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Partial cross-enhancement in models for dengue epidemiology

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HIGHLIGHTS

- Cross-enhancement between serotypes a key factor in dengue epidemiology.
- Reappraisal of data suggests cross-enhancement only affects small number of cases.
- Conventional model framework for cross-enhancement revised.
- If enhancement rare, high intensity required to generate multi-annual oscillations.
- Oscillations generated by other drivers modified by enhancement even if rare.

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ABSTRACT

Four distinct serotypes of dengue virus co-circulate in many parts of the world. Antibodies to one serotype prevent infection with the homologous serotype, but may enhance infections with heterologous serotypes. Enhanced secondary infections have been implicated in the majority of severe cases, termed dengue hemorrhagic fever. Conventionally, mathematical models assume that all heterologous secondary infections are subject to enhanced susceptibility or transmissibility. However, empirical data show that only a minority of secondary infections lead to severe disease, which suggests that only a minority of secondary infections are subject to enhancement. We present a new modelling framework in which the population susceptible to secondary infection is split into a group prone to enhanced infection and a group with some degree of cross-protection. We use this framework to re-evaluate the role of enhanced infections in several well known dengue models that exhibit multi-annual epidemiological oscillations. We show that enhancement is unlikely to be driving such oscillations but may be modifying the effects of other drivers.

1. Introduction

Dengue is a mosquito-borne virus that infects people throughout tropical and subtropical regions. It causes dengue fever and a more severe form, dengue hemorrhagic fever (DHF). It is estimated that over 2.5 billion people are at risk (World Health Organization, 2012) and that there are 390 million dengue infections per year (Bhatt et al., 2013). There are four distinct serotypes of dengue, DENV-1, 2, 3, 4. In hyper-endemic regions the prevalence of each serotype is oscillatory with an 8–10 year cycle (Nisalak et al., 2003; Recker et al., 2009). The epidemiological dynamics of the four serotypes are interwoven by immune cross-reaction. Infection with any serotype results in long-term homologous immunity and probably a short period of heterologous immunity (Sabin, 1952; Reich et al., 2013). As this heterologous immunity wanes, antibody-dependent enhancement (ADE) may occur when non-neutralising antibodies bind to infecting viruses and facilitate cell entry. The intracellular antiviral response may also be compromised. Consequently ADE accelerates viral production, potentially leading to higher viremia and more severe disease. See Guzman and Vazquez (2010) for a review of the ADE mechanism in dengue. Heterologous secondary infections are implicated in the majority of dengue hemorrhagic fever (DHF) cases (Gubler and Kuno, 2004).

The standard framework for incorporating ADE into epidemiological models assumes that all individuals that experience a primary infection then become prone to an enhanced secondary infection. This enhancement may act by increasing susceptibility to infection (due to the facilitation of viral entry) and/or increasing transmission once infection has occurred and/or increasing the mortality associated with infection (both due to higher viremia). In the standard modelling framework, enhanced secondary infections can drive compelling epidemiological dynamics. The impact

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is similar whether enhancement acts through susceptibility or transmission (Ferguson and Andreasen, 2002; Adams and Boots, 2006). Pioneering mathematical modelling studies showed that in an unforced two serotype system a relatively small degree of transmissibility enhancement in secondary infections can result in periodic or chaotic dynamics with recurrent epidemics each spanning several years (Ferguson et al., 1999a). It was consequently suggested that ADE may be driving similar underlying multi-annual epidemiological oscillations observed in dengue prevalence data. Many studies have explored the phenomenon of these 'enhancement-induced' oscillations (Aguiar et al., 2011), documenting fascinating dynamics for a range of epidemiological conditions (Ferguson and Andreasen, 2002; Schwartz et al., 2005; Adams and Boots, 2006; Billings et al., 2007; Bianco et al., 2009; Recker et al., 2009; Wikramaratna et al., 2010). Other research has used similar frameworks to model enhancement but investigated alternatives to ADE that may be driving epidemiological oscillations. Stochastic seasonal variation in transmission can sustain long period oscillations in prevalence, with immune cross-reaction between serotypes determining the phase relationship between the time series of their prevalences (Adams et al., 2006). Complete but temporary heterologous cross-protection can lead to 'immunity-induced' oscillatory dynamics in systems where secondary infections are enhanced or neutral (Wearing and Rohani, 2006), or even have reduced transmissibility if severe disease associated with enhanced infection results in rapid hospitalisation (Aguiar et al., 2008, 2011).

These conventional frameworks assume that all secondary infections are enhanced. However, in an outbreak of DENV-2 in Cuba in 1997 only 2–4% of individuals with a secondary infection had DHF. Genetic predisposition was implicated as a risk factor (Guzmán et al., 2002; Guzmán and Kouri, 2002). A cohort study of children in Thailand from 2006 to 2009 found that 96% of DHF cases had secondary infections, but only 13% of secondary infections were DHF cases (Sabchareon et al., 2012). A sample of 1009 children in Thailand in 1980 found multitypic seroconversion in 80% of 10–11 year olds (Sangkawibha et al., 1984; Ferguson et al., 1999b); it is unlikely that such a large proportion also experienced DHF. Antibody dependent enhancement may occur without leading to DHF. However, given that accelerated viral replication underlies the enhancement of susceptibility, transmission and disease severity, the prevalence of DHF is likely to be a reasonable estimate for the prevalence of ADE.

These empirical observations lead us to propose a new framework for modelling antibody-dependent enhancement of dengue. In this framework, the population susceptible to secondary infections is split into a group prone to enhancement, and a group that is not prone to enhancement and may have some degree of protection with respect to secondary infection. We introduce this framework as a generalisation of the conventional two serotype model (Ferguson et al., 1999a). With reference to the conventional model we explore how ADE prevalence and ADE intensity combine to determine the absence or occurrence of oscillatory dynamics. We then investigate how the new framework for ADE affects the behaviour of long period oscillations in a model with stochastic seasonality (Adams et al., 2006) and a model with temporary heterologous cross-immunity (Wearing and Rohani, 2006; Aguiar et al., 2011). It is not our purpose to compare these models with one another in terms of their capacity to replicate the epidemiological dynamics of dengue. Rather, we have chosen these models as representative examples of the main approaches to modelling epidemiological oscillations induced by immune cross-reaction, and our purpose is to assess the impact of refining the model framework for cross-enhancement in each of these contexts.

Mathematical modelling is a key part of modern epidemic control analysis. The core of any dengue model is likely to be similar to one of the frameworks we consider here. These models may be used to assess how key properties of the epidemiological dynamics, for instance prevalence or periodicity, are affected by intervention or contextual modification, for instance vaccines, vaccine administration programmes, climate changes or the emergence of new serotypes. Enhanced infections are a key component of dengue epidemiology and so need to be modelled correctly. Here we argue that this may require some modification of the conventional framework for modelling enhancement. We focus on the role of enhancement in long period epidemic cycles. We show that models with the same 'average' cross-reaction in the population behave similarly. But breaking down the components of this average in our modified framework shows that enhancement is unlikely to be driving these cycles but is likely to be influencing the effects of other drivers.

2. Model 1: Two serotype SIR model with partial cross-enhancement

We now introduce our new framework for modelling cross-enhancement by modifying the conventional two-serotype SIR model with enhancement of transmission (Ferguson et al., 1999a; Adams and Boots, 2006). This model does not permit co-infection and so can be written as five intersecting compartments or, as here, eight disjoint compartments (Fig. 1a) corresponding to: susceptible to both serotypes (S_0), primary infected with serotype i (I_i), susceptible to secondary infection with serotype i (S_i), secondary infected with serotype i ($I_{j,i}$), immune to both serotypes (R). Natural mortality occurs at rate μ in all compartments. Individuals susceptible to both serotypes are born at rate μN to maintain a constant population size N. The vector population is not explicitly modelled. The immune cross-reaction acts on transmission. So susceptible individuals are infected with serotype i at rate $\lambda_i = \beta_0(I_i + \sigma I_{j,i})/N$ where β_0 is the transmission rate, $0 < \sigma < 1$ corresponds to cross-protection and $\sigma > 1$ corresponds to cross-enhancement. All infected individuals recover at rate γ. Those that recover from a primary infection become susceptible to secondary infection, those that recover from a secondary infection become immune to all further infections. No additional mortality is associated with any infection.

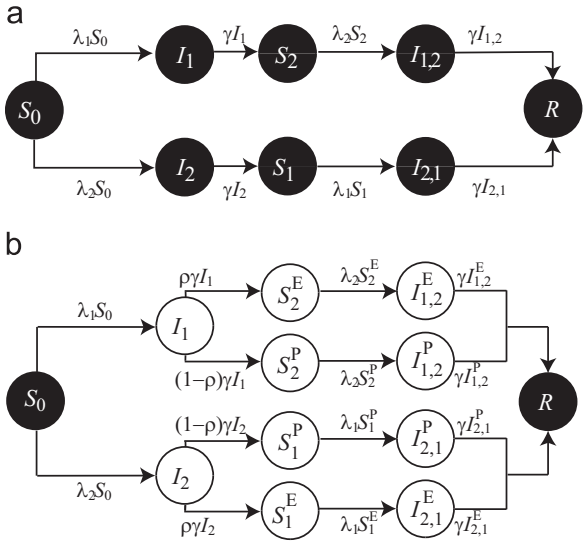

Fig. 1. Flow diagrams showing (a) the conventional structure for two serotype SIR models with cross-protection or cross-enhancement with intensity σ acting on transmission and (b) the modified structure incorporating partial cross-enhancement with prevalence ρ and intensity χ and partial cross-protection with prevalence $1-\rho$ and intensity η. For clarity demographic turnover has been omitted from both diagrams.