Estimation of the basic reproduction number for dengue virus transmission

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Resume

1. Background
Dengue virus is a widely prevalent pathogen throughout tropical countries. Infection with dengue virus (DENV) results in asymptomatic (inapparent) infection, dengue fever (DF) or dengue hemorrhagic fever (DHF) [1]. DHF is the most severe form of clinical manifestations which can lead to death. There are 4 closely related serotypes. Pathogenesis of DHF is associated with secondary infection with heterologous serotypes. Whereas epidemiologic risks of DHF have been explored for more than 30 years, transmission dynamics of dengue are yet to be clarified. In particular, although there have been various theoretical works which stressed out ecological interests [2] (e.g., super-annual cycle of the epidemic, co-circulation of heterologous strains in relation to antibody-dependent enhancement, and spatial spread and heterogeneity), there are few operational researches which offered practical and quantitative epidemiologic implications for dengue control. This study was aimed at estimating the transmission potential of dengue using DHF incidence only.

2. Methods
This study assumes that dengue is endemic (i.e. endemic steady state) and estimates the force of infection only using age-specific profile of infection. When the force of infection, λ, is age-independent, analytical solution of a static SI model (e.g. age-specific proportion of infected individuals at age a) is given by:

\[ I(a) = 1 - \exp(-\lambda a) \]  

(1)

where \( I(0) = 0 \). Usually, eqn (1) is applied to age-specific seroprevalence data [3]. This study estimated \( \lambda \) from incidence data using the similar analytical solution of SISI model:

\[ \frac{dS_0}{da} = -\lambda S_0 \]
\[ \frac{dS_1}{da} = \delta I_1 - p_1 \lambda S_1 \]
\[ \frac{dI_2}{da} = \lambda S_0 - p_1 \lambda S_1 \]

where \( \delta \) is the rate to loose cross-protective immunity and \( p_1 \) is the reduction of the force of
infection during secondary infection. Assuming that the force of infection is identical between serotypes, $p_1$ is 3/4 (since immunity against the same serotype is life-long). The cumulative distribution of those experiencing secondary infection until age $a$ is:

$$I_2(a) = \frac{p_1 \lambda^2 \delta}{\delta - \lambda} \left[ \frac{\exp(-p_1 \lambda a) - 1}{p_1 \lambda} - \frac{\exp(-\lambda a) - 1}{\lambda} \right]$$

Maximum likelihood estimates of $\lambda$ and $\delta$ were obtained by minimizing binomial deviance between the eqn (3) and observed data. With regard to observed age-specific data of DHF and those experiencing secondary infection, observed DHF incidence reported to surveillance and age-specific probability of secondary infection (among all DHF) in Bangkok were used.

The effective reproduction number, $R$, is given by:

$$R = R_0 s^*$$

where $R_0$ is the basic reproduction number and $s^*$ is the proportion of susceptible. In an endemic equilibrium, $R = 1$ and thus $R_0$ is given by an inverse of the proportion of susceptible individuals [4]. I assume that Bangkok population approximately follows so called “Type-II survivorship” function, exponentially distributed age-specific survivorship, $l(a)$:

$$l(a) = \exp(-\mu a)$$

where $\mu$ is the force of death. Under this assumption, the number of susceptible individuals, $S^*$, and total population, $N^*$, in an endemic equilibrium are given by:

$$S^* = \frac{N(0)}{\lambda + \mu}$$
$$N^* = \frac{N(0)}{\mu}$$

where $N(0)$ is the population size at birth. $s^*$ in eqn (4) is given by $S^*/N^*$ [5]. Thus, $R_0$ is:

$$R_0 = 1 + \lambda L$$

where $L$ is the average life expectancy at birth and equals to $\mu^{-1}$. Using the estimated $\lambda$ and $L$, estimate of $R_0$ was obtained.

3. Results and Conclusion

Using DHF incidence during 1990s, $R_0$ (and the corresponding 95% confidence intervals (CI)) was estimated to be 15.4 (95% CI: 14.3, 29.6). The maximum likelihood estimate of $\delta$ was 3.12 (2.65, 3.89) per year. The same model was applied to the incidence during 1980s. $R_0$ was estimated as 18.4 (16.3, 31.4). In addition, this model permitted a dual estimation of the
age-specific risk of DHF following secondary infection, the qualitative pattern of which was consistent with a previous observation on innate susceptibility to DHF in Cuba.

Thus, serotype-unspecific $R_0$ should be assumed to be larger than 15 in endemic areas (where 4 serotypes are co-circulating). The discrepancy seen in different estimates of $R_0$ (in previous studies using DF epidemic data) might be largely attributable to the different vector ecology and virulence, but, most importantly, this also reflects that substantial proportion of asymptomatic infections and unreported DF would exist. It would be appropriate to assume that serotype-unspecific $R_0$ for dengue is approximately 16, at least, to design the monovalent vaccination strategies. It is difficult to eradicate dengue by vector control only. Compared to the difficulty of eradication using monovalent mass vaccination only (which necessitates to cover > 94%), it is easier to eradicate dengue if tetravalent vaccine equally covers four different serotypes. If this is the case, the critical coverage of vaccination should be assumed to be one-fourth of the above serotype-unspecific $R_0$ (i.e. approximately 4) since $\lambda$ in the above model should have been $4\lambda$ in a serotype-specific manner [6].

It is interesting to note that the force of infection significantly decreased from 1980s to 1990s. Indeed, elevated average age at contracting DHF in 1990s compared to 1980s reasonably reflects the decrease in the force of infection. In Bangkok, the habitation of Aedes spp, vector of dengue, may have been reduced. Moreover, the model confirmed that the qualitative pattern of age-specific risk of DHF following secondary infection was consistent with previous suggestion on the innate susceptibility to DHF. During secondary infections, small children are more vulnerable to DHF than adolescents and adults.

4. Acknowledgements

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5. References (Note: original paper describing the above work is under review)