Models for the Transmission Dynamics of Gonorrhea in a Homosexually-Active Population

Sharon K. Lima
PURDUE UNIVERSITY
Mabel Torres
UNIVERSITY OF MIAMI

Abstract

The purpose of this project is to study two questions associated with the transmission dynamics of gonorrhea in a homosexually-active population. First, we examine the impact of a partially effective vaccine on gonorrhea dynamics. Second, we analyze the role of an antibiotic-driven mutation with respect to the survival and spread of resistant gonorrhea strains. Third, we study a model that combines the factors– vaccination and multiple strains of gonorrhea –considered in the first two models. We also explore the influence of heterogeneity and age-structure. Finally, we give a partial mathematical analysis of the system, including the computation of its basic reproduction number.

1 Introduction

Over the last three decades, the scientific community has realized that Neisseria gonorrhoeae seriously affects society. Because its symptoms were not initially considered life threatening, it was not until the early 1970s that gonorrhea was acknowledged as a significant sexually transmitted disease. Since that realization, there has been a decrease in the number of people infected by gonorrhea; however, the number of people presently infected is still high. Since 1975, the national average of the number of reported cases of gonorrhea has dropped from 475 out of 100,000 to 150 out of every 100,000 people (CDC, 1995).

The purpose of this research project is to study how a partially effective vaccine and an antibiotic-driven mutation of gonorrhea affect the transmission dynamics of the disease. The

three systems that we will analyze will consist of partial differential equation models. These models also incorporate age structure, in an active homosexual population, to determine how this will affect the disease dynamics of the infection rate of gonorrhea.

The first model introduces a temporary vaccine into a constant population to determine if there is a deterioration of infected individuals. We consider a temporary vaccine because of the rapid rate of mutation of gonorrhea strains. The second model describes the possibility of multiple strains of gonorrhea existing in a population. In this case, antibiotics can successfully treat the original strain of gonorrhea; however, due to an antibiotic-driven mutation, other strains resist the usual treatment. Therefore, we determine what conditions will permit these two strains to coexist in a population or if one will dominate the population. The final model is a fusion of the preceding models. This system incorporates the possibility of a temporary vaccine and treatment for the original strain of gonorrhea. We study how the system's long-term behavior changes given those factors. Analyses and suggestions for improvements of the models follows.

2 Gonorrhea

Gonorrhea and syphilis are the two venereal diseases most frequently reported across the U.S. Reducing the number of infected individuals is crucial, especially because epidemiological studies strongly indicate that both of these sexually transmitted diseases promote HIV transmission. Although syphilis has more severe consequences, gonorrhea is easier to contract, and due to a short incubation period, it spreads quickly.

Gonorrhea is so contagious that many people spread the disease before noticing their own symptoms. Once an individual becomes infected with gonorrhea, he or she develops the disease after a short incubation period of 1 - 2 days. Until the individual seeks treatment, the active period of infection persists. Moreover, an infected individual's recovery period is a constant rate and is independent of the length of time that the individual has had the disease. Gonorrhea is a non-seasonal disease; therefore, an individual has equal probability of becoming infected at any time of the year. This characteristic accounts for the coefficients of the model being time-independent.

Gonorrhea affects men and women differently. Approximately 90 percent of all infected men usually yield symptoms, a burning sensation when urinating and/or abdominal pains, that cause them to seek medical treatment immediately. It is the remaining 10 percent, who have minimal or no symptoms, that infect the susceptible population. Unlike men, most

women do not realize they carry the infection because their symptoms are transient. Between 50 to 70 percent of the infected women do not develop visible symptoms until the disease has become more severe (Hethcote & Yorke 1984). Like the men with minimal symptoms, this large percentage of women infects most of the susceptible population.

If gonorrhea goes undetected, complications for both sexes can include arthritis, sterility, and heart problems. Women can also have more severe complications that lead to Pelvic Inflammatory Disease (PID) and, although rare, even death (Hethcote & Yorke 1984).

Due to the dynamics of gonorrhea, we model it with SIS equations (Susceptible $\rightarrow$ Infected $\rightarrow$ Susceptible). This system shows that any individual, who is sexually active, is susceptible to gonorrhea. Since there is no permanent immunity or vaccination for gonorrhea, if an individual becomes infected, and seeks treatment, then he or she is once again susceptible.

3 Model 1: Vaccination

In this first model, we consider a basic system that accounts for a vaccination that offers temporary protection in a constant population. We study how this vaccine affects the percentage of the population that can become infected at time t. Hence, we examine how it will affect the dynamics of the infected population.

To determine how effective this vaccine will be, we use the following system of ordinary differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= (1-p)\rho - \mu S(t) - \frac{\beta S(t) I(t)}{N(t)} + \gamma I(t) + \delta V(t) \\
\frac{dI}{dt} &= \frac{\beta S(t) I(t)}{N(t)} - (\gamma + \mu) I(t) \\
\frac{dV}{dt} &= -(\delta + \mu) V(t) + p\rho
\end{aligned}$$

where $\beta = \lambda c$, with c denoting the average number of partners per unit of time and λ the average number of effective contacts per partner.

The variables in the equations denote the following:

μ = mortality rate

β = transmission rate

γ = recovery rate of the infective population

δ = recovery rate of the vaccinated population

p = proportion of the susceptible births that has been successfully vaccinated

ρ = birth rate.

3.1 Asymptotically autonomous system

Although we have a variable total population, it rapidly approaches a steady state. We can use this fact to reduce the system of equations. Defining the total population as $N = S + I + V$, we can write the following:

$$\frac{dN}{dt} = \rho - \mu N,$$

which has the solution,

$$N(t) = N(0)e^{-\mu t} + \frac{\rho}{\mu}(1 - e^{-\mu t}).$$

Therefore, when take the limit as $t \longrightarrow \infty$, we have an asymptotically constant population $N^* = \frac{\rho}{\mu}$. Similarly the equation for the vaccinated

$$\frac{dV}{dt} = -(\delta + \mu)V(t) + p\rho$$

has the solution

$$V(t) = V(0)e^{-(\delta+\mu)t} + \frac{p\rho}{(\delta + \mu)}(1 - e^{-(\delta+\mu)t}),$$

and as $t \longrightarrow \infty$,

$$V(t) \longrightarrow V^* = \frac{p\rho}{\delta + \mu}.$$

Using the fact that $V(t) \longrightarrow \frac{p\rho}{\delta+\mu}$, and $N \longrightarrow \frac{\rho}{\mu}$, we can reduce system of equations to obtain the equivalent autonomous system

$$\frac{dS}{dt} = (1-p)\rho - \frac{\beta\mu}{\rho}SI - \mu S + \gamma I + p\rho\frac{\delta}{\delta+\mu} \quad (1)$$

$$\frac{dI}{dt} = \frac{\beta\mu}{\rho}SI - (\mu+\gamma)I. \quad (2)$$

3.2 Basic Reproductive Number, R_0

Next, we want to calculate the basic reproductive number for this two-dimensional model. R_0 gives the expected number of secondary infections to primary infections when the disease is introduced into a population of susceptibles. The disease free equilibrium for this system is

$$\begin{aligned} S^* &= \left(1 - \frac{p\mu}{\delta + \mu}\right)\frac{\rho}{\mu}, \\ I^* &= 0. \end{aligned}$$

If we start from this disease free state, the infection will grow when

$$\frac{\mu}{\rho}\beta S^* - (\mu + \gamma) > 0$$

and decline when

$$\frac{\mu}{\rho}\beta S^* - (\mu + \gamma) < 0.$$

Thus

$$R_0 = \frac{\beta}{\mu + \gamma}\left(1 - \frac{p\mu}{\delta + \mu}\right).$$

3.3 Equilibria points and Stability

As noted above the disease free equilibrium is

$$\begin{aligned} S^* &= \left(1 - \frac{p\mu}{\delta + \mu}\right)\frac{\rho}{\mu}, \\ I^* &= 0. \end{aligned}$$

For the endemic state we assume $I^* > 0$ and solve the system of differential equations set to zero.

$$\begin{aligned} S^* &= \left(\frac{\gamma + \mu}{\beta}\right)\frac{\rho}{\mu}, \\ I^* &= \left(1 - \frac{p\mu}{\delta + \mu} - \frac{\gamma + \mu}{\beta}\right)\frac{\rho}{\mu}. \end{aligned}$$

Expressed in terms of R_0 and N^* we have

$$\begin{aligned} S^* &= \frac{1}{R_0}\left(1-\frac{p\mu}{\delta+\mu}\right)N^*, \\ I^* &= \left(1-\frac{1}{R_0}\right)\left(1-\frac{p\mu}{\delta+\mu}\right)N^*. \end{aligned}$$

To study the stability of the infection-free state we must calculate the Jacobian matrix for the system, and then we evaluate it at the infection-free point. The Jacobian is given by

$$J = \begin{pmatrix} -\mu-\beta\frac{I^*}{N^*} & \gamma-\beta\frac{S^*}{N^*} \\ \beta\frac{I^*}{N^*} & -(\gamma+\mu)+\beta\frac{S^*}{N^*} \end{pmatrix}.$$

If we evaluate it at

$$E_0 = \left(\left(1-\frac{p\mu}{\delta+\mu}\right)N^*, 0\right),$$

we get

$$J_0 = \begin{pmatrix} -\mu & \gamma-\beta\left(1-\frac{p\mu}{\delta+\mu}\right) \\ 0 & -(\gamma+\mu)+\beta\left(1-\frac{p\mu}{\delta+\mu}\right) \end{pmatrix},$$

or, noting that $\beta\left(1-\frac{p\mu}{\delta+\mu}\right) = R_0(\gamma+\mu)$, we get

$$J_0 = \begin{pmatrix} -\mu & \gamma-R_0(\gamma+\mu) \\ 0 & (R_0-1)(\gamma+\mu) \end{pmatrix}.$$

To check for stability, we must have that the $\det J_0 > 0$ and $\mathrm{tr}J_0 < 0$. For $\det J_0 > 0$ we must have $R_0 < 1$. And for the $\mathrm{tr}J_0 < 0$, we must have $R_0 < 1 + \frac{\mu}{\gamma+\mu}$. Hence, if the first inequality holds then so most the second, and the infection-free point is locally stable whenever $R_0 < 1$. Next, we consider the endemic equilibrium; therefore, evaluating the Jacobian at the endemic point,

$$E_1 = \left(\frac{1}{R_0}\left(1-\frac{p\mu}{\delta+\mu}\right)N^*, \left(1-\frac{1}{R_0}\right)\left(1-\frac{p\mu}{\delta+\mu}\right)N^*\right),$$

we get

$$J_1 = \begin{pmatrix} \gamma-R_0(\gamma+\mu) & -\mu \\ (R_0-1)(\gamma+\mu) & 0 \end{pmatrix}.$$

For $\det J_1 > 0$, we must have $R_0 > 1$, and for $\mathrm{tr}J_0 < 0$ we must have $\frac{\gamma}{\gamma+\mu} < R_0$ which is always true if $R_0 > 1$. Therefore, the endemic state is stable whenever it exists.

3.4 Vaccination with Age Structure

The following model incorporates age structure into our model of the transmission of gonorrhea in a homosexually active population.

$$\begin{aligned}
\frac{\partial s}{\partial a}+\frac{\partial s}{\partial t} &= -\mu(a)s(a,t)-\frac{\beta(a)s(a,t)I(t)}{N(t)}+\gamma(a)i(a,t)+\delta(a)v(a,t),\\
\frac{\partial i}{\partial a}+\frac{\partial i}{\partial t} &= \frac{\beta(a)s(a,t)I(t)}{N(t)}-(\gamma(a)+\mu(a))i(a,t),\\
\frac{\partial v}{\partial a}+\frac{\partial v}{\partial t} &= -(\delta(a)+\mu(a))v(a,t).
\end{aligned}$$

where

$$\begin{aligned}
I(t) &= \int_0^\infty i(a,t)da,\\
V(t) &= \int_0^\infty v(a,t)da \text{ and}\\
N(t) &= \int_0^\infty n(a,t)da.
\end{aligned}$$

The initial and boundary conditions for this system are:

$$\begin{aligned}
s(0,t) &= (1-p)\rho, & s(a,0) &= s_0(a),\\
i(0,t) &= 0, & i(a,t) &= i_0(a),\\
v(0,t) &= p\rho, & v(a,t) &= 0.
\end{aligned}$$

The variables in the equations denote the following:

$\mu(a)$ = mortality rate dependent on age class,

$\beta(a)$ = age-dependent transmission rate,

$\gamma(a)$ = age-dependent recovery rate of the infective population,

$\delta(a)$ = age-dependent loss of immunity rate of the vaccinated population,

p = proportion of the susceptible births that have been sucessfully vaccinated,

ρ = birth rate.

Unlike our system of ordinary differential equations, in this system the basic reproductive number, R_0, is no longer based solely on time but also on age. Therefore, to calculate the basic reproductive number for this partial differential equation model, we use the methodology called the next generation operator. After we calculate R_0 with age structure we will then check the special case when all parameters are constant, and we should obtain the same basic reproductive number that we calculated for the ordinary differential equations.

First we assume that all parameters are age dependent. We will assume separable functions in order to obtain tractable equations in the form

$$A(\tau, a, a+\tau) = g(\tau, a+\tau) f(a) \phi(a).$$

The survival probability of an infective of age a to $a+\tau$ is

$$g(\tau, a+\tau) = e^{-\int_a^{a+\tau} (\mu(\theta)+\gamma(\theta)) d\theta}.$$

The probability of successful transmission and contact rate is $f(a) = \beta(a)$.

Next, we calculate the demographic steady state. The demographic steady state occurs when there is an infection free state, and this steady state is independent of time. The differential equations that we must solve are

$$\begin{aligned} \frac{ds^*}{da} &= \mu(a) s^*(a) + \delta(a) v^*(a) \\ \frac{dv^*}{da} &= -(\delta(a) + \mu(a)) v^*(a). \end{aligned}$$

If

$$\phi^* = s^* + v^*,$$

then

$$\frac{d\phi^*}{da} = -\mu(a) \phi^*(a)$$

or

$$\phi^*(a) = \rho e^{-\int_0^a \mu(\theta) d\theta}$$

and hence

$$s^*(a) = (1-p) \rho e^{-\int_0^a (\mu(\theta)+\delta(a)) d\theta} + \int_0^a \delta(l) \rho e^{-\int_0^a \mu(\theta) d\theta - \int_l^a \delta(\theta) d\theta} dl.$$

Thus

$$\begin{aligned} R_0 &= \int_0^\infty \int_0^\infty \phi(a) f(a) g(\tau, a+\tau) d\tau da \\ &= \int_0^\infty \int_0^\infty s^*(a) \frac{\beta(a)}{N^*} e^{-\int_a^{a+\tau} (\mu(\theta)+\gamma(\theta)) d\theta} d\tau da. \end{aligned}$$

To see if this R_0 is reasonable, let all the parameters in the double integral be constant. We see that $R_0 = \frac{\beta}{\mu+\gamma}\left(1 - \frac{\mu p}{\mu+\delta}\right)$, which agrees with the earlier analysis with the ordinary differential equations.

Now that we have calculated the basic reproductive number with age structure, we proceed to determine stability. This is established by analyzing the characteristic equation. The incidence equation is:

$$i(t,a) = \int_0^\infty \int_0^\infty \rho s^*(a)\beta(a)e^{-\int_\alpha^{a+\tau}(\mu(\theta)+\gamma(\theta))d\theta}\frac{i(t,a+\tau)}{N^*}d\tau d\alpha \tag{3}$$

where $i(t,a)$ is defined as the distribution of infection at time t with respect to age a. Assume $i(t,a) = \xi(a)e^{\lambda t}$ and substitute into (3):

$$\xi(a)e^{\lambda t} = \int_0^\infty \int_0^\infty s^*(a)\beta(a)e^{-\int_\alpha^{a+\tau}(\mu(\theta)+\gamma(\theta))d\theta}\frac{\xi(\alpha)}{N^*}e^{\lambda(t-\tau)}d\tau d\alpha.$$

Dividing through by $e^{\lambda t}$

$$\xi(a) = \int_0^\infty \int_0^\infty s^*(a)\beta(a)e^{-\int_\alpha^{a+\tau}(\mu(\theta)+\gamma(\theta))d\theta}\frac{\xi(\alpha)}{N^*}e^{\lambda\tau}d\tau d\alpha.$$

Multiply by $e^{-\int_\alpha^{a+\tau}(\mu(\theta)+\gamma(\theta))d\theta}e^{-\lambda\tau}$ and integrate over a and τ. After simplifying, the resulting characteristic equation is:

$$F(\lambda) = \int_0^\infty \int_0^\infty s^*(a)\beta(a)e^{-\int_a^{a+\tau}(\mu(\theta)+\gamma(\theta))d\theta}e^{-\lambda\tau}d\tau da = 1$$

where $F(0) = R_0$. Notice that $\frac{dF}{d\lambda} < 0$. Hence, $F(0) < 1$ implies stability, and the infection-free state distribution is unstable provided that $F(0) > 1$. We suspect that when $F(0) > 1$ there exists a unique endemic age-distribution.

4 Model 2: Multiple Strains

In this next model, we consider a basic system that incorporates a mutated strain of the original gonorrhea disease. We explore cases of competition and coexistence with a constant population.

To determine how productive studying the influence of multiple strains of a disease in a population will be, we use the following system of ordinary differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= \rho - \mu S(t) - \frac{c\lambda_1 S(t) I_1(t)}{N(t)} - \frac{c\lambda_2 S(t) I_2(t)}{N(t)} + (1-p)\gamma_1 I_1(t) + \gamma_2 I_2(t) \\
\frac{dI_1}{dt} &= \frac{c\lambda_1 S(t) I_1(t)}{N(t)} - (\mu + \gamma_1) I_1(t) \\
\frac{dI_2}{dt} &= \frac{c\lambda_2 S(t) I_2(t)}{N(t)} - (\mu + \gamma_2) I_2(t) + p\gamma_1 I_1(t)
\end{aligned}$$

The initial conditions for this system are:

$$\begin{aligned}
S(0) &= S_0, \\
I_1(t) &= I_{10} > 0, \\
I_2(t) &= I_{20} > 0.
\end{aligned}$$

The variables in the equations denote the following:

μ = mortality rate;

c = probability of successful contact;

λ_i = transmission rate of the ith-strain of the disease;

γ = recovery rate of the infective population;

p = proportion of the original infected population that becomes infected by the mutated strain;

ρ = birth rate.

4.1 Asymptotically autonomous model

To simplify the dynamics of the population we make the following observations; let $N = S + I_1 + I_2$. This results in $\frac{dN}{dt} = \rho - \mu N$, and $N \to N^* = \rho/\mu$. Therefore, as $t \to \infty$, $S \to N^* - I_1 - I_2$

Now, we can substitute this value into our original equations and reduce the system to a two-dimensional equivalent model.

$$\frac{dI_1}{dt} = \frac{c\mu\lambda_1}{\rho}\left(\frac{\rho}{\mu} - I_1 - I_2\right) I_1 - (\mu+\gamma_1)I_1, \tag{4}$$

$$\frac{dI_2}{dt} = \frac{c\mu\lambda_2}{\rho}\left(\frac{\rho}{\mu} - I_1 - I_2\right) I_2 - (\mu+\gamma_2)I_2 + p\gamma_1 I_1. \tag{5}$$

4.2 Basic Reproductive Number

To determine the basic reproductive number, we let our susceptible population be constant while increasing the infection rates. First, we linearize our equations (4-5):

$$\begin{aligned} I_1 &= \frac{c\lambda_1 S}{(\mu+\gamma_1)N} I_1 \\ I_2 &= \frac{c\lambda_2 S}{(\mu+\gamma_2)N} I_2 + \frac{p\gamma_1}{\mu+\gamma_2} I_1 \end{aligned}$$

Since we are working with a steady state, we can set $F\begin{pmatrix} I_1 \\ I_2 \end{pmatrix} = \begin{pmatrix} I_1 \\ I_2 \end{pmatrix}$ to solve for the values that fulfill this property. We evaluate the Jacobian matrix at this state x^* and the result is:

$$J(x^*) = \begin{pmatrix} \frac{c\lambda_1 S}{(\mu+\gamma_1)N} & 0 \\ \frac{p\gamma_1}{\mu+\gamma_2} & \frac{c\lambda_2 S}{(\mu+\gamma_2)N} \end{pmatrix}$$

The eigenvalues of this matrix determine the two possible reproductive numbers for the system, $R_1 = \frac{c\lambda_1}{\mu+\gamma_1}$ and $R_2 = \frac{c\lambda_2}{\mu+\gamma_2}$, depending on which infection is presently larger in the population. Therefore, $R_0 = \max\{R_1, R_2\}$ which may alternate throughout the progression of the system.

4.3.1 Equilibria points and Stability

Again, we want to determine the equilibrium values for the system. However, this model is slightly more complex than the previous one and we ultimately have three important points. Using the same method as in the first model, we arrive at the following three points:

$E_0 = (0,0)$,

$$E_1 = \left(0, -\frac{\rho(\mu+\gamma_2-c\lambda_2)}{c\mu\lambda_2}\right),$$
$$E_2 = \left(\frac{\rho(c\lambda_1-\mu-\gamma_1)((\mu+\gamma_2)\lambda_1-(\mu+\gamma_1)\lambda_2)}{c\mu\lambda_1((\mu-p\gamma_1+\gamma_2)\lambda_1-(\mu+\gamma_1)\lambda_2)}, \frac{-p\rho\gamma_1(c\lambda_1-\mu-\gamma_1)}{c\mu((\mu-p\gamma_1+\gamma_2)\lambda_1-(\mu+\gamma_1)\lambda_2)}\right).$$

Three steady states can be accounted for, an infection-free state; a state where the original strain of the disease goes extinct; and a state where both strains coexist in the population. It is important that threshold conditions are found for these states to be positive. Otherwise, the equilibria are biologically irrelevant.

4.3.2 Threshold Conditions:

E_1 is biologically relevant, that is, is positive if

$$\left(\frac{c\lambda_2}{\mu+\gamma_2}\right) > 1.$$

E_2 is positive if

$$\frac{c\lambda_1}{\mu+\gamma_1} > 1 \quad \text{and} \quad \frac{\mu+p\gamma_1+\gamma_2}{\mu+\gamma_1}\cdot\frac{\lambda_1}{\lambda_2} > 1$$

These conditions are used to evaluate the Jacobian at these equilibria. J at E_0 it is equal to

$$J_0 = \begin{pmatrix} c\lambda_1-\mu-\gamma_1 & 0 \\ \gamma_1 p & c\lambda_2-\mu-\gamma_2 \end{pmatrix}.$$

E_0 is stable if and only if $\mathrm{tr}J_0 < 0$ and $\det J_0 >$ if and only if $R_0 < 1$. E_0 is unstable if and only if $R_0 > 1$.

The stability of E_1 is determined by the Jacobian J_1 at E_1, where

$$J_1 = \begin{pmatrix} -\gamma_1-\mu+\frac{\lambda_1}{\lambda_2}(\mu+\gamma_2) & 0 \\ \mu+\gamma_2-c\lambda_2-\gamma_1 p & \mu+\gamma_2-c\lambda_2 \end{pmatrix}.$$

Hence E_1 is stable if and only if $\det J_1 > 0$ and $\mathrm{tr}J_1 < 0$, which if only if

$$\frac{c\lambda_1}{\mu+\gamma_1} > \frac{c\lambda_2}{\mu+\gamma_2} > 1$$

as E_1 is feasible if and only if $\frac{c\lambda_2}{\mu+\gamma_2} > 1$.

The stability analysis of E_2 is cumbersome and we omit it albeit simulations strongly suggest that the conditions

$$\frac{c\lambda_1}{\mu+\gamma_1} > 1 \qquad \text{and} \frac{\lambda_2(\mu+\gamma_1}{\lambda_1(\mu+p\gamma_1+\gamma_2)} < 1$$

not only guarantee the existance of E_2 but also its local stability.

5 Conclusion

In studying these three models, we have arrived at the following conclusions. In our first model the temporary vaccine had an initial positive result. However, further research is necessary to determine if a long-term effect is present in the behavior of the vaccine. This study may be carried out via the incorporation of age-structure. Hence if this vaccine provides temporary immunity, further research would determine the age at which this vaccine would produce the most significant decrease in the infected class.

Our model with two strains clearly show the role of mutations due to antibiotic resistance. Ways of reducing the role of resistant gonorrhea strains need to be further studied.

Acknowledgements

This study was supported by the following institutions and grants: National Science Foundation (NSF Grant DMS-9600027); National Security Agency (NSA Grants MDA 904-96-1-0032 and MDA 904-97-1-0074); Presidential Faculty Fellowship Award (NSF Grant DEB 925370) and Presidential Mentoring Award (NSF Grant HRD 9724850) to Carlos Castillo-Chavez; and the Office of the Provost of Cornell University.

We would like to thank Carlos Castillo-Chavez, Jorge Velasco-Hernández, Song Baojun, Steve Cooper and Carlos William Castillo-Garsow for their moral support, suggestions and assistance in this project. Thanks to Pam Archin for proof-reading the project manuscript and providing a lot of insightful information. The authors are solely responsible for the views and opinions expressed in this project.

References

1. Castillo-Chavez, Carlos. 1989. Some applications of structured models in population dynamics. *Applied Mathematical Ecology*

2. Castillo-Chavez, C., H. W. Hethcote, V. Andreasen, S. Levin, and W. M. Liu. 1989. Epidemiological models with age-strucuture, proportionate mixing and cross immuniuty. *Journal of Math. Biology*

3. Heesterbeek, Hans. R_0. Thesis

4. Hethcote, H. *Three basic epidemiological models*

5. Hethcote, H. and James A. Yorke. 1984. Gonorrhea Transmission Dynamics and Control. *Lecture Notes in Biomathematics* **56** NY:Springer-Verlag.

6. Hoppensteadt, Frank. Mathematical theories of populations: demographics, genetics, and epidemics. *SIAM*

7. NY Legislative Comission on Expenditure Review. 1977. *Venereal Diseases Control* Program Audit 6.1.77.

8. Survaillence, 1995. U.S. Department of Health and Human Services, Public Health Service. Atlanta: Center for Disease Control and Prevention.