Analysis of an age-structured epidemic model with a chronic state

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Abstract

In this work we study an age-structured epidemic model with a chronic state for Cytomegalovirus. We divide the population in three groups: susceptible, infectious and chronic, where the chronic state is structured by the amount of time spent in that state. It is assumed that susceptible individuals can be infected by infectious and by chronic. Infectious individuals may recover or become chronic. We study the stability of the model around the disease-free equilibrium and interpret it in terms of the parameters associated with the model's basic reproductive number.

1 Introduction

The purpose of this paper is to study the role that the presence of a chronic stage may have on disease persistence and epidemiology. There is a wide spectrum of diseases that show such stage during their development. We take as case study the Cytomegalovirus infection. Cytomegalovirus is a virus member of the herpes family that includes the Epstein-Barr, herpes simplex, and varicella-zoster viruses. Individuals infected with these viruses are highly infectious for a variable period of time which could be months or even years. Infected individuals eventually become latent with the possibility of periodic reactivation later in life (Jordan, Jordan, Stevens and Miller, 1984).

Cytomegalovirus (CMV) affects mainly pregnant women, who can transmit the disease to newborns. Most babies infected with CMV present no symptoms; however, 10 to 20 percent of the cases there is damage to hearing, mental ability, neuromuscular function, or vision because of damage during gestation or through the development of late sequelae in childhood

(Berge, 1989; Nankervis, Kumar, Cox and Gold, 1984; Pass, Little, Stagno et al, 1987; Preece, Blount, Glover et al, 1983; Stagno, Pass, Cloud et al, 1986; Stagno, Pass, Dworky and Alford, 1982; Stagno and Whitley, 1985). The likelihood of pregnant women of becoming infected with CMV is highly correlated with socioeconomic status, age, birth place, number of children, and sexual activity (Chandler, Alexander and Holmes, 1985). Although the sources of infection are not clearly understood, there is strong evidence that the disease is transmitted to a significant proportion of children in day care centers (Pass, 1985; Pass, August, Dworsky and Reynolds, 1987; Pass, Little, Stagno et al, 1987) where infants between one and three years of age have direct contact with each other. Respiratory transmission does not seem to play an important role in transmission although the virus can persist on surfaces for hours making its transfer the virus through saliva in hands or toys Faix, 1985).

Perinatal and day care center transmission are the most likely sources of infection. Another sources are through blood transfusion, organ transplants, and sexual activity, albeit these last three sources seem to be less critical in the spread of the virus.

The asymptomatic characteristics of CMV infection make it difficult to visualize the role of the chronic state on disease persistance. It is estimated that 50-100% of women in both developed and developing countries (Pass, 1985) are seropositive when they reach childbearing age, and many may develop recurrent infections during pregnancy. In developing countries, 85-95% of children are seropositive, while only 5-30% are seropositive in developed countries (Pass, 1985). Differences are attributed to nutrition levels, driven by culture and/or socioeconomic status (Chandler, Alexander and Holmes, 1985; Pass, 1985).

As for the modelling approach, we decided to stratify chronically infected individuals by age of infection. We assume that suceptible individuals may suffer a primary infection (characterized by high infectivity) from which they cannot recover. Instead they can be transferred either passively or by contact with another infectious individual to the chronic stage. Within this stage individuals possess lower infectivity than the one they have in the acute (primary) infection. Chronic individuals may relapse into the acute infection stage several times.

Our model is based on, although differs substantially from, the model analyzed by Thieme and Castillo-Chávez (1989). We incorporate variable infectivity through the age of the chronic infection and, moreover, chronically infected individuals are the only compartment that is stratified by age. Our contact rates are of the simplest form of proportionate mixing.

This paper is organized in the following way. In Section 2 we present the model to be studied, and study the asymptotic behavior of the population including the disease-free equilibrium. The chronic state is assumed to be age-structured by the amount of time that an

individual has spent in that state. In Section 3 we analyze the non-structured version of our model. We calculate its basic reproductive number and show that an endemic point exists when the disease-free equilibrium is unstable. In Section 4 we analyze the stability properties of the age-structured model near the disease-free equilibrium and show the existence of an endemic point. Finally, in Section 5 we present the conclusions and discuss topics for future research.

2 The model

We consider the following age structured model. Suppose we divide the target human population into three classes: susceptible, (acute) infectious, and (subacute) chronic. We assume the chronic state to be structured by the amount of time spent in this state, τ, the age of infection. Both infectious and chronic individuals may infect susceptible individuals. The infectivity of infectious upon susceptible individuals is proportional to the product of the number of infectious and the proportion of susceptibles in the population, with constant transmission rate β_0. The infectivity of chronic individuals on susceptibles is assumed to be dependent on τ, proportional to the product of the proportion of susceptibles in the population, and to the integral of density of chronic weighted by the transmission rate $\beta_1(\tau)$, where we assume $\beta_1(\tau) < \beta_0$ for all τ. These contact rates have been widely studied and are the simplest that one can assume (see for example Castillo-Chavez, Velasco-Hernández and Fridman (1994) for a review). We also assume that, once being infected by a chronic individual, there is a probability q of becoming a chronic and a complimentary probability $(1-q)$ of becoming an infectious. An infectious individual may become chronic at a constant rate φ, while a chronic may become infectious at the age-dependent rate $\theta(\tau)$. If we consider constant recruitment rate Λ and constant per capita death rate μ. Then we have the following system of equations:

$$\frac{dS}{dt} = \Lambda - \beta_0 S\frac{I}{N} - \frac{S}{N}\int_0^\infty \beta_1(\tau)c(\tau,t)d\tau - \mu S \tag{1}$$

$$\frac{dI}{dt} = \beta_0 S\frac{I}{N} - (\mu+\varphi)I + \int_0^\infty \theta(\tau)c(\tau,t)d\tau + (1-q)\frac{S}{N}\int_0^\infty \beta_1(\tau)c(\tau,t)d\tau \tag{2}$$

$$\left(\frac{\partial}{\partial\tau} + \frac{\partial}{\partial t}\right)c(\tau,t) = -\mu c(\tau,t) - \theta(\tau)c(\tau,t) \tag{3}$$

with initial-boundary conditions

$$\begin{aligned} c(0,t) &= \varphi I + q\frac{S}{N}\int_0^\infty \beta_1(\tau)c(\tau,t)d\tau \quad (4)\\ c(\tau,0) &= c_0(\tau) \quad (5)\\ S(0) &= S_0, I(0) = I_0. \quad (6) \end{aligned}$$

Here, the total population is given by $N = S + I + C$, where

$$C(t) = \int_0^\infty c(\tau,t)d\tau. \quad (7)$$

Integrating equations (3) and (4) over τ we get

$$\frac{dC}{dt} = \varphi I + q\frac{S}{N}\int_0^\infty \beta_1(\tau)c(\tau,t)d\tau - \int_0^\infty \theta(\tau)c(\tau,t)d\tau - \mu C, \quad (8)$$

and hence the total population is governed by

$$\frac{dN}{dt} = \Lambda - \mu N. \quad (9)$$

Therefore

$$N = \frac{\Lambda}{\mu} - \left(\frac{\Lambda}{\mu} - N_0\right)e^{-\mu t} \quad (10)$$

and the population is asymptotically constant with limit

$$\lim_{t\to\infty} N(t) = \frac{\Lambda}{\mu}. \quad (11)$$

The disease-free stationary solution of the system (1-4) is therefore given by

$$S = \frac{\Lambda}{\mu}, I = C = 0. \quad (12)$$

We do not show in this paper proofs of existence and uniqueness of solutions of model (1-6). However, these properties can be guaranteed by routine application of results in Webb (1985).

In the following sections we study the asymptotic dynamics around the equilibrium (12). We give conditions of stability and prove the existence of an endemic state when the disease-free equilibrium is unstable.

3 The case when θ and β_1 are independent of age

Here, we analyze the System (1-6) for the case when θ, β_1 are constants independent of τ. Integrating equation (3) over τ leads to the 3-dimensional system

$$\frac{dS}{dt} = \Lambda - \beta_0 \frac{S}{N} I - \beta_1 \frac{S}{N} C - \mu S \tag{13}$$

$$\frac{dI}{dt} = \beta_0 \frac{S}{N} I + (1-q)\beta_1 \frac{S}{N} C - (\mu + \varphi) I + \theta C \tag{14}$$

$$\frac{dC}{dt} = q\beta_1 \frac{S}{N} C + \varphi I - (\mu + \theta) C. \tag{15}$$

Linearizing the system (13-15) around the disease-free equilibrium, equation(12), gives

$$\dot{X} = BX, \tag{16}$$

where $X = (S\ A\ C)^T$ and

$$B = \begin{pmatrix} -\mu & \beta_0 & \beta_1 \\ 0 & \beta_0 - (\mu + \varphi) & \theta + (1-q)\beta_1 \\ 0 & \varphi & q\beta_1 - (\mu + \varphi) \end{pmatrix}. \tag{17}$$

The basic reproductive number is the spectral radius of the next-generation operator (Diekman, Hesterbeek and Metz, 1990) of (13-15) and is given by

$$R_0 = \frac{1}{2}(R_I + R_C) + \sqrt{\left(\frac{1}{2}(R_I - R_C)\right)^2 + \frac{\varphi}{\mu + \varphi}\left(\frac{\theta}{\mu + \theta} + \frac{(1-q)\beta_1}{\mu + \theta}\right)}, \tag{18}$$

where R_I and R_C,

$$R_I = \frac{\beta_0}{\mu + \varphi} \text{ and } R_C = \frac{q\beta_1}{\mu + \theta},$$

can be interpreted as the basic reproductive numbers of the infectious and chronic states. The second term inside the square root is the product of the expected number of chronics produced by an infectious individual times the expected number of infectious produced by a chronic individual during their respective time of infectivity.

Proposition 3.1 *If $R_0 > 1$ then there is a unique endemic solution to (13-15).*

Proof: Assume $R_0 > 1$. Setting equations (14-15) equal to zero, together with the equation for the total population, give rise to the system of equations:

$$\begin{aligned} -(\mu+\varphi)(1-sR_I)i + (\theta + (1-q)\beta_1 s)c &= 0, \quad (19)\\ \varphi i - (\mu+\theta)(1-sR_C)c &= 0, \quad (20)\\ i + c &= 1-s, \quad (21) \end{aligned}$$

where

$$s = \frac{S}{N}, i = \frac{I}{N}, c = \frac{C}{N}.$$

The homogeneous linear system (19-20) has positive solutions for i, c if and only if its determinant

$$F(s) = (\mu+\varphi)(\mu+\theta)(1-sR_I)(1-sR_C) - \varphi(\theta + (1-q)\beta_1 s) \quad (22)$$

is zero for some s^* with

$$0 \leq s^* < \min\{1, 1/R_I, 1/R_C\}. \quad (23)$$

Since

$$F(0) = (\mu+\varphi)(\mu+\theta) - \varphi\theta > 0,$$

$$F(1/R_I) = -\varphi(\theta + (1-q)\beta_1/R_I) < 0,$$

and

$$F(1/R_C) = -\varphi(\theta + (1-q)\beta_1/R_C) < 0,$$

together with the fact that F is a strictly decreasing function in $(0, \min\{1/R_I, 1/R_C\})$, we have a unique solution s^* with

$$0 \leq s^* < \min\{1/R_I, 1/R_C\}.$$

We observe that $R_0 < 1$ if and only if

$$R_I < 1, R_C < 1 \quad (24)$$

and

$$\frac{\varphi}{\mu+\varphi}\left(\frac{\theta}{\mu+\theta} + \frac{(1-q)\beta_1}{\mu+\theta}\right) < (1-R_I)(1-R_C). \quad (25)$$

If both $1/R_I$ and $1/R_C$ are greater than 1 (since $R_0 > 1$) we have the reverse inequality in (25). Since

$$F(1) = (\mu+\varphi)(\mu+\theta)(1-R_I)(1-R_C) - \varphi(\theta + (1-q)\beta_1) < 0,$$

there is a solution s^* satisfying (23). From this solution s^* it follows that

$$i^* = \frac{(1-s^*)(\theta+(1-q)\beta_1 s^*)}{\theta+(1-q)\beta_1 s^*+(\mu+\varphi)(1-s^* R_I)}, \tag{26}$$

$$c^* = = \frac{(1-s^*)\varphi}{\varphi+(\mu+\theta)(1-s^* R_C)}, \tag{27}$$

is the solution for (19-21). Therefore, a unique endemic point exists whenever $R_0 > 1$. Q.E.D

4 Age-dependent rates $\beta_1(\tau), \theta(\tau)$.

The case when $\beta_1(\tau), \theta(\tau)$ depend on the chronic age τ leads to similar results albeit the analysis is different. To find the conditions for stability around the disease-free equilibrium, we first linearize the system (1-6) around the point $(\Lambda/\mu, 0, 0)$. The linearization is given by

$$\frac{dS}{dt} = \mu S - \beta_0 I - \int_0^\infty \beta_1(\tau) c(\tau,t) d\tau, \tag{28}$$

$$\frac{dI}{dt} = (\beta_0 - (\mu+\varphi))I + \int_0^\infty (\theta(\tau)+(1-q)\beta_1(\tau)) c(\tau,t) d\tau, \tag{29}$$

$$\left(\frac{\partial}{\partial\tau}+\frac{\partial}{\partial t}\right) c(\tau,t) = -\mu c(\tau,t) - \theta(\tau) c(\tau,t), \tag{30}$$

with the initial-boundary conditions

$$c(0,t) = \varphi I + q\int_0^\infty \beta_1(\tau) c(\tau,t) d\tau, \tag{31}$$

$$S(0) = S_0, I(0) = I_0, c(\tau,0) = c_0(\tau). \tag{32}$$

Integrating equation (30) along characteristics gives

$$c(\tau,t) = \begin{cases} c_0(\tau-t)\Pi(\tau-t,\tau) & \text{if } t \le \tau \\ B(t-\tau)\Pi(\tau) & \text{if } \tau < t \end{cases} \tag{33}$$

where

$$B(t) = c(0,t) \tag{34}$$

and $\Pi(a,b)$ is the survival probability function in the chronic state from chronic age $\tau = a$ to $\tau = b$, explicitly

$$\Pi(a,b) = e^{-\int_a^b (\mu+\theta(s))ds}, \tag{35}$$

and $\Pi(\tau) = \Pi(0,\tau)$. Substituting (33) in the boundary condition (31) leads to the integral equation

$$B(t) = \varphi I + q\int_0^t \beta_1(\tau)\Pi(\tau)B(t-\tau)d\tau + q\int_t^\infty \beta_1(\tau)\Pi(\tau-t,\tau)c_0(\tau-t)d\tau. \tag{36}$$

Thus we have reduced our system to a set of coupled linear integro-differential equations

$$I'(t) = \xi I + \int_0^t k(\tau)B(t-\tau)d\tau + K(t) \tag{37}$$

$$B(t) = \varphi I + q\int_0^t f(\tau)B(t-\tau)d\tau + F(t) \tag{38}$$

where

$$\xi = \beta_0 - (\mu+\varphi), \tag{39}$$

$$k(\tau) = (\theta(\tau) + (1-q)\beta_1(\tau))\Pi(\tau), \tag{40}$$

$$f(\tau) = \beta_1(\tau)\Pi(\tau), \tag{41}$$

$$K(t) = \int_t^\infty (\theta(\tau) + (1-q)\beta_1(\tau))\Pi(\tau-t,\tau)c_0(\tau-t)d\tau, \tag{42}$$

$$F(t) = q\int_t^\infty \beta_1(\tau)\Pi(\tau-t,\tau)c_0(\tau-t)d\tau. \tag{43}$$

We can now apply the Laplace transform to equations (37-38) (see e.g Pipkin, 1991) leading to

$$p\hat{I}(p) - I_0 = \xi\hat{I}(p) + \hat{k}(p)\hat{B}(p) + \hat{K}(p) \tag{44}$$

$$\hat{B}(p) = \varphi\hat{I}(p) + q\hat{f}(p)\hat{B}(p) + \hat{F}(p) \tag{45}$$

where the symbol "$\hat{}$" means Laplace transform. Rearranging terms in (44-45) we obtain the equivalent 2-dimensional linear system of equations in $\hat{I}$ and $\hat{B}$

$$(\xi - p)\hat{I}(p) + \hat{k}(p)\hat{B}(p) = -I_0 - \hat{K}(p), \tag{46}$$

$$\varphi\hat{I}(p) + (q\hat{f}(p) - 1)\hat{B}(p) = -\hat{F}(p). \tag{47}$$

Therefore the characteristic equation is given by

$$\varphi\hat{k}(p) - (\xi - p)(q\hat{f}(p) - 1) = 0 \tag{48}$$

which is equivalent to the equation

$$q\hat{f}(p) + \frac{\varphi\hat{k}(p)}{p-\xi} = 1. \tag{49}$$

Theorem 4.1 *The characteristic equation (49) has a unique real solution p^* in the interval (ξ, ∞). Moreover, p^* is the dominant eigenvalue of the system (37-38).*

Proof: Let

$$F(p) = q\hat{f}(p) + \frac{\varphi\hat{k}(p)}{p-\xi}.$$

It is not hard to see that when restricted to the real interval (ξ, ∞), F is a real valued strictly decreasing function with $\lim_{p\to\xi^-} F(p) = \infty$ and $\lim_{p\to\infty} F(p) = 0$. Hence the equation $F(p) = 1$ has a unique solution p^* in (ξ, ∞).

Now suppose $p = \lambda + i\omega$ is a complex solution to the equation

$$F(\lambda + i\omega) = 1, \tag{50}$$

with $\lambda \in (\xi, \infty)$. The real part of (50) gives the equation

$$\begin{aligned} 1 \;=\; & q\int_0^\infty e^{-\lambda\tau} f(\tau)\cos\omega\tau\, d\tau + \\ & \frac{\varphi(\lambda-\xi)}{(\lambda-\xi)^2+\omega^2}\int_0^\infty e^{-\lambda\tau}k(\tau)\left[\cos\omega\tau - \frac{\omega}{\lambda-\xi}\sin\omega\tau\right]d\tau, \end{aligned} \tag{51}$$

where the function

$$\cos\omega\tau - \frac{\omega}{\lambda-\xi}\sin\omega\tau$$

is bounded by

$$\frac{\sqrt{(\lambda-\xi)^2+\omega^2}}{\lambda-\xi}.$$

Hence

$$\begin{aligned} \frac{\varphi(\lambda-\xi)}{(\lambda-\xi)^2+\omega^2}\int_0^\infty e^{-\lambda\tau}k(\tau)\left[\cos\omega\tau - \frac{\omega}{\lambda-\xi}\sin\omega\tau\right]d\tau &\le \varphi\int_0^\infty \frac{e^{-\lambda\tau}k(\tau)}{\sqrt{(\lambda-\xi)^2+\omega^2}}d\tau \\ &\le \frac{\varphi}{\lambda-\xi}\int_0^\infty e^{-\lambda\tau}k(\tau)d\tau. \end{aligned} \tag{52}$$

From (51) and (52) we arrive at the relation

$$F(p^*) \leq F(\lambda). \tag{53}$$

Since F is decreasing in (ξ, ∞) then $\lambda \leq p^*$. Therefore p^* is the dominant eigenvalue of (37-38). Q.E.D

We conclude that the conditions for stability are $\xi < 0$ and $p^* < 0$, that is, that

$$R_I < 1 \tag{54}$$

and

$$F(0) < 1, \tag{55}$$

where F(0) is given by

$$F(0) = R_C + \frac{\varphi}{(\mu+\varphi)(1-R_I)} \int_0^\infty (\theta(\tau) + (1-q)\beta_1(\tau))\Pi(\tau)d\tau, \tag{56}$$

where R_C is the basic reproductive number of the chronic state,

$$R_C = q \int_0^\infty \beta_1(\tau)\Pi(\tau)d\tau. \tag{57}$$

After some algebra we verify that conditions (54-55) are equivalent to the condition

$$R_0 < 1 \tag{58}$$

where R_0 is the basic reproductive number of the system and is given, after appliying the method of Diekman, Hesterbeek and Metz (1990), by

$$R_0 = \frac{1}{2}(R_I + R_C) + \sqrt{\left(\frac{1}{2}(R_I - R_C)\right)^2 + \frac{\varphi}{\mu+\varphi} \int_0^\infty (\theta(\tau)+(1-q)\beta_1(\tau))\Pi(\tau)d\tau}, \tag{59}$$

the same expression obtained in Section 3 for R_0. In the next theorem we prove the existence of an endemic solution.

Theorem 4.2 *If $R_0 > 1$ then an endemic solution exists.*

Proof: Assume $R_0 > 1$. The equations for the endemic solution are given by

$$-(\mu+\varphi)(1-sR_I)I + \int_0^\infty (\theta(\tau)+s(1-q)\beta_1(\tau))c(\tau)d\tau = 0 \tag{60}$$

$$\frac{dc}{d\tau} = -(\mu+\theta(\tau))c(\tau) \tag{61}$$

$$c(0) = \varphi I + qs\int_0^\infty \beta_1(\tau)c(\tau)d\tau \tag{62}$$

$$I + \int_0^\infty c(\tau)d\tau = N(1-s) \tag{63}$$

where

$$s = \frac{S}{N}.$$

From equation (61) we obtain

$$c(\tau) = c(0)\Pi(\tau). \tag{64}$$

Now, integrating (61), together with (62), we get the equation

$$\varphi I + qs\int_0^\infty \beta_1(\tau)c(\tau)d\tau - \int_0^\infty (\mu+\theta(\tau))c(\tau)d\tau. \tag{65}$$

Substituting (64) in (60), (65) and (63) we obtain the system

$$-(\mu+\varphi)(1-sR_I)I + \int_0^\infty (\theta(\tau)+s(1-q)\beta_1(\tau))\Pi(\tau)d\tau c(0) = 0 \tag{66}$$

$$\varphi I - (1-sR_C)c(0) = 0 \tag{67}$$

$$I + c(0)\int_0^\infty \Pi(\tau)d\tau = N(1-s), \tag{68}$$

since

$$\int_0^\infty (\mu+\theta(\tau))\Pi(\tau)d\tau = 1.$$

Similarly as in the proof of Proposition 3.1, it is easily established that the determinant of the homogeneous linear system for $I, c(0)$ (67-68),

$$F(s) = (\mu+\varphi)(1-sR_I)(1-sR_C) - \varphi\int_0^\infty (\theta(\tau)+s(1-q)\beta_1(\tau))\Pi(\tau)d\tau$$

is zero for some s^* satisfying

$$0 \le s^* < \min\{1, 1/R_I, 1/R_C\}.$$

Hence we have positive solutions for $I, c(0)$ for (66-68), which are given by

$$I^* = \frac{N(1-s^*)\int_0^\infty(\theta(\tau)+s^*(1-q)\beta_1(\tau))\Pi(\tau)d\tau}{\int_0^\infty(\theta(\tau)+s^*(1-q)\beta_1(\tau))\Pi(\tau)d\tau+(\mu+\varphi)(1-s^*R_I)\int_0^\infty\Pi(\tau)d\tau} \tag{69}$$

and

$$c(0) = \frac{N(1-s^*)\varphi}{\varphi\int_0^\infty\Pi(\tau)d\tau+(1-s^*R_C)}. \tag{70}$$

Finally, from (64) and (70) we have

$$c^*(\tau) = \frac{N(1-s^*)\varphi\Pi(\tau)}{\varphi\int_0^\infty\Pi(\tau)d\tau+(1-s^*R_C)}. \tag{71}$$

We have then proved the existence of an endemic solution. Q.E.D

5 Discussion

The main purpose of the present paper has been to explore the role that subacute chronic stages play in the dynamics of an infectous disease. Our case study is the cytomegalovirus infection. This first model is a rough caricature of this disease but it has helped us to understand the basic role that an age-structured chronic stage has in a disease with two types of infections (acute and subacute). We have seen that the interaction between the infectious and chronic groups has a very important role in the dynamics around the disease-free equilibrium. The square root on the expression (59) for the basic reproductive number describes this interaction. We can see that the term

$$\left(\frac{1}{2}(R_I - R_C)\right)^2 \tag{72}$$

can be interpreted as competition for susceptibles by the infectious and chronic groups. Note that if the second term inside the square root of (59) is zero, then R_0 is given by

$$R_0 = \max\{R_I, R_C\}, \tag{73}$$

and since the chronic individuals are less infectious than the acutely infectious group, then we see that in this case the infectious group leads the local dynamics around $(N^*, 0, 0)$. Thus in particular, the asymptotic dynamics of the disease is not affected by the presence of age of infection when passive transit from the acute to the subacute stage (represented by φ) is not

significant (i.e., $\varphi = 0$). However, this condition just mentioned is only one possible reason. We proceed now to provide a more ample interpretation.

While the first term inside the square root represents competition, the second term,

$$\frac{\varphi}{\mu+\varphi}\int_0^\infty (\theta(\tau) + (1-q)\beta_1(\tau))\Pi(\tau)d\tau, \tag{74}$$

represents coexistence between the two groups, in the sense that it describes how each infection group produces individuals that recruit into the other group. Note that in the case when $R_I = R_C$, it is this second term the one that determines which one of the groups takes the leading role in the dynamics.

One particular important result is that the asymptotic dynamics for the age-structured and the non-structured models are essentially the same, both around the disease-free equilibrium and in the conditions for existence and number of endemic points; even the expressions for the endemic points are the same. This tells us that age-structure imposed on the chronic state only does not provide any critical changes in the dynamics of the system (compared with its ODE counterpart), which in turn implies the necessity of the inclusion of another compartment in the system in order to comprehend more clearly the effects of secondary infections and relapse-recovery dynamics. In summary, the results obtained here show that the chronic state simply behaves as another unstructured infectious state, with different transmission rates, and does not give any information on how the recovered group participates in the dynamics specially during the relapse-recovery phases.

Furthermore, since we know from our analysis that structuring the chonic stage by age does not affect the dynamics near the disease-free equilibrium (and therefore infectivity and relapse of chronic individuals are independent of the chronic age), we can expect then that treatment of chronic individuals must be independent of how long the individual has been chronically infected (cf. Hadeler and Müler, (1993a,b)).

In future research, we need to produce a model that sufficiently differentiates between chronic individuals (not infectious) and secondary infections. Moreover, it is not enough just to include a fourth state to the system (secondary infections)if we want to have a realistic model for the epidemiology of CMV, since secondary infections are present only in adult women, and not in children. Thus we have to construct a model which separates adults from infants in the dynamics of the epidemic. We are continuing our research in this direction.

Acknowledgements

This study was supported by the following institutions and grants: National Science Foundation (NSF Grant DMS-9600027); National Security Agency (NSA Grants MDA 904-96-1-0032 and MDA 904-97-1-0074); Presidential Faculty Fellowship Award (NSF Grant DEB 925370) and Presidential Mentoring Award (NSF Grant HRD 9724850) to Carlos Castillo-Chavez; and the Office of the Provost of Cornell University. The author would like to give special thanks to Carlos Castillo-Chavez and Jorge X. Velasco-Hernández for their help during this research.

References

1. Berge, P., 1989 *Cytomegalovirus infection during pregnancy: Maternal anthropometry and birth outcomes.* Ph.D. Thesis, Cornell University.

2. Castillo-Chávez, C., JX Velasco-Hernández and S Fridman, 1995. Modeling contact structures in biology. In *Frontiers in Mathematical Biology*, Lecture Notes in Biomathematics **100** pp:454-491. Springer Verlag, Berlin.

3. Chandler SH, ER Alexander and KK Holmes, 1985. Epidemiology of cytomegalovirus infection in a heterogeneous population of pregnant women. *J Infect Dis* **152**pp:249-56.

4. Diekman, O, JAP Hesterbeek and JAJ Metz, 1990. On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biology* **28** pp:365-382.

5. Faix, RG. 1985. Survival of cytomegalovirus on environmental surfaces. *J Pediatr* **106** pp:649-52.

6. Hadeler, KP and J Müler, 1993a. Vaccination in age-structured populations I: The reproduction number. In *Epidemic models: their Structure and Relation to Data.* Cambridge University Press, Cambridge.

7. Hadeler, KP and J Müler, 1993b. Vaccination startegies in sexually transmitted diseases. In *Proceedings of the Third International Conference on Mathematical Population Dynamics.* Pau, France.

8. Jordan, MC, GW Jordan, JG Stevens and G Miller, 1984. Latent herpesviruses of humans. *Ann Intern Med* **100** pp:866-80

9. Nankervis GA, ML Kumar, FE Cox and E Gold, 1984. A prospective study of maternal cytomegalovirus infection and its effect on the fetus. *Am J Obstet Gynecol* **149**pp:435-40

10. Pass RF., 1985. Epidemiology and transmission of cytomegalovirus. *J Infect Dis* **152**pp:243-7

11. Pass RF, Am August, M Dworsky and DW Reynolds, 1982. Cytomegalovirus infection in a day care center. *New Engl J Med* **307** pp:477-9

12. Pass RF, EA Little, S Stagno, et. al., 1987. Young children as a probable source of maternal and congenital cytomegalovirus infection. *New Engl J Med* **316** pp:1366-70

13. Pass RF, S Stagno, GJ Myers and CA Alford, 1980. Outcome of symptomatic congenital cytomegalovirus infection: results of long-term longitudinal follow-up. *Pediatrics* **66** pp:758-62.

14. Pipkin, AC., 1991. *A course on Integral Equations.* Texts in Applied Mathematics **9**. Springer Verlag, New York.

15. Preece PM, JM Blount, J Glover, et. al., 1983. The consequences of primary cytomegalovirus infection in pregnancy. *Arch Dis Child* **58** pp:970-5

16. Stagno S, RF Pass, G Cloud, et. al., 1986. Primary cytomegalovirus infection in pregnancy: Incidence, transmission to fetus, and clinical outcome. *JAMA* **256** pp:1904-8

17. Stagno S, RF Pass, ME Dworsky and CA Alford, 1982. Maternal cytomegalovirus infection and perinatal transmission. *Clin Obstet Gynecol* **23** pp:563-76

18. Stagno S and RJ Whitley, 1985. Herpesvirus infections of pregnancy. *New Engl J Med* **313** pp:1270-4

19. Thieme, HR and C Castillo-Chávez, 1989. On the role of variable infectivity in the dynamics of the Human Immunodeficiency Virus epidemic, in *Mathematical and Statistical Approaches to AIDS Epidemiology*, Lecture Notes in Biomathematics **83**, pp:157-176, Springer Verlag Berlin.

20. Webb, GF, 1985. *Theory of Nonlinear Age-Dependent Population Dynamics.* Marcel Dekker, New York.