ESTIMATING REPRODUCTION NUMBER OF DENGUE TRANSMISSION IN 2013 AND 2014, SINGAPORE

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Abstract. In order to evaluate the reproduction number of vector-borne diseases, which are prevalent in regions for decades and, as a result, the human population is no longer completely susceptible to the disease due to development of natural immunity or vaccination, it is necessary to develop a mathematical model of the disease transmission, the solution of which gives the number of infected cases periodically reported by surveillance organizations. We generated a model and applied it to a dengue epidemic in Singapore in 2013 and 2014. A new estimation formula for the reproduction number was obtained under the assumption that the human population was not completely susceptible to the disease. Using the actual dengue data, we evaluated the reproduction number of dengue transmission in Singapore in 2013 and 2014. The new formula is effective in estimating the reproduction number of a vector-borne disease under the circumstances that the human population is not completely susceptible to the disease.

Keywords: dengue, reproduction number estimation, mathematical model, vector-borne disease

INTRODUCTION

The basic reproduction number R_0, defined as the average number of secondary cases induced by a typical infectious individual in a completely susceptible population (Hethcote, 2000), plays a key important role both in theoretical studies and in practice to control transmission of infectious diseases (Diekmann *et al*, 1990). The value of R_0 is associated with the transmission potential of a disease, the possible maximum number of infected individuals and the strength of the control measures for that particular disease (Heesterbeek, 2002). Usually, the disease will die out gradually in a population if R_0 is <1, while the disease will be endemic in the population if R_0 is >1. Hence, in the practice of controlling the spread of a disease, measures should be taken to reduce the value of R_0. In fact, it is a well known result that a disease will cease its prevalence if the vaccination rate for the susceptible population is >1-1/R_0 (Dietz, 1993). Therefore, it is very important to estimate the value of R_0 to control disease outbreak.

Mathematical models have been widely used to quantitatively analyze transmissions of various infectious diseases (Hethcote, 2000). These models are

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mainly compartmental models that divide a population into different compartments that correspond to the different courses of a disease, such as susceptible, exposed, infected and recovered populations (Hethcote, 2000). In certain theoretical methods, R_0 can be expressed in terms of the parameters of the compartmental models (Van den Driessche and Watmough, 2002). Hence, it appears that the value of R_0 can be obtained via the estimation of the relevant model parameters. However, in most cases, some model parameters included in the calculation of R_0 are very difficult to estimate. As an example, in the mathematical models for the transmission of malaria or dengue, vector-borne diseases transmitted by certain types of mosquitoes, one parameter involved in the determination of R_0 is the amount of the total number of the particular type of mosquitoes. It is a big challenge and perhaps even impossible to obtain the exact number of the pertinent types of mosquitoes in the region.

On the other hand, there is readily available information regarding a disease outbreak, such as the number of newly infected cases, which is announced by disease surveillance organizations daily or weekly. It is therefore more fruitful to look for methods that employ such data to estimate R_0 of the disease in question.

In fact, there are methods to estimate R_0 from the initial growth data of a disease. For example, in the case of dengue transmission, under the assumption that the cumulative cases of the early outbreak are exponential, Marques *et al* (1994) derived an estimation of R_0 as

$$R_0 = 1 + \frac{\lambda}{\mu + \gamma}. \qquad (1)$$

Subsequently, Massad *et al* (2001) proposed the following equation

$$R_0 = \left(1 + \frac{\lambda}{\mu}\right)\left(1 + \frac{\lambda}{\gamma}\right), \qquad (2)$$

and Favier *et al* (2006) established that

$$R_0 = \left(1 + \frac{\lambda}{\mu}\right)\left(1 + \frac{\lambda}{\gamma}\right)e^{\lambda(\tau_i + \tau_e)}, \qquad (3)$$

where in (1), (2) and (3), μ is the natural mortality death rate, and γ is the recovery rate of the infection, τ_i and τ_e are respectively the intrinsic and extrinsic incubation period of the parasites.

In all the above estimations of R_0, we need to estimate the exponential growth rate λ of the cumulative cases in the early outbreak of the disease, while the other parameters can be obtained from the demography of the host population together with other observations. Hence, it is possible to estimate R_0 from the initial growth data of a disease using the above formulas. However, formulas (1) - (3) are developed under the circumstances of an early outbreak of a disease, *ie*, it is assumed that the whole population is susceptible to the disease. Therefore, for diseases, such as dengue, that have been prevalent in a population for decades and only a proportion, not the whole, of the population in a region is susceptible to these diseases (Egger *et al*, 2008), the application of formulas (1) - (3) in estimating R_0 for these diseases will inevitably cause errors. Moreover, as mentioned above, compartmental models have achieved much progress in the studies of infectious diseases, we therefore were motivated, in this paper, to obtain an estimation of R_0 via a combination of compartmental models and information implied by the factual data of infected cases, under the assumption that the population is partially susceptible to the disease concerned. We shall illustrate our methodology by considering

Table 1
Biological meaning and values of parameters used in model (4).

Parameter	Biological meaning	Value
S_H, I_H, R_H	number of susceptible, infectious, recovered subjects	variable
S_V, I_V	number of susceptible, infectious mosquitoes	variable
λ_H	recruitment rate of human population	$=\mu_H$
μ_H	natural death rate of human population	demographical
λ_V	recruitment rate of vector population	$=\mu_V$
μ_V	natural death rate of vector population	0-0.2 day^{-1}
a	bite by *Aedes aegypti* per day per vector per host	0-0.5 day^{-1}
b	proportion of bites leading to human infection	0-1
c	proportion of bites leading to vector infection	0-1
γ	recovery rate of subjects from infection	0-0.5 day^{-1}

a particular case of dengue transmission and using factual dengue data to estimate R_0. The new formula for R_0 can also be applied to other vector-borne diseases.

METHODS

Estimation of R_0

Dengue transmission model. Compartmental models have been established to analyze the transmission and control of dengue (Esteva *et al*, 1998; Erickson *et al*, 2010). For the model given below, the human population is divided into three compartments: susceptible (S_H), infected (I_H) and recovered (R_H). It is assumed that the total human population (N_H) remains constant, *ie*, $S_H+I_H+R_H$ is constant at all time t. The vector population is divided into two compartments: susceptible (S_V) and the infectious (I_V). It is also assumed that the number of mosquitoes (N_V) remains constant in the region considered, *ie*, S_V+I_V is constant. There is no death of the infected vectors induced by the infection.

Thus, the following model was established to describe the dynamics of dengue transmission between the human and mosquito populations:

$$\begin{cases} \dfrac{dS_H}{dt} = \lambda_H(S_H + I_H + R_H) \\ \qquad\qquad -\dfrac{ab}{N_H} S_H I_V - \mu_H S_H, \\ \dfrac{dI_H}{dt} = \dfrac{ab}{N_H} S_H I_V - \gamma I_H - \mu_H I_H, \\ \dfrac{dS_V}{dt} = \lambda_V(S_V + I_V) - \dfrac{ac}{N_H} S_V I_H \\ \qquad\qquad - \mu_V S_V, \\ \dfrac{dI_V}{dt} = \dfrac{ac}{N_H} S_V I_H - \mu_V I_V. \end{cases} \quad (4)$$

The biological meaning and the values of the parameters in the model (4) are listed in Table 1. Due to the assumption that both the human and mosquito populations are constant, we have $\lambda_H=\mu_H$ and $\lambda_V=\mu_V$. Details regarding the derivation of the model (4) have previously been described (Esteva *et al*, 1998; Burattini *et al*, 2008; Erickson *et al*, 2010).

Applying the survival method (Hefferman *et al*, 2005; Wan and Cui, 2013), the basic reproduction number of model (4) is

$$R_0 = \frac{N_V}{N_H} \cdot \frac{a^2 bc}{(\gamma + \mu_H)\mu_V}. \quad (5)$$

Clearly, if one applies formula (5) to calculate R_0, one needs to estimate the value of N_V. As mentioned above, it is a challenge to estimate accurately the total number of *Aedes aegypti* in the region (N_V). Also ubiquitous difficulties also occur in the estimations of *a*, *b* and *c*. Therefore, we developed a new estimation formula for R_0 that does not involve parameters that are difficult to determine.

New estimation formula. In standard practice, surveillance organizations will report newly infected cases daily or weekly to the public. The newly infected cases are clearly related to the solutions of model (4), which in turn would involve parameters such as N_V, *a*, *b* and *c*. Therefore, instead of estimating these parameters directly, we can consider the solutions of model (4) with a view to using the information of the newly infected cases.

As the newly infected cases are related to the dynamics of I_H, we rewrote the second and the last equations of (4) as

$$\begin{cases} \dfrac{dI_H}{dt} = \dfrac{ab}{N_H}(N_H - I_H - R_H)I_V \\ \qquad\qquad - \gamma I_H - \mu_H I_H, \\ \dfrac{dI_V}{dt} = \dfrac{ac}{N_H}(N_V - I_V)I_H - \mu_V I_V, \end{cases} \tag{6}$$

where we used the constant population assumptions $N_H = S_H + I_H + R_H$ and $N_V = S_V + I_V$.

Due to the fact that partial immunity is gained when the infected person recovers from infection, we assumed that $S_H = N_H - I_H - R_H \sim \eta N_H$, where η is the proportion of susceptible people in the human population at time t. Also, we set $S_V = N_V - I_V \sim N_V$ due to the relatively short lifespan of the mosquitoes. Consequently, from (6) we obtained an approximate model of the disease evolution as

$$\begin{cases} \dfrac{dI_H}{dt} = ab\eta I_V - \gamma I_H - \mu_H I_H, \\ \dfrac{dI_V}{dt} = acmI_H - \mu_V I_V, \end{cases} \tag{7}$$

where $m = N_V/N_H$.

Model (7) is a linear system and can be expressed as

$$\begin{pmatrix} \dfrac{dI_H}{dt} \\ \dfrac{dI_V}{dt} \end{pmatrix} = A \begin{pmatrix} I_H \\ I_V \end{pmatrix},$$

where

$$A = \begin{pmatrix} -(\gamma + \mu_H) & \eta ab \\ acm & -\mu_V \end{pmatrix}.$$

It is well known that the solutions of (7) are

$$\begin{pmatrix} I_H \\ I_V \end{pmatrix} = C_1 e^{\lambda_1 t}\mathbf{v_1} + C_2 e^{\lambda_2 t}\mathbf{v}_2, \tag{8}$$

where λ_1, λ_2 are eigenvalues of *A*, $\mathbf{v_1}$, $\mathbf{v_2}$ are the corresponding eigenvectors and C_1, C_2 are constants determined by the initial values. A direct computation and combining with (5) yields

$$\lambda_{1,2} = \frac{1}{2}[-(\gamma + \mu_H + \mu_V) \pm \sqrt{(\gamma + \mu_H + \mu_V)^2 - 4(\gamma + \mu_H)\mu_V(1 - \eta R_0)}],$$

which in turn gives

$$R_0 = \frac{1}{\eta}\left[1 + \frac{\lambda_1^2 + \lambda_1(\gamma + \mu_H + \mu_V)}{(\gamma + \mu_H)\mu_V}\right], \tag{9}$$

as λ_1 is the principal (dominant) eigenvalue of *A*.

The new estimation formula (9) does not involve the parameters N_V, *a*, *b* and *c*, so the difficult problem of estimating these parameters is solved, but the new parameters λ_1 and η have to be estimated. Noting (8), we have

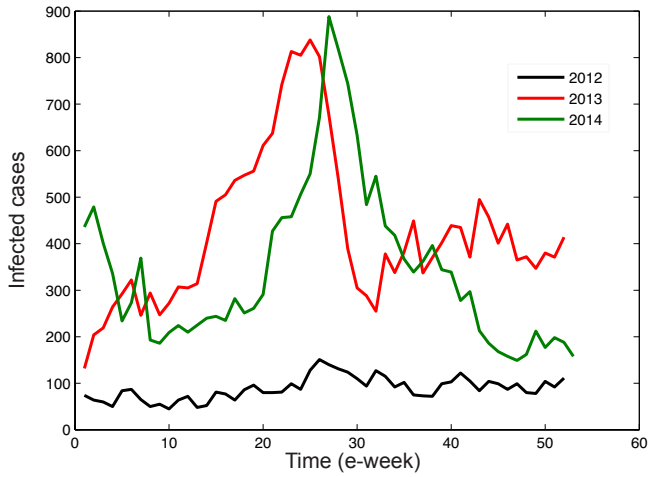

Fig 1–Dengue infected cases in 2012, 2013 and 2014 in Singapore.

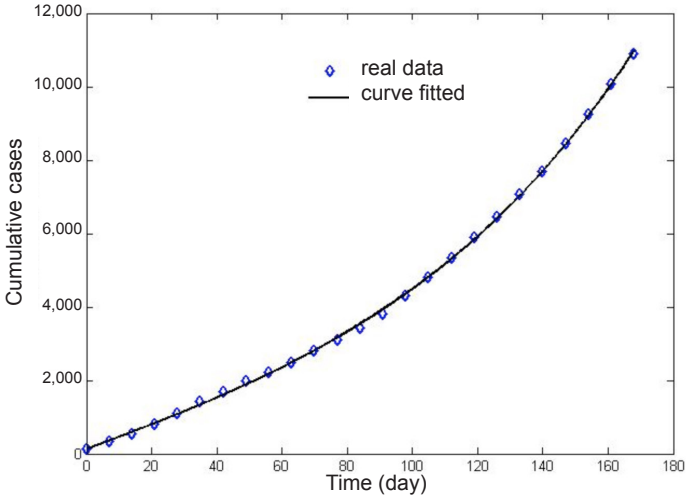

Fig 2–Cumulative Singapore dengue cases in the interval <1, 25> of 2013 fitted by the equation $p_1e^{p_2t} + p_3e^{p_4t}$, where p_1, p_2, p_3, p_4 are constants corresponding to $c_1^{(0)}$, λ_1, $c_2^{(0)}$, λ_2 in (10), respectively.

$$I_H = c_1^{(0)}e^{\lambda_1 t} + c_2^{(0)}e^{\lambda_2 t}, \qquad (10)$$

where $c_1^{(0)}$ and $c_2^{(0)}$ are constants determined by the initial values of $I_H(0)$ and $I_V(0)$. Therefore, λ_1 and λ_2 can be obtained from the newly infected cases announced by the surveillance organizations by appropriate curve fitting. The value of η can be estimated by methods such as described by Egger *et al* (2008).

RESULTS

The newly infected cases of dengue in Singapore are reported by the Ministry of Health, Singapore, on a weekly basis (MOH SGP, 2014-2015). The number of dengue cases in 2013 and 2014 is dramatically elevated compared with that in 2012 (Fig 1). Hence, it is reasonable to claim that there was a dengue outbreak in 2013 and 2014.

It is obvious that the accuracy of the estimation of R_0 is dependent on the estimation of λ_1. It is worth noting that the cumulative infected cases correspond to the integration of I_H, which, from (10), has the interesting form

$$c_1^{(1)}e^{\lambda_1 t} + c_2^{(2)}e^{\lambda_2 t},$$

where λ_1 and λ_1 are the same as those in the expression of I_H. Hence, we can make use of the cumulative cases of a disease to estimate λ_1 (and λ_2), as was performed in (1)-(3) to estimate λ.

Year 2013

Let the interval $<1, n>$ denotes the period from the first e-week to the nth e-week in 2013. For different values of n, we can fit the curve and record the R-square value. R-square, a value between 0 and 1, is a descriptive statistics of Matlab curve

Table 2
Values of R-square for different intervals in 2013 used in curve fitting.

Interval	R-square
<1, 10>	0.9986
<1, 22>	0.9996
<1, 24>	0.999684
<1, 25>	0.999689
<1, 26>	0.999618
<1, 27>	0.9994
<1, 30>	0.9957
<1, 40>	0.7329

Table 3
Values of R-square for different intervals of 2014 used in curve fitting.

Interval	R-square
<1, 10>	0.9983
<1, 19>	0.9996
<1, 20>	0.9997
<1, 21>	0.9996
<1, 27>	0.9971
<1, 33>	0.9965
<1, 35>	0.9933
<1, 42>	0.8294

fitting toolbox, which evaluates the goodness of fit, the larger the R-square is, the more accurate is the fit. Hence, we shall choose the fit with the largest *R*-square to obtain the estimated values of λ_1 and λ_2, which are respectively given by p_2 and p_4.

The largest R-square, 0.999689 (Matlab R2011a), occurs when $n = 25$ (Table 2), and the curve fitting is depicted in Fig 2. Thus $\lambda_1 \approx 0.01209$ and $\lambda_2 \approx 0.0115$ were obtained. All the estimated values are the mean values of the corresponding 95% confidence intervals.

We set $\mu_H = 3.32 \times 10^{-5}$ days^{-1} [life expectancy statistics of Singapore in 2013 (MOH SGP, 2015)] and $\mu_V = 0.25$ days^{-1} (Massad *et al*, 2010). In model (4), γ is the recovery rate of humans from dengue infection, *ie*, $1/\gamma$ is the infectious period of a viremic subject (with virus in the blood that can cause infection of susceptible mosquitoes). The intrinsic incubation period, which is the latent period of the exposed subject before the onset of symptoms, is 4-10 days and the symptoms of dengue last 5-7 days (Rigau-Perez *et al*, 1998; Miranda and Johansson, 2012). Hence, we set the infectious period of a viremic subject $1/\gamma = 10$ days, which includes the time that causes the infection of susceptible mosquitoes during the latent period. This infectious period of 10 days is consistent with the 24 days generation time of dengue transmission (Hsieh and Ma, 2009).

It was observed that <60% of the population in Singapore is susceptible to dengue infection (Egger *et al*, 2008). Therefore, we set the proportion of the susceptible human population $\eta = 60\%$. Now all the parameters in (9) have estimated, and it follows immediately from (9) that R_0 for the year 2013 is 2.77.

Alternatively, instead of using the cumulative cases in <1,25>, we can use the newly infected cases in <1,25> directly for curve fitting (Fig 3). Here, the *R*-square value is 0.9633, which is lower than that of using the cumulative cases (0.999689). Hence, the accuracy of the curve fitting is better when cumulative cases are applied. The reason for this is that as the infected cases cumulate, the number of cumulative cases is monotonically increasing over time, and this is better fitted by functions such as $p_1 e^{p_2 t} + p_3 e^{p_4 t}$. If the cases are not cumulated, the numbers may not be monotonically increasing and subsequently the fit is not as good.

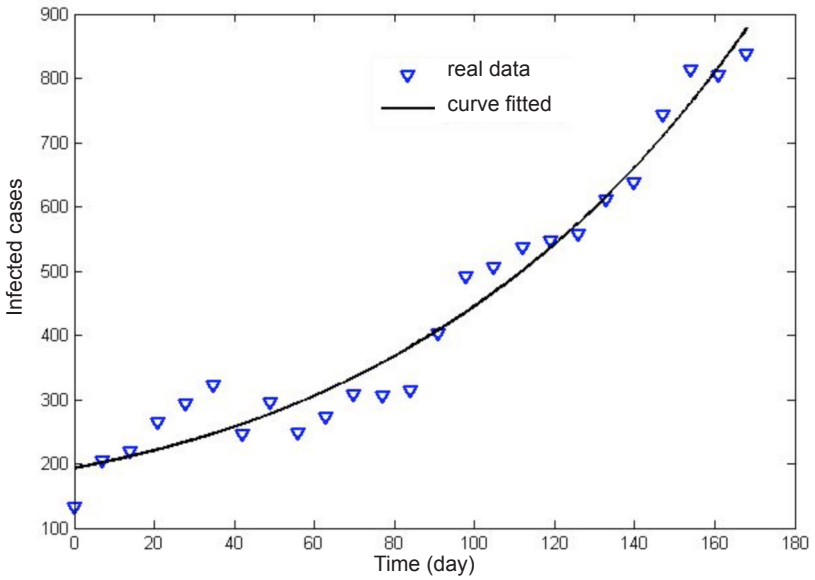

Fig 3–Singapore dengue infected cases in the interval <1, 25> of 2013 fitted by the equation $p_1 e^{p_2 t} + p_3 e^{p_4 t}$, where p_1, p_2, p_3, p_4 are constants corresponding to $c_1^{(0)}$, λ_1, $c_2^{(0)}$, λ_2 in (10), respectively.

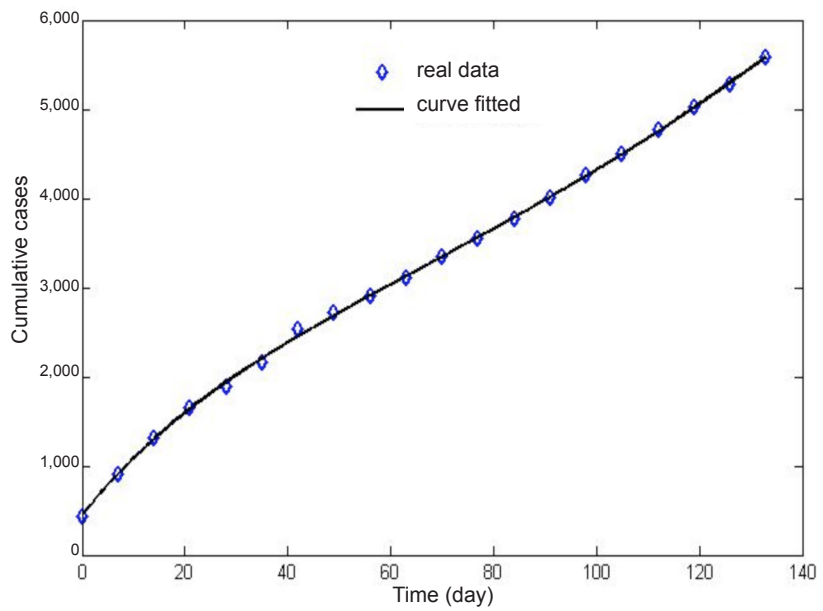

Fig 4–Cumulative Singapore dengue infected cases in the interval <1, 20> of 2014 fitted by the equation $p_1 e^{p_2 t} + p_3 e^{p_4 t}$, where p_1, p_2, p_3, p_4 are constants corresponding to $c_1^{(0)}$, λ_1, $c_2^{(0)}$, λ_2 in (10), respectively.

Year 2014

In 2014, we found that the largest R-square, 0.9997, occurred when $n = 20$ (Table 3). The curve fitting in the interval <1,20> yielded $\lambda_1 \approx 0.007544$ (Fig 4).

With γ, μ_H, μ_V and η having the values as indicated above, R_0 for the year 2014 is 2.33.

During dengue outbreak periods

In the above, R_0 for the years 2013 and 2014 were estimated in the time interval <1,n>, where n^{th} e-week ($1 \le n \le 52$) is selected such that the R-square value of curve fitting is the largest. Clearly, this method can only be applied after we have the whole year's data. The R_0 value obtained can be considered as the annual R_0 for the particular year and it reflects the overall severity of the disease transmission in that particular year.

In practice, however, it is more important to estimate the R_0 value during the early stage of a disease outbreak

Table 4
Variations of R_0 in the interval <9, n> during Singapore dengue outbreak of 2014.

Interval	λ_1	R-square	R_0
<9, 14>	0.008965	0.9997	2.47
<9, 15>	0.008849	0.9997	2.46
<9, 16>	0.002088	0.9999	1.84
<9, 17>	0.00796	0.9999	2.37
<9, 18>	0.006832	0.9999	2.27
<9, 19>	0.002395	0.9999	1.87
<9, 20>	0.008904	0.9978	2.46
<9, 21>	0.01239	0.999	2.80
<9, 22>	0.008904	0.9979	2.46
<9, 23>	0.008904	0.9979	2.46
<9, 24>	0.008314	0.9992	2.41
<9, 25>	0.008273	0.9993	2.40
<9, 26>	0.008231	0.9994	2.40
<9, 27>	0.008268	0.9996	2.40
<9, 28>	0.008066	0.9996	2.38
<9, 29>	0.00746	0.9993	2.33

(Favier *et al*, 2006; Massad *et al*, 2010), so that the severity and trend of the outbreak as well as the effectiveness of control measures can be monitored in a timely manner.

However, formula (9) can also be used to estimate R_0 in the early stage of disease outbreak. The newly infected cases in 2014 are in a down-trend from the first e-week to the 9th e-week followed by an up-trend from the 9th e-week to the 27th e-week, *ie*, the dengue outbreak of 2014 in Singapore began from the 9th e-week (Fig 1). Applying formula (9), we can estimate R_0 in each interval <9, n> and observe the changes of its value during the outbreak of 2014. We observed that the value of R_0 varies during the outbreak, and this can provide useful information for disease control organizations to take appropriate control measures.

In Table 4, we noted that the curve fitting in the interval <9, n> starts from $n = 14$ as at least 6 groups of data are needed to perform the curve fitting to guarantee accuracy. Moreover, in order to give more timely information, one can use the daily data of newly infected cases to estimate R_0 during the disease outbreak.

DISCUSSION

The definition of R_0 involves a completely susceptible population. Because dengue has been prevalent in Singapore for decades (Hsieh and Ma, 2009) and not the whole population in Singapore is susceptible to dengue (Egger *et al*, 2008), it is reasonable to interpret the estimated value of R_0 of dengue transmission in Singapore as "reproduction number", rather than as basic reproduction number.

Hsieh and Ma (2009) estimated that the reproduction number of dengue transmission in Singapore in 2005 is 2.23, while Massad *et al* (2008) estimated R_0 of 1.9

for dengue transmission in Singapore for 2002. The estimated R_0 for different cities in Brazil varies from 2.26 to 11.39 (Coelho *et al*, 2008), and from 1.3 to 11.6 (Nishiura, 2006). Thus, the estimated R_0 values of 2.77 (for 2013) and 2.33 (for 2014) obtained in this paper for the dengue transmission in Singapore are within similar range.

The methodology in this paper involves a combination of (i) the theoretical expression of R_0 obtained from a mathematical model of dengue transmission, and (ii) the actual new infected cases announced by the disease surveillance organizations at regular time intervals. As a result, a *new* estimation formula (9) was obtained to estimate R_0, the dengue "reproduction number". This method can be generalized to derive estimation of the "reproduction number" of other infectious diseases.

In the process to establish the estimation formula, an approximate model was used such that the analytical solution could be obtained. Hence, if the approximate model is more accurate, so will the estimation of R_0. In general, it is not possible to obtain the analytical solutions of nonlinear compartmental models for infectious diseases, such as model (4). Hence, it is more meaningful to seek better approximate models for these compartmental models to improve the accuracy of estimation of the basic reproduction number.

The time interval $<i,j>$ should be selected based on the type of information of interest. For example, if knowledge of the overall severity of the disease transmission in a particular year is desired, then intervals $<1,n>$ of $(1\leq n\leq 52)$ should be used. On the other hand, if the focus is on tracking the severity of transmission during an outbreak, then intervals $<i^*, j>$ should be used, where i^* is the time when the number of new infected cases starts to increase.

In order to estimate the reproduction number when the human population is not completely susceptible to a disease, the method established in this communication is different from that proposed by Pinho *et al* (2010), and our method is easier to apply in practice and also is more efficient.

Finally, we note that our method can only be applied to estimate the reproduction number based on the data of infected cases previously notified, *ie*, the formula in this report cannot be used to compute R_0 in advance using past data of infected cases. However, it will be worthwhile to develop methods that can predict the value of reproduction number for the immediate future based on current data.

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