Deterministic and Stochastic Models of the Spread of Streptococcal Disease and Its Sequel

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Abstract

The beta-hemolytic group A *Streptococcus* (GAS) is responsible for its sequel, acute rheumatic fever (ARF), which may lead to the more serious condition on other heart diseases. To gain a better understanding of the transmission in a population, we formulated epidemic models using a standard compartmental model and a continuous-time Markov chain. The models allow for the contribution of disease carrier and the effect of treatment. The equilibrium points and stability are analyzed in relation to the basic reproduction number based on the deterministic model. For the stochastic model, numerical simulation of sample paths is performed. The results indicate that the dynamic behavior for the two approaches depends on the epidemic threshold. Under stable endemic condition, most sample paths fluctuate around its mean and deterministic curve. On the other hand, when the basic reproduction number is less than one, the stochastic system undergoes a minor outbreak, while the deterministic curve approaches zero. The results are expected to be the first step of a deeper analysis of stochastic treatment linked to its deterministic counterpart.

Keywords: group A *Streptococcus*; acute rheumatic fever; deterministic model; stochastic model; carriers
DOI……..

1. Introduction

The beta-hemolytic group A *Streptococcus* (GAS) bacteria [1] is the main cause of infections of the throat and skin such as pharyngitis, tonsillitis, sinusitis, impetigo, rheumatic fever, and meningitis. These can occur in any gender and at any age. The most common of GAS occurs in children ages 5-15 [2-8]. GAS are carried in the throat or on the skin of individuals where the individuals may have no symptoms of illness [9-11] and infections can be spread from person to person by direct contact or inhalation of the secretions in the nasopharynx such as mucus and saliva [8]. Treatment of a GAS with an antibiotic such as penicillin can reduce the risk of ARF by about 90%. In about 10% of cases, GAS still remain in the throat even though the individual has had a full course of treatment [12]. Treatment failures of GAS may arise from the ineffectiveness of antibiotic therapy

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or an incomplete course of the prescribed antibiotic. The patients who failed from these treatments may be asymptomatic or classified as carriers, which can be a significant impact on the GAS epidemic, since they do not take any special precautions to prevent transmission [1, 13-15].

Untreated GAS pharyngitis or treatment failures may develop into acute rheumatic fever (ARF), which is a non-communicable disease caused by disorders of an autoimmune [16]. ARF is most common in 5-15 years old [4]. The symptoms of ARF are swelling, skin inflammation, blisters or bulges underneath the skin, heart tissue damage, and inflammation of the brain, which causes a movement disorder called Chorea. About 0.3%-3.0% of people will develop ARF following a GAS infection. In addition, patients who have had previous attacks of ARF have a recurrence of ARF following a GAS infection in 30%-80% of cases [12]. There are about 5 million individuals worldwide with rheumatic heart disease and there are about 282,000 new cases per year and 233,000 deaths from this disease each year due to lack of proper infection prevention of GAS [16-18].

Mathematical models have been used widely as a tool to study the propagation of diseases [1, 12]. In addition to deterministic formulation, stochastic model can be used to treat the realistic contact pattern given by unpredictable individual behaviors. In this research, we study the dynamics of infectious and asymptomatic GAS infections that affect the dynamics of ARF. Deterministic and associated stochastic models are constructed to compare the system behaviors. An analytic framework is based on the deterministic analysis while a numerical simulation is the main approach used to solve the stochastic model.

2. Materials and Methods

2.1 Basic assumptions and the deterministic model

We employ the standard compartmental SIS model for the models of GAS and ARF [19]. The model is formulated under the assumption that individuals infected with GAS can be treated by using an antibiotic such as penicillin or amoxicillin [5]. In addition to the possible failure of antibiotic treatment with several reasons [18, 20-23], we assume that even if a full course of the antibiotic is taken, a small fraction of GAS may remain in the throat. Therefore, asymptomatic carriers will be defined as errors of treatment which is different from the previous study [24]. By the term 'error of treatment', we mean that some treated patients may have not complied with the treatment steps or may not have completed the full course of drug administration and dosage.

Suppose that the total population, N is constant. We denote S as the number of susceptible individuals, I as the number of symptomatic GAS individuals, C as the number of asymptomatic GAS individuals or carriers and, A as the number of individuals that develop ARF. Figure 1 shows the flow diagram of GAS infection and ARF development. Since both I and C individuals have positive throat cultures for GAS [23, 25], new ARF patients may develop from these two groups [26]. The differential equations describing the transition rates are given by

$$\frac{dS}{dt} = \Lambda - (\beta_1 I + \beta_2 C)S + \gamma_2 A + \theta\gamma_1 I - \mu S \tag{1}$$

$$\frac{dI}{dt} = (\beta_1 I + \beta_2 C)S + \text{ò}C - (\gamma_1 + \delta_1 + \mu)I \tag{2}$$

$$\frac{dC}{dt} = (1-\theta)\gamma_1 I - (\text{ò} + \delta_2 + \mu)C \tag{3}$$

$$\frac{dA}{dt} = \delta_1 I + \delta_2 C - (\gamma_2 + \mu)A \tag{4}$$

where the definitions of the parameter values used in the above model and their corresponding values are given in Table 1. Since carriers are thought to have a lower density of GAS in their pharynx, compared to those with an acute infection [25-28], and GAS carriers are at little risk for developing acute rheumatic fever [26], we presume that $\beta_2 < \beta_1$ and $\delta_2 < \delta_1$. We note that given the nonnegative initial conditions, the solutions are nonnegative for all time, and if the initial condition is positive, then the set

$$\Omega = \left\{ \left(S(t), I(t), C(t), A(t) \right) \in \text{¡}^4_+ : 0 \le S, I, C, A \le \Lambda / \mu \right\}$$

is a positively invariant.

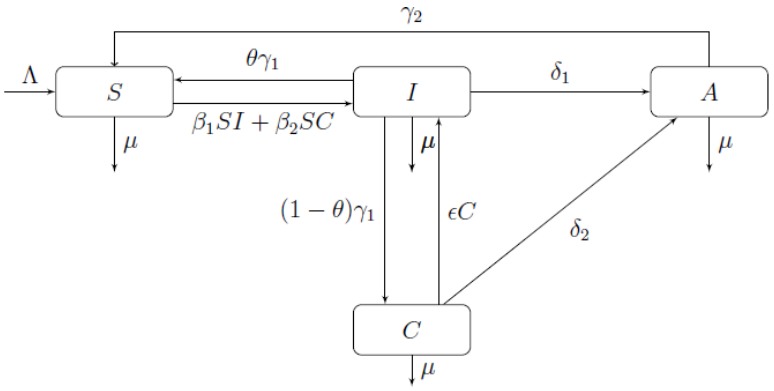

Figure 1. Flowchart describing the transition between compartments

Table 1. Symbols and definition of the parameters

Parameters	Description
Λ	recruitment rate of susceptible class
γ_1	rate at which the infectious individual gets antibiotic treatment
θ	proportion of effectiveness of antibiotic treatment
γ_2	per capita recovery rate of ARF individual
β_1	rate at which a symptomatic GAS individual can infect a susceptible
β_2	rate at which a GAS carrier can infect a susceptible
μ	per capita natural death rate of all compartment
Ò	rate at which a carrier becomes symptomatic GAS individual
δ_1	rate at which a symptomatic GAS individual develops ARF
δ_2	rate at which a carrier develops ARF

2.2 Stochastic model

A continuous time Markov chain (CTMC) associated with the deterministic counterpart is presented. As opposed to the deterministic model, the stochastic model better explains the uncertainty and variability in a real epidemic due to the complex pattern of human contact, which is unpredictable [29-31]. In this study, however, the aim is to demonstrate the random nature via the simulated trajectories which can be compared with the numerical solution of the deterministic model, while we left the stochastic analysis as the future extension.

The multivariate random process is assumed to obey the Markov property where the meaning is the same as in the deterministic model. Hence, we denote $S(t)$, $I(t)$, $C(t)$ and $A(t)$ as the stochastic processes that have a common state space $\{1,2,3,...,N\}$ where $t \in [0,\infty)$. We note that the values of discrete random variables are denoted by the lower case. The transition probabilities related with a small period of time $\Delta t > 0$ is given by

$$P\Big(\big(S(t+\Delta t), I(t+\Delta t), C(t+\Delta t), A(t+\Delta t)\big) = (s+j, i+k, c+m, a+n) \mid \big(S(t), I(t), C(t), A(t)\big) = (s,i,c,a)\Big). \tag{5}$$

The transition probability is time-homogeneous and satisfies the Markov property. Summarized in Table 2 are the changes, $\Delta S, \Delta I, \Delta C$ and ΔA associated with thirteen events. Given $I(0) = i > 0$ and $C(0) = c > 0$, the state (s,i,c,a), where $I = 0$ and $C = 0$ refer to absorbing states; the epidemic ends at time t when an absorbing state is reached.

Table 2. Model assumptions

Event	Change ($\Delta S, \Delta I, \Delta C, \Delta C$)	Probability
Infection to I	$(-1,1,0,0)$	$s(\beta_1 i + \beta_2 c)\Delta t + o(\Delta t)$
Death of S	$(-1,0,0,0)$	$\mu s \Delta t + o(\Delta t)$
Recruitment	$(1,0,0,0)$	$\Lambda \Delta t + o(\Delta t)$
Recover from A to S	$(1,0,0,-1)$	$\gamma_2 a \Delta t + o(\Delta t)$
Recover from I to S	$(1,-1,0,0)$	$\theta \gamma_1 i \Delta t + o(\Delta t)$
Recover from I to C	$(0,-1,1,0)$	$(1-\theta)\gamma_1 i \Delta t + o(\Delta t)$
Recover from I to A	$(0,-1,0,1)$	$\delta_1 i \Delta t + o(\Delta t)$
Death of I	$(0,-1,0,0)$	$\mu i \Delta t + o(\Delta t)$
Moving from C to I	$(0,1,-1,0)$	$\grave{o} c \Delta t + o(\Delta t)$
Develop from C to A	$(0,0,-1,1)$	$\delta_2 c \Delta t + o(\Delta t)$
Death of C	$(0,0,-1,0)$	$\mu c \Delta t + o(\Delta t)$
Death of A	$(0,0,0,-1)$	$\mu a \Delta t + o(\Delta t)$

For any event other than in Table 2, we let $(\Delta S, \Delta I, \Delta C, \Delta A) = (0,0,0,0)$.

2.3 Simulation and the basic reproduction number

Here, we implement numerical simulation for stochastic realization (sample path) of the process. Gillespie [29] developed a numerical method for the simulation of CTMC models, which is known

as the Gillespie algorithm or the stochastic simulation algorithm. The Markov property implies that inter-event time is exponentially distributed, where a parameter λ is the sum of the rates for all possible events:

$$\lambda = \Lambda + s\left(\beta_1 i + \beta_2 c\right) + \gamma_2 a + \theta\lambda_1 i + \left(1-\theta\right)\gamma_1 i + \delta_1 i + \grave{o}c + \delta_2 c + \mu\left(s + i + c + a\right), \tag{6}$$

where (s, i, c, a) is specific for the state of (S , I , C , A) at a given time t. From the inverse method, we obtain the value of the inter-event time τ by

$$\tau = -\frac{\ln u_1}{\lambda} \tag{7}$$

where u_1 is a uniform random generator. To determine which event will occur, we construct a probability distribution of twelve events, i.e., p_i , $i = 1, 2, \text{K}\ 12$, and hence apply the inverse method by generating a second uniform random value, u_2 such that if u_2 lies in k-th subinterval among [0, p_1], (p_1, $p_1 + p_2$] ,…, ($p_1 + p_2 + ... + p_{11}$, 1], then the k-th event occurs.

Since $A = N - S - I - C$, we denote the disease-free equilibrium of the model as

$$E_0 = (S_0, I_0, C_0) = (\Lambda / \mu, 0, 0) .$$

We then derive the basic reproduction number, R_0 by using the next generation method [32]. Therefore, we obtain

$$R_0 = \frac{\Lambda}{\mu}\left\{\frac{\beta_1(\grave{o} + \delta_2 + \mu) + \beta_2(1-\theta)\gamma_1}{\gamma_1(\delta_2 + \mu + \grave{o}\theta) + (\delta_1 + \mu)(\grave{o} + \delta_2 + \mu)}\right\}. \tag{8}$$

3. Results and Discussion

3.1 Stability analysis

Let us begin with the existence and uniqueness of the endemic equilibrium $E^* = (S^*, I^*, C^*)$. By solving the system of algebraic equations, and rewriting in terms of R_0 , we have

$$S^* = \frac{\Lambda}{\mu R_0}, \tag{9}$$

$$I^* = \frac{\Lambda}{\mu}\left(1 - \frac{1}{R_0}\right)\left(\grave{o} + \delta_2 + \mu\right)\eta, \tag{10}$$

and

$$C^* = \frac{\Lambda}{\mu}\left(1 - \frac{1}{R_0}\right)\left(1-\theta\right)\gamma_1\eta \tag{11}$$

where

$$\eta = \frac{\left(\grave{o} + \delta_2 + \mu\right)}{\left(\gamma_2 + \delta_1 + \mu\right)\left(\grave{o} + \delta_2 + \mu\right) + \gamma_1\left(1-\theta\right)\left(\gamma_2 + \delta_2 + \mu\right)}.$$

Since the endemic equilibrium is biological meaningful when all variables are positive, from above expression, E^* can be uniquely determined when $R_0 > 1$.

The stability of E_0 can be determined by calculating the Jacobian matrix

$$J(E_0)=\begin{pmatrix} -(\gamma_2+\mu) & \theta\gamma_1-\gamma_2-\dfrac{\beta_1\Lambda}{\mu} & -\left(\dfrac{\beta_2\Lambda}{\mu}+\gamma_2\right) \\ 0 & \dfrac{\beta_1\Lambda}{\mu}-(\gamma_1+\delta_1+\mu) & \dfrac{\beta_2\Lambda}{\mu}+\grave{o} \\ 0 & (1-\theta)\gamma_1 & -(\grave{o}+\delta_2+\mu) \end{pmatrix}. \tag{12}$$

The characteristic equation is given by

$$(\lambda+\gamma_2+\mu)\left(\lambda^2+c_1\lambda+c_2\right)=0 \tag{13}$$

where

$$c_1=2\mu+\grave{o}+\delta_1+\delta_2+\gamma_1-\frac{\beta_1\Lambda}{\mu}, \tag{14}$$

$$c_2=-(\grave{o}+\delta_2+\mu)\left(\frac{\beta_1\Lambda}{\mu}-\gamma_1-\delta_1-\mu\right)-\gamma_1(1-\theta)\left(\frac{\beta_2\Lambda}{\mu}+\grave{o}\right). \tag{15}$$

Due to the presence of trivial eigenvalue, the problem is reduced to the second order equation. Suppose that $R_0<1$, from equation (15), we find $c_2>0$. Hence, it follows that $c_1>0$. Therefore, we find that the disease-free equilibrium E_0 is locally asymptotically stable if $R_0<1$.

Next, we will derive the conditions for which the endemic is stable. Let us suppose that $R_0>1$, and define

$$R_0^{(1)}=\frac{1}{(\grave{o}+\delta_2+\mu)\eta}, \qquad R_0^{(2)}=\frac{1}{(1-\theta)\gamma_1\eta}.$$

We calculate a Jacobian matrix at $E^*=(S^*,I^*,C^*)$,

$$J=\begin{pmatrix} -\beta_1I^*-\beta_2C^*-\gamma_2-\mu & -\beta_1S^*-\gamma_2+\theta\gamma_1 & -\beta_2S^*-\gamma_2 \\ \beta_1I^*+\beta_2C^* & \beta_1S^*-(\gamma_1+\delta_1+\mu) & \beta_2S^*+\grave{o} \\ 0 & (1-\theta)\gamma_1 & -(\grave{o}+\delta_2+\mu) \end{pmatrix},$$

and hence obtain the characteristic equation

$$\lambda^3+a_1\lambda^2+a_2\lambda+a_3=0 \tag{16}$$

where

$$a_1=\beta_1(I^*-S^*)+\beta_2C^*+\gamma_2+\mu+\gamma_1+\delta_1+\mu+\grave{o}+\delta_2+\mu,$$

$$a_2=\beta_1I^*\left(\delta_1+(1-\theta)\gamma_1\right)+\beta_1\left(I^*-S^*\right)\left(2\mu+\gamma_2+\grave{o}+\delta_2\right)+\beta_2C^*\left(\delta_1+\mu+\gamma_2\right)+\left(\gamma_2+\mu\right)\left(\gamma_1+\delta_1+\mu\right)$$
$$+\left(\beta_2C^*+\gamma_2+2\mu+\delta_1\right)\left(\grave{o}+\delta_2+\mu\right)+\gamma_1\left(\delta_2+\mu+\grave{o}\theta\right)+(1-\theta)\gamma_1\beta_2\left(C^*-S^*\right),$$

$$a_3=\beta_1I^*(1-\theta)\gamma_1\left(\delta_2+\mu\right)+\beta_2C^*(1-\theta)\gamma_1\delta_2+\beta_2\left(C^*-S^*\right)(1-\theta)\gamma_1+\left(\beta_1I^*+\beta_2C^*\right)\delta_1\left(\grave{o}+\delta_2+\mu\right)$$
$$+\left(\beta_1\left(I^*-S^*\right)+\beta_2C\right)\left(\grave{o}+\delta_2+\mu\right)\left(\mu+\gamma_2\right)+\left(\mu+\gamma_2\right)\left(\gamma_1\left(\delta_2+\mu\right)+\left(\delta_1+\mu\right)\left(\grave{o}+\delta_2+\mu\right)\right)$$
$$+\gamma_2(1-\theta)\gamma_1\left(\beta_1I^*+\beta_2\left(C^*-S^*\right)+\grave{o}\theta\gamma_1\left(\mu+\gamma_2\right)\right).$$

According to Routh-Hurwitz criteria [33], the necessary condition for the real parts of all eigenvalues are negative is that the coefficients of the characteristic equation (16) must be positive.

Observe that if $R_0 > R_0^{(1)}$, then $I^* - S^* > 0$ leads to $a_1 > 0$, and hence $C^* - S^* > 0$ which leads to $a_3 > 0$. Thus, it is immediate that if $R_0 > R_0^{(1)}$, and $R_0 > R_0^{(2)}$ then $a_2 > 0$. Finally, after some tedious work, it can be verified that if such two conditions hold, then we find $a_1 a_2 - a_3 > 0$. The last condition fulfills the necessary and sufficient conditions in Routh-Hurwitz criterion.

In summary, we have that the endemic equilibrium is asymptotically stable if

$$R_0 > 1 + \max\left\{R_0^{(1)}, R_0^{(2)}\right\}.$$

In order to assure the stability of the endemic state, the value of the basic reproduction number must satisfy the above condition. The additional parameters, such as $R_0^{(1)}$ and $R_0^{(2)}$, merely provide the sufficient conditions for this to happen. Further analysis, such that the above condition does not hold while $R_0 > 1$, requires a deeper investigation into the parameter relationship which is beyond the scope of this study.

3.2 Numerical results

To support our theoretical results, we present numerical results where the total population is assumed as $N = 1000$ and other parameter values, including the references are provided in Table 3. In this section, the numerical solutions of deterministic models will be compared with the sample paths of the stochastic model.

From the range of parameter values, we first choose $\beta_1 = 0.00089$, $\beta_2 = 0.000001$, $\grave{o} = 0.0027$ and $\gamma_1 = 0.8$. From the analytic results, it follows that $E_0 = (1,000, 0, 0)$ and $R_0 = 0.8926$. Thus, these parameter values combined with the rest in Table 3, form a set of parameters at which the disease will eventually die out. Figure 2 (a) illustrates the time-dependent solutions of the deterministic model confirming the accordance with theoretical prediction.

Table 3: The values of the parameters

Parameters	Values	Units	Reference
γ_1	0.1−1	day^{-1}	[12]
θ	0.9	-	[12]
γ_2	0.8 0.8	day^{-1}	[12]
μ	0.00004	day^{-1}	[1]
$\grave{o}$	0.0027 – 0.0110	day^{-1}	[1]
δ_1	0.2	day^{-1}	[12]
δ_2	0.1	day^{-1}	Estimated
Λ	0.04	$\text{person}\cdot\text{day}^{-1}$	[1]
β_1	0.00089 – 0.0099	$\text{person}^{-1}\cdot\text{day}^{-1}$	[1]
β_2	0.000001 – 0.0005	$\text{person}^{-1}\cdot\text{day}^{-1}$	[1]

The graph of the solutions shown in Figure 2 (b) illustrates the dynamic behavior of deterministic model when we choose $\beta_1 = 0.00356, \beta_2 = 0.000004$, and The difference from the previous case is that we increase the contact rates from both infected groups and reduce the treatment rate. Based on these parameter values, we find that $E^* = (252.1, 370.9, 252.7, 124.3)$ $R_0^{(1)} = 2.0162$,

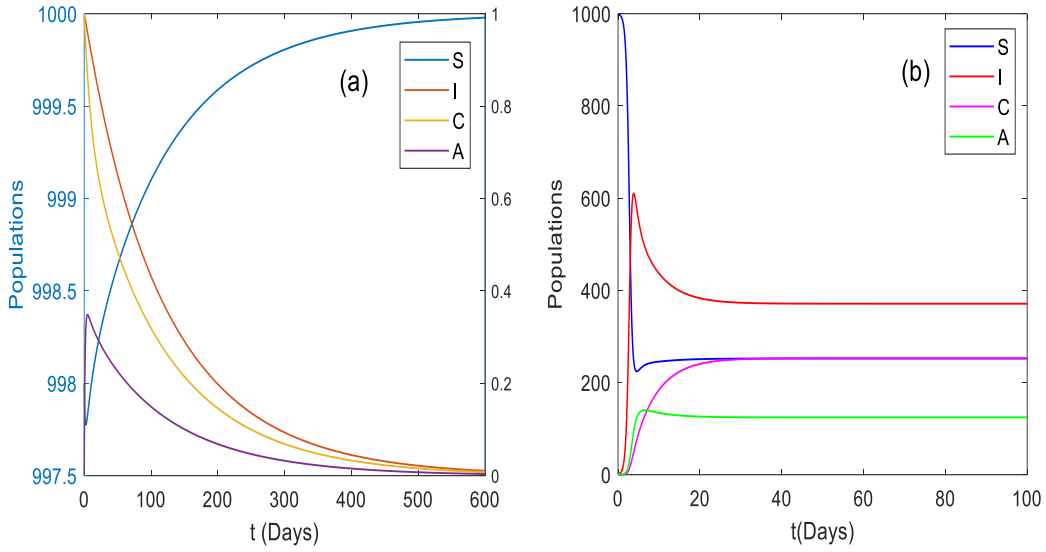

Figure 2. The solution curves of deterministic model with initial conditions $S(0)=999$ and $I(0)=1$. (a) Disease-free equilibrium E_0 is asymptotically stable when $R_0<1$ and (b) endemic equilibrium E^* is asymptotically stable when $R_0>1+\max(R_0^{(1)},R_0^{(2)})$.

$R_0^{(2)}=2.5903$ and $R_0=3.9666$, respectively. To consider the long-term epidemic pattern, we see that, on average, there will be about 37% who have symptomatic infections, and about 12.43% are expected to develop the ARF condition in the future. We note that rate of increase of the force of infection by the contact rates from each infectious group is the same at 300%, while the treatment rate is reduced by only 12.5%.

Let us now focus on the sample paths of the stochastic model. As in the deterministic case, the graph will be plotted in the case $R_0<1$ and $R_0>1+\max(R_0^{(1)},R_0^{(2)})$ using the same parameter values and initial conditions. In the absence of the theoretical conjecture, it can be argued that, for $R_0<1$, a minor outbreak may exist with a positive probability [24]. This implies that under the small number of infectious individuals, there is a fraction of realizations that indicates the presence of successful transmission of a small magnitude and a finite time interval, while the remaining paths are instantly extinct in the successive step by chance. This is referred to as the minor epidemic. In our case, the minor outbreak is observed in Figure 3 (a).

In contrast to the minor outbreak, the system may possess the major outbreak or endemic persistence. The fifty sample paths are plotted in Figure 3 (b), demonstrating a random fluctuating pattern around its mean. In this case (but not always), the paths also fluctuate around the solution of deterministic model. It is possible that the more samples, the more deviation is observed. However, most of the paths fluctuate around the endemic level under the degree of variability.

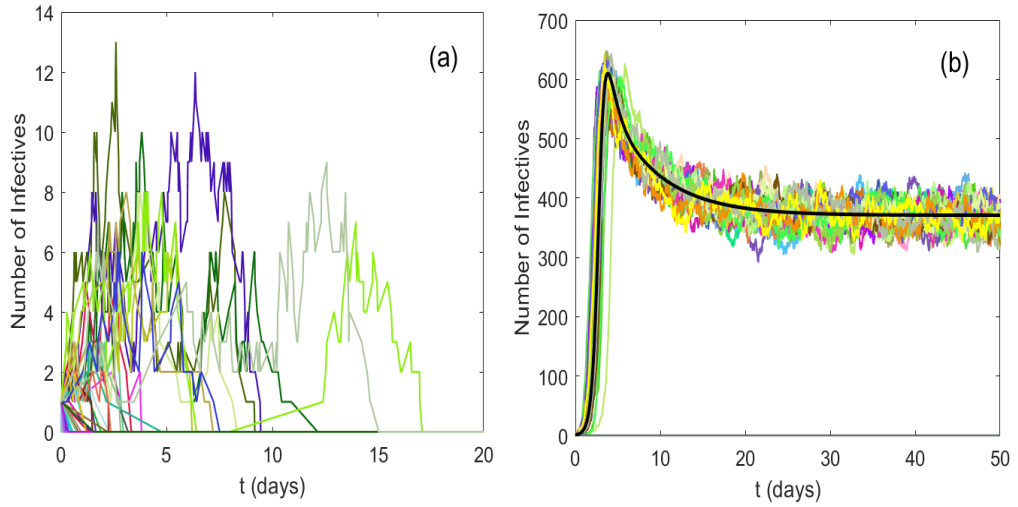

Figure 3. Simulations of ample paths. (a) The fifty sample paths when $R_0 < 1$. (b) The dashed curve is the ODE solution (black solid line) and the other curves are fifty sample paths when $R_0 = 3.9666$.

4. Conclusions

In the deterministic model, we found two equilibrium points. The disease-free equilibrium is locally asymptotically stable when the basic reproduction number less than one. The endemic equilibrium is locally asymptotically stable when the basic reproduction number is greater than one plus the maximum of two additional parameters. Due to the complexity of parameter relations, these two parameters are difficult to interpret in terms of biological meaning. In fact, further analysis to establish the stronger stability condition is required.

Qualitative comparison between deterministic and stochastic dynamics can be made via numerical simulations. Although the trend of stochastic realizations behaves in the similar fashion with the deterministic solutions subject to the stable condition of endemic state, when the basic reproduction number is less than one, their behaviors are quite different. This is because of the stochastic nature of individuals. The further extension should be determination of the probability of extinction and the probability of the outbreak, analysis of the stochastic fade out, and quantification of variance.

From sensitivity analysis, the most effective parameter relevant to the outbreaks of disease is the rate at which an infected individual can infect a susceptible one. From sensitivity index, we note that the parameter that can be practically controlled to directly reduce the outbreak of disease is β_1 . While these analyses can be easily done for the deterministic model, the role of parameter variation can alter the stochastic behaviors if they are quantified. We conclude that the cooperation between the two approaches may be mutually supportive and produce insight into the disease dynamics, knowledge that can facilitate disease management and control.

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