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GLOBAL DYNAMICS OF A VACCINATION MODEL FOR INFECTIOUS DISEASES WITH ASYMPTOMATIC CARRIERS

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Abstract. In this paper, an epidemic model is investigated for infectious diseases that can be transmitted through both the infectious individuals and the asymptomatic carriers (i.e., infected individuals who are contagious but do not show any disease symptoms). We propose a dose-structured vaccination model with multiple transmission pathways. Based on the range of the explicitly computed basic reproduction number, we prove the global stability of the disease-free when this threshold number is less or equal to the unity. Moreover, whenever it is greater than one, the existence of the unique endemic equilibrium is shown and its global stability is established for the case where the changes of displaying the disease symptoms are independent of the vulnerable classes. Further, the model is shown to exhibit a transcritical bifurcation with the unit basic reproduction number being the bifurcation parameter. The impacts of the asymptomatic carriers and the effectiveness of vaccination on the disease transmission are discussed through through the local and the global sensitivity analyses of the basic reproduction number. Finally, a case study of hepatitis B virus disease (HBV) is considered, with the numerical simulations presented to support the analytical results. They further suggest that, in high HBV prevalence countries, the combination of effective vaccination (i.e. ≥ 3 doses of HepB vaccine), the diagnosis of asymptomatic carriers and the treatment of symptomatic carriers may have a much greater positive impact on the disease control.

1. **Introduction.** Besides the greatest disasters to human populations like tsunami and earthquakes, are the infectious diseases. It is well documented that the infectious diseases outbreaks cause mortality of millions of people as well as expenditure of enormous amount of money in health care and disease control [29]. It is therefore important that adequate attention is paid to stop the spread of such diseases by using effective control measures. Vaccination of people at risk of contamination is

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commonly used to prevent and control the epidemic spread. For the majority of diseases, to be efficient, the vaccine need to be administrated in many doses. This has been totally successful for some diseases such as Smallpox, polio, measles, etc... [3]. Mathematical models that incorporate vaccination as a control measure have been used to drive some strategies, and to determine changes in qualitative behavior that could result from such a control measure [3, 22, 26, 27]. A vaccine may fail to confer any protection in a proportion of vaccinees. In this case, the vaccine is not totally effective and vaccinated individuals can be directly infected [7]. When these aspect are included in the model, a rich dynamical behavior may arise including bi-stability, backward and forward bifurcation [3, 13, 22].

For many infectious diseases, the transmission occurs in a heterogeneous population. So, the epidemiological model must divide the population into groups, in which the members have similar characteristics. This division into groups can be based on the mode of transmission, contacts patterns, infectious period, genetic susceptibility and amount/strategies of vaccination. For some infectious diseases, there are asymptomatic carriers (i.e. infected individuals who are able to transmit their illness but do not exhibit any symptoms). Asymptomatic carriers play an important role in the transmission of diseases. They can be regarded as "lost sight of" because they are likely unaware of their conditions, and therefore are more likely to infect others. An infectious disease that produces asymptomatic carriers is the Typhoid fever caused by the bacteria salmonella Typhi. Typhoid fever infects 21 millions people and kills $200,000$ worldwide every year. Asymptomatic carriers play an essential role in the transmission of Typhi, and their presence greatly hinders the eradication of Typhoid fever using treatment and vaccination [24]. Another major infectious disease that causes long-term asymptomatic carriers is hepatitis B, a liver disease caused by the HBV virus of the Hepadnavirus family. It is a major global health problem, and the most serious type of viral hepatitis [29]. Several people living with the disease do not show any symptoms, these are chronic HBV carriers. There is no widely available effective treatment for chronic HBV carrier and immunization with hepatitis B vaccine (HepB) is the most important prevention measure. Several vaccines have been developed for the prevention of HBV infection and the main vaccinations include the 3-dose HepB vaccination [27, 28]. The efficacy of available vaccinations for infectious diseases such as hepatitis B is not perfect. Vaccinated individuals may still contract the disease and the susceptibility varies from individual to individual [8]. Infections of other pathogens are also know to produce asymptomatic carriers (e.g. Epstein-Barr Virus, Clostridium Difficile) [23].

Mathematical models have been used to study the effects of carriers on the transmission dynamics of the disease. One of the earlier attempt is the work in [17]. Later, the authors in [2] proposed a simple compartmental model to investigate the effects of carriers on the transmission of HBV. Several studies used the mathematical models for hepatitis B with carriers to discuss the effects of vaccination on HBV transmission [11, 21, 26, 27]. Others studies using large-scale computational models with carriers are aimed at other diseases [9, 22, 23]. More recently, a model in [16] was proposed to analyze the effects of carriers on the transmission dynamics of diseases. In their work [16], the authors considered an efficacy vaccine, i.e the recovered and vaccinated subgroups are not distinguished, and did not take into account of the effect of ineffectiveness of vaccination. In fact, for certain diseases (e.g. Cholera, Hepatitis B,...), vaccination process is divide into several stages upon a given period and vaccine can be effective only if all the stages during which many

doses of the vaccine are administrated. For instance, for Hepatitis B infection, the vaccination schedule recommends three doses given over 6 to 18 months depending on vaccine type [27, 28] and three doses must be taken for efficiency.

Therefore, the objective of this work is threefold: (1) - to propose a more general mathematical model extending the works in [14–16] by the incorporation of the effectiveness of vaccination and multiple doses/stages of vaccines; (2) - to rigorously analyze the resulting model by addressing the global stability of the model; (3) - to perform local and global sensitivity analyses of the basic reproduction and the numerical simulations through which, the impacts of the effectiveness of both the vaccination and the presence asymptomatic carriers on the transmission of some infectious diseases (e.g. HBV infection).

The model is constructed based on the model proposed in [16]. We make a more realistic assumption that the vaccine is not totally effective, and extend this model by incorporating three vaccinated classes, V_i $(i = 1, 2, 3)$, and three important factors : (1) vaccine coverage, (2) effectiveness of vaccination and (3) susceptibilities of susceptible individuals. We derive the basic reproduction number $\mathcal{R}_0$, and show, using the method of global Lyapunov functions, that the global dynamics of the model is completely determined by the range of $\mathcal{R}_0$. Through a sensitivity analysis of $\mathcal{R}_0$, we are able to discuss the impact of parameters that significantly affect $\mathcal{R}_0$. We have also carried out numerical simulations to illustrate our theoretical results. The Lyapunov functions used in this paper to prove the global stability of endemic equilibrium have the same form as those used in [14–16, 18].

The manuscript is organized as follows: In the next section, we formulate the model and derive its basic properties. In section 3, The reproduction number is derived, and the global stability of disease-free equilibrium is established. Existence, uniqueness and global stability of an endemic equilibrium are shown in section 4. While section 5 is devoted to the numerical simulations for the case study of HBV disease to support our analytical results. Section 6 concludes the paper and provides a discussion for future and ongoing works.

2. **The model.**

2.1. **Model formulation.**

We formulate a $S - V_i - I_c - I - R$, $i = 1, 2, 3$, compartmental model where S, V_i, I_c, I and R stand for the susceptible, vaccinated, asymptomatic carrier, symptomatic carrier, and removed class, respectively. A fraction of the susceptible population is vaccinated and $\theta_i > 0$, $i = 1, 2, 3$, represents the transition vaccination rate of vaccinated individuals from stage V_i to V_{i+1}. Since the vaccine may fail to confer any protection in a proportion of vaccinees, the vaccinated individuals on whom vaccine fails can be infected but with different susceptibilities than that of S-compartment individuals. Here, the susceptible individuals in each group have homogeneous susceptibility but the susceptibilities of individuals from different groups are distinct. The vaccinated individuals on whom the vaccine is successful, are immunized and fully protected by the vaccine. Susceptible individuals can be infected through direct contact with an asymptomatic carrier or a symptomatic carrier. A newly infected susceptible from group S (respectively from groups V_i) can become an asymptomatic carrier with probability π_{11} (respectively, π_{i1}, $i = 2, 3, 4$) or a symptomatic carrier with probability π_{12} (respectively, π_{i2}, $i = 2, 3, 4$), and $\pi_{i1} + \pi_{i2} = 1$, $i = 1, 2, 3, 4$. We assume that the average number of contacts per individual is proportional to the population size. Hence, the rate of infection for susceptibles in compartments S and V_i, $i = 1, 2, 3$ is given

by $\lambda_i = \alpha_i(\beta_1 I_c + \beta_2 I)$, $i = 1,2,3,4$, where α_1, α_2, α_3, α_4 ($\alpha_1 > \alpha_2 > \alpha_3 > \alpha_4$) denote the susceptibilities of susceptible individuals of compartments S and V_i, respectively. β_1, β_2 are the infectiousness of infected individuals of compartments I_c and I respectively. Note that $\beta_{ij} = \alpha_i\beta_j$, $i = 1,2,3,4$, $j = 1,2$. We assume that, the susceptibilities α_2, α_3, α_4 of vaccinated individuals are proportional to the susceptibility α_1 of S-compartment individuals, with $\alpha_i = (1-\varepsilon)^{i-1}\alpha_1$, $i = 2,3,4$, where $\varepsilon \in [0,1]$ is effectiveness of the vaccine. An asymptomatic carrier can become symptomatic at a rate α. For infections such as HBV for which carriage can remain life-long, α can be regarded as the rate of diagnosis. α can also represents the rate at which people carrying the disease became aware of their infection, either through testing or through appearance of symptoms. We assume a constant influx b of susceptibles, and let d_i, $i = 1,\cdots,7$, denote the death rates of those in the susceptible, vaccinated, asymptomatic carriers, symptomatic carrier, and removed classes, respectively. Different parameters d_1, d_2, d_3, d_4 and d_7 are used for natural death rate (though these rates are epidemiologically equal, we distinguish them just for mathematical elegance). The death rates d_5 and d_6 may include both natural and disease-related death. Symptomatic carriers recover with rate π, and we assume that recovered individuals are permanently immune.

The parameters in the model are summarized and epidemiologically explained in Table 1. They are assumed non-negative. The model flowchart is depicted in Figure1 from which we derive the system of ordinary differential equations in system (1) governing the dynamics of the constructed model.

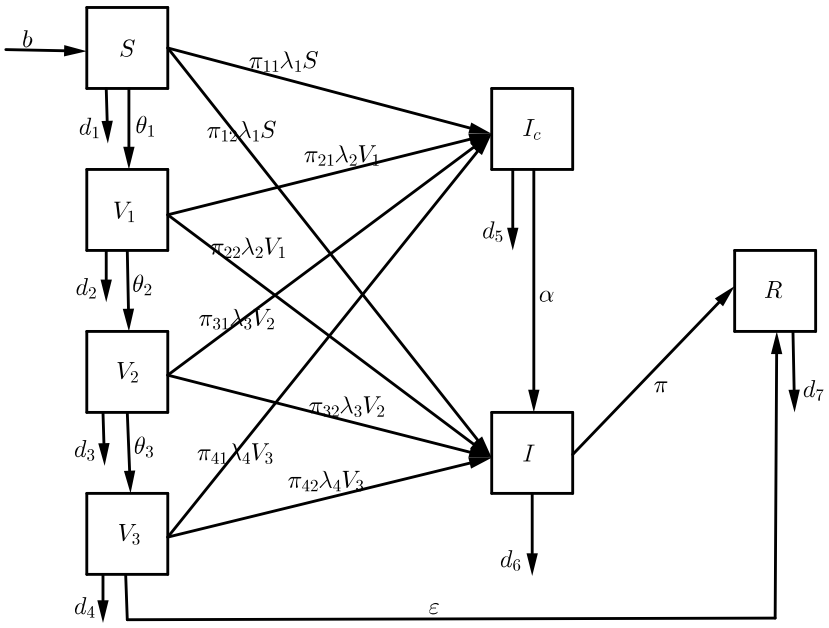

FIGURE 1. Transfer diagram $S - V_i - I_c - I - R$, $i = 1,2,3$ model: $\lambda_j = \alpha_j(\beta_1 I_c + \beta_2 I)$, $j = 1,2,3,4$.

TABLE 1. Variables and parameter values.

Symbols	Definitions	Estimate for HBV	Source
S	Susceptible human individuals	$ind.^*$	
V_i	Vaccinated human individuals	$ind.$	
I_c	Carrier human individuals	$ind.$	
I	Infected human individuals	$ind.$	
R	Recovered human individuals	$ind.$	
b	Recruitment of susceptible human individuals	$20\ ind.day^{-1}$	As.**
α_1	Susceptibilities of susceptible individuals	0.65	As.
β_2	Contact rate of symptomatically infected (I)	$0.05\ ind^{-1}.day^{-1}$	As.
$\beta_1 = 1.5\beta_2$	Contact rate of carriers (I_c)	$ind^{-1}.day^{-1}$	[16]
d_1, d_7	Natural death rate of human individuals	$0.0125\ day^{-1}$	[16]
d_2, d_3, d_4	Natural death rate of human individuals	$0.0125\ day^{-1}$	[16]
d_5, d_6	Death rates for I_c and I compartments, including both natural and disease-caused death	$0.0165\ day^{-1}$	[16]
α	Rate at which carriers develop symptoms	$0-1\ day^{-1}$	
π	Recovered rate of human individuals	$0.75\ day^{-1}$	[16]
ε	Effectiveness of the vaccine	$0-100\%$	
π_{i1}, $i = 1,2,3,4$	Probabilities of becoming an asymptomatic carrier	0.885	[27]
π_{i2}, $i = 1,2,3,4$	Probabilities of becoming a symptomatic carrier	0.115	[27]
θ_i	Transition vaccination rate of vaccinated individuals	$0-100\%$	

*individuals **Assumed

$$
\begin{cases}
\dot{S} &= b-(d_1+\theta_1)S-\alpha_1(\beta_1 I_c+\beta_2 I)S,\\
\dot{V}_1 &= \theta_1 S-(d_2+\theta_2)V_1-\alpha_2(\beta_1 I_c+\beta_2 I)V_1,\\
\dot{V}_2 &= \theta_2 V_1-(d_3+\theta_3)V_2-\alpha_3(\beta_1 I_c+\beta_2 I)V_2,\\
\dot{V}_3 &= \theta_3 V_2-(d_4+\varepsilon)V_3-\alpha_4(\beta_1 I_c+\beta_2 I)V_3,\\
\dot{I}_c &= \pi_{11}\alpha_1(\beta_1 I_c+\beta_2 I)S+\sum_{i=2}^{4}\pi_{i1}\alpha_i(\beta_1 I_c+\beta_2 I)V_{i-1}-(d_5+\alpha)I_c,\\
\dot{I} &= \pi_{12}\alpha_1(\beta_1 I_c+\beta_2 I)S+\sum_{i=2}^{4}\pi_{i2}\alpha_i(\beta_1 I_c+\beta_2 I)V_{i-1}+\alpha I_c-(d_6+\pi)I,\\
\dot{R} &= \pi I+\varepsilon V_3-d_7 R.
\end{cases}
\tag{1}
$$

Our model (1) extend the existing works in [14–16] by incorporating the:

- vaccinated classes and taking account the ineffectiveness of vaccination $1-\varepsilon$. In the case where $\varepsilon = 1$, the vaccine is completely effective. When $\varepsilon = 0$, the vaccine has no effect and is completely useless. This leads to the model without vaccination;
- vaccination transition rates since the vaccination campaign is divided into three different doses;

- different susceptibilities and infectivities, since the vaccinated individuals can be infected with certain susceptibility and new infections from I_c or I may enter either compartment with certain probability. This yields a differential susceptibility and infectivity epidemic model with staged progression.

The system (1) can be written in the following compact form :

$$\left\{\begin{array}{lcl} \dot{X} &=& \Lambda - DX - CXB^T Y + A_X X, \\ \dot{Y} &=& P^T CXB^T Y + A_Y Y + EY, \\ \dot{x_7} &=& ZX + QY - d_7 x_7, \end{array}\right. \tag{2}$$

where $X = (x_1, x_2, x_3, x_4)^T = (S, V_1, V_2, V_3)^T$, $Y = (x_5, x_6)^T = (I_c, I)^T$, $x_7 = R$,

$B = (\beta_1, \beta_2)^T$, $Q = (0\ \pi)$, $\Lambda = (b, 0, 0, 0)^T$, $Z = (0\ 0\ 0\ \varepsilon)$, $D = \mathrm{diag}(d_1, d_2, d_3, d_4)$,

$C = \mathrm{diag}(\alpha_1, \alpha_2, \alpha_3, \alpha_4)$, $A_Y = \mathrm{diag}\,(-d_5 - \alpha, -d_6 - \pi)$, $E = \begin{pmatrix} 0 & 0 \\ \alpha & 0 \end{pmatrix}$,

$$P^T = \begin{pmatrix} \pi_{11} & \pi_{21} & \pi_{31} & \pi_{41} \\ \pi_{12} & \pi_{22} & \pi_{32} & \pi_{42} \end{pmatrix} \quad \text{and} \quad A_X = \begin{pmatrix} -\theta_1 & 0 & 0 & 0 \\ \theta_1 & -\theta_2 & 0 & 0 \\ 0 & \theta_2 & -\theta_3 & 0 \\ 0 & 0 & \theta_3 & -\varepsilon \end{pmatrix}.$$

2.2. **Basic properties.**

Proposition 1. *Let the initial data be $S(0) > 0$, $V_i(0) > 0$, $i = 1, 2, 3$, $I_c(0) \geq 0$, $I(0) \geq 0$ and $R(0) \geq 0$. Then, the solutions $(S, V_1, V_2, V_3, I_c, I, R)$ of model (1) are positive for all $t > 0$, whenever they exist.*

Proof. Set $\lambda_1 = \alpha_1(\beta_1 I_c + \beta_2 I)$, then the first equation of model (1), can be written as

$$\frac{dS}{dt} = b - (d_1 + \theta_1 + \lambda_1)S, \quad \text{where.}$$

Assume the solution of (1) exists in a certain interval $J \subset [0, +\infty[$, then $\forall t \in J$, the above equation can be solved as,

$$\frac{d}{dt}\left[S(t)\exp\left\{(d_1 + \theta_1)t + \int_0^t \lambda_1(s)ds\right\}\right] \geq b\exp\left\{(d_1 + \theta_1)t + \int_0^t \lambda_1(s)ds\right\}.$$

Thus,

$$S(t)\exp\left\{(d_1 + \theta_1)t + \int_0^t \lambda_1(s)ds\right\} - S(0) \geq \int_0^t b\exp\left\{(d_1 + \theta_1)u + \int_0^u \lambda_1(w)dw\right\}du,$$

so that,

$$\begin{aligned} S(t) \quad \geq \quad & S(0)\exp\left\{-\Big((d_1 + \theta_1)t + \int_0^t \lambda_1(s)ds\Big)\right\} \\ & + \exp\left\{-\Big((d_1 + \theta_1)t + \int_0^t \lambda_1(s)ds\Big)\right\} \times \\ & \int_0^t b\exp\left\{(d_1 + \theta_1)u + \int_0^u \lambda_1(w)dw\right\}du > 0. \end{aligned}$$

Hence $S(t) > 0$, $\forall t \in J$. Next, using the fact $S(t) > 0$, we have from the second equation of model (1), that

$$\frac{d}{dt}\left[V_1(t)\exp\left\{(d_2+\theta_2)t+\int_0^t \lambda_2(s)ds\right\}\right] \geq \theta_1 S \exp\left\{(d_2+\theta_2)t+\int_0^t \lambda_2(s)ds\right\}.$$

Thus,

$$\begin{aligned} V_1(t) &\geq V_1(0)\exp\left\{-\left((d_2+\theta_2)t+\int_0^t \lambda_2(s)ds\right)\right\} \\ &\quad + \exp\left\{-\left((d_2+\theta_2)t+\int_0^t \lambda_2(s)ds\right)\right\} \times \\ &\quad \int_0^t \theta_1 S(u)\exp\left\{(d_2+\theta_2)u+\int_0^u \lambda_2(w)dw\right\}du > 0. \end{aligned}$$

Similarly, it can be shown that $V_2(t) > 0$ and $V_3(t) > 0$. Finally, from system (2), we have

$$\dot{Y} = (P^T C X B^T + A_Y + E)Y.$$

Since $X > 0$, the matrix $(P^T C X B^T + A_Y + E)$ is a Metzler matrix, and it is well known that linear Metzler matrices let invariant the non-negative orthant. Thus, $I_c(t) \geq 0$ and $I(t) \geq 0$, for all $t > 0$, $t \in J$. □

Proposition 2. *Whenever they exist, the solutions of the model (1) are bounded.*

Proof. Let $(S(t), V_1(t), V_2(t), V_3(t), I_c(t), I(t), R(t))$ be any solution of system. Let

$$N(t) = S(t) + \sum_{i=1}^{3} V_i(t) + I_c(t) + I(t) + R(t).$$

The derivative of $N(t)$ along the positive solutions of system (1) is

$$\begin{aligned} \dot{N}(t) &= b - d_1 S(t) - \sum_{i=2}^{4} d_i V_{i-1}(t) - d_5 I_c(t) - d_6 I(t) - d_7 R(t), \\ &\leq b - dN(t), \end{aligned} \tag{3}$$

where $d = \min\{d_1, d_2, d_3, d_4, d_5, d_6, d_7\}$. It follows from (3) that,

$$\lim_{t\to+\infty} \sup N(t) \leq \frac{b}{d}.$$

Also from (1), we have

$$\dot{S}(t) \leq b - c_1 S \quad \text{and} \quad \dot{V}_i(t) \leq \prod_{j=1}^{i} \frac{b\,\theta_j}{c_j} - c_{i+1} V_i, \quad i = 1,2,3,$$

where $c_j = d_j + \theta_j$, $j = 1,2,3$ and $c_4 = d_4 + \varepsilon$.

Thus,

$$\lim_{t\to+\infty} \sup S(t) \leq \frac{b}{c_1} \quad \text{and} \quad \lim_{t\to+\infty} \sup V_i(t) \leq \prod_{j=1}^{i+1} \frac{b\,\theta_{j-1}}{c_j}, \quad i = 1,2,3, \quad \text{with} \quad \theta_0 = 1.$$

This completes the proof. □

Theorem 2.1. *System (1) is a dynamical system in the biological feasible region given by*

$$\Omega = \left\{ (S, V_1, V_2, V_3, I_c, I, R) \in \mathbb{R}_+^7 : S \leq \frac{b}{c_1},\ V_i \leq \prod_{j=1}^{i+1} \frac{b\ \theta_{j-1}}{c_j},\ i = 1,2,3\ ,\ N \leq \frac{b}{d} \right\}.$$

Proof. The differentiability of the right-hand side of the system (1) implies, thanks to Cauchy-Lipschitz theorem, the existence of the unique maximal solution for any associated Cauchy problem. Thus, the initial value problem for this system is mathematically well posed and biologically reasonable since all variables remain non-negative. Hence, it is sufficient to study the dynamics of the flow generated by the model (1) in Ω. Moreover, since the solutions of the model (1) are positive and bounded, it remains to show that the vector field defined by this system is transversal to the boundary of Ω on all its faces. The face corresponding to $S = \frac{b}{c_1}$ has direction $(1,0,0,0,0,0,0)$, and the inner product with the vector field is $b - c_1 S - \alpha_1 W S \leq b - c_1 S \leq 0$. Similarly, we can check for the faces $V_i = \prod_{j=1}^{i+1} \frac{b\ \theta_{j-1}}{c_j}$, $i = 1,2,3$. Finally, the face corresponding to $N = \frac{b}{d}$ has direction $(1,1,1,1,1,1,1)$, and the inner product with the vector field is $b - \sum_{i=1}^{7} d_i x_i \leq b - dN \leq 0$. Thus, the vector field on these faces point toward the region Ω. This completes the proof. □

The first six equations of (1) are independent of the state variable R. Thus, once the dynamics of S, V_1, V_2, V_3, I_c, and I are understood, that of R can then be easily determined from the linear equation

$$\dot{R} = \pi I + \varepsilon V_3 - d_7 R.$$

Consequently, after decoupling the equation for R from system (1), we devote the analysis to the remaining equations of system (2) which becomes

$$\begin{cases} \dot{x}_1 = f_1 &= b - (d_1 + \theta_1)x_1 - \alpha_1(\beta_1 x_5 + \beta_2 x_6)x_1, \\ \dot{x}_2 = f_2 &= \theta_1 x_1 - (d_2 + \theta_2)x_2 - \alpha_2(\beta_1 x_5 + \beta_2 x_6)x_2, \\ \dot{x}_3 = f_3 &= \theta_2 x_2 - (d_3 + \theta_3)x_3 - \alpha_3(\beta_1 x_5 + \beta_2 x_6)x_3, \\ \dot{x}_4 = f_4 &= \theta_3 x_3 - (d_4 + \varepsilon)x_4 - \alpha_4(\beta_1 x_5 + \beta_2 x_6)x_4, \\ \dot{x}_5 = f_5 &= \sum_{i=1}^{4} \pi_{i1}\alpha_i(\beta_1 x_5 + \beta_2 x_6)x_i - (d_5 + \alpha)x_5, \\ \dot{x}_6 = f_6 &= \sum_{i=1}^{4} \pi_{i2}\alpha_i(\beta_1 x_5 + \beta_2 x_6)x_i + \alpha x_5 - (d_6 + \pi)x_6. \end{cases} \tag{4}$$

3. Basic reproduction number $\mathcal{R}_0$ and disease-free equilibrium.

3.1. **Computation of $\mathcal{R}_0$.** In the absence of infection, that is $x_5 = x_6 = 0$, the model (4) has a disease-free equilibrium (DFE),

$$X^0 = \left(\frac{b}{c_1}, \frac{\theta_1 b}{c_1 c_2}, \frac{\theta_1 \theta_2 b}{c_1 c_2 c_3}, \frac{\theta_1 \theta_2 \theta_3 b}{c_1 c_2 c_3 c_4}, 0, 0 \right)^T,$$

which is obtained by setting the right-hand side of the system (4) to zero.

A key quantity in classic epidemiological models is the basic reproduction number, denoted by $\mathcal{R}_0$. It is a useful threshold in the study of a disease for predicting a

disease outbreak and for evaluating the control strategies. Based on the work in [6], the next generation operator approach can be used to derive an explicit formula for $\mathcal{R}_0$, as the spectral radius of the next-generation matrix. From system (2), we define

$$\mathcal{F}(X,Y) = \left(0, P^T CXB^T Y\right)^T \quad \text{and} \quad \mathcal{V}(X,Y) = \left(\Lambda - DX - CXB^T Y + A_X X, (A_Y + E)Y\right)^T.$$

Then,

$$D\mathcal{F}(X,Y) = \begin{pmatrix} 0 & 0 \\ P^T CB^T Y & P^T CXB^T \end{pmatrix}, \quad D\mathcal{V}(X,Y) = \begin{pmatrix} -D - CB^T Y + A_X & -CXB^T \\ 0 & A_Y + E \end{pmatrix}.$$

At the DFE X^0,

$$D\mathcal{F}(X^0,0) = \begin{pmatrix} 0 & 0 \\ 0 & P^T CX^0 B^T \end{pmatrix} \quad \text{and} \quad D\mathcal{V}(X^0,0) = \begin{pmatrix} -D + A_X & -CX^0 B^T \\ 0 & A_Y + E \end{pmatrix}.$$

Therefore, $F = P^T CX^0 B^T$ and $V = A_Y + E$. But

$$F = \begin{pmatrix} \sum_{i=1}^{4} \pi_{i1}\beta_{i1}x_i^0 & \sum_{i=1}^{4} \pi_{i1}\beta_{i2}x_i^0 \\ \sum_{i=1}^{4} \pi_{i2}\beta_{i1}x_i^0 & \sum_{i=1}^{4} \pi_{i2}\beta_{i2}x_i^0 \end{pmatrix} \quad \text{and} \quad -V^{-1} = \begin{pmatrix} \frac{1}{d_5+\alpha} & 0 \\ \frac{\alpha}{(d_5+\alpha)(d_6+\pi)} & \frac{1}{d_6+\pi} \end{pmatrix},$$

where $\beta_{ij} = \alpha_i \beta_j$, $i = 1,2,3,4$, $j = 1,2$. Hence,

$$-FV^{-1} = \begin{pmatrix} \frac{\sum_{i=1}^{4} \pi_{i1}\beta_{i1}x_i^0}{d_5+\alpha} + \frac{\alpha \sum_{i=1}^{4} \pi_{i1}\beta_{i2}x_i^0}{(d_5+\alpha)(d_6+\pi)} & \frac{\sum_{i=1}^{4} \pi_{i1}\beta_{i2}x_i^0}{d_6+\pi} \\ \frac{\sum_{i=1}^{4} \pi_{i2}\beta_{i1}x_i^0}{d_5+\alpha} + \frac{\alpha \sum_{i=1}^{4} \pi_{i2}\beta_{i2}x_i^0}{(d_5+\alpha)(d_6+\pi)} & \frac{\sum_{i=1}^{4} \pi_{i2}\beta_{i2}x_i^0}{d_6+\pi} \end{pmatrix}.$$

Since $\det(-FV^{-1}) = 0$, one has

$$\mathcal{R}_0 = \rho(-FV^{-1}) = \sum_{i=1}^{4} \left(\frac{\pi_{i1}\beta_{i1}}{d_5+\alpha} + \frac{\alpha \pi_{i1}\beta_{i2}}{(d_5+\alpha)(d_6+\pi)} + \frac{\pi_{i2}\beta_{i2}}{d_6+\pi} \right) x_i^0. \tag{5}$$

Remark 1. Rewrite $\mathcal{R}_0$ in (5) as

$$\mathcal{R}_0 = \sum_{i=1}^{4} \left[\pi_{i2} \cdot \beta_{i2} \cdot \frac{1}{d_6+\pi} + \pi_{i1} \left(\beta_{i1} \cdot \frac{1}{d_5+\alpha} + \frac{\alpha}{d_5+\alpha} \cdot \beta_{i2} \cdot \frac{1}{d_6+\pi} \right) \right] x_i^0. \tag{6}$$

When a single infective is introduced into the susceptible population (in group x_i, $i = 1,2,3,4$), with probability π_{i2} it is a symptomatic carrier, hence makes β_{i2} effective contacts per unit time. This is multiplied by the average infectious period $\frac{1}{d_6+\pi}$ for symptomatic carriers ; with probability π_{i1} the infective is an asymptomatic carrier, and hence makes β_{i1} effective contacts per unit time during the average period $\frac{1}{d_5+\alpha}$ it remains a carrier. This number should be augmented by the number of infections $\beta_{i2} \cdot \frac{1}{d_6+\pi}$ caused by this infective after it becomes a

symptomatic carrier, with probability $\frac{\alpha}{d_5+\alpha}$ to survive the asymptomatic carrier stage. Therefore, the expression in the big square brackets in (6) is the per capita average number of secondary infections. This number multiplied by the number of susceptibles at the disease-free equilibrium, x_i^0, gives $\mathcal{R}_0$.

3.2. **Sensitivity analysis of $\mathcal{R}_0$.** Sensitivity analysis is used to determine the relative importance of model parameters to disease transmission and its prevalence. We perform the analysis by calculating the sensitivity indices of the basic reproduction number, $\mathcal{R}_0$ to the parameters in the model using both local and global methods. According to [1, 10, 20], sensitivity analysis is commonly used to determine the robustness of model predictions to parameter values, since there are usually uncertainties in data collection and estimated values. We are thus interested in parameters that significantly affect the basic reproduction number, since these are the parameters that should be taken into consideration when considering intervention strategies. Sensitivity analysis also permits us to measure the relative change in a state variable when a parameter changes.

3.2.1. *Local sensitivity analysis.* The local sensitivity analysis is based on the normalised sensitivity index of $\mathcal{R}_0$. The normalized forward sensitivity index of a variable to a parameter is the number of the relative change in the variable to the relative change in the parameter. Since the basic reproduction number is a differentiable function of the parameters, the sensitivity index may alternatively be defined using partial derivatives [10].

To this aim, denoting by Ψ the generic parameter of system (4), we evaluate the normalized sensitivity index

$$S_\Psi = \frac{\Psi}{\mathcal{R}_0}\frac{\partial \mathcal{R}_0}{\partial \Psi},$$

which indicates how sensitive $\mathcal{R}_0$ is to a change of parameter Ψ. A positive (resp. negative) index indicates that an increase in the parameter value results in an increase (resp. decrease) in the $\mathcal{R}_0$ value.

Here, for simplicity we assume that the changes of displaying the disease symptoms are independent of the vulnerable states variables, that is $\pi_{11} = \pi_{i1}$ and $\pi_{12} = \pi_{i2}$, $i = 2, 3, 4$. We consider the parameter values in the Table 1 with $\theta_1 = 0.8$, $\theta_2 = \theta_3 = 0.9$, $\alpha = 0.2$ and $\varepsilon = 0.5$. We tabulate the indices of the remaining parameters in Table 2.

TABLE 2. Sensitivity indices for $\mathcal{R}_0$ with respect to some chosen parameters.

Parameter	Sensitivity index	Value	Parameter	Sensitivity index	Value
α_1	S_{α_1}	+1	d_5	S_{d_5}	−0.0772
α	S_α	−0.7864	d_6	S_{d_6}	−0.0037
ε	S_ε	−0.8813	π	S_π	−0.1677
θ_1	S_{θ_1}	−0.5268	β_1	S_{β_1}	+0.8637
θ_2	S_{θ_2}	−0.2314	β_2	S_{β_2}	+0.1713
θ_3	S_{θ_3}	−0.1142	π_{11}	$S_{\pi_{11}}$	+0.8513

From Table 2, we can observe that the parameters α_1, π_{11}, β_1 and β_2 respectively have a positive influence in the value of $\mathcal{R}_0$. This means that the increase or the

decrease of these parameters say by 10%, then $\mathcal{R}_0$ will increase or decrease by 10%, 8.5%, 8.6% and 1.7% respectively. The index for parameters α, ε and π which represent the diagnosis rate, the effectiveness of vaccination and recovered rate respectively, show that increasing their values by 10% will decrease the value of $\mathcal{R}_0$ by 7.8%, 8.8% and 1.7% respectively. Similarly, the index for the transition vaccination rate show that increasing their values by 10% will decrease $\mathcal{R}_0$ almost by 5.2%. When ε increases, θ_1 has a higher sensitivity index. From these analysis, it is worth noting that a higher diagnosis rate α, effectiveness of vaccination ε and transition vaccination rate θ_1 decreases $\mathcal{R}_0$. Using parameter values in Table 1 with $\theta_2 = \theta_3 = 0.9$, the numerical results displayed in Figure 2 illustrate the role of α, ε, θ_1 and π on the basic reproduction number $\mathcal{R}_0$, from which we observe that $\mathcal{R}_0$ decreases whenever the parameters α, θ_1, ε, π increase. This suggest that, an optimal control measure could be the combination of the effective vaccination of susceptible individuals, the screening of asymptomatic carriers and the treatment of symptomatic carriers.

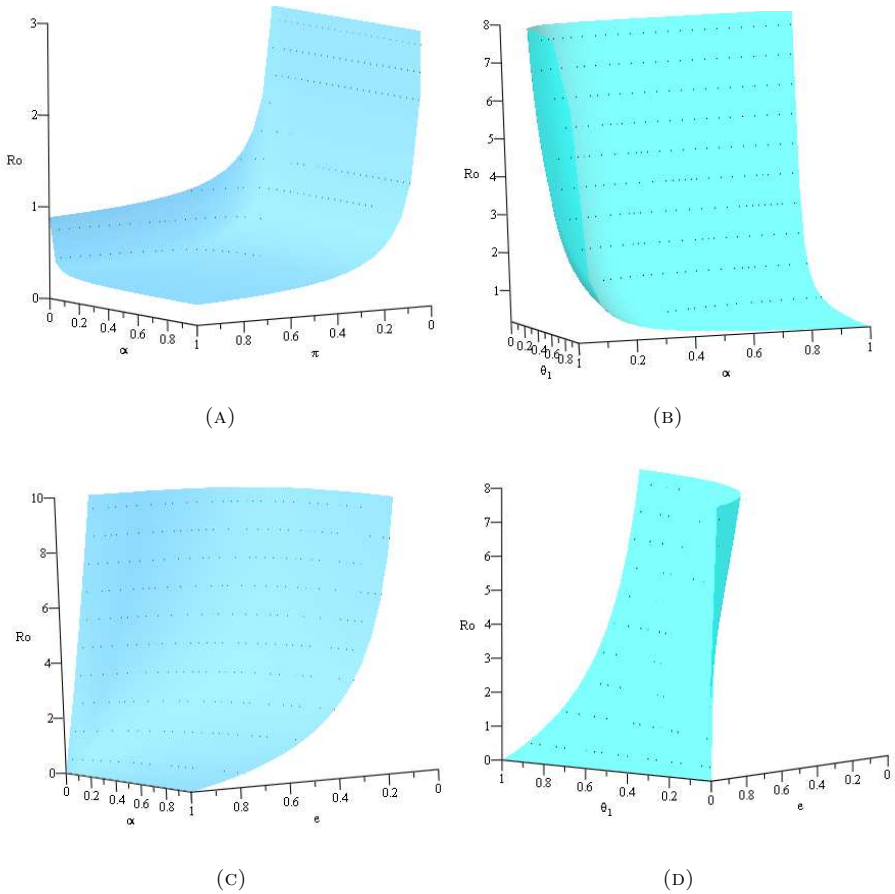

FIGURE 2. The graphs of the basic reproduction number $\mathcal{R}_0$ versus some parameters: (a) $\mathcal{R}_0$ versus α and π, (b) $\mathcal{R}_0$ versus α and θ_1, (c) $\mathcal{R}_0$ versus α and ε, and (d) $\mathcal{R}_0$ versus θ_1 and ε.

3.2.2. *Uncertainty and global sensitivity analysis.* Local sensitivity analysis assesses the effects of individual parameters at particular points in parameter space without taking into account of the combined variability resulting from considering all input parameters simultaneously. Here, we perform a global sensitivity analysis to examine the model responses to parameter variation within a wider range in the parameter space. The mean values of parameters are listed in Table 1, and the range values of these parameters are given in Table3.

TABLE 3. Parameter value ranges of model (1) used as input for the LHS method.

Parameter	Range	Parameter	Range	Parameter	Range
b	[10 , 50]	d_6	[0.01 , 0.03]	α_1	[0.1 , 0.95]
d_1	[0.01 , 0.02]	d_7	[0.01 , 0.02]	θ_1	[0.1 , 0.98]
d_2	[0.01 , 0.02]	α	[0.05 , 0.85]	θ_2	[0.1 , 0.98]
d_3	[0.01 , 0.02]	ε	[0.2 , 0.95]	θ_3	[0.1 , 0.98]
d_4	[0.01 , 0.02]	π	[0.5 , 0.95]	β_1	[0.01 , 0.1]
d_5	[0.01 , 0.03]	π_{11}	[0.2 , 0.95]	β_2	[0.01 , 0.1]

It is important to notice that, variations of these parameters in our deterministic model lead to uncertainty to model predictions since the basic reproductive number varies with parameters. Following the approach in [1, 20], partial rank correlation coefficients (PRCC) between the basic reproduction number $\mathcal{R}_0$ and each parameter for model (1) are derived. Due to the absence of data on the distribution function, a uniform distribution is chosen for all parameters. The sets of input parameter values sampled using the Latin Hypercube Sampling (LHS) method were used to run 1000 simulations. We compute the Partial Rank Correlation Coefficients between $\mathcal{R}_0$ and each parameter of model (1). The results of the PRCC are displayed in Table 4.

TABLE 4. PRCC between $\mathcal{R}_0$ and each parameter

Parameter	PRCCs	P-values	Parameter	PRCCs	P-values
b	$^{**}0.7702$	$8.4837E-194$	ε	$^{**}-0.6762$	$2.62E-132$
d_1	-0.0389	0.2228	π	-0.2691	$9.04E-18$
d_2	-0.0380	0.2334	π_{11}	0.4550	$2.21E-51$
d_3	-0.0269	0.3994	α_1	$^{***}0.8262$	$9.56E-247$
d_4	0.0546	0.0870	θ_1	$^{**}-0.6704$	$2.77E-129$
d_5	-0.0217	0.4977	θ_2	-0.3584	$3.67E-31$
d_6	-0.0375	0.2405	θ_3	-0.1528	$1.48E-06$
d_7	-0.0156	0.6242	β_2	$^{*}0.5889$	$7.9203E-93$
α	$^{**}-0.6426$	$1.32E-115$	β_1	$^{**}0.6235$	$5.3962E-107$

According to [12], the parameters with large PRCC values (> 0.5 or < -0.5) as well as corresponding small p-values (< 0.05) are most influential in model (1). Table 4 shows that the parameter α_1 have the highest influence on the reproduction number $\mathcal{R}_0$, followed in decreasing order by the parameters b, ε, θ_1, α, β_1 and β_2. The other parameters have not almost any effect on $\mathcal{R}_0$. We can observe that parameters α, ε and θ_1 allow us to considerably reduce the reproduction number. Hence, the

sensitivity analysis consistently reinforces our suggestion that the most effective manner to reduce the infection is to increase both the screening of asymptomatic carriers and the effectiveness vaccination rate of susceptible individuals.

We note that the order of the most important parameters for $\mathcal{R}_0$ from the local sensitivity analysis not match those from the global sensitivity analysis, showing that the local results are not enough robust.

3.3. **Global stability of the disease-free equilibrium.** Using Theorem 2 in [6], the following result is straightforward.

Lemma 3.1. *The disease-free equilibrium X^0 of model system (4) is locally asymptotically stable whenever $\mathcal{R}_0 < 1$ and unstable otherwise.*

Theorem 3.2. *The disease-free equilibrium, X^0 is globally asymptotically stable in the feasible region Ω if $\mathcal{R}_0 \leq 1$.*

Proof. To prove the global asymptotic stability of X^0, we use the Lyapunov function approach. Define

$$L = L(x_1, x_2, x_3, x_4, x_5, x_6) = \left(\frac{\beta_1}{d_5+\alpha} + \frac{\alpha\beta_2}{(d_5+\alpha)(d_6+\pi)}\right)x_5(t) + \frac{\beta_2}{d_6+\pi}x_6(t).$$

Then,

$$\begin{aligned}
\dot{L} &= \left(\frac{\beta_1}{d_5+\alpha} + \frac{\alpha\beta_2}{(d_5+\alpha)(d_6+\pi)}\right)\Big[\sum_{i=1}^{4}\pi_{i1}\alpha_i(\beta_1 x_5+\beta_2 x_6)x_i - (d_5+\alpha)x_5\Big] \\
&\quad + \frac{\beta_2}{d_6+\pi}\Big[\sum_{i=1}^{4}\pi_{i2}\alpha_i(\beta_1 x_5+\beta_2 x_6)x_i + \alpha x_5 - (d_6+\pi)x_6\Big], \\
&= \sum_{i=1}^{4}\Big(\frac{\pi_{i1}\alpha_i\beta_1}{d_5+\alpha} + \frac{\alpha\pi_{i1}\alpha_i\beta_2}{(d_5+\alpha)(d_6+\pi)} + \frac{\pi_{i2}\alpha_i\beta_2}{d_6+\pi}\Big)(\beta_1 x_5+\beta_2 x_6)x_i - (\beta_1 x_5+\beta_2 x_6), \\
&= \Big[\sum_{i=1}^{4}\Big(\frac{\pi_{i1}\alpha_i\beta_1}{d_5+\alpha} + \frac{\alpha\pi_{i1}\alpha_i\beta_2}{(d_5+\alpha)(d_6+\pi)} + \frac{\pi_{i2}\alpha_i\beta_2}{d_6+\pi}\Big)x_i - 1\Big](\beta_1 x_5+\beta_2 x_6).
\end{aligned}$$

Since $x_i \leq x_i^0$, $i = 1, 2, 3, 4$, we have

$$\dot{L} \leq (\mathcal{R}_0 - 1)(\beta_1 x_5 + \beta_2 x_6) \leq 0, \quad \text{whenever} \quad \mathcal{R}_0 \leq 1.$$

Moreover, $\dot{L} = 0 \Leftrightarrow x_5 = x_6 = 0$ or $x_i = x_i^0$, $i = 1, 2, 3, 4$ and $\mathcal{R}_0 = 1$.

Thus, the largest invariant set $\mathcal{H}$ such as $\mathcal{H} \subset \{(x_1, x_2, x_3, x_4, x_5, x_6) \in \mathbb{R}_+^6/\dot{L} = 0\}$ is the singleton $\{X^0\}$. By LaSalle's Invariance Principle [19], X^0 is globally asymptotically stable in Ω, completing the proof. □

4. Endemic equilibrium.

4.1. **Existence and uniqueness.** We have shown in Section 3 that if $\mathcal{R}_0 > 1$, the infection-free equilibrium is unstable, and then the disease spreads if a small infection is introduced into the population. Now we assume $\mathcal{R}_0 > 1$ and show that there exists an endemic equilibrium all of whose components are positive.

The endemic equilibrium of model (4) needs to satisfy the following equations

$$\begin{aligned} b - c_1x_1 - \alpha_1 W x_1 &= 0,\\ \theta_1 x_1 - c_2x_2 - \alpha_2 W x_2 &= 0,\\ \theta_2 x_2 - c_3x_3 - \alpha_3 W x_3 &= 0,\\ \theta_3 x_3 - c_4x_4 - \alpha_4 W x_4 &= 0,\\ \sum_{i=1}^{4} \pi_{i1}\alpha_i W x_i - (d_5+\alpha)x_5 &= 0,\\ \sum_{i=1}^{4} \pi_{i2}\alpha_i W x_i + \alpha x_5 - (d_6+\pi)x_6 &= 0. \end{aligned} \tag{7}$$

Solving (7) for x_i yields

$$x_i = b\prod_{j=1}^{i}\frac{\theta_{j-1}}{c_j+\alpha_j W}, \quad i=1,2,3,4, \quad x_5 = \sum_{i=1}^{4}\frac{\pi_{i1}\alpha_i W x_i}{d_5+\alpha},$$

$$x_6 = \sum_{i=1}^{4}\frac{\pi_{i2}\alpha_i W x_i}{d_6+\pi} + \alpha\sum_{i=1}^{4}\frac{\pi_{i1}\alpha_i W x_i}{(d_5+\alpha)(d_6+\pi)} = \sum_{i=1}^{4}\Big(\frac{\pi_{i2}}{d_6+\pi} + \frac{\alpha\pi_{i1}}{(d_5+\alpha)(d_6+\pi)}\Big)\alpha_i W x_i.$$

Hence

$$\begin{aligned} W = \beta_1 x_5 + \beta_2 x_6 &= \sum_{i=1}^{4}\frac{\pi_{i1}\alpha_i\beta_1 W x_i}{d_5+\alpha} + \sum_{i=1}^{4}\beta_2\Big(\frac{\pi_{i2}}{d_6+\pi} + \frac{\alpha\pi_{i1}}{(d_5+\alpha)(d_6+\pi)}\Big)\alpha_i W x_i,\\ &= W\sum_{i=1}^{4}\Big(\frac{\pi_{i1}\alpha_i\beta_1}{d_5+\alpha} + \frac{\pi_{i2}\alpha_i\beta_2}{d_6+\pi} + \frac{\alpha\pi_{i1}\alpha_i\beta_2}{(d_5+\alpha)(d_6+\pi)}\Big)x_i,\\ &= Wb\sum_{i=1}^{4} a_i\prod_{j=1}^{i}\frac{\theta_{j-1}}{c_j+\alpha_j W}, \end{aligned}$$

where $a_i = \dfrac{\pi_{i1}\alpha_i\beta_1}{d_5+\alpha} + \dfrac{\pi_{i2}\alpha_i\beta_2}{d_6+\pi} + \dfrac{\alpha\pi_{i1}\alpha_i\beta_2}{(d_5+\alpha)(d_6+\pi)}$.

- If $W = 0$, then we obtain the disease-free equilibrium.
- If $W \neq 0$, then $\quad b\displaystyle\sum_{i=1}^{4} a_i\prod_{j=1}^{i}\frac{\theta_{j-1}}{c_j+\alpha_j W} = 1.$

  Define

$$G(W) = b\sum_{i=1}^{4} a_i\prod_{j=1}^{i}\frac{\theta_{j-1}}{c_j+\alpha_j W} - 1.$$

  Then there exists an endemic equilibrium for system (4) if and only if there exists a positive solution to $G(W) = 0$.

  Since on the one hand, $\lim\limits_{W\to\infty} G(W) = -1$ and

$$G'(W) = -\sum_{i=1}^{4} a_i\prod_{j=1}^{i}\frac{b\alpha_j\theta_{j-1}}{(c_j+\alpha_j W)^2} < 0,$$

  the equation $G(W) = 0$ has a unique positive root if $G(0) > 0$. On the other hand,

$$G(0) = \sum_{i=1}^{4} a_i\prod_{j=1}^{i}\frac{b\,\theta_{j-1}}{c_j} - 1 = \mathcal{R}_0 - 1, \quad \text{and} \quad \mathcal{R}_0 > 1,$$

we have $G(0) > 0$.

Hence, there exists a unique endemic equilibrium whenever $\mathcal{R}_0 > 1$. We have shown the following result.

Theorem 4.1. *The model (4) has a unique endemic equilibrium T^*, whenever $\mathcal{R}_0 > 1$.*

4.2. **Global stability.** In epidemiology, the bifurcation theory is concerned with how solutions of a differential equation depend on parameters, and it can explain how the changes in dynamics take place from a resting state to oscillations. It plays a relevant role in disease control and eradication. Theorem 4.1 establishes that $\mathcal{R}_0 = 1$ is a bifurcation parameter. In fact, across $\mathcal{R}_0 = 1$ the disease-free equilibrium, X^0 changes its stability property from local stability to unstable (see Theorem 3.2). In the result below, the Centre Manifold Theory [5] is used to investigate the appearance of the transcritical bifurcation at $\mathcal{R}_0 = 1$ where the stable disease-free equilibrium X^0 becomes unstable when $\mathcal{R}_0$ crosses one from below and gives rise to the stable endemic equilibrium T^*. We have the following theorem.

Theorem 4.2. *The ODE system (4) has a forward bifurcation at $\mathcal{R}_0 = 1$.*

Proof. $\mathcal{R}_0 = 1$ is equivalent to $\alpha_1 = \overline{\alpha}_1 = \dfrac{1 - \sum_{i=2}^{4} \alpha_i e_i x_i^0}{e_1 x_1^0}$, with $e_i = \dfrac{\pi_{i1}\beta_1}{d_3 + \alpha} + \dfrac{\alpha \pi_{i1}\beta_2}{(d_3 + \alpha)(d_4 + \pi)} + \dfrac{\pi_{i2}\beta_2}{d_4 + \pi}$.

The Jacobian of system (4) calculated at the DFE X^0 with $\alpha_1 = \overline{\alpha}_1$ is

$$A(X^0) = \begin{pmatrix} -\dfrac{b}{x_1^0} & 0 & 0 & 0 & -\alpha_1\beta_1 x_1^0 & -\alpha_1\beta_1 x_1^0 \\ \theta_1 & -\dfrac{\theta_1 x_1^0}{x_2^0} & 0 & 0 & -\alpha_2\beta_1 x_1^0 & -\alpha_2\beta_2 x_2^0 \\ 0 & \theta_2 & -\dfrac{\theta_2 x_2^0}{x_3^0} & 0 & -\alpha_3\beta_1 x_3^0 & -\alpha_3\beta_2 x_3^0 \\ 0 & 0 & \theta_3 & -\dfrac{\theta_3 x_3^0}{x_4^0} & -\alpha_4\beta_1 x_4^0 & -\alpha_4\beta_2 x_4^0 \\ 0 & 0 & 0 & 0 & A_{55} & A_{56} \\ 0 & 0 & 0 & 0 & A_{65} & A_{66} \end{pmatrix},$$

where

$$A_{55} = \beta_1 \sum_{i=1}^{4} \pi_{i1}\alpha_i x_i^0 - (d_5 + \alpha); \qquad A_{56} = \beta_2 \sum_{i=1}^{4} \pi_{i1}\alpha_i x_i^0;$$

$$A_{65} = \beta_1 \sum_{i=1}^{4} \pi_{i2}\alpha_i x_i^0 + \alpha; \qquad A_{66} = \beta_2 \sum_{i=1}^{4} \pi_{i2}\alpha_i x_i^0 - (d_6 + \pi).$$

Since $\mathcal{R}_0 = 1$,

$$\beta_1 \sum_{i=1}^{4} \frac{\pi_{i1}\alpha_i}{d_5 + \alpha} x_i^0 + \beta_2 \sum_{i=1}^{4} \frac{\pi_{i2}\alpha_i}{d_6 + \pi} x_i^0 = 1 - \sum_{i=1}^{4} \frac{\pi_{i1}\alpha_i\beta_2}{(d_5 + \alpha)(d_6 + \pi)} x_i^0 < 1.$$

This implies that

$$\beta_1 \sum_{i=1}^{4} \frac{\pi_{i1}\alpha_i}{d_5+\alpha} x_i^0 < 1 \quad \text{and} \quad \beta_2 \sum_{i=1}^{4} \frac{\pi_{i2}\alpha_i}{d_6+\pi} x_i^0 < 1$$

or equivalently

$$A_{55} < 0 \quad \text{and} \quad A_{66} < 0.$$

The eigenvalues of the matrix $A(X^0)$ with $\alpha_1 = \overline{\alpha}_1$ are:

$$\lambda_1 = 0; \quad \lambda_2 = -\frac{b}{x_1^0}; \quad \lambda_3 = -\frac{\theta_1 x_1^0}{x_2^0}; \quad \lambda_4 = -\frac{\theta_2 x_2^0}{x_3^0}; \quad \lambda_5 = -\frac{\theta_3 x_3^0}{x_4^0}; \quad \lambda_6 = A_{55} + A_{66} < 0.$$

So, for $\alpha_1 = \overline{\alpha}_1$, $A(X^0)$ has a zero eigenvalue, with all the other eigenvalues having negative real parts. The centre manifold theory can be used to analyse dynamics of system (4).

Eigenvectors of $A(X^0)|_{\alpha_1=\overline{\alpha}_1}$: The right eigenvector corresponding to the zero eigenvalue is

$$w = (w_1, w_2, w_3, w_4, w_6)^T$$

where

$$w_i = -A_i w_5, \quad i = 1,2,3,4; \quad w_5 > 0 \quad \text{and} \quad w_6 = \left(-\frac{\beta_1}{\beta_2} + A_0\right) w_5,$$

with $A_0 = \dfrac{d_5+\alpha}{A_{56}}$; $A_1 = \dfrac{\alpha_1\beta_2 A_0 (x_1^0)^2}{b}$; $A_i = \dfrac{A_{i-1}x_{i-1}^0}{x_{i-2}^0} + \dfrac{\beta_2\alpha_{i-1}(x_{i-1}^0)^2}{\theta_{i-1}x_{i-2}^0}$, $i = 2,3,4$.

The left eigenvector corresponding to the zero eigenvalue is given by

$$v = (v_1, v_2, v_3, v_4, v_5, v_6)^T$$

where

$$v_1 = v_2 = v_3 = v_4 = 0, \quad v_5 > 0 \quad \text{and} \quad v_6 = -\frac{A_{55}}{A_{65}} v_5.$$

Calculation of a: For the system (4), the corresponding non-zero partial derivatives of f_i $(i = 1,2,3,4,5,6)$ calculated at the disease free equilibrium are given by

$$\frac{\partial^2 f_5}{\partial x_i \partial x_6} = \pi_{i1}\alpha_i\beta_2; \quad \frac{\partial^2 f_5}{\partial x_i \partial x_5} = \pi_{i1}\alpha_i\beta_1; \quad \frac{\partial^2 f_6}{\partial x_i \partial x_5} = \pi_{i2}\alpha_i\beta_1; \frac{\partial^2 f_6}{\partial x_i \partial x_6} = \pi_{i2}\alpha_i\beta_2, \ i = 1,2,3,4,$$

$$\frac{\partial^2 f_5}{\partial x_5 \partial \alpha_1} = \pi_{11}\beta_1 x_1^0 ; \quad \frac{\partial^2 f_5}{\partial x_6 \partial \alpha_1} = \pi_{11}\beta_2 x_1^0 ; \quad \frac{\partial^2 f_6}{\partial x_5 \partial \alpha_1} = \pi_{12}\beta_1 x_1^0 ; \quad \frac{\partial^2 f_6}{\partial x_6 \partial \alpha_1} = \pi_{12}\beta_2 x_1^0.$$

Consequently, we calculate the associated bifurcation coefficient a

$$\begin{aligned} a &= \sum_{k,i,j=1}^{6} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(X^0), \\ &= -A_0\beta_2 v_5 w_5^2 \sum_{i=1}^{4} A_i \pi_{i1}\alpha_i + \frac{A_{55}}{A_{65}} \beta_2 A_0 v_5 w_5^2 \sum_{i=1}^{4} A_i \pi_{i2}\alpha_i, \\ &= -A_0\beta_2 v_5 w_5^2 \left(\sum_{i=1}^{4} A_i \pi_{i1}\alpha_i - \frac{A_{55}}{A_{65}} \sum_{i=1}^{4} A_i \pi_{i2}\alpha_i \right) < 0. \end{aligned}$$

Calculation of b: We compute the associated bifurcation coefficient b

$$\begin{aligned} b &= \sum_{k,i=1}^{6} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \alpha_1}(X^0), \\ &= v_5 w_5 \pi_{11} \beta_1 x_1^0 + v_5 w_6 \pi_{11} \beta_2 x_1^0 + v_6 w_5 \pi_{12} \beta_1 x_1^0 + v_6 w_6 \pi_{12} \beta_2 x_1^0, \\ &= A_0 \beta_2 x_1^0 v_5 w_5 \left(\pi_{11} - \pi_{12} \frac{A_{55}}{A_{65}}\right) > 0. \end{aligned}$$

Thus, the bifurcation coefficient a is always negative. Furthermore, the bifurcation coefficient b is always positive. Hence, it follows from Theorem 4.1 in [5], that model (4) does undergo the forward or transcritical bifurcation. □

The application of Theorem 4.1 in [5] to prove Theorem 4.2, also establish the local asymptotic stability of T^*, but this result applies only for small values of $\mathcal{R}_0 > 1$. The following theorem extend Theorem 4.2 by showing the global asymptotic stability of T^* for all values of $\mathcal{R}_0$ above one.

When the changes of displaying the disease symptoms are independent of the vulnerable classes S, V_1, V_2 and V_3, we are able to establish the following global result regarding the stability of the unique endemic equilibrium.

Theorem 4.3. *The endemic equilibrium of system (4), T^* is globally asymptotically stable in the interior of Ω whenever $\mathcal{R}_0 > 1$, $\pi_{11} = \pi_{i1}$ and $\pi_{12} = \pi_{i2}$, $i = 2, 3, 4$.*

Proof. Suppose that $\mathcal{R}_0 > 1$, $\pi_{11} = \pi_{i1}$ and $\pi_{12} = \pi_{i2}$, $i = 2, 3, 4$. To study the global stability of the endemic equilibrium, we make use of a Lyapunov function V of the form

$$V(x_1, \cdots, x_6) = b_1 \sum_{i=1}^{4} (x_i - x_i^* \ln x_i) + b_2 (x_5 - x_5^* \ln x_5) + b_3 (x_6 - x_6^* \ln x_6), \tag{8}$$

where b_1, b_2, $b_3 > 0$ are constants to be specified shortly. The function V has a global minimum at T^* and $V(x_1, \cdots, x_6) - V(T^*)$ is positive definite. We show that suitable constants b_1, b_2, b_3 can be chosen such that the Lyapunov derivative of V is negative with respect T^*. Differentiating this function with respect to time yields

$$\begin{aligned} \frac{dV}{dt} &= b_1 \sum_{i=1}^{4} \left(\dot{x}_i - \frac{x_i^*}{x_i}\dot{x}_i\right) + b_2 \left(\dot{x}_5 - \frac{x_5^*}{x_5}\dot{x}_5\right) + b_3 \left(\dot{x}_6 - \frac{x_6^*}{x_6}\dot{x}_6\right), \\ &= b_1 \left[b - d_1 x_1 - \theta_1 x_1 - \alpha_1 W x_1 - b\frac{x_1^*}{x_1} + d_1 x_1^* + \theta_1 x_1^* + \alpha_1 W x_1^*\right] + b_1 \left[\theta_1 x_1 - d_2 x_2\right. \\ &\quad \left. - \theta_2 x_2 - \alpha_2 W x_2 - \theta_1 x_1^* \frac{x_1 x_2^*}{x_1^* x_2} + d_2 x_2^* + \theta_2 x_2^* + \alpha_2 W x_2^*\right] + b_1 \left[\theta_2 x_2 - d_3 x_3\right. \\ &\quad \left. - \theta_3 x_3 - \alpha_3 W x_3 - \theta_2 x_2^* \frac{x_2 x_3^*}{x_2^* x_3} + d_3 x_3^* + \theta_3 x_3^* + \alpha_3 W x_3^*\right] + b_1 \left[\theta_3 x_3 - (d_4 + \varepsilon) x_4\right. \\ &\quad \left. - \alpha_4 W x_4 - \theta_3 x_3^* \frac{x_3 x_4^*}{x_3^* x_4} + (d_4 + \varepsilon) x_4^* + \alpha_4 W x_4^*\right] + b_2 \left[\pi_{11} W \sum_{i=1}^{4} \alpha_i x_i - (d_5 + \alpha) x_5\right. \\ &\quad \left. - \pi_{11} \sum_{i=1}^{4} \alpha_i x_i \left(\beta_1 x_5^* + \beta_2 \frac{x_5^* x_6}{x_5}\right) + (d_5 + \alpha) x_5^*\right] + b_3 \left[\pi_{12} W \sum_{i=1}^{4} \alpha_i x_i + \alpha x_5\right. \end{aligned}$$

$$-(d_6+\pi)x_6-\pi_{12}\sum_{i=1}^{4}\alpha_i x_i\left(\beta_1\frac{x_5x_6^*}{x_6}+\beta_2x_6^*\right)-\alpha\frac{x_5x_6^*}{x_6}+(d_6+\pi)x_6^*\Big],$$

where $W=\beta_1x_5+\beta_2x_6$ and $W^*=\beta_1x_5^*+\beta_2x_6^*$. Considering (7), we have the following equilibrium relations

$$b=\sum_{i=1}^{3}d_ix_i^*+(d_4+\varepsilon)x_4^*+\sum_{i=1}^{4}\alpha_ix_i^*W^* \quad ; \quad \theta_2x_2^*=d_3x_3^*+(d_4+\varepsilon)x_4^*+\sum_{i=3}^{4}\alpha_ix_i^*W^* \tag{9}$$

$$\theta_1x_1^*=\sum_{i=2}^{3}d_ix_i^*+(d_4+\varepsilon)x_4^*+\sum_{i=2}^{4}\alpha_ix_i^*W^* \quad ; \quad \theta_3x_3^*=(d_4+\varepsilon)x_4^*+\alpha_4x_4^*W^*$$

$$\sum_{i=1}^{4}\alpha_ix_i^* = \frac{(d_5+\alpha)(d_6+\pi)}{\pi_{11}\beta_1(d_6+\pi)+\beta_2[\pi_{12}(d_5+\alpha)+\pi_{11}\alpha]}, \tag{10}$$

$$\pi_{11}(d_6+\pi)x_6^* = [\pi_{12}(d_5+\alpha)+\pi_{11}\alpha]x_5^*. \tag{11}$$

Using the relations (9) in $\frac{dV}{dt}$, one has

$$\begin{aligned}
\frac{dV}{dt} &= b_1\Bigg[d_1x_1^*+d_2x_2^*+d_3x_3^*+(d_4+\varepsilon)x_4^*+\sum_{i=1}^{4}\alpha_ix_i^*W^*-d_1x_1-\theta_1x_1-\alpha_1Wx_1\\
&\quad -d_1x_1^*\frac{x_1^*}{x_1}-d_2x_2^*\frac{x_1^*}{x_1}-d_3x_3^*\frac{x_1^*}{x_1}-(d_4+\varepsilon)x_4^*\frac{x_1^*}{x_1}-\sum_{i=1}^{4}\alpha_ix_i^*W^*\frac{x_1^*}{x_1}+d_1x_1^*+d_2x_2^*\\
&\quad +d_3x_3^*+(d_4+\varepsilon)x_4^*+\sum_{i=2}^{4}\alpha_ix_i^*W^*+\alpha_1Wx_1^*\Bigg]+b_1\left[\theta_1x_1-d_2x_2-\theta_2x_2-\alpha_2Wx_2\right.\\
&\quad +d_2x_2^*+\alpha_2Wx_2^*+d_3x_3^*+(d_4+\varepsilon)x_4^*+\sum_{i=3}^{4}\alpha_ix_i^*W^*-\Big(d_2x_2^*+d_3x_3^*+(d_4+\varepsilon)x_4^*\\
&\quad \left.+\sum_{i=2}^{4}\alpha_ix_i^*W^*\right)\frac{x_1x_2^*}{x_1^*x_2}\Bigg]+b_1\Big[\theta_2x_2-d_3x_3-\theta_3x_3-\alpha_3Wx_3+d_3x_3^*+(d_4+\varepsilon)x_4^*\\
&\quad +\alpha_4x_4^*W^*+\alpha_3Wx_3^*-\left(d_3x_3^*+(d_4+\varepsilon)x_4^*+\sum_{i=3}^{4}\alpha_ix_i^*W^*\right)\frac{x_2x_3^*}{x_2^*x_3}\Bigg]+b_1\Big[\theta_3x_3\\
&\quad -(d_4+\varepsilon)x_4-\alpha_4Wx_4-\Big((d_4+\varepsilon)x_4^*+\alpha_4x_4^*W^*\Big)\frac{x_3x_4^*}{x_3^*x_4}+(d_4+\varepsilon)x_4^*+\alpha_4Wx_4^*\Big]\\
&\quad +b_2\left[\pi_{11}W\sum_{i=1}^{4}\alpha_ix_i-(d_5+\alpha)x_5-\pi_{11}\sum_{i=1}^{4}\alpha_ix_i\left(\beta_1x_5^*+\beta_2\frac{x_5^*x_6}{x_5}\right)+(d_5+\alpha)x_5^*\right]\\
&\quad +b_3\left[\pi_{12}W\sum_{i=1}^{4}\alpha_ix_i+\alpha x_5-(d_6+\pi)x_6-\pi_{12}\sum_{i=1}^{4}\alpha_ix_i\left(\beta_1\frac{x_5x_6^*}{x_6}+\beta_2x_6^*\right)\right.\\
&\quad \left.-\alpha\frac{x_5x_6^*}{x_6}+(d_6+\pi)x_6^*\Big],\right.\\
&= b_1d_1x_1^*\left(2-\frac{x_1^*}{x_1}-\frac{x_1}{x_1^*}\right)+b_1d_2x_2^*\left(3-\frac{x_1^*}{x_1}-\frac{x_2}{x_2^*}-\frac{x_1x_2^*}{x_1^*x_2}\right)+b_1d_3x_3^*\left(4-\frac{x_1^*}{x_1}-\frac{x_3}{x_3^*}\right.
\end{aligned}$$

$$-\frac{x_1x_2^*}{x_1^*x_2}-\frac{x_2x_3^*}{x_2^*x_3}\Big)+b_1(d_4+\varepsilon)x_4^*\Big(5-\frac{x_1^*}{x_1}-\frac{x_4}{x_4^*}-\frac{x_1x_2^*}{x_1^*x_2}-\frac{x_2x_3^*}{x_2^*x_3}-\frac{x_3x_4^*}{x_3^*x_4}\Big)$$
$$+b_1\left(\alpha_1x_1^*+2\alpha_2x_2^*+3\alpha_3x_3^*+4\alpha_4x_4^*\right)(\beta_1x_5^*+\beta_2x_6^*)+b_2(d_5+\alpha)x_5^*+b_3(d_6$$
$$+\pi)x_6^*+\sum_{i=1}^{4}\alpha_ix_iW\left(-b_1+b_2\pi_{11}+b_3\pi_{12}\right)+\sum_{i=1}^{4}x_i\left(-b_2\pi_{11}\beta_{i1}x_5^*-b_3\pi_{12}\beta_{i2}x_6^*\right)$$
$$+x_5\left[b_1\sum_{i=1}^{4}\beta_{i1}x_i^*-b_2(d_5+\alpha)+b_3\alpha\right]+x_6\left[b_1\sum_{i=1}^{4}\beta_{i2}x_i^*-b_3(d_6+\pi)\right]$$
$$+\frac{x_1^*}{x_1}\left[-b_1\sum_{i=1}^{4}\alpha_ix_i^*W^*\right]+\frac{x_1x_2^*}{x_1^*x_2}\left[-b_1\sum_{i=2}^{4}\alpha_ix_i^*W^*\right]+\frac{x_2x_3^*}{x_2^*x_3}\left[-b_1\sum_{i=3}^{4}\alpha_ix_i^*W^*\right]$$
$$+\frac{x_3x_4^*}{x_3^*x_4}\left[-b_1\alpha_4x_4^*W^*\right]+\sum_{i=1}^{4}\frac{x_ix_5x_6^*}{x_i^*x_5^*x_6}\left[-b_3\pi_{12}\beta_{i1}x_5^*x_i^*\right]+\frac{x_5x_6^*}{x_5^*x_6}\left[-b_3\alpha x_5^*\right]$$
$$+\sum_{i=1}^{4}\frac{x_ix_5^*x_6}{x_i^*x_5x_6^*}\left[-b_2\pi_{11}\beta_{i2}x_6^*x_i^*\right].$$

We choose the positive constants b_1, b_2, b_3 such as the expressions of x_5 and x_6 vanish ; we obtain

$$b_1=1;b_2=b_1\left(\frac{\beta_1}{d_5+\alpha}+\frac{\alpha\beta_2}{(d_5+\alpha)(d_6+\pi)}\right)\cdot\left(\sum_{i=1}^{4}\alpha_ix_i^*\right);b_3=b_1\frac{\beta_2}{d_6+\pi}\cdot\left(\sum_{i=1}^{4}\alpha_ix_i^*\right). \quad (12)$$

Using relations (12) and (10), it follows that

$$(\beta_1x_5^*+\beta_2x_6^*)\cdot\left(\sum_{i=1}^{4}\alpha_ix_i^*\right) = b_2(d_5+\alpha)x_5^*+b_3(d_6+\pi)x_6^*-b_3\alpha x_5^*, \quad (13)$$
$$-b_1+b_2\pi_{11}+b_3\pi_{12} = 0. \quad (14)$$

Using the relations (13) and (14), we have

$$V_1 =b_1\left(\alpha_1x_1^*+2\alpha_2x_2^*+3\alpha_3x_3^*+4\alpha_4x_4^*\right)(\beta_1x_5^*+\beta_2x_6^*)+b_2(d_5+\alpha)x_5^*+b_3(d_6+\pi)x_6^*,$$
$$=(b_2\pi_{11}+b_3\pi_{12})\left(2\alpha_1x_1^*+3\alpha_2x_2^*+4\alpha_3x_3^*+5\alpha_4x_4^*\right)(\beta_1x_5^*+\beta_2x_6^*)+b_3\alpha x_5^*, \quad (15)$$

Replacing the relations (14) and (15) in $\frac{dV}{dt}$, one obtains

$$\frac{dV}{dt} = b_1d_1x_1^*\left(2-\frac{x_1^*}{x_1}-\frac{x_1}{x_1^*}\right)+b_1d_3x_3^*\left(4-\frac{x_1^*}{x_1}-\frac{x_3}{x_3^*}-\frac{x_1x_2^*}{x_1^*x_2}-\frac{x_2x_3^*}{x_2^*x_3}\right)+b_1d_2x_2^*\left(3-\frac{x_1^*}{x_1}\right.$$
$$\left.-\frac{x_2}{x_2^*}-\frac{x_1x_2^*}{x_1^*x_2}\right)+b_1(d_4+\varepsilon)x_4^*\left(5-\frac{x_1^*}{x_1}-\frac{x_4}{x_4^*}-\frac{x_1x_2^*}{x_1^*x_2}-\frac{x_2x_3^*}{x_2^*x_3}-\frac{x_3x_4^*}{x_3^*x_4}\right)$$
$$+(b_2\pi_{11}+b_3\pi_{12})\left(2\alpha_1x_1^*+3\alpha_2x_2^*+4\alpha_3x_3^*+5\alpha_4x_4^*\right)(\beta_1x_5^*+\beta_2x_6^*)+b_3\alpha x_5^*, \quad (16)$$
$$+\sum_{i=1}^{4}\frac{x_i}{x_i^*}\left(-b_2\pi_{11}\beta_{i1}x_5^*x_i^*-b_3\pi_{12}\beta_{i2}x_6^*x_i^*\right)+\frac{x_3x_4^*}{x_3^*x_4}\left[-(b_2\pi_{11}+b_3\pi_{12})\alpha_4x_4^*(\beta_1x_5^*\right.$$

$$
\begin{aligned}
&+\beta_2 x_6^*\Big] + \frac{x_1^*}{x_1}\Big[-(b_2\pi_{11}+b_3\pi_{12})\cdot\left(\alpha_1 x_1^*+\alpha_2 x_2^*+\alpha_3 x_3^*+\alpha_4 x_4^*\right)(\beta_1 x_5^*+\beta_2 x_6^*)\Big]\\
&+\frac{x_1 x_2^*}{x_1^* x_2}\Big[-(b_2\pi_{11}+b_3\pi_{12})\cdot\left(\alpha_2 x_2^*+\alpha_3 x_3^*+\alpha_4 x_4^*\right)(\beta_1 x_5^*+\beta_2 x_6^*)\Big]\\
&+\frac{x_5 x_6^*}{x_5^* x_6}\Big[-b_3\alpha x_5^*\Big] + \frac{x_2 x_3^*}{x_2^* x_3}\Big[-(b_2\pi_{11}+b_3\pi_{12})\cdot\left(\alpha_3 x_3^*+\alpha_4 x_4^*\right)(\beta_1 x_5^*+\beta_2 x_6^*)\Big]\\
&+\sum_{i=1}^{4}\frac{x_i x_5^* x_6}{x_i^* x_5 x_6^*}\Big[-b_2\pi_{11}\beta_{i2}x_6^* x_i^*\Big] + \sum_{i=1}^{4}\frac{x_i x_5 x_6^*}{x_i^* x_5^* x_6}\Big[-b_3\pi_{12}\beta_{i1}x_5^* x_i^*\Big].
\end{aligned}
$$

We expanding (16), the coefficients in $\frac{x_1^*}{x_1}$, $\frac{x_1 x_2^*}{x_1^* x_2}$, $\frac{x_2 x_3^*}{x_2^* x_3}$, $\frac{x_3 x_4^*}{x_3^* x_4}$ and gathering some terms, one has

$$
\begin{aligned}
\frac{dV}{dt} &= \left(b_1 d_1 x_1^* + b_2\pi_{11}\beta_{11}x_5^* x_1^* + b_3\pi_{12}\beta_{12}x_6^* x_1^*\right)\left(2-\frac{x_1^*}{x_1}-\frac{x_1}{x_1^*}\right)\\
&+(b_1 d_2 x_2^* + b_2\pi_{11}\beta_{21}x_5^* x_2^* + b_3\pi_{12}\beta_{22}x_6^* x_2^*)\left(3-\frac{x_1^*}{x_1}-\frac{x_2}{x_2^*}-\frac{x_1 x_2^*}{x_1^* x_2}\right)\\
&+(b_1 d_3 x_3^* + b_2\pi_{11}\beta_{31}x_5^* x_3^* + b_3\pi_{12}\beta_{32}x_6^* x_3^*)\left(4-\frac{x_1^*}{x_1}-\frac{x_3}{x_3^*}-\frac{x_1 x_2^*}{x_1^* x_2}-\frac{x_2 x_3^*}{x_2^* x_3}\right)\\
&+\left(b_1(d_4+\varepsilon)x_4^* + b_2\pi_{11}\beta_{41}x_5^* x_4^* + b_3\pi_{12}\beta_{42}x_6^* x_4^*\right)\left(5-\frac{x_1^*}{x_1}-\frac{x_4}{x_4^*}-\frac{x_1 x_2^*}{x_1^* x_2}-\frac{x_2 x_3^*}{x_2^* x_3}\right.\\
&\left.-\frac{x_3 x_4^*}{x_3^* x_4}\right) + 2b_2\pi_{11}\beta_{12}x_6^* x_1^* + 3b_2\pi_{11}\beta_{22}x_6^* x_2^* + 4b_2\pi_{11}\beta_{32}x_6^* x_3^* + 5b_2\pi_{11}\beta_{42}x_6^* x_4^*\\
&+2b_3\pi_{12}\beta_{11}x_5^* x_1^* + 3b_3\pi_{12}\beta_{21}x_5^* x_2^* + 4b_3\pi_{12}\beta_{31}x_5^* x_3^* + 5b_3\pi_{12}\beta_{41}x_5^* x_4^* + b_3\alpha x_5^*\\
&+\frac{x_1^*}{x_1}\Big[-b_2\pi_{11}\beta_{12}x_6^* x_1^* - b_2\pi_{11}\beta_{22}x_6^* x_2^* - b_2\pi_{11}\beta_{32}x_6^* x_3^* - b_2\pi_{11}\beta_{42}x_6^* x_4^*\\
&-b_3\pi_{12}\beta_{11}x_5^* x_1^* - b_3\pi_{12}\beta_{21}x_5^* x_2^* - b_3\pi_{12}\beta_{31}x_5^* x_3^* - b_3\pi_{12}\beta_{41}x_5^* x_4^*\Big]\\
&+\frac{x_1 x_2^*}{x_1^* x_2}\Big[-b_2\pi_{11}\beta_{22}x_6^* x_2^* - b_2\pi_{11}\beta_{32}x_6^* x_3^* - b_2\pi_{11}\beta_{42}x_6^* x_4^* - b_3\pi_{12}\beta_{21}x_5^* x_2^*\\
&-b_3\pi_{12}\beta_{31}x_5^* x_3^* - b_3\pi_{12}\beta_{41}x_5^* x_4^*\Big] + \frac{x_2 x_3^*}{x_2^* x_3}\Big[-b_2\pi_{11}\beta_{32}x_6^* x_3^* - b_2\pi_{11}\beta_{42}x_6^* x_4^*\\
&-b_3\pi_{12}\beta_{31}x_5^* x_3^* - b_3\pi_{12}\beta_{41}x_5^* x_4^*\Big] + \frac{x_3 x_4^*}{x_3^* x_4}\Big[-b_2\pi_{11}\beta_{42}x_6^* x_4^* - b_3\pi_{12}\beta_{41}x_5^* x_4^*\Big]\\
&+\sum_{i=1}^{4}\frac{x_i x_5^* x_6}{x_i^* x_5 x_6^*}\Big[-b_2\pi_{11}\beta_{i2}x_6^* x_i^*\Big] + \sum_{i=1}^{4}\frac{x_i x_5 x_6^*}{x_i^* x_5^* x_6}\Big[-b_3\pi_{12}\beta_{i1}x_5^* x_i^*\Big] + \frac{x_5 x_6^*}{x_5^* x_6}\Big[-b_3\alpha x_5^*\Big].
\end{aligned}
$$

Using the relations (11) and (12), it can be verified that

$$
b_2\pi_{11}\beta_{i2}x_6^* x_i^* = b_3\pi_{12}\beta_{i1}x_5^* x_i^* + \alpha b_{3i}x_5^*, \quad i=1,2,3,4, \tag{17}
$$

where $b_{3i} = \dfrac{\alpha_i\beta_2 x_i^*}{d_6+\pi}$, $i=1,2,3,4$, with $b_3 = b_{31}+b_{32}+b_{33}+b_{34}$.

Thus, substituting the expressions (17) in $\frac{dV}{dt}$, we obtain

$$\begin{aligned}
\frac{dV}{dt} &= \left(b_1d_1x_1^* + b_2\pi_{11}\beta_{11}x_5^*x_1^* + b_3\pi_{12}\beta_{12}x_6^*x_1^*\right)\left(2 - \frac{x_1^*}{x_1} - \frac{x_1}{x_1^*}\right)\\
&+(b_1d_2x_2^* + b_2\pi_{11}\beta_{21}x_5^*x_2^* + b_3\pi_{12}\beta_{22}x_6^*x_2^*)\left(3 - \frac{x_1^*}{x_1} - \frac{x_2}{x_2^*} - \frac{x_1x_2^*}{x_1^*x_2}\right)\\
&+(b_1d_3x_3^* + b_2\pi_{11}\beta_{31}x_5^*x_3^* + b_3\pi_{12}\beta_{32}x_6^*x_3^*)\left(4 - \frac{x_1^*}{x_1} - \frac{x_3}{x_3^*} - \frac{x_1x_2^*}{x_1^*x_2} - \frac{x_2x_3^*}{x_2^*x_3}\right)\\
&+\left(b_1(d_4+\varepsilon)x_4^* + b_2\pi_{11}\beta_{41}x_5^*x_4^* + b_3\pi_{12}\beta_{42}x_6^*x_4^*\right)\left(5 - \frac{x_1^*}{x_1} - \frac{x_4}{x_4^*} - \frac{x_1x_2^*}{x_1^*x_2} - \frac{x_2x_3^*}{x_2^*x_3}\right.\\
&\left.-\frac{x_3x_4^*}{x_3^*x_4}\right) + 4b_3\pi_{12}\beta_{11}x_5^*x_1^* + 6b_3\pi_{12}\beta_{21}x_5^*x_2^* + 8b_3\pi_{12}\beta_{31}x_5^*x_3^* + 10b_3\pi_{12}\beta_{41}x_5^*x_4^*\\
&+3b_{31}\alpha x_5^* + 4b_{32}\alpha x_5^* + 5b_{33}\alpha x_5^* + 6b_{34}\alpha x_5^* - yb_2\pi_{11}\beta_{12}x_6^*x_1^*\left(\frac{x_1^*}{x_1} + \frac{x_1x_5^*x_6}{x_1^*x_5x_6^*}\right)\\
&-\alpha b_{31}x_5^*\frac{x_5x_6^*}{x_5^*x_6} - (1-y)b_2\pi_{11}\beta_{12}x_6^*x_1^*\left(\frac{x_1^*}{x_1} + \frac{x_1x_5^*x_6}{x_1^*x_5x_6^*}\right) - b_3\pi_{12}\beta_{11}x_5^*x_1^*\left(\frac{x_1^*}{x_1}\right.\\
&\left.+\frac{x_1x_5x_6^*}{x_1^*x_5^*x_6}\right) - yb_2\pi_{11}\beta_{22}x_6^*x_2^*\left(\frac{x_1^*}{x_1} + \frac{x_2^*x_1}{x_2x_1^*} + \frac{x_2x_5^*x_6}{x_2^*x_5x_6^*}\right) - \alpha b_{32}x_5^*\frac{x_5x_6^*}{x_5^*x_6}\\
&-(1-y)b_2\pi_{11}\beta_{22}x_6^*x_2^*\left(\frac{x_1^*}{x_1} + \frac{x_2^*x_1}{x_2x_1^*} + \frac{x_2x_5^*x_6}{x_2^*x_5x_6^*}\right) - b_3\pi_{12}\beta_{21}x_5^*x_2^*\left(\frac{x_1^*}{x_1} + \frac{x_1x_2^*}{x_1^*x_2}\right.\\
&\left.+\frac{x_2x_5x_6^*}{x_2^*x_5^*x_6}\right) - yb_2\pi_{11}\beta_{32}x_6^*x_3^*\left(\frac{x_1^*}{x_1} + \frac{x_1x_2^*}{x_1^*x_2} + \frac{x_2x_3^*}{x_2^*x_3} + \frac{x_3x_5^*x_6}{x_3^*x_5x_6^*}\right) - \alpha b_{33}x_5^*\frac{x_5x_6^*}{x_5^*x_6}\\
&-(1-y)b_2\pi_{11}\beta_{32}x_6^*x_3^*\left(\frac{x_1^*}{x_1} + \frac{x_1x_2^*}{x_1^*x_2} + \frac{x_2x_3^*}{x_2^*x_3} + \frac{x_3x_5^*x_6}{x_3^*x_5x_6^*}\right) - b_3\pi_{12}\beta_{31}x_5^*x_3^*\left(\frac{x_1^*}{x_1}\right.\\
&\left.+\frac{x_1x_2^*}{x_1^*x_2} + \frac{x_2x_3^*}{x_2^*x_3} + \frac{x_3x_5x_6^*}{x_3^*x_5^*x_6}\right) - yb_2\pi_{11}\beta_{42}x_6^*x_4^*\left(\frac{x_1^*}{x_1} + \frac{x_1x_2^*}{x_1^*x_2} + \frac{x_2x_3^*}{x_2^*x_3} + \frac{x_3x_4^*}{x_3^*x_4}\right.\\
&\left.+\frac{x_4x_5^*x_6}{x_4^*x_5x_6^*}\right) - \alpha b_{34}x_5^*\frac{x_5x_6^*}{x_5^*x_6} - (1-y)b_2\pi_{11}\beta_{42}x_6^*x_4^*\left(\frac{x_1^*}{x_1} + \frac{x_1x_2^*}{x_1^*x_2} + \frac{x_2x_3^*}{x_2^*x_3} + \frac{x_3x_4^*}{x_3^*x_4}\right.\\
&\left.+\frac{x_4x_5^*x_6}{x_4^*x_5x_6^*}\right) - b_3\pi_{12}\beta_{41}x_5^*x_4^*\left(\frac{x_1^*}{x_1} + \frac{x_1x_2^*}{x_1^*x_2} + \frac{x_2x_3^*}{x_2^*x_3} + \frac{x_3x_4^*}{x_3^*x_4} + \frac{x_4x_5x_6^*}{x_4^*x_5^*x_6}\right),
\end{aligned}$$

where

$$y = \frac{\alpha\pi_{11}}{[\pi_{12}(d_5+\alpha)+\pi_{11}\alpha]\pi_{11}b_2}, \quad \text{and} \quad 1-y = \frac{\pi_{12}\beta_1\sum_{i=1}^{4}\alpha_ix_i^*}{[\pi_{12}(d_3+\alpha)+\pi_{11}\alpha]b_2}. \tag{18}$$

Further, using the relations (11) and (18), we have the following equalities

$$yb_2\pi_{11}\beta_{i2}x_6^*x_i^* = \alpha b_{3i}x_5^* \quad \text{and} \quad (1-y)b_2\pi_{11}\beta_{i2}x_6^*x_i^* = b_3\pi_{12}\beta_{i1}x_5^*x_i^*, \quad i = 1,2,3,4.$$

Thus,

$$\frac{dV}{dt} = \left(b_1d_1x_1^* + b_2\pi_{11}\beta_{11}x_5^*x_1^* + b_3\pi_{12}\beta_{12}x_6^*x_1^*\right)\left(2 - \frac{x_1^*}{x_1} - \frac{x_1}{x_1^*}\right)$$

$$
\begin{aligned}
&+(b_1d_2x_2^* + b_2\pi_{11}\beta_{21}x_5^*x_2^* + b_3\pi_{12}\beta_{22}x_6^*x_2^*)\left(3 - \frac{x_1^*}{x_1} - \frac{x_2}{x_2^*} - \frac{x_1x_2^*}{x_1^*x_2}\right)\\
&+(b_1d_3x_3^* + b_2\pi_{11}\beta_{31}x_5^*x_3^* + b_3\pi_{12}\beta_{32}x_6^*x_3^*)\left(4 - \frac{x_1^*}{x_1} - \frac{x_3}{x_3^*} - \frac{x_1x_2^*}{x_1^*x_2} - \frac{x_2x_3^*}{x_2^*x_3}\right)\\
&+\left(b_1(d_4+\varepsilon)x_4^* + b_2\pi_{11}\beta_{41}x_5^*x_4^* + b_3\pi_{12}\beta_{42}x_6^*x_4^*\right)\left(5 - \frac{x_1^*}{x_1} - \frac{x_4}{x_4^*} - \frac{x_1x_2^*}{x_1^*x_2} - \frac{x_2x_3^*}{x_2^*x_3}\right.\\
&\left.-\frac{x_3x_4^*}{x_3^*x_4}\right) + \alpha b_{31}x_5^*\left(3 - \frac{x_1^*}{x_1} - \frac{x_5x_6^*}{x_5^*x_6} - \frac{x_1x_5^*x_6}{x_1^*x_5x_6^*}\right) + \alpha b_{32}x_5^*\left(4 - \frac{x_1^*}{x_1} - \frac{x_2^*x_1}{x_2x_1^*} - \frac{x_5x_6^*}{x_5^*x_6}\right.\\
&\left.-\frac{x_2x_5^*x_6}{x_2^*x_5x_6^*}\right) + \alpha b_{33}x_5^*\left(5 - \frac{x_1^*}{x_1} - \frac{x_1x_2^*}{x_1^*x_2} - \frac{x_2x_3^*}{x_2^*x_3} - \frac{x_5x_6^*}{x_5^*x_6} - \frac{x_3x_5^*x_6}{x_3^*x_5x_6^*}\right)\\
&+\alpha b_{34}x_5^*\left(6 - \frac{x_1^*}{x_1} - \frac{x_1x_2^*}{x_1^*x_2} - \frac{x_2x_3^*}{x_2^*x_3} - \frac{x_5x_6^*}{x_5^*x_6} - \frac{x_3x_4^*}{x_3^*x_4} - \frac{x_4x_5^*x_6}{x_4^*x_5x_6^*}\right)\\
&+b_3\pi_{12}\beta_{11}x_5^*x_1^*\left(4 - 2\frac{x_1^*}{x_1} - \frac{x_1x_5^*x_6}{x_1^*x_5x_6^*} - \frac{x_1x_5x_6^*}{x_1^*x_5^*x_6}\right)\\
&+b_3\pi_{12}\beta_{21}x_5^*x_2^*\left(6 - 2\frac{x_1^*}{x_1} - 2\frac{x_1x_2^*}{x_1^*x_2} - \frac{x_2x_5x_6^*}{x_2^*x_5^*x_6} - \frac{x_2x_5^*x_6}{x_2^*x_5x_6^*}\right)\\
&+b_3\pi_{12}\beta_{31}x_5^*x_3^*\left(8 - 2\frac{x_1^*}{x_1} - 2\frac{x_1x_2^*}{x_1^*x_2} - 2\frac{x_2x_3^*}{x_2^*x_3} - \frac{x_3x_5x_6^*}{x_3^*x_5^*x_6} - \frac{x_3x_5^*x_6}{x_3^*x_5x_6^*}\right)\\
&+b_3\pi_{12}\beta_{41}x_5^*x_4^*\left(10 - 2\frac{x_1^*}{x_1} - 2\frac{x_1x_2^*}{x_1^*x_2} - 2\frac{x_2x_3^*}{x_2^*x_3} - 2\frac{x_3x_4^*}{x_3^*x_4} - \frac{x_4x_5^*x_6}{x_4^*x_5x_6^*} - \frac{x_4x_5x_6^*}{x_4^*x_5^*x_6}\right).
\end{aligned}
$$

Finally, using the arithmetic-geometric means inequality, $n-(y_1+y_2+\cdots+y_n)\leq 0$, where $y_1y_2\cdots y_n = 1$ and $y_1, y_2, \cdots, y_n > 0$, it follows that $\frac{dV}{dt} \leq 0$. Furthermore, $\frac{dV}{dt} = 0 \Leftrightarrow (x_1,\cdots,x_6) = (x_1^*,\cdots,x_6^*)$. The global stability of the endemic equilibrium follows from the classical stability theorem of Lyapunov and the LaSalle's Invariance Principle. □

5. **Numerical simulations: Case study of Hepatitis B (HBV).** In this section, we use model (4) to further investigate the impact of some control strategies on the spread of chronic Hepatitis B infection among an adult population. Based on the sensitivity analysis of the basic reproduction number on parameters, we seek optimal measures to control the transmission of disease using parameter values in Table 1 related to Hepatitis B, which have been found into literature. Hepatitis B is a disease that is characterised by inflammation of the liver and the risk of developing the disease is primarily related to sexual, household or perinatal exposure to infected individuals. According WHO statistics, more than a billion people around the world have serological indicators of past or present infection with HBV. Over 240 millions people are chronic carriers of the virus. An estimated $780,000$ persons die each year due to the acute or chronic consequence of Hepatitis B. Safe and effective vaccines have been available to prevent HBV infection since 1981. The efficacy of a complete Hepatitis B vaccination series (i.e. ≥ 3 doses of Hepatitis B vaccine) in preventing perinatal, early childhood and late infection was estimated to provide protection for $85-90\%$ of individuals [27]. A complete vaccination series was assumed to provide lifelong protection from clinical acute and chronic HBV infection [11]. In many countries, vaccination has reduced the rate of chronic infection to less than 1% among immunised children [28, 29]. For all simulations below,

we use parameters values in Table 1 related to Hepatitis B virus disease. We fix $\theta_2 = \theta_3 = 90\%$ and vary θ_1 since his sensitivity index is the highest. We will also vary some parameters to investigate their impacts.

5.1. **Simulations of stability results.** To illustrate the stability results contained in this paper, the model (4) is simulated using the parameter values in Table 1 with $\theta_1 = 0.8$, $\theta_2 = \theta_3 = 0.9$, $\varepsilon = 0.85$, and $\alpha = 0.2$.

Figure 3 presents the trajectories of model (4) for different initial conditions when $b = 2$ and $\mathcal{R}_0 \leq 1$. From this figure, we can see that there are always susceptibles in the population while the infected individuals disappear. Thus, the trajectories converge to the disease-free equilibrium. This means that the disease disappears in the host population as shown in Theorem 3.2.

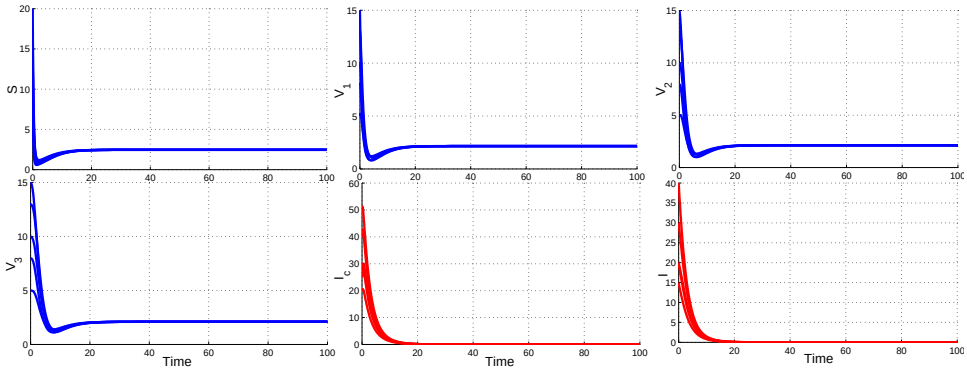

FIGURE 3. Simulation results showing the global stability of disease-free equilibrium.

Figure 4 gives the trajectory plot when $b = 9$ and $\mathcal{R}_0 > 1$. From this figure, we can observe that the infected individuals are always present in the population. This means that the trajectories converge to the endemic equilibrium point. Thus, whenever $\mathcal{R}_0 > 1$, the disease persists in the host population as established in Theorem 4.3.

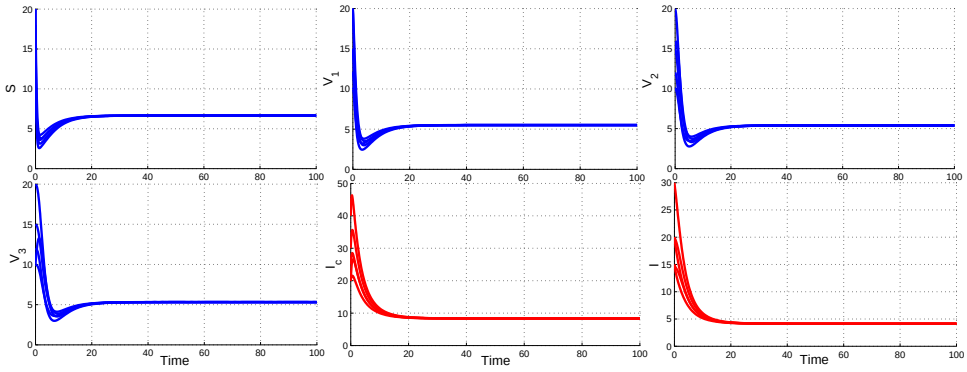

FIGURE 4. Simulation results showing the global stability of endemic equilibrium.

5.2. **Impact of effectiveness of vaccination.** Firstly, we fix $\alpha = 0.2$, $\varepsilon = 0.5$, $\pi = 0.65$ and vary θ_1 to observe the effect of increasing the vaccination rate with a low effectiveness.

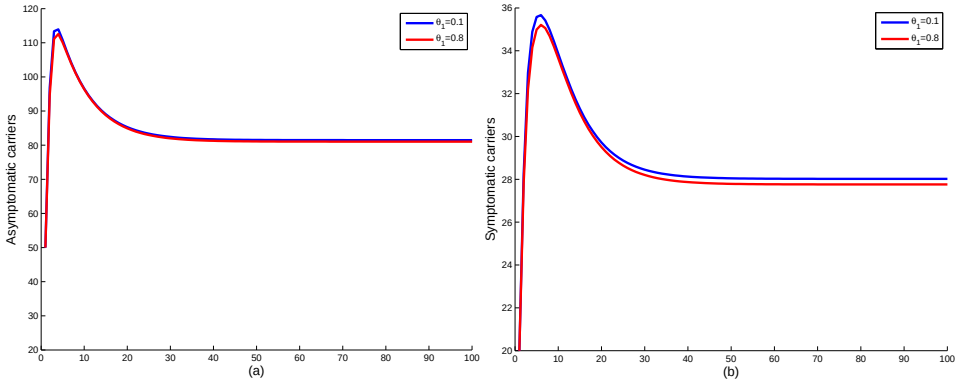

FIGURE 5. Simulation results showing the impact of vaccination with low effectiveness.

We see from Figure 5 that, the variation of θ_1 from 10% to 80% has almost no effect on infected population since the difference between both curves is very small for cases (a) and (b). When we vary ε from 0.5 to 0.9 by fixing $\theta_1 = 80\%$, $\alpha = 0.2$ and $\pi = 0.65$, we see now in Figure 6 that the impact of vaccination is a bit larger, especially for the symptomatic carriers. This shows the close link that exists between vaccination and its effectiveness. Thus, vaccination with a high effectiveness can be a control measure against HBV infection in high HBV prevalence countries. Despite that the impact is a bit larger in this case, the number of infected individuals always remains high, especially for the asymptomatic carriers that are infected individuals taking no treatment because they are unaware of their condition. This implies that vaccination alone is not sufficient to control the disease effectively.

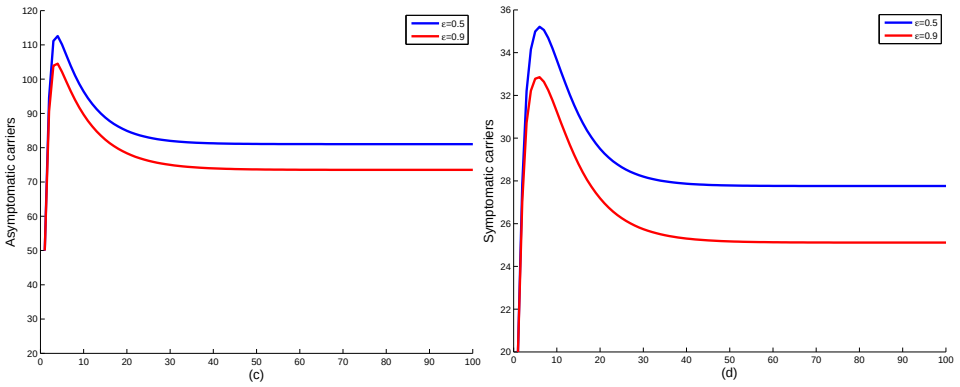

FIGURE 6. Simulation results showing the impact of vaccination with high effectiveness.

5.3. **Impact of asymptomatic carriers on the transmission dynamics.** Secondly, for study the impact of diagnosis rate at which asymptomatic carriers move into symptomatic class either through testing or through appearance of symptoms, we fix $\theta_1 = 80\%$, $\varepsilon = 0.9$ and $\pi = 0.65$. From Figure 7 that, if only 20% of asymp-

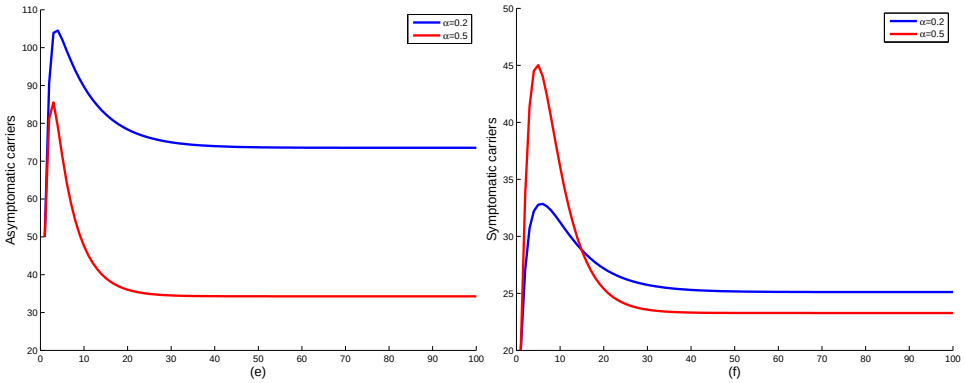

FIGURE 7. Simulation results showing the impact of testing and diagnosis of asymptomatic carriers.

tomatic carriers become aware of their condition, the number of infected individuals decreases, but the number of asymptomatic carriers is still high. This is not a desirable result because asymptomatic carriers are responsible for most of the new infections since they are unaware of their illness. When we increase α from 20% to 50%, the number of asymptomatic carriers shows a much greater decline while the number of symptomatic infected remains low. This shows that testing and diagnosis can be an effective control measure.

Finally, we fix $\theta_1 = 80\%$, $\varepsilon = 0.9$ and $\alpha = 0.5$. If we consider the recovered rate as a treatment rate, then we can see in Figure 8 that increasing π from 10%, the number of asymptomatic does almost not vary while the number of symptomatic carriers is lower.

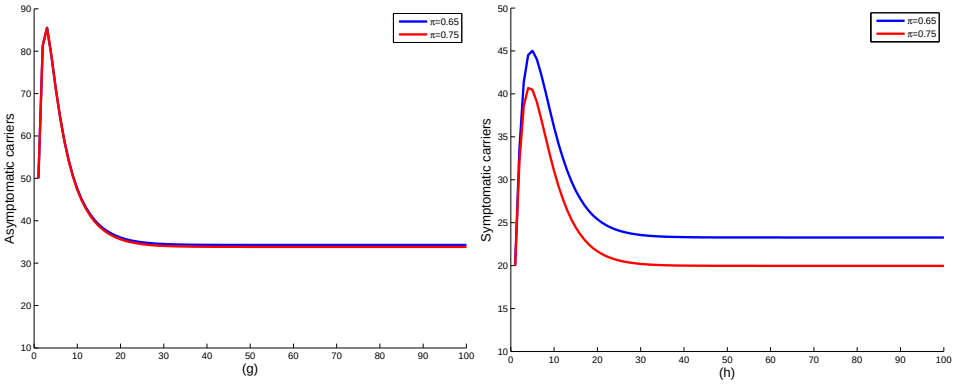

FIGURE 8. Simulation results showing the impact of treatment of symptomatic carriers.

These numerical simulations of the model (1) show that effective vaccination is a good control strategy for HBV infection, however, a combination with the diagnosis

and treatment is a better control measure for the disease. We conclude that in high HBV prevalence countries, combination of effective vaccination (i.e. ≥ 3 doses of Hepatitis B vaccine), testing and increasing awareness of asymptomatic carriers, and treatment of symptomatic carriers will have a much greater impact on the disease burden.

6. **Conclusion-discussion.** This paper have studied the impact of control strategies on the transmission of infectious diseases that can be transmitted through infected individuals who are contagious but do not show any disease symptoms. The model formulated in Section 2 incorporates vaccination for carriers dependent diseases, with clear distinction between vaccinated individuals class and the recovered/removed individuals compartment. This more realistic distinction have contrasted with some models (e.g. [16]) where these two classes are combined and constitutes an improvement. We investigated the effects of the efficacy of the vaccine and asymptomatic carriers (or "lost of sight") on the spread of infectious diseases. The susceptibles and infectives were divided into 4 and 2 subgroups based on their susceptibilities and infectivities, respectively. Using the next generation operator approach, we have derived an explicit formula for the basic reproductive number, $\mathcal{R}_0$, which has been the key parameter in our model. Important parameters in the expression for $\mathcal{R}_0$ are the efficacy of the vaccine and the diagnosis rates (or rates at which asymptomatic carriers become aware of their illness). Using the method of global Lyapunov functions, we have established the global stability results of equilibrium points. Precisely, we have shown that the disease-free equilibrium is globally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable otherwise. For the case where $\mathcal{R}_0 > 1$, we have proven that there exists a unique endemic equilibrium, who is globally asymptotically stable. Furthermore, using the Centre Manifold Theory, we have shown that a forward bifurcation occurs at the critical value $\mathcal{R}_0 = 1$. Our model simulations have suggested the challenges of chronic HBV infection: the existence of a large number of asymptomatic carriers, because they are unaware of their illness and will not be part of any treatment program. Comparing our simulation results in Figures 5, 6, 7 and 8, we have concluded that in high HBV prevalence countries, combination of effective vaccination (i.e. ≥ 3 doses of HepB vaccine), diagnosis of asymptomatic carriers and treatment of symptomatic carriers will have a much greater impact on the disease burden.

In this work, we have considered vaccination and diagnosis as continuous states. In many countries, the control strategies such that vaccination or screening, used to large-scale against infectious diseases are discontinuous or seasonal. It will be interesting to consider an epidemic model with a double impulsion, where after a time T (fixed or variable), one vaccinates and detects. This case can be modelled by impulsive differential equations, which is one of our future works. Due to the fact that most of the vaccination campaigns are age-dependent and that for some diseases with long-term asymptomatic carriers disease such as HBV, the vaccines are recommended for infants and children under the age of 18 and young adults, a more complicated age-structured- dose-structured model will be more appropriate for this setting. This is one of the modelling aspect and extension of the present paper we are actively working on.

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