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A MODEL FOR HEPATITIS B DISEASE WITH AGE-DEPENDENT SUSCEPTIBILITY

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Abstract. In this paper, a SEI model for hepatitis B is constructed in a closed population where the susceptibility depends on the chronological age and the basic reproduction rate R_0 is derived. Under suitable (biological and mathematical) assumptions, it is shown that the disease free equilibrium is globally asymptotically stable (GAS) if $R_0 < 1$. In other hand $R_0 > 1$ induces that endemic equilibrium is GAS and the system is uniformly persistent.

Keywords: PDE model, Hepatitis B, global (asymptotic) stability, Lyapunov-LaSalle functionals.

2000 AMS Subject Classification: 35K55, 92D30, 92D25

1. Introduction

This paper studies a system of equations modelling the dynamic of hepatitis B with age-dependent susceptibility. Its manifestations in human body are shown by Hepatitis B antigens (small spherical particles, tubular forms and a large shelled spherical particles) because of their association with a high risk of hepatitis[21]. Hepatitis B caused acute hepatitis and severe

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chronic liver disease. Hepatitis is endemic in Africa [3, 19]. According to Pasquini *et al.*[15] (with a computer model), Bonzi *et al.*[1](with an EDOs model), Inaba *et al.*[7](theoretically with a PDE) or D. J. Nokes *et al.*[14](with statistics tools) and L. Zou *et al.*[22](with PDE by fitting model to data), age factor is important in epidemiology of disease like hepatitis and reveals most of time useful informations on the dynamics of the epidemic.

In this study, we consider the following (chronological) age-dependent susceptibility model:

$$\begin{aligned}
 & (\partial_t + \partial_a) S(t, a) = -m(a)S(t, a) - \lambda(t, a)S(t, a), \quad t > 0, a > 0, \\
 & S(t, 0) = \Lambda, \\
 (1) \quad & \frac{dE(t)}{dt} = \int_0^{+\infty} p\lambda(t, a)S(t, a)da - \mu_E E(t), \\
 & \frac{dI(t)}{dt} = \int_0^{+\infty} q\lambda(t, a)S(t, a)da - \mu_I I(t) + \varepsilon E(t)
 \end{aligned}$$

posed for $t > 0$ and $a > 0$. Here $s(t, a)$ denotes the age-specific number of susceptible, $E(t)$ and $I(t)$ denotes respectively the age-specific numbers of acute infected (that can be symptomatic or asymptomatic) and chronic carriers. In addition p is a given real number such that $0 < p \leq 1$ while $q \equiv 1 - p$. q represents the age-specific probability to become a chronic carrier when becoming infected. p denotes the probability to develop an acute infection when getting the infection. Parameter $m(a) > 0$ denotes the natural death rate at age a , $\mu_I > 0$ and μ_E denotes the exit rates associated to each infected class. Clearly at each age a , $0 \leq m(a) \leq \min(\mu_I, \mu_E)$. $\varepsilon > 0$ is the transition rate from E to I . Obviously, $\mu_E \geq \varepsilon$. In some studies (like Kouakep *et al.*[8]) authors set $\mu_E \geq \mu_I$. The term $\lambda(t, a)$ corresponds to the age-specific force of infection and follows the usual law of mass-action, that reads as

$$\lambda(t, a) = \beta_I(a)I(t) + \beta_E(a)E(t).$$

This problem (1) is supplemented together with the boundary conditions:

$$\begin{aligned}
 & S(t, 0) = \Lambda \geq 0, \quad (\text{constant influx}) \\
 (2) \quad & E(0) = E_0 \geq 0, \\
 & I(0) = I_0 \geq 0,
 \end{aligned}$$

and initial data

$$(3) \quad S(0, a) = S_0(a).$$

This model (1) is suggested by Melnik *et al.*[13] for the age-dependent susceptibility concept supplemented with Kouakep *et al.*[8] introducing p and q .

We recall that according to WHO[19], Bonzi *et al.*[1] and Fall *et al.*[3], asymptomatic carriers has a low infectious rate. As a consequence in most part of this work one will assume that

$$(4) \quad 0 \approx \beta_E(a) \ll \beta_I(a).$$

Then

$$(5) \quad \lambda(t, a) = \beta_I(a)I(t).$$

In the above model (1)-(5) in a closed population, we do not take into account possible vertical transmission and we do not consider any control strategy such as vaccination campaign. It seems to be relevant together the assumption of WHO [19] that considers that vertical transmission of the disease do occur in sub-Saharan Africa, but its influence on the dynamics of the disease is rather small because the proportion of chronic infections acquired perinatally is low.

Under the above assumption, we assume that the chronological age for the infective classes do not play an important role. The work is organized as follows. After the presentation of the main results in Section 2, Section 3 studies the well posedness of the PDE and derives preliminary results useful to study the long term behaviour of the model. Section 3 deals with the wellposedness of the model and Section 4 proves the global asymptotic stability (GAS) of the disease free equilibrium when the basic reproduction number $R_0 < 1$ and GAS-stability of the endemic equilibrium (EE) with β_E small enough to be considered as zero. In Section 5, these results are verified through numerical simulations extended by a discussion.

2. Main results

The basic reproduction rate is defined by

$$R_0 = \frac{1}{\mu_I \mu_E} \int_0^{+\infty} (\varepsilon p + \mu_E q) \beta_I(a) S_F(a) da.$$

The DFE is defined by

$$(S_F(a), E_F, I_F) = \left(\Lambda \exp \left(- \int_0^a m(\sigma) d\sigma \right); 0; 0 \right).$$

For endemic equilibrium, we obtain only in the case $R_0 \geq 1$,

$$S_e(a) = \Lambda \exp \left(- \int_0^a m(\sigma) + I_e \beta_I(\sigma) d\sigma \right)$$

linked to

$$\frac{1}{\mu_I \mu_E} \int_0^{+\infty} (\varepsilon p + \mu_E q) \beta_I(a) S_e(a) da = 1.$$

That means

$$\frac{1}{\mu_I \mu_E} \int_0^{+\infty} (\varepsilon p + \mu_E q) \beta_I(a) S_F(a) \exp \left(- \int_0^a I_e \beta_I(\sigma) d\sigma \right) da = 1.$$

Assumption 2.1. Assume that the maps $a \mapsto \beta_i(a)$ is bounded and uniformly continuous from $[0, +\infty)$ into itself.

The global asymptotic stability of the steady states is resumed in the following Theorem 2.2.:

Theorem 2.2. *Assume Assumption 2.1. Then:*

- *If $R_0 = \frac{1}{\mu_I \mu_E} \int_0^{+\infty} (\varepsilon p + \mu_E q) \beta_I(a) S_F(a) da < 1$, then the DFE, the disease free equilibrium is globally asymptotically stable.*
- *If $R_0 > 1$, then there exists an endemic equilibrium that is globally asymptotically stable for all $S > 0$, $E > 0$, $I > 0$. Moreover, in that case ($R_0 > 1$) the system is uniformly persistent.*

Remark 2.3. We will see that disease free equilibrium exists whenever $R_0 > 1$ or $R_0 \leq 1$. But the endemic equilibrium exists only when $R_0 \geq 1$.

3. Preliminaries: well posedness of the model (1)–(5)

Let us introduce the Banach space $X = L^1([0; +\infty[, \mathbb{R}) \times \mathbb{R}^3$ and $X_0 = L^1([0; +\infty), \mathbb{R}) \times \{0\} \times \mathbb{R}^2$ endowed with the usual product norm as well as its positive cone X_+ defined by:

$$X_+ = L^1([0; +\infty[, [0; +\infty[) \times [0; +\infty[\times [0; +\infty[\times [0; +\infty[$$

with $X_{0+} = X_0 \cap X_+$.

We consider also the linear operator $A : D(A) \subset X \rightarrow X$ defined by

$$A \begin{pmatrix} \varphi \\ 0 \\ \alpha_E \\ \alpha_I \end{pmatrix} = \begin{pmatrix} -\varphi' - m(\cdot)\varphi \\ -\varphi(0) \\ -\mu_E \alpha_E \\ -\mu_I \alpha_I \end{pmatrix}$$

with the non densely domain $D(A) = W^{1,1}(\mathbb{J}0; +\infty) \times \{0\} \times \mathbb{R} \times \mathbb{R}$ in X : $\overline{D(A)} = X_0 \neq X$.

Finally let us introduce the nonlinear and Frechet differentiable map $F : \overline{D(A)} \rightarrow X$ defined by:

$$F \begin{pmatrix} \varphi \\ 0 \\ \alpha_E \\ \alpha_I \end{pmatrix} = \begin{pmatrix} -\beta_I(\cdot)\alpha_I\varphi \\ \Lambda \\ \int_0^{+\infty} p\beta_I(a)\alpha_I\varphi(a)da \\ \int_0^{+\infty} q\beta_I(a)\alpha_I\varphi(a)da + \varepsilon\alpha_E \end{pmatrix}.$$

Identifying $(S(t, \cdot), E(t), I(t))$ and $u(t) = (S(t, \cdot), 0, E(t), I(t))^T$, one obtains that System (1)-(5) re-writes as the following non-densely defined Cauchy problem (6):

$$(6) \quad \frac{du(t)}{dt} = Au(t) + F(u(t)) \quad , \quad t > 0,$$

$$(7) \quad u(0) = (S_0(\cdot), 0, E_0, I_0) \in X_{0+}.$$

We first derive that the above abstract Cauchy problem (6)-(7) generates a unique globally defined and positive semiflow. Moreover A satisfies the Hille-Yosida property. Then standard methodologies apply to provide the existence and uniqueness of mild solution for system (6)-(7) (see for instance [11, 12, 18, 2, 8]):

Proposition 3.1. Let Mathematical Assumption 2.1 be satisfied. Then there exists a continuous semiflow that is bounded dissipative $\{U(t)\}_{t \geq 0}$ on X_{0+} into itself such that for each $x \in X_{0+}$, the map $t \rightarrow U(t)x$ is the unique integrated solution of (6)-(7) with initial data x , namely $t \rightarrow U(t)x$ satisfies

$$(i) \quad \int_0^t U(s)x ds \in D(A), \quad \forall t \geq 0,$$

$$(ii) \quad U(t)x = x + A \int_0^t U(s)x ds + \int_0^t F(U(s)x) ds \quad \text{for each } t \geq 0.$$

Remark 3.2. One can prove the proposition by using ideas of corollaries 1 and 2 in Melnik *et al.*[13].

By using results in Sell and You[17], one can prove that $\{U(t)\}_{t \geq 0}$ is asymptotically smooth. Then using results of Hale [4, 5], Hale *et al.*[6], one obtains the following proposition.

Proposition 3.3. Let Mathematical Assumption 2.1 be satisfied. Then there exists a compact set $\mathcal{A} \subset X_{0+}$ such that

- (i) \mathcal{A} is invariant under the semiflow $\{U(t)\}_{t \geq 0}$.
- (ii) \mathcal{A} attracts the bounded sets of X_{0+} under $\{U(t)\}_{t \geq 0}$. This means that for each bounded set $B \subset X_{0+}$ we have

$$\lim_{t \rightarrow +\infty} \delta(U(t)B, \mathcal{A}) = 0,$$

where δ is defined as

$$\delta(A, B) = \sup_{x \in A} \inf_{y \in B} \|x - y\|.$$

Moreover \mathcal{A} is locally asymptotically stable.

4. Technical materials: global asymptotic stability of steady states

We will widely adapt ideas of Magal *et al.*[10] and Melnik *et al.*[13] here with Lyapunov functionals well defined on \mathcal{A} for the global asymptotic stability of DFE and EE.

4.1. Stability of the DFE: $R_0 < 1$

Let $G(x) = x - \ln x - 1$ and introduce the positive map defined on \mathbb{R} :

$$V(t) = \int_0^{+\infty} S_F(a) G\left(\frac{S(t, a)}{S_F(a)}\right) da + \frac{\varepsilon}{\varepsilon p + \mu_E q} E(t) + \frac{\mu_E}{\varepsilon p + \mu_E q} I(t)$$

is positive definite at the DFE. We evaluate $\frac{dV(t)}{dt}$ as

$$\int_0^{+\infty} S_F(a) G\left(\frac{1}{S_F(a)} - \frac{1}{S(t, a)}\right) \frac{\partial S(t, a)}{\partial t} da + \frac{\varepsilon}{\varepsilon p + \mu_E q} \frac{dE(t)}{dt} + \frac{\mu_E}{\varepsilon p + \mu_E q} \frac{dI(t)}{dt}$$

with equations of the system 1, one gets for $\frac{dV(t)}{dt}$:

$$- \int_0^{+\infty} S_F(a) \left(\frac{S(t, a)}{S_F(a)} - 1\right) \left(\frac{\partial_a S(t, a)}{S(t, a)} + m(a)\right) da + \int_0^{+\infty} \beta_I(a) I(t) S_F(a) da - \frac{\mu_E \mu_I}{\varepsilon p + \mu_E q} I(t).$$

Finally by integrating by part, $\frac{dV(t)}{dt}$, gives

$$- \left[S_F(a) G \left(\frac{S(t,a)}{S_F(a)} \right) \right]_{a=+\infty} + \int_0^{+\infty} \partial_a S_F(a) G \left(\frac{S(t,a)}{S_F(a)} \right) da + \frac{\mu_E \mu_I}{\varepsilon p + \mu_E q} (R_0 - 1) I(t).$$

Then

$$\frac{dV(t)}{dt} \leq \frac{\mu_E \mu_I}{\varepsilon p + \mu_E q} (R_0 - 1) I(t).$$

Hence by recalling that $R_0 < 1$,

$$\frac{dV(t)}{dt} \leq 0.$$

Finally by global stability Lyapunov-LaSalle theorem [9, 13, 10], the DFE= $(S_F(a), 0, 0)$ is globally asymptotically stable because the largest invariant set of orbits $(S(t,a), I(t), E(t))$ verifying $\frac{dV(t)}{dt} = 0$ is reduced for all positive t and a , to $S(t,a) = S_F(a)$, $I(t) = 0$ and $E(t) = 0$ corresponding to the disease free steady state (DFE), $(S_F(a), 0, 0)$.

4.2. Stability of the endemic equilibrium: $R_0 > 1$

Any solution of system (1)-(5) with positive initial condition remains positive indefinitely: then the system (1)-(5) is uniformly persistent.

Let $G(x) = x - \ln x - 1$. The function G has only one extremum which is a global minimum 0 at 1, satisfying $G(1) = 0$ (see [10]). Then, we will analyse the Lyapunov functional

$$V(t) = \int_0^{+\infty} S_e(a) G \left(\frac{S(t,a)}{S_e(a)} \right) da + \frac{\varepsilon}{\varepsilon p + \mu_E q} E_e G \left(\frac{E(t)}{E_e} \right) + \frac{\mu_E}{\varepsilon p + \mu_E q} I_e G \left(\frac{I(t)}{I_e} \right).$$

We notice that $V(S_e(a), E_e, I_e) = 0$ and V is positive definite at EE= $(S_e(a), E_e, I_e)$ that provides the minimum of V . Moreover V is defined for all $S > 0$, $E > 0$, $I > 0$ and

$$\begin{aligned} \frac{dV(t)}{dt} &= \int_0^{+\infty} S_e(a) \left(\frac{1}{S_e(a)} - \frac{1}{S(t,a)} \right) \frac{\partial S(t,a)}{\partial t} da \\ &+ \frac{\varepsilon}{\varepsilon p + \mu_E q} E_e \left(\frac{1}{E_e} - \frac{1}{E(t)} \right) \frac{dE(t)}{dt} + \frac{\mu_E}{\varepsilon p + \mu_E q} I_e \left(\frac{1}{I_e} - \frac{1}{I(t)} \right) \frac{dI(t)}{dt}. \end{aligned}$$

By using equations of system (1), and introducing the term $\beta_I(a)I_e$ in the integral, we obtain:

$$\begin{aligned} \frac{dV(t)}{dt} = & - \int_0^{+\infty} S_e(a) \left(\frac{S(t,a)}{S_e(a)} - 1 \right) \left(\frac{\partial_a S(t,a)}{\partial t} + m(a) + \beta_I(a)I_e \right) da \\ & + \frac{\varepsilon p}{\varepsilon p + \mu_{E}q} \int_0^{+\infty} S_e(a) \left(\frac{S(t,a)}{S_e(a)} - 1 \right) \beta_I(a)I_e da \\ & - \frac{\varepsilon p}{\varepsilon p + \mu_{E}q} \int_0^{+\infty} \beta_I(a)I_e S_e(a) \left(\frac{I_e E(t)}{E_e I(t)} - 1 \right) da \\ & - \frac{\varepsilon p}{\varepsilon p + \mu_{E}q} \int_0^{+\infty} \beta_I(a)I_e S_e(a) \left(\frac{S(t,a)E_e I(t)}{S_e(a)I_e E(t)} - 1 \right) da. \end{aligned}$$

Finally by integrating by part:

$$\begin{aligned} \frac{dV(t)}{dt} = & - \left[S_e(a)G \left(\frac{S(t,a)}{S_e(a)} \right) \right]_0^{+\infty} + \int_0^{+\infty} \partial_a S_e(a)G \left(\frac{S(t,a)}{S_e(a)} \right) da \\ & + \frac{\varepsilon p}{\varepsilon p + \mu_{E}q} \int_0^{+\infty} S_e(a) \left(\frac{S(t,a)}{S_e(a)} - 1 \right) \beta_I(a)I_e da \\ & - \frac{\varepsilon p}{\varepsilon p + \mu_{E}q} \int_0^{+\infty} \beta_I(a)I_e S_e(a) \left(\frac{I_e E(t)}{E_e I(t)} - 1 \right) da \\ & - \frac{\varepsilon p}{\varepsilon p + \mu_{E}q} \int_0^{+\infty} \beta_I(a)I_e S_e(a) \left(\frac{S(t,a)E_e I(t)}{S_e(a)I_e E(t)} - 1 \right) da. \end{aligned}$$

Moreover, it is clear that:

$$\int_0^{+\infty} \beta_I(a)I_e S_e(a) \left(\ln \frac{S(t,a)E_e I(t)}{S_e(a)I_e E(t)} + \ln \frac{I_e E(t)}{E_e I(t)} - \ln \frac{S(t,a)}{S_e(a)} \right) da = 0.$$

By adding that value to $\frac{dV(t)}{dt}$, we get:

$$\begin{aligned} \frac{dV(t)}{dt} = & - \left[S_e(a)G \left(\frac{S(t,a)}{S_e(a)} \right) \right]_{a=+\infty} + \int_0^{+\infty} \partial_a S_e(a)G \left(\frac{S(t,a)}{S_e(a)} \right) da \\ & - \frac{\varepsilon p}{\varepsilon p + \mu_{E}q} \int_0^{+\infty} \beta_I(a)I_e S_e(a)G \left(\frac{S(t,a)E_e I(t)}{S_e(a)I_e E(t)} \right) da \\ & - \frac{\varepsilon p}{\varepsilon p + \mu_{E}q} \int_0^{+\infty} \beta_I(a)I_e S_e(a)G \left(\frac{I_e E(t)}{E_e I(t)} \right) da \\ & + \frac{\varepsilon p}{\varepsilon p + \mu_{E}q} \int_0^{+\infty} S_e(a)G \left(\frac{S(t,a)}{S_e(a)} \right) \beta_I(a)I_e da. \end{aligned}$$

The previous computations with $\partial_a S_e(a) = -m(a)S_e(a) - \beta_I(a)I_e S_e(a)$ and $S_e(0) = S(t, 0) = \Lambda$ imply that:

$$\begin{aligned} \frac{dV(t)}{dt} = & - \left[S_e(a)G \left(\frac{S(t, a)}{S_e(a)} \right) \right]_{a=+\infty} - \int_0^{+\infty} m(a)S_e(a)G \left(\frac{S(t, a)}{S_e(a)} \right) da \\ & - \frac{\varepsilon p}{\varepsilon p + \mu_E q} \int_0^{+\infty} \beta_I(a)I_e S_e(a)G \left(\frac{S(t, a)E_e I(t)}{S_e(a)I_e E(t)} \right) da \\ & - \frac{\varepsilon p}{\varepsilon p + \mu_E q} \int_0^{+\infty} \beta_I(a)I_e S_e(a)G \left(\frac{I_e E(t)}{E_e I(t)} \right) da \\ & - \frac{\mu_E q}{\varepsilon p + \mu_E q} \int_0^{+\infty} S_e(a)G \left(\frac{S(t, a)}{S_e(a)} \right) \beta_I(a)I_e da \leq 0. \end{aligned}$$

Then by global stability Lyapunov-LaSalle theorem [9, 13, 10], the endemic equilibrium (EE) is globally asymptotically stable because the largest invariant set of orbits $(S(t, a), I(t), E(t))$ verifying $\frac{dV(t)}{dt} = 0$ is reduced for all positive t and a , to $S(t, a) = S_e(a)$, $I(t) = I_e$ and $E(t) = E_e$ corresponding to the endemic steady state $(S_e(a), E_e, I_e)$.

5. Numerical simulations and Discussion

We denote in tables 1 and 2: "p" for people(s), "yr" for year and "nbb" for "new born babies". We made simulations with the values in tables 1 and 2. We consider the following parameters for DFE case ($R_0 < 1$):

Age	p	β_I	ε	μ_I	μ_E	$m(a)$	Λ
[0;A= 60]	$1 - \exp(-0.645)$	0.000000008	0.00001	0.2018458	8.1	0.18	10
yr	probability	$(\mathbf{p} * \text{yr})^{-1}$	$(\mathbf{p} * \text{yr})^{-1}$	yr^{-1}	yr^{-1}	yr^{-1}	nbb/yr

TABLE 1. Values for $R_0 < 1$

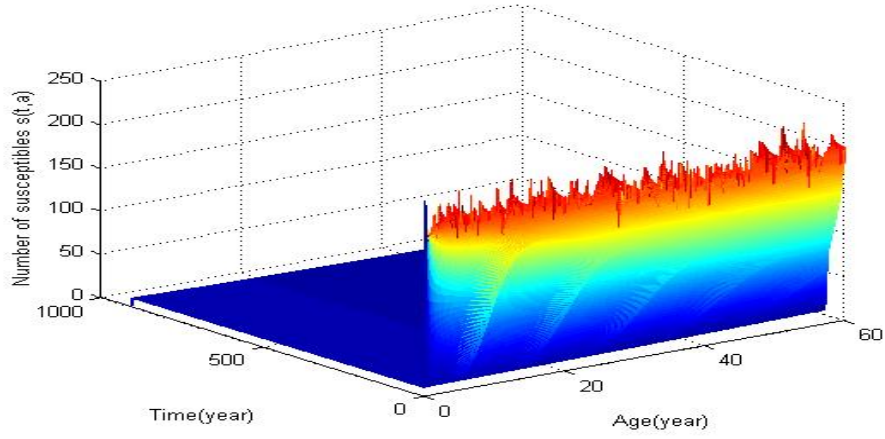


FIGURE 1. Function $S(t, a)$ with $R_0 < 1$

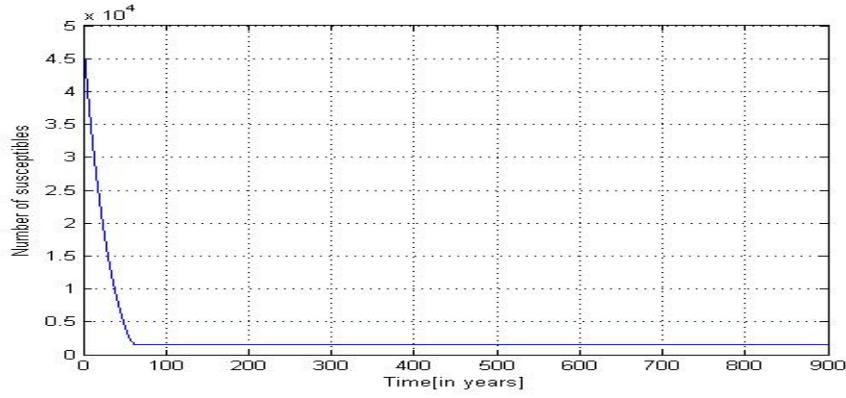
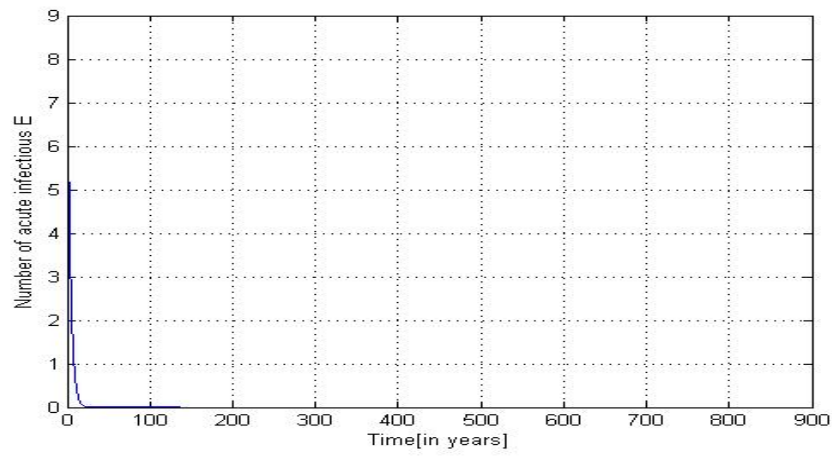
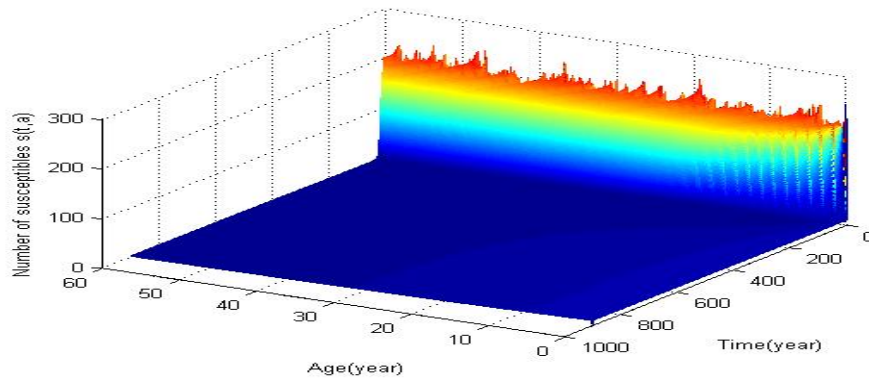


FIGURE 2. Function $t \mapsto \int_0^A S(t, a) da$ with $R_0 < 1$

For endemic case ($R_0 > 1$), let consider the following table 2.

Age	p	β_I	ε	μ_I	μ_E	$m(a)$	Λ
[0;A= 60]	$1 - \exp(-0.645)$	0.0001	0.1	0.02018458	0.1	0.018	10
yr	probability	$(p * yr)^{-1}$	$(p * yr)^{-1}$	yr^{-1}	yr^{-1}	yr^{-1}	nbb/yr

TABLE 2. Values for $R_0 > 1$

FIGURE 3. Function $E(t)$ with $R_0 < 1$ FIGURE 4. Function $S(t,a)$ with $R_0 > 1$

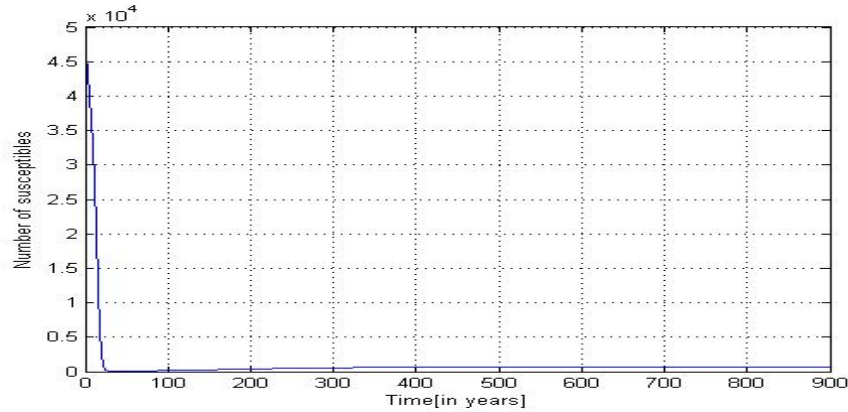


FIGURE 5. Function $t \mapsto \int_0^A S(t, a) da$ with $R_0 > 1$

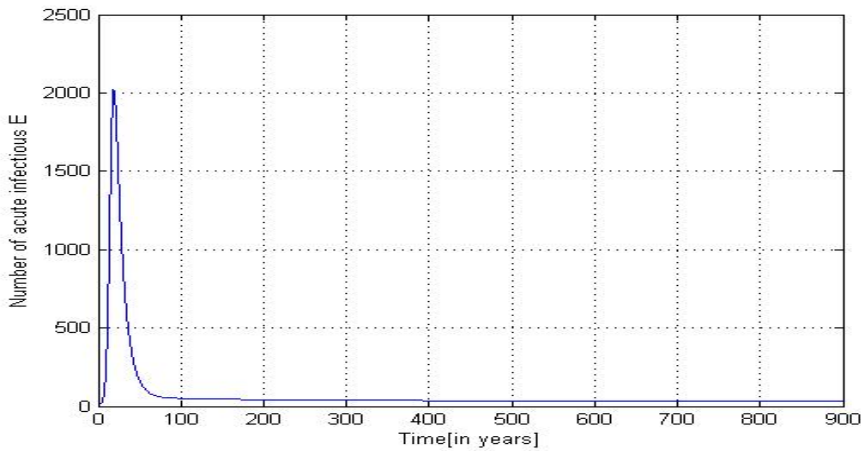
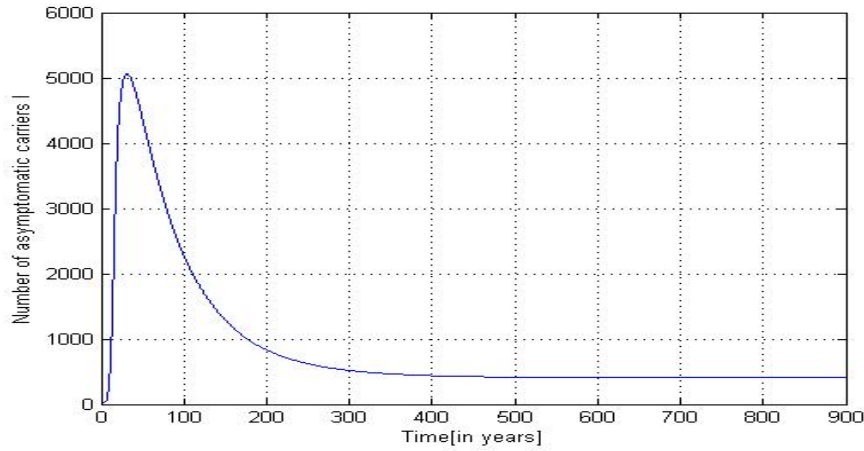
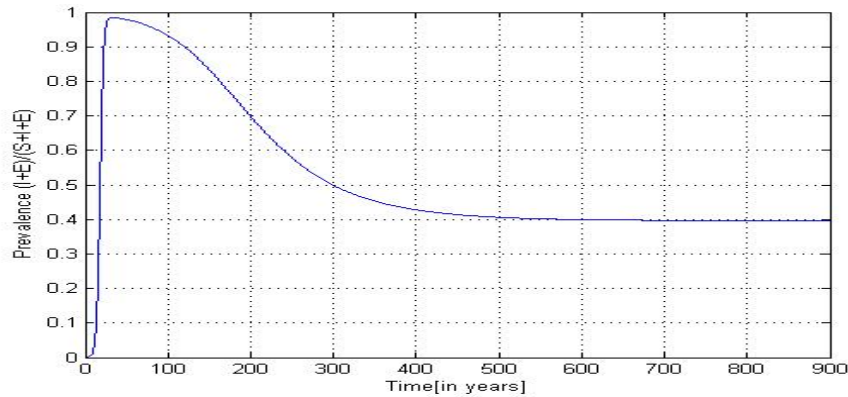


FIGURE 6. Function $E(t)$ with $R_0 > 1$

We observe that our computations for stability of DFE and EE are confirmed by simulations. It is also established that increasing the transmission coefficient β_I , increases the basic reproduction rate. A better model could consider age-dependent p and q as shown by Nokes *et al.* in [14]. In a forthcoming work, we will introduce then age-dependent functions p and q , vertical transmission (because of the controversial article Sall *et al.* [16] on WHO's[20] neglect of vertical transmission in sub-Saharan Africa), studies of (optimal) vaccination strategies and immigration by other ways than birth. It is important to see the difference between our work and those of Melnik *et al.* [13] for the age-dependent susceptibility concept supplemented with Kouakep *et al.* [8] introducing p and q . Melnik *et al.*[13] do not consider proportions p and q

FIGURE 7. Function $I(t)$ with $R_0 > 1$ FIGURE 8. Function prevalence with $R_0 > 1$

from S to $E-I$ and Kouakep et al.[8] neglect transition ε from E to I but add ages of infection on $E-I$ and consider β_E in a more general case (not necessarily zero).

Conflict of Interests

The authors declare that there is no conflict of interests.

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