Modelling Tuberculosis and Hepatitis B Co-infections

S. Bowong[1,2,4,*] **and J. Kurths**[2,3]

[1] Laboratory of Applied Mathematics, Department of Mathematics and Computer Science,
Faculty of Science, University of Douala, P.O. Box 24157 Douala, Cameroon
[2] Postdam Institute for Climate Impact Research (PIK),
Telegraphenberg A 31, 14412 Potsdam, Germany
[3]Department of Physics, Humboldt Universitat zu Berlin, 12489 Berlin, Germany
[4] UMI 209 IRD/UPMC UMMISCO, Bondy, Projet MASAIE INRIA Grand Est, France
Projet Grimcape, LIRIMA, Cameroun

Abstract. Tuberculosis (TB) is the leading cause of death among individuals infected with the hepatitis B virus (HBV). The study of the joint dynamics of HBV and TB present formidable mathematical challenges due to the fact that the models of transmission are quite distinct. We formulate and analyze a deterministic mathematical model which incorporates of the co-dynamics of hepatitis B and tuberculosis. Two sub-models, namely: HBV-only and TB-only sub-models are considered first of all. Unlike the HBV-only sub-model, which has a globally-asymptotically stable disease-free equilibrium whenever the associated reproduction number is less than unity, the TB-only sub-model undergoes the phenomenon of backward bifurcation, where a stable disease-free equilibrium co-exists with a stable endemic equilibrium, for a certain range of the associated reproduction number less than unity. Thus, for TB, the classical requirement of having the associated reproduction number to be less than unity, although necessary, is not sufficient for its elimination. It is also shown, that the full HBV-TB co-infection model undergoes a backward bifurcation phenomenon. Through simulations, we mainly find that i) the two diseases will co-exist whenever their partial reproductive numbers exceed unity; (ii) the increased progression rate due to exogenous reinfection from latent to active TB in co-infected individuals may play a significant role in the rising prevalence of TB; and (iii) the increased progression rates from acute stage to chronic stage of HBV infection have increased the prevalence levels of HBV and TB prevalences.

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*Corresponding author. E-mail: sbowong@gmail.com

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1.   Introduction

Of the seven biggest killers worldwide, TB, malaria, hepatitis, and, in particular, HIV/AIDS continue to surge, with HIV/AIDS and TB likely to account for the overwhelming majority of deaths from infectious diseases in developing countries by 2020 [1-20]. Sub-Saharan Africa accounting for nearly half of infectious disease deaths globally will remain the most vulnerable region. The death rates for many diseases, including HIV/AIDS, tuberculosis, malaria and hepatitis B, exceed those in all other regions. Sub-Saharan Africa's health care capacity, the poorest in the world, will continue to lag [4,5]. Tuberculosis is an old disease whose world-wide prevalence had been diminishing even before vaccination and prophylaxis strategies were firstly accomplished. Its recent return in developing countries, mainly in Southeast Asia, have attracted renewed interest in it. The current world estimate of prevalence is about 33% while the number of deaths per year that it is causing reaches more than 3 million people [2]. Depending of the kind and the intensity of immune response that the host immune system performs after initial infection with M. tuberculosis bacillus, the individual can suffer latent infection, in which the bacteria are under a growth-arrest regime and the individual neither suffer any clinical symptom nor becomes infectious or active infection, where the host suffers clinical symptoms and can transmit the pathogen by air. Latently infected individuals can, generally after an immune-depression episode, reach the active phase. Estimating the probability of developing direct active infection after a contact, or alternatively, the lifetime's risk for a latent infected individual to evolve into the active phase, are not easy tasks. However, it is generally accepted that only 5-10% of the infections directly produce active TB, while the ranges concerning the estimation of typical "half-life" of latent state rounds about 500 years [4, 9].

On the other hand, Hepatitis B is a disease caused by the hepatitis B virus (HBV) which infects the liver of hominoidae, including humans, and causes an inflammation called hepatitis. Originally known as "serum hepatitis", [3,10] the disease has caused epidemics in parts of Asia and Africa [10-20]. It can cause inflammation (swelling) of the liver, and sometimes significant liver damage. Many people do not even realize that they have been infected with that virus, because the typical flu-like symptoms may not develop immediately, or even at all. You can become infected with hepatitis B if you are not immune (resistant) to the virus and have been exposed to the blood or body fluids of an infected person. A vaccine is available to protect against hepatitis B. The hepatitis B virus is present in body fluids such as blood, saliva, semen and vaginal fluid. It can be passed from person to person through unprotected sex (without using a condom) or by sharing needles to inject drugs, for example. Hepatitis B is 100 times more infectious than HIV. Infected mothers can also pass the virus to their baby during childbirth, often without knowing that they are infected. The incubation period (the time it takes from coming into contact with the virus to developing infection) is between one and six months. About a third of the world's population, more than 2 billion people, have been infected with the hepatitis B virus [3]. This includes 350 million chronic carriers of the virus. In developing countries, it is estimated that 5 to 15% of persons are chronic carriers, whereas only about 1% of the population is chronically infected in North America and Western Europe [3,10].

It is important to emphasize that the occurrence of tuberculosis (TB), human immunodeficiency

virus (HIV), and viral hepatitis infections in the same patient poses unique clinical and public health challenges, because medications to treat TB and HIV are hepatotoxic [21]. In developing countries, the scale up of HIV treatment takes place within overlapping epidemics of TB and HBV, particularly in populations where injection drug use and poverty are widespread. The presence of all three infections creates conditions for a perfect storm in medical management, as treatments for TB and HIV each affect the liver already weakened by HBV. In the southwest provinces and some areas of central China, and sub-Saharan Africa, for example, many patients present with all three infections, leading to unique challenges in their medical care [22]. Tuberculosis and hepatitis B are the two common co-infections in patients infected with HIV [21-27]. TB remains an important public health problem in the world that has been exacerbated by the HIV epidemic, resulting in increased morbidity and mortality worldwide. Successful treatment of tuberculosis patients with viral hepatitis and HIV co-infection is a challenging task.

The symbiotic relationship between HBV and TB is a double blow to developing countries and in particular sub-Saharan Africa regions because of the high prevalence of TB and incidence of HBV. HBV and TB exhibit a unique symbiosis, despite biological differences. Therefore, there is a need for a strong qualitative assessment of the population-level implication of the consequences due to the interaction of these two diseases. Tuberculosis and HBV have become a major public health problem and show a danger mark even for the future generations, especially in Asian and sub-Saharan Africa. The main interest in studying HBV and TB model is to understand the long and short term behavior of the dynamics of both diseases and to predict whether the diseases will die out or will persist. A brief survey on previous studies provides the context of this paper.

Blal, et al. [21] studied the prevalence of hepatitis B virus infection among tuberculosis patients with and without HIV in Rio de Janeiro (Brazil). They showed that hepatitis B infection is highly prevalent in tuberculosis patients in Brazil and they suggested that a vaccination program for the general population should be considered in order to prevent further hepatitis B infections. In [22], the authors studied the risk factors and algorithms to identify hepatitis C, hepatitis B, and HIV among Georgian tuberculosis patients. They recruited 300 individuals at in-patient tuberculosis hospitals in three cities in Georgia, administered a behavioral questionnaire, and tested for antibody to HIV, hepatitis C (HCV), hepatitis B core antigen (anti-HBc), and the hepatitis B surface antigen (HBsAg). They found that HIV infection was rare but HBV and HCV infections were common among Georgian tuberculosis patients. High and increasing prevalence of HBV has been reported among both tuberculosis patients and blood donors in Georgia between 1998 and 2001. But this study was the first to indicate that HBV is a significant problem among patients with tuberculosis in Georgia. Bellamy et al. [23] analyzed the co-infection of tuberculosis and chronic hepatitis B virus infection in Africans. They found that persons with VDR genotype tt may be resistant to TB and persistence of HBV infection.

The study of infectious disease co-epidemics is critical for understanding how the diseases are related, and how prevention and treatment efforts can be most effective. Mathematical models can provide insight into the complicated infection dynamics, and into effective control measures. Most mathematical epidemic models evaluate a single disease [28,29], although a growing number of studies have considered co-epidemics. Mathematical studies of co-infection models are not very common. There are a few co-infection models (cf. [30-37]) in the literature. Nevertheless,

Naresh, et al. [31] developed a nonlinear mathematical model for TB/HIV co-infection. Bacaer, et al. [33] developed a mathematical model for the joint dynamics of HIV and TB using numerical simulations to estimate parameters and predict the future transmission of TB in a South Africa township. Sharomi et al. [34] analyzed a mathematical model of the transmission dynamics of HIV/TB co-infection in the presence of treatment, while Mukandavire et al. [35] study a model for HIV-malaria co-infection. In [36], Expeditho, et al. presented an mathematical analysis of malaria and tuberculosis co-dynamics. Roeger, et al. [37] studied HIV/TB co-infection using a mathematical model which does not preclude the possibility of joint infections.

In this paper, we formulate and analyze a realistic mathematical model for HBV-TB co-infection, which incorporates the key epidemiological and biological features of each of the two diseases. The main contribution of this study is to carry out a detailed qualitative analysis of the resulting model. It is our view that this study represents the very first modelling work that provides an in-depth analysis of the qualitative dynamics of HBV-TB co-infection

The rest of this paper is organized as follows. The model is formulated in Section 2. The sub-models for HBV and TB are presented and analyzed in Sections 3. The analysis of the full HBV-TB co-infection model is carried out in Section 4. Numerical results are presented to illustrate the analytical results. Finally, section 5 contains concluding remarks.

2. Modeling of tuberculosis and HBV co-dynamics

2.1. Model construction

The formulation of this co-infection closely follows the epidemiological dynamics of the two diseases.

2.1.1. Basic framework

The model sub-divides the total population at time t denoted by $N(t)$, into various mutually-exclusive compartments depending on their disease status: Susceptible individuals to both diseases ($S(t)$), immune individuals following vaccination to HBV disease ($V(t)$), individuals with latent TB, $E_T(t)$, individuals with active TB ($I_T(t)$), individuals with HBV acute infection ($I_H(t)$), HBV chronic carriers ($C_H(t)$), HBV recovered individuals with protective immunity ($R_H(t)$) dually-infected individuals with HBV acute infection, in the TB latent stage ($E_{TI}(t)$), dually-infected individuals with HBV acute infection, in the TB active stage ($I_{TI}(t)$), dually-infected individuals with HBV chronic carrier, in the TB latent stage ($E_{TC}(t)$), dually-infected individuals with HBV chronic carrier, in the TB active stage ($I_{TC}(t)$), HBV recovered individuals with protective immunity in the TB latent stage ($E_{TR}(t)$) and HBV recovered individuals with protective immunity in the TB active stage ($I_{TR}(t)$).

The total population is

$$
\begin{aligned}
N(t) &= S(t) + V(t) + E_T(t) + I_T(t) + I_H(t) + C_H(t) + R_H(t) + E_{TI}(t) + I_{TI}(t) \\
&+ E_{TC}(t) + I_{TC}(t) + E_{TR}(t) + I_{TR}(t).
\end{aligned}
\tag{2.1}
$$

The compartmental diagram in Fig. 1 illustrates the flow of individuals as they face the possibility of acquiring specific-disease infections or even co-infections.

The model is based on the following assumptions. The mixing between individuals is homogeneous. The population of individuals infected with active-TB is only generated from latent TB class following infection. Latently infected individuals are assumed to acquire some immunity as a result of infection, which reduces the risk of subsequent infection but does not fully prevent it. HBV carrier mothers can pass the virus to their baby during the childbirth. The vaccine-induced immunity acquired by vaccinated individuals is supposed to wane and the way for vaccinated individuals to acquire HBV infection is through the waning of vaccine-induced protection, and individuals therefore enter the HBV acute infection class.

All HBV infected individuals (those in the I_H, C_H and R_H classes) are susceptible to TB infection and TB infected individuals (those in the E_T and I_T classes) are susceptible to HBV infection. Dually infected individuals with TB in the acute and chronic stage of HBV infection (those in the E_{TI}, I_{TI}, E_{TC} and I_{TC} classes) are assumed to transmit HBV at the same rate λ_H as those with only HBV infection (I_H or C_H class). Individuals in the I_{TI}, I_{TC} and I_{TR} classes can transmit TB at the same rate λ_T as individuals with active TB alone (I_T class). Susceptible and HBV vaccinated individuals acquire TB infection following effective contact with TB-infected individuals in the infectious stage (at rate λ_T). Also, susceptible who have never been successfully vaccinated, or who have been vaccinated but the protective effect of vaccination worn off acquire infection with HBV following effective contact with individuals in the acute and chronic carriers stage of HBV infection (at rate λ_H).

The force of infection associated with the HBV infection, denoted by λ_H, is given by

$$
\lambda_H = \beta_H \frac{I_H + \eta_1(E_{TI} + \eta_{1c}I_{TI}) + \eta(C_H + \eta_2(E_{TC} + \eta_{2c}I_{TC}))}{N},
\tag{2.2}
$$

where β_H is the effective contact rate for HBV infection (contact sufficient to result in HBV infection), the modification parameter $\eta_1 \geq 1$ accounts for the relative infectiousness of individuals with HBV acute infection in the TB latent stage (E_{TI}) or displaying active TB (I_{TI}) in comparison to those with HBV infection alone but with acute infection (I_H). In other words, it is assumed that HBV-infected individuals (with acute infection) who are also infected with TB are more infectious than HBV-infected individuals with acute infection and no TB infection (similar comparisons are made for HBV chronic carriers alone in relation to those with HBV chronic carriers and TB infection). Further, the parameter η_{1c} (with $\eta_{1c} \geq \eta_1 \geq 1$) captures the fact that dually-infected individuals with HBV acute infection, but displaying active TB (I_{TI}), are more infectious than the corresponding dually-infected individuals with HBV acute infection in the TB latent stage (E_{TI}). The parameter η models the reduced transmission rate of individuals in the chronic stage of HBV infection with respect to the infectiousness of individuals in the acute infection of HBV
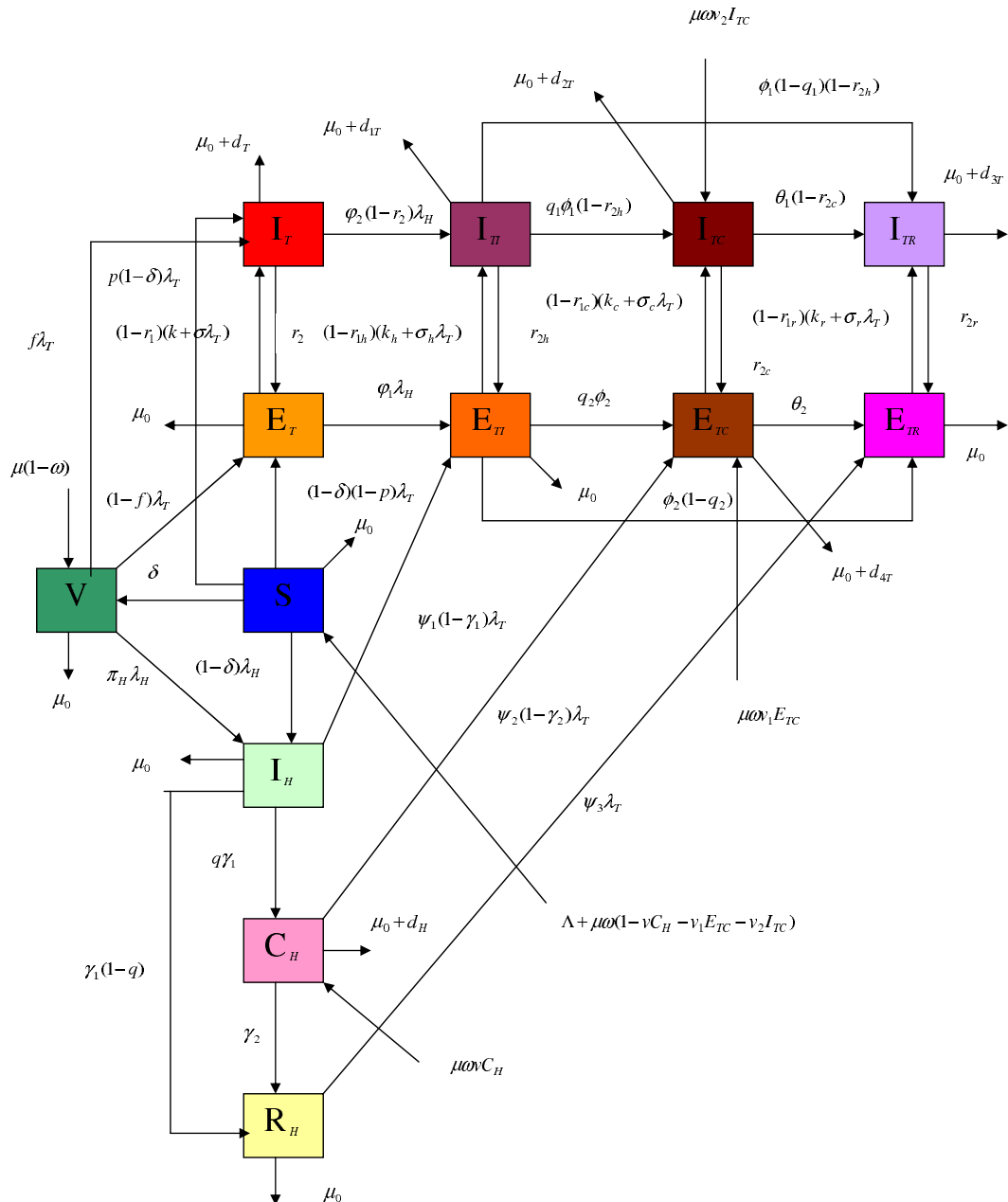
Figure 1: Flowchart of the transmission dynamics of the co-infection TB/HBV.

infection alone. This is due to the fact that individuals in the acute stage of HBV infection have higher viral load compared to individuals in the chronic stage of HBV infection(this is owing to the aforementioned correlation between HBV viral load and infectiousness). Also, η_2 models the relative infectiousness of dually-infected individuals with chronic infection of HBV in the latent stage of TB (E_{TC}) or displaying active TB (I_{TC}) in comparison to those with HBV chronic infec-

tion alone (C_H). Finally, η_{2c} (with $\eta_{2c} \geq \eta_2$) is the modification parameter accounting the fact that dually-infected individuals with HBV chronic infection, but displaying active TB (I_{TC}), are more infectious than the corresponding dually-infected individuals with HBV chronic infection in the TB latent stage (E_{TC}).

Similarly, susceptible and HBV vaccinated individuals acquire TB infection following contact with people in the active stage of TB (that is, those in I_T, I_{TI}, I_{TC} and I_{TR} classes) at rate λ_T defined as follows:

$$\lambda_T = \beta_T \frac{I_T + \varepsilon(I_{TR} + \varepsilon_t I_{TI} + \varepsilon_c I_{TC})}{N}, \tag{2.3}$$

where β_T is the contact rate associated with the TB infection. The modification parameter $\varepsilon > 1$ accounts for the relative risk of infectiousness of dually-infected individuals in the active-TB classes (I_{TI}, I_{TC} and I_{TR}) in comparison to those in the only active TB class (I_T). Further, the modification parameter ε_t (with $\varepsilon_t > \varepsilon > 1$) accounting to the fact that dually-infected individuals with HBV acute infection, but displaying that active TB (I_{TI}) are more infectious than the corresponding HBV recovered individuals in the TB active stage (I_{TR}). Finally, ε_c (with $\varepsilon_c \geq \varepsilon_t > 1$) accounts for the assumed increase in infectiousness for dually-infected individuals in the chronic stage of HBV infection, but displaying active TB (I_{TC}), compared to dually-infected individuals with HBV acute infection in the TB active stage (I_{TI}).

We define by ω the proportion of births without successful vaccination. Children born by carrier mothers (in the C_H, E_{TC} and I_{TC} classes) who are unsuccessfully immunized by vaccination or have not been vaccinated can be infected by carrier mothers and will enter the C_H, E_{TC} and I_{TC} classes at rates $\mu\omega$, $\mu\omega v_1$ and $\mu\omega v_2$, respectively.

The susceptible class is generated by the recruitment of individuals into the population from immigration and children born by carrier women without successful vaccination who have not been infected by the HBV virus at the rates, Λ and $\mu\omega(1-vC_H-v_1E_{TC}-v_2I_{TC})$, respectively. The HBV vaccinated population increases by births who are successful immunized, and are protected from perinatal and postnatal infection at rate $\mu(1-\omega)$. Every susceptible vaccinated neonate enters the vaccinated class V at rate δ, representing the assumption that vaccination prevents perinatal transmission from infectious women. We assume that this protection is not lifelong. Further, natural death rate occurs in all compartments at the rate μ_0.

Individuals with latent TB who have been infected with Mycobacterium tuberculosis but have no clinical symptoms/illness and are non-infectious. Fraction p of newly infected susceptible individuals is assumed to undergo a fast progression directly to the infectious class I_T, while the remainder is latently infected and enter the latent class E_T. Similarly, a fraction f of HBV vaccinated individuals who acquire TB infection move to the TB latent class (E_T), while the remaining fraction, $1 - f$, enters the TB active class (I_T). Once latently infected with M. Tuberculosis, an individual will remain so for life unless reactivation occurs. To account for treatment, we define by r_1E_T the fraction of latently infected individuals receiving effective chemoprophylaxis, and r_2 as the rate of effective per capita therapy of individuals in the active TB alone. Chemoprophylaxis of latently infected individuals reduces their reactivation at the rate r_1 and the initiation of therapeutics immediately removes individuals from active status I_T and places them into a latent state E_T at the rate r_2. Due to endogenous reactivation, a fraction $1 - r_1$ of latently infected individuals who

did not received effective chemoprophylaxis become infectious with a rate k, and some become reinfected (exogenously) after effective contact with individuals in the active TB classes only at rate $\sigma \lambda_T$. σ models the factor reducing the risk of infection as a result of acquiring immunity for latently infected individuals. Individuals with active-TB alone suffer a disease-induced death rate d_T.

The population of individuals infected with TB only (in the E_T or I_T class) is also reduced following acquisition of HBV-infection, which can result following effective contacts with individuals in the HBV acute and chronic infection stage (in the I_H, C_H, E_{TI}, E_{TC}, I_{TI} and I_{TC} classes). Individuals exposed to TB can be infected with HBV (at a rate λ_H). That is, individuals in the E_T class are moved into the E_{TI} class upon acquiring HBV infection at rate $\varphi_1 \lambda_H$ where φ_1 accounts for the assumed increase in the probability of acquiring HBV infection for TB latently infected individuals only. Furthermore, individuals in the active stage of TB infection alone can acquire HBV infection, at rate $\varphi_2(1 - r_2)\lambda_H$ where φ_2 (with $\varphi_2 > \varphi_1$) models the probability of acquiring HBV infection for individuals in the active stage of TB infection alone. Individuals in the E_{TI} class progress to the E_{TC} and E_{TR} classes at rates $q_2\phi_2$ and $\phi_2(1 - q_2)$, respectively, where q_2 is the average probability that an individual in the E_{TI} class fails to clear an acute infection and develops a carrier state (E_{TC}). Similarly, individuals in the I_{TI} class progress to the I_{TC} and I_{TR} classes at rates $q_1\phi_1$ and $\phi_1(1 - q_1)$, respectively, where q_1 is the average probability that an individual in the I_{TI} class fails to clear an acute infection and develops a carrier state (I_{TC}). Dually infected individuals with HBV acute and chronic infection, and HBV recovered individuals in the TB latent stage are assumed to receive effective chemoprophylaxis at rates r_{1h}, r_{1c} and r_{1r} (with $r_{1r} > r_{1h} > r_{1c}$), respectively.

Dually infected individuals with HBV acute and chronic infection, and HBV recovered individuals in the TB latent stage (in the E_{TI}, E_{TC} and E_{TR} classes) who did not receive effective chemoprophylaxis can develop an active TB and will move to the I_{TI}, I_{TC} and I_{TR} classes at rates $k_h(1 - r_{1h})$, $k_c(1 - r_{1c})$ and $k_r(1 - r_{1r})$ for endogenous reactivation and $\sigma_h\lambda_T$, $\sigma_c\lambda_T$ and $\sigma_r\lambda_T$ for exogenous re-infection, respectively. σ_h, σ_c and σ_r are respectively, the factors reducing the risk of infection as a result of acquiring immunity for individuals in the E_{TI}, E_{TC} and E_{TR} classes. The initiation of therapeutics immediately removes individuals from active status I_{TI}, I_{TC} and I_{TR} and places them into latent states E_{TI}, E_{TC} and E_{TR} at rates r_{2h}, r_{2c} and r_{2r} (with $r_{2r} > r_{2h} > r_{2c}$), respectively. Furthermore, individuals in the I_{TI} and I_{TR} classes die due to TB at rates d_{1T} and d_{3T} (with $d_{1T} > d_{3T}$), respectively, while, individuals in the E_{TC} class die due to HBV at rate d_{4T}. In addition, individuals in the I_{TC} class suffer death due to TB and HBV at rate d_{2T} (with $d_{2T} > d_{4T} > d_H$). We point out that since the chemoprophylaxis of latently infected individuals only reduces their reactivation to active TB, chemoprophylaxis of dually-infected individuals with latent TB and HBV infection (those in the E_T, E_{TI} and E_{TC} classes) have no effect on the progression of the HBV infection. This is why there, the terms $1 - r_1$, $1 - r_{1h}$ and $1 - r_{1c}$ which are associated to the chemoprophylaxis of individuals in the E_T, E_{TI} and E_{TC} classes do not exist in the expressions of the transfer rates from E_T to E_{TI}, from E_{TI} to E_{TC} and from E_{TC} to E_{TR}, respectively.

Table 1: Description of the variables of the model

Variable	Description
$S(t)$	Susceptible individuals
$V(t)$	HBV vaccinated individuals
$E_T(t)$	TB infected individuals in the TB latent stage
$I_T(t)$	TB-infected individuals in the active stage of TB
$E_{TI}(t)$	Dually-infected individuals with HBV acute infection in the TB latent stage
$I_{TI}(t)$	Dually-infected individuals with HBV acute infection that displaying active TB
$E_{TC}(t)$	Dually-infected individuals with HBV chronic carrier in the TB latent stage
$I_{TC}(t)$	Dually-infected individuals with HBV chronic carrier that displaying active TB
$E_{TR}(t)$	HBV recovered individuals with protective immunity in the TB latent stage
$I_{TR}(t)$	HBV recovered individuals with protective immunity that displaying active TB
$I_H(t)$	HBV acute infection individuals
$C_H(t)$	HBV chronic carriers
$R_H(t)$	HBV recovered individuals with protective immunity

Susceptible individuals whose HBV vaccination was successful enter in the HBV vaccinated class V at rate δ, while the remaining who can be infected with HBV and will move to the I_H class with the force of infection $(1-\delta)\lambda_H$. The vaccine-induced immunity acquired by vaccinated individuals is supposed to wane at rate π_H and the way to vaccinated individuals to acquire HBV infection is through the waning of vaccine-induced protection, and individuals therefore enter the HBV acute infection class I_H. Thus, HBV vaccinated individuals can experience break-through infection (due to incomplete protection provided by vaccine) and can become infected with HBV at rate $\pi_H\lambda_H$. We define by q the average probability that an individual in the HBV acute class I_H fails to clear an acute infection but develops a chronic state (C_H). Then, individuals in the I_H class progress to the C_H class at rate $q\gamma_1$, while the remainders enter the R_H class at rate $\gamma_1(1-q)$. Further, individuals in the C_H class progress to the HBV recovered class (R_H), at rate γ_2. Individuals in the I_H, C_H and R_H classes are also reduced due to the TB infection (following effective contacts with individuals in the I_T, I_{TI}, I_{TC} and I_{TR} classes). The parameters ψ_1, ψ_2 and ψ_3 (with $\psi_3 < \psi_1 < \psi_2$) account for the assumed increase in probability of acquiring TB infection for HBV-infected individuals alone. The parameters ψ_1, ψ_2 and ψ_3 are associated, respectively, with those with acute infection (I_H), carrier state (C_H) and recovered state (R_H). It is assumed that individuals with HBV infection are more prone to TB infection than all susceptible individuals. Further, those with HBV chronic state acquire TB infection at a higher rate than those in the acute stage of HBV infection which also acquire TB infection at a higher rate than recovered individuals owing to the weaker immune status of the former. Once infected by Mycobacterium

tuberculosis, individuals in the I_H, C_H and R_H classes move to the E_{TI}, E_{TC} and E_{TR} classes at rates $\psi_1(1 - \gamma_1)\lambda_T$, $\psi_2(1 - \gamma_2)\lambda_T$ and $\psi_3\lambda_T$, respectively. Carriers are prone to the background death rate that applies to the whole community but have an additional death rate d_H because of their hepatitis B carrier status.

The model variables and parameters are further described in Tables 1 and 2 for elucidation.

Table 2: Description of parameters of the model

Parameters	Description
Λ	Recruitment rate of susceptible individuals into the population
β_T	Transmission rate of TB
β_H	Transmission rate of HBV
η_1, η_{1c}	Factors taking into account the infectivity of individuals in the HBV acute infection stage
η, η_2, η_{2c}	Infectiousness of individuals in the chronic stage of HBV infection
ε, ε_t, ε_c	Factors taking into account the infectivity of active TB individuals
π_H	Rate of waning vaccine-induced immunity
p	Fraction of newly-infected susceptible individuals with latent TB
f	Fraction of newly-infected HBV vaccinated individuals with latent TB
φ_1	Probability of acquiring HBV infection of individuals in the E_T class
φ_2	Probability of acquiring HBV infection of individuals in the I_T class
ψ_1	Probability of acquiring TB of individuals in the I_H class
ψ_2	Probability of acquiring TB of individuals in the C_H class
ψ_3	Probability of acquiring TB of individuals in the R_H class
k	Progression rate from the E_T class to the I_T class
k_h	Progression rate from the E_{TI} class to the I_{TI} class
k_c	Progression rate from the E_{TC} class to the I_{TC} class
k_r	Progression rate from the E_{TR} class to the I_{TR} class
σ, σ_h, σ_c, σ_r	Re-infection parameters in the E_T, E_{TI}, E_{TC} and E_{TR} classes
μ_0	Natural death rate of people
μ	Birth rate in the population
ω	Proportion of births without successful vaccination
v, v_1, v_2	Proportions of perinatally infected born by carriers mothers in the C_H, E_{TC} and I_{TC} classes
δ	Vaccination rate
γ_1, ϕ_1, ϕ_2	Rate moving from acute to carrier
q, q_1, q_2	Average probability that an individual in the HBV acute infection fail to clear an acute state and develops a carrier state
γ_2, θ_1, θ_2	Rate moving from carrier classes to recovered classes
d_H	HBV induced death rate of individuals in the HBV chronic carriers class C_H

d_T	TB induced death rate of individuals in the TB active class I_T
d_{1T}	TB induced death rate of individuals in the I_{TI} class
d_{2T}	HBV and TB induced death rate of individuals in the I_{TC} class
d_{3T}	TB induced death rate of individuals in the I_{TR} class
d_{4T}	HBV induced death rate of individuals in the E_{TC} class
r_2	TB recovery rate of individuals in the I_T class
r_{2h}	TB recovery rate of individuals in the I_{TI} class
r_{2c}	TB recovery rate of individuals in the I_{TC} class
r_{2r}	TB recovery rate of individuals in the I_{TR} class
r_1	Rate of TB effective chemoprophylaxis of individuals in the E_T class
r_{1h}	Rate of TB effective chemoprophylaxis of individuals in the E_{TI} class
r_{1c}	Rate of TB effective chemoprophylaxis of individuals in the E_{TC} class
r_{1r}	Rate of TB effective chemoprophylaxis of individuals in the E_{TR} class

2.1.2. The model

Putting the above formulations and assumptions together gives the following system of differential equations:

$$
\begin{cases}
\dot{S} &= \Lambda + \mu\omega(1 - vC_H - v_1 E_{TC} - v_2 I_{TC}) - (1-\delta)(\lambda_T + \lambda_H)S - (\mu_0 + \delta)S, \\[2mm]
\dot{V} &= \mu(1-\omega) + \delta S - (\lambda_T + \pi_H \lambda_H)V - \mu_0 V, \\[2mm]
\dot{I}_H &= [\pi_H V + (1-\delta)S]\lambda_H - \psi_1(1-\gamma_1)\lambda_T I_H - (\mu_0 + \gamma_1)I_H, \\[2mm]
\dot{C}_H &= \mu\omega v C_H + q\gamma_1 I_H - \psi_2(1-\gamma_2)\lambda_T C_H - (\mu_0 + d_H + \gamma_2)C_H, \\[2mm]
\dot{R}_H &= \gamma_1(1-q)I_H + \gamma_2 C_H - \psi_3 \lambda_T R_H - \mu_0 R_H, \\[2mm]
\dot{E}_T &= [(1-f)V + (1-\delta)(1-p)S]\lambda_T + r_2 I_T - (1-r_1)(k + \sigma\lambda_T)E_T \\[1mm]
&\quad - \varphi_1 \lambda_H E_T - \mu_0 E_T, \\[2mm]
\dot{I}_T &= [fV + p(1-\delta)S]\lambda_T + (1-r_1)(k + \sigma\lambda_T)E_T - \varphi_2(1-r_2)\lambda_H I_T \\[1mm]
&\quad - (\mu_0 + d_T + r_2)I_T, \\[2mm]
\dot{E}_{TI} &= \varphi_1 \lambda_H E_T + \psi_1(1-\gamma_1)\lambda_T I_H + r_{2h} I_{TI} - \sigma_h(1-r_{1h})\lambda_T E_{TI} \\[1mm]
&\quad - [\mu_0 + k_h(1-r_{1h}) + \phi_2]E_{TI},
\end{cases}
\tag{2.4}
$$

$$
\begin{cases}
\dot{I}_{TI} &= \varphi_2(1 - r_2)\lambda_H I_T + (1 - r_{1h})(k_h + \sigma_h\lambda_T)E_{TI} \\
&\quad - [\mu_0 + d_{1T} + r_{2h} + \phi_1(1 - r_{2h})]I_{TI}, \\[2mm]
\dot{E}_{TC} &= \mu\omega v_1 E_{TC} + q_2\phi_2 E_{TI} + \psi_2(1 - \gamma_2)\lambda_T C_H + r_{2c}I_{TC} \\
&\quad - \sigma_c(1 - r_{1c})\lambda_T E_{TC} - [\mu_0 + d_{4T} + \theta_2 + k_c(1 - r_{1c})]E_{TC}, \\[2mm]
\dot{I}_{TC} &= \mu\omega v_2 I_{TC} + q_1\phi_1(1 - r_{2h})I_{TI} + (1 - r_{1c})(k_c + \sigma_c\lambda_T)E_{TC} \\
&\quad - [\mu_0 + d_{2T} + r_{2c} + \theta_1(1 - r_{2c})]I_{TC}, \\[2mm]
\dot{E}_{TR} &= \psi_3\lambda_T R_H + \theta_2 E_{TC} + \phi_2(1 - q_2)E_{TI} + r_{2r}I_{TR} \\
&\quad - (1 - r_{1r})\sigma_r\lambda_T E_{TR} - [\mu_0 + k_r(1 - r_{1r})]E_{TR}, \\[2mm]
\dot{I}_{TR} &= \theta_1(1 - r_{2c})I_{TC} + \phi_1(1 - q_1)(1 - r_{2h})I_{TI} + (1 - r_{1r})(k_r + \sigma_r\lambda_T)E_{TR} \\
&\quad - (\mu_0 + d_{3T} + r_{2r})I_{TR}.
\end{cases}
$$

We assume that the population of new born carriers (born by carrier mothers) is less than the sum of the death of carriers and the population moving from carrier to immune state. In this case, we have $\mu\omega v < \mu_0 + d_H + \gamma_2$. Otherwise, carriers would keep increasing rapidly as long as there is infection, i.e., $dC_H/dt > 0$ for $C_H \neq 0$ or $I_H \neq 0$ and $t \geq 0$.

The parameter values used for numerical simulation are given in Table 3.

Table 3: Numerical values for the parameters of the model

Parameters	Estimated values/range	Reference
Λ	500 per year	Assumed
β_T	Variable	
β_H	Variable	
π_H	0.1 per year	[12]
η	0.16 per year	[11]
$\eta_1,\ \eta_{1c},\ \eta_2,\ \eta_{2c}$	0.6, 1.1, 1.2, 1.4 per year	Assumed
$\varepsilon,\ \varepsilon_t,\ \varepsilon_c$	1.1, 1.3, 1.5 per year	Assumed
p	0.7 per year	Assumed
f	0.6 per year	Assumed

$\varphi_1,\ \varphi_2$	0.3, 0.5 per year	Assumed
$\psi_1,\ \psi_2,\ \psi_3$	0.4, 0.6, 0.1 per year	Assumed
k	0.00013 per year	[40]
$k_h,\ k_c,\ k_r$	0.00015, 0.00016, 0.00014 per year	Assumed
$\sigma,\ \sigma_h,\ \sigma_c,\ \sigma_r$	0.7, 0.75, 0.8, 0.9 per year	Assumed
μ_0	0.019896 per year	[42]
μ	0.0121 per year	[42]
ω	0.1 per year	Assumed
v	0.11 per year	[11]
$v_1,\ v_2$	0.12, 0.13 per year	Assumed
δ	0.7 per year	Assumed
γ_1	4 per year	[11]
$\phi_1,\ \phi_2$	2, 3 per year	Assumed
q	0.0885 per year	[39]
$q_1,\ q_2$	0.9, 0.95 per year	Assumed
γ_2	0.025 per year	[11]
$\theta_1,\ \theta_2$	0.015, 0.01 per year	Assumed
d_H	0.002 per year	Assumed
d_T	0.0575 per year	[41]
$d_{1T},\ d_{2T},\ d_{3T},\ d_{4T}$	0.06, 0.08, 0.05, 0.07 per year	Assumed
r_2	0.7311 per year	[41]
$r_{2h},\ r_{2c},\ r_{2r}$	0.5, 0.4, 0.6 per year	[41]
$r_1,\ r_{1h},\ r_{1c},\ r_{1r}$	0, 0, 0, 0 per year	[38]

2.2. Positivity of solutions

For the system (2.4) to be epidemiologically meaningful, it is important to prove that all its state variables are non-negative for all time. In other word, solutions of system (2.4) with positive initial data remain positive for all time $t > 0$. This can be verified as follows. Suppose, for example, the variable I_H becomes zero for some time $\bar{t} > 0$, i.e., $I_H(\bar{t}) = 0$, while all other variables are positive. Then, from the I_H equation we have $dI_H(\bar{t})/dt > 0$. Thus, $I_H(t) \geq 0$ for all $t > 0$. Similarly, it can be shown that all variables remain nonnegative for all $t > 0$.

2.3. Invariant region

The TB-HBV transmission model (2.4) will therefore be analyzed in a suitable feasible region, obtained as follows.

We first show that all feasible solutions are uniformly-bounded in a proper subset of Ω. Let, $(S, V, I_H, C_H, R_H, E_T, I_T, E_{TI}, E_{TC}, E_{TR}, I_{TI}, I_{TC}, I_{TR}) \in \mathbb{R}_{\geq 0}^{13}$ be any solution of the system with non-negative initial conditions. Adding all the equations in system (2.4) gives the following equation for N, the total population

$$\dot{N} = \Lambda + \mu - \mu_0 N - (d_H C_H + d_T I_T + d_{1T} I_{TI} + d_{4T} E_{TC} + d_{2T} I_{TC} + d_{3T} I_{TR}).$$

Then, one gets $\dot{N} < \Lambda + \mu - \mu_0 N$. Thus, applying Birkhoff's and Rota's Theorem on differential inequality [43], as $t \to \infty$, one obtains $0 \leq N \leq \dfrac{\Lambda + \mu}{\mu_0}$. Therefore, all feasible solutions of components of system (2.4) enter the region

$$\Omega = \left\{ (S, V, I_H, C_H, R_H, E_T, I_T, E_{TI}, E_{TC}, E_{TR}, I_{TI}, I_{TC}, I_{TR}) \in \mathbb{R}^{13}_{\geq 0}, \quad N(t) \leq \frac{\Lambda + \mu}{\mu_0} \right\}.$$

(2.5)

Thus, it follows from (2.5) that all possible solutions of system (2.4) will enter the region. Hence, the region Ω, of biological interest, is positively-invariant under the flow induced by system (2.4). Further, it can be shown using the theory of permanence [44] that all solutions on the boundary of Ω eventually enter the interior of Ω. Furthermore, in Ω, the usual existence, uniqueness and continuation results hold for system (2.4). Hence, system (2.4) is well posed mathematically and epidemiologically and it is sufficient to consider the dynamics of the flow generated by the system (2.4) in Ω.

Having established a biologically feasible region where the model is biologically and mathematically well-posed [45], the next step is to consider the dynamics of the two sub-models, namely; HBV-only and TB-only models. This would help to lay down the foundation for the qualitative analysis of the full model.

3. Mathematical analysis of the HBV and TB sub-models

3.1. HBV-only sub-model

Hepatitis B is a potentially life-threatening liver infection caused by the HBV and is a major global health problem and the most serious type of viral hepatitis [3]. It has caused epidemics in parts of Asia and Africa. Worldwide, about 2 billion people have been infected with the virus and about 360 million live with this chronic infection. Estimated 600,000 persons die each year due to the acute or chronic consequences of hepatitis B [3, 46].

The HBV-only model is obtained by setting $E_T = I_T = E_{TI} = I_{TI} = E_{TC} = I_{TC} = E_{TR} = I_{TR} = 0$. Thus, we have,

$$
\begin{cases}
\dot{S} &= \Lambda + \mu\omega(1 - vC_H) - (1 - \delta)\lambda_H S - (\delta + \mu_0)S, \\[2mm]
\dot{V} &= \mu(1 - \omega) + \delta S - \pi_H \lambda_H V - \mu_0 V, \\[2mm]
\dot{I}_H &= [\pi_H V + (1 - \delta)S]\lambda_H - (\mu_0 + \gamma_1)I_H, \\[2mm]
\dot{C}_H &= \mu\omega v C_H + q\gamma_1 I_H - (\mu_0 + d_H + \gamma_2)C_H, \\[2mm]
\dot{R}_H &= \gamma_1(1 - q)I_H + \gamma_2 C_H - \mu_0 R_H,
\end{cases}
\tag{3.1}
$$

where $\lambda_H = \beta_H \dfrac{I_H + \eta C_H}{N}$ with $N = S + V + I_H + C_H + R_H$. It should be pointed out that the HBV-only model is a slight modification of HBV models proposed in Refs. [11-14]. In the model (3.1), we have assumed that the vaccine-induced immunity acquired by vaccinated individuals is suppose to wane and the way for vaccinated individuals to acquire HBV infection is through the waning of vaccine-induced protection, and individuals therefore enter the HBV acute infection class. This is no the case of the models proposed in Refs. [11-14] where the authors have supposed that when the vaccine-induced immunity wanes, vaccinated individuals return to the susceptible before acquire HBV infection.

The feasible region for this sub-model is

$$\Omega_H = \left\{ (S, V, I_H, C_H, R_H) \in \mathbb{R}^5_{\geq 0}, \quad S + V + I_H + C_H + R_H \leq \frac{\Lambda + \mu}{\mu_0} \right\}. \qquad (3.2)$$

Next, we show that the region Ω_H is positively invariant, so that it is sufficient to consider the dynamics of the above model in Ω_H.

Adding all equations in (3.1) gives

$$\dot{N} = \Lambda + \mu - \mu_0 N - d_H C_H.$$

Since the right hand side of the above equation is bounded by $\Lambda + \mu - \mu_0 N(t)$, it follows that $\dot{N} < 0$ if $N(t) > \dfrac{(\Lambda + \mu)}{\mu_0}$. Using a standard comparison theorem [47-49], it can be shown that $N(t) \leq N(0)e^{-\mu_0 t} + \dfrac{(\Lambda + \mu)}{\mu_0}(1 - e^{-\mu_0 t})$. Thus, Ω_H is positively-invariant. If $N(0) > \dfrac{\Lambda + \mu}{\mu_0}$, then, either the solution enters Ω_H in finite time, or $N(t)$ approaches $\dfrac{\Lambda + \mu}{\mu_0}$ asymptotically, and the infected variables I_H, C_H and R_H approach zero. Hence, Ω_H is attracting.

One of the most important concerns in the analysis of epidemiological models is the determination of the asymptotic behavior of their solutions which is usually based on the stability of the associated equilibria [50]. These models typically consist of a disease-free equilibrium and at least one endemic equilibrium. The local stability of the disease-free equilibrium (DFE) is determined based on a threshold parameter, known as the basic reproductive number [51, 52].

3.1.1. Local stability of the disease-free equilibrium (DFE) of the HBV-only model

The DFE of the HBV-only model (3.1) is given by,

$$Q_0^H = (S_0, \ V_0, \ 0, \ 0, \ 0),$$

where

$$S_0 = \frac{\Lambda + \mu\omega}{\mu_0 + \delta} \qquad \text{and} \qquad V_0 = \frac{\delta(\mu + \Lambda) + \mu\mu_0(1 - \omega)}{\mu_0(\mu_0 + \delta)}.$$

The local stability of the DFE of the HBV-onlymodel is determined by its basic reproduction number $\mathcal{R}_0^H$, which is computed using the next generation operator method proposed by van den Driessche and Watmough [52].

Using the notations in [52], the matrices F and V, for the new infection and the remaining transfer, are, respectively, given by

$$F = \frac{\beta_H}{N_0}[\pi_H V_0 + (1-\delta)S_0] \begin{bmatrix} 1 & \eta & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} \mu_0 + \gamma_1 & 0 & 0 \\ -q\gamma_1 & A & 0 \\ -\gamma_1(1-q) & -\gamma_2 & \mu_0 \end{bmatrix},$$

where $N_0 = S_0 + V_0$ and $A = \mu_0 + d_H + \gamma_2 - \mu\omega v$. Then, the basic reproduction ratio is defined as the dominant eigenvalue of the next generation matrix, FV^{-1}:

$$\mathcal{R}_0^H = \frac{\beta_H(A + \eta q\gamma_1)[\pi_H[\delta(\mu + \Lambda) + \mu\mu_0(1-\omega)] + \mu_0(1-\delta)(\Lambda + \mu\omega)]}{A(\mu_0 + \delta)(\mu_0 + \gamma_1)(\Lambda + \mu)}. \tag{3.3}$$

We can also interpret $\mathcal{R}_0^H$ as the average number of secondary HBV acute and chronic infection cases produced by a HBV acute or chronic individual during his or her effective infectious period when introduced in a population of mostly HBV susceptible. The threshold quantity $\mathcal{R}_0^H$ is the reproduction number for HBV. Then, we claim the following result.

Lemma 1. *: The DFE Q_0^H of the HBV-only model is locally asymptotically stable (LAS) if $\mathcal{R}_0^H < 1$, and unstable if $\mathcal{R}_0^H > 1$.*

Biologically speaking, Lemma 1 implies that HBV can be eliminated from the community (when $\mathcal{R}_0^H < 1$) if the initial size of the sub-populations of the model is in the basin of attraction of Q_0^H.

Now let us analyze the basic reproduction ratio $\mathcal{R}_0^H$. The parameters ω and δ are important for the prevalence of HBV infection. They influence the dynamics of HBV, in particular the equilibrium states, including the states of susceptible, acute infective, and carriers. It is evident from (3.3) that

$$\lim_{\delta \to 1} \mathcal{R}_0^H = \frac{\beta_H\pi_H(A + \eta q\gamma_1)[\mu + \Lambda + \mu_0\mu(1-\omega)]}{A(\mu_0 + 1)(\mu_0 + \gamma_1)(\Lambda + \mu)} > 0. \tag{3.4}$$

Thus, a sufficiently effective HBV vaccination program can lead to effective disease control if it results in making the right-hand side of (3.4) less than unity, that is,

$$\pi_H < \frac{A(\mu_0 + 1)(\mu_0 + \gamma_1)(\Lambda + \mu)}{\beta_H(A + \eta q\gamma_1)[\mu + \Lambda + \mu_0\mu(1-\omega)]}.$$

Further, sensitivity analysis on the vaccination parameter of susceptible individuals is carried out by computing the partial derivative of $\mathcal{R}_0^H$ with respect to δ yielding

$$\frac{\partial \mathcal{R}_0^H}{\partial \delta} = -\frac{\beta_H\mu_0(\Lambda + \mu\omega)(A + \eta q\gamma_1)(\mu_0 + 1 - \pi_H)}{A(\mu_0 + \gamma_1)(\Lambda + \mu)(\mu_0 + \delta)^2} < 0. \tag{3.5}$$

Thus, increasing the vaccination parameter δ will have a positive impact in reducing the propagation of HBV in the community.

To find better control strategies for HBV infection, we would like to see what parameters can reduce the basic reproduction ratio $\mathcal{R}_0^H$ given by (3.3).

Figure 2 presents the 3-D plot showing the effects of β_H, $1 - \omega$ and δ on the basic reproduction ratio $\mathcal{R}_0^H$. All other parameters are as in Table 3. From Fig. 2(a), we can see that $\mathcal{R}_0^H$ decreases if β_H decreases (see Fig. 2(a)) even in the case of large values of $1 - \omega$. This means that if the transmission coefficient β_H is sufficiently small HBV infection could be eliminated even if $1 - \omega = 0$. Also, it clearly appears from Fig. 2(b) that $\mathcal{R}_0^H$ decreases if δ increases or β_H decreases. However, it is difficult to control β_H. Figure 2(c) shows the effects of δ and $1 - \omega$ on the basic reproduction ratio $\mathcal{R}_0^H$ when $\beta_H = 5$. As expected, $\mathcal{R}_0^H$ might be smaller than 1 as long as δ and $1 - \omega$ are large enough. Therefore, immunization of both newborns and susceptible individuals is an efficient intervention. Thus, combining immunization with reduction of contacts can reduce $\mathcal{R}_0^H$ to be less than 1. Then, the optimal control strategy will be a combination of immunization of newborns, immunization of susceptible individuals (at least young adults), and reduction of contacts.
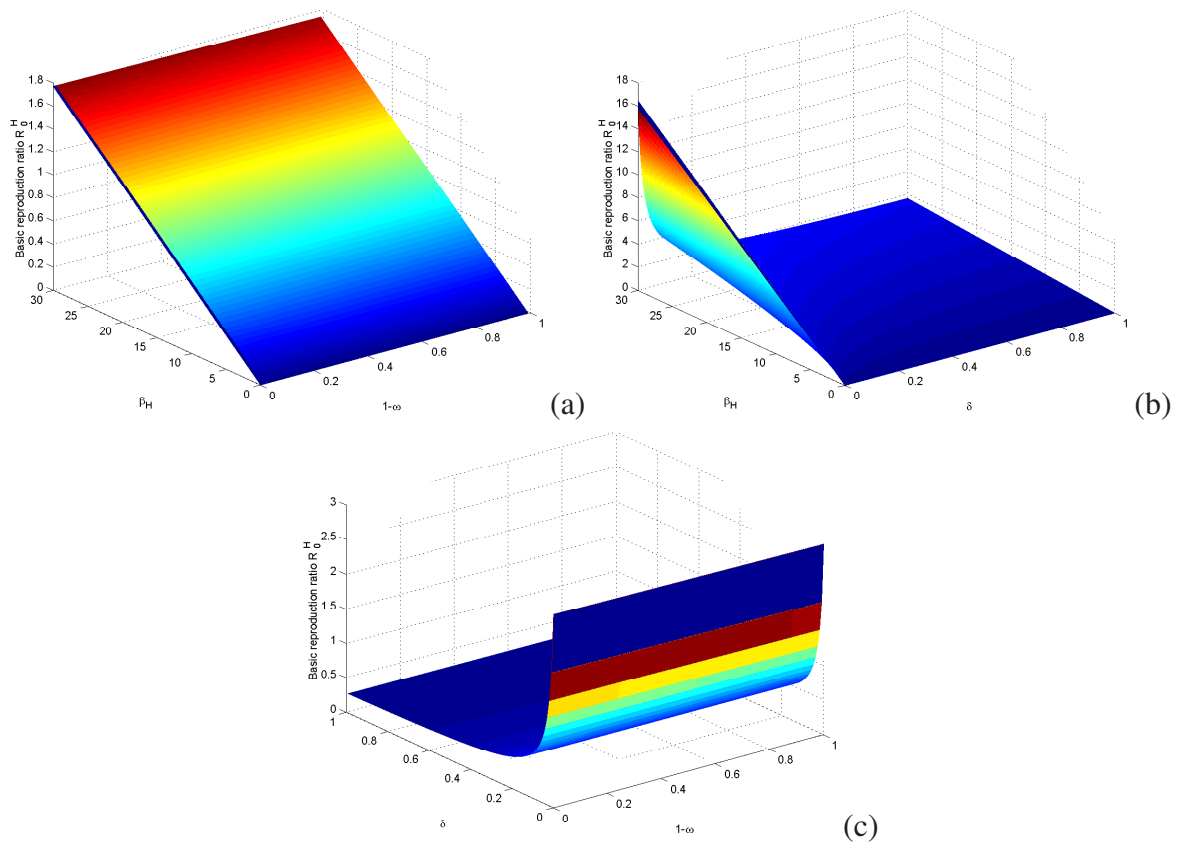
Figure 2: Graphs of the basic reproduction ratio $\mathcal{R}_0^H$ of system (3.1) in dependence on some parameters: (a) $\mathcal{R}_0^H$ in terms of $1 - \omega$ and β_H, (b) $\mathcal{R}_0^H$ in terms of δ and β_H, and (c) $\mathcal{R}_0^H$ in terms of $1 - \omega$ and δ when $\beta_H = 5$. All other parameters are as in Table 3.

3.1.2. Global stability of DFE of the HBV-only model

We get the following result concerning the stability of the DFE Q_0^H of system (3.1).

Theorem 2. *The DFE of system (3.1), given by Q_0^H, is globally-asymptotically stable (GAS) in Ω_H whenever $\mathcal{R}_0^H \leq 1$.*

Proof: Consider the following LaSalle-Lyapunov candidate function:

$$\mathcal{L}(I_H, C_H) = a_1 I_H + a_2 C_H, \tag{3.6}$$

where

$$a_1 = A \qquad \text{and} \qquad a_2 = \frac{\beta_H \eta [\pi_H V_0 + (1-\delta)S_0]}{S_0 + V_0}.$$

Its time derivative along the trajectories of system (3.1) satisfies

$$
\begin{aligned}
\dot{\mathcal{L}} &= a_1 \dot{I}_H + a_2 \dot{C}_H \\
&= a_1 \left(\frac{\beta_H [\pi_H V + (1-\delta)S]}{N}(I_H + \eta C_H) - (\mu_0 + \gamma_1) I_H \right) + a_2(q\gamma_1 I_H - A C_H).
\end{aligned}
\tag{3.7}
$$

Since the state variables of the model when the HBV is endemic in the population do not exceed the state variables of the model in a population free of HBV, one has that $\dfrac{[\pi_H V + (1-\delta)S]}{N} \leq \dfrac{[\pi_H V_0 + (1-\delta)S_0]}{S_0 + V_0}$, one has

$$
\begin{aligned}
\dot{\mathcal{L}} &\leq \left(\frac{a_1 \beta_H [\pi_H V_0 + (1-\delta)S_0]}{S_0 + V_0} - a_1(\mu_0 + \gamma_1) + a_2 q\gamma_1 \right) I_H \\
&+ \left(\frac{a_1 \beta_H \eta [\pi_H V_0 + (1-\delta)S_0]}{S_0 + V_0} - a_2 A \right) C_H.
\end{aligned}
\tag{3.8}
$$

Now, plugging the positive constants a_1 and a_2 given in Eq. (3.6) into Eq. (3.8), one finally obtains

$$
\begin{aligned}
\dot{\mathcal{L}} &\leq \left(\frac{\beta_H(A + \eta q\gamma_1)[\pi_H V_0 + (1-\delta)S_0]}{S_0 + V_0} - A(\mu_0 + \gamma_1) \right) I_H, \\
&\leq A(\mu_0 + \gamma_1) \left(\frac{\beta_H(A + \eta q\gamma_1)[\pi_H V_0 + (1-\delta)S_0]}{A(S_0 + V_0)(\mu_0 + \gamma_1)} - 1 \right) I_H, \\
&\leq A(\mu_0 + \gamma_1)(\mathcal{R}_0^H - 1) I_H.
\end{aligned}
\tag{3.9}
$$

Thus, $\dot{\mathcal{L}} \leq 0$ when $\mathcal{R}_0^H \leq 1$. By LaSalle's invariance principle, the largest invariant set in Ω_H contained in $\{(S, V, I_H, C_H, R_H) \in \mathbb{R}_{\geq 0}^5 \quad \dot{\mathcal{L}} = 0\}$ is reduced to the DFE. This proves the global asymptotic stability on Ω_H ([55, Theorem 3.7.11, page 346]). Since Ω_H is absorbing, this proves

the global asymptotic stability on the nonnegative orthant when $\mathcal{R}_0^H \leq 1$. We stress the need to consider a positively invariant compact set to establish the stability of the DFE since the function $\mathcal{L}$ is not positive definite. Generally the LaSalle's invariance principle only proves the attractivity of the equilibrium. Considering Ω_H permits us to conclude for the stability [53-55]. This fact is often overlooked in the literature using the LaSalle's invariance principle. This concludes the proof.

□

Figure 3 shows simulation results converging to the disease free equilibrium for the total number of HBV infected individuals using various initial conditions when $\beta_H = 10$ (so that $\mathcal{R}_0^H = 0.5805$). All other parameters are as in Table 3. This result shows that HBV can be eliminated from the community if the associated threshold quantity, $\mathcal{R}_0^H$, can be brought to a value less than unity.
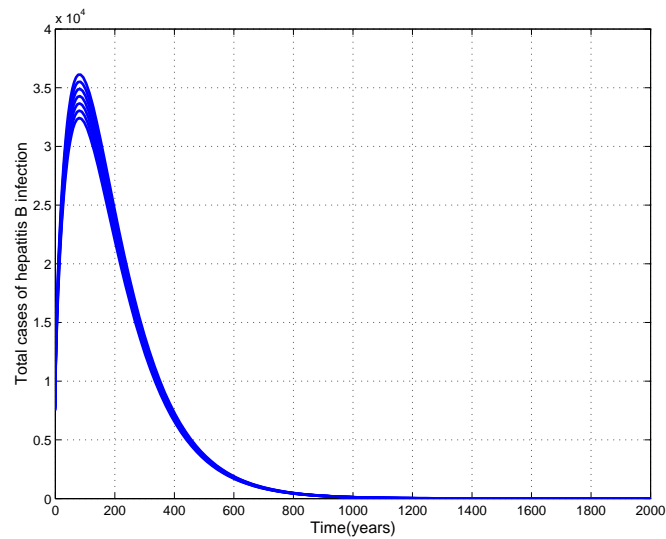
Figure 3: Time series of HBV-only model (3.1) showing the total number of the HBV infected individuals as a function of time, using various initial conditions for $\beta_H = 10$ (so that $\mathcal{R}_0^H = 0.5805$). All other parameters are as in Table 3.

3.1.3. Existence and stability of the endemic equilibrium

Because R_H appears only in the fifth equation of the model, we can discuss the steady states without this variable. To find conditions for the existence of an endemic equilibrium for which HBV is endemic in the population (i.e., at least one of I_H^* and C_H^* is non-zero), denoted by $Q_H^* = (S_H^*, V_H^*, I_H^*, C_H^*)$, equations in (3.1) are solved in terms of the force of infection at the steady-state (λ_H^*) yields

$$\lambda_H^* = \frac{\beta_H(I_H^* + \eta C_H^*)}{N_H^*}. \tag{3.10}$$

Setting the right hand sides of the model to zero (and noting that $\lambda_H = \lambda_H^*$ at equilibrium) gives

$$
\begin{cases}
\Lambda + \mu\omega(1 - vC_H^*) - (1 - \delta)\lambda_H^* S_H^* - (\delta + \mu_0)S_H^* = 0, \\[2mm]
\mu(1 - \omega) + \delta S_H^* - \pi_H \lambda_H^* V^* - \mu_0 V^* = 0, \\[2mm]
(\pi_H V_H^* + (1 - \delta)S_H^*)\lambda_H^* - (\mu_0 + \gamma_1)I_H^* = 0, \\[2mm]
\mu\omega v C_H^* + q\gamma_1 I_H^* - (\mu_0 + d_H + \gamma_2)C_H^* = 0.
\end{cases}
\tag{3.11}
$$

Solving the above equations in (3.11) at steady state gives

$$
\begin{cases}
I_H^* = \dfrac{A(\Lambda + \mu)\lambda_H^*}{\beta_H \mu_0(A + \eta q\gamma_1) + d_H q\gamma_1 \lambda_H^*}, \\[4mm]
C_H^* = \dfrac{q\gamma_1(\Lambda + \mu)\lambda_H^*}{\beta_H \mu_0(A + \eta q\gamma_1) + d_H q\gamma_1 \lambda_H^*}, \\[4mm]
S_H^* = \dfrac{1}{(1 - \delta)\lambda_H^* + \delta + \mu_0}\left[\Lambda + \mu\omega\left(1 - \dfrac{q\gamma_1 v(\Lambda + \mu)\lambda_H^*}{\beta_H \mu_0(A + \eta q\gamma_1) + d_H q\gamma_1 \lambda_H^*}\right)\right], \\[4mm]
V_H^* = \dfrac{1}{\pi_H \lambda_H^* + \mu_0}\left[\mu(1 - \omega)\right. \\[4mm]
\quad + \left. \dfrac{\delta}{(1 - \delta)\lambda_H^* + \delta + \mu_0}\left[\Lambda + \mu\omega\left(1 - \dfrac{q\gamma_1 v(\Lambda + \mu)\lambda_H^*}{\beta_H \mu_0(A + \eta q\gamma_1) + d_H q\gamma_1 \lambda_H^*}\right)\right]\right].
\end{cases}
\tag{3.12}
$$

Substituting (3.12) in (3.10), it can be shown that the non-zero equilibria of system (3.1) satisfy the following quadratic equation in term of λ_H^*:

$$
b_2(\lambda_H^*)^2 + b_1 \lambda_H^* + b_0 = 0,
\tag{3.13}
$$

where

$$
\begin{aligned}
b_2 &= (1 - \delta)(\Lambda + \mu)[\pi_H[A(\mu_0 + \gamma_1) - d_H q\gamma_1] + \mu\omega v q\gamma_1(1 - \delta)], \\[2mm]
b_1 &= -\pi_H \mu(1 - \omega)[\beta_H \mu_0(1 - \delta)(A + \eta q\gamma_1) + d_H q\gamma_1(\mu_0 + \delta)], \\[2mm]
&\quad - d_H q\gamma_1 \pi_H \delta(\Lambda + \mu\omega) + \pi_H \delta\mu v q\gamma_1(\Lambda + \mu) \\[2mm]
&\quad - (1 - \delta)(\Lambda + \mu\omega)[\pi_H \beta_H \mu_0(A + \eta q\gamma_1) + \mu_0 d_H q\gamma_1] \\[2mm]
&\quad + \mu\omega v q\gamma_1(1 - \delta)(\mu_0 + \delta)(\Lambda + \mu) \\[2mm]
&\quad + A(\mu_0 + \gamma_1)(\Lambda + \mu)[\pi_H(\mu_0 + \delta) + \mu_0(1 - \delta)], \\[2mm]
b_0 &= A\mu_0(\mu_0 + \gamma_1)(\mu_0 + \delta)(\Lambda + \mu)(1 - \mathcal{R}_0^H).
\end{aligned}
$$

It is worth noting that the coefficient b_2 is always positive and b_0 is positive if $\mathcal{R}_0^H$ is less than unity, and negative if $\mathcal{R}_0^H$ is greater than unity. Thus, the number of possible real roots of Eq. (3.13) can have depends on the signs of b_2, b_1 and b_0. This can be analyzed using the Descartes Rule of Signs on the polynomial

$$f(\lambda_H^*) = b_2(\lambda_H^*)^2 + b_1\lambda_H^* + b_0. \tag{3.14}$$

Since $\lambda_H^* \in [0, \beta_H(1 + \eta)]$, one can easily verify that

$$f(0) \quad = \quad b_0 = A\mu_0(\mu_0 + \gamma_1)(\mu_0 + \delta)(\Lambda + \mu)(1 - \mathcal{R}_0^H),$$

$$f(\beta_H(1 + \eta)) \quad = \quad b_2(\beta_H(1 + \eta))^2 + b_1(\beta_H(1 + \eta)) + b_0.$$

A simple calculation proves that $f(\beta_H(1 + \eta) > 0$. It is now a trivial matter to see that $f(0) < 0$ when $\mathcal{R}_0^H > 1$. The existence follows from the intermediate value theorem. Now, $f(\lambda_H^*)$ is monotone increasing , so that $f(\lambda_H^*) = 0$ has only one positive root in the interval $[0, \beta_H(1 + \eta)]$. Thus, we have established the following result.

Lemma 3. *When $\mathcal{R}_0^H > 1$, the model (3.1) has a unique endemic equilibrium $Q_H^* = (S_H^*, V_H^*, I_H^*, C_H^*, R_H^*)$ with $S_H^*, V_H^*, I_H^*, C_H^*$ and R_H^* all nonnegative.*

Now, let us study the stability of the endemic equilibrium guaranteed by Lemma 3. Using standard linearization of the HBV-only model around the endemic equilibrium is laborious and not really tractable mathematically. Here, the center manifold theory [56], as described in [57] (Theorem 4.1), will be used to establish the local asymptotic stability of the endemic equilibrium (see also [52, 58]).

Then, we claim the following result (the proof is given in Appendix A):

Lemma 4. *The unique endemic equilibrium guaranteed by Lemma 3 is LAS for $\mathcal{R}_0^H$ near 1.*

It should be pointed out that this result holds for $\mathcal{R}_0^H > 1$ but close to 1.

Figure 4 shows convergence to the endemic equilibrium for the total number of infected individuals using various initial conditions when $\beta_H = 20$ (so that $\mathcal{R}_0^H = 1.1609$). All other parameters are as in Table 3.

In summary, the HBV-only model (3.1) has a globally-asymptotically stable DFE whenever $\mathcal{R}_0^H \leq 1$, and a unique endemic equilibrium point whenever $\mathcal{R}_0^H > 1$. The unique endemic equilibrium point is LAS at least near $\mathcal{R}_0^H = 1$. The dynamics of TB-only is also explored as below.

3.2. TB-only sub-model

The high prevalence of tuberculosis in developing countries and recent resurgence of tuberculosis in many developed countries suggest that current control strategies are suboptimal. More than 36 million patients have been successfully treated via the World Health Organization strategy for tuberculosis control since 1995. Despite predictions of a decline in global incidence, the number of new cases continues to grow, approaching 10 million in 2010 [1, 2]. This rise has been attributed
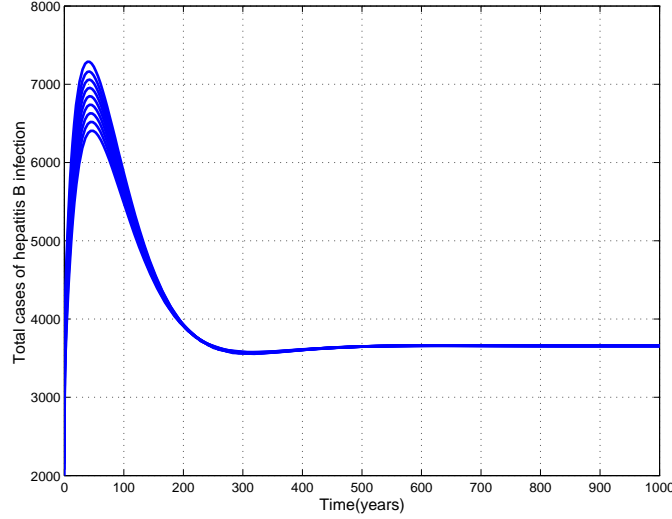
Figure 4: Time series of HBV-only model (3.1) showing the total number of infected individuals as a function of time, using various initial conditions for $\beta_H = 20$ (so that $\mathcal{R}_0^H = 1.1609$). All other parameters are as in Table 3.

to the spread of HIV, the collapse of public health programs and the emergence of drug-resistant strains of *M. tuberculosis*. Another issue that is essential to the epidemiology of TB is the exogenous re-infection, where a latently-infected individual acquires a new infection from another infectious (see [34, 61] and references therein).

The TB-only model is obtained by setting $V = I_H = C_H = R_H = E_{TI} = I_{TI} = E_{TC} = I_{TC} = E_{TR} = I_{TR} = 0$ and $\delta = \omega = 0$, which gives,

$$\begin{cases} \dot{S} &=& \Lambda - \lambda_T S - \mu_0 S, \\[2mm] \dot{E}_T &=& (1-p)\lambda_T S + r_2 I_T - (1-r_1)\sigma\lambda_T E_T - [\mu_0 + k(1-r_1)]E_T, \\[2mm] \dot{I}_T &=& p\lambda_T S + (1-r_1)(k + \sigma\lambda_T)E_T - (\mu_0 + d_T + r_2)I_T, \end{cases} \quad (3.15)$$

where $\lambda_T = \beta_T \dfrac{I_T}{N}$ and $N = S + E_T + I_T$. Note that since the population is free of HBV, there is no HBV infected individuals who can transmit HBV infection to susceptible individuals. Therefore, it is not necessary to vaccine people with respect to HBV. So, in this case, one has $\delta = \omega = 0$. We point out that the TB-only model (3.15) is an extension of the model proposed by Kirchner et al. [66], which, in our opinion, captures the essentials of *Mycobacterium tuberculosis* transmission. In our model, exogenous reinfections have been take into account.

The feasible region for this sub-model is

$$\Omega_T = \left\{ (S, E_T, I_T) \in \mathbb{R}^3_{\geq 0}, \quad N(t) \leq \frac{\Lambda}{\mu_0} \right\}. \quad (3.16)$$

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Likewise Ω_H above, it can be shown that all solutions of system (3.15) starting in Ω_T remain in Ω_T for all $t \geq 0$. Thus, Ω_T is positively invariant (hence, it is sufficient to consider the dynamics of (3.15) in Ω_T).

3.2.1.   Local stability of the DFE of the TB-only model

The TB-only model (3.15) has a DFE given by

$$Q_0^T = \left(\frac{\Lambda}{\mu_0}, 0, 0 \right).$$

The stability of this equilibrium will be investigated using the next generation operator method [51, 52]. Using the notations in [52] on system (3.15), the matrices F and V, for the new infection terms and the remaining transfer terms are, respectively, given by

$$F = \left[\begin{array}{cc} 0 & \beta_T(1-p) \\ 0 & \beta_T p \end{array} \right] \qquad \text{and} \qquad V = \left[\begin{array}{cc} A_1 & -r_2 \\ -k(1-r_1) & A_2 \end{array} \right],$$

where $A_1 = \mu_0 + k(1-r_1)$ and $A_2 = \mu_0 + d_T + r_2$. The spectral radius or the largest eigenvalue of its next generation operator is given by

$$\mathcal{R}_0^T = \frac{\beta_T[p\mu_0 + k(1-r_1)]}{\mu_0(\mu_0 + d_T + r_2) + k(1-r_1)(\mu_0 + d_T)}. \tag{3.17}$$

Thus, from Theorem 2 in [52], the following result holds.

Lemma 5. *The DFE of the TB-only model given by the subsystem (3.15) is LAS if $\mathcal{R}_0^T < 1$, and unstable if $\mathcal{R}_0^T > 1$.*

Now let us analyze the basic reproduction ratio $\mathcal{R}_0^T$. The objective here is to determine, using the threshold quantity $\mathcal{R}_0^T$, whether or not chemoprophylaxis of latently infected individuals and treatment of infectious lead to an effective control or elimination of TB in the population. Figure 5 shows the effects of the chemoprophylaxis rate r_1 and the treatment rate r_2 on the basic reproduction ratio $\mathcal{R}_0^T$ when $\beta_T = 0.5$. All other parameters are as in Table 3. As expected, when r_1 is fixed, the basic reproduction ratio, $\mathcal{R}_0^T$, decreases as r_2 increases and vice versa. Then, combining the chemoprophylaxis of latently infected individuals and treatment of infectious can reduced $\mathcal{R}_0^T$ to less than unity. Therefore, the best control strategy will be the chemoprophylaxis of latently infected individuals and treatment of infectious or a combinaison of chemoprophylaxis and treatment.

The threshold quantity $\mathcal{R}_0^T$ is the reproduction number for TB. Biologically speaking, Lemma 4 implies that TB can be eliminated from the community (when $\mathcal{R}_0^T < 1$) if the initial size of the sub-populations of the model is in the basin of attraction of Q_0^T. Since TB models may undergo the phenomenon of backward bifurcation (see [58] and references therein), it is instructive to determine whether the present sub-model exhibits this phenomenon.
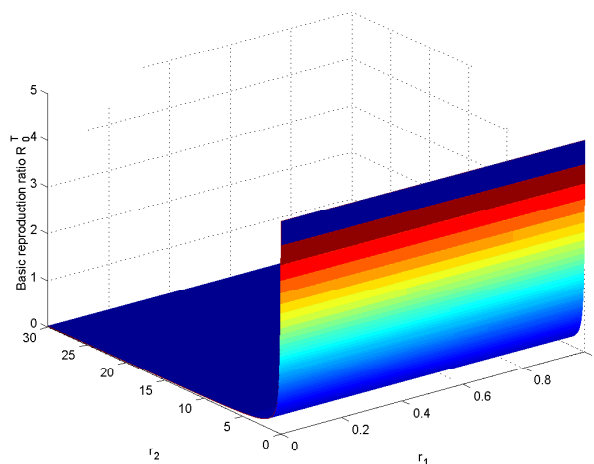
Figure 5: Graphs of the basic reproduction ratio $\mathcal{R}_0^T$ of system (3.15) in terms of r_1 and r_2 when $\beta_T = 0.5$. All other parameters are as in Table 3.

3.2.2.   Existence of backward bifurcation

System (3.15) has one disease-free equilibrium, $Q_0^T = (S_0, \, 0, \, 0)$ and one or two endemic equilibria of the form $Q_T^* = (S_T^*, E_T^*, I_T^*)$. On the other hand, from Lemma 4, the DFE of the TB-only model is locally asymptotically stable (LAS) if $\mathcal{R}_0^T < 1$. However, this equilibrium may not be globally asymptotically stable (GAS) in Ω_T for $\mathcal{R}_0^T < 1$, owing to the possibility of backward bifurcation, where the stable DFE co-exists with a stable endemic equilibrium when $\mathcal{R}_0^T < 1$ (see for instance [58-65]) and references therein). In general, substitution of standard incidence with mass action incidence in some differential models removes their backward bifurcation property [63]. The standard incidence together with a large disease induced death rate are the driving force herein. The public health implication of backward bifurcation is that the classical requirement of having the basic reproductive number less than unity, although necessary, is no longer sufficient for curtailing the outbreak of the disease [64]. The possibility of this phenomenon in (3.15) is investigated below. Solving the TB-only model at an arbitrary equilibrium $Q_T^* = (S_T^*, E_T^*, I_T^*)$ gives

$$
\begin{cases}
\Lambda - \lambda_T^* S^* - \mu_0 S_T^* = 0, \\[2mm]
(1-p)\lambda_T^* S^* - \sigma(1-r_1)\lambda_T^* E_T^* + r_2 I_T^* - A_1 E_T^* = 0, \\[2mm]
p\lambda_T^* S^* + \sigma(1-r_1)\lambda_T^* E_T^* + k(1-r_1)E_T^* - A_2 I_T^* = 0,
\end{cases}
\tag{3.18}
$$

where A_1 and A_2 are defined as in Eq. (3.17), and

$$
\lambda_T^* = \beta_T \frac{I_T^*}{N^*},
\tag{3.19}
$$

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is the force of infection at the steady state. Solving the equations in (3.18) at the steady state gives

$$
\begin{aligned}
S_T^* &= \frac{\Lambda}{\mu_0 + \lambda_T^*}, \\[2mm]
E_T^* &= \frac{\lambda_T^* S^*[(1-p)A_2 + r_2 p]}{A_1 A_2 - r_2 k(1-r_1) + \sigma(1-r_1)(A_2 - r_2)\lambda_T^*}, \\[2mm]
I_T^* &= \frac{\lambda_T^* S^*[(1-p)k(1-r_1) + pA_1 + \sigma(1-r_1)\lambda_T^*]}{A_1 A_2 - r_2 k(1-r_1) + \sigma(1-r_1)(A_2 - r_2)\lambda_T^*}.
\end{aligned}
\tag{3.20}
$$

Substituting the expressions in (3.20) in Eq. (3.19), it can be shown that the non-zero equilibria of the system (3.15) satisfy the following quadratic equation in term of λ_T^*:

$$
c_2(\lambda_T^*)^2 + c_1(\lambda_T^*) + c_0 = 0,
\tag{3.21}
$$

where

$$
\begin{aligned}
c_2 &= \sigma(1 - r_1), \\[2mm]
c_1 &= \sigma(1 - r_1)(\mu_0 + d_T - \beta_T) + (1-p)(\mu_0 + d_T) + r_2 + p\mu_0 + k(1 - r_1), \\[2mm]
c_0 &= [[\mu_0 + k(1 - r_1)](\mu_0 + d_T) + r_2\mu_0](1 - \mathcal{R}_0^T).
\end{aligned}
$$

Thus, positive endemic equilibria Q_T^* are obtained by solving for λ_T^* from the quadratic equation (3.21) and substituting the result (positive values of λ_T^*) into (3.19). Clearly, the coefficient c_2 of Eq. (3.21) is always positive, and c_0 is positive or negative if $\mathcal{R}_0^T$ is less than or greater than unity, respectively. Thus, the number of possible real roots of the polynomial (3.21) can have depends on the signs of c_2, c_1 and c_0. Then, the following result holds:

Lemma 6. *System (3.15) with TB alone has*
(i) a unique endemic equilibrium when $c_0 < 0$, i.e., $\mathcal{R}_0^T > 1$;
(ii) a unique endemic equilibrium when $c_1 < 0$, and $c_0 = 0$ or $c_1^2 - 4c_2c_0 = 0$,
(iii) two endemic equilibria when $c_0 > 0$, $c_1 < 0$ and $c_1^2 - 4c_2c_0 > 0$;
(iv) no endemic equilibria in all other cases.

It should be pointed out that the case (iii) indicates the possibility of a backward bifurcation phenomenon (where locally asymptotically stable DFE co-exists with a locally asymptotically stable endemic equilibrium when $\mathcal{R}_0^T < 1$, (see for instance, [58-64]) in system (3.15) with TB alone. To check this, the discriminant $c_1^2 - 4c_2c_0$ is set to zero and solved for the critical value of $\mathcal{R}_0^T$, denoted by $\mathcal{R}_c^T$, given by

$$
\mathcal{R}_c^T = 1 - \frac{c_1^2}{4c_2\mathcal{R}^*}.
\tag{3.22}
$$

where

$$
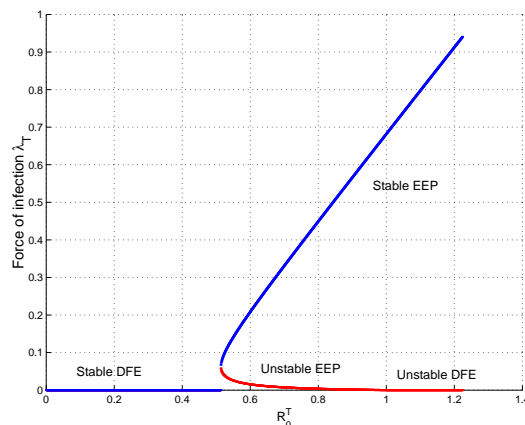\mathcal{R}^* = \mu_0(\mu_0 + d_T + r_2) + k(1 - r_1)(\mu_0 + d_T).
$$

Figure 6: Bifurcation diagram for the model (3.15) where the notation EEP stands for endemic equilibrium point. All other parameters are as in Table 1.

The associated backward bifurcation diagram is depicted in Fig. 6.

The backward bifurcation phenomenon is also illustrated by simulating the system (3.15) with different initial conditions, parameters of Table 3 and $\beta_T = 1$ (so that $\mathcal{R}_0^T = 0.8733$). Figure 7 shows the convergence to both the disease-free equilibrium and the endemic equilibrium for the trajectories of system (3.15) when $\mathcal{R}_0^T < 1$. In other words, from this figure, the profiles can converge to either the disease free equilibrium or an endemic equilibrium point, depending on the initial sizes of the population of the model (owing to the phenomenon of backward bifurcation).

Finally, it is worth stating that, unlike in the HBV-only model, the DFE of the TB-only model (Q_0^T) is not globally-asymptotically stable when the associated reproductive number ($\mathcal{R}_0^T$) is less than unity, owing to the phenomenon of backward bifurcation. Consequently, this study shows that the control of TB spread in a population when $\mathcal{R}_0^T < 1$ depends on the initial sizes of the sub-populations of the TB-only model (3.15).

4.   Analysis of the full HBV-TB model

Having analyzed the dynamics of the two sub-models, that is HBV-only and TB-only models, the full HBV-TB model (2.4) is now considered (the analysis is done in the positively invariant region Ω).

4.1.   Local stability of the disease-free equilibrium

The HBV-TB model (2.4) has a DFE given by

$$Q_0 = \left(S_0, \quad V_0, \ 0, \ 0, \ 0, \ 0, \ 0, \ 0, \ 0, \ 0, \ 0, \ 0, \ 0\right).$$

where

$$S_0 = \frac{\Lambda + \mu\omega}{\mu_0 + \delta} \qquad \text{and} \qquad V_0 = \frac{\delta(\mu + \Lambda) + \mu\mu_0(1 - \omega)}{\mu_0(\mu_0 + \delta)}.$$
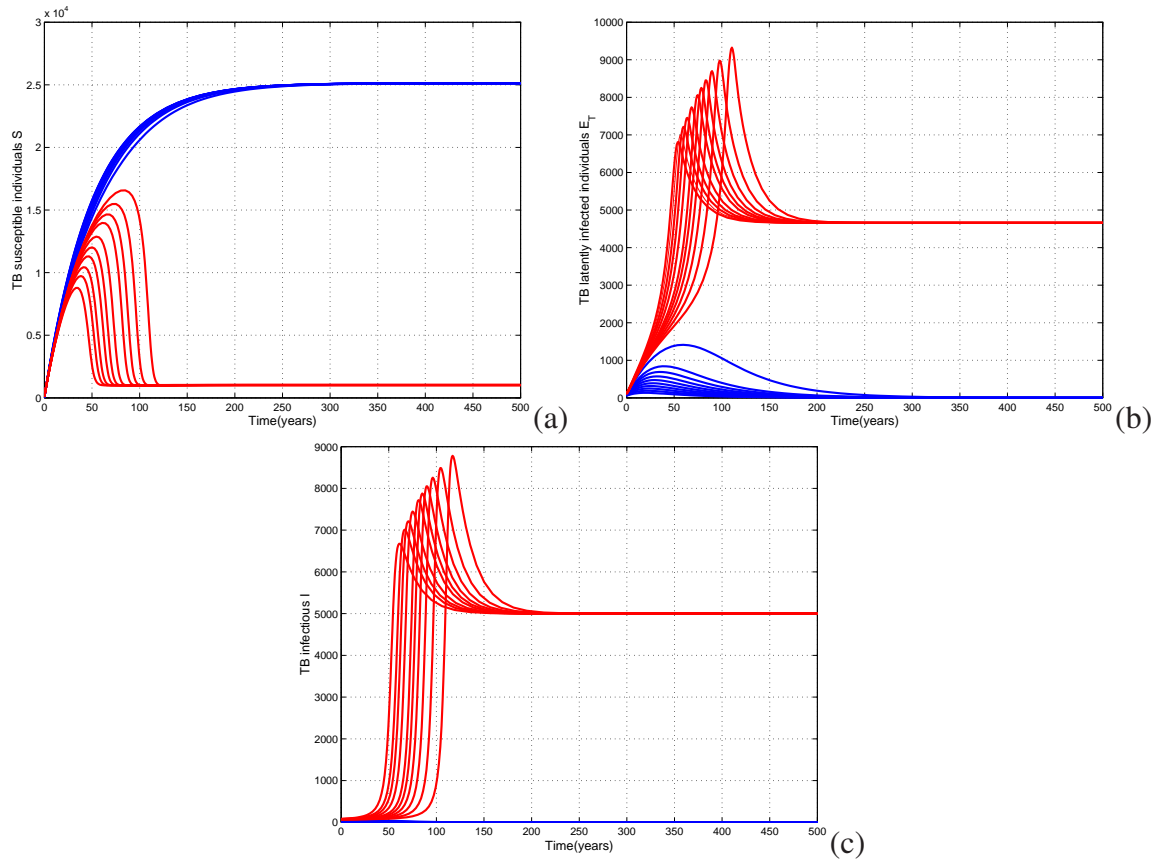
Figure 7: Simulation of system (3.15). Time series of (a) susceptible individuals, (b) latently infected individuals and (c) infectious when $\beta_T = 1$ (so that $\mathcal{R}_0^T = 0.8733$). All other parameters are as in Table 3.

The spectral radii of the next generation matrix FV^{-1} are independent and given in terms of HBV and TB-only associated reproduction numbers (see details in Appendix B). It is therefore evident that the associated reproduction number for the full HBV-TB model denoted by $\mathcal{R}_0$ is given by

$$\mathcal{R}_0 = \max\{\mathcal{R}_H^T, \mathcal{R}_0^H\}, \tag{4.1}$$

where

$$\mathcal{R}_0^H = \frac{\beta_H(A + \eta q \gamma_1)[\pi_H[\delta(\mu + \Lambda) + \mu\mu_0(1-\omega)] + \mu_0(1-\delta)(\Lambda + \mu\omega)]}{A(\mu_0 + \delta)(\mu_0 + \gamma_1)(\Lambda + \mu)},$$

$$\mathcal{R}_H^T = \frac{\beta_T[f\mu_0 + k(1-r_1)]V_0}{(S_0 + V_0)[\mu_0(\mu_0 + d_T + r_2) + k(1-r_1)(\mu_0 + d_T)]} + \frac{(1-\delta)S_0}{S_0 + V_0}\mathcal{R}_0^T, \tag{4.2}$$

with $\mathcal{R}_0^T$ the basic reproduction ratio of the TB-only model defined in Eq. (3.17).

$\mathcal{R}_H^T$ gives the number of secondary TB infectious cases produced by a TB infectious individual during his or her effective infectious period when introduced in a population of mostly TB sus-

ceptible. $\mathcal{R}_0^H$ is the HBV reproduction number in the absence of TB, which gives the number of secondary HBV acute or chronic individuals produced by an HBV acute or chronic individual (but not infected with TB) during his or her infectious period when introduced in a population of HBV susceptible who have no TB. Note that the reproductive numbers defined above do not involve the parameters associated with individuals who are co-infected with both TB and HBV. But, from Eq. (4.2), one can see that the basic reproduction ratio $\mathcal{R}_H^T$ depends on the parameters δ, ω and μ which are parameters associated with the HBV disease. Additionally, using the expression of $\mathcal{R}_H^T$, it is evident that $\mathcal{R}_H^T \leq \mathcal{R}_0^T$.

A threshold condition for endemicity is given by $\mathcal{R}_0 = 1$: the disease dies out if $\mathcal{R}_0 < 1$, and becomes endemic if $\mathcal{R}_0 > 1$. Then, we can claim the following result.

Lemma 7. *The DFE Q_0 of system (2.4) is LAS if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.*

Figure 8 shows the 3-D plots showing the effects of β_T, $1 - \omega$ and δ on the basic reproduction ratio $\mathcal{R}_H^T$. All other parameters are as in Table 3. It clearly appears that $\mathcal{R}_H^T$ decreases when β_T decreases even if $1 - \omega$ or δ has a large value. But, if the transmission coefficient β_T is sufficiently small, TB could be eliminated even if $1 - \omega = 0$ or $\delta = 0$. However, it is difficult to control β_T.
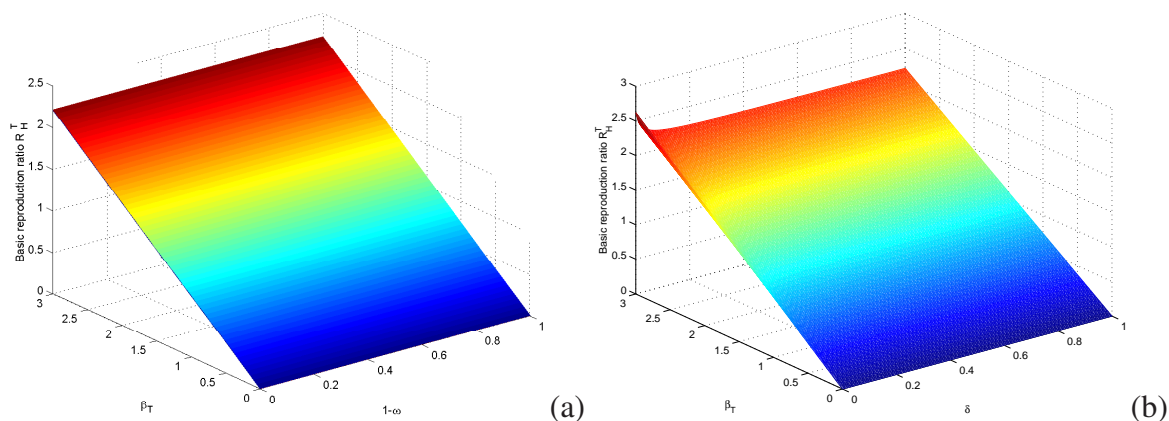

Figure 8: Graphs of the basic reproduction ratio $\mathcal{R}_H^T$ in terms of some parameters. (a) $\mathcal{R}_H^T$ in terms of β_T and $1 - \omega$, and (b) $\mathcal{R}_H^T$ of system (2.4) in terms of β_T and δ. All other parameters are as in Table 3.

It is worth noting that the DFE of the HBV-TB is not GAS, owing to the presence of the TB-induced backward bifurcation. Like in the case of the TB-only model (3.15), the full HBV-TB model (2.4) also undergoes a backward bifurcation phenomenon.

4.1.1. Existence of boundaries equilibria and bifurcation parameter

System (2.4) has three possible nonnegative boundary equilibria on Ω: one disease-free equilibrium, $Q_0 = (S_0, V_0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)$ and one endemic equilibrium of the form $Q_H^* = (S_H^*, V_H^*, I_H^*, C_H^*, R_H^*, 0, 0, 0, 0, 0, 0, 0, 0, 0)$, one or two endemic equilibria of the form $Q_T^* = (S_T^*, 0, 0, 0, 0, E_T^*, I_T^*, 0, 0, 0, 0, 0, 0)$, and

$Q^* = (S^*, V^*, I^*, C^*, R^*, E^*, I_T^*, E_{TI}^*, I_{TI}^*, E_{TC}^*, I_{TC}^*, E_{TR}^*, I_{TR}^*)$, corresponding, respectively, to states where only HBV, only TB, or both HBV/TB are present. HBV-only (TB-free) equilibrium Q_H^* exists if and only if $\mathcal{R}_0^H > 1$ and the number of TB-only (HBV-free) equilibria Q_0^T depends on the threshold parameters $\mathcal{R}_0^T$ and $\mathcal{R}_H^T$. Thus, there exists one TB-only (HBV-free) equilibrium if $\mathcal{R}_0^T > \mathcal{R}_H^T > 1$ or $\mathcal{R}_0^T = 1$ (cases (i) and (ii) of Lemma 6), one or two endemic equilibria if $\mathcal{R}_H^T < \mathcal{R}_0^T < 1$, $c_1 > 0$ and $c_1^2 - 4c_0c_2 > 0$ (case (iii) of Lemma 6)) is satisfied.

The TB-only model is shown to exhibit the phenomenon of backward bifurcation and consequently, the full HBV-TB model will exhibits the same feature. Therefore, we shall only derive the bifurcation parameters for the full model. By computing the eigenvalues of the Jacobian of the full HBV-TB model (2.4), it can be shown that $\mathcal{R}_0 = \max\{\mathcal{R}_H^T, \mathcal{R}_0^H\}$, where $\mathcal{R}_H^T$ and $\mathcal{R}_0^H$ are defined as earlier. $\mathcal{R}_0 = \max\{\mathcal{R}_H^T, \mathcal{R}_0^H\}$, therefore, there is no competitive exclusion and the two diseases enhance each other. Thus, when both reproduction numbers exceed unity (that is, $\mathcal{R}_H^T > 1$ and $\mathcal{R}_0^H > 1$), there is always a co-existence no matter which of the reproduction numbers is greater. Even though $\mathcal{R}_0$ does not combine the two reproduction numbers, it is worth not studying the two diseases in isolation because we will miss the dual HBV-TB only co-infection.

If $\max\{\mathcal{R}_H^T, \mathcal{R}_0^H\} = \mathcal{R}_H^T$, then, from Lemma 6, the HBV-TB model exhibits backward bifurcation for values of $\mathcal{R}_H^T$ less than unity.

The backward bifurcation phenomenon of the full HBV-TB model (2.4) is illustrated by depicting time series plots, based on simulating the model (2.4) with various initial conditions when $\beta_T = 1$ and $\beta_H = 10$ (so that $\mathcal{R}_0^H = 0.5805$, $\mathcal{R}_0^T = 0.8733$, $\mathcal{R}_H^T = 0.7363$ and $\mathcal{R}_0 = 0.7363$). They show convergence to either the DFE (Q_0) or an endemic equilibrium (Figure 9).

Numerical simulations are also carried out to monitor the dynamics of the full model (2.4) using different initial conditions for the case where the associated basic reproduction number $\mathcal{R}_H^T$ does not exceed the unity. The results are reported in Figs. 10-11.

Figure 10 illustrates the solution profiles of the total of new TB cases, new HBV cases and dually-infected cases of the full model (2.4), using various initial conditions. Simulating the model using the parameter values in Table 3 with $\beta_T = 0.1$ and $\beta_H = 10$ (so that $\mathcal{R}_0^H = 0.5805$, $\mathcal{R}_0^T = 0.0873$ and $\mathcal{R}_H^T = 0.0736$) shows convergence to the disease-free equilibrium (Fig. 10), in line with Lemma 7. Then, one can conclude that for smaller values of the $\mathcal{R}_0^H$ and $\mathcal{R}_H^T$, the DFE (Q_0) is LAS. This has been verified via numerical simulations.

Now, we first select $\beta_T = 1$ and $\beta_H = 20$ such that ($\mathcal{R}_0^H = 1.1609$, $\mathcal{R}_0^T = 0.8733$ and $\mathcal{R}_H^T = 0.7363$). This corresponds to $\mathcal{R}_0^H > 1$ and $\mathcal{R}_H^T < 1$. From Fig. 11, one can see that depending on the initial conditions, the trajectories of system (2.4) converge either to the disease-free equilibrium or to the endemic equilibrium. This means that if $\mathcal{R}_0^H > 1$, then it is possible that HBV disappears in the community (i.e., Q_0^H is LAS) and it is also possible that TB becomes prevalent even if $\mathcal{R}_H^T < 1$.

Numerical simulations for the case where the associated basic reproduction number $\mathcal{R}_H^T$ exceeds unity is carried out and depicted in Figs. 12-13. Choosing $\beta_T = 2$ and $\beta_H = 20$ (so that $\mathcal{R}_0^H = 1.1609$, $\mathcal{R}_0^T = 1.7467$ and $\mathcal{R}_H^T = 1.4725$. This corresponds to $\mathcal{R}_0^H > 1$ and $\mathcal{R}_H^T > 1$. From Fig. 12, one can observe the convergence of the trajectories of the full model (2.4) to an endemic equilibrium. As expected, for $\mathcal{R}_0^T$ and $\mathcal{R}_H^T$ greater than unity, there is always co-existence of the two diseases no matter which of the reproduction numbers is greater.
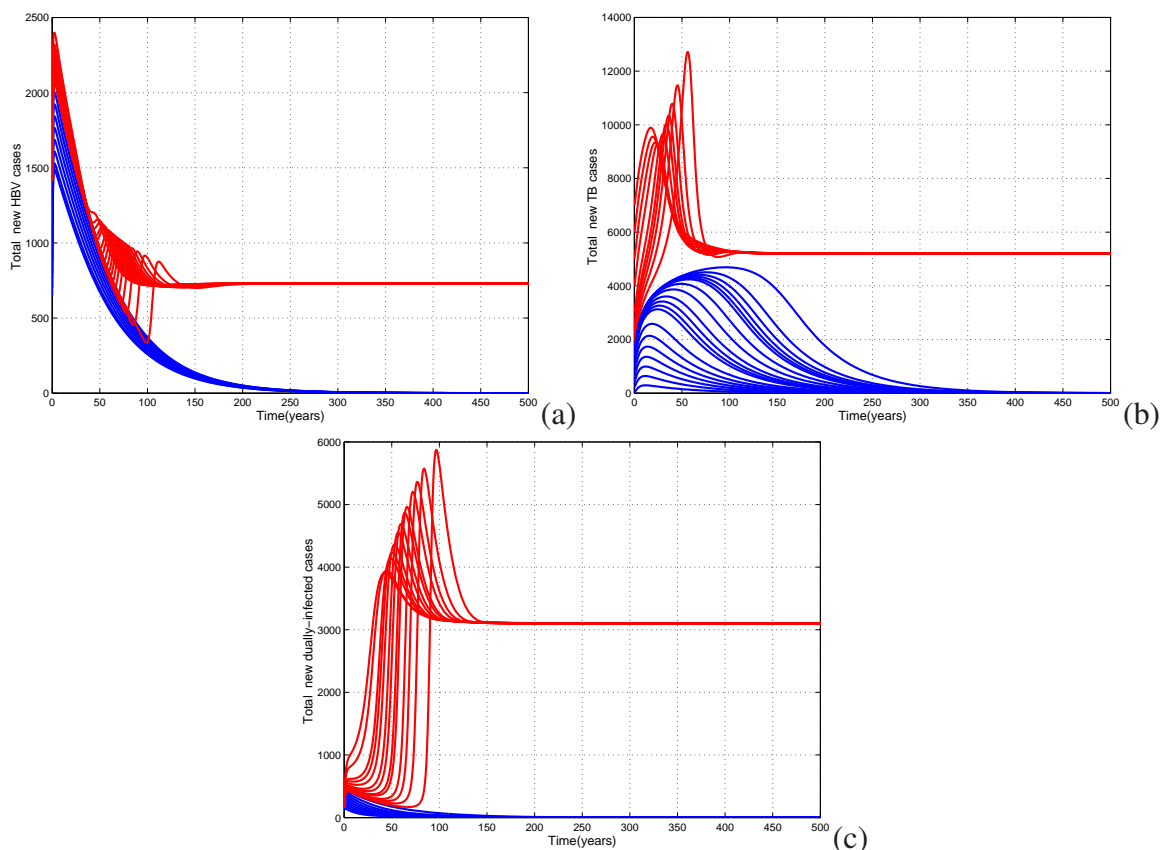
Figure 9: Simulations of the HBV-TB model (2.4) with different initial conditions illustrating the phenomenon of backward bifurcation when $\beta_T = 1$ and $\beta_H = 10$ (so that $\mathcal{R}_0^H = 0.5805$, $\mathcal{R}_0^T = 0.8733$, $\mathcal{R}_H^T = 0.7363$ and $\mathcal{R}_0 = 0.7363$). This corresponds to the case $\mathcal{R}_0^H < \mathcal{R}_H^T < 1$. All other parameters are as in Table 3.

Now, we choose $\beta_T = 2$ and $\beta_H = 10$ (so that $\mathcal{R}_0^H = 0.5805$ and $\mathcal{R}_H^T = 1.4725$. This corresponds to $\mathcal{R}_0^H < 1$ and $\mathcal{R}_H^T > 1$. Numerical results are depicted in Fig. 13. From this figure, it clearly appears that the HBV-free equilibrium is stable. This implies that when $\mathcal{R}_H^T > 1$, then it is possible that HBV becomes prevalent even though it cannot persist in the absence of TB (as $\mathcal{R}_0^H < 1$).

4.1.2. Impact of HBV on the prevalence level of TB infection

In many epidemiological models, the magnitude of the reproduction number is associated with the level of infection. The same is true in the model (2.4). That is, the basic reproduction numbers for TB and HBV infections, $\mathcal{R}_H^T$ and $\mathcal{R}_0^H$ (see Eq. (4.2)), are directly related to the infection levels of the respective diseases (in the absence of the other disease). Thus, we consider the impact of HBV on TB by first examining the effect of k, k_c, k_h and k_r on the prevalence of TB. After, we also examine the effect of σ_c, σ_h and σ_r on the prevalence of TB. The basic reproductive numbers
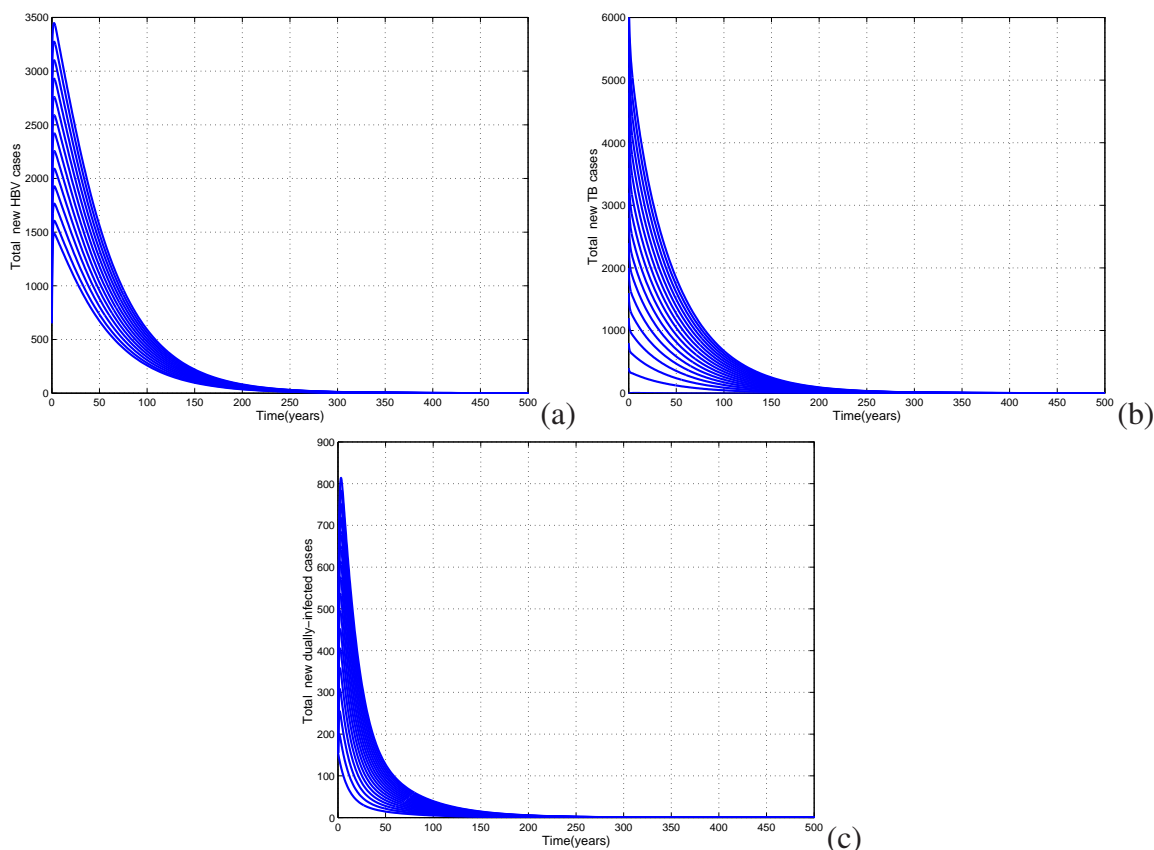
Figure 10: Simulations of the HBV-TB model (2.4) with different initial conditions when $\beta_T = 0.1$ and $\beta_H = 10$ (so that $\mathcal{R}_0^H = 0.5805$, $\mathcal{R}_0^T = 0.0873$ and $\mathcal{R}_H^T = 0.0736$). This corresponds to the case where $\mathcal{R}_H^T < \mathcal{R}_0^H < 1$. All other parameters are as in Table 3.

are the same for both plots: $\mathcal{R}_0^H = 1.609$ ($\beta_H = 20$) and $\mathcal{R}_H^T = 1.4725$ ($\beta_T = 2$). All other parameter values are given in Table 3 except that $r_{2h} = r_{2c} = r_{2r} = 0.5r_2$ (i.e., it takes twice as long to treat a TB infected person with HBV than without). Figure 14 plots the fraction of active TB $(I_T + \varepsilon(I_{TR} + \varepsilon_t I_{TI} + \varepsilon_c I_{TC})/N$ and the fraction of HBV acute and chronic carriers $(I_H + \eta_1(E_{TI} + \eta_{1c} I_{TI}) + \eta(C_H + \eta_2(E_{TC} + \eta_{2c} I_{TC}))/N$.

Figures 14(a) and 14(b) present the results of the numerical simulation for different values of k, k_c, k_h and k_r. It clearly appears that increase the parameters k, k_c, k_h and k_r due to TB has no effect on the prevalence levels of HBV and TB. This illustrates that the assumption $k_c > k_h > k_r > k$ does not automatically lead to an increase in TB prevalence. One of the reasons is that a person with both HBV acute and TB infection (E_{TI} and I_{TI}) may progress at a faster rate ($q_1 > q_2$) to the both HBV chronic and TB infection (E_{TC} and I_{TC}) which is associated with an excess death rate ($d_{2T}, d_{4T} > 0$). Figure 14(c) and 14(d) show the results for different values σ_c, σ_h and σ_r. It shows that the increased the parameters σ_c, σ_h and σ_r due to TB have increased the prevalence level of TB but does not automatically lead to an increase in the HBV prevalence. In summary, conditions $k_c > k_h > k_r > k$ alone may not be sufficient for HBV to have a significant impact on TB.
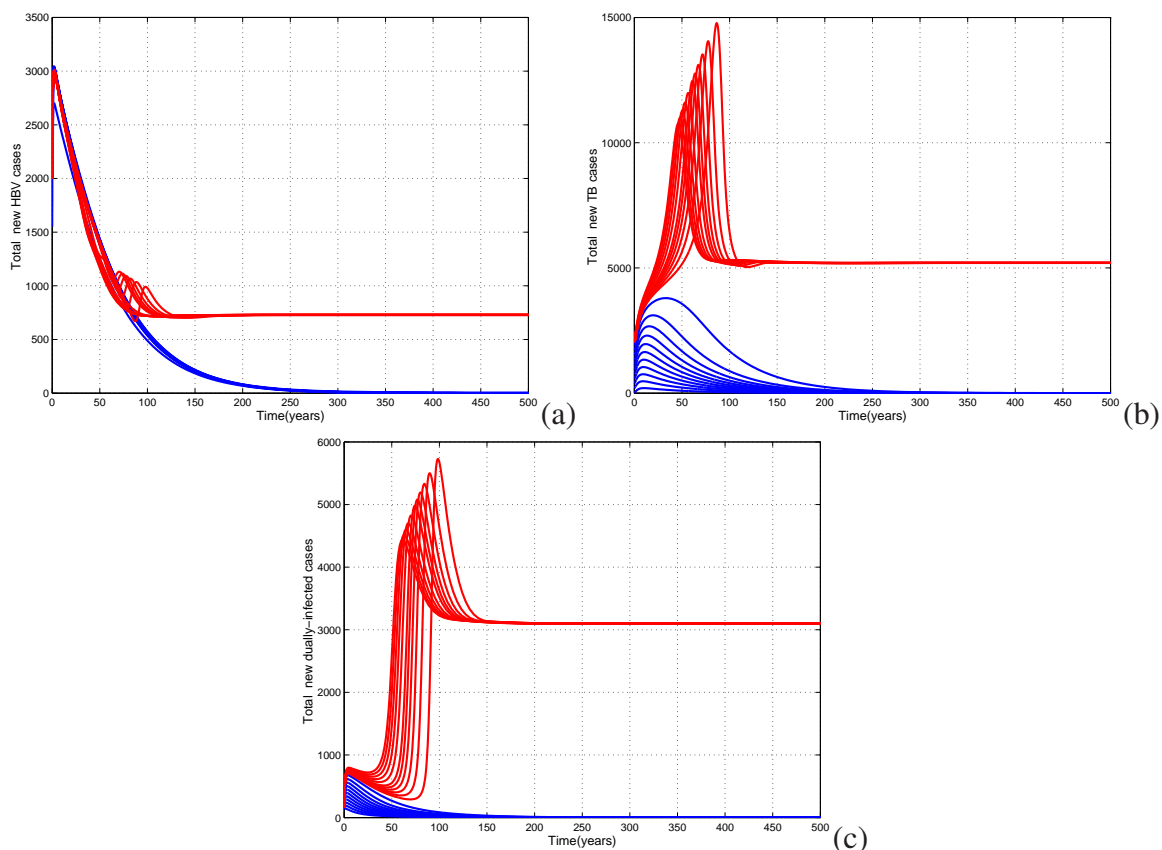
Figure 11: Time plots of trajectories of the HBV-TB model (2.4) with different initial conditions when $\beta_T = 1$ and $\beta_H = 20$ (so that ($\mathcal{R}_0^H = 1.1609$, $\mathcal{R}_0^T = 0.8733$ and $\mathcal{R}_H^T = 0.7363$). This corresponds to $\mathcal{R}_0^H > 1$ and $\mathcal{R}_H^T < 1$. All other parameters are as in Table 3.

Other factors may also play an important role, e.g., the probability that individuals who are also infected with TB in the HBV acute infection fail to clear an acute state and develop a carrier state (q_1 and q_2).

4.1.3. Influence of TB on HBV dynamics

Our numerical simulations also suggest that the presence of TB may have a significant impact on HBV dynamics. Simulation results are demonstrated in Fig. 14. This figure shows time plots of $(I_T + \varepsilon(I_{TR} + \varepsilon_t I_{TI} + \varepsilon_c I_{TC})/N$ (fraction of active TB) and $(I_H + \eta_1(E_{TI} + \eta_{1c}I_{TI}) + \eta(C_H + \eta_2(E_{TC} + \eta_{2c}I_{TC}))/N$ (fraction of HBV acute and chronic carriers) for different values of q, q_1 and q_2 (probability that an individual in the HBV acute infection fail to clear an acute state and develops a carrier state). Other parameter values are the same as in Fig. 14.

Figure 15(a) is for the case of $q = q_1 = q_2$ (i.e., the probability that an individual in the HBV acute infection fail to clear an acute state and develops a carrier state is the same for a person with or without TB infection), while Fig. 15(b) is for the case of $q_1 = 10q$ and $q_2 = 2q$ (i.e., for HBV
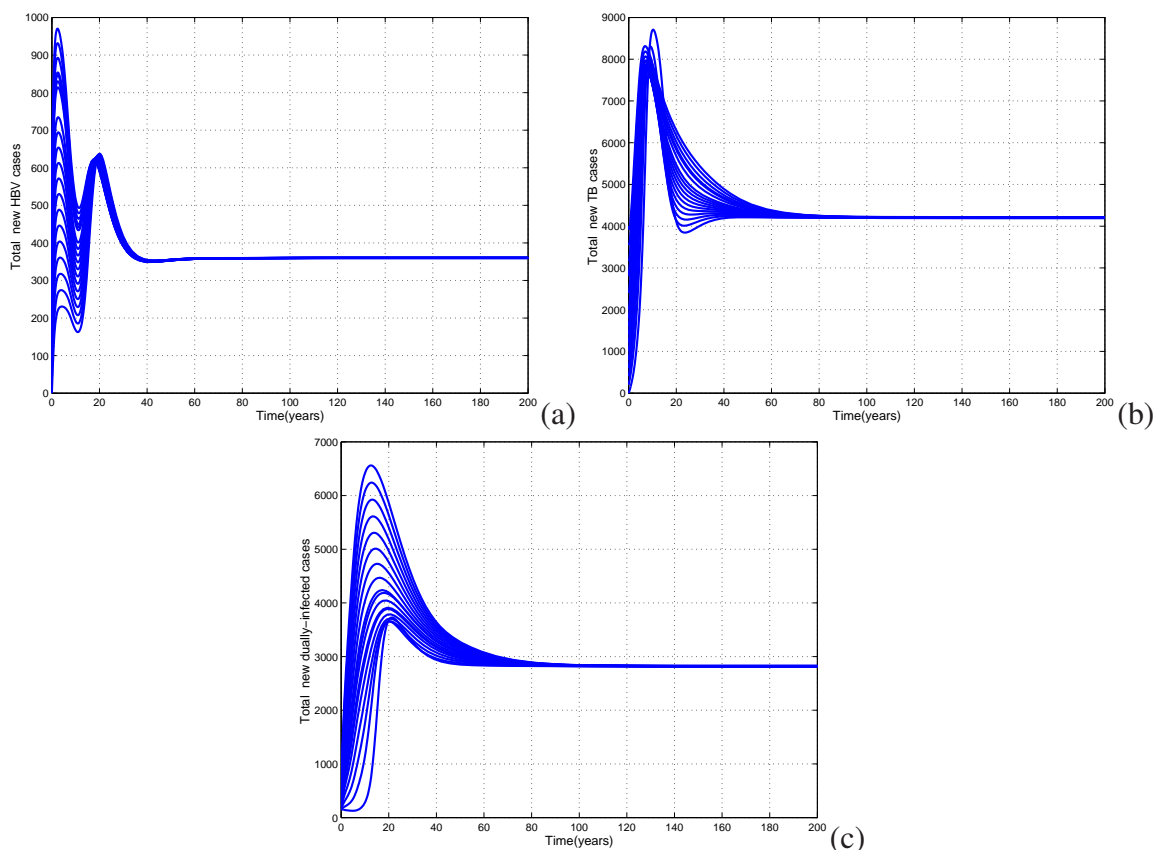
Figure 12: Time plots of trajectories of the HBV-TB model (2.4) with different initial conditions when $\beta_T = 2$ and $\beta_H = 20$ (so that $\mathcal{R}_0^H = 1.1609$, $\mathcal{R}_0^T = 1.7467$ and $\mathcal{R}_H^T = 1.4725$). This corresponds to $\mathcal{R}_0^H > 1$ and $\mathcal{R}_H^T > 1$. All other parameters are as in Table 3.

dually infected individuals with TB infection, the progression from acute stage to chronic stage of infection is respectively ten and two times faster than a person without TB infection). It shows that the increased the parameters q_1 and q_2 due to TB have increased the prevalence levels of HBV and TB. This means that condition $q_1 > q_2 > q$ alone may be sufficient for TB to have a significant impact on HBV.

5.   Discussions

A realistic deterministic ODE based compartmental model for the transmission of hepatitis B and tuberculosis co-dynamics in a population has been proposed and analyzed. The HBV-only and TB-only models were qualitatively examined, first of all. The main theoretical results obtained are as follows:

1. We are able to compute independent reproduction numbers for TB ($\mathcal{R}_H^T$) and HBV ($\mathcal{R}_0^H$) and the total reproduction number for the system, $\mathcal{R}_0 = \max\{\mathcal{R}_H^T, \mathcal{R}_0^H\}$.
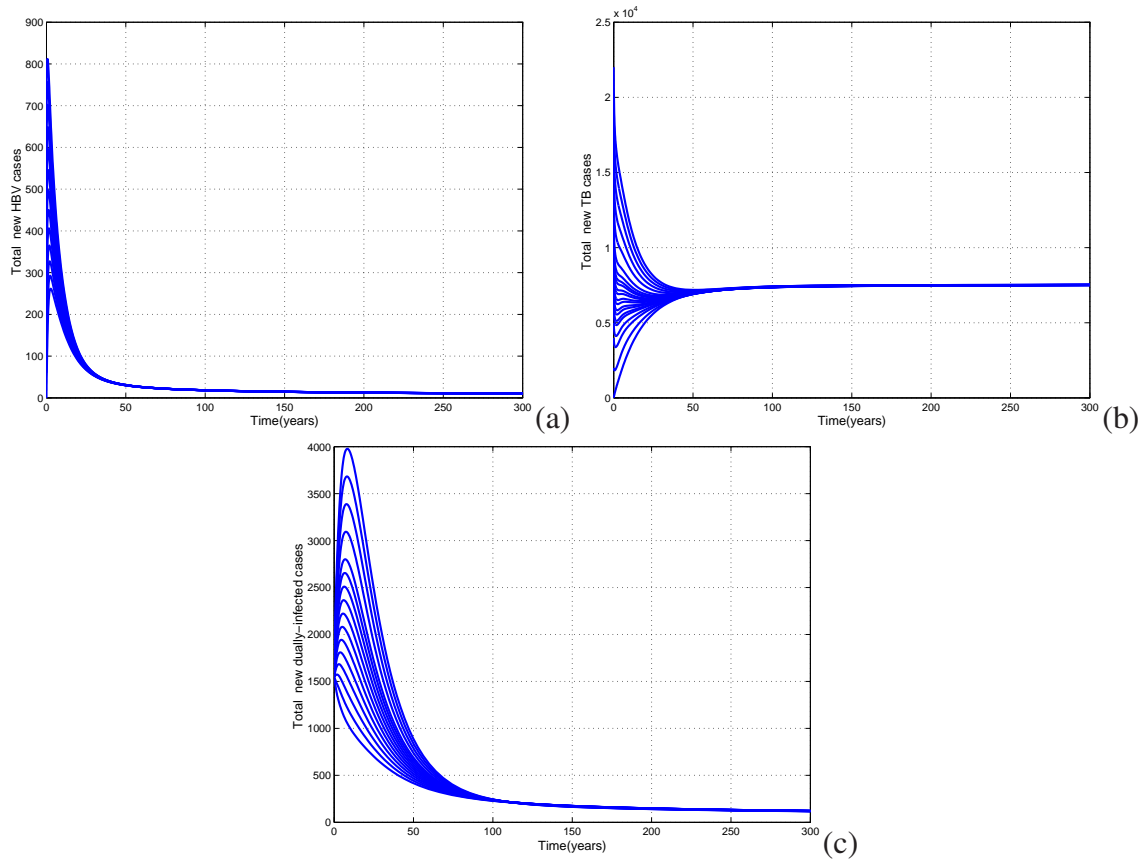
Figure 13: Simulations of the HBV-TB model (2.4) with different initial conditions when $\beta_T = 2$ and $\beta_H = 10$ (so that $\mathcal{R}_0^H = 0.5805$ and $\mathcal{R}_H^T = 1.4725$). This corresponds to $\mathcal{R}_0^H < 1$ and $\mathcal{R}_H^T > 1$. All other parameters are as in Table 3.

2. The HBV-only model has a globally-asymptotically stable disease-free equilibrium whenever a certain epidemiological threshold ($\mathcal{R}_0^H$) is less than unity and unstable if this threshold exceeds unity;

3. The HBV-only model has a unique endemic equilibrium whenever the aforementioned threshold exceeds unity. This endemic equilibrium is locally asymptotically stable at least near $\mathcal{R}_0^H = 1$ whenever it exists;

4. Unlike the HBV-only model, the TB-only model undergoes the phenomenon of backward bifurcation, where the associated stable disease-free equilibrium co-exists with a stable endemic equilibrium when the corresponding reproduction number ($\mathcal{R}_0^T$) is less than unity;

5. The full HBV-TB model is shown to have a locally-asymptotically stable disease-free equilibrium when its reproductive threshold is less than unity, and unstable if the threshold exceeds unity. It also undergoes the phenomenon of backward bifurcation under certain conditions;
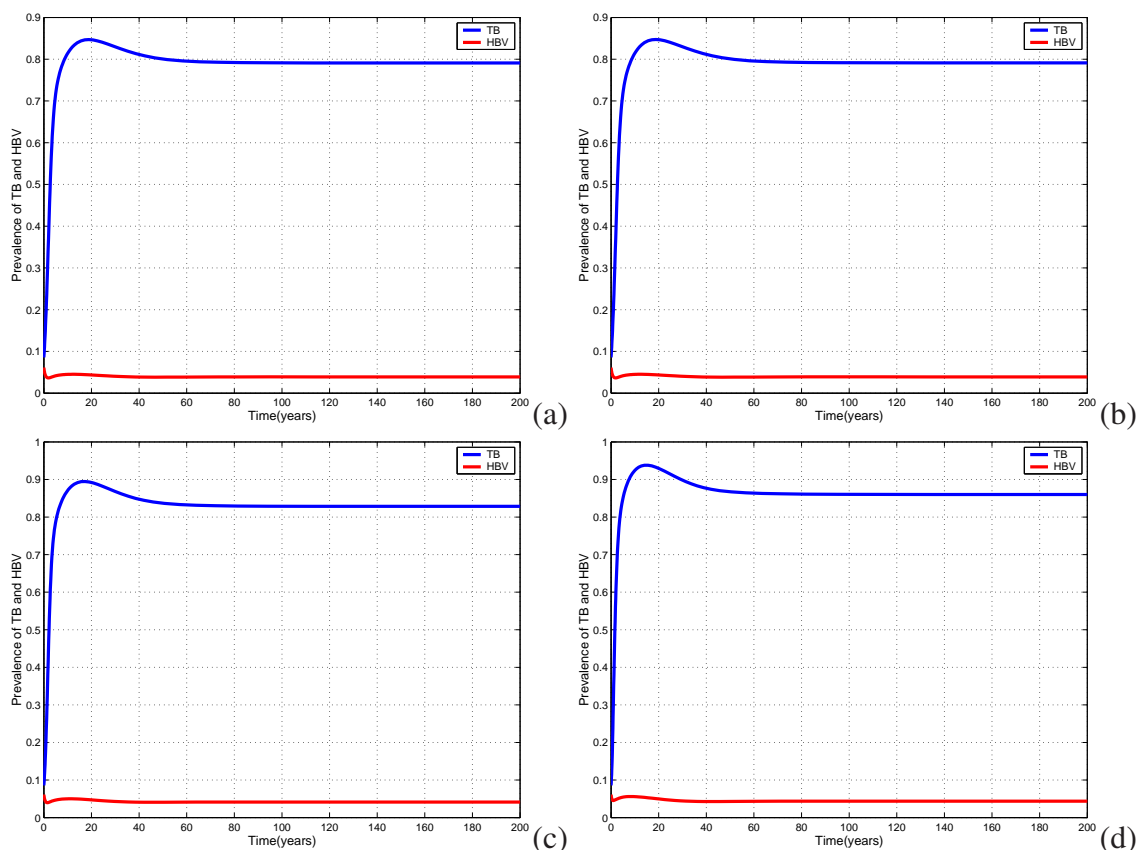
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Figure 14: Time plots of fraction of active TB and fraction of HBV acute and chronic carriers when $\beta_T = 2$ and $\beta_H = 20$ (so that $\mathcal{R}_0^H = 1.609$ and $\mathcal{R}_H^T = 1.4725$) and $r_{2h} = r_{2c} = r_{2r} = 0.5 r_2$. (i) For different values of k, k_h, k_c and k_r: (a) $k = k_h = k_c = k_r$ and (b) $k_c = 5k$, $k_h = 3k$ and $k_r = 2k$; and (ii) for different values of σ, σ_h, σ_c and σ_r (c) $\sigma = \sigma_h = \sigma_c = \sigma_r$ and (d) $\sigma_c = 5\sigma$, $\sigma_h = 3\sigma$ and $\sigma_r = 2\sigma$. All other parameter values are given in Table 3 except that $r_{2h} = r_{2c} = r_{2r} = 0.5 r_2$ (i.e., it takes twice as long to treat a TB infected person with HBV than without).

The simulation results provided many interesting insights into the effect of the dynamical interactions between TB and HBV. Mainly, the following are observed:

(i) The HBV only sub-model has a DFE which is GAS.

(ii) The analysis shows that the TB-only model exhibits a mechanism known as backward bifurcation by allowing for reactivation of latent TB individuals by infected individuals.

(iii) The two diseases disappear in the population whenever their reproduction numbers are very small and less than unity.

(iv) The HBV-free equilibrium is stable when $\mathcal{R}_H^T > 1$ and $\mathcal{R}_0^H < 1$. However, the symmetric result does not hold. That is, the TB-free equilibrium may not be stable when $\mathcal{R}_H^T < 1$ and $\mathcal{R}_0^H > 1$.

(v) The two diseases co-exist whenever their reproduction numbers exceed unity (regardless
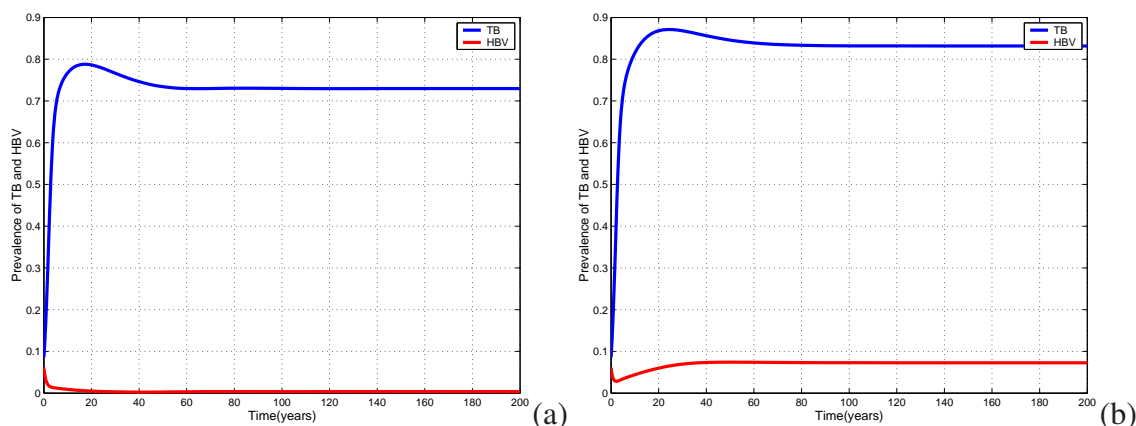
Figure 15: Time plots of fraction of active TB and fraction of HBV acute and chronic carriers for different values of q, q_1 and q_2. (a) $q = q_1 = q_2$, and (b) $q_1 = 10q$ and $q_2 = 2q$. Other parameter values are the same as in Fig. 14.

which of the numbers is larger).

(vi) Condition $k_c > k_h > k_r > k$ alone does not always lead to a significant increase in TB in the presence of HBV. However, when $\sigma_c > \sigma_h > \sigma_r > \sigma$, the presence of HBV may have a significant influence on TB dynamics. Also, when $q_1 > q_2 > q$, the presence of TB may have a significant influence on the HBV dynamics.

Numerical results suggest that to reduce or control the impact of TB, investing more in reducing the prevalence of HBV can be an effective option. Such reductions would not be easy due to the waning vaccine-induced immunity and lack of effective medication. There is no 'cure' at this time for HBV. However, significant reductions may be obtained through programs that accelerate the treatment of active TB cases. Since there are about 8 million new cases of active TB per year, a program may be feasible. It has worked well in countries that allocate substantial resources to public health. Naturally, accelerating the treatment rate of individuals with active TB is more critical in areas where HIV prevalence is high since approximately 10% of the HIV-infected population worldwide is infected with HBV. Unfortunately, the areas with the highest prevalence of co-infections have limited resources and cannot implement to accelerated TB treatment programs.

It is worth stressing that our models and observations are rather crude for multiple reasons. The results are not only based on local mathematical analysis but they are from a model that does not incorporate multiple and common forms of the possibility of increases in antibiotic resistant TB, and the impact of human behavior, particularly the role of core groups (prostitution, injection drug, etc.). A research program that tackles some of these possibilities is still viable, since it is the first time the dynamics of HBV-TB co-infection is studied and therefore they are still poorly understood from a theoretical or mathematical perspective.

Acknowledgements

Appendix A: Local stability of the unique endemic equilibrium of the HBV-only model (3.1)

In this Appendix, we shall give the proof of Lemma 4, using the Centre Manifold theory. To apply this theory, the following simplification and change of variables are made first of all. Let $x_1 = S, x_2 = V, x_3 = I_H, x_4 = C_H$ and $x_5 = R_H$ so that $N = x_1 + x_2 + x_3 + x_4 + x_5$. Further, by using vector notation $x = (x_1, x_2, x_3, x_4, x_5)^T$, the HBV-only model (3.1) can be written in the form $\dot{x} = f(x)$, with $f = (f_1, f_2, f_3, f_4, f_5)^T$, as follows:

$$\begin{cases} \dot{x}_1 = f_1 = \Lambda + \mu\omega(1 - vx_4) - (1 - \delta)\lambda_H x_1 - (\delta + \mu_0)x_1, \\ \dot{x}_2 = f_2 = \mu(1 - \omega) + \delta x_1 - \pi_H \lambda_H x_2 - \mu_0 x_2, \\ \dot{x}_3 = f_3 = [\pi_H x_2 + (1 - \delta)x_1]\lambda_H - (\mu_0 + \gamma_1)x_3, \\ \dot{x}_4 = f_4 = \mu\omega vx_4 + q\gamma_1 x_3 - (\mu_0 + d_H + \gamma_2)x_4, \\ \dot{x}_5 = f_5 = \gamma_1(1 - q)x_3 + \gamma_2 x_4 - \mu_0 x_5, \end{cases} \tag{5.1}$$

where

$$\lambda_H = \frac{\beta_H(x_3 + \eta x_4)}{x_1 + x_2 + x_3 + x_4 + x_5}.$$

The Jacobian of system (5.1), at the DFE Q_0^H, is given by

$$J(Q_0^H) = \begin{pmatrix} -(\mu_0 + \delta) & 0 & -J_1 & -J_2 & 0 \\ \delta & -\mu_0 & -J_3 & -J_4 & 0 \\ 0 & 0 & J_5 & J_6 & 0 \\ 0 & 0 & q\gamma_1 & -A & 0 \\ 0 & 0 & \gamma_1(1 - q) & \gamma_2 & -\mu_0 \end{pmatrix}$$

where

$$J_1 = \frac{\beta_H(1 - \delta)x_{01}}{x_{01} + x_{02}}, \quad J_2 = \mu\omega v + \frac{\beta_H\eta(1 - \delta)x_{01}}{x_{01} + x_{02}}, \quad J_3 = \frac{\beta_H\pi_H x_{02}}{x_{01} + x_{02}},$$
$$J_4 = \frac{\beta_H\pi_H\eta x_{02}}{x_{01} + x_{02}}, \quad J_5 = \frac{\beta_H[\pi_H x_{02} + (1 - \delta)x_{01}]}{x_{01} + x_{02}} - \mu_0 - \gamma_1,$$
$$J_6 = \frac{\beta_H\eta[\pi_H x_{02} + (1 - \delta)x_{01}]}{x_{01} + x_{02}},$$

with

$$x_{01} = \frac{\Lambda + \mu\omega}{\mu_0 + \delta} \qquad \text{and} \qquad x_{02} = \frac{\delta(\mu + \Lambda) + \mu\mu_0(1 - \omega)}{\mu_0(\mu_0 + \delta)}.$$

Consider, next, the case when $\mathcal{R}_0^H = 1$. Suppose, further, that $\beta_H = \beta_H^*$ is chosen as a bifurcation parameter. Solving for β_H from $\mathcal{R}_0^H = 1$ gives

$$\beta_H = \frac{A(\mu_0 + \delta)(\mu_0 + \gamma_1)(\Lambda + \mu)}{(A + \eta q\gamma_1)[\pi_H[\delta(\mu + \Lambda) + \mu\mu_0(1 - \omega)] + \mu_0(1 - \delta)(\Lambda + \mu\omega)]}.$$

It follows that the Jacobian $(J(Q_0^H))$ of (5.1) at the DFE, with $\beta_H = \beta_H^*$, denoted by $J_{\beta_H^*}$ has a simple zero eigenvalue (with all other eigenvalues having negative real part). Hence, the Centre Manifold theory [56] can be used to analyze the dynamics of the model (5.1). In particular, the theorem in [57] (see also [52, 56, 58]), reproduced below for convenience, will be used to show that the unique endemic equilibrium of the model (5.1) (or, equivalently, (3.1)) is locally asymptotically stable for $\mathcal{R}_0^H$ near 1.

Theorem 8. *(Castillo-Chavez & Song [57]). Consider the following general system of ordinary differential equations with a parameter ϕ:*

$$\frac{dx}{dt} = f(x, \phi), \qquad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R} \qquad \text{and} \qquad f \in C^2(\mathbb{R}^n, \mathbb{R}), \qquad (5.2)$$

where 0 is an equilibrium point of the system (that is, $f(0, \phi) \equiv 0$ for all ϕ) and assume

1. $A = D_x f(0, 0) = \left(\dfrac{\partial f_i}{\partial x_j}(0, 0) \right)$ is the linearization matrix of system (5.1) around the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;

2. Matrix A has a right eigenvector u and a left eigenvector z (each corresponding to the zero eigenvalue).

Let f_k be the kth component of f and

$$a = \sum_{k,i,j=1}^{n} z_k u_i u_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0),$$

$$b = \sum_{k,i=1}^{n} z_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0, 0),$$

then the local dynamics of the system around the equilibrium point 0 is totally determined by the signs of a and b.

1. $a > 0$, $b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable and there exists a positive unstable equilibrium; when $0 < \phi \ll 0$, 0 is unstable and there exists a negative, locally asymptotically stable equilibrium;

2. $a < 0$, $b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0 is locally asymptotically stable equilibrium, and there exists a positive unstable equilibrium;

3. $a > 0$, $b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable, and a positive unstable equilibrium appears;

4. $a < 0$, $b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.

Particularly, if $a > 0$ and $b > 0$, then a backward bifurcation occurs at $\phi = 0$.

In order to apply the above theorem, the following computations are necessary (it should be noted that we are using β_H^* as the bifurcation parameter, in place of ϕ in Theorem 8).

Eigenvectors of $J_{\beta_H^*}$: For the case when $\mathcal{R}_0^H = 1$, it can be shown that the Jacobian of (5.1) at $\beta_H = \beta_H^*$ (denoted by $J_{\beta_H^*}$) has a right eigenvector (corresponding to the zero eigenvalue), given by $u = (u_1, u_2, u_3, u_4, u_5)^T$, where,

$$
\begin{cases}
u_1 &= -\dfrac{(AJ_1 + q\gamma_1 J_2)u_3}{A(\mu_0 + \delta)}, \\[3mm]
u_2 &= -\dfrac{[\delta(AJ_1 + q\gamma_1 J_2) + (\mu_0 + \delta)(AJ_3 + q\gamma_1 J_4)]u_3}{A\mu_0(\mu_0 + \delta)}, \\[3mm]
u_3 &= u_3 > 0, \\[3mm]
u_4 &= \dfrac{q\gamma_1}{A}u_3, \\[3mm]
u_5 &= \dfrac{\gamma_1}{\mu_0}\left(1 - q + \dfrac{q\gamma_2}{A}\right)u_3.
\end{cases}
\tag{5.3}
$$

Similarly, the components of the left eigenvectors of J_{β^*} (corresponding to the zero eigenvalue), denoted by $z = (z_1, z_2, z_3, z_4, z_5)^T$, are given by,

$$
\begin{cases}
z_1 &= 0, \\[3mm]
z_2 &= 0, \\[3mm]
z_3 &= z_3 > 0, \\[3mm]
z_4 &= \dfrac{J_6}{A}z_3, \\[3mm]
z_5 &= 0.
\end{cases}
\tag{5.4}
$$

Computation of a: For system (5.1), the associated non-zero partial derivatives of f (at the DFE) are given by

$$\frac{\partial^2 f_3}{\partial x_3^2} = -\frac{2\beta_H^*[\pi_H x_{02} + (1 - \delta)x_{01}]}{(x_{01} + x_{02})^2},$$

$$\frac{\partial^2 f_3}{\partial x_3 \partial x_4} = \frac{\partial^2 f_3}{\partial x_4 \partial x_3} = -\frac{\beta_H^*(1 + \eta)[\pi_H x_{02} + (1 - \delta)x_{01}]}{(x_{01} + x_{02})^2},$$

$$\frac{\partial^2 f_3}{\partial x_1 \partial x_3} = \frac{\partial^2 f_3}{\partial x_3 \partial x_1} = -\frac{\beta_H^*(\pi_H + \delta - 1)x_{02}}{(x_{01} + x_{02})^2}, \qquad \frac{\partial^2 f_3}{\partial x_2 \partial x_3} = \frac{\partial^2 f_3}{\partial x_3 \partial x_2} = \frac{\beta_H^*(\pi_H + \delta - 1)x_{01}}{(x_{01} + x_{02})^2},$$

$$\frac{\partial^2 f_3}{\partial x_1 \partial x_4} = \frac{\partial^2 f_3}{\partial x_4 \partial x_1} = -\frac{\beta_H^*\eta(\pi_H + \delta - 1)x_{02}}{(x_{01} + x_{02})^2}, \qquad \frac{\partial^2 f_3}{\partial x_2 \partial x_4} = \frac{\partial^2 f_3}{\partial x_4 \partial x_2} = \frac{\beta_H^*\eta(\pi_H + \delta - 1)x_{01}}{(x_{01} + x_{02})^2},$$

$$\frac{\partial^2 f_3}{\partial x_4^2} = -\frac{2\beta_H^*\eta[\pi_H x_{02} + (1 - \delta)x_{01}]}{(x_{01} + x_{02})^2}, \qquad \frac{\partial^2 f_3}{\partial x_5 \partial x_3} = \frac{\partial^2 f_3}{\partial x_3 \partial x_5} = -\frac{\beta_H^*[\pi_H x_{02} + (1 - \delta)x_{01}]}{(x_{01} + x_{02})^2},$$

$$\frac{\partial^2 f_3}{\partial x_5 \partial x_4} = \frac{\partial^2 f_3}{\partial x_4 \partial x_5} = -\frac{\beta_H^*\eta[\pi_H x_{02} + (1 - \delta)x_{01}]}{(x_{01} + x_{02})^2}.$$

Then, it follows that

$$a = z_3 \sum_{i,j=1}^{5} u_i u_j \frac{\partial^2 f_3}{\partial x_i \partial x_j},$$

$$= -\frac{2\beta_H^* z_3(u_3 + \eta u_4)}{(x_{01} + x_{02})^2} \left[[\pi_H x_{02} + (1 - \delta)x_{01}](u_3 + u_4 + u_5) + (\pi_H + \delta - 1)(-x_{01}u_2 + x_{02}u_1) \right].$$

Now, using Eq. (5.3) and after a calculation, one finally obtains

$$a = -\frac{2\beta_H^* z_3 u_3(u_3 + \eta u_4)}{A\mu_0(\mu_0 + \delta)(x_{01} + x_{02})^2}[\mathcal{A}_1 + \pi_H \mathcal{A}_2 + (1 - \delta)\mathcal{A}_3], \qquad (5.5)$$

where

$$\mathcal{A}_1 = \frac{\beta_H \mu_0(A + q\gamma_1\eta)(\pi_H + \delta - 1)^2 x_{01} x_{02}}{N_0}$$

$$\mathcal{A}_2 = \frac{\beta_H \delta(A + q\gamma_1\eta)[\pi_H x_{02} + (1 - \delta)x_{01}]x_{01}}{N_0} + x_{02}(\mu_0 + \delta)[\mu_0 + \gamma_1(1 - q)]A,$$

$$+ \frac{q\gamma_1}{\mu_0}[\mu\mu_0(1 - \omega)(\mu_0 + \gamma_2 - \mu\omega v) + \delta(\Lambda + \mu)(\mu_0 + \gamma_2)],$$

$$\mathcal{A}_3 = q\gamma_1\mu^2\omega v(1 - \omega) + x_{01}q\gamma_1(\mu_0 + \gamma_2) + x_{01}A[\mu_0 + \gamma_1 + \mu_0(\mu_0 + \delta) + \gamma_1(1 - q)(\mu_0 + \delta)].$$

At this stage, remind that we have assumed that $\mu\omega v < \mu_0 + d_H + \gamma_2$ because if this inequality do not hold, $dC_H/dt > 0$ for $C_H \neq 0$ or $I_H > 0$ and $t \geq 0$. Note also that when $\mu\omega v < \mu_0 + \gamma_2$, carriers would also not keep increasing rapidly as long as there is infection. Then, we can also assumed that $\mu_0 + \gamma_2 - \mu\omega v > 0$. In this case, one has $a < 0$.

Computation of b: For the sign of b, it can be shown that the associated non-vanishing partial derivatives of f are

$$\frac{\partial^2 f_3}{\partial x_3 \partial \beta_H^*}(0,0) = \frac{\pi_H x_{02} + (1-\delta)x_{01}}{x_{01} + x_{02}} \quad \text{and} \quad \frac{\partial^2 f_3}{\partial x_4 \partial \beta_H^*}(0,0) = \frac{\eta[\pi_H x_{02} + (1-\delta)x_{01}]}{x_{01} + x_{02}},$$

Substituting the respective partial derivatives into the expression

$$b = z_3 \sum_{i=1}^{5} u_i \frac{\partial^2 f_3}{\partial x_i \beta_H^*}(0,0) + z_4 \sum_{i=1}^{5} u_i \frac{\partial^2 f_4}{\partial x_i \beta_H^*}(0,0).$$

gives

$$b = \frac{z_3(u_3 + \eta u_4)}{x_{01} + x_{02}}[\pi_H x_{02} + (1-\delta)x_{01}] > 0. \tag{5.6}$$

Thus, $a < 0$ and $b > 0$. So (by Theorem 8, Item (4)), we have established the result about the local stability of the endemic equilibrium of the HBV-only model (note that this result holds for $\mathcal{R}_0^H > 1$ but close to 1). This achieves the proof.

$\square$

Appendix B: Calculation of the basic reproduction ratio for system (2.4)

In order to compute the basic reproduction ratio, it is important to distinguish new infections from all other class transitions in the population. The infected classes are $I_H, C_H, R_H, E_T, I_T, I_{TI}$, $E_{TI}, I_{TC}, E_{TC}, I_{TR}$ and E_{TR}. Following Van den Driessche and Watmough [52], we can write the model (2.4) as

$$\dot{x} = f(x) = \mathcal{F}(x) - \mathcal{V}(x) = \mathcal{F}(x) - (\mathcal{V}^-(x) - \mathcal{V}^+(x)), \tag{5.7}$$

where $x = (I_H, C_H, R_H, E_T, I_T, E_{TI}, I_{TI}, E_{TC}, I_{TC}, E_{TR}, I_{TR}, S, V)$, $\mathcal{F}$ is the rate of appearance of new infections in each class, $\mathcal{V}^+$ is the rate of transfer into each class by all other means and $\mathcal{V}^-$ is the rate of transfer out of each class. Hence,

$$\mathcal{F}(x) = ([\pi_H V + (1-\delta)S]\lambda_H S, \, 0, \, 0, \, [(1-f)V + (1-\delta)(1-p)S]\lambda_T,$$

$$[fV + p(1-\delta)S]\lambda_T, 0, 0, 0, 0, 0, 0, 0, 0)^T.$$

The Jacobian matrices of $\mathcal{F}$ and $\mathcal{V}$ at the disease-free equilibrium Q_0 are

$$D\mathcal{F}(Q_0) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix}, \qquad D\mathcal{V}(Q_0) = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix},$$

where F and V correspond to the derivatives of $\mathcal{F}$ and $\mathcal{V}$ with respect to the infected classes:

$$
F = \begin{bmatrix} F_H & 0 & F_{TH} \\ 0 & F_T & \tilde{F}_{TH} \\ 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} V_H & 0 & 0 \\ 0 & V_T & 0 \\ 0 & 0 & V_{TH} \end{bmatrix},
$$

where

$$
F_H = \frac{\beta_H[\pi_H V_0 + (1-\delta)S_0]}{S_0 + V_0} \begin{bmatrix} 1 & \eta & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \qquad F_T = \frac{\beta_T}{S_0 + V_0} \begin{bmatrix} 0 & F_{01} \\ 0 & F_{02} \end{bmatrix},
$$

$$
F_{TH} = \frac{\beta_H[\pi_H V_0 + (1-\delta)S_0]}{S_0 + V_0} \begin{bmatrix} \eta_1 & \eta_2 & \eta_1\eta_{1c} & \eta_2\eta_{2c} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},
$$

$$
\tilde{F}_{TH} = \frac{\beta_T}{S_0 + V_0} \begin{bmatrix} 0 & \varepsilon\varepsilon_1 F_{01} & 0 & \varepsilon\varepsilon_2 F_{01} & 0 & \varepsilon F_{01} \\ 0 & \varepsilon\varepsilon_1 F_{02} & 0 & \varepsilon\varepsilon_2 F_{02} & 0 & \varepsilon F_{02} \end{bmatrix},
$$

and

$$
V_H = \begin{bmatrix} \mu_0 + \gamma_1 & 0 & 0 \\ -q\gamma_1 & A & 0 \\ -\gamma_1(1-q) & -\gamma_2 & \mu_0 \end{bmatrix}, \qquad V_T = \begin{bmatrix} A_1 & -r_2 \\ -k(1-r_1) & A_2 \end{bmatrix},
$$

$V_{TH} =$

$$
\begin{bmatrix} v_{1T} & -r_{2h} & 0 & 0 & 0 & 0 \\ -k_h(1-r_{1h}) & v_{2T} & 0 & 0 & 0 & 0 \\ -q_2\phi_2 & 0 & v_{3T} & -r_{2c} & 0 & 0 \\ 0 & -q_1\phi_1(1-r_{2h}) & -k_c(1-r_{1c}) & v_{4T} & 0 & 0 \\ -\phi_2(1-q_2) & 0 & -\theta_2 & 0 & v_{5T} & -r_{2c} \\ 0 & -\phi_1(1-q_1)(1-r_{2h}) & 0 & -\theta_1(1-r_{2c}) & -k_r(1-r_{1r}) & v_{6T} \end{bmatrix},
$$

with

$$
F_{01} = (1-f)V_0 + (1-p)(1-\delta)S_0, \qquad F_{02} = fV_0 + p(1-\delta)S_0,
$$

$$
v_{1T} = \mu_0 + k_h(1-r_{1h}) + \phi_2, \qquad v_{2T} = \mu_0 + d_{1T} + r_{2h} + \phi_1(1-r_{2h}),
$$

$$
v_{3T} = \mu_0 + d_{4T} + \theta_2 + k_c(1-r_{1c}), \qquad v_{4T} = \mu_0 + d_{2T} + r_{2c} + \theta_1(1-r_{2c}),
$$

$$
v_{5T} = \mu_0 + k_r(1-r_{1r}) \qquad \text{and} \qquad v_{6T} = \mu_0 + d_{3T} + r_{2r}.
$$

The basic reproduction number is defined, following van den Driessche and Watmough [52], as the spectral radius of the next generation matrix, FV^{-1}:

$$\mathcal{R}_0 = \max\{\mathcal{R}_H^T, \mathcal{R}_0^H\},$$

where $\mathcal{R}_H^T$ and $\mathcal{R}_0^H$ are the two eigenvalues:

$$
\begin{aligned}
\mathcal{R}_0^H &= \frac{\beta_H(A + \eta q \gamma_1)[\pi_H[\delta(\mu + \Lambda) + \mu\mu_0(1 - \omega)] + \mu_0(1 - \delta)(\Lambda + \mu\omega)]}{A(\mu_0 + \delta)(\mu_0 + \gamma_1)(\Lambda + \mu)}, \\
\mathcal{R}_H^T &= \frac{\beta_T[f\mu_0 + k(1 - r_1)]V_0}{(S_0 + V_0)[\mu_0(\mu_0 + d_T + r_2) + k(1 - r_1)(\mu_0 + d_T)]} + \frac{(1 - \delta)S_0}{S_0 + V_0}\mathcal{R}_0^T,
\end{aligned}
\tag{5.8}
$$

with $\mathcal{R}_0^T$ the basic reproduction number for the TB-only sub-model (3.15).

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