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Delay equation formulation for an epidemic model with waning immunity: an application to mycoplasma pneumoniae

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Abstract: We formulate a general epidemic model with two arbitrary probability distributions for describing durations of infectivity and immunity. The model is given as a coupled system of a delay differential equation and a renewal equation for two dynamical variables: susceptible population and the force of infection. It is shown that there exists a unique endemic equilibrium if the basic reproduction number is greater than one. Assuming that a fixed duration of immunity we show that the endemic equilibrium becomes unstable via Hopf bifurcation. We briefly discuss that periodic outbreak of mycoplasma pneumoniae may be interpreted with the result of instability of the endemic equilibrium.

1. INTRODUCTION

In some communicable diseases e.g. measles and pertusis, established immunity after infection wanes through time. Decreased herd immunity due to the waning immunity may induce re-emergence of epidemic. Formulation and analysis of mathematical models that take into account waning immunity are of importance to gain insight into the role of waning immunity that possibly affects the long-term disease transmission dynamics. In some countries periodic outbreak of mycoplasma pneumoniae has been observed, see Nquipdop et al., (2013). It is also reported that some individuals re-infect mycoplasma pneumoniae. Our aim in this paper is to approach to a relation of the periodic outbreak of mycoplasma pneumoniae and the reinfection, but with a *detour* formulating a rather general deterministic epidemic model.

SIRS type epidemic model is one of the simplest deterministic mathematical models taking into account of waning immunity, see Hethcote et al., (1981); Mena-Lorca and Hethcote (1992). In the model individuals change the status cyclically as Susceptible→Infective→Recovered→Susceptible. The SIRS model can be formulated as a system of differential equations:

$$\frac{d}{dt}S(t) = -\beta S(t)I(t) + \delta R(t), \tag{1a}$$

$$\frac{d}{dt}I(t) = \beta S(t)I(t) - \gamma I(t), \tag{1b}$$

$$\frac{d}{dt}R(t) = \gamma I(t) - \delta R(t). \tag{1c}$$

Here $S(t)$, $I(t)$ and $R(t)$ respectively denote susceptible, infective and recovered population at time t. Model (1) has three positive parameters: β is the transmission coefficient, γ is the recovery rate and δ is the rate of waning immunity, see e.g. Gonçalves et al., (2011); Hethcote et al., (1981); Mena-Lorca and Hethcote (1992) for detail. An important feature of the model (1) is existence of a positive constant solution that is referred as an endemic equilibrium, when the basic reproduction number is greater than one. It is known that the endemic equilibrium is asymptotically stable.

In the model (1) one can notice that exponential distributions are assumed for both the recovery process and the waning immunity. Infective individuals who infected time a ago leave the I-compartment and enter to the R-compartment with probability $\gamma e^{-\gamma a}$ per unit of time at time t. Similarly, recovered individuals who entered to the R-compartment time a ago obtain susceptibility to the disease, due to the waning immunity, and enter to the S-compartment with probability $\delta e^{-\delta a}$ per unit of time. The assumptions *stabilise* the endemic equilibrium, as seen in Gonçalves et al., (2011); Hethcote et al., (1981); Mena-Lorca and Hethcote (1992), thus, to explain the observed sustained oscillations, in the mathematical model, it is necessary to take into account of other distributions of infectious and immunity periods: in which time who recover from the infection and in which time who obtains the susceptibility?

Here we formulate a general epidemic model that allows general probability density functions describing the durations of infectivity and immunity. The model is formulated by delay equations, a coupled system of a renewal equation and a delay differential equations, following the spirit of papers, Diekmann and Heesterbeek (1990); Diekmann and Gyllenberg (2012); Diekmann and Metz (2010). Our model is closely related to the one studied in Gonçalves et al., (2011), where the authors formulate a delay differential equation model describing durations of infectivity and immunity by gamma distributions. Our formulation

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explicitly writes the renewal process of the infection with easily incorporating the variable infectivity.

In the following section we formulate an epidemic model with waning immunity by delay equations. In Section 3 we show existence of an endemic equilibrium and compute the characteristic equation. In Section 4, for a special case, we analyse the characteristic equation and discuss periodic outbreak of mycoplasma pneumoniae relating the result of instability of the endemic equilibrium.

2. DELAY EQUATION FORMULATION

We structure infective and recovered populations by age since infection (the time elapsed since the last infection established) and by age since recovery, respectively. We refer these two structuring variables as infection-age and recovery-age for short. Let $i(t,a)$ and $r(t,a)$ be the density of infected individuals at time t with respect to infection-age a and then the density of recovered population at time t with respect to recovery-age a. Infected and recovered populations are expressed as

$$I(t)=\int_0^\infty i(t,a)da,\ R(t)=\int_0^\infty r(t,a)da.$$

The SIRS-type transmission dynamics can be described by a system of partial differential equations:

$$\begin{aligned}\frac{d}{dt}S(t) =& -S(t)\int_0^\infty \beta(a)i(t,a)da \\ &+\int_0^\infty \delta(a)r(t,a)da, \qquad (2a)\end{aligned}$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)i(t,a) = -\gamma(a)i(t,a), \qquad (2b)$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)r(t,a) = -\delta(a)r(t,a) \qquad (2c)$$

with boundary conditions

$$\begin{aligned}i(t,0) =& S(t)\int_0^\infty \beta(a)i(t,a)da,\\ r(t,0) =& \int_0^\infty \gamma(a)i(t,a)da.\end{aligned}$$

For simplicity, here we ignore population demography as in Gonçalves et al., (2011). The parameters have same interpretations as in (1) but now depend on either infection-age or recovery-age.

To derive an equivalent model in terms of *delay equations*, we introduce a variable Λ to denote the force of infection at time t:

$$\Lambda(t)=\int_0^\infty \beta(a)i(t,a)da. \qquad (3)$$

Let us denote by $G_I(a)$ probability per unit of time that an infected individual whose infection-age is a recovers so that

$$\begin{aligned}\mathcal{F}(a) :=& 1-\int_0^a G_I(s)ds\\ =& \text{probability to be still infected for an individual}\\ & \text{after } a \text{ unit time passed since the infection.}\end{aligned}$$

Note that the probability density function G_I can be expressed

$$G_I(a)=\gamma(a)e^{-\int_0^a \gamma(s)ds}$$

using the recovery rate γ used in the PDE model (2).

The interpretations lead to the following identity

$$i(t,a)=S(t-a)\Lambda(t-a)\mathcal{F}(a) \qquad (4)$$

thus, from (3) and (4), we get the following nonlinear renewal equation

$$\Lambda(t)=\int_0^\infty \beta(a)S(t-a)\Lambda(t-a)\mathcal{F}(a)da.$$

We then denote by $G_R(a)$ probability per unit of time that a recovered individual whose recovery-age is a obtains susceptibility to the disease. Similarly the probability density function G_R can be expressed as

$$G_R(a)=\delta(a)e^{-\int_0^a \delta(s)ds},$$

where δ is the rate of waning immunity used in the PDE model (2). The number of newly susceptible individuals per unit of time at time t is

$$\int_0^\infty \delta(a)r(t,a)da=\int_0^\infty S(t-a)\Lambda(t-a)\mathcal{G}(a)da,$$

where

$$\mathcal{G}(a):=\int_0^a G_R(s)G_I(a-s)ds.$$

Here $\mathcal{G}(a)$ is probability per unit of time that an individual who infected at time $t-a$ obtains susceptibility again to the disease at time t.

SIRS model (2) is now formulated by only two dynamical variables: the susceptible population S and the force of infection Λ:

$$\frac{d}{dt}S(t) = -S(t)\Lambda(t)+\int_0^\infty S(t-a)\Lambda(t-a)\mathcal{G}(a)da, \qquad (5a)$$

$$\Lambda(t)=\int_0^\infty \beta(a)S(t-a)\Lambda(t-a)\mathcal{F}(a)da. \qquad (5b)$$

Here we briefly discuss an extension of the model (5) by incorporating spatial heterogeneity. For example, consider a metapopulation structure for spatial heterogeneity such that movement of individuals among nodes can be described. If one assumes that infection occurs only in the node and that no infection occur during the transportation, formulation of delay equation would be straightforward. Many systems like (5) can be coupled so that each of them describes disease dynamics in a node, certainly paying attention to writing the spatial movement of individuals among nodes. If one considers infection during the transportation, the model formulation and analysis seem to be challenging as there are infinitely many "birth" states distributed along the edge, see Nakata and Röst (2015) regarding this topic and for references to papers on deterministic epidemic models with spatial heterogeneity.

3. EXISTENCE OF AN ENDEMIC EQUILIBRIUM

The basic reproduction number denotes the expected numbers of secondary infective individuals produced by a typical infective individual during an entire infectious period, in a completely susceptible population, which can be assumed $S\approx 1$ without loss of generality. The basic reproduction number is given as the dominant eigenvalue of a positive linear operator, see Diekmann and Heesterbeek