predorminance 2 years later. Epidemic in stage 3 is lowest but 10 years later Epidemic in 1 drops to be lower than Epidemic in stage 3.

As noted before whether one is vaccinated or not is not a vaccine variant. The curves are the same as the ones obtained in the previous graph. The SAS code generating these curves is in Appendix 4. with delta parameter value changed to 0.5. Meaning half of the population is vaccinated at any given time. The rest of vaccine variants; phi, omega and epsilon are set to zero.

5.3: Half the population vaccinated had immunological response induced

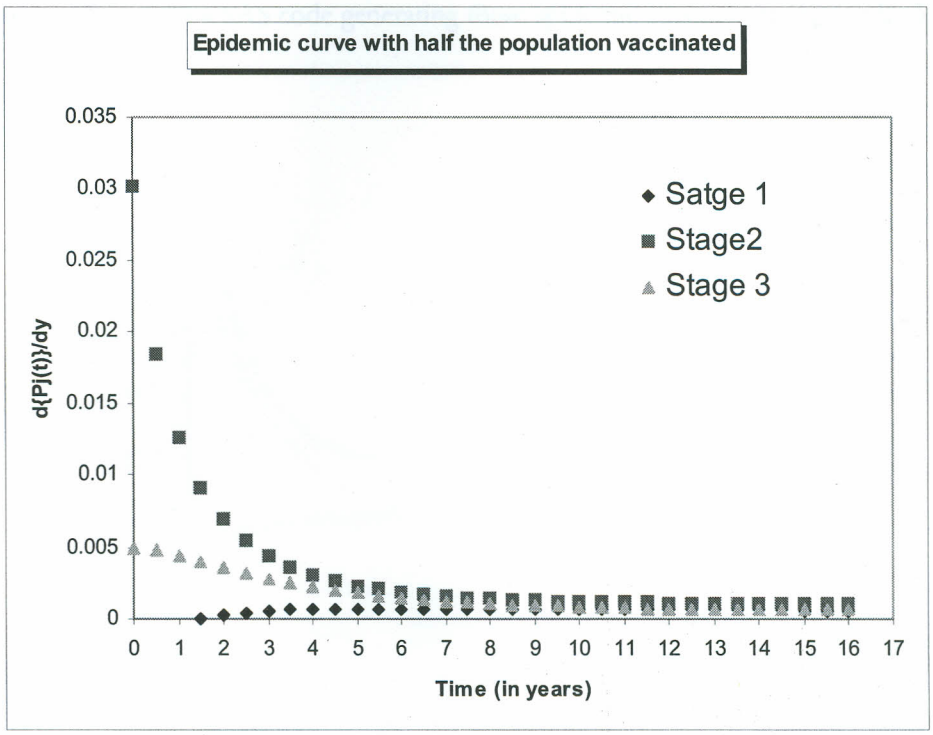

Fig. 5.3; for half of the population vaccinated, 0.1-0.9 of them had their effective immune response induced. We note that the epidemic is effectively reduced. This is a case of an effective vaccine in which the vaccine administered 'took' 0.1 – 0.9 of the population vaccinated, vaccine induced immunity waned also between 0.1 – 0.9 with time and the degree of protection is also varied between 0.1 – 0.9, meaning the 'successfully' vaccinated individuals can subsequently become infected, such that the vaccine did not offer full protection. The epidemic is

contained in the first stratum. The epidemic is not so pronounced in the third stage where it dies off only after the fifth year of vaccine introduction into the population. The second stage even though is high at the beginning later dies off at the 5th year. The SAS code generating these epidemic curves is in Appendix 5 .

5.4: HIV Epidemic curves with the population vaccinated with a good vaccine.

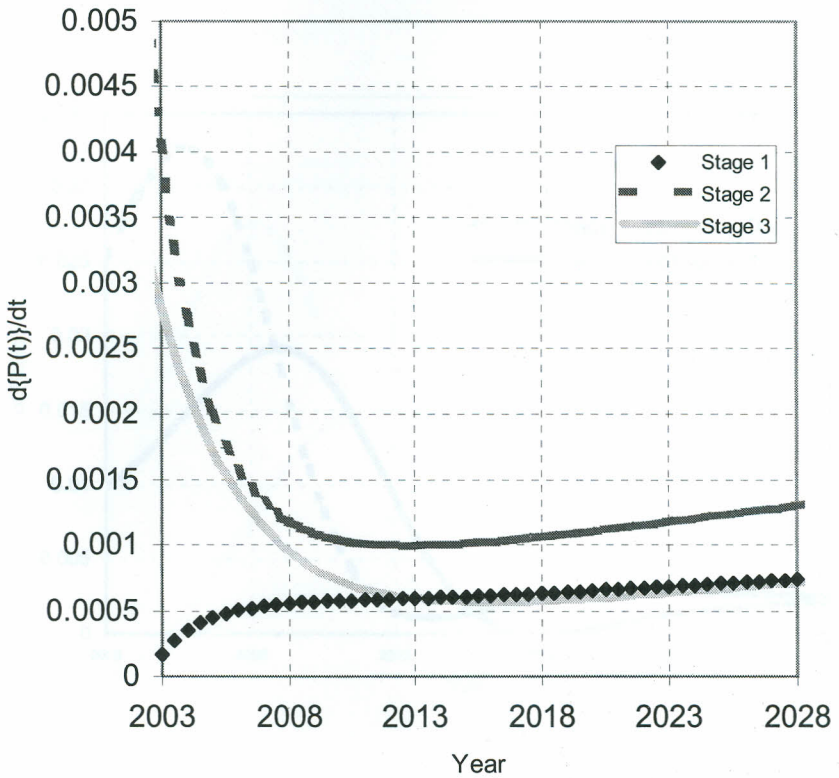

Fig. 5.4; with an effective vaccine the epidemic is very low. Even though the HIV infection might never be done away with as evidenced from the graph. Stage 2 still leads in the epidemic dynamic with the current rate if an effective vaccine was available in 2003 standing at 0.004. The infection rate in the first stage is the lowest, maintained below 0.0005.

5.5: HIV epidemic curves with ε as a vaccine parameter.

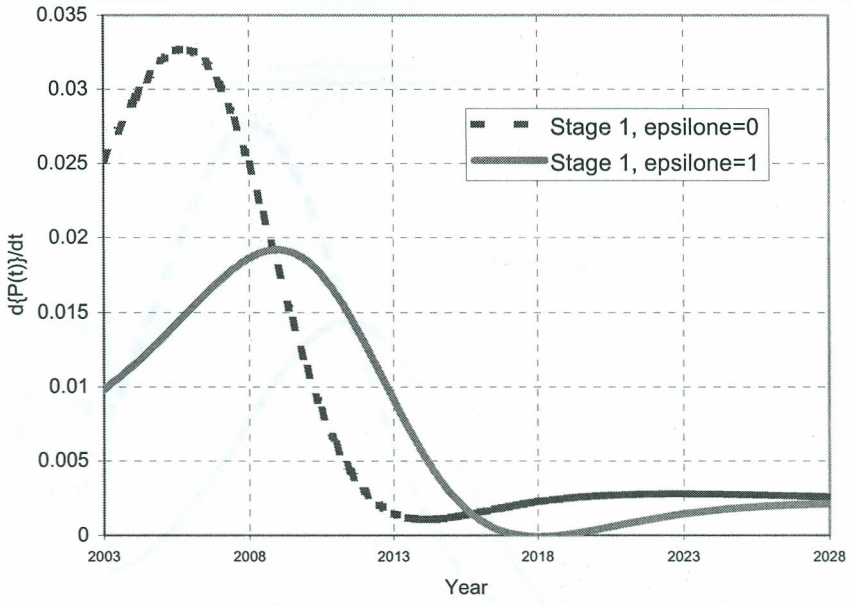

Fig. 5.5 ε is the proportion in whom the vaccine 'took'. The eidemics start at 0.025 and 0.010, rapidly rises to peaks of 0.033 and 0.019 in the years 2005 and 2010, and finally drop to near zero in the year 2013 and 2017 for ε=0 and ε=1 respectively.

5.6: HIV epidemic curves with ε as a vaccine parameter for stage 2 of HIV epidemic.

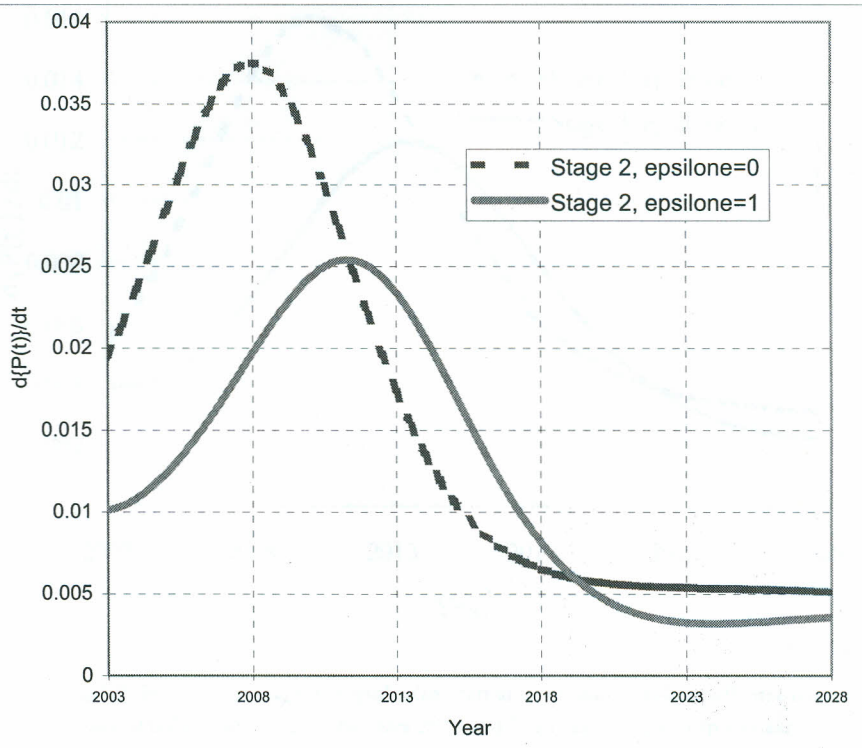

Fig. 5.6 For the 2nd stage, the eidemics start at 0.02 and 0.010, rapidly rises to peaks of 0.036 and 0.025 in the years 2008 and 2012, and finally drop to near zero in the year 2018 and 2022 for ε=0 and ε=1 respectively.

5.7: HIV epidemic curves with ε as a vaccine parameter for stage 3 of HIV epidemic.

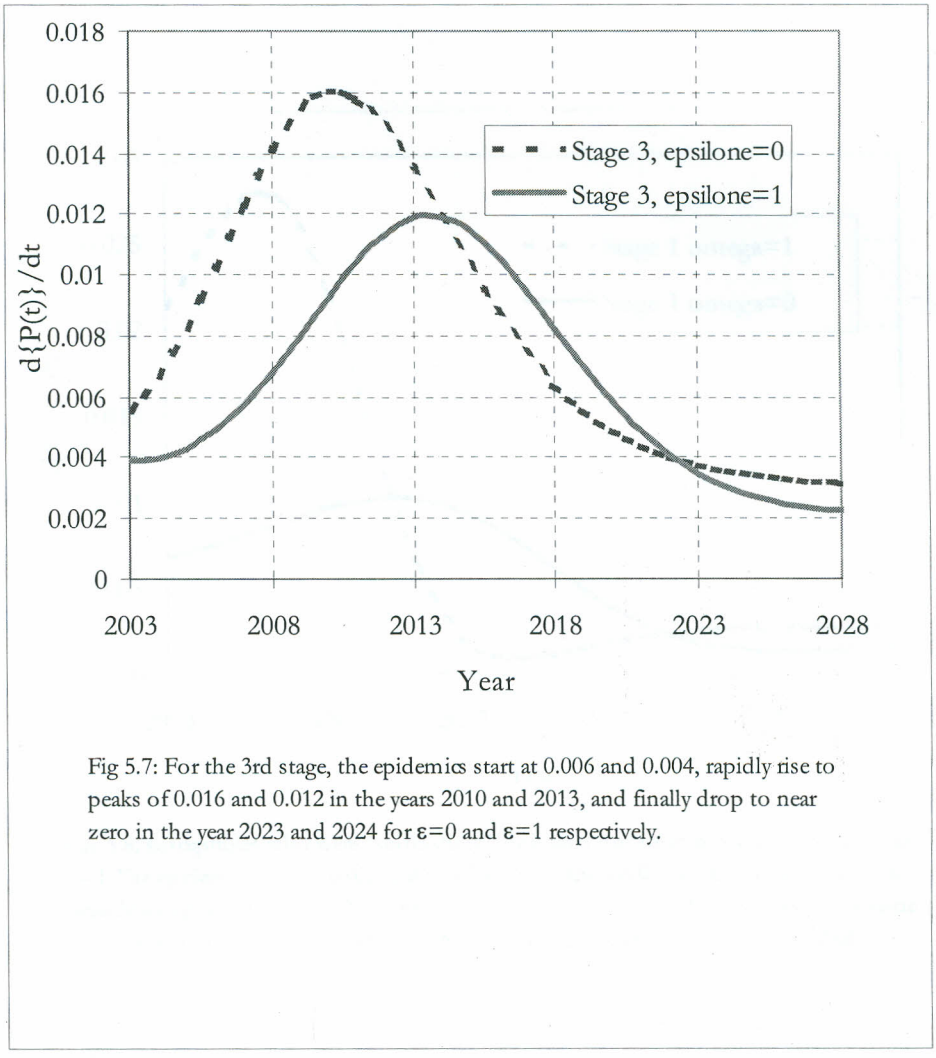

Fig 5.7: For the 3rd stage, the epidemics start at 0.006 and 0.004, rapidly rise to peaks of 0.016 and 0.012 in the years 2010 and 2013, and finally drop to near zero in the year 2023 and 2024 for ε=0 and ε=1 respectively.

5.8: HIV epidemic curves with ω as a vaccine parameter for stage 1 of HIV epidemic.

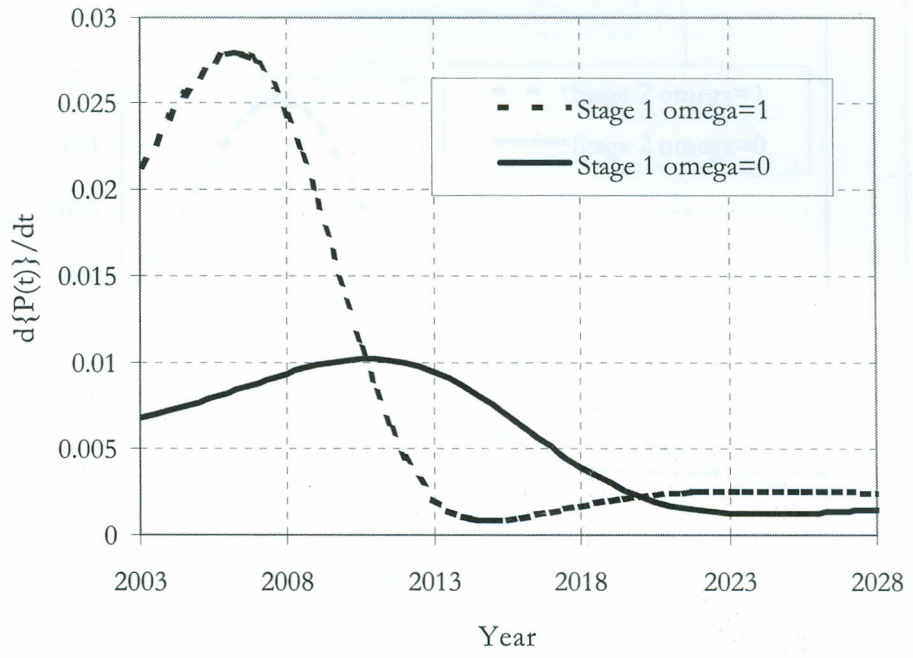

Fig. 5.8; susceptibles who were "successfully" vaccinated had their immune systems wane, ω=1.The epidemic starts at 0.022 and 0.007 for ω=1 and ω=0 respectively, curve ω=1 rises steadily to a peak of 0.027 in 2005 then drops to a near zero in 2015. For ω=0 in the same stage, a peak of 0.01 is reached in 2010 and drops down to a near zero in 2020.

5.9: HIV epidemic curves with ω as a vaccine parameter for stage 2 of HIV epidemic.

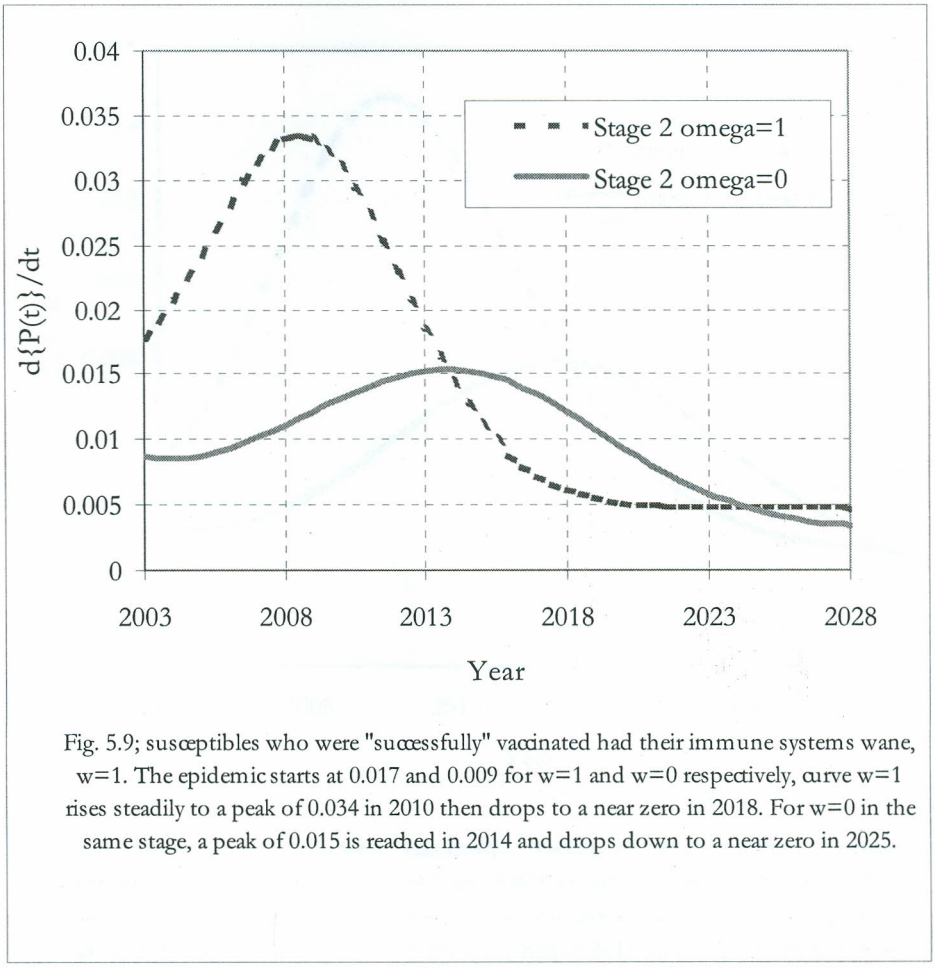

Fig. 5.9; susceptibles who were "successfully" vaccinated had their immune systems wane, w=1. The epidemic starts at 0.017 and 0.009 for w=1 and w=0 respectively, curve w=1 rises steadily to a peak of 0.034 in 2010 then drops to a near zero in 2018. For w=0 in the same stage, a peak of 0.015 is reached in 2014 and drops down to a near zero in 2025.

5.10: HIV epidemic curves with ω as a vaccine parameter for stage 3 of HIV epidemic.

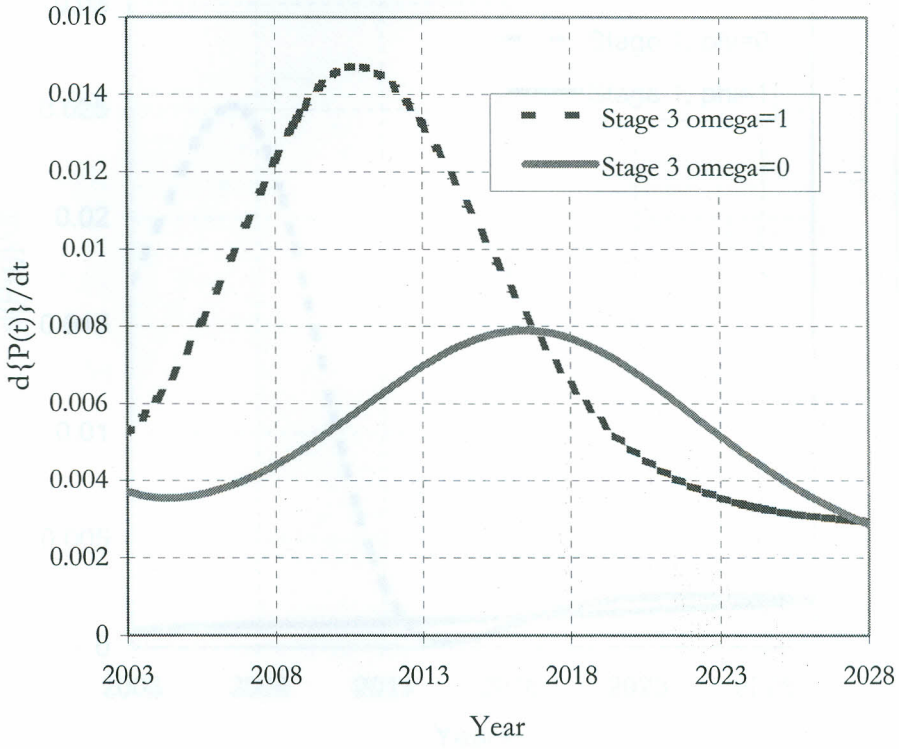

Fig. 5.10; susceptibles who were "successfully" vaccinated had their immune systems wane, ω=1.The epidemic starts at 0.005 and 0.004 for ω=1 and ω=0 respectively, curve ω=1 rises steadily to a peak of 0.014 in 2010 then drops to a near zero in 2023. For ω=0 in the same stage, a peak of 0.008 is reached in 2016 and drops down to a near zero in 2028.

5.11: HIV epidemic curves with ψ as a vaccine parameter for stage 1 of HIV epidemic.

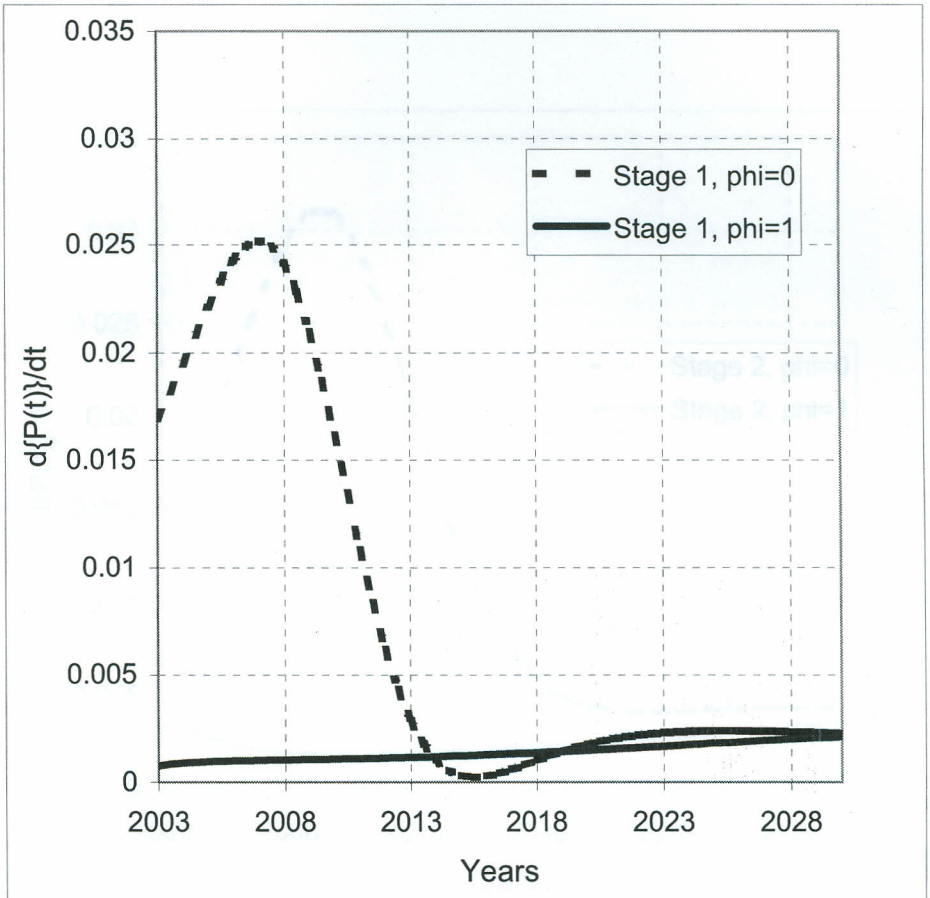

Fig. 5.11; ψ is the degree of protection offered by HIV vaccine to vaccinated individual. The epidemic starts at 0.017, rapidly rises to a peak of 0.025 in the year 2007 and finally drops to near zero in the year 2013 for ψ=0. But the epidemic is stopped immediately for ψ=1.

5.12: HIV epidemic curves with ψ as a vaccine parameter for stage 2 of HIV epidemic.

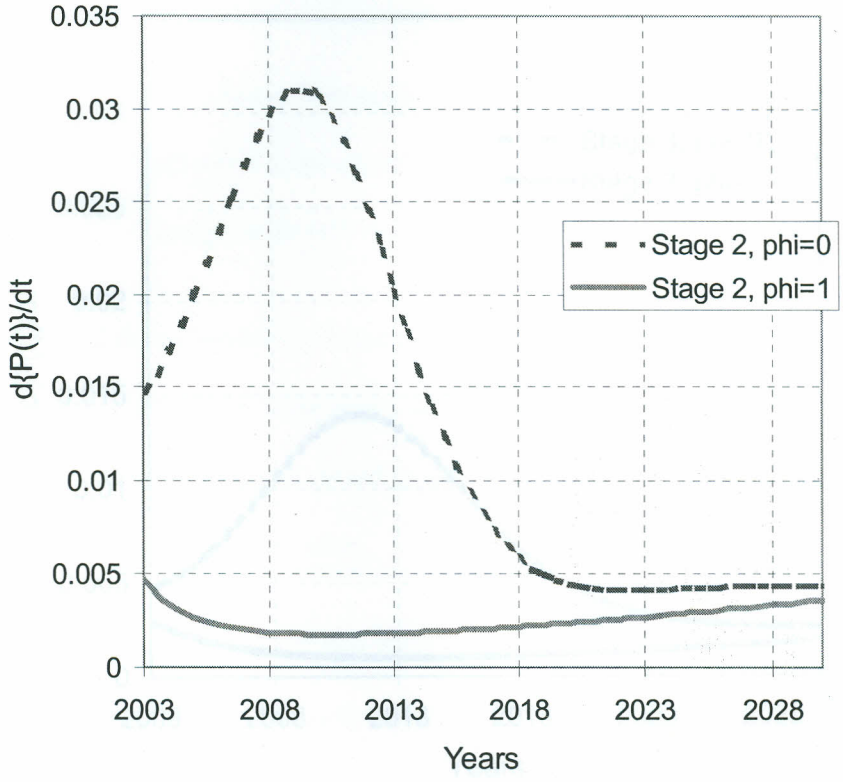

Fig. 5.12; for stage 2; the epidemic starts at 0.015, rapidly rises to a peak of 0.031 in the year 2010 and finally drops to near zero in the year 2018 for $\psi=0$. But the epidemic is stopped immediately for $\psi=1$.

5.13: HIV epidemic curves with ψ as a vaccine parameter for stage 3 of HIV epidemic.

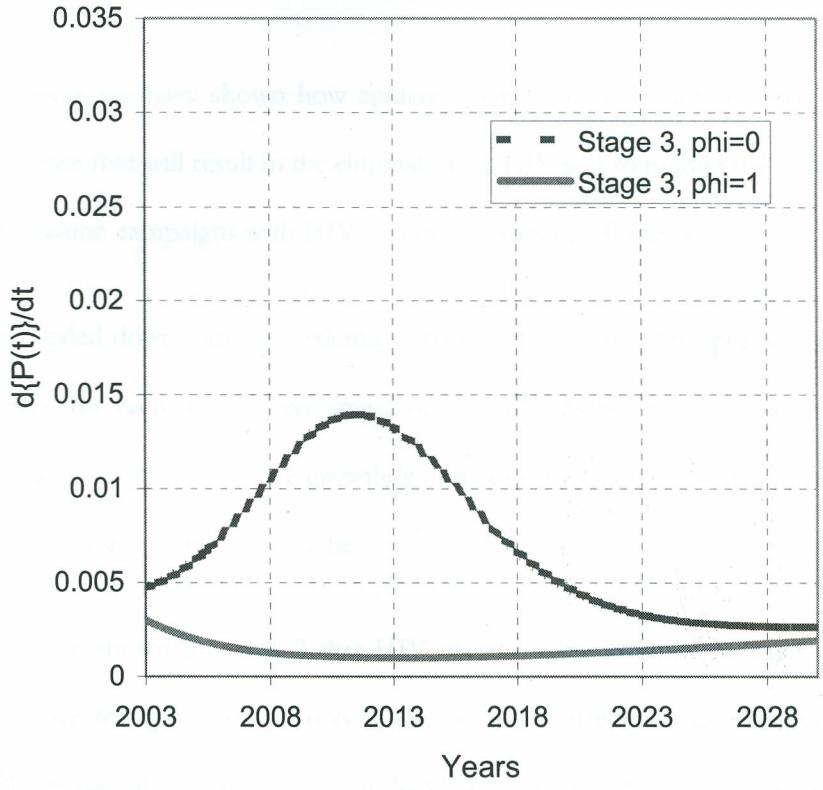

Fig. 5.13;for stage 3; the epidemic starts at 0.005, rapidly rises to a peak of 0.014 in the year 2011 and finally drops to near zero in the year 2023 for ψ=0. But the epidemic is stopped immediately for ψ=1.

5. 3. DISCUSSIONS

An effective vaccine is yet to be found, and in contrast to the successful immunization efforts against many other viral infections, there are inadequate immunological clues from human studies as to how such a vaccine might be constructed.

However, we have shown how epidemic control models can be used to design strategies that will result in the elimination of HIV and to predict the outcomes of vaccination campaigns with HIV vaccines of varying efficacies.

The scaled down vaccine epidemic curves, and thus the corresponding epidemic curves, for each of the three stages of the HIV disease progression are seen to indicate that the prevalence growth is non-zero for each stage for at least 5 years since the introduction of vaccine.

We have shown in curve 2 that HIV vaccine administration in itself does not influence the epidemic but only if the vaccine is effective. An effective vaccine will change the transmission probabilities for the inoculated individuals. It reduces the probability of infection given exposure, and as has been noted by *Blower et al*, lowering of probability of infection is not all. A highly effective vaccine should have a high 'take' ($\varepsilon=1$), a high 'degree' ($\psi=1$) of protection and a low rate of waning ($\omega=0$).

Once a highly effective vaccine is found the vaccine should be administered to all new recruits into the susceptible populations. In the meantime the people should be sensitized on the dynamics of HIV epidemic. If the number of sexual partners per year is reduced and people use condoms not only as a family planning method but also as a means of guarding against fresh HIV infection, then the per capita infection rate will reduce and the epidemic will not be as heavy.

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5. 4. CONCLUSION

From the graphs, it is clear that the epidemic shall have been contained if an effective vaccine was available by the year 2003 and by then, half of the Kenyan population was vaccinated.

However, in our model we have assumed a constant rate of vaccination, since we do not yet have data to that effect. More information would be needed for precise estimation of the vaccine parameters. The closest we can get currently to estimate the parameters is comparing the HIV epidemic in Kenya to that in Uganda, because in Uganda the research on HIV epidemic is in more advanced stage than in Kenya.

The Kenyan government can use this model as a yardstick to evaluate the best vaccine for the Kenyan population. It should keep blood samples of individuals vaccinated such that periodically, it contaminates the samples with the HIV virus

and evaluates the above-mentioned parameters. It should have in mind the following;

1. That an effective vaccine should be that, for everyone vaccinated, immune response is induced ($\varepsilon=1$)
2. Once immune response is induced, there should be no or little waning of the vaccine ($\omega=0$)
3. Finally, the vaccine should be effective over mutations of the virus and any other future strains that may arise ($\psi=1$)
4. In summary, an effective vaccine is that which 'take' (ε)=1, 'degree of protection' (ψ)=1 and 'waning' (ω)=0
5. In this paper we expect the HIV epidemic to end after the fifth year of vaccinating half of the population with an effective vaccine.

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5. 5. FINDINGS AND RECOMMENDATIONS

1. Data collection and management of incidences and factors affecting transmission of HIV must be taken very seriously
2. Sensitizing the public on HIV transmission dynamics creates awareness that impact positively on HIV transmission probability
3. Publications which help more research on HIV should not be patented but should readily be available over the internet

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