

The role of vaccination in controlling the outbreak of infectious diseases: a mathematical approach

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ABSTRACT

Introduction: Infectious diseases threaten the public health; hence understanding their propagation mechanisms may help to control them. Mathematical models are tools that can help the scientists to understand the pathogens' propagations and can provide strategies for their control in future. **Methods:** Using mathematical theorems and MATLAB software, a continuous-time model known as susceptible-infected-susceptible (SIS) for transmission of infection in a population was described and the effects of a vaccination program based on this framework was investigated. **Results:** It was shown that the model had two equilibria: the infection-free equilibrium and the infected equilibrium. A specific threshold in terms of model parameters was obtained and then the existence of the equilibria and asymptotic stability of the system were stated with respect to this threshold. The theoretical results were also verified numerically by providing several simulations. **Conclusion:** The results indicated the stability of this model which emphasized that parameters such as restricting the immigration, reducing harmful contacts between the susceptible and the infected individuals, increasing awareness level of people, and most-importantly vaccination will reduce the basic reproduction number and help to control the disease. Moreover, a relation to calculate the minimum doses for vaccinating of the new-comers and the susceptible individuals, was obtained.

KEYWORDS: Dynamical system, Epidemiological model, SIS model, Stability, Vaccine.

INTRODUCTION

The spread of various infections is a constant threat for the public health. Thus, understanding the mechanisms of propagation of pathogens and then finding ways to control them are a serious challenge for the public health authorities. Mathematical models are instruments that can help scientists to understand how the infections spread, how to identify them, how to provide strategies for controlling the diseases and how to forecast the possible outbreaks of diseases in the future. In mathematical epidemiology, each person, based on his/her disease status, lies in only one sub-population or compartment. All per capita changes in each compartment are obtained by identifying the number of individuals who enter, exit, or transmit in a unit of time. Therefore, the spread of infectious diseases can be described by using mathematical models. Such compartmental models which are often called "epidemic models" have been introduced for various types of diseases [1-5]. The infectious disease modeling is often deterministic and is mainly formulated by differential equations for continuous-time models [6, 7] or by difference equations for discrete-time models [8, 9]. In recent years, stochastic modeling has been gaining more attention because it also considers randomness effects on a dynamical system and thus leads to providing more

realistic models [10, 11]. Here, an epidemic model is investigated and its properties and stability are investigated. Moreover, the theoretical results have been discussed by providing several numerical examples and simulations.

MATERIALS and METHODS

The SIS model

The susceptible-infected-susceptible (SIS) epidemic models are one of the well-known types of epidemic models. In these models, susceptible individuals become infectious immediately after a successful contact with infected individuals (transition from compartment *S* to *I*) while the infected individuals recover from the infection and will return to compartment *S* after a period of time (transition from compartment *I* to *S*). Thus, a SIS model is appropriate for those infections in which the infected individuals do not get permanent immunity after recovery and become susceptible again after a period of time. The SIS models are widely addressed in the literature. For instance, some authors have specially discussed a SIS model [12-14] while some others have investigated the SIS-based models and have also considered the effects of some issues such as treatment [15], quarantine [16] and vaccination [17] on the studied population. Selecting a suitable SIS model depends on the disease under study and its corresponding population in which the study is conducted. Obviously, an enriched model

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with more details can better describe a population behavior. However, additional details will make the model analysis more difficult and complicated. These models may consider a constant or a variable number for the population size. They may also contain vital dynamics such as natural births and deaths, immigration, disease-caused deaths and various incidence functions.

The following version of the SIS model contains vital dynamics as births or immigration, natural deaths, and disease-related deaths:

$$\begin{aligned}\frac{dS}{dt} &= r - \frac{\beta SI}{S+I} - dS + \sigma I, \\ \frac{dI}{dt} &= \frac{\beta SI}{S+I} - (d + \sigma + \delta)I,\end{aligned}\quad (1)$$

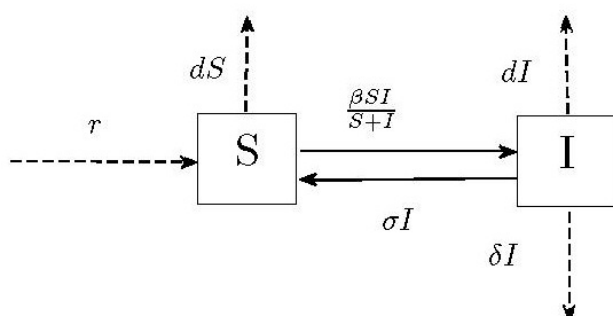


Fig. 1. Diagram of possible transitions of individuals in a SIS model.

As it is shown in Fig. 1, a population has been divided into two sub-populations as susceptible and infectious individuals with S and I individuals at time t in each one. The letters r and d are the recruitment rate and the natural death rate, respectively while δ denotes the rate of death due to an infection. The susceptible individuals become infectious at standard incidence rate $\beta SI / N$ (where β is the transmission coefficient; contact rate) and recover from the infection with the rate of σ . All parameters are assumed to be non-negative, in addition to $r \neq 0$ and $d \neq 0$.

The equilibria of the model in the form (\bar{S}, \bar{I}) are obtained by solving the following system:

$$\begin{aligned}r - \frac{\beta \bar{S} \bar{I}}{\bar{S} + \bar{I}} - d\bar{S} + \sigma \bar{I} &= 0, \\ \frac{\beta \bar{S} \bar{I}}{\bar{S} + \bar{I}} - (d + \sigma + \delta)\bar{I} &= 0.\end{aligned}\quad (2)$$

As it can be seen, two equilibria exist. The equilibrium $E^0 = \left(\frac{r}{d}, 0\right)$ is called the infection-free equilibrium and the

equilibrium $E^* = \frac{r}{dR_0 + \delta(R_0 - 1)}(1, R_0 - 1)$ is called

the infected equilibrium. Here, R_0 is the basic reproduction number of model (1) and it can be found [18, 19] as

$$R_0 = \frac{\beta}{d + \sigma + \delta}. \quad (3)$$

It is seen that E^* exists, if $R_0 > 1$. Therefore, we can state the following lemma:

Lemma 1: For system (1), the infected-free equilibrium E^0 always exists while the infected equilibrium E^* exists only when $R_0 > 1$.

In the following theorem, we consider the local asymptotic stability of the system.

Theorem 1: For system (1)

(I) E^0 is stable if $R_0 < 1$ and it is unstable if $R_0 > 1$,

(II) E^* is stable if $R_0 > 1$.

For the proof, please see Appendix A.

The SIS model and vaccination

To control and eliminate the infectious diseases, vaccination is usually a preferred mean of action due to its efficiency, compared with the other measures. The effect of a vaccine can be studied in an infectious disease modeling by considering a compartment for the vaccinated individuals in addition to the other compartments (e.g. the susceptible, the infected, etc.) [20-22]. Therefore, we consider the vaccinated individuals as a separate sub-population in the model (1). The vaccination program is applied on both the new members (with rate ν) and the susceptible individuals (with rate ρ). Although it is assumed to be completely effective, the conferred immunity is lost by passage of time (with rate θ). The under study SIS model with vaccination (also known as SIVS model), is stated by a system of differential equations as (4). Furthermore, Fig. 2 shows all possible changes in the compartments of the model and Table 1 describes its variables and parameters.

$$\begin{aligned}\frac{dS}{dt} &= (1-\nu)r + \sigma I + \theta V - \frac{\beta SI}{S+I+V} - (d + \rho)S, \\ \frac{dI}{dt} &= \frac{\beta SI}{S+I+V} - (d + \sigma + \delta)I, \\ \frac{dV}{dt} &= \nu r + \rho S - (d + \theta)V.\end{aligned}\quad (4)$$

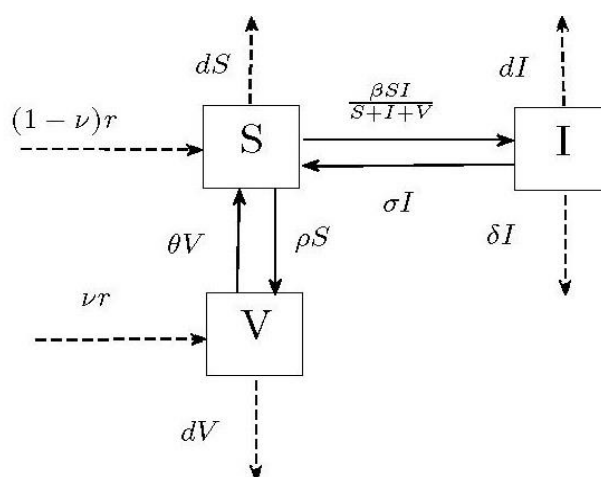


Fig. 2. Diagram of possible transitions in SIS model with vaccination.

Table 1. Notations used in model (4) and their interpretations

Notation	Name	Category	Description
t	Time	Independent variable	Length of time passed from entering the infection to the population
S	Susceptible individuals	Dependent variable	Number of individuals at time t who can get the infection if they are exposed to it
I	Infected Individuals	Dependent variable	Number of individuals at time t who are capable to spreading the infection
V	Vaccinated Individuals	Dependent variable	Number of individuals at time t who are immune from the infection by vaccination
r	Recruitment rate	Parameter, Constant	Number of newborns or immigrant individuals who enter the population per unit of time
β	Contact rate	Parameter, Constant	Rate at which the susceptible individuals become infected
σ	Treatment rate	Parameter, Constant	Rate at which the infected individuals recover from the infection
d	Natural death rate	Parameter, Constant	Rate at which the individuals die from the natural causes
δ	Disease death rate	Parameter, Constant	Rate at which the infected individuals die from the infection
ν	Vaccination proportion of new members	Parameter, Constant	Proportion of new members who are vaccinated
ρ	Vaccination rate of susceptible individuals	Parameter, Constant	Rate at which the susceptible individuals are vaccinated
θ	Immunity lost rate	Parameter, Constant	Rate at which the vaccinated individuals lose their immunity

System (4) has two equilibria in form of $(\bar{S}, \bar{I}, \bar{V})$. The infection-free equilibrium of the model is:

$$EV^0 = \left(\frac{r(d(1-\nu)+\theta)}{d(d+\theta+\rho)}, 0, \frac{r(d\nu+\rho)}{d(d+\theta+\rho)} \right),$$

and the infected equilibrium is:

$$EV^* = \left(\frac{r(d+\sigma+\delta)}{\beta d} \left(1 - \frac{\delta(\bar{R}_0-1)}{dR+\delta(R-1)} \right), \frac{r(\bar{R}_0-1)}{dR+\delta(R-1)}, \frac{\nu r}{d+\theta} \left(1 + \frac{\rho(d+\delta\nu+\theta)/(d+\rho+\theta)}{dR+\delta(R-1)} \right) \right),$$

in which:

$$\bar{R}_0 = \frac{\beta(d(1-\nu)+\theta)}{(d+\sigma+\delta)(d+\rho+\theta)},$$

is the basic reproduction number of model (4) and

$$R = \frac{\beta(d+\theta)}{(d+\sigma+\delta)(d+\rho+\theta)}.$$

Similar to the previous section we can show:

Lemma 2: System (4) has only the infection-free equilibrium EV^0 when $\bar{R}_0 \leq 1$ and it also has a unique infected equilibrium EV^* if $\bar{R}_0 > 1$.

In the following theorem, the local asymptotic stability of the infected equilibrium is considered:

Theorem 2: For model (4),

(I) the infection-free equilibrium EV^0 is stable if $\bar{R}_0 < 1$ and it is unstable if $\bar{R}_0 > 1$,

(II) the infected equilibrium EV^* is stable if $\bar{R}_0 > 1$.

For the proof, please see Appendix B.

RESULTS and DISCUSSION

By implementing some codes in MATLAB software (version 7) and using various values for the parameters, as well as for the number of initial individuals in each sub-population, we numerically challenged the theoretical results obtained in the preceding sections. Supposing that the value of parameters in model (1) are $r = 60$, $\beta = 0.08$, $d = 0.05$, $\sigma = 0.05$, and $\delta = 0.25$; these values imply that $R_0 = 0.2286 < 1$ and according to Theorem 1, the infection-free equilibrium E^0 is stable. This result can also be concluded from Table 2, using eigenvalues of the Jacobian matrix (7) of the model (1) at E^0 . We see that eigenvalues λ_1 and λ_2 are both negative and thus E^0 is stable. From a biological point of view, this means the disease will be extinct in this case. On the other hand, Fig. 3 displays the solutions of $S(t)$ and $I(t)$, and also a phase portrait of the solutions when different initial values are used for the number of individuals in each sub-population. It can be seen that the solutions tend to the disease-free equilibrium $E^0 = (1200, 0)$.

Table 2. Stability of the model (1) for parameter values as $r = 60$, $\beta = 0.08$, $d = 0.05$, $\sigma = 0.05$, and $\delta = 0.25$.

Equilibrium	\bar{S}	\bar{I}	λ_1	λ_2	Stability
E^0	1200	0	-0.05	-0.27	Stable
E^*	-33.07	255.12	0.11+ 0.45i	0.11- 0.45i	Unstable

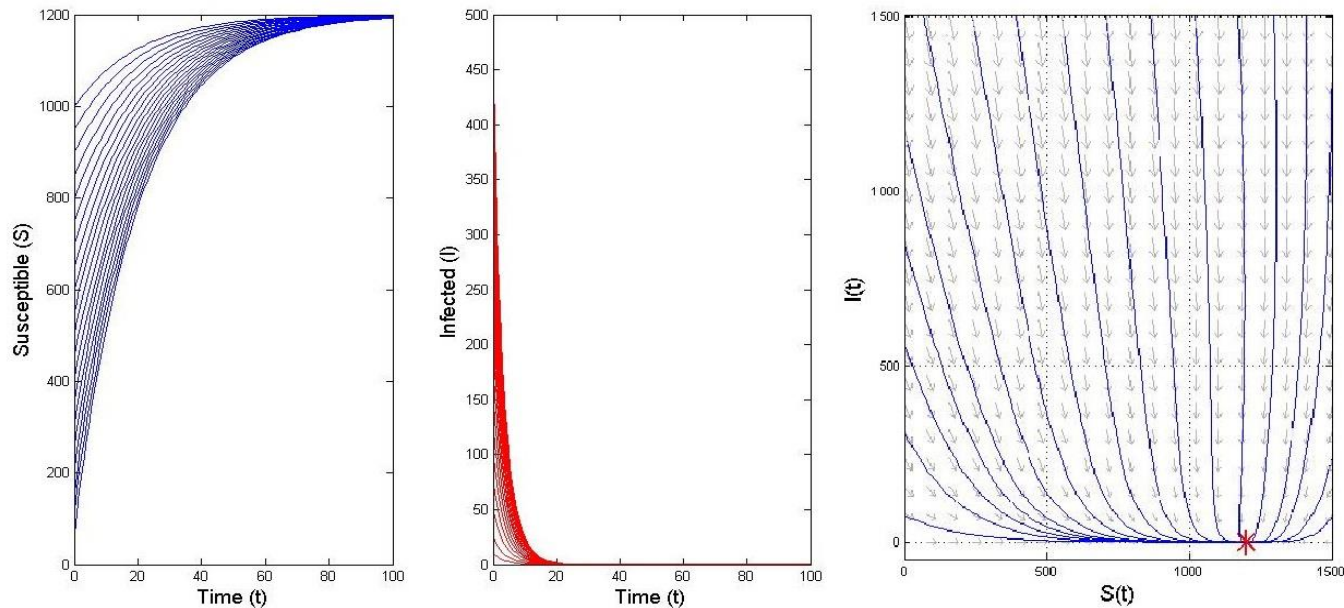


Fig. 3. Solutions of SIS epidemic model (1) for different initial numbers $S(0)$ and $I(0)$ with parameters of the model as $r = 60$, $\beta = 0.08$, $d = 0.05$, $\sigma = 0.05$, and $\delta = 0.25$. For these values, $R_0 = 0.2286 < 1$ and disease will be vanished.

Now, we consider different values for $\beta = 0.8$, $\sigma = 0.2$, and $\delta = 0.1$. For these values, $R_0 = 2.2857 > 1$ and thus the infected equilibrium E^* is stable as it was stated in Theorem 1. Table 3 also verifies this behavior. Furthermore, Fig. 4 shows

how solutions of the model (1) with different initial values, converge to $E^* = (247.06, 317.65)$. In this case, disease will remain at a positive level in the population and it will be endemic.

Table 3. Stability of the model (1) for parameter values as $r = 60$, $\beta = 0.8$, $d = 0.05$, $\sigma = 0.2$, and $\delta = 0.1$.

Equilibrium	\bar{S}	\bar{I}	λ_1	λ_2	Stability
E^0	1200	0	-0.05	0.45	Unstable
E^*	247.06	317.65	-0.37	-0.13	Stable

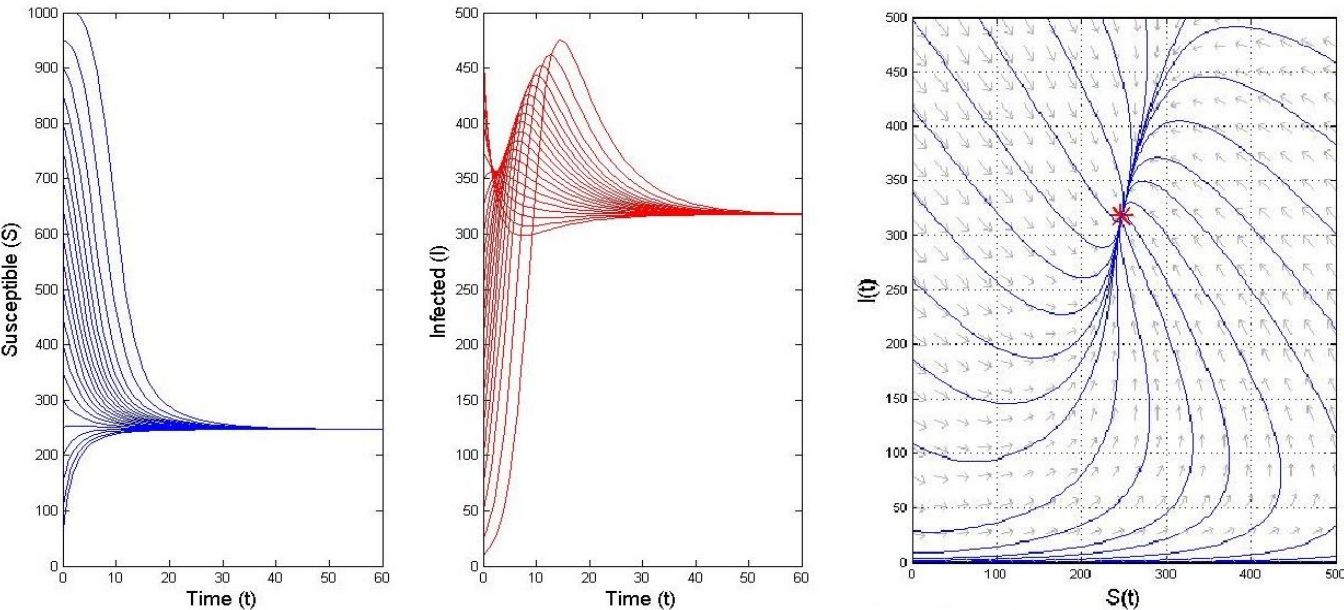


Fig. 4. Solutions of SIS epidemic model (1) for different initial numbers $S(0)$ and $I(0)$ with parameters of the model as $r = 60$, $\beta = 0.8$, $d = 0.05$, $\sigma = 0.2$, and $\delta = 0.1$. For these values, $R_0 = 2.2857 > 1$ and disease will remain in the population.

In such a situation (*i.e.* when $R_0 > 1$), we introduce a vaccination program to the population as stated in model (4), in

order to control and eliminate the disease. The vaccination program includes both new the members and the susceptible

individuals and the vaccine doses must consider at such level that $\check{R}_o < 1$. Obviously, $\check{R}_o = R_o \left(\frac{d(1-\nu) + \theta}{d + \rho + \theta} \right)$, and thus $\check{R}_o < R_o$. This relation states that the basic reproduction in presence of the vaccine is less than another one in the absence of the vaccine and therefore the disease is more controllable. For this purpose, the vaccine doses ν and ρ must be chosen as such that the following inequality holds:

$$R_0 d \nu + \rho > (d + \theta)(R_0 - 1). \tag{5}$$

If we take $\nu = 0.25$, $\rho = 0.2$ and $\theta = 0.08$ together with the previous parameter values, we find that $\check{R}_o = 0.8139 < 1$. Thus, according to Theorem 2, the infection-free equilibrium EV^0 is stable and disease extinction occurs (see Table 4 and Fig. 5). On the other hand, when we only change $\nu = 0.125$ and $\rho = 0.1$, we have $\check{R}_o = 1.2298 > 1$ and the infected equilibrium EV^* is stable. Therefore, the vaccine doses are not enough to eradicate the infection and the disease will persist in the population (see Table 5 and Fig. 6).

Table 4. Stability of the model (4) for parameter values as $r = 60$, $\beta = 0.8$, $d = 0.05$, $\sigma = 0.2$, $\delta = 0.1$, $\nu = 0.25$, $\rho = 0.2$ and $\theta = 0.08$.

Equilibrium	\bar{S}	\bar{I}	\bar{V}	λ_1	λ_2	λ_3	Stability
EV^0	427.27	0	772.73	-0.12	-0.38	-0.07	Stable
EV^*	0.8037e3	-0.3185e3	1.3519e3	-0.34	-0.12	0.10	Unstable

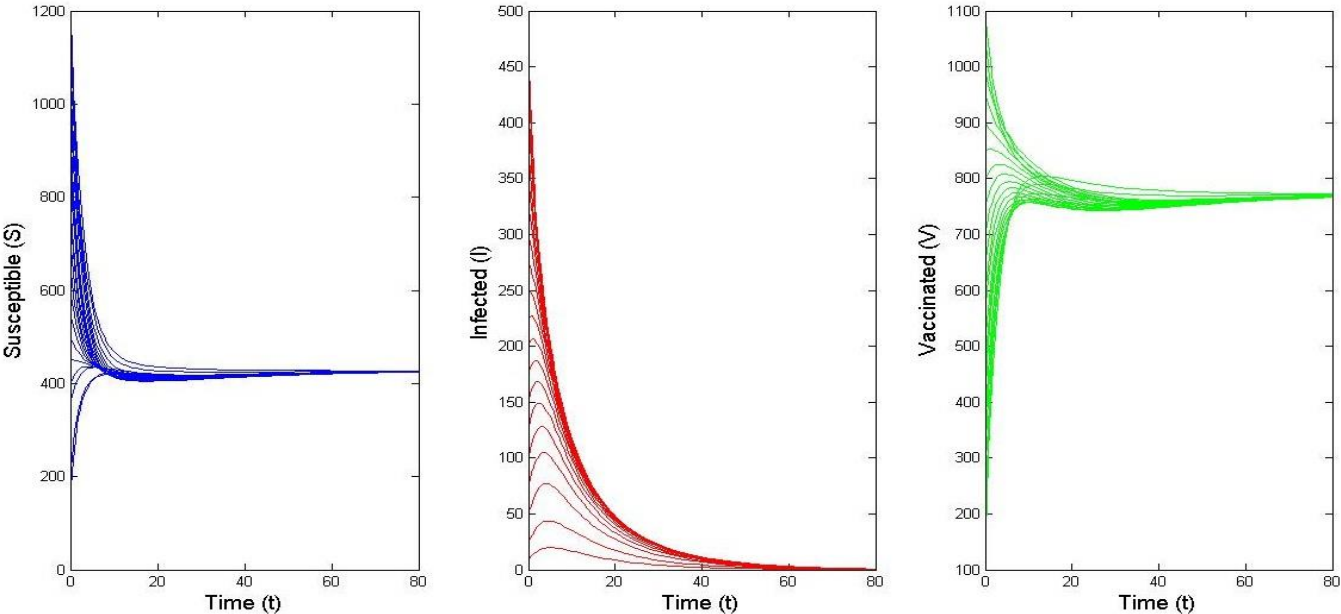


Fig. 5. Solutions of epidemic model (4) for different initial numbers $S(0)$, $I(0)$ and $V(0)$ with parameters of the model as $r = 60$, $\beta = 0.8$, $d = 0.05$, $\sigma = 0.2$, $\delta = 0.1$, $\nu = 0.25$, $\rho = 0.2$ and $\theta = 0.08$. These values yield to $\check{R}_o = 0.8139 < 1$.

Table 5. Stability of the model (4) for parameter values as $r = 60$, $\beta = 0.8$, $d = 0.05$, $\sigma = 0.2$, $\delta = 0.1$, $\nu = 125$, $\rho = 0.1$ and $\theta = 0.08$.

Equilibrium	\bar{S}	\bar{I}	\bar{V}	λ_1	λ_2	λ_3	Stability
EV^0	645.65	0	554.35	-0.06	-0.24	0.08	Unstable
EV^*	396.36	147.02	362.58	-0.28	-0.08+ 0.01 <i>i</i>	-0.08- 0.01 <i>i</i>	Stable

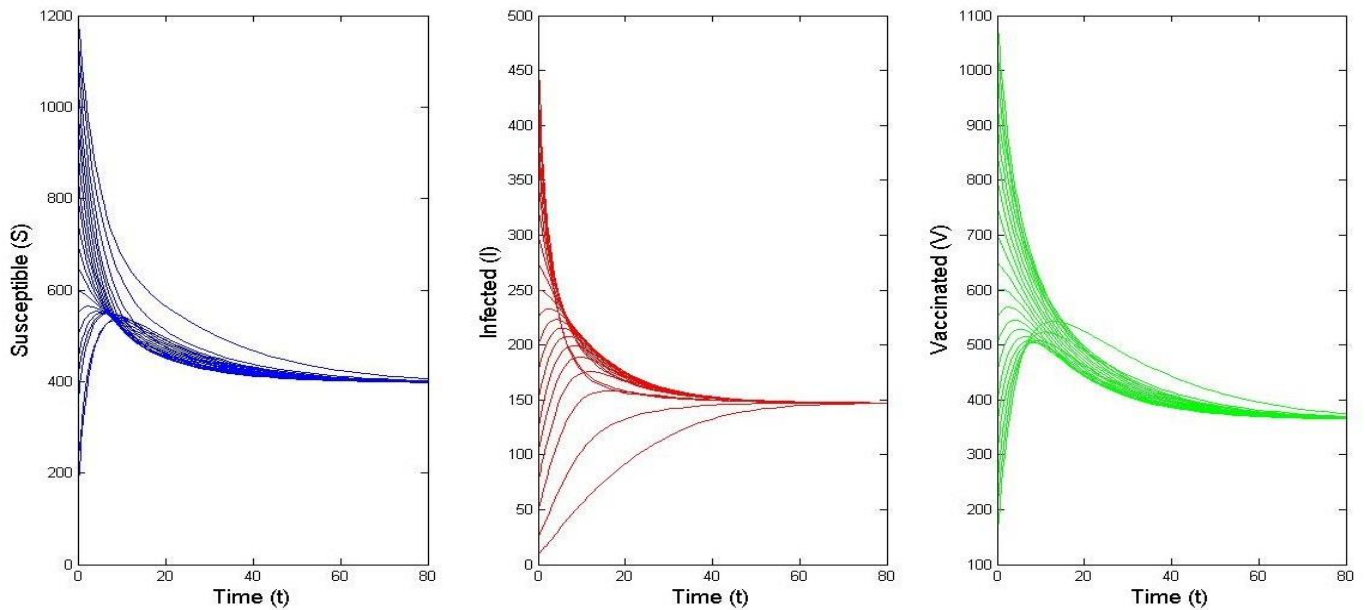


Fig. 6. Solutions of epidemic model (4) for different initial values with parameters of the model as $r = 60$, $\beta = 0.8$, $d = 0.05$, $\sigma = 0.2$, $\delta = 0.1$, $v = 125$, $\rho = 0.1$ and $\theta = 0.08$. For these values $\tilde{R}_0 = 1.2298 > 1$.

Theorems 1 and 2 are confirmed by Fig. 3- 6 and Tables 2- 5, indicating that when the basic reproduction number is less than unity, the infection dies out and otherwise the infection persists in the population and for any initial values, the solutions of models (1) and (4) stably converge to the equilibria.

Considering the basic reproduction number:

$$\tilde{R}_0 = \frac{\beta(d(1-v) + \theta)}{(d + \sigma + \delta)(d + \rho + \theta)},$$

We see r has not been appeared in this quantity and thus \tilde{R}_0 is independent of the incoming members, whereas the number of the infected individuals is directly affected by r . Therefore, reducing fertility and immigration to the population will decrease the number of the infected individuals and helps to control the spread of the disease. All other parameters are contained in \tilde{R}_0 and somehow affect the dynamics of the model. The rates δ and σ are inversely related to \tilde{R}_0 and state an increase in disease-caused deaths (elimination of the infected) and recovery rate (disinfection) will lead to control of the disease. The contact rate β directly affects \tilde{R}_0 and it is clear that this parameter changes the basic reproduction number, more quickly than others. When the contact rate between the infected and the susceptible individuals is very small, the disease can be eliminated. Moreover, informing the people can lead to decrease in harmful contacts and thus awareness level may also be contained in β . It is easy to see that \tilde{R}_0 decreases when vaccination rates v and ρ increase. Thus, certain doses of the vaccine can give appropriate immunity to the individuals and will make \tilde{R}_0 less than unity. This shows that vaccination is a useful strategy for the disease control. Another important attribute of a vaccine is related to its duration of immunity. When the rate of loss of vaccine-induced immunity θ is small, the duration of the immunity becomes

significant. Hence, the efficiency of a vaccine to be used would be important for the public health management. Furthermore, regarding the relation (5), the small rate of loss of immunity θ leads to smaller minimum vaccine doses v and ρ that are required for the disease elimination.

In conclusion, a susceptible-infected-susceptible (SIS) model was introduced. In this model, the total population size is not constant and the demographic changes contain the recruitments (births and immigration) as well as natural deaths and infection-induced deaths. The infection takes place at a standard incidence rate and the infected individuals who recover from the infection can become susceptible to the reinfection, after a period of time. The basic reproduction number (BRN) of this model was obtained and it was shown that the model has two equilibria: the infection-free equilibrium (IFE) and the infected equilibrium (IE). It was proved that IFE always exists and it is stable, if $R_0 < 1$, while IE exists and is stable, if $R_0 > 1$.

Next, in addition to the previous assumptions, a vaccination program was introduced into the SIS model. The vaccination was assumed to be perfect but temporary and included both the new members and the susceptible individuals. BRN of this model, namely, the SIVS model was also obtained and it was shown that this model has also two equilibria. We proved a stability statement similar to the statement we mentioned for the SIS model; however, in terms of its corresponding BRN. It was found that BRN of the SIVS model is less than the corresponding quantity for the SIS model and thus the disease is more controllable in the model with vaccination. Also, following the trace of all model parameters in BRN, it was revealed that restricting the immigration (or births), reducing harmful contacts between the susceptible and the infected individuals, increasing awareness level of people, and of course vaccination will reduce the BRN and help to control the disease. Furthermore, a relation was made that can be used to calculate the minimum doses for vaccinating of the new-comers and the susceptible individuals, in order to eradicate the infection (*i.e.* relation (5)).

The theoretical results were also verified numerically by providing several simulations. The stability of each system for various parameter values was studied by obtaining eigenvalues of the corresponding Jacobian matrices. Also, the solutions of each model with different initial numbers of individuals in the sub-populations were presented. The figures clearly illustrated that the solutions are stable and converge either to IFE when BRN is less than unity (*i.e.* disease extinction) or to IE when BRN is greater than unity (*i.e.* disease persistence).

For further studies, one can use real data about a disease that fits in this model and compare the real outcomes with the theoretical findings of this study. Moreover, more details can be included in these models and then the properties of the obtained models can be investigated mathematically. For instance, the recruitment rate can be considered as a function of time or a multiplication of the total population size. Moreover, the standard incidence rate used in this model can be replaced by other incidence rates such as bilinear incidences or saturated incidences. The vertical transmission of infection may also be included in the model. This means the model also contains infected newborn members (*i.e.* a proportion of newborns with an infection who enter a population). It is envisaged that confirmed and robust models of this nature can shape the future attempts to control and prevent infectious diseases by the public health authorities.

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APPENDICES

Appendix A. Proof of Theorem 1:

The Jacobian of system at (S, I) is as follows:

$$J = \begin{pmatrix} -\beta \frac{I^2}{(S+I)^2} - d & -\beta \frac{S^2}{(S+I)^2} + \sigma \\ \beta \frac{I^2}{(S+I)^2} & \beta \frac{S^2}{(S+I)^2} - (d + \delta + \sigma) \end{pmatrix}. \quad (6)$$

At E^0 the Jacobian matrix is

$$J(E^0) = \begin{pmatrix} -d & -\beta + \sigma \\ 0 & \beta - (d + \delta + \sigma) \end{pmatrix}, \quad (7)$$

and its eigenvalues are $\lambda_1 = -d$ and $\lambda_2 = \beta - (d + \delta + \sigma)$. Therefore, the eigenvalues have negative real part if and only if $R_0 < 1$. On the other hand, the Jacobian matrix at E^* is

$$J(E^*) = \begin{pmatrix} -\beta(1 - \frac{1}{R_0})^2 - d & -\beta(\frac{1}{R_0})^2 + \sigma \\ \beta(1 - \frac{1}{R_0})^2 & \beta(\frac{1}{R_0})^2 - (d + \delta + \sigma) \end{pmatrix}, \quad (8)$$

The characteristic equation of matrix $J(E^*)$ is

$$p(\lambda) = \lambda^2 + a_1\lambda + a_2, \quad (9)$$

where:

$$\begin{aligned}
 a_1 &= -tr(J(E^*)) = -\beta + 2\beta\left(\frac{1}{R_0}\right) - d - (d + \delta + \sigma) \\
 &= (d + \delta + \sigma) - \beta - d < 0, \\
 a_2 &= det(J(E^*)) = (d + \delta)\beta\left(1 - \frac{1}{R_0}\right)^2 - d\beta\left(\frac{1}{R_0}\right)^2 + d(d + \delta + \sigma) \\
 &= (d + \delta)\beta\left(1 - \frac{1}{R_0}\right)^2 - d\beta\left(\frac{1}{R_0}\right)^2 + d(d + \delta + \sigma) > 0.
 \end{aligned}$$

Thus the Routh-Harwitz criterion is satisfied and all eigenvalues of $J(E^*)$ have negative real parts.

Appendix B. Proof of Theorem 2:

Part (I) can be easily proven as in Theorem 1. For proving Part (II), denoting the force of infection as $\Upsilon = \frac{\beta SI}{S + I + V}$, we

obtain the Jacobian matrix of system (4) at an equilibria as follows:

$$J = J(S, I, V) = \begin{pmatrix} -\Upsilon_S - (d + \rho) & \sigma - \Upsilon_I & \theta - \Upsilon_V \\ \Upsilon_S & \Upsilon_I - (d + \sigma + \delta) & \Upsilon_V \\ \rho & 0 & -(d + \theta) \end{pmatrix} \quad (10)$$

In which, Υ_S , Υ_I and Υ_V are partial derivatives of force of infection $\Upsilon(t)$ with respect to S , I and V , respectively and are:

$$\begin{aligned}
 \Upsilon_S &= \frac{\beta I (S + I + V) - \beta SI}{(S + I + V)^2}, \\
 \Upsilon_I &= \frac{\beta S (S + I + V) - \beta SI}{(S + I + V)^2}, \\
 \Upsilon_V &= -\frac{\beta SI}{(S + I + V)^2}.
 \end{aligned}$$

At EV^* , we have $\frac{\beta S^*}{S^* + I^* + V^*} = (d + \sigma + \delta)$ and the following relations can be obtained:

$$\begin{aligned}
 \Upsilon_S &= (\beta - (d + \sigma + \delta)) \frac{I^*}{S^* + I^* + V^*}, \\
 \Upsilon_I &= (d + \sigma + \delta) \left(1 - \frac{I^*}{S^* + I^* + V^*}\right), \\
 \Upsilon_V &= -(d + \sigma + \delta) \frac{I^*}{S^* + I^* + V^*},
 \end{aligned}$$

Moreover:

$$\begin{aligned}
 -\Upsilon_S + \Upsilon_V &= -\beta \frac{I^*}{S^* + I^* + V^*}, \\
 \Upsilon_I - (d + \sigma + \delta) &= -(d + \sigma + \delta) \frac{I^*}{S^* + I^* + V^*}, \\
 -\Upsilon_S + \Upsilon_I - (d + \sigma + \delta) &= -\beta \frac{I^*}{S^* + I^* + V^*}.
 \end{aligned}$$

We have:

$$\begin{aligned}
 tr(J(EV^*)) &= -\Upsilon_S - (d + \rho) + \Upsilon_I - (d + \sigma + \delta) - (d + \theta) \\
 &= -(\beta - (d + \sigma + \delta)) \frac{I^*}{S^* + I^* + V^*} - (d + \rho) \\
 &\quad - (d + \sigma + \delta) \frac{I^*}{S^* + I^* + V^*} - (d + \theta) \\
 &= -\beta \frac{I^*}{S^* + I^* + V^*} - (2d + \rho + \theta) < 0.
 \end{aligned}$$

Taking determinant of $J(EV^*)$ with respect to the third row, we get

$$\begin{aligned}
 det(J(EV^*)) &= \rho \begin{vmatrix} -\Upsilon_I + \sigma & -\Upsilon_V + \theta \\ \Upsilon_I - (d + \sigma + \delta) & \Upsilon_V \end{vmatrix} \\
 &\quad - (d + \theta) \begin{vmatrix} -\Upsilon_S - (d + \rho) & -\Upsilon_I + \sigma \\ \Upsilon_S & \Upsilon_I - (d + \sigma + \delta) \end{vmatrix} \\
 &= \rho(-\Upsilon_V(d + \delta) - \theta(\Upsilon_I - (d + \sigma + \delta))) \\
 &\quad + (d + \theta)(-\Upsilon_S(d + \delta) + (d + \rho)(\Upsilon_I - (d + \sigma + \delta))) \\
 &= \frac{I^*}{S^* + I^* + V^*} \{ \rho(d + \sigma + \delta)(d + \delta + \theta) + (d + \delta)(d + \theta)(d + \sigma + \delta) \\
 &\quad - \beta(d + \delta)(d + \theta) - (d + \rho)(d + \theta)(d + \sigma + \delta) \} \\
 &= \frac{I^*}{S^* + I^* + V^*} \{ \delta(d + \rho + \theta)(d + \sigma + \delta) - \beta(d + \theta)(d + \delta) \} \\
 &< -\frac{I^*}{S^* + I^* + V^*} d(d + \rho + \theta)(d + \sigma + \delta) < 0,
 \end{aligned}$$

Because, $\overset{v}{R}_0 > 1$ implies $\beta(d + \theta) > (d + \rho + \theta)(d + \sigma + \delta)$.

The second additive compound matrix of a 3×3 matrix

$$A = \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix},$$

can be obtained as [23]

$$A^{[2]} = \begin{pmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{pmatrix}.$$

The second additive compound matrix of $J(EV^*)$ is then obtained as:

$$J^{[2]}(EV^*) = \begin{pmatrix} -Y_S - (d + \rho) & Y_V & Y_V - \theta \\ +Y_I - (d + \sigma + \delta) & & \\ 0 & -Y_S - (d + \rho) - (d + \theta) & -Y_I + \sigma \\ -\rho & Y_S & Y_I - (d + \sigma + \delta) - (d + \theta) \end{pmatrix}$$

$$= \begin{pmatrix} -\beta \frac{I^*}{S^* + I^* + V^*} - (d + \rho) & Y_V & Y_V - \theta \\ 0 & -Y_S - (d + \rho) - (d + \theta) & -Y_I + \sigma \\ -\rho & Y_S & Y_V - (d + \theta) \end{pmatrix}.$$

Now, subtracting the third row from the first row and adding the third to the second row, determinant of $J^{[2]}$ becomes:

$$\det(J^{[2]}(EV^*)) = \begin{vmatrix} -\beta \frac{I^*}{S^* + I^* + V^*} - d & -\beta \frac{I^*}{S^* + I^* + V^*} & d \\ -\rho & -(2d + \rho + \theta) & -(2d + \delta + \theta) \\ -\rho & (\beta - (d + \sigma + \delta)) \frac{I^*}{S^* + I^* + V^*} & -(d + \sigma + \delta) \frac{I^*}{S^* + I^* + V^*} - (d + \theta) \end{vmatrix}$$

$$= d \{ -\rho(\beta - (d + \sigma + \delta)) \frac{I^*}{S^* + I^* + V^*} - \rho(2d + \rho + \theta) \}$$

$$+ (2d + \delta + \theta) \{ -(\beta \frac{I^*}{S^* + I^* + V^*} + d)(\beta - (d + \sigma + \delta)) \frac{I^*}{S^* + I^* + V^*} - \rho\beta \frac{I^*}{S^* + I^* + V^*} \}$$

$$- \{ (d + \sigma + \delta) \frac{I^*}{S^* + I^* + V^*} + (d + \theta) \}$$

$$\{ (\beta \frac{I^*}{S^* + I^* + V^*} + d)(2d + \rho + \theta) - \rho\beta \frac{I^*}{S^* + I^* + V^*} \} < 0.$$

It was found that $\text{tr}(EV^*) < 0$, $\det(EV^*) < 0$ and $\det(J^{[2]}(EV^*)) < 0$. Thus, all real parts of eigenvalues of

matrix $J(EV^*)$ are negative [24] and $J(EV^*)$ is stable. This means that the infected equilibrium EV^* is stable.