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Intervention Measures, Turning Point, and Reproduction Number for Dengue, Singapore, 2005

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Abstract. The 2005 dengue outbreak in Singapore cumulated in > 14,000 cases and 27 reported dengue deaths. We fit the single-phase Richards model to weekly dengue notification numbers to detect the turning point for the outbreak, which enables us to study the impact of intervention measures relating to the turning point. The results indicate that turning point had most likely occurred in late August or early September, before large-scale intervention measures were implemented. The "initial" reproduction number for the outbreak is estimated to be ~1.89–2.23 (95% confidence interval: 1.15–3.00). One of the lessons learned from the 2003 severe acute respiratory syndrome (SARS) outbreak is that multiple phases of outbreak were observed in some affected countries when efforts to intensify intervention or to sustain vigilance were compromised. Intensive and continuing efforts in the implementation of control measures are essential in reducing further dengue occurrences during any resurgence of dengue.

INTRODUCTION

Dengue is an old disease that has become endemic in many parts of Africa, Latin America, and Asia and has shown increased prevalence in recent decades.[1] It is estimated by the World Health Organization (WHO) that, in the early 21st century, ~2.5 billion people—two fifths of the world's population—are now at risk from dengue.[2] Moreover, WHO estimated in 2002 that there may be 50 million cases of dengue infection worldwide annually.

In some tropical countries such as Singapore, dengue transmission occurs on a year-round basis. In 2005, a significantly rise in the number of dengue fever (DF)/dengue hemorrhagic fever (DHF) cases was reported in Singapore, which peaked in September/October.[3] A total of 14,209 laboratory-confirmed cases of DF/DHF were reported in 2005 in Singapore, comprising 13,816 cases of DF and 393 cases of DHF, which was an increase of 50.2% from the 9,459 dengue cases reported in 2004 (which in turn was an increase of 97.6% from the 4,788 dengue cases reported in 2003[4]).

At the peak of the epidemic, the government implemented, in addition to the regular vector control strategy used every year,[5] country-wide adulticidal and larvicidal control measures, also known as "carpet-combing." The carpet-combing campaign was an intensive "search-and-destroy" operation led by the National Environmental Agency (NEA) and carried out during six weekends by thoroughly searching out and eliminating mosquito breeding sites in common outdoor areas of all public and private residential estates. A detailed summary of the campaign can be found elsewhere.[6]

Since the outbreak, several studies on the impact of control strategies were carried out. Burattini and others[7] used a model for dengue infection that takes into account the seasonal variation in incidence and showed, using weekly DF/DHF data of Singapore for 2003–2005 and simulation studies of the actual intervention strategy implemented by the government in 2005, that the mixed strategy of adulticide and larvicide methods introduced by the government seemed to be very effective in reducing the number of cases in the first weeks after the start of control.

In another study,[6] a retrospective study was carried out using regression analysis on the weekly number of case notifications for dengue received in 2005 stratified by the carpet-combing exercises for each of the six mutually exclusive groups of pre-identified locations, to estimate the unique predictive importance attributed to the natural progression of time series (they termed "time-component") and to the impact of the carpet-combing operations. Their results indicated that the average number of dengue notifications decreased significantly by about one half an SD as a result of the intervention efforts caused by the first carpet-combing operation started in the 37th epidemiologic week (or e-week), which was in fact the largest one in its scope compared with that of subsequent exercises. Moreover, they observed that there was a decreasing rate of "returns" in terms of the reduction in dengue notifications from carpet-combing operations, and interestingly, the contribution of the time-component was deemed to be greater than that of the carpet-combing operations in the reduction of dengue notifications, which was observed for all the six exercises.

Recently, in an effort to assess the effectiveness of intervention measures during the severe acute respiratory syndrome (SARS) pandemic, Zhou and Yan[8] used the Richards model, a logistic-type model,[9] to fit the cumulative number of SARS cases reported daily in Singapore, Hong Kong, and Beijing. In that article, they obtained estimates for the cumulative case number and basic reproduction number for each affected area. However, only partial case data during the outbreak was used, which influenced the accuracy of the results. More seriously, the inflection point of the logistic (S-shaped) curve, which could provide vital information pertaining to the changing trends of the epidemic and possibly indicating changes in intervention and control, was not discussed.

Hsieh and others[10] proposed to use the Richards model, along with the complete Taiwan SARS case data from the beginning of the outbreak to its end, to obtain an estimate of the cumulative case number. Moreover, the inflection point of the S-shaped epidemic curve was obtained, which indicates the "turning point" of the outbreak in Taiwan when the daily number of infections starts to decrease. More recently, Hsieh and Cheng[11] used the SARS case data of the Greater Toronto

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area (GTA) to show that, even for a multi-staged epidemic, the Richards model can still be used for real-time prediction of outbreak severity and real-time detection of turning points. A comprehensive examination of the Richards model and its application to all major SARS infected regions in 2003, namely Beijing, Hong Kong, Taiwan, Singapore, and Greater Toronto, can be found in Hsieh.[12]

In this article, we will apply the Richards model to Singapore weekly notifications of DF/DHF data to identify the turning point of the outbreak and to ascertain the impact of intervention and control measures implemented during the 2005 dengue outbreak in Singapore.

MATERIALS AND METHODS

In 1959, Richards[9] proposed the following model to study the growth of biological populations:

$$I'(t) = rI(t)\left[1 - \left(\frac{I}{K}\right)^{a}\right].$$

Here the prime "′" denotes the time rate of change and the time unit is e-week. As a model for the growth of an epidemic outbreak, $I(t)$ is the cumulative number of notification cases at time t (in weeks), K is the maximum case number over the course of the outbreak, r is the per capita intrinsic growth rate of the infected population, and a is the exponent of the deviation for the S-shaped epidemic curve for $I(t)$.

The model is a generalization of the well-known logistic equation first proposed by Verhulst in 1838.[13] The differential equation given above is a special case of the Bernoulli equation, named after the famous mathematician Jacob Bernoulli and first solved by Leibnitz at the end of 17th century. The explicit solution of the Richards model is known to be $I(t) = K[1 + e^{-r(t-t_m)}]^{1/a}$. Here the parameter t_m is related to the turning point t_i of the epidemic by the simple formula $t_m = t_i + (\ln a)/r$, where ln denotes the natural logarithm function. For more technical details regarding the Richards model or the Bernoulli equation, the readers are referred elsewhere.[12,14]

Unlike the susceptible-infective-removal (SIR) compartmental model commonly used to predict the spread of disease, the Richards model considers only the cumulative infective population size with saturation in growth as the outbreak progresses caused by implementation of control measures. The basic premise of the Richards model is that the daily incidence curve consists of a single peak of high incidence, resulting in an S-shaped epidemic curve and a single turning point of the outbreak. The turning point, defined as the points in time at which the rate of accumulation changes from increasing to decreasing or *vice versa*, can be easily located by finding the inflection point of the epidemic curve, the moment at which the trajectory begins to decline. This quantity has obvious epidemiologic importance, indicating either the beginning (i.e., moment of acceleration after deceleration) or the end (i.e., moment of deceleration after acceleration) of a phase.

The data used for model fitting is the e-weekly notification of DF/DHF cases, 2004–2005 (Figure 1), extracted from the "Communicable Diseases Surveillance in Singapore, 2005" report[15] (accessible from Singapore Ministry of Health website). The weekly data were converted into cumulative case numbers, starting from e-week 17. Although dengue cases occur year-round in Singapore, e-week 17 was chosen because the outbreak had clearly occurred after e-week 17. The cumulative case data were fitted to the cumulative case function $I(t)$ in the Richards model with the initial time $t_0 = 0$ being e-week 17 and the initial case number $S_0 = S(0) = 118$, the number of new cases in that week. The data fit can be easily evaluated and efficiently performed using any standard software with a least-squares approximation tool.

RESULTS

Turning point of outbreak. The estimation results of the model parameters are given in Table 1, showing the estimation runs for different time periods all starting in e-week 17. The initial estimates using shorter time periods (or insufficient data) were clearly not meaningful. The estimated values of the turning point t_i started to converge with the estimation using the data of the time period ending with e-week 45. Because e-week 17 is the initial time or $t = 0$, the estimated turning point of $t_i = 18.10$ (95% confidence interval [CI]: 16.44–19.77), denoting e-week 35.10 (i.e., 17 + 18.10), indicates that the turning point had occurred approximately in e-week 35 or 36, the 18th or 19th week after e-week 17. Therefore, we conclude that the turning point for the dengue

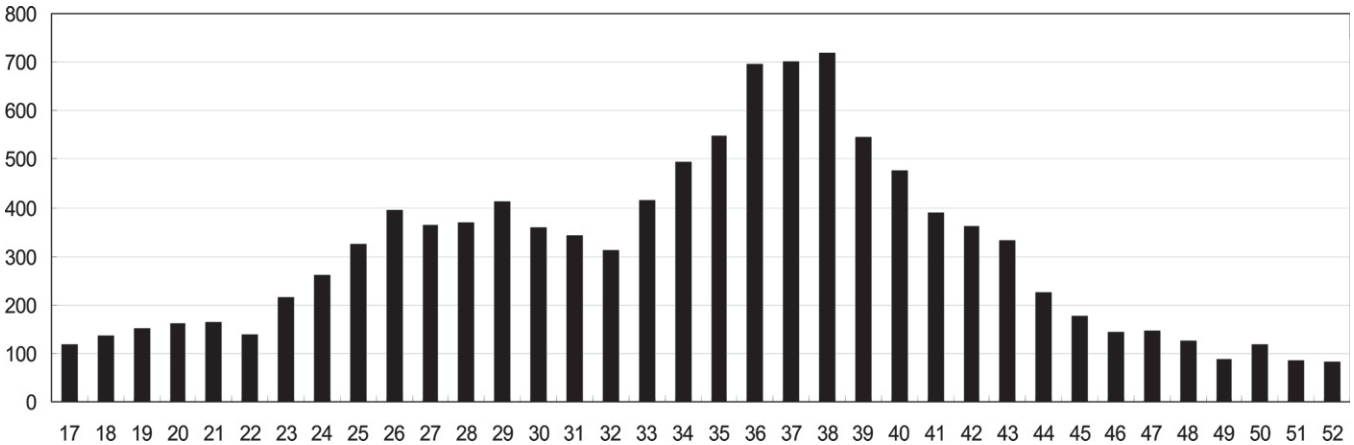

FIGURE 1. E-weekly distribution of DF/DHF cases, 2004–2005 in Singapore. Source: "Communicable Diseases Surveillance in Singapore 2005" Report (accessed from http://www.moh.gov.sg/mohcorp/publicationsreports.aspx?id=15272).

TABLE 1
Estimation results of the model parameters starting from e-week 17 with 95% CI, using data from e-week 17 to various time past the turning point at e-week 35

Time period	Exponent of deviation (95% CI)	Turning point (95% CI)	Growth rate (95% CI)	Maximum case no. (95% CI)
17–35	0.001 (0*–30.041)	10.90 (0*–42,5501.04)	0.085 (0*–3.155)	4,954.6 (0*–101,480)
17–43	0.061 (0*–0.567)	20.72 (0*–152.19)	0.077 (0.02–0.135)	19,474.6 (9,408.2–29,541.0)
17–44	0.389 (0*–0.936)	18.70 (3.47–33.93)	0.118 (0.057–0.178)	14,749.0 (10,982.0–18,515.9)
17–45	0.729 (0.147–1.311)	18.10 (12.15–24.06)	0.157 (0.095–0.219)	12,808.5 (10,944.1–14,672.8)
17–46	1.014 (0.418–1.610)	17.99 (14.48–21.51)	0.189 (0.127–0.251)	11,953.8 (10,833.4–13,074.3)
17–47	1.201 (0.617–1.785)	18.01 (15.38–20.64)	0.210 (0.151-0.269)	11,583.0 (10,807.7–12,358.4)
17–48	1.316 (0.758–1.874)	18.05 (15.84–20.26)	0.223 (0.167–0.278)	11,408.6 (10,824.7–11,992.5)
17–52	1.425 (0.988–1.861)	18.10 (16.440–19.77)	0.234 (0.194–0.275)	11,275.1 (10,992.9–11,557.4)

Note that the estimate for maximum (cumulative) case number was the whole time period of e-weeks 17–52. The true cumulated case number from e-weeks 17–52 was 11,076.
* Max(0, lower bound).

outbreak occurred in e-weeks 35–36, or August 28–September 10 of that year, which can be detected using data of e-weeks 17–45 only, or ~8 weeks after the occurrence of the turning point. We also note that, because the data used were stamped by a notification date, the actual turning point for dengue infection most likely occurred even earlier. In addition, given the vector–host cycle, the actual impacts on human dengue infections would not become noticeable until 2–3 weeks after any carpet-combing exercises on controlling mosquitoes had started.

The fitted (cumulative) epidemiologic curve obtained from the Richards model using data between e-weeks 17 and 52 is given in Figure 2, along with the observed data for comparison, which exhibit a very good fit.

Basic reproduction number. The basic reproduction number R_0 is an important epidemiologic parameter, which, in describing degree of vector–host transmissibility, is defined to be the expected number of hosts who would be infected after one generation of the parasite by a single infectious person who had been introduced into an immunologically naïve population.[16] Our result can be used to compute the basic reproduction number $R_0 = \exp(rT)$, where T is the generation time of the disease, the average interval from infection of one individual to when their contacts are infected (see elsewhere[8,11] for application to SARS). r is the per capita intrinsic growth rate in the Richards model, the estimate of which is given in Table 1.

We use the estimated value for r in the last row of Table 1 (i.e., r = 0.234; 95% CI: 0.194–0.275), which is the converging estimate for r obtained by using the complete data set of weeks 17–52 and hence is more reliable (see the column of estimates for r in Table 1). For the generation time of vector–host disease transmission, MacDonald has argued (see, eg,[17,18]) that one should consider the average number of cases in the host population arising from one case in the host population through vector cases. For the generation time, we know that the intrinsic incubation period within a human, or the time from a human being bitten to onset of symptoms, averages from 4 to 7 days. Moreover, it could range from 3 to 14 days according to dengue information provided from the US CDC website.[19] Period with symptoms in human caused by dengue infection may last 3–10 days, with an average of 5 days after the onset of symptoms. The viremia begins slightly before the onset of symptoms, which also lasts for ~5 days. During the viremic period, an uninfected female *Aedes aegypti* mosquito bites the person and ingests blood that contains dengue virus. Then, within the mosquito, the virus replicates during an extrinsic incubation period of 8–12 days. The mosquito bites a susceptible person and transmits the virus to him or her, thus beginning the next generation of infection. Assuming a mean extrinsic incubation period of 10 days, we arrive at a mean generation of 19–22 days, with a range of 14–36 days. Using a mean generation of 19 days (or 19/7 weeks, because our data and the estimates are given in time units of weeks), we obtain

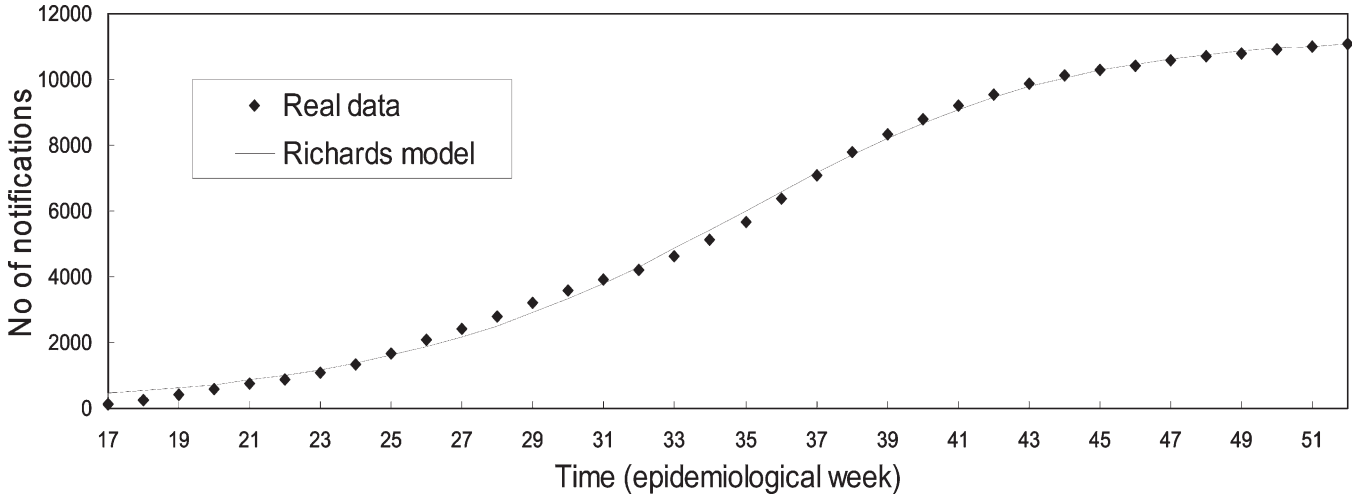

FIGURE 2. Epidemic curve for the cumulative DF/DHF notifications in Singapore during e-weeks 17–52 of 2005 using the Richards model.

an estimate for the reproduction number of 1.89 (95% CI: 1.15–2.62). On the other hand, if we use 22 days for the mean generation, the estimate is 2.09 (95% CI: 1.26–2.92). Note that we do not use the term "basic" reproduction number for reasons to be given later.

Massad and others[20] used an extrinsic incubation period of ~14 days, ranging from 10 to 16 days from Halstead,[21] and the duration of viremia (or presence of virus in the blood) of 5 days with a range of 3–8 days for dengue. For the purpose of comparisons, we used their values for extrinsic incubation period and viremia (along with the US CDC value for the intrinsic incubation period) to arrive at the estimated generation time of 24 days, ranging from 16 to 34 days. Again, using the formula for R_0, we obtain $R_0 = 2.23$ (95% CI: 1.47–3.00).

DISCUSSION

The data between e-weeks 17 and 52 fitted the Richards model well, exhibiting a typical single wave outbreak. The turning point was pinpointed to be around e-weeks 35–36, before the implementation of the first carpet-combing exercise in e-week 37. This seems to corroborate with the conclusion of Ang and others[6] that temporal decline of the outbreak, which they called time-component, had more impact on containing the outbreak than the carpet-combing exercises. Moreover, this turning point was detectable ~9 weeks after the occurrence of this turning point.

It is interesting to also note that e-weeks 35–36 in 2005 was August 28–September 10. An earlier event that could have had alerted the public and hence have an impact on mitigating the spread of dengue, as reported by ChannelNewsAsia[22] on August 24, was the action taken by the NEA to recruit more field inspectors that year with a target of > 500 inspectors by the end of the year, or four times more than the number for previous year, mainly because of the alarm over the number of new dengue cases doubling over the previous year.

The Richards model also could be useful for modeling multi-wave outbreaks and detecting multiple turning points.[11] However, in this instance, delayed detection of the turning point 9 weeks later does make its practical usefulness doubtful. We believe this is more because of the unique features of dengue, namely, vector–host cycle and delay in notifications, which makes this model less than ideal for the purpose of real-time prediction.

Dengue has re-emerged in Singapore over the past two decades as an infectious disease of public health importance. Disease incidence increased from 4.9 cases/100,000 population in 1985 to 322.5 cases/100,000 population in 2005. During this period, there were inter-year cyclic patterns of an upward temporal trend, with peaks in 1992, 1998, and 2005, each followed by a short period of respite. In addition, there were also intra-year cycles of incidence increasing from April to a peak at September of each year. Our results indicate that the 2005 dengue outbreak in Singapore was of the single-phase nature. One of the lessons learned from the SARS outbreak in 2003 is that multiple phases of an outbreak were observed in various affected countries when the efforts to intensify intervention or the degree of maintaining vigilance were compromised (e.g., Toronto[11,23] and Singapore[24]). Likewise, without intensive and continuing efforts in the implementation of various control measures, maximum impact in reducing further dengue occurrences could not have been achieved during this resurgence of dengue in 2005.

The effect of climate also cannot be easily discarded. The observation made by Ang and others[6] that the contribution of the time-component was deemed to be greater than that of the carpet-combing operations in the reduction of dengue notifications can be easily interpreted in terms of climate effects. Using local Singapore data from 1985 to 2007, the highest correlation between monthly notifications of dengue incidence and mean temperature was found in a lag of ~2–3 months ($r > 0.37$, $P = 0.000$; data not shown; the detailed correlational analysis between various climate factors and dengue incidence is currently under study by the second author but is beyond the scope of this work). Other studies such as Chowell and Sanchez[25] also used data from the 2002 dengue epidemic in Colima, Mexico, to determine that the highest correlation between monthly reported the number of confirmed dengue incidence and maximum temperature had a lag of 1 month, whereas the highest correlation between dengue incidence and evaporation had a lag of 3 months.

It has been noted that emergency response to dengue outbreaks, usually in terms of vector control, has become common practice.[26] However, by the time a response is carried out, transmission is usually at or near its peak, at which time vector control has little impact. Our result seems to highlight this common dilemma. However, as a tool for weekly real-time assessment of epidemic severity during the ongoing outbreak,[11] our estimate for turning point converged around e-week 45, whereas weekly incidence was still high, offering assurance that the outbreak was coming under control, provided that the mass vector control that was implemented after the peak (but before e-week 45) was not terminated, which could possibly cause a second wave of outbreak. On the other hand, a divergence of weekly real-time estimates usually indicates a new wave of infections, enabling quicker response.

We also obtained estimates for the basic reproduction number of the 2005 dengue outbreak to be between 1.89 and 2.23, with 95% CIs ranged between 1.15 and 3.00. Many good models appropriate for modeling initial density-independent phase are available for estimation of R_0.[20] For comparison, Koopman and others[27] estimated R_0 for 70 locations in Mexico from serologic data and obtained values of 1.33–2.41. Marques and others[28] estimated R_0 for dengue in Sao Paulo state, Brazil, from the rate of growth of clinical cases seen early in the 1990–1991 epidemic and obtained estimates between 1.6 and 2.4 for different cities. Using the classic definition of R_0 as inversely related to the proportion of susceptibles in the population in endemic areas with random mixing[29] and assuming all four serotypes are equally represented and cross-reactivity between the strains did not occur, Khoa and others[30] concluded that estimates of R_0 for each strain would range from 1.25 to 1.75. Chowell and others[31] proposed to use two competing methods to estimate the "mean reproduction number" R_p for the 2002 dengue epidemic in Colima, Mexico, arguing, perhaps correctly so, that R_p is a more appropriate quantification for recurrent infectious diseases such as dengue where a fraction of the population is already immunologically protected at the beginning of an outbreak. They obtained estimates of 3.09 (95% CI: 2.34–3.84) for their method 1 and 2.0 (95% CI: 1.75–2.23) for method 2. Our results for basic reproduction number for dengue are in close agreement with these studies.

However, other studies using distinctly different methods have resulted in vastly different basic reproduction numbers for dengue. Luz and others[32] proposed a model that incorporates vector density spatial heterogeneity and parameterized the model using *a priori* probability density functions covering a range of plausible values for each parameter. Using Latin Hypercube Sampling procedure, they obtained a 95% CI range of 0.66–22.4 for high urban vector infestation areas in Rio de Janeiro city and a 95% CI range of 0.03–14.4 for low urban vector infestation areas. Favier and others[33] proposed a method of deriving the reproductive number from the early epidemic curves and applied the model to several dengue epidemics in different climatic regions of Brazil to obtain a wide range of R_0 for nine dengue epidemics in several cities in Brazil during 1996–2003, from the lowest value of 2.0 for Fortaleza in 2003 to as high as 103 for Brasilia in 2001. Ferguson and others[34] analyzed serologic survey data collected in Thailand to obtain estimates of the force of infection and basic reproduction numbers for each strain under a variety of different assumptions regarding the degree of cross-protection and/or enhancement conferred by primary or later infections. Taking into account the interaction between different strains and immunologic response, their strain-specific estimates of R_0 ranged from ~4 to 8. More recently, Massad and others[35] used the estimated dengue seroprevalence[36] to deduce that R_0 is ~1.9 for dengue in Singapore. A recent review on basic reproduction number for dengue with detailed discussions on mathematical modeling of dengue can be found elsewhere.[37]

The above-mentioned discrepancy in estimation results for R_0 highlights the difficulty in quantifying dengue using basic reproduction number, because of the additional challenges of, among other factors, the nature of vector-borne infectious disease cycle of infection, the four strains of dengue, and variations in location and climate. It is also important to note that R_0 is defined to be the number of secondary infections by an index case in an immunologically "naïve" population, which is certainly not the case for most of the above-mentioned regions for which R_0 was estimated. For example in Singapore, Wilder-Smith and others[36] found 45% of 298 enrolled subjects had a positive dengue serology. Moreover, Egger and others[26] determined that, during 1960–2000, < 60% of the population in Singapore was susceptible to dengue. A sizable immunoprotected population typically leads to substantial underestimation of R_0, because many of the contacts of the index case are not susceptible to infection with the same serotype of dengue virus. Subsequently, the value for R_0 that we have obtained through the Richards model is in fact the number of secondary infections caused by a new infective at the initial stages of the outbreak (e.g., in our case, e-week 17). Therefore, perhaps a more appropriate term for our estimate is the "initial" reproduction number of the outbreak, which coincides with the basic reproduction number only when disease prevalence is low.

To fully account for this concern, multi-strain model taking into account cross-protection[34] might be desirable to adequately resolve this problem. Moreover, further studies using data from regions where dengue is not endemic, and perhaps even more detailed serologic dengue serotype data, are needed in the future to elucidate this issue of epidemiologic importance.

Finally, a recent modeling study on the impact of intervention for dengue[38] raised the possibility that decreases in dengue transmission may act to increase DHF incidence, and DHF incidence can be effectively controlled with a sufficiently large reduction in R_0, but moderate reductions may be counterproductive. This hypothetical scenario further highlights the need for reliable mathematical models for dengue outbreaks to discover the likely outcome of intervention measures for dengue. Our use of the simple Richards model to obtain quantitatively and qualitatively useful information regarding turning points and basic reproduction number of an outbreak is one step in that direction.

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