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An exploration of the role of asymptomatic infections in the epidemiology of dengue viruses through susceptible, asymptomatic, infected and recovered (SAIR) models

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ABSTRACT

It is estimated that 20–97% of all dengue infections could be asymptomatic. I used SIR models to investigate the epidemiological role of such infections, by adding an asymptomatic class (SAIR models). Upon infection in one of the models, a human becomes either symptomatic or asymptomatic. In the other, a human becomes asymptomatic and may progress to being symptomatic. The robustness of results from these models is examined by incorporating the mosquito-vector into one of the models, followed by simulating epidemic dynamics stochastically. Results from the first two models were very similar, with epidemics typically lasting less than one year. When mosquitoes were explicitly modelled in a high-transmission setting, if the level or duration of infectivity from asymptomatic infections was high relative to symptomatic infections, dengue would become endemic. Under stochastic simulation this effect of asymptomatic infections leading to dengue persisting was no longer guaranteed. Longer durations in asymptomatic infections had a higher chance of causing dengue's persistence in stochastic simulation, indicating that this may be more of a key determinant for dengue's persistence to 10 years than the infectivity of such infections. Otherwise, the level and duration of infectivity from asymptomatic infections had similar effects on R_0 and other epidemiological measures. With all models, outbreaks often led to a larger proportion of the population being immune than suggested by monitoring symptomatic dengue infections. This population would be at risk of developing severe dengue in a subsequent outbreak with a different dengue serotype, and would have to be determined via expansion factors.

1. Introduction

Recent work by Bhatt et al. (2013) estimates that there are 390 million dengue infections a year, but only 96 million episodes of dengue illness. This raises the question, how important are unreported infections to the epidemiology of dengue viruses? After heterotypic immunity to a dengue serotype wanes (Guzman et al., 2010; Reich et al., 2013; Rodenhuis-Zybert et al., 2010) infection with another dengue serotype can lead to dengue haemorrhagic fever (DHF) (Andraud et al., 2012; Guzman et al., 2010; Rodenhuis-Zybert et al., 2010; WHO, 2015), which can cause dengue shock syndrome (DSS). Severe dengue, including both DHF and DSS, has been estimated to cause 500,000 cases of illness resulting in a mortality rate of 2.5% (WHO, 2015). Asymptomatic dengue infections may not only affect dengue's persistence and spread, but determine the proportion of the population left immune to a dengue serotype after an epidemic. This population would be at risk of developing severe dengue in a subsequent epidemic of a differing dengue serotype.

Since the 1980s there has been a growing number of studies attempting to quantify the proportion of dengue virus infections that are asymptomatic (Grange et al., 2014). A recent review found that across 23 studies, 20–97% of dengue virus infections were subclinical (Grange et al., 2014). Recent findings by Duong et al. (2015) suggest that *Aedes aegypti* become more readily infected when feeding off pre-symptomatic or asymptomatic hosts infected with dengue virus when compared to symptomatic hosts, with a similar viral load; *Ae. aegypti* being the principle vector of dengue viruses (Lambrechts et al., 2010; Service, 2012). However, it should be noted that Duong et al. (2015) point to pre-symptomatic and asymptomatic hosts having typically lower viremias than symptomatic hosts. On the other hand, Perkins et al. (2016) demonstrated that febrile humans, many of whom were infected with dengue virus, experienced a loss in mobility compared to afebrile humans. Considering the diurnal and crepuscular biting behaviour of the *Aedes* mosquitoes which are vectors of dengue (Service, 2012), this could

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Table 1
Variables at starting value and parameters used in the models, along with their sources. Population levels were chosen to be computationally practical.

Symbol	Name	Value in FDT Model A	Value in FDT Model B	Value in MDT Model A	Source
μ_H	Human birth and death rate (per day)	1/(60*365)	1/(60*365)	$1/(60 \times 365)$	Mid-range from Andraud et al. (2012)
C	Coefficient relating infectivity from asymptomatic infections to symptomatic infections	0 to 2	0 to 2	0 to 2	NA
B	Biting rate (per day)	Not in FDT	Not in FDT	0.3–1	Andraud et al. (2012)
β_i	Probability of symptomatic transmission to a vector	Not in FDT	Not in FDT	0–1	Andraud et al. (2012)
β_I	Symptomatic transmission rate (per day)	200/365 to 400/365	200/365 to 400/365	$b\beta_i$	Andraud et al. (2012)
β_A	Asymptomatic transmission rate (per day)	$c\beta_I$	$c\beta_I$	$c\beta_I$	NA
Φ	Days symptomatic	8	8	8	Mid-range from Andraud et al. (2012)
γ_I	Symptomatic recovery rate (per day)	φ^{-1}	φ^{-1}	φ^{-1}	NA
D	Coefficient relating asymptomatic recovery rate to symptomatic recovery rate	0.05 to 2	0.05 to 2	0.05 to 2	NA
γ_A	Asymptomatic recovery rate (per day)	$(d\varphi)^{-1}$	$(d\varphi)^{-1}$	$(d\varphi)^{-1}$	NA
P	Probability of being symptomatic	0 to 1	0 to 1	0 to 1	NA
Δ	Progression rate from asymptomatic to symptomatic (per day)	Not in Model A	$p(\gamma_A+\mu)/(1\text{-}p)$	Not in Model A	NA
S_H	Susceptible human population	10^6–1	10^6–1	10^6–1	NA
A_H	Asymptomatic human population	1	1	1	NA
I_H	Symptomatic human population	0	0	0	NA
R_H	Recovered human population	0	0	0	NA
N_H	Total human population	10^6	10^6	10^6	NA
μ_V	Mosquito birth and death rate (per day)	Not in FDT	Not in FDT	1/6	Average *Ae. aegypti* and *Ae. albopictus* from Brady et al. (2013)
Ω	Mosquito maturation rate (per day)	Not in FDT	Not in FDT	1/11	Service (2012)
β_v	Probability of vector transmission to a human	Not in FDT	Not in FDT	0.425	Mid-range from Andraud et al. (2012)
β_V	Mosquito transmission rate (per day)	Not in FDT	Not in FDT	$b\beta_v$	Mid-range from Andraud et al. (2012)
E	Extrinsic incubation period	Not in FDT	Not in FDT	1/10	Mid-range from Andraud et al. (2012)
S_E	Pre-adult mosquitos	Not in FDT	Not in FDT	$(\omega/\mu_V)N_V$	NA
S_V	Susceptible adult mosquito population	Not in FDT	Not in FDT	9.5×10^6	NA
E_V	Latent adult mosquito population	Not in FDT	Not in FDT	0	NA
I_V	Infectious adult mosquitoes population	Not in FDT	Not in FDT	0	NA
N_V	Total adult mosquito population	Not in FDT	Not in FDT	9.5×10^6	NA

increase dengue virus transmission through a greater opportunity of asymptomatically infected humans being bitten by such mosquitoes.

For all of these reasons it is likely that the epidemiology of dengue viruses is strongly influenced by asymptomatic infections. In order to investigate this role, I adapted two SIR models of flu transmission by Robinson and Stilianakis (2013) that included an asymptomatic class (SAIR models). Upon infection in one of these models a human becomes either symptomatic or asymptomatic. In the other model a human becomes asymptomatic and may progress to being symptomatic. The robustness of results from these models is examined by explicitly adding the vector to one of the models and then simulating dynamics stochastically, via τ-leap methodology.

2. Methods

2.1. Models

Studies on asymptomatic dengue infections vary in their definition of asymptomatic dengue infection (Bhatt et al., 2013; Duong et al., 2015; Grange et al., 2014). For the purposes of this study, I define asymptomatic infections as those that do not cause an alteration of the daily movements of the host, and symptomatic infections as those that do. My first model assumes that infections lead either to symptomatic or to asymptomatic states. This model was sourced from Robinson and Stilianakis (2013). Here it is referred to as model A (see Eqs. (1)–(4), Fig. 1A and Table 1). I began by assuming frequency dependent transmission (FDT) (Andraud et al., 2012; Johansson et al., 2011), modelling vector transmission into an aggregated mean vector mediated transmission rate (Johansson et al., 2011). Many justify FDT assuming that the vector population is dense and the timescale of transmission is sufficiently short (Andraud et al., 2012; Johansson et al., 2011). The Basic Reproductive Number R_0 of model A under FDT was sourced from Robinson and Stilianakis (2013) (see Eq. (5)).

$$\frac{\Delta S_H}{\Delta t} = \mu_H N_H - \frac{S_H(\beta_A A_H + \beta_I I_H)}{N_H} - \mu_H S_H \tag{1}$$

$$\frac{\Delta A_H}{\Delta t} = (1-p)\frac{S_H(\beta_A A_H + \beta_I I_H)}{N_H} - \gamma_A A_H - \mu_H A_H \tag{2}$$

$$\frac{\Delta I_H}{\Delta t} = p\frac{S_H(\beta_A A_H + \beta_I I_H)}{N_H} - \gamma_I I_H - \mu_H I_H \tag{3}$$

$$\frac{\Delta R_H}{\Delta t} = \gamma_I I_H + \gamma_A A_H - \mu_H R_H \tag{4}$$

$$R_0 = (1-p)\left(\frac{\beta_A}{\gamma_A + \mu_H}\right) + p\frac{\beta_I}{\gamma_I + \mu_H} \tag{5}$$

The total human population (N_H) is divided into susceptible (S_H), asymptomatically infected (A_H), symptomatically infected (I_H), and recovered (R_H) classes. Each human class experiences loss due to death rate μ_H, but the human population remains constant as