# AN SIS MODEL OF STREPTOCOCCAL DISEASE WITH A CLASS OF BETA-HEMOLYTIC CARRIERS

**BU-1524-M** **August 1999**

MTBI

**Kevin Doura**
**Julio D. Meléndez-Morales**
**Gigi G. Meyer**
**Luis E. Pérez**

**Keywords**: none provided.

**Abstract**:
We analyzed the dynamics of an epidemic in a population infected with *Streptococcal pyogenes* (*S. pyogenes*), the causative agent in strep throat, with a *Susceptible--Infected--Susceptible (S-I-S)* model that includes an extra class of infectious carriers. Our model represents a three dimensional nonlinear differential equation system, which describes the spread of the disease in a population with three epidemiological classes: susceptible *(S)*, infected *(I)* and beta--hemolytic carriers *(C)*. We focus on the impact that the classes *(I)* and *(C)* have on *(S)*, and the rate at which groups move in and out of the infectious state. Lastly, we study the long term dynamics of the disease in the population.

BU-1524-M

# An S–I–S Model of Streptococcal Disease with a Class of Beta–Hemolytic Carriers

Kevin Doura
HOWARD UNIVERSITY

Julio D. Meléndez-Morales
UNIVERSITY OF PUERTO RICO, HUMACAO

Gigi G. Meyer
VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY

Luis E. Pérez
UNIVERSITY OF CALIFORNIA, IRVINE

August 10, 1999

**Abstract**

We analyzed the dynamics of an epidemic in a population infected with *Streptococcal pyogenes (S. pyogenes)*, the causative agent in strep throat, with a *Susceptible–Infected–Susceptible (S–I–S)* model that includes an extra class of infectious carriers. Our model represents a three dimensional nonlinear differential equation system, which describes the spread of the disease in a population with three epidemiological classes: susceptible *(S)*, infected *(I)* and beta–hemolytic carriers *(C)*. We focus on the impact that the classes $I$ and $C$ have on $S$, and the rate at which groups move in and out of the infectious state. Lastly, we study the long–term dynamics of the disease in the population.

# Outline

1. **Introduction**
2. **The Model**
   (a) Discussion of the Parameters
   (b) Estimation of the Parameters
   (c) Introduction to the Model
   (d) Determining $R_0$
      i. First Model
      ii. Second Model
3. **Biological Analysis**
   (a) First Model
   (b) Second Model
4. **Simulations**
5. **Conclusions**

# 1 Introduction

Humans are a natural reservoir for the beta-hemolytic group $A$ Streptococcus; transmission from person to person is frequently associated with an asymptomatic carrier who is colonized in the nasopharynx [10]. An asymptomatic carrier is one who carries the infection but does not develop the symptoms of the infection.*Streptococcaceae* is a family made up of gram positive bacteria: round cocci that usually grow in chains of various lengths. Consisting of $A, B, C, D, \ldots, V$ groups, of these $A, B$ and $D$ are of greatest pathogenic significance. Group $A$ streptococcus is classified as the most pathogenic to man; the species *S. pyogenes* causes a variety of infections in humans including pharyngitis, tonsilitis, sinuitis, impetigo, rheumatic fever, and meningitis [6,10,12]. In 1895, Marmorek observed that some of the streptococci were hemolytic, and Schottmuller in 1903 described pathogenic and non-pathogenic streptococci that were not hemolytic [6]. A hemolytic streptococci damages the cell; the process is most easily seen in red blood cells in which the hemolytic process liberates hemoglobin from the red blood cell. These were divided into three groups depending on the amount of hemolysis produced on blood agar. It is questionable how one might carry such damaging cells naturally without any symptoms.

- Alpha Streptococci produce a zone of greenish discoloration around the colony that is 1-2 mm wide and shows partial hemolysis;
- Beta Streptococci produced a completely hemolyzed, clear colorless zone 2-4 mm in diameter;
- Gamma types produce no change in the medium surrounding the colony [6,10].

Since the beginning of the use of antibiotics, strep infections have been easily controlled. Prior to antibiotics being available, no treatment for strep infections prevailed; more serious forms of the infection often occured. By the 1920's hemolytic Streptococcus had been established as the causative agent of several forms of severe tonsilitis. Prior to this, much of the research focused on the tonsils area as "the focus of infection"; this led to widespread tonsillectomy to remove the source of infection. Gradually, though, it was found that this did not protect against subsequent streptococcal infections: colonization and infection can occur throughout the nasopharynx [6].

Therefore we are led to believe that transmission from person to person occurs from asymptomatic infected individuals and symptomatic individuals. Let the symptomatic group represent an "infected" group; a large percentage of individuals will receive treatment by antibiotics for their condition and will no longer be infectious. If we let the asymptomatic individuals represent a carrier group, healthy individuals possibly ignorant of their infection, this group could have a significant impact on an epidemic. This leads us to ask an interesting question, such as "what impact does a beta-hemolytic carrier group have on a susceptible population? What initial amount of carriers must be present in the population to have any significant effect?"

Streptococcus can be transmitted through direct contact, such as touching a contaminated hand to the mouth, or inoculation by breathing in infected air droplets. Crowding is a definite factor in the spread of the disease since the closer a group is to the infected, the more likely that infected air droplets released in a cough or sneeze will successfully infect [2,6,7]. Spread is common in families and may be accentuated by crowding in institutions such as schools and military barracks [2]. The epidemiology of a group can be tested through a simple throat-swab, and plated on blood agar [10]. Infections and carrier status is more common amoung younger age groups; half the children have been shown to carry group A streptococci in their throats during a particular school year [2,3,6]. A study on Malaysian school children in 1982 took specimens from 432 symptom-free individuals mixed from 5 different schools, and included various races and socio-economic groups. Carrier rates averaged 9% (39/432). In Japan, 2,527 specimens were taken from primary and middle school children; 686 group A carrier/infecteds occured; and 66.2% of these experienced cases of pharyngitis [8]. We can conclude that 33.8% must be aymptomatic carriers [8]. We are assuming for our model of the disease that approximately 6% of the population may occur as carriers; this takes into account that carrier rates are much higher amoung children and rare amoung adults. Even though carriers seem to represent a small portion of the population, we must take into account their significance in the spread of the disease. *S. pyogenes* may be harbored for years in a carrier unnoticed, yet this individual may infect others on a daily basis.

# 2 The Model

Now, we are going to present two models that describe the dynamic of the population with streptococcus. The first model presents three groups: susceptible ($S$), infected ($I$) and carriers ($C$). The second one includes four groups. Instead of just one infected group, the second model has two infected groups, infected susceptible ($I_S$) and infected carriers ($I_C$).

## 2.1 Introduction to the model

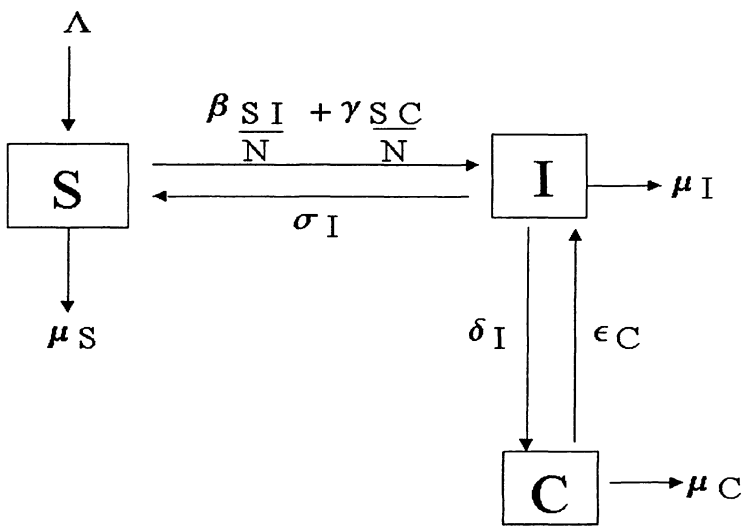


Figure 1: *Flowchart describing the First Model.*

The equations that describe our first model are the following:

$$\frac{dS}{dt} = \Lambda + \sigma I - (\beta\frac{SI}{N} + \gamma\frac{SC}{N}) - \mu S \quad (1)$$

$$\frac{dI}{dt} = \beta\frac{SI}{N} + \gamma\frac{SC}{N} - (\sigma + \mu + \delta)I + \epsilon C \quad (2)$$

$$\frac{dC}{dt} = \delta I - (\epsilon + \mu)C \quad (3)$$

where $S$ refers to the susceptible class, $I$ to infected and $C$ to carriers. $N$ is the total population, where $N = S + I + C$.

$N$ is not necessarily constant since a constant number of new recruits are added to the susceptible class only and death naturally occurs out of all classes.

In our second model, susceptibles move into and out of $I_S$ after being infected by an infective or carrier; a carrier will still move into the "sick" infectious class if their immune system weakens; an individual can move from $I_C$ to susceptible when the symptoms have been noticed and treated by antibiotics; or as mentioned earlier, a small percentage can recover naturally to the susceptible class. An individual can move from $I_S$ to carrier status if the infection goes untreated by antibiotics; some infections go unnoticed at all, and this movement between classes occurs rapidly. Also, in this model, carriers $C$ are not infectious.

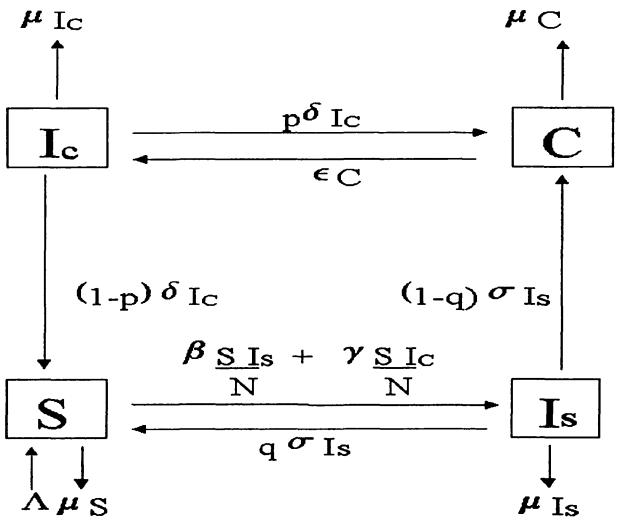


Figure 2: *Flowchart describing the Second Model.*

The equations that describe our second model are the following:

$$\frac{dS}{dt} = \Lambda + q\sigma I_S + (1-p)\delta I_C - (\beta\frac{SI_S}{N} + \gamma\frac{SI_C}{N}) - \mu S \quad (4)$$

$$\frac{dI_S}{dt} = \beta\frac{SI_S}{N} + \gamma\frac{SI_C}{N} - (\sigma+\mu)I_S \quad (5)$$

$$\frac{dC}{dt} = (1-q)\sigma I_S + p\delta I_C - (\epsilon+\mu)C \quad (6)$$

$$\frac{dI_C}{dt} = \epsilon C - (\delta+\mu)I_C \quad (7)$$

where $S$ is susceptible, $I_S$ infected susceptible, $C$ carriers and $I_C$ infected carriers. $N$ is the total population, where $N = S + I_S + C + I_C$.

From both models we get that

$$\frac{dN}{dt} = \Lambda - \mu N$$

$$\Rightarrow N(t) = (N_0 - \frac{\Lambda}{\mu})e^{-\mu t} + \frac{\Lambda}{\mu}$$

Then,

$$\lim_{t\to\infty} N(t) = \frac{\Lambda}{\mu}. \quad (8)$$

## 2.2 Discussion of the Parameters

We have the following parameters:

1. $\mu$: natural death rate out of all classes.
2. $\Lambda$: recruitment rate into susceptible class.
3. infection rates
   (a) $\beta = \phi P_1$: rate at which an infected can infect a susceptible.
   (b) $\gamma = \phi P_2$: rate at which a carrier can infect a susceptible.
   (c) $\phi$ is the contact rate per person per unit time.

(d) $P_1$ is the probability of infection given a contact with an infectious (usually very big) and $P_2$ is the probability of infection given a contact with a carrier (usually very small).

4. recovery rate ($\Omega$)

   (a) $\sigma = \Omega Q$: rate at which the infectious individual recovers to the susceptible class.

   (b) $\delta = \Omega(1 - Q)$: rate at which infectious moves into carrier class.

   (c) Notice that $\Omega = \sigma + \delta$. Usually $\sigma > \delta$, that is, $Q > \frac{1}{2}$, since there are more individuals in $I$ going to $S$ than to $C$ .

   (d) $Q$ is the probability that recovered infectives go to $S$ and $1 - Q$ the probability that recovered infectives go to $C$.

   (e) $\frac{1}{\Omega}$ $yr$: average time it takes to be recovered if you are sick.

5. $\epsilon$: rate at which a carrier moves into the infectious class.
   $\frac{1}{\epsilon}$ $yr$: average time for carrier relapse into infectious class.

The susceptible class is completely free of streptococcus, and will fall prey to infection by direct inoculation, which occurs by close contact with an infected or carrier who is colonized in the nasopharynx. A susceptible can obtain an infection by a strain found in an infected or a carrier; naturally, an infected individual is more contagious than a carrier since their throat area carriers a much larger density of bacteria to transfer. A strain found in the infected individual may also be a more contagious and virulent serotype. An individual that carries streptococcus as part of their natural flora may be able to do so because of a lowered virulence in the strain they carry; their immune system can hold it in check [11]. However, we must consider that a carrier or infected individual may be ignorant of their status and so take no precautions against spreading the disease. A member of the infectious class moves to the susceptible class by antibiotic treatment or a natural recovery that kicks out the streptococcus completely. However, natural recovery may lead to a colony established in the nasopharynx; this condition results in carrier status.

Next we study how the carrier class moves into the infectious class. A carrier is already infected and so needs no outside inoculation; this class moves into the infectious "sick" category when the immune system is compromised by inadequate nutrition and sleep, stress, or an infection by a virus

that diverts the immune system's recources. Within 24 hours the colony can grow out of control and the individual can move to the infectious class; the individual can recover without treatment back into the carrier class, or with antibiotic treatment will move into the susceptible class. First, we make the assumption that a great majority of infectious that recover to the susceptible class do so by antibiotic treatment. Second, the assumption that a carrier that moves to the infectious class can recover without antibiotics to the susceptible class, but a carrier must move through the infectious class first; the movement of carriers directly into susceptibles will not be studied in this model. We may attribute this necessary step into the infectious class first to higher levels of antibodies acquired through a bout of illness to defeat the streptococcus infection entirely. However, we hypothesize that the carrier has a greater tolerance to the streptococcus and can move into the infectious class and recover out quickly; a susceptible individual will need more time to recover since their immune system is not familiar with streptococcus.

For the second model we are going to use the same parameters, the only difference is that in this model we have two more parameters $p$ and $q$ described as follows:

1. $p$: proportion of $I_C$ that recover to $C$ class, then, $1-p$ is the proportion of $I_C$ that recover to $S$ class;

2. $q$: proportion of $I_S$ that recover to $S$ class, then, $1-q$ is the proportion of $I_S$ that recover to $C$ class.

## 2.3 Estimation of the Parameters

Parameter values vary for different outbreaks. The average estimates we will be using are:

1. $\mu = \frac{1}{70}\ yr^{-1}$. That means that on average it takes 70 years for an individual to die.

2. $\Lambda = \mu N_0$, where $N_0$ is the initial size of the population.

3. infection rates

   (a) $\beta = \phi P_1$.

   (b) $\gamma = \phi P_2$.

(c) $\phi$: approximately from 1 to 10 times a day.

(d) $P_1$: from 0.89 to 0.99
$P_2$: from 0.001 to 0.05.

4. recovery rate($\Omega$)

   (a) $\sigma = 364\ yr^{-1}$.

   (b) $\delta = 1\ yr^{-1}$.

5. $\epsilon$: from 1 $yr^{-1}$ to 4 $yr^{-1}$.

## 2.4 Determining $R_0$

### 2.4.1 First Model

The average number of infecteds that one infected individual produces during the entire infectious period in an entirely susceptible population is known as $R_0$. In order to find the $R_0$ for our first model, we have to find values or equilibrium points for $S, I, C$ in the following algebra equations

$$\Lambda + \sigma I - \left(\beta\frac{SI}{N} + \gamma\frac{SC}{N}\right) - \mu S = 0$$
$$\beta\frac{SI}{N} + \gamma\frac{SC}{N} - (\sigma + \mu + \delta)I + \epsilon C = 0$$
$$\delta I - (\epsilon + \mu)C = 0.$$

One of the solutions is

$$(S^o, I^o, C^o) = \left(\frac{\Lambda}{\mu}, 0, 0\right)$$

We will call $(S^o, I^o, C^o)$ the *Disease Free Equilibrium (DFE)* point, because it represents the dynamics of the population when $t \to \infty$ and $I = C = 0$, meaning that there are only susceptibles in the population. The *DFE* is important for the analysis of the dynamics of the population because we can calculate $R_0$ with it.

Now, we are interested to know whether the small deviations away from the equilibrium points will grow larger (instability) or decay (stability). We have to recall that in a continuous model, an equilibrium point will be stable

provided that all the eigenvalues ($\lambda's$) of $J$ are negative (if real) or have negative real parts (if complex) [5]. That is to say that,

$$Re\ \lambda_i < 0,\ \forall\ i.$$

As the reader can see, we are studying a model with constant recruitment rate and logistic total population size K. Then, by (8), we can set $K = \frac{\Lambda}{\mu}$. Now, we have the following limiting system:

$$\begin{aligned} \frac{dI}{dt} &= \beta\frac{(K-I-C)I}{K} + \gamma\frac{(K-I-C)C}{K} - (\sigma+\mu+\delta)I + \epsilon C \quad (9) \\ \frac{dC}{dt} &= \delta I - (\epsilon+\mu)C. \quad (10) \end{aligned}$$

Using the **Castillo–Chavez, Thieme Theorem** [1], we say that the dynamical behavior of the systems (1) - (3) and (9) - (10) is identical. So, to determine the stability of the *DFE* point we first calculate the Jacobian matrix of the system (9) - (10). This leads to

$$J_L(0,0) = \begin{pmatrix} \beta-\delta-\mu-\sigma & \gamma+\epsilon \\ \delta & -(\epsilon+\mu) \end{pmatrix}$$

To prove that the other two eigenvalues are negative, the following conditions must be satisfied:

$$\begin{aligned} Trace(J_L) &< 0 \\ Det(J_L) &> 0 \end{aligned}$$

Thus we need to have

$$\begin{aligned} Trace(J_L) &= (\beta-(\mu+\sigma)-\delta)-\epsilon-\mu < 0 \\ Det(J_L) &= \gamma\delta+\beta(\epsilon+\mu)-(\mu(\delta+\epsilon+\mu)+\sigma(\epsilon+\mu)) > 0 \\ &\Leftrightarrow \frac{\gamma\delta+\beta(\epsilon+\mu)}{\mu(\delta+\epsilon+\mu)+\sigma(\epsilon+\mu)} < 1 \end{aligned}$$

From the latter condition we get that

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

for our first model. Notice that $R_0$ can be rewritten as

$$R_0 = \frac{\beta(\epsilon+\mu)+\gamma\delta}{(\mu+\sigma)(\epsilon+\mu)+\mu\delta} \tag{11}$$

Thus, $R_0 < 1$ implies $\beta-(\mu+\sigma)-\delta\frac{\mu}{\epsilon+\mu} < 0$, which implies $Trace(J_L) < 0$.

So, $(S^o, I^o, C^o)$ is locally stable when $R_0 < 1$; this will be explained biologically in section 3.

Only when $R_0 > 1$ does there exists an equilibrium point $(S^*, I^*, C^*)$ where

$$\begin{aligned} S^* &= \frac{\Lambda}{\mu}\cdot\frac{1}{R_0} \\ I^* &= \frac{\Lambda}{\mu}(1-\frac{1}{R_0})\cdot\frac{\mu+\epsilon}{\mu+\epsilon+\delta} \\ C^* &= \frac{\Lambda}{\mu}(1-\frac{1}{R_0})\cdot\frac{\delta}{\mu+\epsilon+\delta} \end{aligned}$$

$(S^*, I^*, C^*)$ will be known as the *Endemic Equilibrium (EE)* point, because it represents the dynamics of the population when $t \to \infty$ and $I$ or $C$ are positive numbers, meaning that there are infected or carriers individuals in the population.

### 2.4.2 Second Model

To obtain the $R_0$ for the second model we will study the stability of the *DFE* point. First we have to solve the following system:

$$\begin{aligned} &\Lambda + q\sigma I_S + (1-p)\delta I_C - \left(\beta\frac{SI_S}{N} + \gamma\frac{SI_C}{N}\right) - \mu S = 0 \\ &\beta\frac{SI_S}{N} + \gamma\frac{SI_C}{N} - (\sigma+\mu)I_S = 0 \\ &(1-q)\sigma I_S + p\delta I_C - (\epsilon+\mu)C = 0 \\ &\epsilon C - (\delta+\mu)I_C = 0. \end{aligned}$$

From this we get that the *DFE* is

$$(S^o, I_S^o, C^o, I_R^o) = \left(\frac{\Lambda}{\mu}, 0, 0, 0\right)$$

In this case, to determine the stability of the *DFE* we will consider different values for $p$ and $q$; and use the *Routh–Hurwitz Criteria.* Now, following the same steps that we did determining the stability for the *DFE* in the first model, we get that

$$J(\frac{\Lambda}{\mu},0,0,0) = \begin{pmatrix} -\mu & -\beta+q\sigma & 0 & -\gamma+(1-p)\delta \\ 0 & \beta-\mu-\sigma & 0 & \gamma \\ 0 & (1-q)\sigma & -(\epsilon+\mu) & p\delta \\ 0 & 0 & \epsilon & -(\delta+\mu) \end{pmatrix}$$

Also, this matrix reduces to a simpler system since it is easy to see that one of the eigenvalues, $\lambda_1 = -\mu < 0$. From this point, we will analyze the following matrix:

$$B = \begin{pmatrix} \beta-\mu-\sigma & 0 & \gamma \\ (1-q)\sigma & -(\epsilon+\mu) & p\delta \\ 0 & \epsilon & -(\delta+\mu) \end{pmatrix}$$

Now, we will calculate $R_0$ for different values of $p$ and $q$.

1. $q = 1$.
   In the first case, $p = q = 1$, the interactions between $I_C \to S$ and $I_S \to C$ disappear. That is, we will have two separate and closed interactions between $S \to I_S$ and $C \to I_C$. Since there are no born carriers and the carrier status is always an acquired condition, $C$ has no recruitment rate. This means that biologically, when $t \to \infty$, $C$ is always zero because of the death rate. The second case, $0 \leq p < 1$, $q = 1$ is similar to the first case and we obtain the same results. This leads to the standard $R_0$ for an *S–I–S* model

   $$R_0 = \frac{\beta}{\mu+\sigma}$$

   We will not study this case, because we are interested in dynamics in which there are at least one carrier when $t \to \infty$.

2. $p = 0, 0 \leq q < 1$.
Then,

$$B_1 = \begin{pmatrix} \beta - (\sigma + \mu) & 0 & \gamma \\ (1-q)\sigma & -(\epsilon + \mu) & 0 \\ 0 & \epsilon & -(\delta + \mu) \end{pmatrix}$$

In order to have $(S^o, I_S^o, C^o, I_C^o)$ stable in this case, using the *Routh-Hurwitz Criteria*, we have to show that all the coefficients $a_i$, $i = 1, 2, 3$ of the characteristic equation of $B_1$ are positive and $a_1 a_2 > a_3$ [5].

(a) Suppose that
$a_3 = -Det(B_1) = (\sigma + \mu - \beta)((\epsilon + \mu)(\delta + \mu)) - \gamma\epsilon(1-q)\sigma > 0.$

Notice that to have $a_3 > 0$ it is necessary that

$$\beta < \mu + \sigma. \tag{12}$$

As it turns out, $a_3 > 0$ implies that $a_1, a_2 > 0$, by means (12).

(b)

$$\begin{aligned} a_2 &= Det \begin{pmatrix} b_{11} & b_{12} \\ b_{21} & b_{22} \end{pmatrix} + Det \begin{pmatrix} b_{22} & b_{23} \\ b_{32} & b_{33} \end{pmatrix} + Det \begin{pmatrix} b_{11} & b_{13} \\ b_{31} & b_{33} \end{pmatrix} \\ &= (\sigma + \mu - \beta)(\epsilon + \mu) + (\epsilon + \mu)(\delta + \mu) + (\sigma + \mu - \beta)(\delta + \mu) \end{aligned}$$

By using (12), we get that $a_2 > 0$

(c) $a_1 = -Trace(B_1) = (\sigma + \mu - \beta) + (\epsilon + \mu) + (\delta + \mu)$

Also, by (12), we have that $a_1 > 0$.

(d) To show that $a_1 a_2 > a_3$ we will write $a_2$ as follows,

$$a_2 = (\sigma + \mu - \beta)((\epsilon + \mu) + (\delta + \mu)) + (\epsilon + \mu)(\delta + \mu).$$

We get

$$\begin{aligned} a_1 a_2 &= (\sigma + \mu - \beta)^2((\epsilon + \mu) + (\delta + \mu)) + (\sigma + \mu - \beta)(\epsilon + \mu)(\delta + \mu) + \\ &\quad (\sigma + \mu - \beta)((\epsilon + \mu) + (\delta + \mu))^2 + ((\epsilon + \mu) + (\delta + \mu))(\epsilon + \mu)(\delta + \mu). \end{aligned}$$

Now, it is easy to see that $a_1 a_2 > a_3$.

Now, to obtain $a_3 > 0$,

$$\begin{aligned} a_3 &= (\sigma+\mu-\beta)((\epsilon+\mu)(\delta+\mu)) - \gamma\epsilon(1-q)\sigma > 0 \\ &= (\mu+\sigma)(\epsilon+\mu)(\delta+\mu) - \beta(\epsilon+\mu)(\delta+\mu) - \gamma\epsilon(1-q)\sigma > 0 \end{aligned}$$

$$\Rightarrow \frac{\beta(\epsilon+\mu)(\delta+\mu)+\gamma\epsilon(1-q)\sigma}{(\mu+\sigma)(\epsilon+\mu)(\delta+\mu)} < 1.$$

Hence, when $p = 0, 0 \leq q < 1$

$$R_0 = \frac{\beta}{\mu+\sigma} + \frac{(1-q)\sigma}{\mu+\sigma} \cdot \frac{\epsilon}{\mu+\epsilon} \cdot \frac{\gamma}{\mu+\delta} \tag{13}$$

3. $0 < p \leq 1$, $0 \leq q < 1$.
   Following the steps above, we find that $R_0$ is calculated to be

$$R_0 = \frac{\beta}{\mu+\sigma} + \frac{(1-q)\sigma}{\mu+\sigma} \cdot \frac{\gamma\epsilon}{\mu(\mu+\delta+\epsilon)+(1-p)\delta\epsilon} \tag{14}$$

Then, if $R_0 < 1$, the only equilibrium point is $(S^o, I_S^o, C^o, I_C^o)$. On the other hand, if $R_0 > 1$, the $EE$ exists.

# 3 Biological Analysis

In this section we are going to analyze biologically each one of the $R_0$'s that we have obtained in the previous section.

## 3.1 First Model

We recall the $R_0$ for our first model,

$$R_0 = \frac{\beta(\epsilon+\mu)+\gamma\delta}{(\mu+\sigma)(\epsilon+\mu)+\mu\delta}$$

From this $R_0$ we can see many different characteristics. For example, if we take $\epsilon \to \infty$ or $\delta = 0$ we obtain the standard $R_0$ for an $S$–$I$–$S$ model:

$$R_0 = \frac{\beta}{\mu+\sigma}$$

That is, when $\epsilon \to \infty$, an individual carrier relapses very rapidly to the $I$ class. When $\delta = 0$ there is no interaction going from $I$ to $C$, and $C$ has no recruitment rate.

Notice that we can write (11) as follows,

$$R_0 = \frac{\beta + \gamma\frac{\delta}{\epsilon+\mu}}{\mu + \sigma + \mu\frac{\delta}{\epsilon+\mu}}.$$

Notice that $\delta$ is the rate into $C$. On the other hand, $\epsilon+\mu$ is the rate out of $C$. Thus, $\frac{\delta}{\epsilon+\mu}$ gives the "strength" of the $C$ class contribution to an epidemic.

Assuming that $\gamma$ is greater than $\mu$, let $\frac{\delta}{\epsilon+\mu}$ be small. $R_0$ will reduce to $\frac{\beta}{\mu+\sigma}$. However, if we let $\frac{\delta}{\epsilon+\mu}$ be large, then the $R_0$ will reduce to $\frac{\gamma}{\mu}$, and this by assumption is greater than 1. Therefore, if carriers spend enough time in the $C$ class, $R_0 > 1$ and the carrier class is sufficient to propagate the epidemic.

From the flowchart of the first model (1) we gather that

$$\begin{aligned} R_0 \;=\; & \frac{\beta}{\mu+\sigma+\delta}\sum_{i=0}^{\infty}\left(\frac{\delta}{\mu+\sigma+\delta}\cdot\frac{\epsilon}{\mu+\epsilon}\right)^i + \\ & \left(\frac{\gamma}{\mu+\epsilon}\cdot\frac{\delta}{\mu+\sigma+\delta}\right)\sum_{i=0}^{\infty}\left(\frac{\delta}{\mu+\sigma+\delta}\cdot\frac{\epsilon}{\mu+\epsilon}\right)^i. \end{aligned} \tag{15}$$

Here, the term

$$\left(\tfrac{\delta}{\mu+\sigma+\delta}\right)^{i+1}\left(\tfrac{\epsilon}{\mu+\epsilon}\right)^i, \forall i = 0, 1, 2, \ldots$$

is the probability that an infected goes to $C$ given that this infected have been $i$ times in the $C$ class. It is easy to see that, $0 < \frac{\delta}{\mu+\sigma+\delta}\cdot\frac{\epsilon}{\mu+\epsilon} < 1$,

$$\sum_{i=0}^{\infty}\left(\tfrac{\delta}{\mu+\sigma+\delta}\cdot\tfrac{\epsilon}{\mu+\epsilon}\right)^i$$

, is a geometric series. So, (15) reduces to

$$R_0 = \left(\frac{\beta}{\mu+\sigma+\delta} + \frac{\gamma}{\mu+\epsilon}\cdot\frac{\delta}{\mu+\sigma+\delta}\right)\left(\frac{1}{1-\frac{\delta}{\mu+\sigma+\delta}\cdot\frac{\epsilon}{\mu+\epsilon}}\right)$$

Notice that the above $R_0$ is equal to (11).

## 3.2 Second Model

In the previous section we calculated two $R_0$'s when we considered different values for $p$ and $q$. Then let

1. $P_{I_S \to C} = \frac{(1-q)\sigma}{\mu+\sigma}$: the probability that a member of $I_S$ goes to the $C$ class instead of the $S$ class or dying.

2. $P_{C \to I_C} = \frac{\epsilon}{\mu+\epsilon}$: the probability that a carrier goes to the $I_C$ class before dying.

3. $P_{I_C \to C} = \frac{p\delta}{\mu+\delta}$: the probability that a member of $I_C$ returns to the $C$ class instead of going to $S$ or dying (just for the case in which $0 < p \leq 1, 0 \leq q < 1$).

Now we are going to study the two cases.

1. $p = 0, 0 \leq q < 1$
   By (11), we can rewrite $R_0$ as follows,

$$R_0 = \frac{\beta}{\mu+\sigma} + \frac{\gamma}{\mu+\delta} \cdot P_{I_S \to C} \cdot P_{C \to I_C}$$

   where

   (a) $\frac{\beta}{\mu+\sigma}$: this acts like an "$R_0$" for the $I_S$ class.

   (b) $\frac{\gamma}{\mu+\delta}$: this acts like an "$R_0$" for the $I_C$ class.

   Here, if we take $\epsilon \to \infty$, then $P_{C \to I_C} \to 1$. This means that a member of the $I_S$ class moves very rapidly to the $I_C$ class. If we take both $\epsilon \to \infty$ and $\delta \to \infty$, then $P_{C \to I_C} \to 1$ and $\frac{\gamma}{\mu+\delta} \to 0$. This obtains the standard $R_0$ for an $S$–$I$–$S$ model. Therefore, a member of the $I_S$ class returns rapidly to $S$ after passing through the $C$ and $I_C$ classes.

2. $0 < p \leq 1, 0 \leq q < 1$
   In this case, having values for $p$ and $q$ between 0 and 1 will give us some particular characteristics for the $R_0$ in this model. Notice that $0 < p \leq 1$ implies an interaction of $I_C \to C$. There is a considerable difference between the first case of this model and the second one. If an individual is a member of the $I_C$ class, there is a possibility that

this individual will return to the $C$ class many times before going to the $S$ class or dying. Directly from the flowchart of the second model (2) we gather that

$$R_0 = \frac{\beta}{\mu+\sigma} + \left(\frac{\gamma}{\mu+\delta}\cdot P_{I_S\to C}\cdot P_{C\to I_C}\right)\sum_{i=0}^{\infty}\left(\frac{\epsilon}{(\mu+\epsilon)}\cdot\frac{p\delta}{(\mu+\delta)}\right)^i \quad (16)$$

The term

$$\left(\tfrac{\epsilon}{\mu+\epsilon}\right)^{i+1}\left(\tfrac{p\delta}{\mu+\delta}\right)^i,\ \forall i=0,1,2,\ldots$$

in (16) is the probability that a carrier visits $I_C$ given that this carrier has visited $i$ times in the $I_C$ class.

Since $0<\frac{\epsilon}{(\mu+\epsilon)}\cdot\frac{p\delta}{(\mu+\delta)}<1$,

$$\sum_{i=0}^{\infty}\left(\tfrac{\epsilon}{(\mu+\epsilon)}\cdot\tfrac{p\delta}{(\mu+\delta)}\right)^i,$$

is a geometric series. Then (16) reduces to

$$R_0=\frac{\beta}{\mu+\sigma}+\frac{(1-q)\sigma}{\mu+\sigma}\cdot\frac{\gamma}{\mu+\delta}\cdot\frac{1}{1-\left(\frac{\epsilon}{(\mu+\epsilon)}\cdot\frac{p\delta}{(\mu+\delta)}\right)}$$

Notice that the above $R_0$ is the same one we obtained analytically in the previous section.

Now, if we consider $\epsilon\to\infty$ and $p\to 0$, then $P_{C\to I_C}\to 1$ and $P_{I_C\to C}\to 0$. Biologically, this means that a carrier will go rapidly to the $I_C$ class and from there very rapidly to the $S$ class. If we take $\delta\to\infty$ then it follows that $\frac{\gamma}{\mu+\delta}\to 0$. This gives us the standard $R_0$ for an $S$–$I$–$S$ model, and consequently the dynamics of $I_C\to C$ and $I_C\to S$ are very rapid.

# 4 Simulations

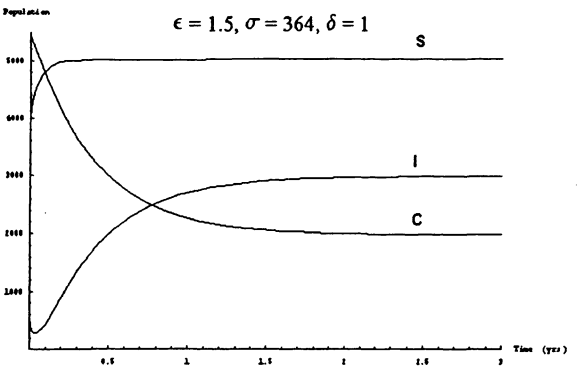


Figure 3: *Dynamics considering 2 contacts with infected people per day. (First Model)*

Here, even though carriers start as the majority of the population, when the carriers move to the $I$ class, it is very likely that they will recover to the $S$ class, since $\sigma$ is large. Notice the stabilization of these three groups over the 3-year period.

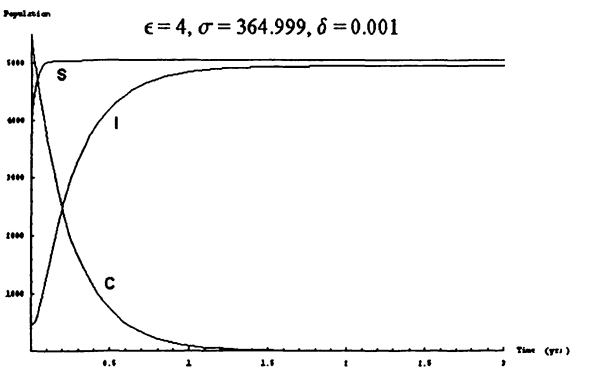


Figure 4: *Dynamics considering 2 contacts with infected people per day. (First Model)*

Notice here that the $\epsilon$ large causes carriers to cycle into the $I$ class quickly. Once there, only a minute fraction ($\delta$ small) may recover back to $C$. Therefore

the large contribution of the $C$ class causes $S$ and $I$ to stablize to the EE majority.

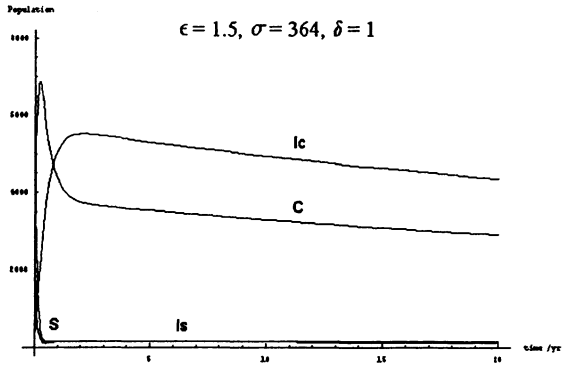


Figure 5: *Dynamics considering 2 contacts with infected people per day. (Second Model with $p = 0$, $q = 0.9$)*

First, notice that $\sigma$ large will cause new recruits to cycle through the $I_S$ class quickly, and a large portion of $I_S$ will move to $C$. There is a build up when $C$ contributes to the $I_C$ class, with the absence of the contribution of $I_C$ to $C$ ($p = 0$). Over a 20-year span the $I_C$ and $C$ classes will stabilize to the majority.

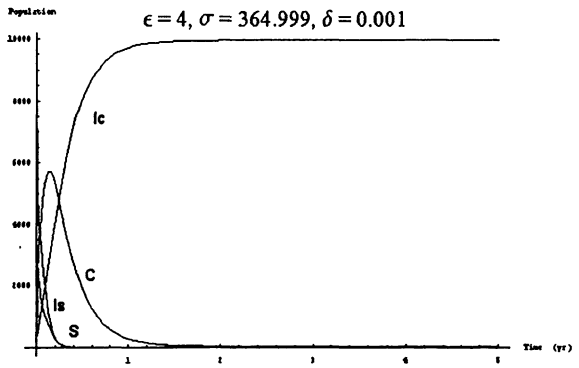


Figure 6: *Dynamics considering 2 contacts with infected people per day. (Second Model with $p = 0$, $q = 0.9$)*

Notice in this simulation, $\delta$ is extremely small and contribution of $I_C$ to $S$ is unlikely. $\epsilon$ large cycles all carriers into $I_C$, such that a member of $S$ is

likely to cycle to $I_S$, and from there rapidly to $C$ and then rapidly $I_C$ and stay there. Our EE shows $I_C$ as the majority over a 5-year span.

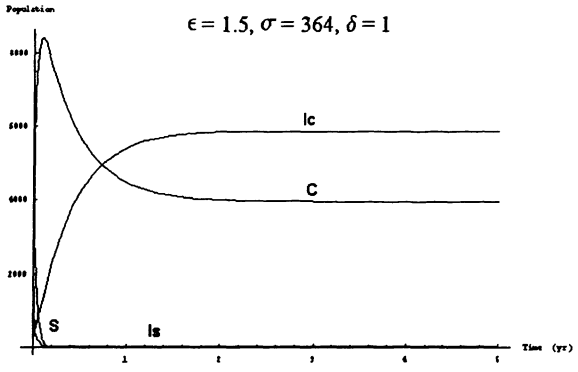


Figure 7: *Dynamics considering 2 contacts with infected people per day. (Second Model with $p = 0.25$, $q = 0.5$)*

Here we consider values of $p$ and $q$ between 0 and 1. Notice that a member of $I_S$ is equally likely to move to $C$ as it is to move to $I_S$, ($q = 0.5$). We may see this condition only in a population that does not have antibiotics readily available, and strep colonies are not immediately killed. Eventually, a majority of the population stays in the $I_C$ and $C$ cycle; this occurs over a 5-year span.

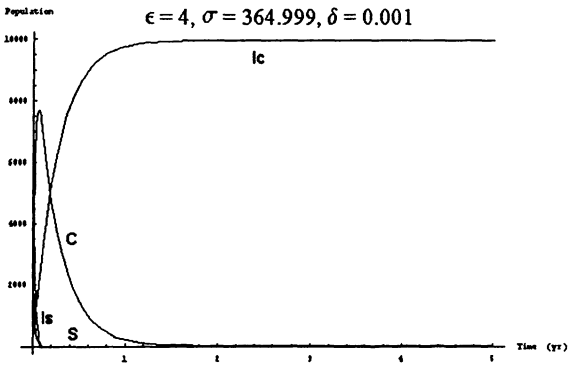


Figure 8: *Dynamics considering 2 contacts with infected people per day. (Second Model with $p = 0.25$, $q = 0.5$)*

Members of $S$ move to $I_S$ and eventually up to $C$. Here, $\epsilon$ large cycles $C$

quickly to $I_C$ with little chance of recovery to $C$. Since $\delta$ is so small, a minute fraction will leak from $I_C$ to $S$. We see that $I_C$ stabilizes to the majority over a 5-year span.

# 5 Conclusions

According to Robert W. Quinn, many recent studies indicate that streptococcal infections are much more common than streptococcal disease [6]. It appears that most children who are carriers and presumably have streptococcal infections do not develop disease. Theoretically, this leaves only a small proportion of susceptibles available for aquisition of the disease, probably too few to result in an epidemic. The strains usually found in children would appear to be moderately contagious, since about half the children have been shown to carry group $A$ streptococci in their throats during a school year. The situation described here seems to have a fairly high initial amount of carriers; yet an epidemic in the population does not follow. The question we may need to ask may be "what effect does a group of susceptibles have on a beta-hemolytic carrier population?" We can partly answer some of this question from the simulations with high initial carrier groups and low susceptible groups. Since the infectiousness of the carrier group was constant, and antibiotics available keep the flow of infecteds recovering to susceptibles, the population was always likely to stabilize to susceptibles larger than both carrier and infected groups. Still, fluctuations may appear in a one or two year span, as expected in a seasonal disease. Still, we can study a population that does not have antibiotics readily available, or is limited only to severe cases [7]. "What impact would the absence of antibiotics have on the carrier class? Would it grow as a sort of natural immune response?" Absence of antibiotics might dramatically increase the recovery rate to the carrier class, and decrease the rate to the susceptible class. One might see a situation similar to this in a region where antibiotics are not readily available. Since medical treatment is readily available to most U.S. schoolchildren, carrier rates may be lower. A carrier in a healthy environment does have an advantage in not contracting infections; could this be a selective force? Here we will discuss options and further work that can stem from our research.

Even though at birth one is sterile and free from bacteria, an individual will gradually colonize different types of bacteria throughout a lifetime; age and exposure, hormonal changes, genetics, and environment play a role in

the natural bacterial flora of an individual throughout their lifetime. At any given time, the natural flora of a percentage of the population may be colonized with streptococcus. Given the following evidence, it seems more likely that a group of susceptibles introduced into a population of beta-hemolytic carriers is more likely to cause an epidemic than vise-versa. U.S. Navy records from WWII show susceptible recruits were introduced at weekly intervals into training centers where there were large numbers of infected individuals. In the years 1942 to 1945, at least a million cases of streptococcal infections occured. Navy recruits, 18 to 21 years of age, came from widely separated regions, many from rural areas. Serotypes 19, 17, and 3 are known predominantly as Army and Navy strains and rarely are they found in civilian populations [6]. We can assume that the recruits represented the susceptible population, and when introduced at intervals into a infected and carrier population, produced a large epidemic amoung them.

A susceptible population introduced at intervals seems to play a role; though Quinn explains that even when opportunity for spread and epidemic are ideal when a new strain of streptococcus is introduced, the epidemics are self-limited because new susceptibles are not introduced periodically [6]. One may ask why an epidemic in a group of susceptibles and beta-hemolytic carriers is limited, and an epidemic in a periodically-introduced population is severe? K. Ryan gives an example with "ping-pong" infections: "Recurrent infections are sometimes seen in families when prompt antimicrobial therapy has prevented the development of type-specific immunity. This situation allows reinfection from other infected of colonized siblings when antimicrobial treatment is stopped. Such "ping-pong" infection-reinfection cycles sometimes require simultaneous treatment of the entire family to prevent continued transmission" [2]. Therefore, epidemics can be controlled with simultaneous infection and treatment of the disease in a group; however, a group introduced on intervals to the disease will theoretically propagate the epidemic. We were unable to study this periodic recruitment epidemic, and normal initial starting values for the C, I, and S classes proved to be a self-limited epidemic; susceptibles always stabilized as the largest amout. We believe the key to finding periodic infection cycles is to recruit by week or month, not by year, since strep throat is a seasonal disease.

We could also address the issue of "what is the critical 'waiting' time for an infectious person?" It has been shown that the longer an infectious individual holds out on antibiotics, the more likely they will develop antibodies that are immune to the particular serotype of the disease. This would help

prevent the "ping-pong" infections mentioned above, but how many more new infections would occur in the contagious waiting period? 'Critical time' allows for natural immunity to the serotype to occur, otherwise the individual may be reinfected as soon as they go off antibiotic treatment. One main assumption we used in our model is that susceptibles never gain immunity to any serotypes; an individual is ready to be infected as soon as he/she reaches the susceptible class [6,9,13]. How necessary are antibiotics with this disease? The use and possible over-use of antibiotics leads us to studying resistant strains. Drug-resistant strep bacteria are becoming more common; up to 25% of cases of infections were not killed by penicillin in 1997, and another 25% had some resistance to penicillin [4]. What effect does resistance have on the population, and on the carrier class? Continually, new antibiotics must be made each year with an approximate cost of $30 million. Can anything be done to slow antibiotic resistance?

It is possible to make still two more models out of our originals. We assumed in our models that direct movement between the susceptible and carriers classes does not occur. But suppose that maybe a percentage of asymptomatic individuals do move directly to the carrier class, and after some time lose thier carrier status without an infection? The assumptions we made were that an individual must move to the infectious class from the carrier class to build up anitbodies to rid him/her from all bacterial colonies in the nasopharynx. We did not take into account that a carrier may simply lose carrier status with changes in bacterial flora in which the strep colony is out-competed. This model may be more accurate to use in an age defined simulation, where bodily flora matures. Lastly, we can use a version of our model rearranged such that the carrier class is an incubation period. Susceptibles move to carrier class, and can either move on to full infection or cure the body before that stage. The infectious class can recover to susceptibles or move on to another matured carrier stage. The "matured" carrier box can move to the first incubation carrier box. This probably represents a more realistic view of the disease, since it allows for an age simulation as well as a probable epidemic model. We are opening this questions and applying to our research, hoping to continue in this direction.

# Acknowledgements

This study was supported by the following institutions and grants: National Science Foundation (NSF Grant DMS 9977919); National Security Agency (NSA Grants MDA 9049710074); Presidential Faculty Fellowship Award (NSF Grant DEB 925370) and Presidential Mentoring Award (NSF Grant HRD9724850) to Carlos Castillo-Chavez; the Office of the Provost of Cornell University; Intel Technology for Education 2000 Equipment Grant. Special thanks to Ted Greenwood of the Sloan Foundation.

The authors would like to give special thanks to Carlos Castillo-Chavez, Maia Martcheva, Gloria Crispino-O'Connor, Ricardo Sáenz, Christopher Kribs-Zaleta and Baojun Song.

# References


1. Castillo-Chavez, C., Thieme, H. R. 1995. *Asymptotically autonomous epidemic models, in Mathematical Population Dynamics: Analysis of Heterogeneity.* Arino, D.E. Axelrod, and M. Kimmel, eds.

2. Champoux, J., Corey, L., Neidhardt, F., Plorde, J., Ray, C., Ryan, K. 1990. *MedicalMicrobiology.* Elsevier New York Publishers.

3. Clark, V.L., Bavoli, P. 1997. *Bacterial Pathogenesis.* Academic Press.

4. Drug-Resistant Strep Spreading In US, Report Says. 1999. *http : //dailynews.yahoo.com/h/ts/st...nm/*19990806*/ts/health*$_s$*trep*$_1$*.html*

5. Edelstein – Keshet, L. 1988. *Mathematical Models In Biology*, Birkhauser Mathematics Series. McGraw-Hill Inc.

6. Evans, A. S., Feldman, H. A. 1982. *Bacterial Infections of Humans.* Plenum Publishing company.

7. Joklik, W., Willett, H., Amos, D. 1980. *Zinsser Microbiology.* Appleton – Century – Crafts.

8. Kimura, Y., Kotami, S., Shiokawa, Y. 1984. *Recent Advances in Streptococci and Streptococcal Diseases.*

9. Lappe, M. 1995. *Breakout, The Evolving Threat of Drug – Resistance Disease.* Sierra Club Books.

10. Lunnette, E.H., Balows, A., Hausler, W.J., Shadomy, H. 1985. *Manual of Clinical Microbiology Fourth Edition.* American Society For Microbiology.

11. Merkel, S. 1999. Interview with member of Cornell University Microbiology Department.

12. Molte, W.A. 1973. *Oral Microbiology.* The Mosly, C.V. Company.

13. Mudd, S. 1970. *Infectious Agents and Host Reactions.* Saunders, W.B. Company.

14. Sáenz, R. 1997. *Analysis of an age-structured epidemic model with a chronic state. Studies in Theoretical BIology: A Collection of Undergraduate Researc.* h1997 Mathematical and Theoretical Biology Institute at Cornell.