COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE 104 (2011) 37–49

journal homepage: www.intl.elsevierhealth.com/journals/cmpb

The use of a formal sensitivity analysis on epidemic models with immune protection from maternally acquired antibodies

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ARTICLE INFO

Article history:
Received 14 December 2009
Received in revised form
13 August 2010
Accepted 31 August 2010

Keywords:
SIR epidemic models
Maternal antibodies
Sensitivity analysis
PDE systems
Age dependency
Serological survey

ABSTRACT

This paper considers the outcome of a formal sensitivity analysis on a series of epidemic model structures developed to study the population level effects of maternal antibodies. The analysis is used to compare the potential influence of maternally acquired immunity on various age and time domain observations of infection and serology, with and without seasonality. The results of the analysis indicate that time series observations are largely insensitive to variations in the average duration of this protection, and that age related empirical data are likely to be most appropriate for estimating these characteristics.

1. Introduction

During early life the immature neonate immune system is highly dependent on the accumulated immunologic experience of the mother. For example, in the case of human respiratory syncytial virus (hRSV), which has a particularly low average age at primary infection, studies such as those by Ogilvie et al. [1] and Hacimustafaoglu et al. [2] have shown a strong correlation between high levels of maternal antibodies (MAb) and reduced risk of infection and severity of disease among young infants. Maternal immunity is only acquired passively in the specific form of immunoglobulin isotopes IgA and IgG [3], where IgA is transferred after birth through breast feeding and remains predominantly within mucosal secretions in the digestive and respiratory tracts of the infant. The majority of IgG transfer occurs during the final four weeks of pregnancy, where antibodies actively enter foetal circulation via the placenta. As a result, MAb are short lived and following birth, concentrations of IgG in the newborn decay exponentially with a typical half life of around 35–40 days [4]. Many seroepidemiological surveys have shown that most infants become seronegative within 6–9 months of age (see the work by Cox et al. [5] and Hacimustafaoglu et al. [2] for hRSV, Williams et al. [6] for measles and Nicoara et al. [4] for measles, mumps and rubella (MMR)).

The focus of this paper is not on the individual, however, but on the analysis of epidemic models developed to investigate the potential influence of MAb on wider, population level infection dynamics. In this case it is not individual MAb decay (typically estimated using mixed effects modelling techniques and longitudinal serological data) that is directly considered,

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doi:10.1016/j.cmpb.2010.08.019

but the resulting population immunity. The most common approach to deterministic modelling of this type is through a compartmental representation of the various stages of the natural history of infection, written as a system of ordinary differential equations (ODEs). This method was first developed by Kermack and McKendrick [7], in the form of a fundamental SIR (Susceptible-Infective-Recovered) type model structure, which was intended to approximate epidemic evolution within large constant size populations (for general examples see the texts by Jacquez [8] and Capasso [9], and for specific examples see the work by Weber et al. [10] and White et al. [11] for hRSV, and Keeling and Grenfell [12] for measles).

Postulated models of this type are often fitted to time series data corresponding to the prevalence (current number of infective cases) or incidence (current rate of emerging cases) of infection, typically recorded from observations of clinical disease. This process is performed in order to estimate parameter values within the model and make inferences about various characteristics of the real system. However, epidemic data are also often collected with respect to age, for example, in the form of age serological surveys where samples of serum are tested for the presence of disease specific antibodies. It is the objective of this work to use a formal sensitivity analysis, applied to a general partial differential equation (PDE) model structure, in order to compare a number of prospective age and time domain output structures, corresponding to observations of infection and serology. The intention is to establish how well parameters associated with maternally acquired immunity might be determined by various observations of the real system and also to consider the potential influence of these processes on various aspects of system behaviour. The analysis is performed according to the work by Vajda et al. [13] on models residing at endemic equilibrium, where analytic results are derived for systems without seasonal forcing and numerical results obtained for those that include annual variation with time.

2. SIR framework models

The general SIR model [7] is used to characterise epidemic systems where the natural history of infection can be approximated into three distinct stages. The total population is therefore divided into non-overlapping classes that represent subpopulations of individuals with a specific state of disease: Susceptible (S), Infective (I) or Recovered (R). The susceptible class includes all individuals who are able to contract the disease and become infectious; the infective class represents only individuals who are currently infected and infectious to susceptibles, and the recovered class contains all individuals who have recovered from infection and consequently acquired some form of immunity.

The fundamental SIR model can be readily extended to incorporate any number of different epidemiological characteristics such as incomplete immunity (see Gomes et al. [14]), altered secondary infection (see Glass and Grenfell [15], and White et al. [11]) and multiple-strain variants (see White et al. [16]), etc. The potential effects of maternally derived protection can be explored with an additional state compartment M(t), see Fig. 1, that corresponds to newborn individuals protected by MAb [17].

Individuals are born into either the maternally protected or susceptible class depending on the previous infection experience of the mother. The total inflow of newborns into the population occurs at a net birth rate equal to μN, where μ (yr^{-1}) is a combined fertility/mortality coefficient and N is the total population size. The parameter ω (yr^{-1}) describes the rate at which maternally protected newborns become fully susceptible, and ν (yr^{-1}) denotes the rate at which infective individuals recover from infection. It is assumed that the average duration of infection, ν^{-1}, is small with respect to the average life expectancy, μ^{-1}, so that the net mortality rate $\mu(M(t)+S(t)+I(t)+R(t))$ can be assumed to equal μN, hence maintaining a constant size population.

Assuming there is an average contact rate c (yr^{-1}) between all individuals within a particular population, then the rate at which infective individuals, $I(t)$, make contact with individuals from the susceptible proportion, $S(t)/N$, can be shown to be $cS(t)I(t)/N$. For each contact between infective and susceptible individuals there is a finite probability, ρ, that the infectious agent will be successfully transmitted. Therefore the incidence of disease (i.e. the rate at which susceptible individuals become infected) can be modelled as $\beta S(t)I(t)/N$, where $\beta = c\rho$, and $\lambda(t) = \beta I(t)/N$ is often used to represent the force of infection [8]. A system of ordinary differential equations (ODEs) can then be defined:

$$\frac{dM(t)}{dt} = \mu R(t) - \omega M(t), \quad M(0) = M_0, \tag{1}$$

$$\frac{dS(t)}{dt} = \mu I(t) + \omega M(t) - \frac{\beta(t)}{N} S(t)I(t), \quad S(0) = S_0, \tag{2}$$

$$\frac{dI(t)}{dt} = \frac{\beta(t)}{N} S(t)I(t) - (\mu + \nu)I(t), \quad I(0) = I_0, \tag{3}$$

$$\frac{dR(t)}{dt} = \nu I(t) - \mu R(t), \quad R(0) = R_0. \tag{4}$$

If necessary the system (1)–(4) can be reduced to a set of three state equations given that $R(t) = N - M(t) - S(t) - I(t)$.

Given that both the effects of human behaviour, c, and the contagiousness of the infectious agent, ρ, are potentially governed by recurring seasonal trends, it is common to include a periodic function of time within the transmission parameter $\beta(t)$. For example, seasonality in measles is primarily driven by the annual school term-time pattern of increased contact between individuals in the classroom [18], and prolonged survival of many pathogens outside the host is significantly affected by varying climatic conditions, such as temperature and humidity [19].

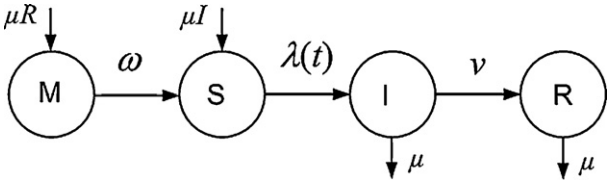

Fig. 1 – MSIR compartmental model.