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An epidemic model with viral mutations and vaccine interventions

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In this paper, we introduce a two-strain SIR epidemic model with viral mutation and vaccine administration. We discuss and analyze the existence and stability of equilibrium points. This model has three types of equilibrium points, namely disease-free equilibrium, dominance equilibrium point of strain two, and coexistence endemic equilibrium point. The local stability of the dominance equilibrium point of strain two and coexistence endemic equilibrium point are verified by using the Routh–Hurwitz criteria, while for the global stability of the dominance equilibrium point of strain two, we used a suitable Lyapunov function. We also carried out the bifurcation analysis using the application of center manifold theory, and we obtained that the system near the disease-free equilibrium point always has supercritical bifurcation. Finally, the numerical simulations are provided to validate the theoretical results. Continuation of the supercritical bifurcation point results in two Hopf bifurcations indicating a local birth of chaos and quasi-periodicity.

Keywords: *epidemic model; virus mutation; vaccination; stability analysis; bifurcation.*

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1. Introduction

Epidemiology is one of the important topics in the field of mathematical modeling. The discussion of epidemic models is usually built through the development of the SIR epidemic model which was first introduced by Kermack–McKendrick in 1927. Up to now, various mathematical models have been developed to study disease transmission, and more importantly, to understand the mechanism of the epidemic so that efforts to prevent or reduce disease transmission can be done through medication or other medical measures. In general, the aim of the modeling is to describe the relationship between susceptible and infected individuals along with the disease transmission process by dividing the population into related compartments. One can cite several recent studies using these models for cholera [1,2], Dengue [3], H1N1 flu [4], tuberculosis [5,6], measles [7,8], hepatitis [9,10], among others. There are various models that also consider factors for preventing and controlling the spread of diseases, such as vaccinations [11–13], treatment [14], quarantine [15,16], and others.

Recently, the world has been rocked by the COVID-19 pandemic. As of January 31, 2022, WHO reported 394 220 821 confirmed cases of COVID-19, including 5 762 014 deaths [17]. The increasing number of cases of COVID-19 has recently been exacerbated by the presence of a mutation strain of the corona virus which is believed to be more contagious. As reported by the CDC, there has been a mutation of the virus strain that causes COVID-19 with the emergence of several new variants. One of the new variants was recognized in the UK on December 14, 2020 and was named SARS-CoV VOC 202012/01 or known as B.1.1.7 (https://cdc.gov/coronavirus/2019-ncov), following other previous variants which appeared in China in June 2020 as reported by Huo et al., namely SARS-CoV-2 D614G [18]. The new variant appeared in southern Africa on December 18, 2020 and was given the

name 501Y.V2 (WHO). The existence of new variants and the possibility of being infected with more than one virus strain, raises new concerns about the increasing number of positive cases and deaths due to COVID-19 [19].

On the other hand, the development of efforts to prevent the transmission of COVID-19 through the use of vaccines is still being carried out. Although it does not guarantee complete protection from a disease, vaccination is one of the biggest achievements in public health, including in preventing COVID-19. Some pathogens can mutate and in some cases, the immune system may still not be able to beat the infection. This is due to the effectiveness of the vaccine. It is interesting to study the effect of vaccination in preventing the continuation of the COVID-19 pandemic. One way to study this is by utilizing mathematical modeling. Through mathematical modeling, various types of infections and infectious diseases involving treatment or vaccination have been studied, such as in [12, 13, 20]. Especially in COVID-19, various models involving intervention strategies have been developed by many researchers. Modeling the spread of COVID-19 with the policies of social isolation, lockdown, or social distancing and travel restrictions have been studied in [21–27]. Meanwhile, the COVID-19 model that considers vaccination as a treatment intervention can be studied in [28–31]. However, no COVID-19 model has yet to consider viral mutations with vaccine interventions. Therefore it is necessary to form a model that takes into account virus mutations and vaccine interventions. Motivated by this point, we propose a Susceptible–Infected–Recovered–Vaccinated (SIRV) model that divides the infected population I into subpopulation with virus strain one ($I_1(t)$) and sub population with virus strain two ($I_2(t)$). This model is expected to be applied not only to COVID-19 but also to the spread of other diseases that involve viral mutations and vaccination interventions.

The rest of this paper is organized as follows. In Section 2, we formulated the mathematical model and present the basic properties of the model, such as positivity and boundedness of solutions. The existence and stability of equilibrium points are discussed in Section 3. The local stability is determined by the sign of the real part of the eigenvalues of the Jacobian matrix at the equilibrium point, Routh–Hurwitz stability criterion and the global stability is determined using the Lyapunov function. Then, in Section 4, we discuss the existence of a supercritical bifurcation using the application of the center manifold theory. In Section 5, we provide the numerical simulation to verify the theorem results. Finally, we discuss and summarize our results in Section 6.

2. Model formulation

In this section, we present an SIR epidemic model with two viral strains and vaccinations. For that purpose, we divided the population into five sub-populations, namely the susceptible individuals $S(t)$, Individuals infected by strain one $I_1(t)$, Individuals infected by strain two $I_2(t)$, Vaccinated individuals $V(t)$, and Recovered individuals $R(t)$. In this model, mutations are counted through terms that transfer an individual infected with one strain to an individual infected with the other. Furthermore, the following hypothesis is taken to formulate a mathematical model that describes the dynamics of the SIR model with virus mutations and vaccine interventions.

Susceptible individuals are recruited at a rate Λ and can become infected by strain one or by strain two at a transmission rate β_1 and β_2, respectively. Those infected by strain one can be mutated into strain two infected individuals at a mutation rate ω and recover at a rate α_1. Those infected individuals with strain two recover at a rate α_2. The related death rates for disease infected by strain one and infected by strain two are denoted by c and d, respectively. We assume that vaccination is only applied to healthy individuals so that only susceptible individuals are vaccinated at the vaccine coverage rate γ. In this model, we assume that strain one is the perfect vaccine strain, whereas, for strain two, the vaccine offers only partial protection. In other words, the vaccines are imperfect for strain two, so that some vaccinated individuals can become infected and infectious by strain two even after being vaccinated. We assume that the vaccine efficacy is also the rate of vaccinated individuals becoming infected by strain two is $1 - \varepsilon$, with $0 < \varepsilon < 1$. An extension of the SIR model with virus mutation

and vaccination will take the form:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta_1 S I_1 - \beta_2 S I_2 - \gamma S - \mu S,\\
\frac{dI_1}{dt} &= \beta_1 S I_1 - (\omega + \alpha_1 + c + \mu) I_1,\\
\frac{dI_2}{dt} &= \beta_2 S I_2 + \omega I_1 + (1-\varepsilon) V I_2 - (\alpha_2 + d + \mu) I_2,\\
\frac{dV}{dt} &= \gamma S - (1-\varepsilon) V I_2 - \mu V,\\
\frac{dR}{dt} &= \alpha_1 I_1 + \alpha_2 I_2 - \mu R.
\end{aligned} \tag{1}$$

with initial conditions $S(0) > 0$, $I_1(0) > 0$, $I_2(0) > 0$, $V(0) > 0$, $R(0) > 0$. The total population at time t is $N(t) = S(t) + I_1(t) + I_2(t) + V(t) + R(t)$, so we have

$$\frac{dN}{dt} = \Lambda - cI_1 - dI_2 - \mu N \leqslant \Lambda - \mu N, \tag{2}$$

with solution

$$0 \leqslant N(t) \leqslant \frac{\Lambda}{\mu} + N(0)e^{-\mu t},$$

where $N(0)$ is the initial value of the total population. Thus for $t \to \infty$

$$0 \leqslant N(t) \leqslant \frac{\Lambda}{\mu}. \tag{3}$$

Hence, it is deduced that $N(t)$ is positive and bounded inside a set

$$\Omega = \left\{ (S, I_1, I_2, V, R) \in R_+^5 : 0 \leqslant N(t) \leqslant \frac{\Lambda}{\mu} \right\}.$$

We state the above result in the following theorem.

Theorem 1. *The set*

$$\Omega = \left\{ (S, I_1, I_2, V, R) \in R_+^5 : 0 \leqslant N(t) \leqslant \frac{\Lambda}{\mu} \right\}$$

is positively-invariant and attracting set for the system (1).

Since the recovered population does not appear in the first four equations of system (1), the rest of the paper will not consider the recovered population. So, it is sufficient to consider the following reduced models:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta_1 S I_1 - \beta_2 S I_2 - \gamma S - \mu S,\\
\frac{dI_1}{dt} &= \beta_1 S I_1 - (\omega + \alpha_1 + c + \mu) I_1,\\
\frac{dI_2}{dt} &= \beta_2 S I_2 + \omega I_1 + (1-\varepsilon) V I_2 - (\alpha_2 + d + \mu) I_2,\\
\frac{dV}{dt} &= \gamma S - (1-\varepsilon) V I_2 - \mu V.
\end{aligned} \tag{4}$$

3. Existence and stability of equilibrium points

In this section, we will study the existence and stability of the equilibria of system (4).

3.1. Disease-free equilibrium

System (4) always has a disease-free equilibrium point in which neither infected by strain one nor strain two is present. The disease free equilibrium is $E_0 = (\frac{\Lambda}{\gamma+\mu}, 0, 0, \frac{\gamma\Lambda}{\mu(\gamma+\mu)})$. Then, we define the

basic reproduction number R_0, that defined as the spectral radius of the next generation matrix $F\Sigma^{-1}$ with F and Σ are the Jacobian matrices of $\mathcal{F}$ and $\mathcal{V}$, where

$$\mathcal{F} = \begin{bmatrix} \beta_1 SI_1 \\ \beta_2 SI_2 + (1-\varepsilon)VI_2 \end{bmatrix} \quad \text{and} \quad \mathcal{V} = \begin{bmatrix} (\omega+\alpha_1+\mu+c)I_1 \\ -\omega I_1 + (\alpha_2+\mu+d)I_2 \end{bmatrix}.$$

The basic reproduction number is given by

$$R_0 = \rho(F\Sigma^{-1}) = \max\{R_1, R_2\}. \tag{5}$$

where

$$R_1 = \frac{\beta_1\Lambda}{(\gamma+\mu)(\omega+\alpha_1+\mu+c)}, \quad R_2 = \frac{\Lambda(\beta_2\mu+(1-\varepsilon)\gamma)}{\mu(\alpha_2+\mu+d)(\gamma+\mu)} \tag{6}$$

We can see that, R_1 and R_2 are the reproduction rates of strain one and strain two, respectively. It is clear that if $R_i < 1$, $i = 1, 2$, then no strain can persist in the population and the infected individuals I_1 and I_2 converge to zero and we have the disease free-equilibrium point $E_0 = \left(\frac{\Lambda}{\gamma+\mu}, 0, 0, \frac{\gamma\Lambda}{\mu(\gamma+\mu)}\right)$. Furthermore, the following theorem states the stability of the disease-free equilibrium point. We will analyze the local stability of the equilibrium point by determining the eigenvalues of the Jacobian matrix of system (4) at the equilibrium point.

Theorem 2. *If $R_0 < 1$ then the disease-free equilibrium is locally asymptotically stable. If $R_0 > 1$ then the disease-free equilibrium is unstable.*

Proof. The Jacobian matrix of system (4) at E_0 is

$$J(E_0) = \begin{bmatrix} -(\gamma+\mu) & -\frac{\beta_1\Lambda}{\gamma+\mu} & -\frac{\beta_2\Lambda}{\gamma+\mu} & 0 \\ 0 & J_{22} & 0 & 0 \\ 0 & \omega & J_{33} & 0 \\ \gamma & 0 & -\frac{(1-\varepsilon)\Lambda\gamma}{\mu(\gamma+\mu)} & -\mu \end{bmatrix},$$

with

$$J_{22} = \frac{\beta_1\Lambda}{\gamma+\mu} - (\omega+\alpha_1+\mu+c) \quad \text{and} \quad J_{33} = \frac{\beta_2\Lambda}{\gamma+\mu} + \frac{(1-\varepsilon)\Lambda\gamma}{\mu(\gamma+\mu)} - (\alpha_2+d+\mu).$$

The Jacobian matrix $J(E_0)$ has two negative eigenvalues, $\lambda_1 = -(\gamma+\mu)$ and $\lambda_2 = -\mu$. Two others eigenvalues are $\lambda_3 = (\omega+\alpha_1+\mu+c)(R_1-1)$ and $\lambda_4 = (\alpha_2+d+\mu)(R_2-1)$, which always negative if $R_1 < 1$ and $R_2 < 1$. Hence, the disease-free equilibrium E_0 of system (4) is locally asymptotically stable if $R_1 < 1$ and $R_2 < 1$ correspond to $R_0 < 1$. If $R_1 < 1$ or $R_2 < 1$, at least one of eigenvalues of the The Jacobian matrix $J(E_0)$ has a positive real part, so that E_0 is unstable. This completes the proof. ∎

Furthermore, we can prove the global stability of E_0 when $R_0 \leqslant 1$.

Theorem 3. *If $R_0 \leqslant 1$, then the disease-free equilibrium is globally asymptotically stable.*

Proof. Consider the following Lyapunov function:

$$L_1 = \omega I_1 + (\alpha_1+\mu+c)I_2. \tag{7}$$

We obtain the Lyapunov derivative

$$\begin{aligned} \frac{dL_1}{dt} &= \omega\frac{dI_1}{dt} + (\alpha_1+\mu+c)\frac{dI_2}{dt} \\ &= \omega\big(\beta_1 SI_1 - (\omega+\alpha_1+c+\mu)I_1\big) + (\alpha_1+\mu+c)\big(\beta_2 SI_2 + \omega I_1 + (1-\varepsilon)VI_2 - (\alpha_2+d+\mu)I_2\big) \\ &\leqslant \omega I_1\big(\beta_1 S - (\omega+\alpha_1+c+\mu)\big) + (\alpha_1+\mu+c)I_2\big(\beta_2 S + (1-\varepsilon)V - (\alpha_2+d+\mu)I_2\big) \\ &= \omega(\omega+\alpha_1+c+\mu)I_1(R_1-1) + (\alpha_1+\mu+c)(\alpha_2+d+\mu)I_2\,(R_2-1) \\ &\leqslant 0, \end{aligned}$$

and $\frac{dL_1}{dt} = 0$ if only if $I_1 = I_2 = 0$. From inspection of system (4), the maximum compact invariant set is the plane $I_1 = 0$, $I_2 = 0$, which implies that the solutions starting there will tend to E_0 as t goes to infinity. Thus, by LaSalle–Lyapunov theorem [32], E_0 is globally asymptotically stable. ∎

3.2. Dominance equilibrium of strain two

From system (4), we can also find the dominance equilibrium of strain two at which the infected individuals by strain one dies out and infected individuals by strain two persists denoted by

$$E_1^* = (S^*, 0, I_2^*, V^*),$$

where

$$S^* = \frac{\alpha_2 + \mu + d - (1-\varepsilon)V^*}{\beta_2}, \quad V^* = \frac{\gamma(\alpha_2 + \mu + d)}{\gamma(1-\varepsilon) + \mu\beta_2 + \beta_2(1-\varepsilon)I_2^*},$$

and I_2^* is the positive solution of the following equation

$$a_2 I_2^2 + a_1 I_2 + a_0 = 0, \tag{8}$$

with

$$\begin{aligned} a_2 &= \beta_2(1-\varepsilon)(\alpha_2 + \mu + d), \\ a_1 &= \beta_2\mu(1-\varepsilon)(\alpha_2 + \mu + d) + (1-\varepsilon)(\gamma + \mu)(\alpha_2 + \mu + d) - (1-\varepsilon)\beta_2\Lambda, \\ a_0 &= \mu(\gamma + \mu)(\alpha_2 + \mu + d)(1 - R_2). \end{aligned} \tag{9}$$

For the existence of the endemic dominance equilibrium point of strain two, the solution of (8) must be real and positive. From (9), we note that a_2 is always nonnegative, a_1 can be positive or negative, and $a_0 < 0$ if only if $R_2 > 1$, $a_0 \geqslant 0$ if only if $R_2 \leqslant 1$. Therefore, we have the following results for existence dominance equilibrium of strain two.

Theorem 4. *The following results hold:*

(i) System (4) has a unique dominance equilibrium of strain two when $R_2 > 1$.
(ii) System (4) has a unique dominance equilibrium of strain two when $R_2 = 1$ and $a_1 < 0$.
(iii) System (4) has no dominance equilibrium point whenever $R_2 \leqslant 1$ and $a_1 > 0$.

Furthermore, we claim the following theorem for local stability of the dominance equilibrium of strain two.

Theorem 5. *Let $R_2 > 1$. The dominance equilibrium point of strain two $E_1 = (S^*, 0, I_2^*, V^*)$ is locally asymptotically stable if $\beta_1 S^* < \omega + \alpha_1 + \mu + c$.*

Proof. The Characteristic equation of the Jacobian matrix of system (4) at E_1 is

$$\begin{vmatrix} \lambda + A & \beta_1 S^* & \beta_2 S^* & 0 \\ 0 & \lambda - B & 0 & 0 \\ -\beta_2 I_2^* & -\omega & \lambda & -(1-\varepsilon)I_2^* \\ -\gamma & 0 & (1-\varepsilon)I_2^* & \lambda + C \end{vmatrix} = 0, \tag{10}$$

where

$$A = \beta_2 I_2^* + \gamma + \mu, \quad B = \beta_1 S^* - (\omega + \alpha_1 + \mu + c), \quad C = (1-\varepsilon)I_2^* + \mu.$$

Inspecting (10) we get $\lambda_1 = \beta_1 S^* - (\omega + \alpha_1 + \mu + c)$ and the other three eigenvalues are the roots of the equation

$$\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0, \tag{11}$$

with $a_2 = A + C$, $a_1 = AC + (1-\varepsilon)I_2^* V^* + \beta_2^2 I_1^* S^*$, and $a_0 = A(1-\varepsilon)I_2^* V^* + C\beta_2^2 I_2^* S^* + \gamma\beta_2(1-\varepsilon)I_2^* S$. Clearly, $a_2 > 0$, $a_1 > 0$, $a_0 > 0$, and it can be verified that $a_2 a_1 - a_0 > 0$. Therefore, by Routh–Hurwitz criteria, we find that all roots of (11) will have negative real parts. Thus the dominance equilibrium point of strain two E_1 is locally asymptotically stable $\lambda_1 = \beta_1 S^* - (\omega + \alpha_1 + \mu + c) < 0$ or $\beta_1 S^* < (\omega + \alpha_1 + \mu + c)$. This completes the proof. ∎

Next, following [33] we can prove the global stability of E_1 in the next theorem.

Theorem 6. *Let $R_2 > 1$ and $\beta_1 S^* - (\omega + \alpha_1 + \mu + c) < 0$, then the dominance equilibrium point of strain two $E_1 = (S^*, 0, I_2^*, V^*)$ is globally asymptotically stable.*

Proof. Divide the second and third equation of (4) by I_1 and I_2, respectively, then we get

$$\begin{aligned}\frac{d\log I_1}{dt} &= \beta_1 S - K_1\\ \frac{d\log I_2}{dt} &= \beta_2 S + \omega\frac{I_1}{I_2} + (1-\varepsilon)V - K_2.\end{aligned} \tag{12}$$

with $K_1 = \omega + \alpha_1 + c + \mu$ and $K_2 = \alpha_2 + d + \mu$. Solve for S in both equations (12),

$$S = \frac{1}{\beta_1}\left(\frac{d\log I_1}{dt} + K_1\right) = \frac{1}{\beta_2}\left(\frac{d\log I_2}{dt} + K_2 - \omega\frac{I_1}{I_2} - (1-\varepsilon)V\right),$$

which leads to the following inequality

$$\frac{1}{\beta_1}\left(\frac{d\log I_1}{dt} + K_1\right) \leqslant \frac{1}{\beta_2}\left(\frac{d\log I_2}{dt} + K_2 - (1-\varepsilon)V\right).$$

Taking $V = V^*$ and integrating both sides

$$\left(\tfrac{I_1(t)}{I_1(0)}\right)^{\frac{1}{\beta_1}} e^{\frac{K_1}{\beta_1}} \leqslant \left(\tfrac{I_2(t)}{I_2(0)}\right)^{\frac{1}{\beta_2}} e^{\frac{1}{\beta_2}(K_2-(1-\varepsilon)V^*)t} \Longleftrightarrow \left(\tfrac{I_1(t)}{I_1(0)}\right)^{\frac{1}{\beta_1}} \leqslant \left(\tfrac{I_2(t)}{I_2(0)}\right)^{\frac{1}{\beta_2}} e^{\left(\frac{1}{\beta_2}(K_2-(1-\varepsilon)V^*)-\frac{K_1}{\beta_1}\right)t}.$$

The last inequality can be rewritten as $\left(\tfrac{I_1(t)}{I_1(0)}\right)^{1/\beta_1} \leqslant \left(\tfrac{I_2(t)}{I_2(0)}\right)^{1/\beta_2} e^{(\beta_1 S^* - K_1)t}$.

Since $\beta_1 S^* - K_1 < 0$ we find $\lim\limits_{t\to\infty}\left(\tfrac{I_1(t)}{I_1(0)}\right)^{1/\beta_1} \leqslant \lim\limits_{t\to\infty}\left(\tfrac{I_2(t)}{I_2(0)}\right)^{1/\beta_2} e^{(\beta_1 S^* - K_1)t} = 0$.

Thus all solutions of (4) will tend to the hyperplane $I_1 = 0$ when $\beta_1 S^* - (\omega + \alpha_1 + c + \mu) < 0$.

Furthermore, to complete the proof of the global stability of the equilibrium point E_1 on hyperplane $I_1 = 0$, the following Lyapunov function is constructed,

$$L = S - S^*\ln S + I_2 - I_2^*\ln I_2 + D, \tag{13}$$

where

$$D = -(S^* - S^*\ln S^* + I_2^* - I_2^*\ln I_2^*).$$

Thus,

$$\begin{aligned}\frac{dL}{dt} &= \left(1-\frac{S^*}{S}\right)\frac{dS}{dt} + \left(1-\frac{I_2^*}{I_2}\right)\frac{dI_2}{dt}\\ &= \left(1-\frac{S^*}{S}\right)(\Lambda - \beta_2 S I_2 - (\gamma+\mu)S) + \left(1-\frac{I_2^*}{I_2}\right)(\beta_2 S I_2 + ((1-\varepsilon)V - K_2)I_2)\\ &= \Lambda - \beta_2 S I_2 - (\gamma+\mu)S - \Lambda\frac{S^*}{S} + \beta_2 S^* I_2 + (\gamma+\mu)S^* + \beta_2 S I_2\\ &\quad + \big((1-\varepsilon)V - K_2\big)I_2 - \beta_2 S I_2^* - \big((1-\varepsilon)V - K_2\big)I_2^*\end{aligned}$$

Substituting $\Lambda = (\gamma+\mu)S^* + \beta_2 I_2^* S^*$, we obtain

$$\begin{aligned}\frac{dL}{dt} &= (\gamma+\mu)S^* + \beta_2 I_2^* S^* - (\gamma+\mu)S - (\gamma+\mu)S^*\frac{S^*}{S} - \beta_2 I_2 S^*\frac{S^*}{S}\\ &\quad + (\gamma+\mu)S^* + \beta_2 S^* I_2 - (K_2 - (1-\varepsilon)V)I_2 - \beta_2 S^* I_2^*\frac{S}{S^*} + (K_2 - (1-\varepsilon)V)I_2^*\end{aligned}$$

Substitute $\beta S^* = (K_2 - (1-\varepsilon)V$ to get the following simplified expression

$$\begin{aligned}\frac{dL}{dt} &= (\gamma+\mu)S^*\left(2 - \frac{S^*}{S} - \frac{S}{S^*}\right) + (K_2 - (1-\varepsilon)V)I_2^*\\ &\quad - (K_2 - (1-\varepsilon)V)I_2^*\frac{S^*}{S} - (K_2 - (1-\varepsilon)V)I_2^*\frac{S}{S^*} + (K_2 - (1-\varepsilon)V)I_2^*\\ &= (\gamma+\mu)S^*\left(2 - \frac{S^*}{S} - \frac{S}{S^*}\right) + (K_2 - (1-\varepsilon)V)I_2^*\left(2 - \frac{S^*}{S} - \frac{S}{S^*}\right)\end{aligned}$$

Since $K_2 - (1-\varepsilon)V \geqslant 0$ and $\left(2 - \frac{S^*}{S} - \frac{S}{S^*}\right) \leqslant 0$, we obtain $\frac{dL}{dt} \leqslant 0$. Therefore, the dominance equilibrium of strain two E_1 is globally asymptotically stable if $R_2 > 1$ and $\beta_1 S^* < \omega + \alpha_1 + c + \mu$. This completes the proof. ∎

3.3. Coexistence endemic equilibrium

The system (4) has a coexistence endemic equilibrium in which both strain one and strain two exist. The coexistence endemic equilibrium is given by

$$E_2 = (S^{**}, I_1^{**}, I_2^{**}, V^{**}),$$

where

$$\begin{aligned} S^{**} &= \frac{\omega + \alpha_1 + \mu + c}{\beta_1}, \\ I_2^{**} &= \frac{1}{\beta_2}\big((\mu+\gamma)(R_1-1) - \beta_1 I_1^{**}\big), \\ V^{**} &= \frac{\gamma(\omega + \alpha_1 + \mu + c)}{\beta_1\big(\mu + \frac{1}{\beta_2}(1-\varepsilon)((\mu+\gamma)(R_1-1) - \beta_1 I_1^{**})\big)}, \end{aligned} \tag{14}$$

and I_1^{**} is the positive solution of

$$b_2 I_1^2 + b_1 I_1 + b_0 = 0, \tag{15}$$

with

$$\begin{aligned} b_2 &= (1-\varepsilon)\beta_1^2\Big(K_1 - \frac{\beta_1}{\beta_2}K_2 - \omega\Big), \\ b_1 &= -(1-\varepsilon)\beta_1\left((\mu+\gamma)(R_1-1)\left(K_1 - \frac{\beta_1}{\beta_2}K_2\right) + \gamma\beta_1 K_1\right) - \left(K_1 - \frac{\beta_1}{\beta_2}K_2 - \omega\right)G, \\ b_0 &= (\mu+\gamma)(R_1-1)\left(\frac{G}{\beta_1}\beta_2\left(K_1 - \frac{\beta_1}{\beta_2}K_2\right) + (1-\varepsilon)\gamma K_1\right), \end{aligned} \tag{16}$$

where $K_1 = \omega + \alpha_1 + \mu + c$, $K_2 = \alpha_2 + \mu + d$, and $G = \beta_1\beta_2((\mu+\gamma)(R_1-1) + \mu)$.

It is clear that from (14), the system (4) has no coexistence endemic equilibrium point when $R_1 < 1$. For the existence of coexistence endemic equilibrium, it must be $R_1 > 1$ and $(R_1 - 1) - \beta_1 I_1^{**} > 0$. In addition, a real positive solution of (15) is required, which can be determined by the Descartes' Rule of Signs. Observe that under the conditions $K_1 - \frac{\beta_1}{\beta_2}K_2 - \omega > 0$, b_2 and b_0 are always positive, while b_1 is always negative, so the equation (15) has two real positive solutions. Whereas if $K_1 - \frac{\beta_1}{\beta_2}K_2 < 0$ then b_2 is always negative and both b_1 and b_0 can be positive or negative. We state these results in the following theorem.

Theorem 7. *Let $R_1 > 1$ and $(R_1 - 1) - \beta_1 I_1^{**} > 0$, then the following results hold:*

(i) If $K_1 - \frac{\beta_1}{\beta_2}K_2 < 0$ and $b_1 < 0$, then the system (4) may have no or one coexistence endemic equilibrium point;

(ii) If $K_1 - \frac{\beta_1}{\beta_2}K_2 < 0$ and $b_1 > 0$, then the system (4) has one coexistence endemic equilibrium point;

(iii) If $K_1 - \frac{\beta_1}{\beta_2}K_2 - \omega > 0$, then the system (4) may have two coexistence endemic equilibrium points.

For the stability of coexistence endemic equilibrium point E_2, we define:

$$\begin{aligned} P &= (1-\varepsilon)I_2^{**} + \mu, \\ Q &= \frac{\beta_2}{\beta_1}K_1 + (1-\varepsilon)V^{**} - K_2, \\ c_3 &= (\mu+\gamma)R_1 + P - Q, \\ c_2 &= \beta_1 K_1 I_1^{**} + (\mu+\gamma)(P-Q) - PQ, \\ c_1 &= K_1 I_1^{**}(\beta_1 + \beta_2\omega) + (1-\varepsilon)I_2^{**}V^{**} + \frac{\beta_2^2}{\beta_1}K_1 I_2^{**} - (\mu+\gamma)R_1 PQ, \\ c_0 &= \beta_1 K_1 I_1^{**}\big((1-\varepsilon)I_2^{**}V^{**} - PQ\big)\beta_2 I_1^{**}K_1\omega P + \frac{\beta_2}{\beta_1}K_1 I_2^{**}\big(\beta_2 P - (1-\varepsilon)\gamma\big). \end{aligned} \tag{17}$$

We consider the characteristic equation of the Jacobian of system (4) at the coexistence endemic equilibrium point $E_2 = (S^{**}, I_1^{**}, I_2^{**}, V^{**})$ is given by

$$\lambda^4 + c_3\lambda^3 + c_2\lambda^2 + c_1\lambda + c_0 = 0. \tag{18}$$

From Routh–Hurwitz stability criterion, E_2 is locally asymptotically stable if and only if $c_3 > 0$, $c_3c_2 - c_1 > 0$, $c_0 > 0$, and $c_3c_2c_1 - c_3^2c_0 - c_1^2 > 0$.

We state the above results in the following theorem.

Theorem 8. *If the coexistence endemic equilibrium of strain one and strain two $E_2 = (S^{**}, I_1^{**}, I_2^{**}, V^{**})$ of system (4) exist, then E_2 is locally asymptotically stable if and only if $c_3 > 0$, $c_3c_2 - c_1 > 0$, $c_0 > 0$, and $c_3c_2c_1 - c_3^2c_0 - c_1^2 > 0$.*

In the next section, we are going to make use the bifurcation method introduced in [34] to study the existence of either forward or backward bifurcation.

4. Bifurcation analysis

Bifurcation analysis plays an important role in the discussion of epidemic models related to disease control and eradication efforts. In this section, we discuss the possibility of the occurrence of forward (supercritical) bifurcation or backward (subcritical) bifurcation. The forward bifurcation guarantee that keeping the basic reproduction number less than one is a sufficient condition for disease elimination. Meanwhile, if backward bifurcation occurs, endemic may still occur even though the basic reproduction number is greater than one. We carry out a bifurcation analysis based on the use of the center manifold theory [34]. We claim the following theorem.

Theorem 9. *Let $\Lambda(\beta_2\mu + (1-\varepsilon)\gamma) < \mu(\alpha_2 + \mu + d)(\gamma + \mu)$. The system (4) near the disease-free equilibrium point E_0 always has supercritical bifurcation at $R_0 = 1$.*

Proof. From (6) we find that $R_0 = 1$ associated with $\beta_1 = \beta_1^* = \frac{K_1(\gamma+\mu)}{\Lambda}$. The eigenvalues of the Jacobian matrix at (E_0, β_1^*) are $\lambda_1 = -(\gamma+\mu)$, $\lambda_2 = 0$, $\lambda_3 = R_2 - 1$, and $\lambda_4 = -\mu$. Since $R_2 < 1$, we have $\lambda_2 = 0$ is a simple eigenvalue and all other eigenvalues are real and negative. Hence, E_0 is a non hyperbolic equilibrium point and system (4) can undergo a bifurcation at β_1^*.

The right eigenvector of Jacobian matrix at (E_0, β_1^*) corresponding to $\lambda_2 = 0$ is given by

$$\mathbf{w} = (w_1, w_2, w_3, w_4)^T,$$

where

$$\begin{aligned} w_1 &= K_1K_2(R_2 - 1) - \frac{\beta_2\Lambda}{\gamma+\mu}, \\ w_2 &= \frac{(1-\varepsilon)\Lambda\gamma}{\mu\omega(\gamma+\mu)}, \\ w_3 &= 1, \\ w_4 &= \frac{\gamma}{K_1\mu} - \frac{(1-\varepsilon)\Lambda\gamma}{\mu(\gamma+\mu)}\left(1 + \frac{\Lambda\gamma\beta_2}{\omega K_1(\gamma+\mu)}\right). \end{aligned} \tag{19}$$

The left eigenvector of the matrix $J(E_0, \beta_1^*)$ corresponding to $\lambda_2 = 0$ satisfying $\mathbf{v} \cdot \mathbf{w} = 1$ is given by

$$\mathbf{v} = \left(0, 0, 0, -\frac{\omega}{K_2(R_2 - 1)}\right).$$

Then, we define the coefficient a and b as

$$a = \sum_{k,i,j=1}^{4} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(E_0, \beta_1^*), \qquad b = \sum_{k,i=1}^{4} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_1}(E_0, \beta_1^*).$$

Since the component $v_1 = v_2 = v_3 = 0$, it follows that

$$\begin{aligned} a &= v_2 w_1 w_2 \frac{\partial^2 f_2}{\partial I_1 \partial S}(E_0, \beta_1^*) + v_2 w_2 w_1 \frac{\partial^2 f_2}{\partial S \partial I_1}(E_0, \beta_1^*) \\ &= 2 w_1 \beta_1^* \\ &= \frac{2}{\omega(\gamma+\mu)} \left(K_1 K_2 (R_2 - 1) - \frac{\beta_2 \Lambda}{\gamma + \mu} \right) \end{aligned}$$

and

$$\begin{aligned} b &= v_2 w_1 \frac{\partial^2 f_2}{\partial S \partial \beta_1}(E_0, \beta_1^*) + v_2 w_2 \frac{\partial^2 f_2}{\partial I_1 \partial \beta_1}(E_0, \beta_1^*) \\ &= \frac{\Lambda}{\gamma + \mu}. \end{aligned}$$

We find that the coefficient b is always positive. Likewise, considering $R_2 < 1$, we also find that the coefficient a is always positive. Hence, by applying Theorem 4 in [34], we conclude that the system (4) exhibits supercritical bifurcation at $\beta_1 = \beta_1^* = \frac{K_1(\gamma+\mu)}{\Lambda}$, corresponding to $R_0 = 1$. ∎

From the Theorem 9, we know that, the backward bifurcation will only occur if $K_1 K_2 (R_2 - 1) - \frac{\beta_2 \Lambda}{\gamma+\mu} > 0$, i.e. $R_2 > 1 + \frac{\beta_2 \Lambda}{K_1 K_2 (\gamma+\mu)}$ In the other word, it is not possible to exhibit backward bifurcation for $R_2 < 1$.

We will give some numerical simulations to illustrate the theoretical results in the next section.

5. Numerical simulation

In this section, we provide the numerical results to study the behavior of the solution of system (4). We begin with the set of feasible parameter values:

$$\begin{aligned} &\Lambda = 411, \quad \beta_1 = 0.00036, \quad \beta_2 = 0.00002, \quad \mu = 0.000386, \quad \alpha_1 = 0.02, \\ &\alpha_2 = 0.2, \quad \omega = 0.16, \quad \gamma = 0.2, \quad c = 0.08, \quad d = 0.05, \quad 1 - \varepsilon = 0.0000002. \end{aligned} \tag{20}$$

With these sets of parameter values (5), we have $R_0 = \max\{R_1, R_2\}$ with $R_1 = 2.844413276$, $R_2 = 1.015860531$ and the conditions of Theorem 4(i), Theorem 7(ii), and Theorem 8 are satisfied. Hence, in addition to the disease-free equilibrium point E_0, the system (4) has a unique dominance equilibrium point of strain two E_1 and a unique coexistence endemic equilibrium point E_2. We found $E_0 = (2054.60, 0, 0, 1.06456 \times 10^7), E_1 = (2048.56, 0, 29.67, 1.04534 \times 10^7)$, and $E_2 = (722.33, 977.56, 851.64, 2.5967 \times 10^6)$. We find that the disease-free equilibrium point E_0 is unstable, since $R_0 > 1$, and the dominance equilibrium point of strain two E_1 is unstable, since $\beta_1 S^* - (\omega + \alpha_1 + \mu + c) = 0.4774 > 0$ does not meet the condition of Theorem 5. Figure 1 illustrates that E_2 is asymptotically stable by depicting phase portrait projection through I_2 versus I_1 with varies initial conditions.

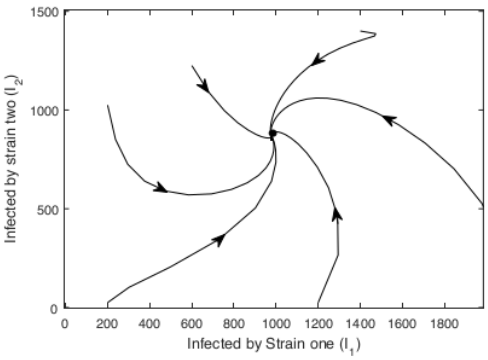
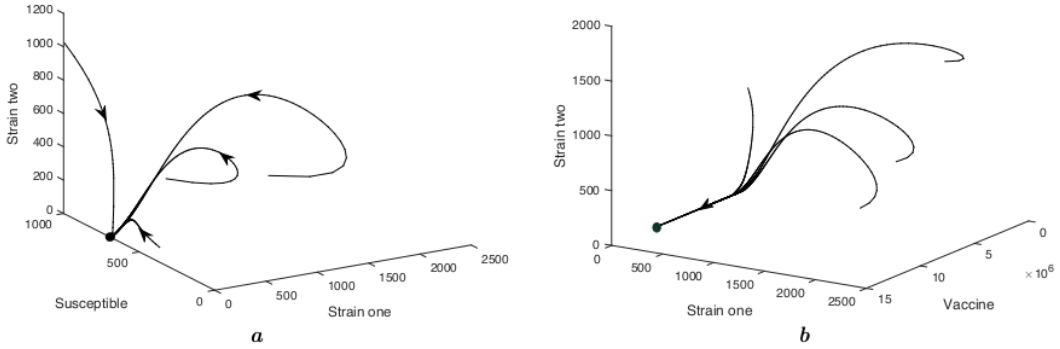


Fig. 1. Phase portrait projection confirms that all trajectories tend to the coexistence endemic equilibrium point $(722.33, 977.56, 851.64, 2.596774 \times 10^6)$.

Now increasing the value of vaccine coverage rate γ from 0.2 to 0.6 eliminates both dominance of strain two and coexistence endemic equilibrium point. The basic reproduction number becomes $R_0 = \max\{R_1, R_2\}$ with $R_1 = 0.9482597$, $R_2 = 0.906415$ and the system only has a disease-free equilibrium point $E_0 = (684.96, 0, 0, 1.0646983 \times 10^7)$. We also find that the conditions of Theorem 2 and Theorem 3 are satisfied. Figure 2 shows that the disease-free equilibrium point is globally asymptotically stable,

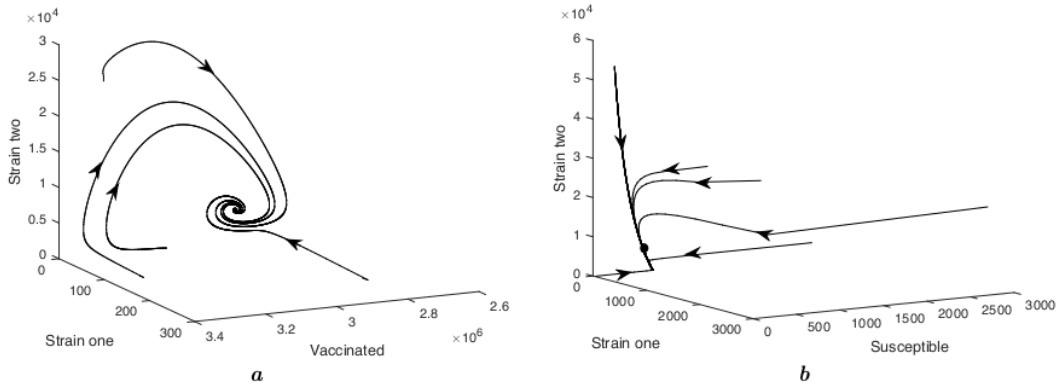
as seen for the varying initial values all trajectories tend to E_0. Medically, this shows that the disease will be cured and no more individuals will be infected, either by strain one or strain two.



a ***b***

Fig. 2. All trajectories tend to the diseases-free equilibrium point $E_0 = (6\ldots.96, 0, 0, 1.0646983 \times 10^7)$. (***a***) Susceptible verses infected by strain one and strain two, (***b***) Vaccinated verses infected by strain one and strain two.

Now, we varying one parameter by set $\alpha_2 = 0.02$ and keep all other parameters as in (5) with $\gamma = 0.6$. With these values, the conditions of Theorem 4(i) are satisfied, in which equation (8) has one positive real root. In this case, we have $R_2 = 3.2359$ and the dominance equilibrium point of strain two $E_1 = (599.6450906, 0, 4268.34, 2.9022849 \times 10^6)$. We also have $\beta_1 S^* - (\omega + \alpha_1 + \mu + c) = -0.044166 < 0$, so that the condition of Theorem 5 and Theorem 6 are satisfied. Hence the dominance equilibrium point of strain two E_1 is globally asymptotically stable. Figure 3 shows that all trajectories which starting from different sets of initial conditions tend to the dominance equilibrium point of strain two E_1. In this case, we could see that with decreasing the recovery rate of infected individual strain two, α_2 leads to destabilizing of the disease-free equilibrium point.



a ***b***

Fig. 3. All trajectories tend to the the dominance strain two equilibrium point E_1. (***a***) Vaccinated verses infected by strain one and strain two, (***b***) Susceptible verses infected by strain one and strain two.

Next, we set $\alpha_2 = 0.02$ and increase the transmission rate of the strain one, $\beta_1 = 0.00066$ to get $R_1 = 1.738476 > 1$ whereas $R_2 = 3.2359$ remains the same as the previous case. With these sets of parameter values, the system (4) has unstable disease-free equilibrium point $E_0 = (684.9559345, 0, 0, 1.0646983 \times 10^7)$, the asymptotically stable dominance equilibrium point of strain two $E_1 = (599.656, 0, 4268.34, 2.9022849 \times 10^6)$, by the fact that $\beta_1 S^* - (\omega + \alpha_1 + \mu + c) = 0.13572 > 0$. In this case, we have $K_1 - \frac{\beta_1}{\beta_2} K_2 < 0$ and $b_1 > 0$, so according to the Theorem 7 the system (4) has one coexistence endemic equilibrium point $E_2 = (393.99, 550.81, 3978.74, 2.000413 \times 10^6)$ which is meet the stability condition in Theorem 8. Figure 4 shows that the coexistence endemic equilibrium point E_2 is asymptotically stable.

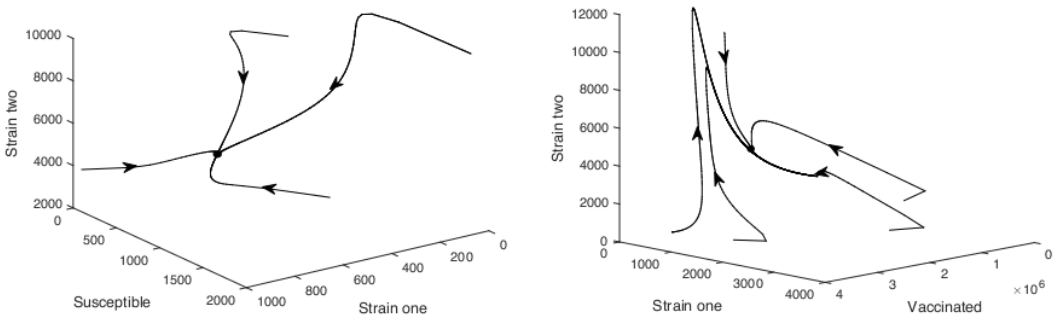


Fig. 4. All trajectories tend to the dominance strain two equilibrium point E_2. (***a***) Vaccinated verses infected by strain one and strain two, (***b***) Susceptible verses infected by strain one and strain two.

Finally, let us look again at the set of parameter values (5) with $\gamma = 0.6$. In codimension one bifurcation, we make a continuation on the disease-free equilibrium point E_0 and let we consider β_1 as a bifurcation parameter, then we have a critical parameter $\beta_1^* = 0.00038037009$, where meet the condition of Theorem 9, in which the system (4) exhibits forward bifurcation, see Figure 5*a*. We find that for $\beta_1 < 0.00038037009$ associated with $R_0 < 1$ (note that in this case $R_0 = R_1$), then we only have a disease-free equilibrium point which is globally asymptotically stable. By increasing β_1, in addition to the disease-free equilibrium point, we get the coexistence equilibrium point E_2 when $\beta_1 > 0.00038037009$. For $\beta_1 > 0.00038037009$, we have $R_0 > 1$ so the disease-free equilibrium point is unstable and the condition of Theorem 7(ii) and Theorem 8 are satisfied. Hence, the system (4) has one coexistence endemic equilibrium point which is stable. A continuation of the supercritical bifurcation point BP as β_1 increases generates two Hopf bifurcations at H_1 when $\beta_1 = 0.00038096393$ and H_2 when $\beta_1 = 0.00041434067$. It means that some cycles of interaction in the system happen as transmission rate of strain one infection increases [35].

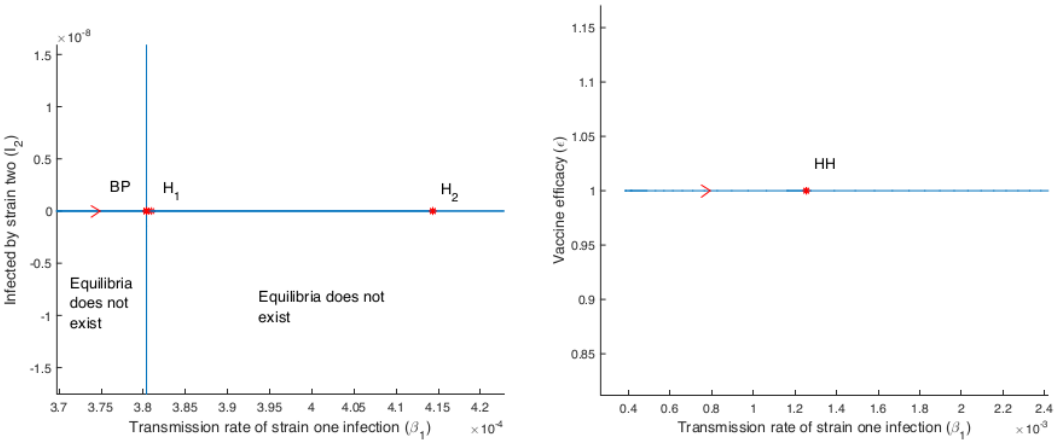
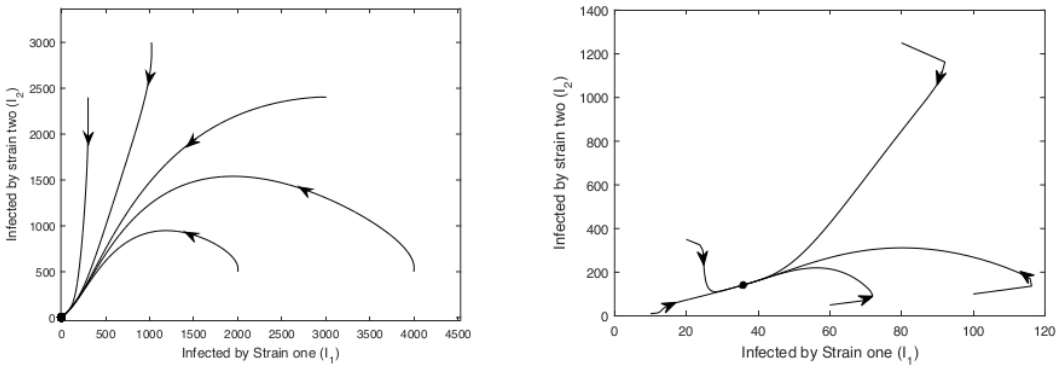


Fig. 5. Bifurcation Diagram: (***a***) Codimension one bifurcation diagram: E_0 continuation by varying β_1, (***b***) Codimension two bifurcation diagram: H_1 continuation by varying β_1 and ε.

In codimension two bifurcation, a double Hopf bifurcation is found through continuation of H_2 by varying β_1 and ε at HH, i.e. $(\beta_1, \varepsilon) = (0.001255, 1)$, see Figure 5*b*. This point is an intersection of two Hopf curves and become the emanation point of two branches of torus bifurcations. It also generates

Shilnikov's homoclinic orbits to the focus-focus equilibrium and a connection between an equilibria and saddle limit cycles through heteroclinic bifurcation. Hence, the bifurcation can become an indicator of a local birth of chaos and quasi-periodicity [36]. It means that an increase in vaccine efficacy can still cause an unpredictable pattern and an irregular periodicity of the subpopulation dynamic when it coincides with an increase in transmission rate of strain one infection. So, it is important to control or suppress the transmission rate of strain one infection in addition to increase the efficacy of the vaccine.



a ***b***

Fig. 6. Phase portrait projection of infected by strain one verses infected by strain two. (***a***) For $\beta_1 = 0.00036$ all trajectories tend to the the equilibrium point E_0. (***b***) For $\beta_1 = 0.00039$ all trajectories tend to the equilibrium point E_2.

Figure 6 shows a phase portrait projection of infected individuals by strain one verses infected individuals by strain two. It can be seen that before the bifurcation point, the disease-free equilibrium point E_0 is asymptotically stable as indicated by all trajectories starting with different initial values always approaching the equilibrium point $E_0 = (684.96, 0, 0, 1.0646983 \times 10^7)$ (Figure 6*a*). Note that under these conditions, E_0 is the only equilibrium point of system (4) which is globally stable. After passing $\beta_1 = 0.0003796428163$, E_0 turns unstable and there is another equilibrium point, that is a stable coexistence equilibrium point E_2. In Figure 6*b*, we show that for $\beta_1 = 0.00039$, there is a stable coexistence endemic equilibrium E_2. In this case we have $E_2 = (666.76, 35.21, 131.96, 9.700913 \times 10^6)$. The higher the value of β_1, the greater the number of infected individuals, both by strain one and strain two. This also suggests that in addition to increasing the vaccine coverage rate, lowering the transmission rate is an attempt to end the disease. Medically, these efforts can take the form of various preventive policies or reduce interactions between infected individuals and susceptible populations.

6. Discussion and conclusion

In this paper, we presented an epidemic model with vaccination by considering two viral strains of diseases. This model is similar to the general SIR epidemic model with vaccination but includes viral mutations to form individuals infected by strain two from individuals infected by strain one with mutation rate γ. In addition, it is assumed that the vaccine is completely perfect for strain one but not for strain two, which is a mutation from strain one. The analytical results started by showing that the solution of the model is positive and bounded in the admissible region. It is observed that system (4) always has a disease-free equilibrium point that is globally asymptotically stable whenever $R_0 < 1$. In addition to the disease-free equilibrium point, the system may have a dominance equilibrium point of strain two and coexistence endemic equilibrium point. The local stability analysis of all equilibrium points was performed using the Routh–Hurwitz criterion, while the global stability was studied using the appropriate Lyapunov functions. We also performed a bifurcation analysis by using the application of the center manifold theory, and observed that for $R_0 < 1$, the solution of the system always tends

to the disease-free equilibrium point, so there is no backward bifurcation. Theorem 9 showed that, when $R_2 < 1$, the system always has forward bifurcation at $R_0 = 1$. This indicates that reducing the basic reproduction number to values less than one is a necessary and sufficient condition for disease eradication.

We provide numerical simulations to verify the analytical results for a suitable set of parameter values. To determine the impact of vaccine administration, we varied the parameter γ. We concluded that the larger the individual covered by the vaccine, the endemic could be eliminated from the community, which agrees with intuition. We also vary the value of recovering rate of infected individuals by strain two and disease strain one transmission rate to confirm our obtained analytical results. The last two parameters are respectively related to the prevention of transmission by strain one and treatment of individuals infected by strain two, in which vaccination was not completely effective. Through numerical simulations, we showed that vaccination and prevention of transmission rate by strain one positively impact disease incidence and prevalence in a community. In future research, we will study this model more intensively by paying attention to more specific cases, and we believe it will be more excitable.

Acknowledgment

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Модель епідемії з вірусними мутаціями та вакцинальними втручаннями

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У цій статті представлено модель епідемії SIR із двома штамами з вірусною мутацією та введенням вакцини. Обговорюється та аналізується існування та стійкість точок рівноваги. Ця модель має три типи точок рівноваги, а саме: рівновагу без захворювань, точку рівноваги домінування другого штаму та точку рівноваги ендемічного співіснування. Локальну стійкість точки рівноваги домінування другого штаму та точку рівноваги ендемічного співіснування перевірено за допомогою критерія Рауса–Гурвіца, тоді як для глобальної стійкості точки рівноваги домінування штаму два використано відповідну функцію Ляпунова. Проведено аналіз біфуркації, використовуючи теорію центрального многовиду, і отримано, що система поблизу точки рівноваги без хвороб завжди має надкритичну біфуркацію. Накінець, чисельне моделювання надано для підтвердження теоретичних результатів. Продовження надкритичної точки біфуркації призводить до двох біфуркацій Хопфа, що вказує на локальне народження хаосу та квазіперіодичності.

Ключові слова: *модель епідемії; мутація вірусу; щеплення; аналіз стійкості; біфуркація.*

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