Modelling and analysis of hepatitis B and HIV co-infections

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RÉSUMÉ. Le virus de l'immunodéficience humaine (VIH) est la principale cause de décès chez les personnes infectés par le virus de l'hépatite B (HBV). L'étude de la dynamique commune du VIH et HBV présente un défis mathématique majeur, en dépit du fait qu'ils ont le même mode de transmission. Un modèle déterministe pour la co-infection du HBV et du VIH au sein d'une population est présenté et rigoureusement analysé. Nous calculons le nombre de reproduction de base ($\mathcal{R}_0$), le point d'équilibre sans maladie, les points d'équilibre frontières, que nous définissons comme l'existence d'une seule maladie en l'absence de l'autre maladie, et le point d'équilibre de co-infection pour des conditions spécifiques. Nous déterminons les critères de stabilité pour le point d'équilibre sans maladie et les points d'équilibre frontières. Les simulation numériques sont présentées pour illustrer les résultats analytiques.

ABSTRACT. The human immunodeficiency virus (HIV) is the leading cause of death among individuals infected with the Hepatitis B virus (HBV). The study of the joint dynamics of HIV and HBV present formidable mathematical challenges in spite the fact that they share similar routes of transmission. A deterministic model for the co-interaction of HBV and HIV in a community is presented and rigorously analyzed. We calculate the basic reproduction number ($\mathcal{R}_0$), the disease-free equilibrium, boundary equilibria, which we define as the existence of one disease along with the complete eradication of the other disease, and the co-infection equilibrium for specific conditions. We determine stability criteria for the disease-free and boundary equilibria. Numerical simulations have been presented to illustrate analytical results.

MOTS-CLÉS : Systèmes dynamiques, Modèles épidémiologiques, VIH/SIDA, HBV, Stabilité.

KEYWORDS : Dynamical systems, Epidemiological models, HIV/AIDS , HBV, Stability.

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1. Introduction

Due to shared models of transmission, co-infection with hepatitis B virus (HBV) and HIV is common. With a reduction in AIDS-related deaths due to highly active antiretroviral therapy (HAART), liver disease has emerged as an important cause of death in patients with HBV-HIV co-infection. Hepatitis B is a dynamic disease and an understanding of its virology and natural history is imperative if complications are to be reduced and disease progression limited. The management of HIV-HBV co-infection is complicated by the use of drugs with activity against both viruses, the risk of flares and hepatic decompensation with immune reconstitution, and the increasing prevalence of antiviral resistance.

More than 350 million people are infected with HBV, with 75% of the world's HBV carriers residing in Asia [1-3]. Forty million people are infected with HIV worldwide. Due to shared modes of transmission, co-infection is common and an estimated 4 million people worldwide are co-infected with HBV-HIV. The prevalence of HBV in HIV infected individuals varies with the population studied. In the United States, up to 10% of all HIV-infected individuals have HBV co-infection [3]. Several studies support an increased prevalence of HBV in HIV-infected populations of sub-Saharan Africa, with more than 80% of HIV-positive individuals in some of those countries carrying serum markers for HBV [1]. People co-infected with both hepatitis B and HIV are 14 to 17 times more likely to die than those with hepatitis B alone. Those co-infected with HIV and HBV also face accelerated liver scarring or cirrhosis. To make matters worse, some medicines used to treat HIV are toxic to the liver, which may already be damaged from the hepatitis B infection [4].

However, the study of infectious disease co-epidemics is critical to 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 [5,6], although a growing number of studies have considered co-epidemics [7-9]. Mathematical studies of co-infection models are not very common. On the other hand, the huge public health burden inflicted by HIV and HBV necessitates the use of mathematical modeling to gain insights into their transmission dynamics and to determine effective control strategies.

In this study, we formulate and analyze a realistic mathematical model for HBV-HIV co-infection, which incorporates the key epidemiological and biological features of each of the two diseases. The main contribution of this study is in carrying 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-HIV co-infection.

2. Model construction

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

2.1. Basic framework

The model sub-divides the total sexually-active population at time t denoted by N, into various mutually-exclusive compartments depending on their disease status : Susceptible individuals to both diseases (S(t)), infected individuals in the asymptomatic stage of HIV infection ($H_1(t)$), HIV-infected individuals with clinical symptoms of AIDS ($H_2(t)$), dually-infected individuals with HBV acute infection, in the asymptomatic stage of HIV infection ($H_{1I}(t)$), dually-infected individuals with HBV acute infection, displaying symptoms of AIDS ($H_{2I}(t)$), dually-infected individuals with HBV chronic infection, in the asymptomatic stage of HIV infection ($H_{1C}(t)$), dually-infected individuals with HBV chronic infection, displaying symptoms of AIDS ($H_{2C}(t)$), HBV recovered individuals with protective immunity in the asymptomatic stage of HIV infection ($H_{1R}(t)$), HBV recovered individuals with protective immunity displaying symptoms of AIDS ($H_{2R}(t)$), HBV vaccinated individuals ($V(t)$), individuals with HBV acute infection ($I_B(t)$), HBV chronic carriers ($C_B(t)$) and HBV recovered with protective immunity ($R_B(t)$).

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.

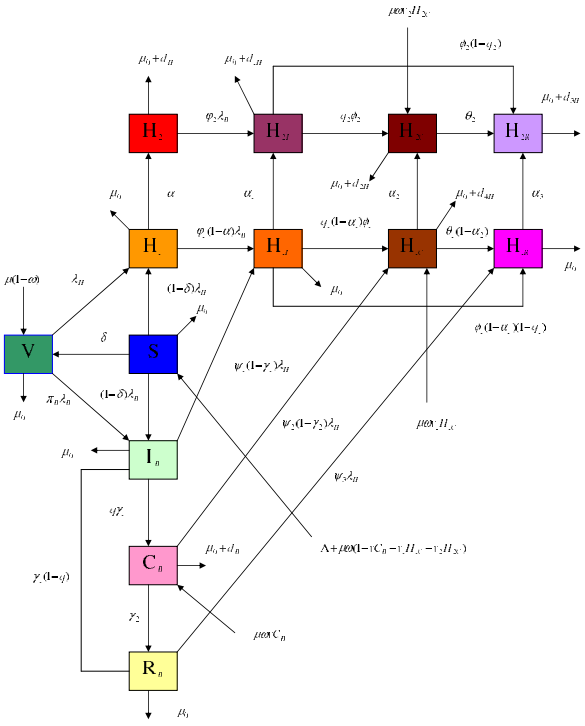

Figure 1. *Flowchart of the transmission dynamics of the co-infection HIV/HBV.*

The force of infection associated with HBV infection is given by

$$\lambda_B = \beta_B \frac{I_B + \eta_1(H_{1I} + \eta_{1h}H_{2I}) + \eta(C_B + \eta_{1c}H_{1C} + \eta_{2c}H_{2C})}{N}, \qquad [1]$$

where β_B is the effective contact rate for HBV transmission and the modification parameters η_1, η_{1h}, η, η_{1c} and η_{2c} model the relative infectiousness of individuals in the C_B H_{1I}, H_{2I}, H_{1C} and H_{2C} classes.

Susceptible and HBV vaccinated individuals acquire HIV infection following contact with people infected with HIV (that is, those in H_1, H_2 H_{1I}, H_{2I}, H_{1C}, H_{2C}, H_{1R} and H_{2R} classes) at rate λ_H defined as follows :

$$\lambda_H = \beta_H \frac{H_1 + \varepsilon H_2 + \varepsilon_1(H_{1I} + \varepsilon_{1h} H_{2I}) + \varepsilon_2(H_{1C} + \varepsilon_{2h} H_{2C}) + \varepsilon_3(H_{1R} + \varepsilon_{3h} H_{2R})}{N}, \quad [2]$$

where β_H is the effective contact rate for HIV infection (contact sufficient to result in HIV infection). Further, the modification parameters ε, ε_1, ε_{1h}, ε_2, ε_{2h}, ε_3 and ε_{3h} account for the relative infectiousness of individuals in the H_2 H_{1I}, H_{2I}, H_{1C}, H_{2C}, H_{1R} and H_{2R} classes.

2.2. The model

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

$$\begin{cases}
\dot{S} = \Lambda + \mu\omega(1 - vC_B - v_1 H_{1C} - v_2 H_{2C}) - (1-\delta)(\lambda_H + \lambda_B)S - (\delta + \mu_0)S, \\
\dot{V} = \mu(1-\omega) + \delta S - (\lambda_H + \pi_B \lambda_B)V - \mu_0 V, \\
\dot{H}_1 = [V + (1-\delta)S]\lambda_H - \varphi_1(1-\alpha)\lambda_B H_1 - (\mu_0 + \alpha)H_1, \\
\dot{H}_2 = \alpha H_1 - \varphi_2 \lambda_B H_2 - (\mu_0 + d_H)H_2, \\
\dot{H}_{1I} = \varphi_1(1-\alpha)\lambda_B H_1 + \psi_1(1-\gamma_1)\lambda_H I_B - [\mu_0 + \phi_1(1-\alpha_1)]H_{1I}, \\
\dot{H}_{2I} = \varphi_2 \lambda_B H_2 + \alpha_1 H_{1I} - (\mu_0 + d_{1H} + \phi_2)H_{2I}, \\
\dot{H}_{1C} = \mu\omega v_1 H_{1C} + q_1\phi_1(1-\alpha_1)H_{1I} \\
+\psi_2(1-\gamma_2)\lambda_H C_B - [\mu_0 + d_{4H} + \alpha_2 + \theta_1(1-\alpha_2)]H_{1C}, \\
\dot{H}_{2C} = \mu\omega v_2 H_{2C} + q_2\phi_2 H_{2I} + \alpha_2 H_{1C} - (\mu_0 + d_{2H} + \theta_2)H_{2C}, \\
\dot{H}_{1R} = \phi_1(1-\alpha_1)(1-q_1)H_{1I} + \theta_1(1-\alpha_2)H_{1C} + \psi_3\lambda_H R_B - (\mu_0 + \alpha_3)H_{1R}, \\
\dot{H}_{2R} = \phi_2(1-q_2)H_{2I} + \theta_2 H_{2C} + \alpha_3 H_{1R} - (\mu_0 + d_{3H})H_{2R}, \\
\dot{I}_B = [\pi_B V + (1-\delta)S]\lambda_B - \psi_1(1-\gamma_1)\lambda_H I_B - (\mu_0 + \gamma_1)I_B, \\
\dot{C}_B = \mu\omega v C_B + q\gamma_1 I_B - \psi_2(1-\gamma_2)\lambda_H C_B - (\mu_0 + d_B + \gamma_2)C_B, \\
\dot{R}_B = \gamma_1(1-q)I_B + \gamma_2 C_B - \psi_3\lambda_H R_B - \mu_0 R_B,
\end{cases} \quad [3]$$

where Λ is the recruitment rate of susceptible individuals into the population ; π_B is the rate of waning vaccine-induced immunity ; φ_1 and φ_2 are the probabilities of acquiring HBV infection of individuals in the H_1 and H_2 classes, respectively ; ψ_1, ψ_2 and ψ_3 are respectively, the probabilities of acquiring HIV of individuals in the I_B, C_B and R_B classes ; μ is the birth rate in the population ; ω is the proportion of births without successful vaccination ; v, v_1 and v_2 are proportions of perinatally infected born by carriers mothers in the C_B, H_{1C} and H_{2C} classes, respectively ; δ is the vaccination rate ; γ_1, ϕ_1 and ϕ_2 are respectively, the rates moving from I_B, H_{1I} and H_{2I} classes to C_B, H_{1C} and H_{2C} classes ; q, q_1, and q_2 are respectively, the average probability that an individual in the I_B, H_{1I} and H_{2I} classes fail to clear an acute state and develops a carrier state (C_B, H_{1C} and H_{2C}), respectively ; γ_2, θ_1 and θ_2 are respectively, rates moving from C_B, H_{1C} and H_{2C} classes to R_B, H_{1R} and H_{2R} classes ; d_B is the HBV induced death rate of individuals in the HBV chronic carriers class C_B ; d_H, d_{1H}, d_{2H}, d_{3H} and d_{4H} are respectively, the HIV induced death rate of individuals in the H_2, H_{1I}, H_{2I}, H_{1C}, H_{2C} and H_{2R} classes.

We show that all feasible solutions of components of system (3) enters the region :

$$\Omega = \left\{ (S, V, H_1, H_2, H_{1I}, H_{2I}, H_{1C}, H_{2C}, H_{1R}, H_{2R}, I_B, C_B, R_B) \in R^{13}_{\geq 0}, \;\; N(t) \leq \frac{\Lambda + \mu}{\mu_0} \right\}. \qquad [4]$$

3. Analysis of the model

3.1. Local stability of the disease-free equilibrium (DFE)

The HBV-HIV model (3) has a DFE given by

$$Q_0 = \left(\frac{\Lambda + \mu\omega}{\mu_0 + \delta}, \frac{\delta(\mu + \Lambda) + \mu\mu_0(1 - \omega)}{\mu_0(\mu_0 + \delta)}, 0,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0 \right).$$

The local stability of the DFE of the HBV-HIV model is determined by its basic reproduction number $\mathcal{R}_0$, which is computed using the next generation operator method proposed by van den Driessche and Watmough [10]. The associated reproduction number for the HBV-HIV model denoted by $\mathcal{R}_0$ is given by

$$\mathcal{R}_0 = \max\{\mathcal{R}_0^B, \mathcal{R}_B^H\}, \qquad [5]$$

where

$$\begin{aligned} \mathcal{R}_0^B &= \frac{\beta_B(A + \eta q \gamma_1)[\pi_B[\delta(\mu + \Lambda) + \mu\mu_0(1 - \omega)] + \mu_0(1 - \delta)(\Lambda + \mu\omega)]}{A(\mu_0 + \delta)(\mu_0 + \gamma_1)(\Lambda + \mu)}, \\ \mathcal{R}_0^H &= \frac{\beta_H(\mu_0 + d_H + \varepsilon_2\alpha)}{(\mu_0 + \alpha)(\mu_0 + d_H)} \qquad \text{and} \qquad \mathcal{R}_B^H = \mathcal{R}_0^H \left(1 - \frac{\mu_0\delta(\Lambda + \mu\omega)}{(\Lambda + \mu)(\mu_0 + \delta)} \right), \end{aligned} \qquad [6]$$

with $A = \mu_0 + d_B + \gamma_2 - \mu\omega v$.

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.

Corollary 1 *: The DFE Q_0 of system (3) is LAS if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.*

3.2. Existence and stability of boundary equilibria

System (3) has four possible nonnegative boundary equilibria in Ω : the disease-free equilibrium (DFE) Q_0, the HBV-only (HIV-free) equilibrium Q_B^*, the HIV-only (HBV-free) equilibrium Q_H^* and the HBV/HIV equilibrium Q_B^H.

At Q_H^*, the components are $V_B = I_B = C_B = H_{1I} = H_{2I} = H_{1C} = H_{2C} = H_{1R} = H_{2R} = 0$,

$$S_H^* = \frac{\Lambda}{\mu_0 + \lambda_H^*}, \qquad H_{1H}^* = \frac{\Lambda\lambda_H^*}{(\mu_0+\alpha)(\mu_0+\lambda_H^*)}, \qquad H_{2H}^* = \frac{\alpha\Lambda\lambda_H^*}{(\mu_0+\alpha)(\mu_0+d_H)(\mu_0+\lambda_H^*)},$$

$$\lambda_H^* = \frac{(\mu_0+\alpha)(\mu_0+d_H)(\mathcal{R}_0^H - 1)}{\mu_0+\alpha+d_H}.$$

At Q_B^*, the components are $H_1 = H_2 = H_{1I} = H_{2I} = H_{1C} = H_{2C} = H_{1R} = H_{2R} = 0$ and

$$\begin{cases} I_B^* &= \dfrac{A(\Lambda+\mu)\lambda_B^*}{\beta_B\mu_0(A+\eta q\gamma_1) + d_B q\gamma_1\lambda_B^*}, \; C_B^* = \dfrac{q\gamma_1(\Lambda+\mu)\lambda_B^*}{\beta_B\mu_0(A+\eta q\gamma_1) + d_B q\gamma_1\lambda_B^*}, \\ S_B^* &= \dfrac{1}{(1-\delta)\lambda_B^* + \delta + \mu_0}\left[\Lambda + \mu\omega\left(1 - \dfrac{q\gamma_1 v(\Lambda+\mu)\lambda_B^*}{\beta_B\mu_0(A+\eta q\gamma_1) + d_B q\gamma_1\lambda_B^*}\right)\right], \\ V_B^* &= \dfrac{1}{\pi_B\lambda_B^* + \mu_0}\left[\mu(1-\omega)\right. \\ &+ \left.\dfrac{\delta}{(1-\delta)\lambda_B^* + \delta + \mu_0}\left[\Lambda + \mu\omega\left(1 - \dfrac{q\gamma_1 v(\Lambda+\mu)\lambda_B^*}{\beta_B\mu_0(A+\eta q\gamma_1) + d_B q\gamma_1\lambda_B^*}\right)\right]\right], \end{cases}$$

where $\lambda_B^* = \dfrac{\beta_B(I_B^* + \eta C_B^*)}{N_B^*}$ (with $N_B^* = S_B^* + V_B^* + I_B^* + C_B^* + R_B^*$) is the force of infection at the steady state Q_B^* which satisfies the following quadratic equation :

$$b_2(\lambda_B^*)^2 + b_1\lambda_B^* + b_0 = 0, \qquad [7]$$

where

$$\begin{aligned} b_2 &= (1-\delta)(\Lambda+\mu)[\pi_B[A(\mu_0+\gamma_1) + d_B q\gamma_1] + \mu\omega v q\gamma_1(1-\delta)], \\ b_1 &= -\pi_B\mu(1-\omega)[\beta_B\mu_0(1-\delta)(A+\eta q\gamma_1) + d_B q\gamma_1(\mu_0+\delta)] - d_B q\gamma_1\pi_B\delta(\Lambda+\mu\omega) \\ &+ \pi_B\delta\mu v q\gamma_1(\Lambda+\mu) - (1-\delta)(\Lambda+\mu\omega)[\pi_B\beta_B\mu_0(A+\eta q\gamma_1) + \mu_0 d_B q\gamma_1] \\ &+ \mu\omega v q\gamma_1(1-\delta)(\mu_0+\delta)(\Lambda+\mu) + A(\mu_0+\gamma_1)(\Lambda+\mu)[\pi_B(\mu_0+\delta) + \mu_0(1-\delta)], \\ b_0 &= A\mu_0(\mu_0+\gamma_1)(\mu_0+\delta)(\Lambda+\mu)(1-\mathcal{R}_0^B). \end{aligned}$$

The stability of these boundary equilibria are described as follows. Two coexistence thresholds must be calculated : the first separates the region where only HBV persists from

the region of coexistence ; the second marks the shift from coexistence to persistence of HIV alone.

In order to derive an expression for the region of stability of the boundary equilibrium Q_H^*, we measure the capacity of HBV to invade and persist in a population where HIV is at equilibrium. Applying the methods in van den Driessche [10], we find the basic reproduction ratio of the HBV in a population where HIV are fixed :

$$\mathcal{R}_0^B(Q_H^*) = \frac{\beta_B(1-\delta)S_H^*[A+\psi_2(1-\gamma_2)\lambda_H^*+\eta q\gamma_1]}{N_H^*[\psi_1(1-\gamma_1)\lambda_H^*+\mu_0+\gamma_1][A+\psi_2(1-\gamma_2)\lambda_H^*]}. \quad [8]$$

This formalism permits the derivation of a threshold condition for coexistence, now equivalent to a threshold condition for HBV endemicity in a population where HIV is at equilibrium, $\mathcal{R}_0^B(Q_H^*) = 1$: only HIV persists for $\mathcal{R}_0^B(Q_H^*) < 1$, while for $\mathcal{R}_0^B(Q_H^*) > 1$ HBV can invade a population where HIV state are fixed, that is, to say coexistence is possible.

Now, let us compute the region of stability of the boundary equilibrium Q_B^*. We use the same reasoning as before. We consider HIV as the phenotype invading a population where HBV is already endemic. Applying the methods in [10] once again, we find the basic reproduction ratio of the HIV in a population where HBV is fixed :

$$\mathcal{R}_B^H(Q_B^*) = \frac{\beta_H[\pi_B V_B+(1-\delta)S_B][\varphi_2\lambda_B^*+\mu_0+d_H+\varepsilon\alpha]}{N_B^*[\varphi_1(1-\alpha)\lambda_B^*+\mu_0+\alpha](\varphi_2\lambda_B^*+\mu_0+d_H)}. \quad [9]$$

Then, HIV can invade a population where HBV is fixed when $\mathcal{R}_B^H(Q_B) > 1$.

To illustrate the theoretical results contained in this paper, the model (3) is simulated using the following set of parameters : $\Lambda = 500$,$\pi_B = 0.1$, $\delta = 0.75$, $\eta = 0.16$, $\eta_1 = 1.1$, $\eta_{1h} = 1.2$, $\eta_{1c} = 1.3$, $\eta_{2c} = 1.4$, $\varepsilon = 1.1$, $\varepsilon_1 = 1.2$, $\varepsilon_{1h} = 1.25$, $\varepsilon_2 = 1.5$, $\varepsilon_{2h} = 1.55$, $\varepsilon_3 = 1.3$, $\varepsilon_{3h} = 1.35$, $\varphi_1 = 0.3$, $\varphi_2 = 0.5$, $\psi_1 = 0.4$, $\psi_2 = 0.5$, $\psi_3 = 0.1$, $\mu_0 = 0.019$, $\mu = 0.012$, $\omega = 0.35$, $\gamma_1 = 4$, $\gamma_2 = 0.025$, $v = 0.11$, $v_1 = 0.12$, $v_2 = 0.13$, $\phi_1 = 2$, $\phi_2 = 3$, $q = 0.885$, $q_1 = 0.9$, $q_2 = 0.95$, $\theta_1 = 0.015$, $\theta_2 = 0.01$, $\alpha = 1/33$, $\alpha_1 = 0.04$, $\alpha_2 = 0.05$, $\alpha_3 = 0.06$, $d_H = 0.01$, $d_{1H} = 0.03$, $d_{2H} = 0.05$, $d_{3H} = 0.02$, $d_{4H} = 0.06$ and $d_B = 0.002$.

Figure 2 examines changes in infection levels over time. It plots the time series of λ_B/β_B (fraction of acute and chronic HBV infection) and λ_H/β_H (fraction of HIV infection). The top two figures are for the case when $\mathcal{R}_B^H = 1.2908 > 1$ ($\beta_H = 0.03$), $\mathcal{R}_0^B(Q_H^*) = 0.8545 < 1$ ($\beta_B = 0.4$) in (a) and $\mathcal{R}_0^B(Q_H^*) = 2.5634 > 1$ ($\beta_B = 1.2$) in (b). It demonstrates that for $\mathcal{R}_B^H > 1$, the HBV free equilibrium Q_H^* is stable when $\mathcal{R}_0^B(Q_H^*) < 1$ and HIV and HBV coexist when $\mathcal{R}_0^B(Q_H^*) > 1$. The bottom two figures are for the case when $\mathcal{R}_0^B = 1.4596 > 1$ ($\beta_B = 1.2$), $\mathcal{R}_H^B(Q_B^*) = 0.4247 < 1$ ($\beta_H = 0.02$) in (c) and $\mathcal{R}_H^B(Q_B^*) = 1.0619 > 1$ ($\beta_H = 0.1$) in (d). It illustrates that for $\mathcal{R}_0^B > 1$, the HIV free equilibrium Q_B^* only persists when $\mathcal{R}_H^B(Q_B^*) > 1$, while when $\mathcal{R}_H^B(Q_B^*) > 1$, HIV and HBV persist. Also, it clearly appears that the increased of $\mathcal{R}_H^B(Q_B^*)$ generated damped oscillations in the system.

4. Bibliographie

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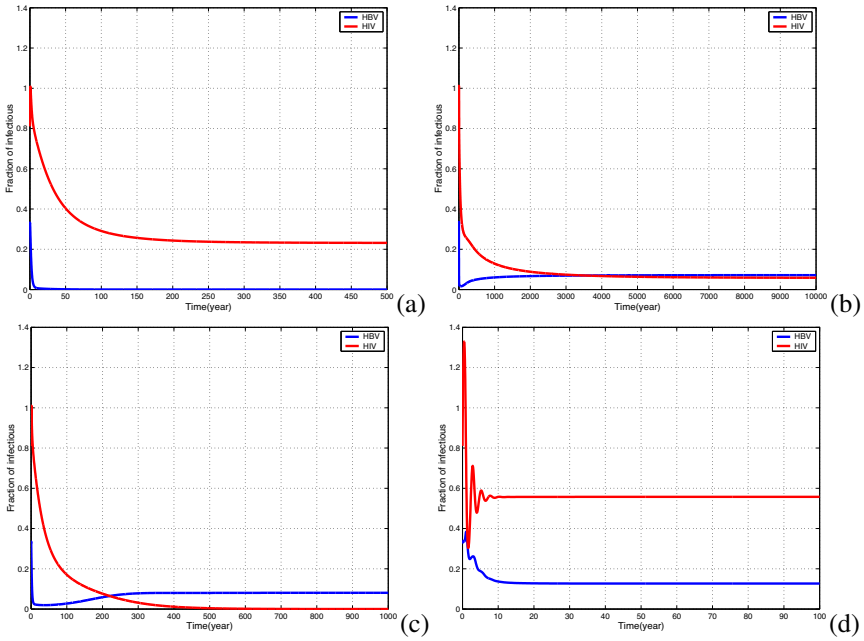

Figure 2. *Time plots of prevalence of HIV and HBV. The top two figures are for the case when* $\mathcal{R}_B^H = 1.2908 > 1$ *(*$\beta_H = 0.03$*),* $\mathcal{R}_0^B(Q_H^*) = 0.8545 < 1$ *(*$\beta_B = 0.4$*) in (a) and* $\mathcal{R}_0^B(Q_H^*) = 2.5634 > 1$ *(*$\beta_B = 1.2$*) in (b). The bottom two figures are for the case when* $\mathcal{R}_0^B = 1.4596 > 1$ *(*$\beta_B = 1.2$*),* $\mathcal{R}_H^B(Q_B^*) = 0.4247 < 1$ *(*$\beta_H = 0.02$*) in (c) and* $\mathcal{R}_H^B(Q_B^*) = 1.0619 > 1$ *(*$\beta_H = 0.1$*) in (d).*

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