Gen. Math. Notes, Vol. 20, No. 1, January 2014, pp.19-26
ISSN 2219-7184;
www.i-csrs.org
Available free online at http://www.geman.in

Optimal Test Strategies for Hepatitis B Vaccination with no Vertical Transmission

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(Received: 12-10-13 / Accepted: 25-11-13)

Abstract

We consider a age-structured model with vaccination and define costs for a vaccination strategy and effect. Two optimization problems in a free disease pattern situation emmerge: to find the strategy with minimal costs at a given level for the effect, and also to find the strategy with maximal effect at given costs. It turns out that there is an optimal strategy that is nonzero in one or two age classes, i.e., consists of a sum of at most two delta-peaks.

Keywords: *Vaccination, Optimization, Age-structure, Public health.*

1 Introduction

This paper investigates age strategies able to optimize the cost (impact and effect[5]) of the vaccination on an hepatitis B model. Our model with application on Hepatitis B (see Pasquini et al.[13] for a good and general description) adds age structure a to the continuous time t and analyses then, some improvements in the comprehension of the disease dynamics (please compare to A.A. Elbab et al.[3] without age or J. Fu et al.[4] with diffusion). We follow methods of Castillo & Feng[2] with Hadeler & Muller[6] and Stoer & Witzgall[14]. The main result (see Theorem 4.3 therein) is that *in a free disease pattern, there is an optimal strategy that is nonzero in one or two age classes, i.e., consists of a sum of at most two delta-peaks.* The paper is organised as follow: second, third, fourth and last sections are devoted to problem formulations,

primary material on the model, results on optimal vaccination strategies and a discussion.

2 Problem Formulations

In this paper we will consider the following (chronological) age-structured model with vaccination

$$\begin{aligned}
&(\partial_t + \partial_a + \Psi(a) + \mu)\, s(t,a) = -\lambda_0(t,a)s(t,a),\\
&(\partial_t + \partial_a + \mu)\, v(t,a) = \Psi(a)s(t,a) - \delta\lambda_0(t,a)v(t,a),\\
&(\partial_t + \partial_a + (\mu_I + \mu))\, i(t,a) = \lambda_0(t,a)p(a)\left(s(t,a) + \delta v(t,a)\right),\\
&(\partial_t + \partial_a + \nu_E)\, e(t,a) = \lambda_0(t,a)q(a)\left(s(t,a) + \delta v(t,a)\right),\\
&(\partial_t + \partial_a + \mu)\, r(t,a) = (\mu_I - \epsilon)i(t,a),
\end{aligned} \tag{1}$$

posed for time $t > 0$, (chronological) age $a > 0$, $\mu_I, \nu_E, \mu, \epsilon \geq 0$, $\nu_E \geq \mu$ and $\mu_I - \epsilon \geq 0$. Here $s(t,a)$ denotes the age-specific density of susceptibles, $e(t,a)$ and $i(t,a)$ denotes respectively the the age-specific density of chronic carriers and acute infected individuals (that can be symptomatic or asymptomatic) while $r(t,a)$ denotes the recovered individuals from acute infection. $v(t,a)$ is the density of vaccinated individuals. The term $\lambda_0(t,a)$ corresponds to the age-specific force of infection and follows the usual law of mass-action, that reads as

$$\lambda_0(t,a) = \int_0^\infty \left[\beta_i(a,a')i(t,a') + \beta_e(a,a')e(t,a')\right] da'.$$

Here $\beta_i(a,a')$ and $\beta_e(a,a')$ respectively denote the contact transmission rate between acute infected (resp. asymptomatic carriers) of age a' with susceptible of age a. $\Psi(a)$ is the proportion of susceptibles vaccinated. $0 \leq \delta \leq 1$ is the reduction in risk due to prior exposure to vaccination. That means: $\delta = 0$ corresponds to a perfect vaccine and $\delta = 1$ corresponds to a totally imperfect vaccine. In addition $p \in L^\infty_+(0,\infty)$ is a given function such that $0 \leq p(a) \leq 1$ *a.e.* while $q(a) \equiv 1 - p(a)$. Function q represents the age-specific probability to become a chronic carrier when becoming infected at age a. Function p denotes the probability to develop an acute infection when getting the infection at age a. We refer to Nokes et al. [12] for more explanation on the age-dependence susceptibility to the infection and Abboubakar [1] for their estimations from data with maximum likewood or least mean square methods. This problem is supplemented together with the boundary conditions:

$$\begin{aligned}
&s(t,0) = \Lambda, \text{ (constant external influx)}\\
&i(t,0) = e(t,0) = 0, \text{ (no vertical transmission)},\\
&r(t,0) = 0, \text{ (no immunity at birth)},
\end{aligned} \tag{2}$$

and initial data

$$s(0,a)=s_0(a),\ \ i(0,a)=i_0(a),\ \ e(0,a)=e_0(a),\ \ r(0,a)=r_0(a),\ \ v(0,a)=v_0(a). \tag{3}$$

Note that the r component of the system is decoupled from the other components and has therefore no impact upon the long time behaviour of the system. To perform our analysis we shall assume that the contact between individuals is homogeneous so that

$$\beta_i(a,a')\equiv\beta_I>0 \text{ and } \beta_e(a,a')\equiv\beta_E\geq 0.$$

By setting

$$I(t):=\int_0^\infty i(t,a)da \text{ and } E(t):=\int_0^\infty e(t,a)da,$$

one obtains that (s,v,I,E) satisfies the following system of equations:

$$\begin{aligned}
&(\partial_t+\partial_a+\mu)\,s(t,a)=-\lambda(t)s(t,a),\ \ t>0,\ a>0,\\
&s(t,0)=\Lambda,\\
&(\partial_t+\partial_a+\mu)\,v(t,a)=\Psi(a)s(t,a)-\delta\lambda(t)v(t,a),\\
&I'(t)=\lambda(t)\int_0^\infty p(a)\left(s(t,a)+\delta v(t,a)\right)da-\nu_I I(t),\\
&E'(t)=\lambda(t)\int_0^\infty q(a)\left(s(t,a)+\delta v(t,a)\right)da-\nu_E E(t),\ \ t>0,
\end{aligned} \tag{4}$$

with

$$\lambda(t)=\beta_I I(t)+\beta_E E(t), \tag{5}$$

The disease free equilibrium is defined as $x_F^\Psi=\left(s_F^\Psi,v_F^\Psi,0,0\right)^T$ wherein we have set $s_F^\Psi(a)=\Lambda e^{-\left(\mu a+\int_0^a\Psi(s)ds\right)}$ and $v_F^\Psi(a)=s_F(a)-s_F^\Psi(a)$. One can see that

$$s_F^\Psi(a)\leq s_F(a)=\Lambda e^{-\mu a},\forall a\geq 0$$

It traduces the benefit of vaccination for population because it reduces population of susceptibles to HBv (Hepatitis B virus).

Like Cameroon Government (see [9]) we choose the situation with no newborn baby vaccination: $v(t,0)=0$.

3 Preliminary Materials

We denote by R_0^Ψ the basic reproduction rate for the new partial model (4). Clearly it is

$$R_0^\Psi:=\left[\int_0^\infty\left(\frac{\beta_I}{\nu_I}p(a)+\frac{\beta_E}{\nu_E}q(a)\right)\left(s_F^\Psi(a)+\delta v_F^\Psi(a)\right)da\right] \tag{6}$$

With $\left(s_F^{\Psi}(a) + \delta v_F^{\Psi}(a)\right) = s_F(a) - (1-\delta)\left(s_F(a) - s_F^{\Psi}(a)\right)$. We recall the basic reproduction rate for our previous model (1) without vaccination

$$R_0 := \left[\int_0^{\infty} \left(\frac{\beta_I}{\nu_I} p(a) + \frac{\beta_E}{\nu_E} q(a)\right) s_F(a) da\right] = R_0^0 \tag{7}$$

The wellposedness of this model is studied as in Inaba[7] or Kouakep et al.[8]. It can be show that there is a unique positive nontrivial stationary solution if the reproduction number R_0 is greater than one, while for $R_0 < 1$ there is only the noninfected stationary solution.

We see that $R_0 \geq R_0^{\Psi}$. As mentioned by Castillo & Feng[2], "the infection-free state may be locally/globally asymptotically stable if $R_0^{\Psi} < 1$ and unstable if $R_0^{\Psi} > 1$. Also an endemic steady state exists when $R_0^{\Psi} > 1$. We have not shown whether or not endemic steady states exist for parameters that satisfy $R_0^{\Psi} < 1 < R_0$. This may suggest the existence of a backwards bifurcation of nontrivial equilibria for some parameter values in that range".

We define $F(\Psi) = R_0 - R_0^{\Psi}$ and $C(\Psi) = \int_0^{+\infty} u(a)\Psi(a)s_F^{\Psi}(a)da$ with $u(a)$ is a positive function representing the cost associated with one vaccination at age a. We define also a useful function in the next lines:

$$\phi(a) = -\frac{d}{da}\left(e^{-\int_0^a \Psi(s)ds}\right)$$

It follows that $1 - e^{-\int_0^a \Psi(s)ds} = \int_0^a \phi(x)dx$ and $\Psi(a) = \frac{\phi(a)}{1-\int_0^a \phi(s)ds}$.

We set also $\bar{F}(\phi) := F(\Psi)$ and $\bar{C}(\phi) := C(\Psi)$.

4 Optimization Problems and Results

Two optimization problems can be defined as follows. Let R_* and C_* be two constants.

(I) Find a vaccination strategy $\Psi(a)$ that minimizes $C(\Psi)$ constrained by

$$R_0^{\Psi} \leq R_*$$

(II) Find a vaccination strategy $\Psi(a)$ that minimizes R_0^{Ψ} constrained by

$$C(\Psi) \leq C_*$$

Hadeler and Muller[6] and Castillo & Feng[2] show how to transform the nonlinear maps $F(\Psi)$ and $C(\Psi)$ respectively into linear functionals $\bar{F}(\phi)$ and $\bar{C}(\phi)$. One can easily see possibly with an integral transformation:

$$\bar{F}(\phi) = \int_0^{+\infty} K(a)\phi(a)da$$

and

$$\bar{C}(\phi) = \int_0^{+\infty} B(a)\phi(a)da$$

if we set

$$K(a) = \int_a^{+\infty} (1-\delta)\, s_F(s) \left[\frac{\beta_I}{\nu_I} p(s) + \frac{\beta_E}{\nu_E} q(s)\right] ds$$

and

$$B(a) = u(a)\Lambda e^{-\mu a}$$

Remark 4.1 *It is possible to generalise the concept of δ by considering it as a positive function of age.*

Letting $Q(\phi) = \int_0^{+\infty} \phi(a)da$ and $\rho = R_0 - R_*$. We observe also that $Q(\phi) \leq 1$. We see that:

(I)$\Leftrightarrow$ **(I')** minimize $\bar{C}(\phi)$ when $f(\phi) \leq 0$ and $\phi \geq 0$ where we have set $f(\phi) \equiv \big(\rho - \bar{F}(\phi); Q(\phi) - 1\big)$. $f(\phi) \leq 0$ means that $f_i(\phi) \leq 0$, $(i = 1, 2)$.

Remark 4.2 *One can follow ideas in Muller[10] in order to prove existence of optimal stategies for **(I)**, **(I')** or **(II)** (by a property of a continue fonction on a compact set in a "good" space) and caracterizes some of them as extremal points in suitable spaces with convexity and Krein-Milman Theorem.[[15], p. 362]*

Like Castillo and Feng[2], one can use the Saddle Point Theorem of Kuhn and Tucker for the convex optimization problem (see Ref.[14]) we can show that **(I')** is mathematically equivalent to (P1) in Ref.[6]. Hence, using the same arguments we arrive at the following conclusion.

Theorem 4.3 *Letting $\delta_* := \frac{R_*}{R_0}$ for $R_0 \neq 0$, we assume that $R_0 = 0$ or $\delta_* > \delta$. 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.

For the two vaccination strategies, the optimal ages can be calculated in the following way: Note that $K(a)$ is a strictly decreasing function with $K(0) = (1-\delta)\, R_0 > \rho$ and $K(a) \to 0$ when $a \to \infty$. Hence, we can find $A^* > 0$ such that $K(A^*) = \rho$. Let A be the minimum of the quotient $\frac{B(a)}{K(a)}$. (See [6] 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 $C_{R_*}(A_1; A_2)$ on $A_1 \in [0; A^*]$ and $A_2 \in (A^*; +\infty)$, where

$$C_{R_*}(A_1; A_2) = \frac{\rho - K(A_2)}{K(A_1) - K(A_2)} B(A_1) + \frac{K(A_1) - \rho}{K(A_1) - K(A_2)} B(A_2)$$

*For **(II)**, a similar conclusion to Result above can be obtained; i.e., the optimal vaccination strategy is either one- or two-age, and the optimal ages can be determined.*

Remark 4.4 *We think that $K(0) = (1 - \delta) R_0$. For us argument "$K(0) = R_0 > \rho$" of Castillo & Feng[2] fails in page 149 for general cases. It surely holds for perfect vaccine ($\delta = 0$). There is a level of "inefficacity" for δ precisely $\delta_* = \frac{R_*}{R_0}$ if $R_0 \neq 0$, above wich all strategies seems to be inefficient.*

5 Discussion and Conclusion

The fact that we found one or two age strategies could be explained also by the fact that we neglect vertical transmission. Cameroon Ministry of Public Health[9] chooses a three ages strategy at 6th, 10th and 14th weeks after birth. For most studies (see D. Greenhalgh[5] for a good review), it seems to be enough even if we consider vertical transmission. We expect to include vertical transmission and study a model similar to the first model with

$$\begin{aligned} s(t,0) &= \Lambda, \text{ (constant external influx)} \\ i(t,0) &= \Lambda_2(t), \text{ (vertical transmission)}, \\ e(t,0) &= \Lambda_3(t), \text{ (vertical transmission)}, \\ r(t,0) &= 0, \text{ (no immunity at birth)}, \end{aligned} \tag{8}$$

and maybe include $v(t,0) = \Lambda_4(t)$.

Another remark on this note is the fact that we have not proved that optimal ages are consistent with human life time or life expectancy to avoid cases where for example ages go beyond 200 years.

Moreover we see the link between "level of inefficiency" δ_* for the vaccine and the security upper bound R_* condition for the effect. It partially explains why a bad quality vaccine could not protect a population with an optimal n-age strategy with n not big at all. We understand also that there is a tradeoff between minimizing the cost $C(\Psi)$ and setting the effect's upper bound R_*. In a forthcoming work, we will study discrete structures of optimal vaccination strategies in the endemic pattern case for our model using methods similar to J. Muller [11].

Acknowledgements: We would like to thank Pr Arnaud Ducrot, Dr Damakoa Irepran, Pr Bekolle David, Pr Djoya Oudou and Dr Tewa J.-J. for their valuable comments. This work was partially supported by AIMS-Senegal where the first author conducted a part of his PhD thesis work as student at University of Ngaoundere.

References

[1] H. Abboubakar, Modelling Hepatitis B virus infection (HvB) - Modélisation de l'infection au virus de l'hépatite B (VHB), *Master Thesis*, University of Ngaoundere, Cameroon, (2010).

[2] C. Castillo-Chavez and Z. Feng, Global stability of an age-structure model for TB and its applications to optimal vaccination strategies, *Math. Biosci.*, 151(1998), 135-154.

[3] A.A. Elbab, K.M. Hemida and M. Elsaid, On the behavior of numerical solutions with natural of stability and controllability of viral dynamical models, *Gen. Math. Notes*, 9(2) (2012), 42-55.

[4] J. Fu, R. Chen and X. Hou, An optimal distributed control for age-dependent population diffusion system, *Gen. Math. Notes*, 6(1) (2011), 73-85.

[5] D. Greenhalgh, Age-structured models and optimal control in mathematical epidemiology: A survey, In: *Optimal Control of Age-Structured Populations in Economy, Demography and the Environment*, Routledge Explorations in Environmental Economics, Routledge, Taylor & Francis Group, (2010).

[6] K.P. Hadeler and J. Muller, Vaccination in age structured populations II: Optimal vaccination strategies, In: V. Isham and G. Medley (Eds.), *Models for Infectious Human Diseases: Their Structure and Relation to Data*, Cambridge University, Cambridge, (1996).

[7] H. Inaba, Threshold and stability results for an age-structured epidemic model, *J. Math. Biol.*, 28(1990), 411-434.

[8] T.Y. Kouakep, A. Ducrot and D.D.E. Houpa, A model for Hepatitis B with chronological and infection ages, *Appl. Math. Sci.*, 7(117) (2013), 5977-5993, http://dx.doi.org/10.12988/ams.2013.37420.

[9] Ministry of Public Health of Cameroon, Plan D'introduction du vaccin contre l'Hépatite virale B dans le PEV de routine 2005-2009,

http://www.gavialliance.org/country/cameroon/documents/proposals/vaccine-introduction-plan-for-nvs—hep-b-support–cameroon–fran%C3%A7ais-/.

[10] J. Muller, Optimal vaccination patterns in age-structured populations, *SIAM J. Appl. Math.*, 59(1) (1998), 222-241.

[11] J. Muller, Optimal vaccination patterns in age-structured populations: Endemic case, *Math. and Comp. Modelling*, 31(2000), 149-160.

[12] D. J. Nokes, A. J. Hall, W. J. Edmunds, G. F. Medley and H. C. Whittle The influence of age on the development of the hepatitis B carrier state. *Proc R Soc Lond. B Biol. Sci.*, (1993).

[13] P. Pasquini and B. Cvjetanović, Mathematical models of Hepatitis B infection, *Ann. Ist. Super. Sanitá.*, 24(2) (1988), 245-250.

[14] J. Stoer and Chr. Witzgall, *Convexity and Optimization in Finite Dimension I*, Springer, Berlin, (1970).

[15] K. Yosida, *Functional Analysis*, Springer-Verlag, Berlin, New York, (1980).