

Mathematical and Statistical Analyses of the Spread of Dengue

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Abstract

This paper is aimed at clarifying the contributions of mathematical and statistical approaches to dengue epidemiology without delving into mathematical details and sharing the basic theory and its applications regardless of the reader's mathematical background. The practical importance of the basic reproduction number, R_0 , for dengue is highlighted in relation to the critical proportion of vaccination required to eradicate the disease in the future, and three different methods to estimate R_0 , (i) final size equation; (ii) intrinsic growth rate; and (iii) age distribution, are concisely explained with published estimates and examples. Although the estimates of R_0 most likely depend on the ecological characteristics of the vector population, it would be appropriate to assume that serotype-nonspecific R_0 for dengue is approximately 10, at least in planning vaccination strategies in endemic areas. Statistical approaches to determining the periodicity of epidemics, cocirculation of different serotypes (relevant to pathogenesis of dengue haemorrhagic fever), and the significance of spatial heterogeneity are subsequently discussed. Whereas the dengue epidemic is partly characterized by a super-annual cycle with 3–4-year intervals, it is known only that this pattern is determined by the intrinsic dynamics of dengue and not by environmental factors. Although antibody-dependent enhancement was determined as a factor permitting the coexistence of the four serotypes of dengue, a more detailed understanding requires further data. To base the transmission dynamics of dengue on firm evidence and apply the results to dengue control, it is essential that field and laboratory professionals and theoretical specialists interact more.

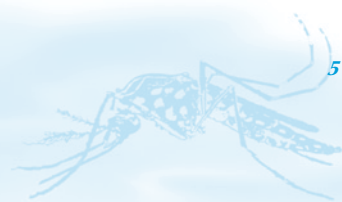
Keywords: Dengue, epidemiology, mathematical model, statistical model, basic reproduction number, periodicity, population theory.

Introduction

Numerous approaches have been used to clarify the epidemiology of dengue fever (DF) and dengue haemorrhagic fever (DHF). The epidemiology of dengue virus (DENV) infection possesses several specific ecological

characteristics, and thus, the epidemiological determinants have often been explored using mathematical and statistical methods. Whereas various epidemiological studies using mathematical and statistical models have appeared so far, their insights and implications have not been successfully shared with dengue

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researchers or epidemiologists. One of the reasons for this might be attributed to the difficult and complicated mathematical expressions in the original articles. In particular, although the value of predictability seems to be frequently accentuated, mathematical and statistical approaches of dengue are more likely to offer significant implications from other viewpoints (e.g. evolutionary biology). Since the pathogenesis of DHF and ecological characteristics of both DF and DHF are yet to be clarified, it is of practical importance to share common interests and questions between dengue specialists and theoretical epidemiologists in order to specify directions for future research. This paper is aimed at clarifying the contributions of mathematical and statistical approaches to dengue epidemiology and ecology without delving into too many professional mathematical notations and to share knowledge of the basic theory, regardless of the reader's mathematical background.

A simple mathematical model

Table 1 shows a summary of the theoretical models relevant to dengue epidemiology that have been published to date.^[1-37] The thirty-seven publications included in the table differ from each other in the approaches taken and the underlying assumptions. For example, whereas the series of studies by Focks et al. investigated the quantitative value of models using entomological data and simulations,^[9,10,12,19] others focused purely on the qualitative patterns of the equation system motivated by ecological interests.^[16,27,30] Despite the different purposes, these studies share a common methodology for the underlying structure of population dynamics,^[6,38,39] which was originally proposed for malaria by Ross and thereafter formalized by Macdonald.^[40,41] Since the basic theory of malaria is detailed elsewhere,^[42,43] here I briefly discuss a model for dengue, which was initially proposed by Dietz^[6] and Bailey.^[44]

Figure 1: Compartments of human and vector populations

[Whereas the human population consists of three compartments (susceptible (S_h), infectious (I_h) and removed (R_h)), the mosquito population is classified into two, susceptible (S_v) and infectious (I_v)]

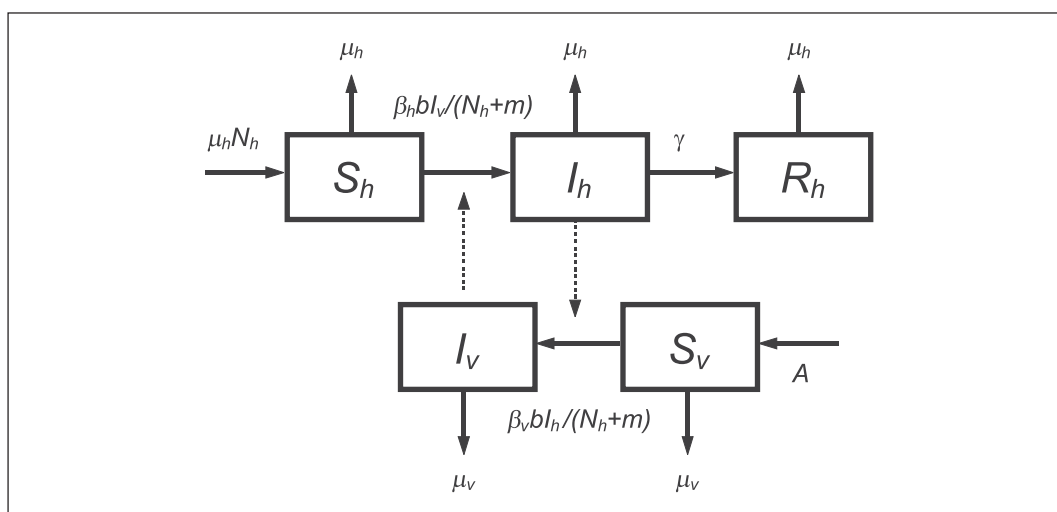
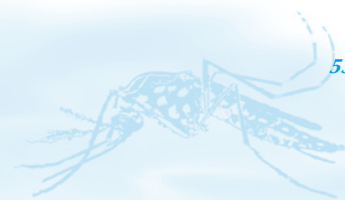


Table 1: Mathematical and statistical studies on dengue

First author, year	Population	Model	R_0	Conclusions
Bartlett, 1964 ^[1]	Not available (N/A)	Stochastic compartmental model		Extinction plays an important role in vector-borne dynamics
Fischer, 1970 ^[2]	Thailand	Double sequential infection model with stationary assumptions		Secondary infection was validated using age distribution of DHF
de Moor, 1970 ^[3]	South Africa (Chikungunya)	Stochastic individual-based model		Survival probability of the vector is the critical factor in the cycle
Griffiths, 1972 ^[4]	N/A	Stochastic birth-death process model		The behaviour of the process conditional on extinction is examined
Radcliffe, 1974 ^[5]	N/A	Stochastic model		The typical interval between epidemics based on the model parameters is obtained
Dietz, 1975 ^[6]	N/A	Deterministic compartmental model with vaccination	27	Analytical solution, critical population size, spatial heterogeneity, vaccination strategy, and age-structure are formally presented
Koopman, 1991 ^[7]	Mexico	Final size equation based on discrete-time model	1.3	The low R_0 for dengue indicates reductions through modest efforts
Newton, 1992 ^[8]	N/A	Deterministic compartmental model with vector control	1.9	Ultra-low volume (ULV) aerosols have little impact on disease incidence
Focks, 1993 ^[9,10]	USA	Weather-driven life table simulation model (CIMSIM)		Useful in simulation studies concerning vector control strategies
Marques, 1994 ^[11]	Brazil	Simplified deterministic compartmental model	1.6–2.5	Dengue virus is only moderately infectious in Brazil
Focks, 1995 ^[12]	Honduras	Entomologic information-based dengue simulation model (DENSIM)		The model accounts for virus development within individuals and its passage between both populations



First author, year	Population	Model	R_0	Conclusions
Feng, 1997 ^[13]	N/A	Deterministic compartmental model with two pathogen strains		Competitive exclusion is the interplay between the host superinfection process and biting frequency
Esteva, 1998 ^[14]	N/A	Deterministic compartmental model		The global stability of the endemic equilibrium is given
Esteva, 1999, 2000 ^[15,16]	N/A	Deterministic compartmental model		Three threshold parameters exist which regulate the endemic equilibrium
Ferguson, 1999 ^[17]	Thailand	Non-stationary age- and serotype-specific model	4.3–5.8	The force of infection varies on a 3- to 4-year time period
Ferguson, 1999 ^[18]	Mexico	Deterministic compartmental model with two strains		Antibody-dependent enhancement generates complex and persistent cyclical or chaotic epidemic behaviour
Focks, 2000 ^[19]	Trinidad and others	CIMSiM and DENSiM		Entomological threshold condition is developed
Hay, 2000 ^[20]	Thailand	Time-series analysis in contrast to equation of inter-epidemic period		Intrinsic population dynamics explain the observed inter-epidemic periods
Massad, 2001, 2003 ^[21,22]	Brazil	Deterministic compartmental model with yellow fever	2.7–11.6	R_0 for dengue would also suggest a transmission potential of yellow fever
Pongsumpun, 2001, 2002 ^[23,24]	Cuba, Thailand	Deterministic compartmental model with age-structure		Secondary infection explained age-specific incidence of DHF
Bartley, 2002 ^[25]	Thailand	Deterministic compartmental model with seasonality and secondary infection		The time to peak the prevalence corresponds to a delay in the system
Esteva, 2003, 2005 ^[26,27]	N/A	Deterministic compartmental model with two serotypes		Coexistence is permitted for a large range of parameters



First author, year	Population	Model	R_0	Conclusions
Derouich, 2003 ^[28]	N/A	Deterministic compartmental model with vaccination		Combination of environmental measures and vaccination would be required as a short term policy
Luz, 2003 ^[29]	N/A	Continuous-time Markov chain for uncertainty analysis		Spatial heterogeneity of the vector population increase the risk of epidemics and complicates the control strategies
Kawaguchi, 2003 ^[30]	N/A	Deterministic compartmental model with antibody-dependent enhancement and two serotypes		Mortality enhancement supports an evolutionary stable viral community and allows co-circulation
Pongsumpun, 2004 ^[31]	N/A	Deterministic compartmental model with mobile susceptible		The number of travellers' dengue is obtained as a function of the length of time to stay in infested area
Cummings, 2004 ^[32]	Thailand	Spatial-temporal model to show the traveling wave		Bangkok acts as a pacemaker of DHF for the surrounding regions
Favier, 2005 ^[33]	Easter Island	Hybrid stochastic compartmental model with heterogeneous mixing		Spatial heterogeneity on a local scale explained epidemic curve
Takahashi, 2005 ^[34]	N/A	Dispersal dynamics based on a continuous model including diffusion and advection		Travelling wave frequently exists and invasion containment should be more emphasized
Cummings, 2005 ^[35]	N/A	Deterministic compartmental model with antibody-dependent enhancement		At high levels of enhancement, the probability of extinction increases. Otherwise, the enhancement would ease the transmissions
Favier, 2006 ^[36]	Brazil	Deterministic compartmental model with statistical determination of exponential growth cut-off	3.8–5.1	Previously suggested R_0 are underestimated. High vectorial capacity could allow yellow-fever epidemics
Wearing, 2006 ^[37]	Thailand	Hybrid stochastic compartmental model with antibody-dependent enhancement and serotypes		A short-lived period of cross-immunity sufficiently explains periodicity of DHF



The simplest model for dengue is governed by the following equations:

$$\begin{aligned}\frac{dS_h}{dt} &= \mu_h(N_h - S_h) - \frac{\beta_h b}{N_h + m} S_h I_v, \\ \frac{dI_h}{dt} &= \frac{\beta_h b}{N_h + m} S_h I_v - (\mu_h + \gamma) I_h, \\ \frac{dR_h}{dt} &= \gamma I_h - \mu_h R_h, \\ \frac{dS_v}{dt} &= A - \frac{\beta_v b}{N_h + m} S_v I_h - \mu_v S_v, \\ \frac{dI_v}{dt} &= \frac{\beta_v b}{N_h + m} S_v I_h - \mu_v I_v,\end{aligned}\quad (1)$$

where μ_h and μ_v are the per capita mortality rates of humans and mosquitoes, respectively; γ , the recovery rate of humans (i.e. the average

infectious period being given by γ^{-1}); b , the biting rate (i.e. average number of bites per mosquito per day); m , the number of alternative hosts available as the blood source; A , a constant recruitment rate for the vector; and β_h and β_v , the transmission probabilities from the vector to human and human to vector, respectively. Although the differential equations might look complicated, the underlying theory can be understood by comparing the compartments in Figure 1 and the right-hand side of equations (1). The model consists of a set of parameters ('rates' at specified time intervals), where the parameters entering into a compartment are positive and then leave negative after application of equations (1).

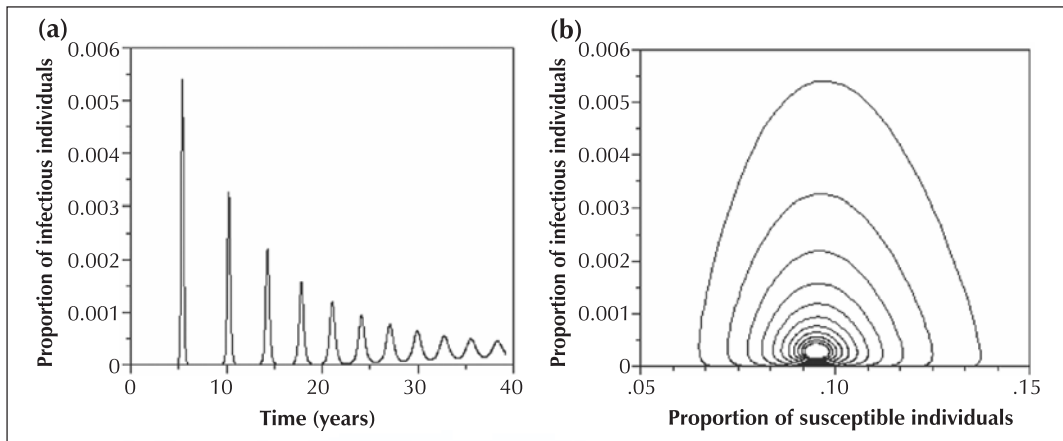
The population dynamics of the vector are given by the following equation:

$$\frac{dN_v}{dt} = A - \mu_v N_v. \quad (2)$$

Figure 2: Numerical solutions of equations (1)

(a) The proportion of infectious humans versus time

(b) Phase-plane plot of I_h - S_h . The parameters employed were: $\mu_h = 0.0000457/\text{day}$, $\mu_v = 0.25/\text{day}$, $b = 1.0$, $\gamma = 0.167/\text{day}$, $\beta_h = 0.4$, $\beta_v = 0.4$, $m = 0$, $N = 10000$, $A = 5000$,^[14,23] and consequently, R_0 was assumed to be 7.7



Usually, for mathematical convenience, N_v is assumed to be constant, and thus, the right-hand side of equation (2) is zero and $N_v = A/\mu_v$. A simple simulation result of equations (1) is given in Figure 2a. In this model, with the allocated parameters, the proportion of infectious individuals in each population approaches endemic proportions (e.g. $I_h=0.0028$, $I_v=0.00057$) after damped oscillations. In other words, the system gradually reaches an endemic steady state (i.e. stable state), where the relationship between S_h and I_h given in Figure 2b applies (the panel is referred to as a phase-plane plot). The term “stable state” is the origin of the epidemiological distinction “stable and unstable malaria” (i.e. the technical term arose from the stability of the equation system).^[41] Most mathematical studies attempt to explain parts of the transmission dynamics in detail, and for this purpose, mathematical studies are frequently interested in finding analytical solutions and discussing global or local stability based on the assumed equation system (i.e. to offer biological interpretations of the epidemiological process). Analytical studies of the dengue model have been extensively published to characterize the ecological features of dengue transmission.^[6,13-16]

Here, the most fundamental epidemiological parameter of population dynamics is discussed. Following Bailey’s analysis, it is suggested that the product $N_h N_v$ has to be larger than the product $\rho_h \rho_v$ (where $\rho_h = (N_h + m)(\gamma + m_h)/\beta_h b$ and $\rho_v = (N_h + m)\mu_v/\beta_v b$, respectively) for dengue to be transmitted sustainably.^[6,44] That is, the relationship can be re-arranged as follows:

$$R_0 = \sqrt{\frac{N_h N_v}{\rho_h \rho_v}} = \sqrt{\frac{b^2 \beta_h \beta_v N_h A / \mu_v}{(N_h + m)^2 \mu_v (\gamma + m_h)}} > 1, \quad (3)$$

where R_0 is the basic reproduction number, defined as the average number of new infections generated by a single infectious

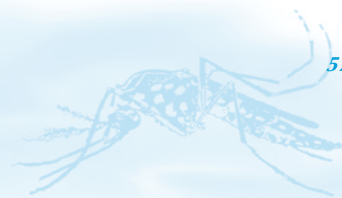
individual in a fully susceptible population.^[38,45] As the estimate of R_0 determines if dengue can sustain its chain of transmission, R_0 is also referred to as the threshold parameter and equation (3) as the threshold condition.^[46] In a more formal manner, the analytical expression of R_0 for vector-borne diseases is derived using the next generation matrix and from the dominant eigenvalue.^[38,47] R_0 summarizes the transmission potential and is the most common measure for quantifying the strength (or the severity) of epidemics. Mathematical approaches, therefore, enable us to examine the threshold condition and determine local or global stability through analytical exercises. Further, it is also possible to examine the impact of various intervention strategies (e.g. vector control) on epidemic progression in a hypothetical population by extending the extrinsic assumptions of equations (1).^[8-10,27]

Estimates of R_0 for dengue

Before discussing the estimates of R_0 for dengue, it is of critical importance to first understand the contribution of R_0 to dengue control. Since the threshold parameter determines if the transmission is persistent, estimates are useful in determining the required vaccination coverage to eradicate dengue transmission.^[48] The critical proportion, p_c , is given by:

$$p_c > \frac{1}{\varepsilon} \left(1 - \frac{1}{R_0} \right), \quad (4)$$

where ε denotes the direct effectiveness (or efficacy) of vaccination (where $0 < \varepsilon < 1$). Although the vaccines against dengue are still under development,^[49,50] equation (4) allows us to roughly estimate the required coverage. Since it has been suggested that secondary infection with a heterologous strain is a risk factor for DHF,^[51,52] tetravalent vaccines, which

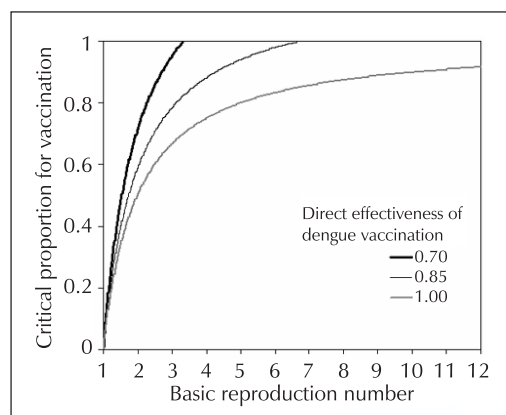


protect the vaccinated subjects against all four serotypes, are required, but have not yet achieved acceptable reactogenicity. The critical proportion for different values of R_0 and levels of direct effectiveness are shown in Figure 3. If monovalent vaccines for each serotype were completely efficacious, i.e. $\varepsilon = 1.0$, it might be possible that dengue would be eradicated with more than 90% coverage even with a large R_0 . However, if the effectiveness were small (e.g. $\varepsilon = 0.7$), it would not be possible to contain dengue using vaccination only (i.e. for $R_0 > 3.4$). This implies that we need highly efficacious monovalent vaccines to realistically discuss eradication by means of mass monovalent vaccination.

R_0 for dengue has been estimated in eight publications.^[6-8,11,17,21,22,36] The estimate of Newton and Reiter, $R_0 = 1.9$, was given by

Figure 3: The critical proportion of individuals needing to be vaccinated with different R_0 and degrees of direct effectiveness

[The areas above the lines indicate the vaccination coverage that is needed to eradicate dengue using mass vaccination only. As the effectiveness of vaccination decreases, and as R_0 increases, the required coverage increases considerably]



allocating parameters for the density of vectors and number of bites into equation (3), while that of Dietz was derived from mathematical discussion of the periodicity of yellow fever.^[6,8] In more recent studies, R_0 for dengue has been estimated using one of the following three methods.

Final size equation

The estimate of R_0 for dengue was initially suggested by Koopman et al.^[7] by applying the following formula, determined from an analytical solution, to the observed epidemic record in Mexico:^[44]

$$R_0 = \frac{-\ln(1-p)}{p}, \quad (5)$$

where p is the final attack rate, the proportion of those who experienced infection during an epidemic (note: precisely, p is not a rate but a proportion). R_0 was estimated to be approximately 1.3, from which it was concluded that the transmission potential of dengue is relatively small, compared to other infectious diseases (e.g., R_0 for measles ranges from 9–16) and that dengue can be significantly reduced by modest efforts. However, it appeared later that dengue infection involves a substantial fraction of asymptomatic infections,^[53,54] and thus, the suggested R_0 may have been considerably underestimated. Equation (5) remains useful if the population at risk is identified and the number of exposed individuals during an epidemic is precisely estimated with serological support.

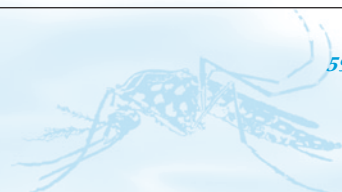
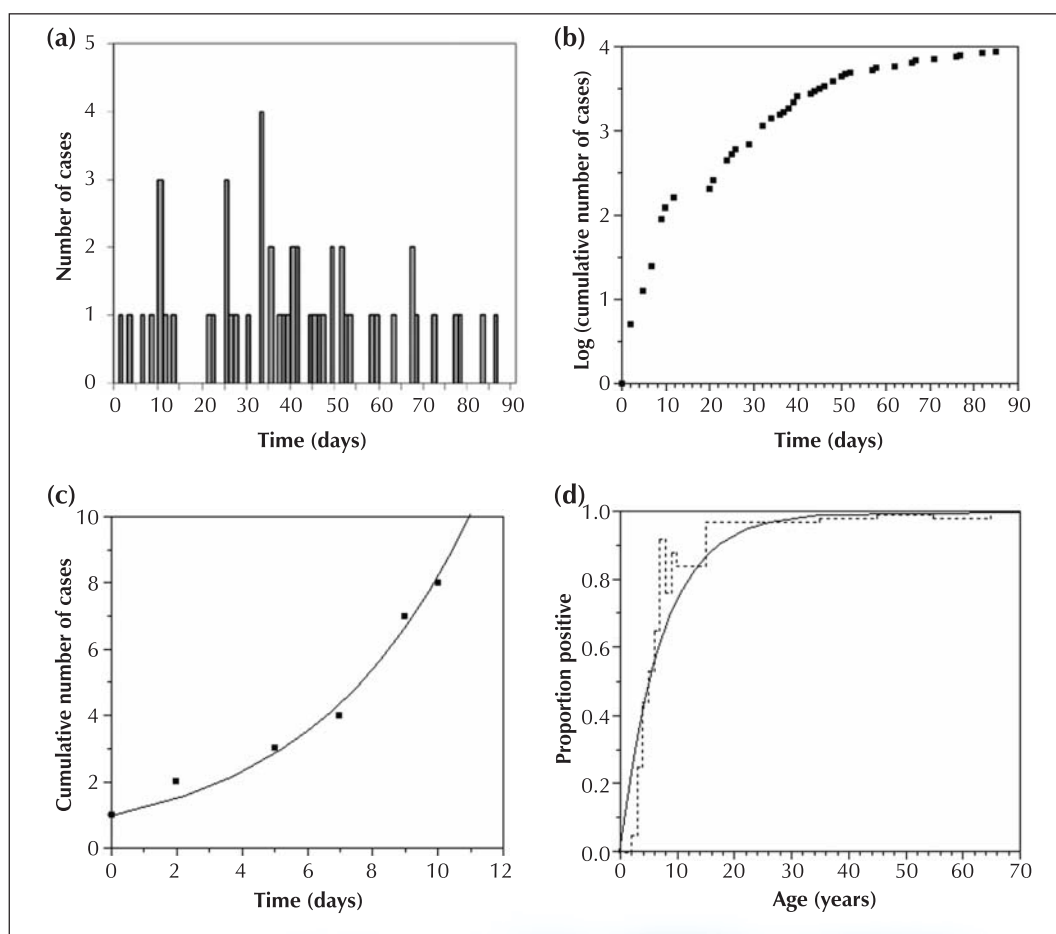
Initial intrinsic growth rate

Estimates of the intrinsic growth rate can be obtained using the epidemic curve of dengue at the very initial stage (Figure 4).



Figure 4: *Epidemiologic description of temporal dynamics and age distribution*

- (a) Temporal distribution of chikungunya in Malaysia from 1998-99 ($n = 51$), restructured from a previous outbreak.^[53]
- (b) Logarithmic temporal distribution of the cumulative number of chikungunya cases in Malaysia.
- (c) Exponential fit of the initial growth of chikungunya (up to 11 days after the start of the epidemic). Intrinsic growth rate, r_0 is estimated to be 0.21, and subsequently, with the following parameters: $\gamma = 0.5/\text{day}$, $\mu_v = 0.5/\text{day}$, $\tau_h = 8$ days and $\tau_v = 3$ days, R_0 was estimated as 20.4. The χ^2 goodness-of-fit test did not reveal significant deviations between the observed and expected data ($\chi^2_5 = 0.97$, $p = 0.96$).
- (d) Distribution of the age at infection, showing the observed and predicted proportions of those exposed to dengue at least once in the Dominican Republic, 2002.^[60] The broken line shows the observed data and the solid line the predicted data. The estimate of the force of infection, λ , is 0.14, and consequently, the estimate of R_0 is 9.5 ($\chi^2_{15} = 9.11$, $p = 0.87$).



For example, Figure 4a shows the daily count of chikungunya cases in Malaysia from 1998–99,^[55] and the cumulative number of cases on a logarithmic scale is given in Figure 4b, showing a linear increase at the initial stage (i.e. during the first 11 days). In other words, exponential growth of cases is seen at this stage. Mathematically, this can be explained by ignoring the decline of susceptible individuals at the initial stage, an approximation of which yields:

$$\frac{dl_h}{dt} = r_0 l_h, \quad (6)$$

where r_0 is referred to as the intrinsic growth rate, the coefficient of initial growth. Using r_0 , R_0 is then given by^[36]:

$$R_0 = \left(1 + \frac{r_0}{\gamma}\right) \left(1 + \frac{r_0}{\mu_v}\right) \exp[r_0(\tau_h + \tau_v)], \quad (7)$$

where τ_h and τ_v denote intrinsic and extrinsic incubation periods, respectively. Figure 4c shows the best fit of exponential growth for the chikungunya data using the least sum of squares method, yielding r_0 of 0.21 (95% confidence interval (CI): 0.20, 0.22) and, consequently, R_0 of 20.4 (95% CI: 18.2, 22.6). Marques et al.^[11] and Massad et al.^[21,22] used a slightly simpler equation to determine the initial growth and R_0 for dengue in Brazil, the estimate of which did not deviate from that of Koopman et al.^[7] However, Favier et al.^[36] later claimed that the estimates of Marques et al. and Massad et al. were underestimated owing to an ignorance of the extrinsic incubation period in equation (7), and suggested estimates ranging from 3.8–5.1.

Despite the methodological improvements, the use of r_0 is seldom considered elegant from a modeling

perspective^[56] and should be avoided unless no alternatives can be conceived. This is because exponential growth involves an approximation, the validity of which is not always statistically supported, and because equation (7) requires various fixed parameters extracted from previous publications. Moreover, it should be noted that the asymptomatic fraction of dengue could be rather large and there is most likely stochasticity in the initial stage (i.e. a lack of predictable order due to randomness).

Age distribution

The age-specific proportion of immune individuals (or more precisely, the proportion of those exposed at least once) has been useful in estimating the force of infection in endemic areas. Pioneering work using age distribution was initially performed in a study of yellow fever,^[57] and thereafter, improvements have accumulated to take into account the age-specificity of the force of infection.^[58,59] When a population experiences a force of infection at age a , $\lambda(a)$, the cumulative distribution function of age at infection, $F(a)$, is given by :

$$F(a) = 1 - \exp\left(-\int_0^a \lambda(\tau) d\tau\right). \quad (8)$$

Here, for mathematical simplicity, it is assumed that λ is an age-independent constant and that the population follows type II survival (e.g. age-specific survivorship is exponentially distributed with a mean life-expectancy at birth $L = 65$ years). The average age at infection, A_{av} , is then given by $A_{av} = 1/\lambda$ and R_0 is approximated by the following formula:^[6]

$$R_0 = 1 + \frac{L}{A_{av}}. \quad (9)$$



The maximum likelihood estimate of λ is obtained by minimizing binomial deviance between the observed and predicted seropositive proportions (given by equation (8)). In a population where dengue is endemic, it is reasonable to assume that the frequency of previous exposure is approximately constant (i.e. stationary). For example, Figure 4(d) shows the age-specific proportion of those positive for dengue, determined by using IgG, in the Dominican Republic.^[60] The estimate of λ is 0.14 (95% CI: 0.12, 0.15), and thus, the average age at infection is 6–7 years. Consequently, serotype-nonspecific R_0 is estimated as 9.5 (95% CI: 8.5, 10.5), which is rather higher than the above estimates.

The discrepancy seen in different estimates of R_0 might be largely attributable to differing vector ecology and virulence, but, most importantly, reflects the fact that a substantial proportion of asymptomatic infections and unreported DF cases exist. Therefore, it would be appropriate to assume that R_0 for dengue, summarized for all cocirculating serotypes, is approximately 10, at least in designing vaccination strategies in endemic areas. Ferguson et al.^[17] extended the method to assume a non-stationary state and simultaneously estimated the previous epidemic potential with time as well as the age-independent force of infection. The extended method confirmed the periodicity of dengue as having a 3–4-year cycle and enabled estimation of the serotype-specific R_0 (ranging from 4–6), which did not significantly differ by strain.

Seasonality and periodicity

To understand the ecological characteristics of dengue based on firm evidence, it is essential to use mathematical and statistical techniques. In particular, these characteristic features are

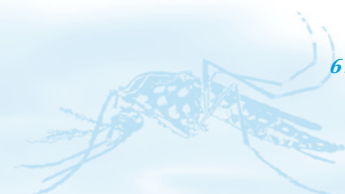
represented by the seasonality and periodicity,^[61] the former of which is mainly influenced by entomological factors and climatic changes. Several studies have attempted to model seasonality not only using simulations with entomologic variables,^[9,10] but also using a simple dynamical model.^[62] Rather than an annual cycle, dengue is also characterized by a super-annual cycle with a 3–4 year interval. The inter-epidemic period, T , has been analytically obtained from the damped oscillations of the dynamic system based on equations (1) (e.g. the oscillations in Figure 2(a)).^[38]

$$T \cong 2\pi \left[(D + D') A_{av} \right]^{\frac{1}{2}},$$

$$= 2\pi \left[\frac{L(D + D')}{R_0 - 1} \right]^{\frac{1}{2}}, \quad (10)$$

where D and D' denote average infectious and latent periods, respectively, and $D + D'$ is the total duration of infection (i.e. serial interval). However, it must be noted that equation (10) is primarily derived from an analytical solution of a model for directly transmitted diseases.^[38] Heesterbeek and Roberts^[63] discussed the threshold conditions under a periodic environment using a simple model for malaria, suggesting that the threshold is more complex. Thus, although equation (10) was previously used to discuss the periodicity of dengue,^[20] an explicit numerical answer for the periodicity of vector-borne diseases is yet to be clarified.^[64]

To analyse observed incidence data, statistical approaches, i.e. time-series analysis, have been more useful, in particular, autocorrelation and spectral analysis.^[65] Spectral analysis is based on the idea of a theoretical power spectrum, which partitions the total



variance of the series among sinusoidal components.^[66]

For example, Figure 5(a) shows monthly reports of DHF in the Central Region (including Bangkok) of Thailand from 1983–2005.^[67] The spectral density of the temporal pattern is shown in Figure 5(b). The spectral density showed a sharp peak at 12 months, corresponding to the annual cycle (seasonality), and another peak at 36 months, corresponding to the 3-year super-annual cycle. Hay et al.^[20] examined the relationship between the latter periodicity and climatic factors, claiming that the association with temperature and rainfall has not been clearly demonstrated and intrinsic epidemic dynamics determine the super-annual cycle. The 3-year period obtained based on spectral analysis was consistent with the above-mentioned suggestion of Ferguson et al.^[17] In a recent study, it was also suggested that short-lived cross protective immunity plays an important role in realizing the periodic cycle based on model predictions.^[37]

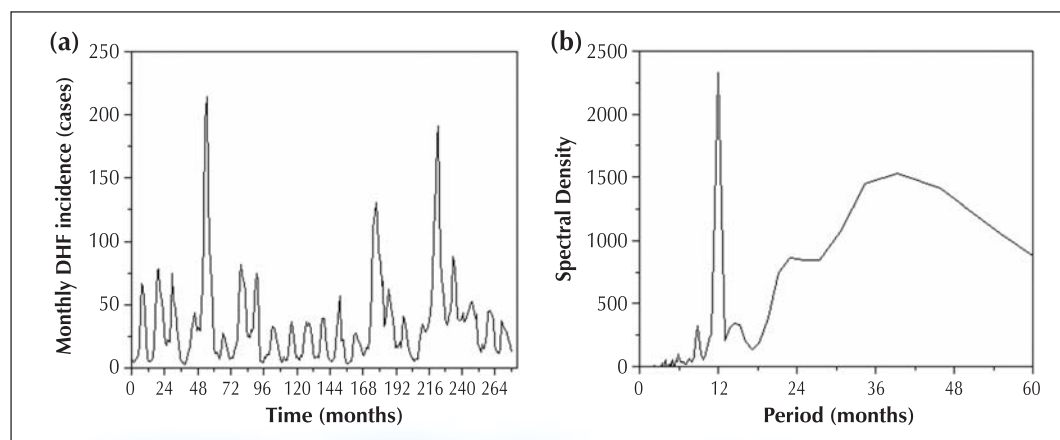
Pathogenesis of DHF and cocirculation

One of the most fascinating ecological features of dengue is represented by the cocirculation of its four closely-related virus serotypes^[68] and the pathogenesis of DHF associated with secondary infection by a heterologous strain.^[51,52] Ecologically, it is of particular interest to understand cocirculation, which is a rather peculiar phenomena considering the competition (or interference) between strains. Mathematical models of dengue have been more interested in this issue than practical or operational research. Whereas usually there should be competition between strains if the infection of one strain generates cross-reactive immunity, dengue is different from the majority of other diseases in that infection of the heterologous strain enhances the severity. Ferguson et al.^[18] found that this fact supports persistent cyclical behaviour. Moreover, the specific pathogenesis, characterized by antibody-dependent enhancement (ADE), appears to be a factor

Figure 5: *Temporal dynamics of dengue in Central Regions, Thailand, from 1983-2005*

(a) Monthly incidence of DHF^[67]

(b) Spectral density plots for dengue incidence. The sharp peak at 12 months corresponds to the annual cycle, and the second peak at 36 months the super-annual cycle



permitting coexistence.^[18,26,30] Kawaguchi et al.^[30] further demonstrated that a high case fatality owing to ADE would support an evolutionarily stable viral community. These implications were suggested based on stability analyses and relevant analytical frameworks based on an extension of the equation system (1). However, since the majority of these qualitative works assumed the population dynamics of humans only (i.e. as if the system was equivalent to that of directly transmitted diseases) and because the mechanism of pathogenesis has yet to be fully clarified, more detailed understanding of the transmission dynamics of dengue, including periodicity, requires further field data.

Other significant aspects

Since a dengue epidemic is characterized by an accumulation of micro-scale epidemics (e.g. local outbreaks owing to habitation of *Ae. aegypti*),^[69] it is essential to take into account spatial heterogeneity for realistic modelling. Indeed, spatial spread of DHF in Thailand was found to be very specific, spreading from a pacemaker, Bangkok, to the surrounding areas.^[32] Luz et al.^[29] investigated the uncertainty of model prediction by examining the regional differences in vector competence, claiming that the geographic heterogeneity of the vector population is a significant factor in dengue transmissions. A more quantitative study demonstrated that the model-based predictions closely fitted the epidemic curve of Easter Island when taking into account spatial heterogeneity.^[33] Because dengue is recognized as a significant problem in urban areas, its geographical characteristics are likely to be more complex, and thus, quantitative reality can be achieved only if we consider entomological details at an individual level.^[12]

Further, as in studies in Brazil, where yellow fever causes occasional outbreaks, R_0 for yellow fever was estimated using R_0 for dengue.^[21,22] This has been useful in determining estimates

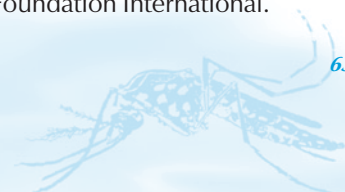
of the critical coverage of vaccination for yellow fever based on equation (4). However, because there are locations where dengue is not endemic (or which are not severely infested with dengue), estimates of R_0 in these areas can only be obtained by using an exponential fit as in equations (6) and (7).^[36] The different estimates of R_0 compared to endemic countries should, therefore, be more explicitly clarified with serological support and entomological detail in the future.

Conclusion

Because of the gap in knowledge and interests between mathematical modellers and field workers, and the lack of a summary of the theoretical frameworks of dengue, this paper reviewed the basic concepts and summarized recent studies of the dengue model without delving into too much mathematical detail. There is very little operational research compared to mathematical and ecological works, partly because of the lack of detailed epidemiological and entomological data needed to clarify dengue dynamics in more detail.^[70,71] For example, the immunoepidemiology and molecular or genetic epidemiology of an open population would be useful for clarification of the spread of dengue. Moreover, if the data were based on hospitalized cases of DHF, evaluation of the severity of DHF (e.g. the threshold and characteristic factors of severe manifestations) might also be useful. As long as the natural history and pathogenesis remain to be fully clarified,^[72] the model will continue to rely on unrealistic assumptions. To base the transmission dynamics on firm evidence and apply it to dengue control, more discussion and interaction between field and laboratory professionals and theoretical specialists is therefore needed.

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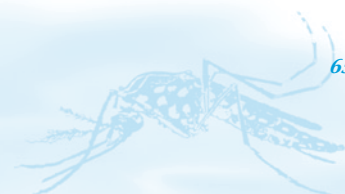


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