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MODELING THE EFFECTS OF CARRIERS ON TRANSMISSION DYNAMICS OF INFECTIOUS DISEASES

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Abstract. An S-I_c-I-R epidemic model is investigated for infectious diseases that can be transmitted through carriers, infected individuals who are contagious but do not show any disease symptoms. Mathematical analysis is carried out that completely determines the global dynamics of the model. The impacts of disease carriers on the transmission dynamics are discussed through the basic reproduction number and through numerical simulations.

1. **Introduction.** For certain infectious diseases, there are individuals who are able to transmit their illness but do not exhibit any symptoms. These individuals are called "carriers" and they play an important role in the transmission of the disease. There are two types of carriers. *Genetic carriers* carry the illness on their recessive genes. They can only pass on their disease to their children and are not contagious. The focus of our study is on *infectious disease carriers*. These individuals are asymptomatic and are likely unaware of their conditions, and therefore are more likely to infect others. An infectious disease that produces long-term asymptotic carriers is the Typhoid fever caused by the bacteria Salmonella Typhi. Typhoid fever reached public notoriety at the beginning of the 20th century with the cases of "Mr. N the milker" in England and Typhoid Mary in the US. These individuals infected hundreds of people over the decades while they worked in the food production industry and private homes. Even today, Typhoid fever infects 21 million people and kills 200,000 worldwide every year. Asymptomatic carriers are believed to play an essential role in the evolution and global transmission of Typhi, and their presence greatly hinders the eradication of Typhoid fever using treatment and vaccination [13].

Another major infectious disease that causes long-term asymptomatic carriage is hepatitis B, a liver disease caused by the HBV virus of the Hepadnavirus family. Most people infected with HBV recover completely and develop a lifelong immunity to the virus. However, about 5-10% of adults will develop chronic HBV infection,

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and 15-25% of these will develop liver disease. Hepatitis B's symptoms include jaundice, abdominal pain, nausea, fatigue and joint pain. About 30% of people with the disease do not show any of these symptoms. A major public-health challenge in the control of hepatitis B infection in many countries is the existence of a large pool of chronic carriers who are responsible for transmitting most of the new infections. Infections of other pathogens are also know to produce asymptomatic carriers. The Epstein-Barr Virus (EBV) of the herpes family is one of the most common viruses in humans. EBV infection commonly causes infectious mononucleosis, also known as glandular fever. Most people infected with EBV are asymptomatic, as it remains dormant in those who have had it for the rest of their lives in the cells of the throat and the immune system. Clostridium difficile is a bacterium that causes Clostridium difficile-associated diseases (CDAD). CDAD remains the most common cause of acute hospital-acquired diarrhea, responsible for more than 300,000 cases of diarrhea annually in acute-care facilities in the United States. Asymptomatic carriage rates of up to 30% have been reported in long-term care facilities. It is believed that carriers are responsible for transmission and large outbreaks of CDAD in Europe and North America [12].

Despite their public health significance, the effects of carriers on the transmission dynamics of the disease have not received adequate research attention in the mathematical modeling literature. One of the earlier attempts was Kemper [7], in which a general mathematical model that incorporates disease carriers was developed and analyzed. Medley et al. [10] used a mathematical model for hepatitis B with carriers to discussed the effects of HBV vaccination. Several other studies using large-scale computational models with carriers are specifically aimed at hepatitis B and other diseases [15, 1, 2, 14, 11]. In the present paper, we propose a general mathematical model for infectious diseases with asymptomatic carriers to investigate the effects of carriers on the transmission dynamics. We have derived the basic reproduction number R_0 and show that the global dynamics of the model are completely determined by the values of R_0. Since R_0 explicitly involves parameters related to disease carriage, we are able to discuss the impact of disease carriage on R_0. We have also carried out numerical simulations of the model using parameter values that are pertinent to hepatitis B infection, and investigated the effects of carriers on the HBV transmission dynamics. Mathematically, our proof of the global stability of the unique endemic equilibrium when $R_0 > 1$ nontrivially utilizes the method of global Lyapunov functions.

The model derivation is given in the next section. The basic reproduction number is derived and discussed in Section 3. Global stability of the disease-free and endemic equilibrium is proved in Section 4 and 5, respectively. In Section 6, effects of carriers on the transmission of chronic hepatitis B infection are discussed.

2. **A general epidemic model with asymptomatic carriers.**

2.1. **Model formulation.**

We formulate an S-I_c-I-R compartmental model where S, I_c, I, and R represent the susceptible, carrier, symptomatically infectious or infectious for short, and removed classes, respectively. A susceptible individual can be infected through direct contact with an infectious individual or a carrier. A newly infected individual can become a carrier with probability p, or shows disease symptoms with probability $1-p$. We assume that the rate of transmission β for carriers is higher than the rate γ of symptomatically infected individuals due to the fact that they are more likely to be unaware of their condition, and therefore continue

with their regular behaviours. Carriers may become symptomatic at a rate α. For infections such as HBV for which carriage can remain life-long, α can be regarded as rate of diagnosis. We assume a constant influx b of susceptibles, and let d_1, d_2, d_3, d_4 denote the death rates of those in the susceptible, carrier, infectious, and removed classes, respectively. Here d_1, d_4 can be considered as natural death rates, while d_2 and d_3 may include both natural and disease-related death. We incorporate a simple vaccination strategy in which a fraction θ of the susceptible population is vaccinated and is fully protected by the vaccine. Symptomatically infected individual recover with rate π, and we assume that recovered individuals are permanently immune. Parameters in the model are summarized and explained in Table 1, and the model is depicted in the transfer diagram in Figure 1. We assume that all parameters in the model are nonnegative and that $b > 0, d_i > 0$, $i = 1, 2, 3, 4$.

Table 1. Parameters in the Model

b :	Rate of influx of susceptibles
d_1, d_4 :	Natural death rates
d_2, d_3 :	Death rates for I_c and I compartments, respectively, including both natural and disease-caused death
β :	Transmission coefficient for the carrier compartment I_c
γ :	Transmission coefficient for the symptomatically infected compartment I
α :	Rate at which carriers develop symptoms
π :	Rate of recovery
p :	Probability of a newly infected individual is asymptomatic
θ :	Vaccination rate

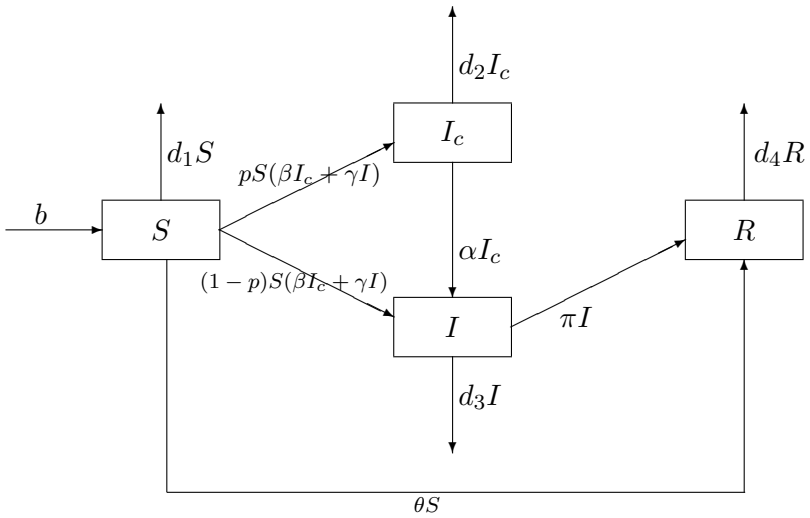

Figure 1. Transfer diagram of model (1).

Based on our assumptions and the transfer diagram, we can derive the following system of differential equations that govern our model.

$$\begin{aligned} S' &= b - d_1 S - S(\beta I_c + \gamma I) - \theta S \\ I_c' &= pS(\beta I_c + \gamma I) - (d_2 + \alpha) I_c \\ I' &= (1-p)S(\beta I_c + \gamma I) - (d_3 + \pi) I + \alpha I_c \\ R' &= \pi I + \theta S - d_4 R. \end{aligned} \tag{1}$$

We note that disease carriage is different from disease latency in that individuals in the carrier state are infectious while those in the latent period are not. Our model (1) is thus different from the traditional SEIR models that incorporate disease latency. In the special case when $\beta = 0$, the I_c class is not infectious and can be considered as latent, and our model becomes a modified SEIR model in which new infections can be either latent or infectious. While both I_c and I are infectious, model (1) is different from the differential infectivity models considered in [5], since new infections from I_c or I may enter either compartment with certain probability. Our model is more general than the carrier model in [7] in that we incorporate demography and disease-caused death. We also allow carriers to become symptomatic over their life time. Our model is different from the carrier model in [10] in that we allow new infections to be either symptomatic or asymptomatic with certain probabilities.

2.2. **Feasible region and equilibria.** From (1) we have that $S' \le b - (d_1 + \theta)S$, and thus $\limsup_{t\to\infty} S(t) \le \frac{b}{(d_1+\theta)}$ along each solution. Also from (1) we see that

$$N' = b - d_1 S - d_2 I_c - d_3 I - d_4 R \le b - \bar{d} N,$$

where $\bar{d} = \min\{d_1, d_2, d_3, d_4\}$. Therefore $\limsup_{t\to\infty} N(t) \le b/\bar{d}$. The equation for R can be omitted in our analysis as R does not appear in the other equations. This shows that the model can be studied in the feasible region

$$\Gamma = \{\, (S, I_c, I) \in \mathbb{R}^3_+ \;:\; S \le b/(d_1 + \theta),\ S + I_c + I \le b/\bar{d} \,\}.$$

It can be verified that Γ is positively invariant with respect to (1). Once the dynamics of (S, I_C, I) are understood, those of R can then be determined from the equation $R' = \pi I + \theta S - d_4 R$.

The first step in our analysis is to find equilibria (S^*, I_c^*, I^*) from equations

$$\begin{aligned} 0 &= b - d_1 S^* - S^*(\beta I_c^* + \gamma I^*) - \theta S^*, \\ 0 &= pS^*(\beta I_c^* + \gamma I^*) - (d_2 + \alpha) I_c^*, \\ 0 &= (1-p)S^*(\beta I_c^* + \gamma I^*) - (d_3 + \pi) I^* + \alpha I_c^*. \end{aligned} \tag{2}$$

Model (1) always has a disease-free equilibrium $P_0 = (\frac{b}{d_1+\theta}, 0, 0)$. An endemic equilibrium $P^* = (S^*, I_c^*, I^*)$ satisfies $S^*, I_c^*, I^* > 0$. From the equilibrium equations we can show that a unique P^* exists with

$$S^* = \frac{(d_3 + \pi)(d_2 + \alpha)}{pd_3\beta + (d_2 + \alpha)\gamma + p(\pi\beta - d_2\gamma)}.$$

For P^* to exist in the feasible region Γ, it is necessary and sufficient that $0 < S^* \le \frac{b}{d_1+\theta}$, or equivalently, $\frac{b}{(d_1+\theta)S^*} \ge 1$. Define

$$R_0 = \frac{1}{S^*}\frac{b}{d_1 + \theta} = \frac{b}{d_1 + \theta}\frac{pd_3\beta + (d_2 + \alpha)\gamma + p(\pi\beta - d_2\gamma)}{(d_3 + \pi)(d_2 + \alpha)}. \tag{3}$$

Then R_0 is a threshold parameter that determines the number of equilibria. We will show in Section 3 that R_0 is the basic reproduction number.

Proposition 1. *If $R_0 \le 1$ then P_0 is the only equilibrium in Γ; if $R_0 > 1$, then there are two equilibria, P_0 and a unique endemic equilibrium P^*.*

3. **The basic reproduction number.** Rewrite R_0 in (3) as

$$R_0 = \Big[(1-p)\,\gamma\,\frac{1}{d_3+\pi} + p\Big(\beta\,\frac{1}{d_2+\alpha} + \frac{\alpha}{d_2+\alpha}\,\gamma\,\frac{1}{d_3+\pi}\Big)\Big]\frac{b}{d_1+\theta}. \tag{4}$$

In the following, we show that R_0 is the *basic reproduction number*, namely, it represents the average number of secondary infections caused by a single infective in an entirely susceptible population during its entire infectious period.

When a single infective is introduced into the population, with probability $1-p$ it is a non-carrier, hence makes γ effective contacts per unit time. This is multiplied by the average infectious period $\frac{1}{d_3+\pi}$ for non-carriers; with probability p the infective is a carrier, and hence makes β effective contacts per unit time during the average period $\frac{1}{d_2+\alpha}$ it remains a carrier. This number should be augmented by the number of infections $\gamma\frac{1}{d_3+\pi}$ caused by this infective after it becomes a non-carrier, with probability $\frac{\alpha}{d_2+\alpha}$ to survive the carrier stage. Therefore, the expression in the big square brackets in (4) is the per capita average number of secondary infections. This number multiplied by the number of susceptibles at the disease-free equilibrium, $\frac{b}{d_1+\theta}$, gives R_0.

The carriers in our system can have a great effect on R_0. The parameters β, α, and p are all related to the carrier class and all appear in the basic reproductive number. It is straightforward from (3) that R_0 increases as β increases. This agrees with the intuition that higher transmissibility increases the basic reproduction number.

To see the effect of p on R_0 we note

$$\begin{aligned}\frac{\partial R_0}{\partial p} &= \Big[-\frac{\gamma}{d_3+\pi} + \frac{\beta}{d_2+\alpha} + \frac{\gamma}{d_3+\pi}\frac{\alpha}{d_2+\alpha}\Big]\frac{b}{d_1+\theta}\\ &= \frac{b(d_2+\alpha)}{d_1+\theta}\Big[\beta - \frac{d_2}{d_3+\pi}\gamma\Big],\end{aligned}$$

and thus $\frac{\partial R_0}{\partial p} > 0$ if

$$\beta > \frac{d_2}{d_3+\pi}\gamma. \tag{5}$$

We see that a greater probability to develop carriage will increase the basic reproduction number under the condition (5).

We can also analyze the effect of diagnosis rate α on R_0. Straightforward computation gives

$$\begin{aligned}\frac{\partial R_0}{\partial \alpha} &= p\Big[-\frac{\beta}{(d_2+\alpha)^2} + \frac{\gamma}{d_3+\pi}\frac{d_2}{(d_2+\alpha)^2}\Big]\frac{b}{d_1+\theta}\\ &= -\frac{bp}{(d_2+\alpha)^2(d_1+\theta)}\Big[\beta - \frac{d_2}{d_3+\pi}\gamma\Big],\end{aligned}$$

and thus $\frac{\partial R_0}{\partial \alpha} > 0$ if the same condition (5) holds.

From these analysis we see that parameter p and α have opposite effects on R_0: while a higher probability p of carriage increases R_0, a higher diagnosis rate α of

carriage decreases R_0. The latter aspect can be a very useful control strategy and will be further explored in Section 6 through numerical simulations. Biologically, condition (5) only requires that the transmissibility β of carriers is not too small compared to that of the symptomatically infected. This is likely to hold for many diseases with carriers since carriers can unknowingly infect many people.

4. **Stability of the disease-free equilibrium.** To examine the local stability of the disease-free equilibrium P_0 we evaluate the Jacobian matrix at $P_0 = (\frac{b}{d_1+\theta}, 0, 0)$

$$J(P_0) = \begin{bmatrix} -d_1-\theta & -\beta(\frac{b}{d_1+\theta}) & -\gamma(\frac{b}{d_1+\theta}) \\ 0 & p\beta(\frac{b}{d_1+\theta}) - (d_2+\alpha) & p\gamma(\frac{b}{d_1+\theta}) \\ 0 & (1-p)\beta(\frac{b}{d_1+\theta}) + \alpha & (1-p)\gamma(\frac{b}{d_1+\theta}) - (d_3+\pi) \end{bmatrix}.$$

We have the following stability result that shows R_0 is a sharp threshold.

Proposition 2. *P_0 is locally asymptotically stable if $R_0 < 1$ and is unstable if $R_0 > 1$.*

Proof. One eigenvalue of $J(P_0)$ is $\lambda_1 = -(d_1+\theta) < 0$. The other two eigenvalues λ_2, λ_3 are eigenvalues of the 2×2 matrix

$$A = \begin{bmatrix} p\beta(\frac{b}{d_1+\theta}) - (d_2+\alpha) & p\gamma(\frac{b}{d_1+\theta}) \\ (1-p)\beta(\frac{b}{d_1+\theta}) + \alpha & (1-p)\gamma(\frac{b}{d_1+\theta}) - (d_3+\pi) \end{bmatrix}.$$

We want to show, when $R_0 < 1$, that the Routh-Hurwitz conditions hold, namely, $\mathrm{tr}(A) < 0$ and $\det(A) > 0$. Simple calculations show that

$$\mathrm{tr}(A) = (d_2+\alpha)\Big[\frac{p\beta\frac{b}{d_1+\theta}}{d_2+\alpha} - 1\Big] + (d_3+\pi)\Big[\frac{(1-p)\gamma\frac{b}{d_1+\theta}}{d_3+\pi} - 1\Big].$$

Using our assumption that $R_0 = \frac{b}{d_1+\theta}[\frac{p\beta}{(d_2+\alpha)} + \frac{p\alpha\gamma}{(d_2+\alpha)(d_3+\pi)} + \frac{(1-p)\gamma}{(d_3+\pi)}] < 1$ we have

$$\frac{p\beta\frac{b}{d_1+\theta}}{d_2+\alpha} < 1 \quad \text{and} \quad \frac{(1-p)\gamma\frac{b}{d_1+\theta}}{d_3+\pi} < 1.$$

Therefore

$$\frac{p\beta\frac{b}{d_1+\theta}}{d_2+\alpha} - 1 < 0 \quad \text{and} \quad \frac{(1-p)\gamma\frac{b}{d_1+\theta}}{d_3+\pi} - 1 < 0.$$

This shows that $\mathrm{tr}(A) < 0$. Now we calculate

$$\begin{aligned} \det(A) &= \Big[p\beta\frac{b}{d_1+\theta} - (d_2+\alpha)\Big]\Big[(1-p)\gamma\frac{b}{d_1+\theta} - (d_3+\pi)\Big] \\ &\quad - \Big[(1-p)\beta\frac{b}{d_1+\theta} + \alpha\Big]p\gamma\frac{b}{d_1+\theta} \\ &= (d_2+\alpha)(d_3+\pi) - (d_3+\pi)p\beta\frac{b}{d_1+\theta} - d_2(1-p)\gamma\frac{b}{d_1+\theta} \\ &= (d_2+\alpha)(d_3+\pi)[1-R_0]. \end{aligned}$$

Therefore, $\det(A) > 0$ if and only if $R_0 < 1$. This proves the proposition. □

Theorem 4.1. *P_0 is globally asymptotically stable in the feasible region Γ if $R_0 \le 1$.*

Proof. To prove the global asymptotic stability of P_0 we use the method of Lyapunov functions. Define

$$L = \Big[\frac{\beta}{d_2+\alpha} + \frac{\gamma\alpha}{(d_3+\pi)(d_2+\alpha)}\Big]I_c + \frac{\gamma}{d_3+\pi}I.$$

Then

$$\begin{aligned}\frac{dL}{dt} &= \Big[\frac{\beta}{d_2+\alpha} + \frac{\gamma\alpha}{(d_3+\pi)(d_2+\alpha)}\Big]I_c' + \frac{\gamma}{d_3+\pi}I' \\ &= \Big[\frac{p\beta}{d_2+\alpha} + \frac{p\gamma\alpha}{(d_3+\pi)(d_2+\alpha)} + \frac{(1-p)\gamma}{d_3+\pi}\Big]S(\beta I_c+\gamma I) - (\beta I_c+\gamma I) \\ &= \Big[\frac{d_1+\theta}{b}R_0 S - 1\Big](\beta I_c+\gamma I).\end{aligned}$$

Using $S \le \frac{b}{d_1+\theta}$ we know

$$\frac{dL}{dt} \le (R_0-1)(\beta I_c+\gamma I) \le 0.$$

So $\frac{dL}{dt} \le 0$ if $R_0 \le 1$. Furthermore, $\frac{dL}{dt} = 0 \Leftrightarrow I_c = I = 0$ or $R_0 = 1$ and $S = \frac{b}{d_1+\theta}$. Therefore the largest invariant set in the closure $\bar{\Gamma}$ of Γ where $\frac{dL}{dt} = 0$ is the singleton $\{P_0\}$. By LaSalle's Invariance Principle [9], P_0 is globally asymptotically stable in Γ, completing the proof. □

5. Stability of the endemic equilibrium P^*.

Theorem 5.1. *If $R_0 > 1$, then P^* is globally asymptotically stable with respect to the interior of Γ.*

Proof. To study the global stability of the endemic equilibrium, we make use of a Lyapunov function V of form

$$V(S, I_c, I) = x_1(S - S^* \ln S) + x_2(I_c - I_c^* \ln I_c) + x_3(I - I^* \ln I), \tag{6}$$

where $x_1, x_2, x_3 > 0$ are constants to be specified. Note that V has a global minimum at $P^* = (S^*, I_c^*, I^*)$ and $V(S, I_c, I) - V(P^*)$ is positive definite. We show that suitable constants x_1, x_2, x_3 can be chosen such that the Lyapunov derivative of V is negative definite with respect to P^*. Direct calculation and applying the identity $b = d_1S^* + \theta S^* + \beta I_c^* S^* + \gamma I^* S^*$ lead to

$$\begin{aligned}\frac{dV}{dt} =& x_1(S' - \frac{S^*}{S}S') + x_2(I_c' - \frac{I_c^*}{I_c}I_c') + x_3(I' - \frac{I^*}{I}I') \\ =& x_1\Big[b - (d_1+\theta)S - (\beta I_c+\gamma I)S - b\frac{S^*}{S} + (d_1+\theta)S^* + (\beta I_c+\gamma I)S^*\Big] \\ &+ x_2\Big[(1-p)(\beta I_c+\gamma I)S - (d_2+\alpha)I_c - (1-p)\frac{\beta I_c S I_c^*}{I_c} - (1-p)\frac{\gamma I S I_c^*}{I_c} \\ &+ (d_2+\alpha)I_c^*\Big] + x_3\Big[p(\beta I_c+\gamma I)S - \alpha I_c - (d_3+\pi)I - p\frac{\beta I_c S I^*}{I} \\ &- p\frac{\gamma I S I^*}{I} - \frac{\alpha I_c I^*}{I} + (d_3+\pi)I*\Big] \\ =& \Big[x_1(d_1+\theta)S^*(2 - \frac{S^*}{S} - \frac{S}{S^*})\Big] \\ &+ \Big[x_1(\beta I_c^* + \gamma I^*)S^* + x_2(d_2+\alpha)I_c^* + x_3(d_3+\pi)I*\Big] \\ &- \Big[x_1\frac{(\beta I_c^* + \gamma I^*)S^{*2}}{S} + x_2(1-p)\beta S I_c^* + x_2(1-p)\frac{\gamma I S I_c^*}{I_c} \\ &+ x_3 p\frac{\beta I_c S I^*}{I} + x_3 p\gamma S I^* - x_3\frac{\alpha I_c I^*}{I}\Big].\end{aligned}$$

Positive constants x_1, x_2, and x_3 are chosen as

$$x_1 = 1, \quad x_2 = \frac{(d_3+\pi)\beta S^* + \gamma\alpha S^*}{(d_2+\alpha)(d_3+\pi)}, \quad x_3 = \frac{\gamma S^*}{(d_3+\pi)}. \tag{7}$$

It can be verified that they satisfy relations

$$\begin{aligned} -x_1 + x_2(1-p) + x_3 p &= 0, \\ x_1\gamma S^* - x_3(d_3+\pi) &= 0, \\ x_1\beta S^* - x_2(d_2+\alpha) + x_3\alpha &= 0. \end{aligned} \tag{8}$$

We re-group terms in $\frac{dV}{dt}$ such that $\frac{dV}{dt} = V_1 + V_2 + V_3$, where

$$\begin{aligned} V_1 &= (d_1+\theta)S^*(2 - \frac{S}{S^*} - \frac{S^*}{S}), \\ V_2 &= x_1(\beta S^* I_c^* + \gamma I^* S^*) + x_2(d_2+\alpha)I_c^* + x_3(d_3+\pi)I^*, \\ V_3 &= -\frac{x_1(\beta I_c^* S^* + \gamma I^* S^*)S^*}{S} - x_2(1-p)\beta S I_c^* - x_3 p\gamma S I^* \\ &\quad - \frac{x_2(1-p)\gamma I S I_c^*}{I_c} - \frac{x_3 p\beta S I_c I^*}{I} - \frac{x_3\alpha I_c I^*}{I}. \end{aligned}$$

We see that $V_1 \le 0$ from the inequality $x + \frac{1}{x} \ge 2$ for all $x > 0$, and that $V_1 = 0$ if and only if $S = S^*$. We are left to show that $V_2 + V_3 \le 0$. We begin by examining V_2. Using the values for x_1, x_2, and x_3 in (7), relations in (8), and the equilibrium relation

$$(pd_2+\alpha)I_c^* = (1-p)(d_3+\pi)I^*, \tag{9}$$

we can rewrite V_2 as

$$V_2 = 2px_3\gamma I^* S^* + 2(1-p)x_2\beta I_c^* S^* + 4px_3\beta I_c^* S^* + \frac{3(1-p)\alpha}{(pd_2+\alpha)}\gamma I^* S^*. \tag{10}$$

Similarly, we can rewrite V_3 as

$$\begin{aligned} V_3 = &\Big[- x_2(1-p)\beta I_c^* S - \frac{(1-p)x_2\beta S^{*2} I_c^*}{S}\Big] \\ &+ \Big[- x_3 p\gamma S I^* - \frac{p x_3\gamma I^* S^{*2}}{S}\Big] \\ &+ \Big[- y\frac{x_2(1-p)\gamma I S I_c^*}{I_c} - \frac{x_3\alpha I_c I^*}{I} - y\frac{(1-p)x_2\gamma I^* S^{*2}}{S}\Big] \\ &+ \Big[- (1-y)\frac{x_2(1-p)\gamma I S I_c^*}{I_c} - \frac{x_3 p\beta I_c S I^*}{I} - (1-y)\frac{(1-p)x_2\gamma I^* S^{*2}}{S} \\ &- \frac{p x_3\beta S^{*2} I_c^*}{S}\Big], \end{aligned}$$

where

$$y = \frac{(1-p)\alpha}{(pd_2+\alpha)(1-p)x_2}, \quad 1-y = \frac{(1-p)p\beta S^*}{(pd_2+\alpha)(1-p)x_2}.$$

Write $V_3 = V_a + V_b + V_c + V_d$, with each term representing the expression enclosed in a pair of big square brackets. We will estimate each term in V_3 by applying the inequality

$$\frac{a_1 + a_2 + \cdots + a_n}{n} \ge (a_1 \cdot a_2 \cdots a_n)^{1/n}, \quad \text{for } a_i > 0.$$

We obtain

$$\begin{aligned} V_a &= -x_2(1-p)\beta I_c^* S - \frac{(1-p)x_2\beta S^{*2} I_c^*}{S} \\ &\le -2\sqrt{(x_2(1-p))^2(\beta I_c^* S^*)^2} = -2(1-p)x_2\beta I_c^* S^*, \end{aligned} \tag{11}$$

and

$$V_b = -x_3 p\gamma S I^* - \frac{px_3\gamma I^* S^{*2}}{S} \le -2\sqrt{(x_3 p)^2(\gamma I^* S^*)^2} = -2px_3\gamma I^* S^*. \tag{12}$$

Similarly,

$$\begin{aligned} V_c &= -y\frac{x_2(1-p)\gamma I S I_c^*}{I_c} - \frac{x_3\alpha I_c I^*}{I} - y\frac{(1-p)x_2\gamma I^* S^{*2}}{S} \\ &\le -3[(x_2(1-p))^2 x_3\alpha I_c^* y^2(\gamma I^* S^*)^2]^{\frac{1}{3}} = -\frac{3(1-p)\alpha}{(pd_2+\alpha)}\gamma I^* S^*, \end{aligned} \tag{13}$$

and

$$\begin{aligned} V_d &= -(1-y)\frac{x_2(1-p)\gamma I S I_c^*}{I_c} - \frac{x_3 p\beta I_c S I^*}{I} - (1-y)\frac{(1-p)x_2\gamma I^* S^{*2}}{S} \\ &\quad - \frac{px_3\beta S^{*2} I_c^*}{S} \\ &\le -4[(x_2(1-p))^2(px_3)^2(1-y)^2\gamma I^* S^* 2\beta I_c^* S^{*2}\gamma\beta I^* I_c^*]^{\frac{1}{4}} = -4px_3\beta I_c^* S^*. \end{aligned} \tag{14}$$

Therefore, (11) - (14) imply

$$V_3 \le -2(1-p)x_2\beta I_c^* S^* - 2px_3\gamma I^* S^* - 4px_3\beta I_c^* S^* - \frac{3(1-p)\alpha}{(pd_2+\alpha)}\gamma I^* S^*. \tag{15}$$

It follows from (10) and (15) that $V_2 + V_3 \le 0$ and thus $\frac{dV}{dt} \le 0$. Furthermore, $\frac{dV}{dt} = 0$ if and only if $V_1 = 0$ and $V_2 + V_3 = 0$. Using (10) - (15), we can show that $\frac{dV}{dt} = 0 \Leftrightarrow (S, I_c, I) = (S^*, I_c^*, I^*)$, and thus $\frac{dV}{dt}$ is negative definite with respect to P^*. The global stability of P^* follows from the classical stability theorem of Lyapunov. □

We remark that the form of Lyapunov function in (6) was motivated by those used in Korobeinikov and Maini [8], Guo [3], and Guo and Li [4].

6. **Impact of carriers on the transmission dynamics: chronic hepatitis B infection.** To further illustrate the impact of disease carriers on the transmission dynamics, we use chronic hepatitis B infection as an example. Hepatitis B is a liver disease caused by the HBV virus. It is transmitted through sexual contact, the sharing of infected needles, or from mother to infant. Chronic HBV infection is more common: children infected with HBV rarely develop acute illness and up to 90% of infected children become chronically infected; adults infected with HBV usually recover from acute illness, but 5-10% will become chronically infected. About 30% of people infected with HBV do not show any symptoms. These people are the asymptomatic carriers. According to WHO statistics, about 2 billion people worldwide have been infected with HBV and about 350 million live with chronic infection. An estimated 600,000 persons die each year due to the acute or chronic consequences of hepatitis B. Safe and effective hepatitis B vaccines became available in 1982. Integration of the HBV vaccines into childhood immunization programs since 1991 has produced a great decline in the amount of children infected. In many countries where 8% to 15% of children used to become chronically infected

with HBV, vaccination has reduced the rate of chronic infection to less than 1% among immunized children [18, 16, 17].

Our model (1) can be used as a crude approximation for the transmission dynamics of chronic hepatitis B infection among an adult population. The compartment S contains individuals who are susceptible to HBV infection, compartment I contains individuals who are chronically infected with HBV and are symptomatic or have been tested and are aware of their condition, and compartment I_c contains individuals who are asymptomatic carriers of HBV and have no knowledge that they are infected. Recall that in this model, α represents the rate of diagnosis - the rate at which people carrying the disease are made aware of their infection, either through testing or through appearance of symptoms. Based on epidemiological data from WHO, CDC (US), and PHAC (Canada) [18, 16, 17], we have estimated the the values of our model parameters as follows:

$$b = 90,000,\ d_1 = 1/80,\ d_2 = d_1 + 0.004,\ d_3 = d_2,\ \beta = 1.5\gamma,\ \pi = 0.75. \tag{16}$$

We carry out numerical simulations of our model (1) in a hypothetical population of size $200,000$. We will vary key parameters to investigate the impact of asymptomatic carriers and HBV vaccinations.

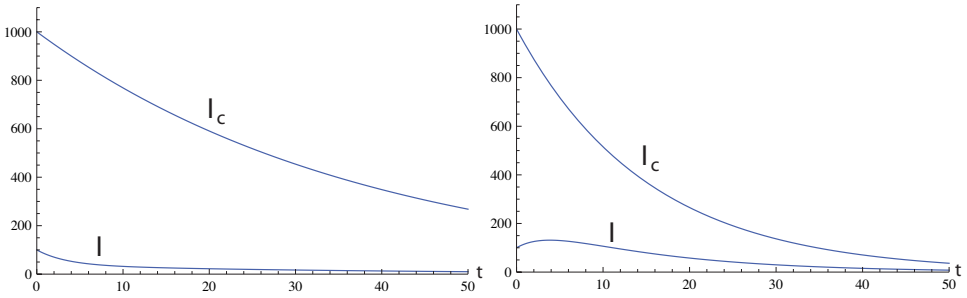

Figure 2. Simulation results showing the impact of testing and diagnosis of carriers. In (a), diagnosis rate $\alpha = 0.1$. In (b), $\alpha = 0.5$. Other parameter values are the same as in (16)

In the first set of simulations, we fix a vaccination coverage rate at 70% where the vaccine has a success rate of 85%. This means that $\theta = 0.85 \times 0.7 = 0.585$. We vary the parameter α to see the effects of diagnosis rate at which carriers move into the infected class.

We see in Figure 2 that, if only 1% of chronic carriers become aware of their disease, the number of symptomatically infected individuals decreases significantly, but the number of carriers is still high. This is not a desirable result as it is the carriers that are responsible for most of the new infections. If we increase α from 1% to 5%, a more dramatic change occurs in the disease dynamics: the number of carriers shows a much greater decline while the number of symptomatically infected remains low. This demonstrates that testing and diagnosis of carriers can be an effective control measure in high HBV prevalence countries.

In the second set of simulations, we will fix $\alpha = 0.01$ and vary θ to see the effect of increasing the vaccination rate. If we set $\theta = 0.1$, we see in Figure 3 that though the number of symptomatically infected reduces rapidly, the number of carriers remains

high. Increasing θ to 0.6 only slightly alters the disease dynamics; the number of carriers only shows a moderate decline.

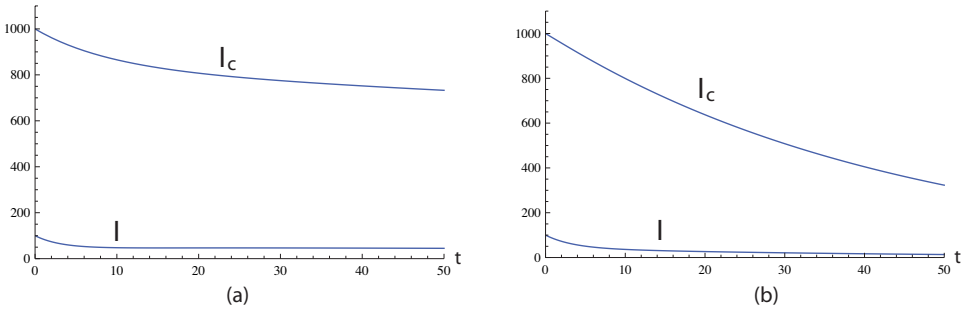

Figure 3. Simulation results showing the impact of vaccination. In (a), vaccination rate $\theta = 0.1$. In (b), $\theta = 0.6$. Other parameter values are the same as in (16)

Our model simulations demonstrate the challenges of chronic HBV infection: the existence of a large number of carriers who are infectious but show no symptoms. Because carriers do not show symptoms, they will not be part of any treatment program. Comparing our simulation results in Figures 2 and 3, we conclude that, in high HBV prevalence countries, testing and increasing awareness of carriers will have a much greater impact on the disease burden than increasing vaccination rates. While this conclusion may have practical implications for the control of chronic HBV infections, more realistic models that are specific for HBV infection and more detailed data need to be employed to further explore its significance in future studies.

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