Appl. Math. J. Chinese Univ.
2023, 38(4): 523-544

Optimal Control of Hepatitis B in a sub-Saharan African rural area

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Abstract. In this paper, we ameliorate the model proposed in [13], by incorporating the influence of hepatitis B e antigen (HBeAg) status of mothers on vertical transmission. We use the improved model to fit reported HBV new infections in the Zhejiang Province of China. Also to predict the course of the Hepatitis B (HBV) infection in this Chinese area, and in Tokombere, located in sub-Saharan Africa(SSA). Furthermore, we apply optimal control techniques in view to re-examine the effects of the newborn vaccination, the universal vaccination and the treatment of chronic carriers in preventing the HBV infection. Simulation results show that treatment slightly steps in the optimal strategy, while immunisation is an effective measure. On the other hand, they indicate that the control measures and immunization programs implemented in Zhejiang Province are effective. Besides, they suggest that in SSA, a package of several policies centred on birth dose vaccination should be implemented.

§1 Introduction

HBV infection continues to be a significant health concern globally, despite the availability of hepatitis B vaccine and effective antiviral therapy. Remarkable progress has been made in the past few decades in understanding the natural history of HBV infection. A substantial modification of the description of the chronic HBV infection has followed lately. In fact, relative to the HBV DNA levels, alanine aminotransferase values, eventually the presence or absence of liver inflammation and the presence of the HBeAg, the chronic HBV infection has been classified into five phases : ***HBeAg-positive chronic HBV infection*** **(or immune tolerant state)**, ***HBeAg-positive chronic hepatitis B*** **(or immune active state)**, ***HBeAg-negative chronic HBV infection*** **(or inactive carrier state)**, ***HBeAg-negative chronic hepatitis B*** **(or immune escape state)** and ***HBsAg-negative state*** [5].

HBeAg is a reliable marker of infectivity. Among infected pregnant women, those who are positive for HBeAg are more likely to infect their babies [33]. It is estimated that transmis-

Received: 2020-12-4. Revised: 2021-03-17.
MR Subject Classification: 34H05, 34C23, 37N25, 92D30, 49K15.
Keywords: hepatitis B virus, chronic carriers, vaccine, treatment, Pontryagin.
Digital Object Identifier(DOI): https://doi.org/10.1007/s11766-023-4332-5.
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sion rates can be as high as 12-25% in HBeAg negative mothers and as 70-90% in HBeAg positive mothers [2]. Fortunately, HBV infection can be prevented by currently available effective vaccines. Besides, current evidence shows that Hepatitis B immune globulin (HBIG) provides HBV-exposed infants with additional protection to the one afforded by the birth-dose vaccine [32]. Moreover, the ideal endpoint of hepatitis B treatment is the hepatitis B s antigen (HBsAg) seroclearance. But it is difficult to eradicate the virus. Indeed, the induction of long-term suppression of HBV DNA levels represents the main endpoint of all current treatments and the induction of HBeAg loss in HBeAg-positive chronic patients is a valuable endpoint [5].

Based on mathematical models, various combinations of policies have been studied to control the spread of HBV infection. In [15, 16], it was suggested that the application of both universal vaccination and treatment controls should respond better than the use of only one of these policies. The models proposed in these papers present a shortcoming in caring for a chronic carrier. Indeed, carriers have been investigated collectively therein for their potential role in disease transmission, their vulnerability to hepatitis B complications and their eligibility to treatment. In the more realistic models studied in [19, 34, 44], the carrier population was split into treated and untreated. Thus, the fact that all chronic HBV carriers are not eligible to currently available treatment was highlighted. On the same path, in the model studied in [21], the infected population was partitioned into three groups: infected individuals who are not infectious, infected individuals who can transmit the infection and individuals who are affected by liver cirrhosis. Thereafter, treatment was considered only for the last group. Investigation in [21, 44] suggested that treatment should be more effective than universal vaccination to minimize disease transmission and, as in [15, 16], the optimal combination of vaccination and treatment should be much more effective. In [19], it was reflected that proper treatment is necessary for the curtailing of HBV infection. In each of these papers, the variable of treatment control in the optimality system was far from negligible.

Chronic carriers were distributed in four groups according to their disease state in the model formulated and investigated in [13]. This makes that model a more biologically relevant one, since the following features were considered: the differential infectivity of carriers, the eligibility of only a small subpopulation of carriers to current treatment, and the fact that recovery happens only among inactive carriers. For simulations, data from Tokombere have been used and sensitivity analysis led to the conclusion that treatment could not be an effective strategy to fight against the propagation of the HBV. Furthermore, universal vaccination and neonate vaccination were both actions which could substantially impact its evolution, aligning with findings in [9].

In the present study, we include in the model proposed in [13], the fact that vertical transmission is related to the HBe status of carrier pregnant women. Model application is done to predict the outcome of HBV infection over the next decades in Tokombere. Intending to make sure that findings in [13] are unchanged, a global sensitivity analysis is performed. Finally, in order to reconsider the impacts of newborn vaccination, universal vaccination and treatment of chronic carriers in fighting against the spread of HBV infection, the corresponding four parameters are regarded as functions of time, resulting in an optimality system.

The paper is organized as follows. In section 2, we present and mathematically analyse

the improved model. In section 3, we generate simulated models to predict the course of the infection in Zhejiang and in Tokombere. Also to carry out sensitivity analysis. The model with control is investigated in section 4. It is numerically solved and the discussion is fulfilled in section 5. In the end, the conclusion is summarized in section 6.

§2 Model Framework

2.1 The model

We make a little modification of the model in [13], in which the proportions of perinatally infected by HBeAg positive and HBeAg negative mothers are supposed equal. In this paper, we consider that they are different and that ν_1 and ν_2 ($\nu_1 > \nu_2$) denote the proportions of perinatally infected by HBeAg positive and HBeAg negative mothers respectively. The total population size is divided into 10 mutually exclusive epidemiological groups:

- Firstly, the susceptibles are divided into three groups: the proportion of susceptible persons without previous vaccination (S), the proportion of vaccinated with one previous dose (V_1) and the proportion of vaccinated with two previous doses (V_2).
- Next, there are the proportion of exposed (L) (those who are infected but not yet infectious), and the proportion of acute infected patients (I).
- Thirdly, the population of carriers is divided into four categories, the proportions of patients: in immune tolerant state (E); in immune active state (C); in inactive carrier state (P) ; in immune escape state (F).
- Finally, there is the proportion of removed (R): those who cannot get the disease, because they either have recovered permanently from the acute or carrier state, or have successfully been immunized after the third vaccination dose.

The model transfer diagram is depicted in Fig. 1. The description, the values and the ranges of most parameters are given in Table 1. We set $\bar{\omega} = 1 - \omega$. Then, $\bar{\omega}\mu$ newborn babies are successfully immunized with one previous dose and move directly to the class (V_1), while $\omega\mu(\nu_1(E+C)+\nu_2(P+F))$ babies are infected in perinatal infection and access to an immune tolerant class. The rest, $\omega\mu(1-\nu_1(E+C)-\nu_2(P+F))$ newborns move to the susceptible class. Denote β_e, β_c, β_p, β_f the infectiousness of patients in the immune tolerant state, immune active state, inactive carrier state and immune escape state respectively. These infectiousness are estimated relative to the infectiousness of acute infected like: $\beta_e = p_e\beta_i$, $\beta_c = p_c\beta_i$, $\beta_p = p_p\beta_i$, $\beta_f = p_f\beta_i$, where $p_e, p_c, p_p, p_f \in]0;1[$. Hence $\beta_{ki} = \tau_k\beta_i$, $k = 0, 1, 2$ is the transmission rate of acute infected for susceptible individuals that corresponds to τ_k. The transmission rates of the sub-groups of carriers are defined in a similar manner. Therefore, $\lambda\tau_k$, $k = 0, 1, 2$, where λ is given by Eq. (1), is the force of infection associated with HBV infection for susceptible individuals in compartments S, V_1 and V_2 respectively.

$$\lambda = \beta_i I + \beta_e E + \beta_c C + \beta_p P + \beta_f F. \tag{1}$$

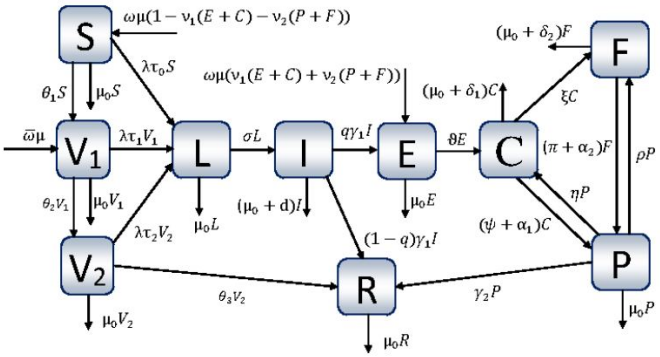


Figure 1. Flow chart of the transmission dynamics of HBV. It has been set $\bar{\omega} = 1 - \omega$.

The model is described by the following system of ordinary differential equations:

$$\begin{cases} \dot{S} = \omega\mu(1 - \nu_1(E + C) - \nu_2(P + F)) - a_0 S - \lambda\tau_0 S, \\ \dot{V}_1 = \bar{\omega}\mu + \theta_1 S - a_1 V_1 - \lambda\tau_1 V_1, \\ \dot{V}_2 = \theta_2 V_1 - a_2 V_2 - \lambda\tau_2 V_2, \\ \dot{L} = \lambda(\tau_0 S + \tau_1 V_1 + \tau_2 V_2) - b_l L, \\ \dot{I} = \sigma L - b_i I, \\ \dot{E} = \omega\mu(\nu_1(E + C) + \nu_2(P + F)) + q\gamma_1 I - b_e E, \\ \dot{C} = \vartheta E + \eta P - b_c C, \\ \dot{P} = (\psi + \alpha_1)C + (\pi + \alpha_2)F - b_p P, \\ \dot{F} = \xi C + \rho P - b_f F, \\ \dot{R} = \theta_3 V_2 + (1 - q)\gamma_1 I + \gamma_2 P - \mu_0 R. \end{cases} \tag{2}$$

where

$$a_0 = \mu_0 + \theta_1, \quad a_1 = \mu_0 + \theta_2, \quad a_2 = \mu_0 + \theta_3, \quad b_l = \sigma + \mu_0, \quad b_i = \mu_0 + d + \gamma_1, \quad b_e = \mu_0 + \vartheta,$$
$$b_c = \mu_0 + \delta_1 + \xi + \psi + \alpha_1, \quad b_p = \mu_0 + \eta + \gamma_2 + \rho, \quad b_f = \mu_0 + \delta_2 + \pi + \alpha_2.$$

For convenience, let the positive constants:

$$D_0 = b_p b_f - \rho(\pi + \alpha_2), \qquad D_1 = b_c b_p b_f - (\rho b_c + \eta\xi)(\pi + \alpha_2) - \eta b_f(\psi + \alpha_1),$$
$$D_2 = \xi(b_p + \pi + \alpha_2) + (\rho + b_f)(\psi + \alpha_1).$$

Throughout this paper, we will assume that $\nu_1 < \dfrac{b_e D_1}{\omega\mu\left[D_1 + \vartheta(D_0 + D_2)\right]}$.

2.2 Basic reproduction number, equilibria and their stability

Model (2) always has a disease-free equilibrium $X_0^* = \left(S^0, V_1^0, V_2^0, 0, 0, 0, 0, 0, 0, R^0\right)^t$, with S^0, V_1^0 and V_2^0 defined by

$$S^0 = \frac{\omega\mu}{a_0}, \; V_1^0 = \frac{\mu\bar{\omega}a_0 + \omega\mu\theta_1}{a_0 a_1}, \; V_2^0 = \frac{\mu\bar{\omega}a_0\theta_2 + \omega\mu\theta_1\theta_2}{a_0 a_1 a_2} \text{ and } R^0 = \frac{\mu\bar{\omega}a_0\theta_2\theta_3 + \omega\mu\theta_1\theta_2\theta_3}{\mu_0 a_0 a_1 a_2}.$$

Table 1. Ranges used for global sensibility analysis and parameter values used to simulate the spread of HBV transmission in Tokombere.

Par	Description	Value	Range	Ref.
μ	Natural birth rate	0.0367 y^{-1}	[0.02 ; 0.05]	[25]
ω	Proportion of births without successful vaccination	0.9	[0.01 ; 0.97]	[25]
ν_1	Proportion of perinatally infected by HBeAg positive mothers	0.75	[0.7 ; 0.9]	[2]
ν_2	Proportion of perinatally infected by HBeAg negative mothers	0.16	[0.12 ; 0.25]	[8]
τ_0	Susceptibility of persons without previous vaccination	1		
τ_1	Susceptibility of persons with one previous vaccination	0.7	[0.6 ; 0.8] ^{a}	[10]
τ_2	Susceptibility of persons with two previous vaccinations	0.3	[0.2 ; 0.4] ^{a}	[10]
θ_1	Rate of vaccination with the first dose	variable	[0 ; 0.9]	
θ_2	Rate of vaccination with the second dose	0.925 y^{-1}	[0.8 ; 1]	[4]
θ_3	Rate of effective vaccination with the third dose	0.879 y^{-1}	[0.7 ; 1]	[4]
β_i	Infectiousness rate of acutes	Variable	[0.1 ; 1.2] ^{b}	[6, 30, 45]
σ	Rate of loss of latency	6 y^{-1}	[3 ; 9]	[6]
γ_1	Rate of leaving the acute state	4 y^{-1}	[3.467 ; 4]	[6, 38]
γ_2	Recovery rate of inactive carriers	0.015 y^{-1}	[0.01 ; 0.03]	[5]
q	Average probability an individual fails to clear an acute infection and develops to carrier state	0.885	[0.05; 0.9]	[12, 45]
ϑ	Rate moving from immune tolerant to immune active state	0.07 y^{-1}	[0.025 ; 0.1]	[42]
ξ	Incidence of immune escape from immune active state	0.011 y^{-1}	[0.0001 ; 0.015]	[24]
ψ	Rate moving from immune active to inactive carrier state	0.139 y^{-1}	[0.018 ; 0.1425]	[24]
ρ	Incidence of immune escape from inactive carrier state	0.02 y^{-1}	[0.01 ; 0.03]	[36]
η	Incidence of HBeAg reversion	0.008 y^{-1}	[0.003 ; 0.016]	[36]
π	Rate of moving from immune escape to inactive carrier state	0.17 y^{-1}	[0.1 ; 0.26]	As.
α_1	Rate of treating immune active carriers	0.2	[0.001 ; 0.95]	As.
α_2	Rate of treating immune escape carriers	0.1	[0.001 ; 0.95]	As.
μ_0	Natural mortality rate	0.0108 y^{-1}	[0.001 ; 0.02]	[39]
d	Mortality rate of acute due to infection	0.00461 y^{-1}	[0,001 ; 0.007]	[1]
δ_1	Mortality rate of immune active carriers due to infection	0.01 y^{-1}	[0.0077 ; 0.0158]	[14]
δ_2	Mortality rate of immune escape carriers due to infection	0.008 y^{-1}	[0.0077 ; 0.0158]	[14]

"Par." stands for Parameter, "As." for Assumed, "y^{-1}" for $year^{-1}$ and "Ref." denotes Reference.

a: We assume that $\tau_0 > \tau_1 > \tau_2$.

b: This range is realistic. Indeed, in [6] the value of β_i is estimated at 0.111. Moreover, for β_i the authors in [30] worked with the value 0.85, while those in [45] used the value 1. About the infectiousness of different chronic carriers, in [6], the infectiousness of patients with the chronic HBV infection relative to acute infection is estimated at 0.16. Thus, for simulation it is relevant to take the values $p_e = 0.165$, $p_c = 0.14$, $p_p = 0.04$, $p_f = 0.07$. Moreover, for global sensitivity analysis we will consider that $p_e \in [0.12; 0.2]$, $p_c \in [0.1; 0.18]$, $p_p \in [0.02; 0.07]$ and $p_f \in [0.05; 0.1]$.

As in [13], we shall focus our attention only on the positive invariant and absorbing compact set

$$\Omega = \left\{(S, V_1, V_2, E, I, L, C, P, F, R) \in [0;1]^{10},\ S(t) \leq S^0,\ V_1(t) \leq V_1^0,\ V_2(t) \leq V_2^0\right\}.$$

The basic reproduction number $\mathcal{R}_0$ is computed in the same way as in [13], we easily have

$$\mathcal{R}_0 = \frac{\sigma \mathcal{A} Y^0}{b_l b_i \left[b_e D_1 - \omega\mu\left(\nu_1(D_1 + \vartheta D_0) + \nu_2 \vartheta D_2\right)\right]}, \tag{3}$$

where

$$\begin{aligned} Y^0 =& \tau_0 S^0 + \tau_1 V_1^0 + \tau_2 V_2^0 = \frac{\tau_0 a_1 a_2 + \theta_1 \tau_1 a_2 + \theta_1 \theta_2 \tau_2 + \theta_1 \theta_2}{a_0 a_1 a_2 b_l b_i b_e b_c D}, \\ \mathcal{A} =& \left[b_e D_1 - \omega\mu\left(\nu_1(D_1 + \vartheta D_0) + \nu_2 \vartheta D_2\right)\right]\beta_i + q\gamma_1 D_1 \beta_e + q\gamma_1 \vartheta D_0 \beta_c \\ &+ q\gamma_1\vartheta\left[b_f(\psi + \alpha_1) + \xi(\pi + \alpha_2)\right]\beta_p + q\gamma_1\vartheta\left[\rho(\psi + \alpha_1) + \xi b_p\right]\beta_f. \end{aligned}$$

Notice that we have assumed $\nu_1 > \nu_2$ and $\nu_1 < \dfrac{b_e D_1}{\omega\mu\left[D_1 + \vartheta(D_0 + D_2)\right]}$. Therefore $\mathcal{A} > 0$. The below proposition follows from Theorem 2 in [35].

Proposition 2.1. *The disease-free equilibrium X_0^* is locally and asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.*

Theorem 2.1. *If $\mathcal{R}_0 \leq 1$, then X_0^* is globally asymptotically stable on Ω.*

The proof of the global and asymptotic stability of the disease-free equilibrium is an easy adaptation of the one provided in [13]. In the same way, regarding the existence and the stability of the endemic equilibrium, the below lemma and the theorem that follows remain true by obvious adaptation of the proofs of corresponding ones in that paper.

Lemma 2.1. *If $\mathcal{R}_0 \leq 1$ then X_0^* is the only equilibrium of System (2). If $\mathcal{R}_0 > 1$, then System (2) has two equilibria: the disease free equilibrium X_0^* and a unique endemic equilibrium $X_e^* = (S^*, V_1^*, V_2^*, L^*, I^*, E^*, C^*, P^*, F^*, R^*)$.*

Theorem 2.2. *(Global stability of the endemic equilibrium X_e^*)*
If $\mathcal{R}_0 > 1$ then

- *when $\nu_1 = \nu_2 = 0$, $\omega = 1$, X_e^* is globally asymptotically stable on Ω;*
- *when $\nu_1 = \nu_2 = 0$, $\omega < 1$, if $\mu_0 V_1^* > \mu\bar{\omega}$ then X_e^* is globally asymptotically stable on Ω;*
- *when $\nu_1 > \nu_2 > 0$ and $\omega < 1$, if $\mu_0 V_1^* > \mu\bar{\omega}$ then X_e^* is globally asymptotically stable on $\Omega_1 \cup \Omega_2$, where*

$$\Omega_1 = \{(S, V_1, V_2, L, I, E, C, P, F, R) \in \Omega, S \geq S^*, R \leq R^*, E \geq E^*, C \geq C^*, P \geq P^*, F \geq F^*\},$$

$$\Omega_2 = \{(S, V_1, V_2, L, I, E, C, P, F, R) \in \Omega, S \leq S^*, R \geq R^*, E \leq E^*, C \leq C^*, P \leq P^*, F \leq F^*\}.$$

§3 Model predictions and sensitivity analysis

3.1 Application to the HBV transmission in a Chinese province

In 2002, China fully integrated hepatitis B vaccine into the routine immunization program. As a result of the introduction of the HBV vaccination and the wide availability of antiviral drugs to treat the primary infection in infected subjects, HBV prevalence has decreased a lot in China. Furthermore the rate of mother-to-infant transmission has since been significantly reduced to approximately 3%–5% [41].

The reported HBV data from the Ministry of Health of China in Zhejiang Province, picture well the success of immunization program implemented in China. The trend of the acute hepatitis B notification rate over a period of twelve years, from 2005 to 2016 is depicted in Fig. 2. From 2005 to 2013 the data are specifically reported in the Zhejiang Province [37] and from 2014 to 2016 they are the general trend in China reported by Ministry of Health of China [28]. The trend showed a steady decline, the only exception was a slight increase in 2011.

The Model (2) is applied to simulate the HBV transmission in this zone. The simulations of our model are carried out with the software MATLAB (R2018a). Initial conditions are

$(0.6424; 0.0511; 0.0365; 0.0001; 0.0001; 0.0119; 0.0056; 0.0475; 0.0049; 0.2)$. They have been chosen on the base of a prevalence of HBV infection equal to 0.0701 %. The initial value of the proportion of acute infected is the one reported in 2005 in the Zhejiang Province. Relatively to the distribution of chronic carriers, we have considered the proportions used in [13]. Moreover, we do not consider HBV induced death here ($d = \delta_1 = \delta_2 = 0$), in view of the effort of improving liver histology by treatment made in this area. We take $\mu = \mu_0 = 0.0121$, $\omega = 0.1$ [30] and we assume $\nu_1 = 0.85$, $\nu_2 = 0.22$, $\beta_i = 0.116$, $\theta_1 = 0.1$, $\theta_2 = 0.96$, $\theta_3 = 0.92$, $\alpha_1 = 0.5$, $\alpha_2 = 0.4$, and the values of the other parameters are as given in Table 1. The simulation result in Fig. 2 matches the HBV reported data. Based on these parameter values, we estimate the basic reproduction number $\mathcal{R}_0 = 0.0092$. Corroborated by Fig. 3, this shows that the control measures implemented in Zhejiang Province are effective.

With the previous values of parameters, Fig. 3 shows the evolution over twelve years from 2005, then a prediction over the next forty height years of the HBV dynamics in Zhejiang Province, under a mass infant immunization rate of 90%. The incidence of acute infection has been immediately impacted and will be near zero from 2030 (Fig. 3a). About the prevalence of chronic infection, the proportion of carriers is progressively affected. It will decrease to around 4.1% by 2030 and will keep decreasing till reach 2.5% by 2055 (Fig. 3b). This slow regression is due to the fact that carriage may last for decades, actually the decline of their number is mostly due to natural death or recovering. Finally, since immune active and immune escape carriers are those who are exposed to the risk of dying from the disease, Fig. 3c shows that the disease burden is also decreasing and will continue to do so.

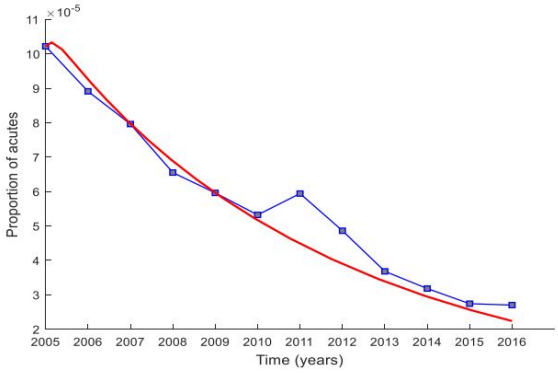
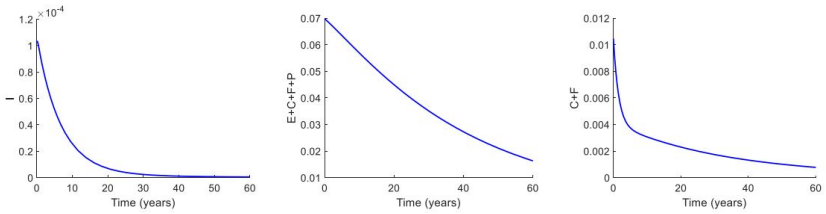


Figure 2. Comparison of the simulation result (solid red curve) and the yearly new reported cases (blue broken line) in Zhejiang Province since 2005-2016.

3.2 Application of the model to the HBV transmission in a sub-Saharan African area

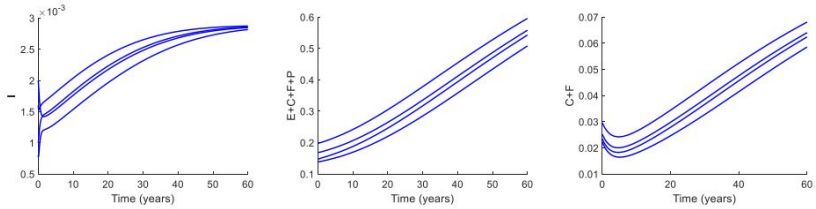
The lack of epidemiological data hinders the prediction of the evolution of HBV infection in SSA, which for instance is sensitive to initial conditions [27]. Demographic data and some



(a) Proportion of acute subjects (b) Proportion of carriers (c) Proportion of exposed to complication

Figure 3. Trend of the spread of hepatitis B since 2005 to 2016 and prediction of new cases, prevalence of carriers and HBV burden in the Zhejiang Province from 2017 to 2065.

epidemiologic data from Tokombere are used to predict the course of HBV infection in this area [13]. Tokombere is located in the Far-North Region of Cameroon, where the average seroprevalence of viral hepatitis B is 17 %. We take $\beta_i = 0.7$ and for other parameters the values are as given in Table 1. For these values, we find $\mathcal{R}_0 = 3.08$. The simulations are also carried out with the software MATLAB (R2018a). In Fig. 4, several initial conditions are used. It appears that if nothing is done to substantially limit the progression of HBV infection in Tokombere, the disease will continue to progress to a stable endemic state.



(a) Proportion of acute subjects (b) Proportion of carriers (c) Proportion of exposed to complication

Figure 4. Evolution of the incidence of acute Hepatitis B and the prevalence of Hepatitis B carriers in Tokombere.

3.3 Threshold's sensitivity analysis

Latin Hypercube Sampling (LHS) scheme is used to sample 10,000 values in the ranges listed in Table 1 for each input parameter. Notice that from the ranges of β_i, p_e, p_c, p_p and p_f, we have $\beta_e \in [0.012, 0.24]$, $\beta_c \in [0.01, 0.216]$, $\beta_p \in [0.002, 0.084]$ and $\beta_f \in [0.005, 0.12]$. Afterwards, the expression of $\mathcal{R}_0$ is used to perform 10,000 model simulations by randomly pairing sampled values for all LHS parameters. Finally, Partial Rank Correlation Coefficients (PRCC) and corresponding p-values between $\mathcal{R}_0$ and each parameter are computed [26]. An input is assumed to significantly influence $\mathcal{R}_0$ if its PRCC is less than -0.5 or greater than $+0.5$ and the corresponding p-value is less than 0.05 [11].

On the whole, as pictured in Fig. 5, the results of global sensitivity analysis are the same as in [13]. They bring out the significant and insignificant parameters in that paper. For intense, the impact of the contact rate between an infectious subject and a susceptible person is depicted in this figure by the $PRCCs$ of parameters β_e, β_p and β_i. Particularly, the basic reproduction number $\mathcal{R}_0$ is strongly and negatively impacted by the time-birth dose vaccine rate $\bar{\omega}$ ($PRCC = -0.8225$) and the initial vaccine dose rate θ_1 ($PRCC = -0.7505$). On the other hand, α_1 ($PRCC = -0.1623$) and α_2 ($PRCC = -0.0315$) have a slight negative influence on $\mathcal{R}_0$. Hence performing sensitivity analysis also leads to the conclusion that treatment could not be an effective measure to control the spread of HBV infection, and that timely birth-dose vaccination and universal vaccination are good options.

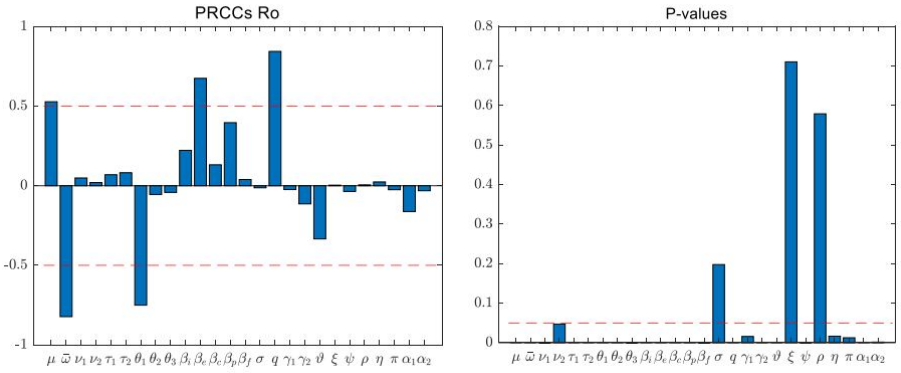


Figure 5. PRCCs and P-values.

Additionally, for the Model (2), results are informative about the loss between two consecutive doses. Indeed, the parameters θ_2 (PRCC,=-0.0547) and θ_3 (PRCC=-0.0418) are significant this time. They do not sensibly impact $\mathcal{R}_0$. By the way, even though initiation of prophylactic nucleoside analogue antiviral therapy in the third trimester of pregnancy contribute to prevent mother-to-child transmission of HBV [32], results suggest that this effort should be of limited utility. Because, the rates of perinatally infected by HBeAg positive and HBeAg negative mothers ν_1 (PRCC=0.0489) and ν_2 (PRCC = 0.0199) do not significantly influence $\mathcal{R}_0$.

§4 The model with control

With a view to re-examine the effect of vaccination and treatment in controlling the spread of HBV infection, the model is now reformulated as an optimal control problem. Our purpose here is to reduce HBV infection among the population of Tokombere by minimizing the proportions of susceptible persons, temporary and chronically infected persons with the exception of inactive carriers; as well as the cost of the control measures. Then, the maximization of the proportions of inactive carriers and recovered should follow. The Pontryagin's maximum principle is used to characterize the optimal controls and the optimality system is solved numerically.

Based on model (2), the four control measures, i.e., newborn vaccination, universal vaccination, treatment of immune active carriers and treatment of immune escape carriers enter the system as control functions denoted by $\bar{\omega}(t)$, $\theta_1(t)$, $\alpha_1(t)$ and $\alpha_2(t)$ respectively. Thus, they are regarded as time-dependent controls in a compact interval of time duration in the optimality system. The dynamics of the model are described by the following system of differential equations, in which the equation of $R(t)$ has been omitted without lost of generality.

$$\begin{cases} \dot{S} =\mu(1-\bar{\omega}(t))(1-\nu_1(E+C)-\nu_2(P+F))-(\mu_0+\theta_1(t))S-\lambda\tau_0 S, \\ \dot{V}_1 =\mu\bar{\omega}(t)+\theta_1(t)S-a_1V_1-\lambda\tau_1V_1, \\ \dot{V}_2 =\theta_2V_1-a_2V_2-\lambda\tau_2V_2, \\ \dot{L} =\lambda(\tau_0S+\tau_1V_1+\tau_2V_2)-b_lL, \\ \dot{I} =\sigma L-b_iI, \\ \dot{E} =\mu(1-\bar{\omega}(t))(\nu_1(E+C)+\nu_2(P+F))+q\gamma_1I-b_eE, \\ \dot{C} =\vartheta E+\eta P-(\mu_0+\delta_1+\xi+\psi+\alpha_1(t))C, \\ \dot{P} =(\psi+\alpha_1(t))C+(\pi+\alpha_2(t))F-b_pP, \\ \dot{F} =\xi C+\rho P-(\mu_0+\delta_2+\pi+\alpha_2(t))F, \end{cases} \tag{4}$$

where

$$a_1=\mu_0+\theta_2,\quad a_2=\mu_0+\theta_3,\quad b_l=\sigma+\mu_0,$$
$$b_i=\mu_0+d+\gamma_1,\quad b_e=\mu_0+\vartheta,\quad b_p=\mu_0+\eta+\gamma_2+\rho.$$

We assume that $\bar{\omega}(t)$, $\theta_1(t)$, $\alpha_1(t)$ and $\alpha_2(t)$ are Lebesgue integrable functions. We restrict the values of our controls so that $0\ \leq\bar{\omega}(t),\theta_1(t),\alpha_1(t),\alpha_2(t)\leq 0.9$, to eliminate the unfeasible situation in which the entire susceptible population is vaccinated and the entire population of eligible carriers is treated.

Our optimal control problem is to find $\bar{\omega}(t)$, $\theta_1(t)$, $\alpha_1(t)$ and $\alpha_2(t)$ and the associated state variables which minimize the objective functional J at a time interval $[0,T]$ given by

$$J(u)=\int_0^T\left(A_SS(t)+A_CC(t)+A_FF(t)+\frac{1}{2}\left(B_1\bar{\omega}^2(t)+B_2\theta_1^2(t)+B_3\alpha_1^2(t)+B_4\alpha_2^2(t)\right)\right)dt,$$

subject to the differential equations (4). Were A_S, A_C, A_F, are positive constants that are represented to keep a balance in the size of $S(t)$, $C(t)$, $F(t)$, respectively. And B_1, B_2, B_3, B_4 are positive weight parameters which are associated with the controls $\bar{\omega}(t)$, $\theta_1(t)$, $\alpha_1(t)$, $\alpha_2(t)$ respectively. Notice that excluding the proportions of acute HBV infected (I), immune tolerant carriers (E), even the one of inactive carriers (P) in the objective functional was suggested by some simulations. In fact, it appeared that including them does not influence the state variables, nor the control functions.

We set $u=(\bar{\omega}(t),\theta_1(t),\alpha_1(t),\alpha_2(t))$, our aim is to decrease the proportions of susceptible persons and eligible chronic carriers to treatment that are immune active and immune escape carriers. In other words, we are looking for optimal $u^*=(\bar{\omega}^*;\theta_1^*;\alpha_1^*;\alpha_2^*)$ such that:

$$J(u^*)=\min\left\{J(u),u\in U\right\},$$

with

$$U=$$

$$\left\{u,\ u(t)=(\bar{\omega}(t),\theta_1(t),\alpha_1(t),\alpha_2(t)):\ 0\le t\le T;\ u\in[0;0.9]^4;\ u \text{ is Lebesgue measurable}\right\}.$$

By applying Pontryagin's Maximum Principle and an existence result for the optimal control, we obtain the following theorem:

Theorem 4.1. *There exist an optimal control* $u^*(t)=(\bar{\omega}^*(t),\theta_1^*(t),\alpha_1^*(t),\alpha_2^*(t))$ *and corresponding solution* $(S^*,V_1^*,V_2^*,L^*,I^*,E^*,C^*,P^*,F^*)$ *that minimizes* $J(u)$ *over* U*. Moreover, there exist adjoint functions* λ_i*,* $i=1,\dots,10$*, satisfying the equations below:*

$$\begin{cases}
\dot{\lambda}_1 = -A_S+\mu_0\lambda_1+\tau_0\lambda(\lambda_1-\lambda_4)+\theta_1(t)(\lambda_1-\lambda_4),\\
\dot{\lambda}_2 = a_1\lambda_2-\theta_2\lambda_3+\tau_1\lambda(\lambda_2-\lambda_4),\\
\dot{\lambda}_3 = a_2\lambda_3+\tau_2\lambda(\lambda_3-\lambda_4),\\
\dot{\lambda}_4 = -A_L+b_l\lambda_4-\sigma\lambda_5,\\
\dot{\lambda}_5 = -A_I+b_i\lambda_5-q\gamma\lambda_6+\beta_i\tau_0S(\lambda_1-\lambda_4)+\beta_i\tau_1V_1(\lambda_2-\lambda_4)+\beta_i\tau_2V_2(\lambda_3-\lambda_4),\\
\dot{\lambda}_6 = -A_E+b_e\lambda_6-\vartheta\lambda_7+\mu\nu_1(1-\bar{\omega}(t))(\lambda_1-\lambda_6)+\beta_e\tau_0S(\lambda_1-\lambda_4)+\beta_e\tau_1V_1(\lambda_2-\lambda_4)\\
\qquad +\beta_e\tau_2V_2(\lambda_3-\lambda_4),\\
\dot{\lambda}_7 = -A_C+(\mu_0+\delta_1+\xi+\psi)\lambda_7-\psi\lambda_8-\xi\lambda_9+\alpha_1(t)(\lambda_7-\lambda_8)+\mu\nu_1(1-\bar{\omega}(t))(\lambda_1-\lambda_6)\\
\qquad +\beta_c\tau_0S(\lambda_1-\lambda_4)+\beta_c\tau_1V_1(\lambda_2-\lambda_4)+\beta_c\tau_2V_2(\lambda_3-\lambda_4),\\
\dot{\lambda}_8 = b_p\lambda_8-\eta\lambda_7-\rho\lambda_9+\mu\nu_2(1-\bar{\omega}(t))(\lambda_1-\lambda_6)+\beta_p\tau_0S(\lambda_1-\lambda_4)+\beta_p\tau_1V_1(\lambda_2-\lambda_4)\\
\qquad +\beta_p\tau_2V_2(\lambda_3-\lambda_4),\\
\dot{\lambda}_9 = -A_f+(\mu_0+\delta_2+\pi)\lambda_9-\pi\lambda_8+\alpha_2(t)(\lambda_9-\lambda_8)+\mu\nu_2(1-\bar{\omega}(t))(\lambda_1-\lambda_6)\\
\qquad +\beta_e\tau_0S(\lambda_1-\lambda_4)+\beta_e\tau_1V_1(\lambda_2-\lambda_4)+\beta_e\tau_2V_2(\lambda_3-\lambda_4),
\end{cases} \tag{5}$$

with transversal conditions

$$\lambda_i(T)=0,\quad i=1,...,9.$$

Besides, the optimal control is given by $u^*=(\bar{\omega}^*,\theta_1^*,\alpha_1^*,\alpha_2^*)$ *where*

$$\begin{cases}
\bar{\omega}^* = \max\left(0;\min\left(0.9;\dfrac{\mu(\lambda_1-\lambda_2)+\mu\left[\nu_1(E^*+C^*)+\mu\nu_2(P^*+F^*)\right](\lambda_6-\lambda_1)}{B_1}\right)\right),\\
\theta_1^* = \max\left(0;\min\left(0.9;\dfrac{(\lambda_1-\lambda_2)S^*}{B_2}\right)\right),\\
\alpha_1^* = \max\left(0;\min\left(0.9;\dfrac{(\lambda_7-\lambda_8)C^*}{B_3}\right)\right),\\
\alpha_2^* = \max\left(0;\min\left(0.9;\dfrac{(\lambda_9-\lambda_8)F^*}{B_4}\right)\right).
\end{cases} \tag{6}$$

Proof The existence of an optimal control results in the convexity of the integrand of J with respect to $u=(\bar{\omega},\theta_1,\alpha_1,\alpha_2)$, a priori boundedness of the state solutions and the Lipschitz property of the system with respect to the state variables [7] (see Corollary 4.1).

The Hamiltonian H for the control problem is defined by:

$$H(L,I,E,C,P,F,u) = A_S S(t) + A_C C(t) + A_F F(t) + \frac{1}{2}\left(B_1\bar{\omega}^2(t) + B_2\theta_1^2(t) + B_3\alpha_1^2(t)\right) + \frac{1}{2}B_4\alpha_2^2(t) + \sum_{i=1}^{9}\lambda_i f_i,$$

where $f_i,\ i = 1,\ldots,9$ is the right hand side of the equation of the i^{th} state variable in System (5).

The adjoint equations and transversality conditions can be obtained by using Pontryagin's Maximum Principle [31]. Hence, we have

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial S},\ \dot{\lambda}_2 = -\frac{\partial H}{\partial V_1},\ \dot{\lambda}_3 = -\frac{\partial H}{\partial V_2},\ \dot{\lambda}_4 = -\frac{\partial H}{\partial E},\ \dot{\lambda}_5 = -\frac{\partial H}{\partial I},$$
$$\dot{\lambda}_6 = -\frac{\partial H}{\partial L},\ \dot{\lambda}_7 = -\frac{\partial H}{\partial C},\ \dot{\lambda}_8 = -\frac{\partial H}{\partial P},\ \dot{\lambda}_9 = -\frac{\partial H}{\partial F}$$

and

$$\lambda_1(T) = \lambda_2(T) = \lambda_3(T) = \lambda_4(T) = \lambda_5(T) = \lambda_6(T) = \lambda_7(T) = \lambda_8(T) = \lambda_9(T) = 0.$$

The optimality conditions are given by

$$\frac{\partial H}{\partial \bar{\omega}} = \frac{\partial H}{\partial \theta_1} = \frac{\partial H}{\partial \alpha_1} = \frac{\partial H}{\partial \alpha_2} = 0.$$

That are

$$\begin{cases} B_1\bar{\omega} + \mu\lambda_2 - \mu\lambda_1(1 - \nu_1(E^* + C^*) - \nu_2(P^* + F^*)) - \mu\lambda_6(\nu_1(E^* + C^*) + \nu_2(P^* + F^*)) = 0, \\ B_2\theta_1 - (\lambda_1 - \lambda_2)S^* = 0, \\ B_3\alpha_1 - (\lambda_7 - \lambda_8)C^* = 0, \\ B_4\alpha_2 - (\lambda_9 - \lambda_8)F^* = 0. \end{cases}$$

Thus taking into account the bounds in U, we easily get $u^* = (\bar{\omega}^*, \theta_1^*\alpha_1^*, \alpha_2^*)$ as given by (6). □

§5 Numerical results and discussion

The optimality system is composed of the state equation (4) and adjoint equation (5). It is solved by using the forward-backward sweep method described in [23]. Numerical solutions are carried out in MATLAB (R2018a). Initial conditions, which have been chosen on the base of a prevalence of 17%, are $(0.572; 0.0455; 0.0325; 0.0007; 0.001; 0.0286; 0.0135; 0.1144; 0.0118; 0.18)$. Once again, about infected and infectious compartments, we have considered the distribution used in [13]. We use the values of parameters used to simulate the spread of the infection in Tokombere. For the weight parameters, we take $B_1 = B_2 = B_3 = B_4 = 1$. In fact, simulations show that: although control functions are sensitive to variations in the values of these parameters, the state variables are not influenced by changing their values. Thus, only A_S, A_C and A_F will vary. Figs. 6, 7, 8, represent the effects of vaccination and treatment as control measures for 20 years. As for Fig. 9, it pictures the outcome of a numerical simulation of Model (4) in the case where all controls are constant and the case where only the percentage of susceptible individuals that take the first dose of vaccine is constant.

5.1 General trend

Initially, we include all control measures: neonatal vaccination ($\bar{\omega}$), universal vaccination (θ_1), treatment of immune active carriers (α_1) and treatment of immune escape carriers (α_2); i.e., $A_S = 2$, $A_C = 1$ and $A_F = 1$. For this choice of the balancing parameters, we can see in Fig. 6b that the proportion of fully susceptible individuals significantly decreases, while the proportions of vaccinated with one previous dose and vaccinated with two previous doses significantly increase. Logically, the proportion of recovered must also increase. At the same time, the proportions of exposed, acute infected, immune tolerant carriers, immune escape carriers and inactive carriers remain steadily around their respective initial values.

This control regime suggests, as depicted in Fig. 6a, that universal vaccination is the key to disease management. Actually, the rate of neonate vaccination start at 5.22% and steadily decreases over the time interval down to zero at the final time, while the universal vaccination rate starts at 85.18% then has the same behaviour as the former rate. On the other hand, the profiles of treatment rates α_1 and α_2 give the impression that treatment is of no importance, they are very far from being at their maxima as in [15,20,34,44]. Indeed, they start respectively at 1.15% and 1.05% and also steadily decrease to zero at the end time.

5.2 Influence of treatment

More simulation results strengthen the idea that treating the immune active and immune escape carriers is of limited interest. Indeed varying the values of A_C and A_F does not sensibly affect the optimal states, except the immune active and immune escape carriers, and therefore the of inactive carrier. In Fig. 7, $A_C = A_F = 300$ and the other parameters are as previously. In this picture, compared to the pictures in Fig. 6, we can see that when the maximum treatment rates of immune active and immune escape carriers are applied for more than the first ten years (Fig. 7a), the proportions of immune active and immune escape carriers in the optimality system are smaller and decrease over the time interval; moreover, the proportion of inactive carriers is bigger and increase. Meanwhile, the changes in the plots of the other state variables are not noticeable (Fig. 6b). In addition, the optimal vaccination strategies are unchanged.

On the whole, the discrepancies with the results in Fig. 6b appear only in the plots of the proportions of immune active and inactive carriers when we change the values of A_C. Likewise only the immune escape and inactive carriers are affected when the value of A_F varies. In both cases, the plots of the other states and the vaccination functions remain almost the same as in that figure. To conclude, Fig. 7 reflect that raising the treatment rate of immune active and immune escape carriers, and then the cost of this two control measures, only impact the disease burden. Because, the death rate due to HBV infection is mainly related to the immune active and immune escape states. Indeed, among HBV chronic carriers, they are the ones who are most at increased risk of progression to cirrhosis and hepatocellular carcinoma, which can lead to a liver-related death. Immune tolerant carriers have little or no inflammation or fibrosis of the liver, while inactive and HBsAg-negative carriers have low risk of progression to cirrhosis or hepatocellular carcinoma [43]. Notice that reaching the state of inactive carrier is a valuable endpoint of current hepatitis B treatment [5]. It must be said that inactive carriers are very lesser infectious than immune active and immune escape carriers. Therefore, they less

propagate the disease. Moreover the higher the proportion of inactive carriers is, the more recovering happens. Nevertheless, in the end, reaching this state through treatment, does not sensibly act upon the appearance of new cases.

5.3 Influence of newborn vaccination

Contrary to treatment, simulation results suggest that seeking strategy to limit the incidence of HBV infection should focus on vaccination, mostly the universal vaccination. The two vaccination rates naturally increase according to the coast of vaccination. From the value 3 of A_S, fully susceptible individuals can be vaccinated at the maximum level over a period of time that increases as the value of A_S rises. Neonate vaccination has the same behaviour from the value 41 of A_S. Besides, the more the vaccination rates increase, faster the proportion of fully susceptible persons declines. And the proportions of vaccinated with one and two doses grow. But from the value 5 there is no more change in the proportion of fully susceptible individuals. Meanwhile the proportions of both incomplete vaccinated groups rise weakly in relation to the value of A_S. However, the proportions of exposed, acute infected and all chronic carrier states are slightly affected in all ways. Unfortunately, implementation of universal vaccination is not feasible in SSA, owing mostly to limited resources. Then the trend in this region is the implementation of newborn vaccination.

According to [3], timely birth-dose vaccination followed by completion of the 3-dose infant-vaccination series is the most cost-effective intervention. It can prevent 75–95 % of the vertical HBV infections. Simulations in Fig. 8 are made in a context where there is no universal vaccination ($\theta_1 = 0$), only newborn vaccination and treatments are considered, $A_S = 60$; $A_C = 80$ and $A_F = 80$ (to come to a realistic policy of treating immune active and immune escape carriers). In Fig. 8a, the rate of neonate vaccination $\bar{\omega}$ starts and remains at its maximal value for more than 10 years. While the treatment rates start at 0.75 for immune active carriers and 0.65 for immune escape carriers, and decrease over the time interval.

In this scenario, the proportion of the tree susceptible classes are fewer than in the previous figures, certainly because of the absence of universal vaccination. The proportion of fully susceptible individuals remains steadily around its initial value. The ones of vaccinated with one and two previous doses decrease and increase slowly respectively. At the same time, the proportions of immune active and immune escape carriers are just a little bit lower than in Fig. 7b, while the one of inactive carrier is slightly larger. This is due to the slackening of the treatment rates of the eligible carriers in this case.

On the other hand, always comparatively with the previous case, the plots of proportions of exposed and acute infected persons have not changed significantly, the one of immune tolerant carriers too. Meaning that in the optimality system, the incidence of acute infection and the prevalence of chronic infection are nearly impacted in the same way as in Fig. 7, although the proportions of susceptible groups are lesser large.

In a word, Fig. 8b shows that in the current case, the epidemic is controlled and its outcome is almost the same as in Fig. 7b where the universal vaccination is regarded. Thus, we can conclude that optimal time-birth vaccination is a valuable option, it can substantially prevent new acute infections and therefore new chronic infections as well as universal vaccination.

5.4 An optimal strategy for SSA

In order to have an insight on reaching targets defined by the WHO in a Sub-saharan African rural zone, in Fig. 9 we show the outcome of a numerical simulation for Model (4) over a time period of 10 years in two scenarios. We first suppose that all controls are constant and have the same respective values used to simulate the spread of HBV infection in Tokombere. That are $\bar{\omega} = 0.1$, $\theta_1 = 0.05$, $\alpha_1 = 0.2$ and $\alpha_2 = 0.1$. Meaning that: 10% of births receive a dose of hepatitis B vaccine within 24 hours from delivery, 5% of susceptible individuals are vaccinated with the first dose, 20% of immune active carriers and 10 % of immune escape carriers are treated every year. Thereafter we consider that only θ_1 is constant and still equal to 0.05, while the other controls are determined by the optimal control process. The former scenario predicts the course of HBV infection in Tokombere and the later outlines how optimizing neonate vaccination and treatment can help reaching the goals defined by the WHO, which aims at reducing new viral hepatitis infections by 90% and reducing deaths cases due to viral hepatitis by 65% by 2030 [40].

In Fig. 9b, the effect of neonatal vaccination can be observed through the discrepancy between the proportions of each of the three susceptible classes. On the other hand, the reduction of the new infections can be seen through the gap between the plots of proportions of exposed and acute infected persons in the two scenarios. In addition, it can be seen that the optimal treatment strategies can reduce the predicted proportion of carriers exposed to complications of the disease, and who as a result can die of it, that is to say immune escape carriers and immune active carriers. Albeit the cost of this strategy is especially high. In effect, the immune active and immune escape carriers should be treated at the maximal rate for the first 2 years. Regarding the neonatal vaccine, its rate must be at it upper bound for almost the first 6 years (Fig. 9a). Actually, when it remains like this for a larger time period, the changes in the plots are small. Nevertheless, in the area of Tokombere, by observing the initial values used for simulations in Fig. 9b, it appears that this optimal combination of strategies alone is not sufficient to achieve the goals targeted by the WHO by 2030. Hence, the recommendation in [32], that SSA will need to actively prioritise implementation of several elimination strategies should be taken.

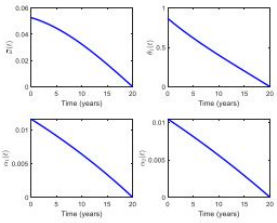
Global sensibility analysis suggested that initiation of prophylactic nucleoside analogue antiviral therapy in the third trimester of pregnancy is of limited use. Investigation in [30] led to the same conclusion about the additional protection provided by the HBIG, when it is combined with HBV birth-dose vaccine. This work tends to support these findings. Given that the upper bound of the birth-dose vaccine rate used for simulations in this paper is 0.9. Then, in the context of SSA where: resources are limited [25, 32]; many HBV–infected patients remain undiagnosed [29]; incomplete immunization coverage after birth remains high [22]; HBIG is not readily available at most primary health care clinics [3]; both knowledge of risk factors and transmission of HBV infection and vaccination status are very low [17, 29]. The additional expenses for the adminstration of HBIG and treatment to carrier pregnant women could be avoided in the national control programs. In contrast, some works established the significant impact of affordable measures such as isolation [18, 19, 34] and educational campaigns [18, 34].

§6 Conclusion

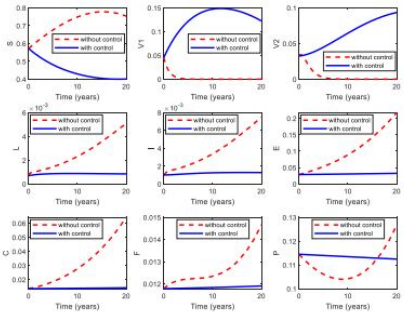
In this paper we have improved the model in [13] by taking into account the HBeAg status of pregnant women. The resulting model has been developed with constant control variables, mathematical results and global sensitivity analysis results in [13] have been found again. It has been applied to fit HBV incidence in the Zhejiang Province of China from 2005 to 2016. And the simulation results have matched the HBV new cases reported data (Fig. 2). Also, it has been used to predict a bright future in this Chinese province. In fact, simulations indicate that the control measures and immunization program implemented in Zhejiang Province are effective. Furthermore, in this area the incidence of acute Hepatitis B and the prevalence of chronic Hepatitis B are declining swiftly and will maintain this tendency (Figs. 3a, 3b). As a consequence, the disease burden is fast lowering too and will be close to eradication by 2064 (Fig. 3c). In contrast, Tokombere faces very bad days in future. Here, the disease is not destined to die out with current weak intervention strategies (Fig. 4). Thereafter, we have modified the proposed model by incorporating four time-dependent control variables.

The optimal controls represent the efforts to enhance time-birth dose vaccination, universal vaccination and treatment of eligible chronic carriers in the context of Tokombere. After investigation, it has been observed that the optimal control strategies have a dramatic effect on the spread and the prevalence of HBV infection as compared with the model without control. Moreover, numerical results corroborated finding in [13] that vaccination is the key tool to control HBV. And that treatment is much more effective for reducing the disease induced death. Actually, it cannot be a reliable strategy to limit new infections. This supports the state in [9] that universal vaccination is better than treatment to limit infection and contradicts finding in [21,44] that the treatment is more effective than vaccination. Also finding in [19] that proper treatment is necessary for the curtailing of HBV infection; and in some ways, finding in [15, 16, 21, 44] that simultaneous use of vaccination and treatment is much more effective than the use of single control policies. In addition, investigation have shown that an effective implementation of the newborn vaccination with high full 3-dose and timely birth dose coverage rates is a decisive strategy, although it is insufficient to reach the elimination targets defined by the WHO in SSA by 2030.

Finally, to achieve the WHO goals, the optimal control strategy in SSA should be made of several elimination strategies. In concrete terms, timely administration of the HBV birth-dose vaccine, and ensuring subsequent full HBV-vaccine coverage should form the cornerstone of the HBV elimination strategy. In addition, programmes aimed at raising public awareness about the HBV among the population generally and the vertical transmission among pregnant women particularly should be considered. In fact, governments should take the responsibility to heighten the level of public awareness about the HBV spread, the rationale of receiving three doses of HBV vaccines and the benefit of being aware of one's infectious status. Furthermore, they should strive to make diagnosis and antiviral therapy affordable, and to improve social conduct in order to limit risky contacts. Given that resources are limited, the adminstration of HBIG and the treatment of all carrier pregnant women could be avoided in control programs.

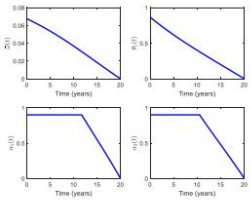


(a) Control profiles.

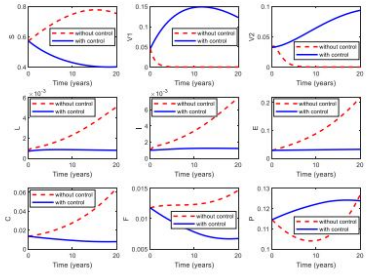


(b) Optimal states.

Figure 6. Comparison in both models: with control system and without control system, $A_S = 2$, $A_C = 1$, $A_F = 1$.

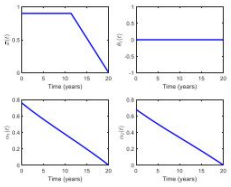


(a) Control profiles.

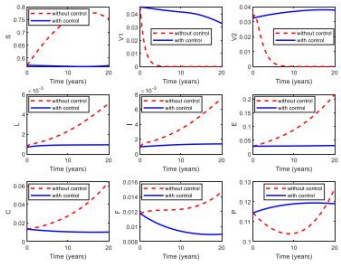


(b) Optimal states.

Figure 7. Emphasizing immune escape carriers treatment. Comparison in both models: with control system and without control system, $A_S = 2$, $A_C = 300$, $A_F = 300$.

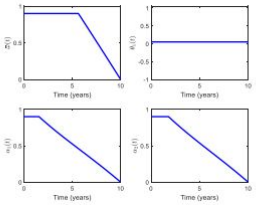


(a) Control profiles.

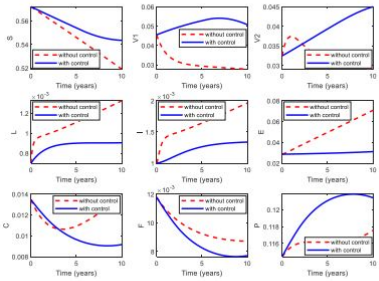


(b) Optimal states.

Figure 8. Emphasizing newborn vaccination in the absence of universal vaccination. Comparison in both models: with control system and without control system, $A_S = 60$, $A_C = 80$, $A_F = 80$.



(a) Control profiles.



(b) Optimal states.

Figure 9. Comparison in a model in which all controls are constant and a model in which only the rate of the first dose of universal vaccination is constant, $A_S = 60$, $A_C = 125$, $A_F = 150$.

Declarations

Conflict of interest The authors declare no conflict of interest.

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