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OPTIMALITY CONDITIONS IN AGE-STRUCTURED HEPATITIS B MODEL WITHOUT VERTICAL TRANSMISSION

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Abstract

This paper deals with the analysis of the optimal test strategy vaccination of a modified age-structured model for the transmission dynamics of hepatitis B without vertical transmission. The proposed model takes into account the additional mortality rate associated with the disease. It appears that the optimal strategies are one or two-age strategies.

1. Introduction

This paper focuses on the analysis of the optimal test strategy vaccination of a modified age-structured model for the transmission dynamics of hepatitis B without vertical transmission. In our previous work [6], we suppose that a vaccinated person may become susceptible if a vaccine is not effective and recovered if a vaccine is

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effective. In this model, we define costs of the vaccination strategy and effect by considering the additional mortality rate associated with the disease. We follow methods of C. Castillo-Chavez and Z. Feng [3], Kouakep and Houpa [4], Hadeler and Muller [10], Stoer and Witzgall [13].

The manuscript is organised as follows: second section is devoted to problem formulation, third section to preliminary result, fourth section to optimization problem and result, we end this work by conclusion and perspectives.

2. Problem Formulation

We consider a general age structured model describing the dynamics of transmission of hepatitis B without vertical transmission. A population of size $N(a, t)$ is stratified into six compartments, namely: susceptible $S(a, t)$, latently infected $E(a, t)$, acutely infected $I(a, t)$, carrier $C(a, t)$, recovered $R(a, t)$ and vaccinated $V(a, t)$ with age distribution at time t. We suppose that all newborns are susceptible. The parameters used are described as follows:

- $b(a)$ birth rate.
- $\mu(a)$ natural mortality rate.
- $\mu_1(a)$ HBV-related mortality rate.
- ε reduced transmission rate from chronic carriers compared to acute infections.
- $\sigma(a)$ rate moving from latent to acute.
- $\gamma_1(a)$ rate moving from acute to carrier.
- $\gamma_2(a)$ rate moving from carrier to recovered.
- $\Psi(a)$ vaccination rate against hepatitis B.
- $q(a)$ probability that an individual fails to clear an acute infection and develops to carrier state.
- $\varphi(a)$ rate moving from vaccinated to susceptible.
- $p(a)$ probability that an individual fails to clear a latent infection and

develops to acute infection state.

• $u(a)$ probability that an individual fails to clear vaccinated and develops to susceptible state.

The variables and model structured are described in the following figure:

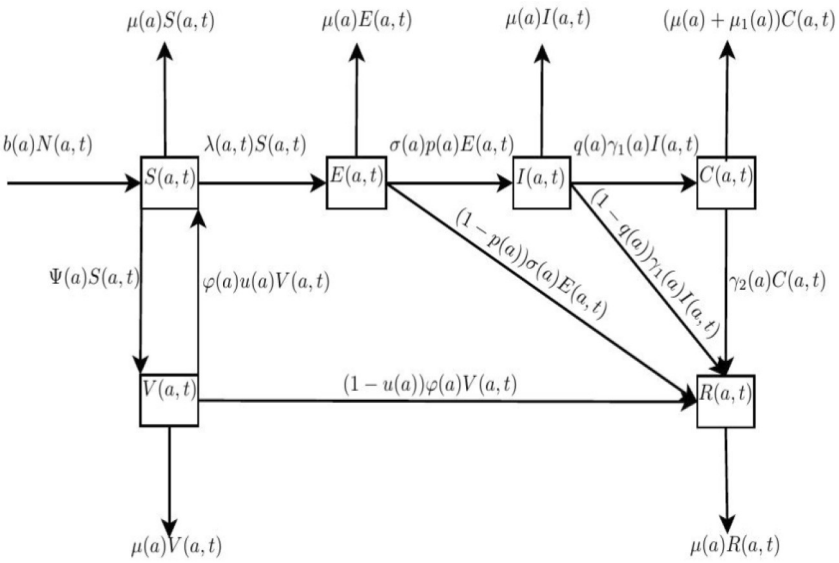

Figure 1. Model of HBV without vertical transmission.

Under the above assumptions and parameters, the dynamic of the disease can be described by the following system of partial differential equations:

$$\begin{cases} \frac{\partial S(a,t)}{\partial t}+\frac{\partial S(a,t)}{\partial a}=b(a)N(a,t)+\varphi(a)u(a)V(a,t)-(\mu(a)+\lambda(a,t)+\Psi(a))S(a,t) \\ \frac{\partial E(a,t)}{\partial t}+\frac{\partial E(a,t)}{\partial a}=\lambda(a,t)S(a,t)-(\mu(a)+\sigma(a))E(a,t) \\ \frac{\partial I(a,t)}{\partial t}+\frac{\partial I(a,t)}{\partial a}=\sigma(a)p(a)E(a,t)-(\mu(a)+\gamma_1(a))I(a,t) \\ \frac{\partial C(a,t)}{\partial t}+\frac{\partial C(a,t)}{\partial a}=q(a)\gamma_1(a)I(a,t)-(\mu(a)+\mu_1(a)+\gamma_2(a))C(a,t) \\ \frac{\partial R(a,t)}{\partial t}+\frac{\partial R(a,t)}{\partial a}=-(1-u(a))\varphi(a)V(a,t)+(1-p(a))\sigma(a)E(a,t)+(1-q(a))\gamma_1(a)I(a,t) \\ \qquad\qquad +\gamma_2(a)C(a,t)-\mu(a)R(a,t) \\ \frac{\partial V(a,t)}{\partial t}+\frac{\partial V(a,t)}{\partial a}=\Psi(a)S(a,t)-(\mu(a)+\varphi(a))V(a,t) \end{cases} \tag{1}$$

with initial and boundary conditions:

$$\begin{cases} S(0, t) = \int_{a_1}^{a_2} b(a)N(a, t)\mathrm{da};\ E(0, t) = I(0, t) = C(0, t) = R(0, t) = V(0, t) = 0, \\ S(a, 0) = S_0(a);\ E(a, 0) = E_0(a);\ I(a, 0) = I_0(a);\ C(a, 0) = C_0(a), \\ R(a, 0) = R_0(a);\ V(a, 0) = V_0(a), \end{cases}$$

where a_1 and a_2 are, respectively, the minimum and maximum age of procreation.

The total population is: $N(a, t) = S(a, t) + E(a, t) + I(a, t) + C(a, t) + R(a, t) + V(a, t)$.

By summing all equations of system (1), we obtain the following equations for the total population $N(a, t)$:

$$\frac{\partial N(a, t)}{\partial t} + \frac{\partial N(a, t)}{\partial \mathrm{a}} = b(a)N(a, t) - \mu(a)N(a, t) - \mu_1(a)C(a, t).$$

$$N(0, t) = \int_{a_1}^{a_2} b(a)N(a, t)\,da.$$

Those relations show that the population dynamics is affected by the disease.

Following [2] one can express the force of infection by:

$$\lambda(a, t) = k(a)\int_0^{a_+} \tilde{\beta}(a')\left(\frac{I(a', t) + \varepsilon C(a', t)}{N(a', t)}\right)da',$$

where a_+ is the maximum age of individual, the function $k(a)$ and $\tilde{\beta}(a')$ are, respectively, the age-specific (average) probability of becoming infected through contact with infectious individuals and the age-specific per-capita contact/activity rate.

Let $s(a, t) = \frac{S(a, t)}{N(a, t)}$, $e(a, t) = \frac{E(a, t)}{N(a, t)}$, $i(a, t) = \frac{I(a, t)}{N(a, t)}$, $c(a, t) = \frac{C(a, t)}{N(a, t)}$, $r(a, t) = \frac{R(a, t)}{N(a, t)}$, and $v(a, t) = \frac{V(a, t)}{N(a, t)}$. Then we obtain the following normalised system of partial differential equations:

$$\begin{cases} \frac{\partial s(a,t)}{\partial t} + \frac{\partial s(a,t)}{\partial a} = b(a) + \varphi(a)u(a)v(a,t) - (-\mu_1(a)c(a,t) + k(a)\lambda(t) + \Psi(a) + b(a))s(a,t) \\ \frac{\partial e(a,t)}{\partial t} + \frac{\partial e(a,t)}{\partial a} = k(a)\lambda(t)s(a,t) - (b(a) - \mu_1(a)c(a,t) + \sigma(a))e(a,t) \\ \frac{\partial i(a,t)}{\partial t} + \frac{\partial i(a,t)}{\partial a} = \sigma(a)p(a)e(a,t) - (b(a) - \mu_1(a)c(a,t) + \gamma_1(a))i(a,t) \\ \frac{\partial c(a,t)}{\partial t} + \frac{\partial c(a,t)}{\partial a} = q(a)\gamma_1(a)i(a,t) - (b(a) - \mu_1(a)c(a,t) + \mu_1(a) + \gamma_2(a))c(a,t) \\ \frac{\partial r(a,t)}{\partial t} + \frac{\partial r(a,t)}{\partial a} = -(1-u(a))\varphi(a)v(a,t) + (1-p(a))\sigma(a)e(a,t) + (1-q(a))\gamma_1(a)i(a,t) \\ \qquad\qquad + \gamma_2(a)c(a,t) - (b(a) - \mu_1(a)c(a,t))r(a,t) \\ \frac{\partial v(a,t)}{\partial t} + \frac{\partial v(a,t)}{\partial a} = \Psi(a)s(a,t) - (b(a) - \mu_1(a)c(a,t) + \varphi(a))v(a,t) \\ \lambda(t) \qquad\qquad = \int_0^{a_+} \tilde{\beta}(a')(i(a',t) + \epsilon c(a',t))da' \end{cases} \tag{2}$$

with initial and boundary conditions:

$$s(0,t) = 1;\ e(0,t) = i(0,t) = c(0,t) = r(0,t) = v(0,t) = 0.$$

3. Previous Result

In the previous work [6], we proove that if $R(\Psi) < R_0 < 1$, the DFE is locally and globally asymptotically stable, and if $R_0 > 1$ unstable, we also prove that there exist an endemic equilibrium. We did not prove the existence and stability in the case when $R(\Psi) < 1 < R_0$. For the wellposedness of our problem (see [6]).

4. Vaccination Strategies and Optimality Conditions

Let define $F(\Psi) = R_0 - R(\Psi)$ and $C(\Psi) = \int_0^{a_+} \kappa(a')\Psi(a')s^0(a')da'$ with $\kappa(a')$ representing the cost associated with one vaccination at age a', $s^0(a')$ a density of susceptible at DFE (Disease free equilibrium). We define also the function $\phi(a') = -\frac{d}{da'}e^{-\int_0^{a'}\Psi(\tau)d\tau}$, then we obtain $1 - e^{-\int_0^{a'}\Psi(\tau)d\tau} = -\int_0^{a'}\phi(\tau)d\tau$ and $\Psi(a') = \frac{\phi(a')}{1 - \int_0^{a'}\phi(a')da'}$. This gives us, linear expression of $F(\Psi)$ and $C(\Psi)$.

Two problems emerged as mentioned by C. C. Chavez in [3]. Let R_* and C_* be two constants.

(I) Find a vaccination strategy $\Psi(a')$ that minimizes $C(\Psi)$ constrained by $R(\Psi) \leq R_*$.

(II) Find a vaccination strategy $\Psi(a')$ that minimizes $R(\Psi)$ constrained by $C(\Psi) \leq C_*$.

It is not easy to overcome the difficulty we have faced without transforming the expression of $F(\Psi)$ and $C(\Psi)$. Hadeler and Muller, and C.C. Chavez [10, 3] show how to transform a non linear maps $F(\Psi)$ and $C(\Psi)$ into linear functionals $\overline{F}(\phi)$ and $\overline{C}(\phi)$ by using the expression of $\phi(a')$. By changing the order of integration twice, in expression of $F(\Psi)$ and some approximation in the neighborhood of zero, we found:

$$\overline{F}(\phi) = \int_0^{a_+} K(a')\phi(a')\,da' \tag{3}$$

and

$$\overline{C}(\phi) = \int_0^{a_+} \kappa(a')\phi(a')\,da' \tag{4}$$

with:

$$K(a') = \int_{a'}^{a_+} \tilde{\beta}(\eta)\int_{a'}^{\eta} e^{-\int_{\lambda}^{\eta} b(\tau)\,d\tau} k(\lambda) e^{-\int_{a'}^{\lambda}(b(\tau)+u(\tau)\varphi(\tau))\,d\tau} \int_{\lambda}^{\eta} e^{-\int_{\lambda}^{\xi}\sigma(\tau)\,d\tau}\sigma(\xi)p(\xi)$$

$$\times\left[e^{-\int_{\xi}^{\eta}\gamma_1(\tau)\,d\tau} + \epsilon\int_{\xi}^{\eta} e^{-\int_{\alpha}^{\eta}(\mu_1(\tau)+\gamma_2(\tau))\,d\tau} q(\alpha)\gamma_1(\alpha) e^{-\int_{\xi}^{\alpha}\gamma_1(\tau)\,d\tau}\,d\alpha\right] d\xi\,d\lambda\,d\eta. \tag{5}$$

So, we have replace two non linear functionals by two linear functionals given by $\overline{F}(\phi)$ and $\overline{C}(\phi)$.

Letting $\rho = R_0 - R_*$ and $Q(\phi) = \int_0^{a'} \phi(a')\,da'$. It is easy to see that $Q(\phi) \leq 1$.

Now, we replace (I) by these new linear optimization problem:

$$\begin{aligned} &\textit{Minimise } \overline{C}(\phi), \\ &\textit{subject to } \quad f(\phi) \le 0, \\ &\phi \ge 0, \end{aligned} \tag{6}$$

where

$$f(\phi) = \begin{pmatrix} f_1(\phi) \\ f_2(\phi) \end{pmatrix} = \begin{pmatrix} \rho - \overline{F}(\phi) \\ Q(\phi) - 1 \end{pmatrix}$$

and $f(\phi) \le 0$ is equivalent to $f_i(\phi) \le 0 (i = 1, 2)$. Like Castillo and Feng [3], we use the Saddle Point Theorem of Khun and Tucker for the convex optimization problem [13]. We can show that (I) is mathematically equivalent to (P1) in [10]. Hence using the same arguments we arrive at the following conclusion.

Theorem 1. *There are two possible optimal vaccination strategies in* (I):

(i) *One age strategy*: *vaccinate the susceptible population at exactly age A*.

(ii) *Two age strategy*: *vaccinate part of the susceptible population at age* A_1 *and the remaining susceptibles at a later age* A_2.

Proposition 2. *We suppose that birth rate* $b(a)$ *add probability an individual fails to clear vaccinated and develops to susceptible state times rate moving from vaccinated to susceptible* $u(a)\varphi(a)$ *is a constant*, *we can say that* $\theta = \int_0^{\lambda} (b(\tau) + u(\tau)\varphi(\tau))\, d\tau$.

For two vaccination strategies, the optimal ages can be calculated in the following way: Note that $K(a')$ is a strictly decreasing function with $K(0) = e^{-\theta} R_0 > \rho$ and $\theta < \ln(\frac{R_0}{\rho})$, also $K(a') \to 0$ when $a' \to +\infty$. Hence we can find $A_* > 0$ such that $K(A_*) = \rho$. Let A be the minimum of the quotient $\frac{\kappa(a')}{K(a')}$ (see [10] for discussions about the existence of A). If $A \in [0, A_*]$, then it gives an optimal age for the one age-strategy. If $A \in (A_*, +\infty)$, then the optimal two age-

strategy is found by minimizing the expression $C(A_1, A_2)$ on $A_1 \in [0, A_*]$ and $A_2 \in (A_*, +\infty)$, where:

$$C(A_1, A_2) = \frac{\rho - K(A_2)}{K(A_1) - K(A_2)} \kappa(A_1) + \frac{K(A_1) - \rho}{K(A_1) - K(A_2)} \kappa(A_2). \quad (7)$$

For (II), we obtain similar results (one or two age-strategies of vaccination).

5. Conclusion and Perspectives

We found one or two age-strategies by considering our model, like in [3, 4, 10], it surely holds because we neglect the vertical transmission. WHO recommend since 1992 a three age-strategies in high endemic areas [1]. In Niger Republic it is at 6th, 10th, 14th weeks after birth. We also found the link between the efficacy of vaccine and newborn population, if $\theta < \ln(\frac{R_0}{\rho})$, we get optimal conditions. This means that if the vaccine is effective and newborn population controlled by vaccination, we will get a good result in the way for controlling this disease. This work is different from Kouakep T. Y. and Houpa D. D. E. [4], they did not take account a latent class who is very important in the transmission dynamics of hepatitis B. They did not prove also the importance of effective vaccine.

In the next step, we will see the impact of vertical transmission to get the best strategy to apply, for eradicating this major public health problem, and maybe to see also possible co-infection with other disease like hepatitis C and VIH [14].

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