Dengue Transmission Dynamics: Assessment And Implications For Control

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Abstract

This paper is essentially a mathematical treatment of the epidemiology of dengue with a view to control. The paper begins with two important mathematical insights central to the development of mathematical epidemiology: *the mass action principal* – the course of an epidemic is dependent on the rate of contact between susceptible hosts and infectious vectors, and *threshold theory* – the introduction of a few infectious individuals into a community of susceptible individuals will not give rise to an outbreak unless the density of vectors exceeds a certain critical level. These insights lie at the heart of two mathematical, mechanistic, and weather-driven models (CIMSiM and DENSiM) used to elucidate the non-linear relationships influencing the dengue system. Transmission thresholds in terms of *Ae. aegypti* pupae per person are discussed in the context of dengue and control. A method, the pupal demographic survey, is described whereby the productivities of various classes of water-holding container can be measured, permitting the development of targeted control strategies that have estimates of endpoints in terms of transmission thresholds, e.g. *Ae. aegypti* pupae per person.

Next, the role of weather is discussed noting that daily, seasonal, and interannual variability in temperature, atmospheric moisture, and rainfall all influence the dengue system in a variety of ways. Whether a particular aspect of weather can exert a controlling influence depends on the state of the system. Several cities are contrasted in terms of rainfall being or not being a driver of the dynamics of *Ae. aegypti* and dengue. Atmospheric moisture is shown under rare conditions to adversely influence egg and adult survival, and transmission dynamics. Under the heading of temperature, the influence of temperature-driven variation on the extrinsic incubation period and gonotrophic cycle length is discussed and examples are given where these two temperature-driven variables are responsible for much of the interannual variability in transmission. Finally, the influence of weather anomalies associated with El Niño/Southern Oscillation (ENSO) is discussed. The section concludes with a discussion of the possible use and potential of early warning systems (EWS) for dengue control.

The section on lags between factors favouring transmission and cases presents examples of how increasingly high initial values of R_0 in the months preceding an epidemic can result in substantially more infections in the subsequent epidemic phase when conditions may have actually moderated and R_0 values are lower. This phenomenon produces a *lag* (temporal autocorrelation) between conditions promoting transmission and the subsequent realization in the epidemic when the number of infections is high.

The final section, viral factors, investigates the role that virus titre and variation in viraemic periods play in transmission dynamics. Also covered is the often underappreciated role that stochastic events play in the dengue system. The section on co-circulation of multiple serotypes includes the following topics: 1) spatial and temporal variation in serotype abundance; 2) the founder or stochastic effect; 3) the influence of herd immunity on serotype abundance; 4) the interaction of different serotypes through the mechanism of heterologous immunity; and 5) the potential influence of antibody-dependent enhancement on the dynamics and persistence of multiple serotypes of virus.

Introduction

A cursory scan of the chapter titles in a text on dengue epidemiology highlights the many facets of the dengue story. Similar to work in other vector-borne infectious systems, as the understanding of the biology became more detailed, our reductionist efforts have necessarily involved a growing variety of highly specialized researchers working on particular problems ranging from molecular to cellular to the whole animal on three entities, the virus, the insect vector, and the human. This has led, on a larger scale, to studies on the dynamics of the dengue system as also influenced by human behaviour, climate, and the movement of viruses and humans. Epidemiology, the branch of medicine that investigates the causes and control of epidemics, involves, implicitly or explicitly, all of the elements contributing to the occurrence or non-occurrence of a disease in a population – in a word, epidemiology deals with the ecology of the disease. Given the many aspects of dengue which interact directly or indirectly and at different temporal and spatial scales and usually in a nonlinear fashion, it is not surprising that it is difficult to identify a single key factor responsible for the particular dynamics of the system as a whole. Yet it is understandable that each specialist tends to see the overall behaviour of the disease from the perspective of his/her discipline. The virologist sees variation in viral virulence as an important determinant of dynamics. Some entomologists are fairly certain that the density and dynamics of the vector population are major influences, yet others uncritically believe that any density of the vector is sufficient for epidemics and causes are to be sought elsewhere. Climatologists suspect that interannual climate variability is a facet that is underappreciated by others in understanding epidemics. Herein, then, lies the utility of mathematical epidemiology—the building of models of infectious diseases to integrate the interacting components of the system—so that its behaviour and causes can be understood. It is simply another tool, a tool potentially and historically useful in understanding the dynamics and control of infectious disease.

Mathematical epidemiology, the application of mathematics to the investigation of infectious disease, was probably begun by Daniel Bernoulli in 1760; he used mathematical techniques to evaluate the effectiveness of variolation against smallpox in an attempt to influence public policy.[1] Today, mathematical epidemiology has evolved, from simply providing quantitative tools useful in the description of incidence of infectious diseases, to statistical models attempting to correlate incidence with various determinants, and more recently, to dynamic, mechanistic, first principal models that serve as tools to investigate the role of one variable against the background of other factors, which in combination, are involved in the dynamics and control. Two important mathematical insights were central to the development of mathematical epidemiology. In 1906, Hamer postulated that the course of an epidemic depended on the rate of contact between susceptible and infectious individuals;[2] this notion, *the mass action principal*, has become a central concept in mathematical epidemiology—the rate of spread of an infection within a population is proportional to the product of the density of susceptible and infectious people. Ross used this principal in his pioneering work on the dynamics of malaria transmission.[3] The insight of Hamer and Ross was further developed by Kermack and McKendrick in 1927 into an understanding of the concept of thresholds.[4] Anderson and May consider this *threshold theory*, coupled with the mass action principal, to be the cornerstone upon which modern epidemiological theory is built.[1] This notion of thresholds indicates that the introduction of a few infectious individuals into a community of susceptibles will not give rise to an epidemic outbreak

unless the density of susceptibles (or vectors) is above a certain critical level. Threshold theory has important control ramifications. More recent advances in the rapid growth of mathematical epidemiology have recognized that spatial aspects cannot be ignored and that variation and the elements of chance are important determinants of the spread and persistence of infection.

It is unfortunate that little use of epidemiological models has been made in empirical studies and in the development of public health policy regarding infectious human diseases – Anderson and May relate this directly to the abstract nature of much of the theoretical work and the lack of ties to field data.[1] They find that "in view of the successes achieved by combining empirical and theoretical work in the physical sciences, it is surprising that many people still question the potential usefulness of mathematical models in epidemiology".

This paper on the epidemiology of dengue differs a bit from the traditional approach of documenting epidemics and their spread by use of insights gained from a pair of weather-driven simulation models that were developed to provide insight into dengue dynamics and control, CIMSiM (Container-Inhabiting Mosquito Simulation Model) and DENSiM (Dengue Simulation Model). The models incorporate the theoretical principals outlined above, but in a computer simulation environment that permits use of site-specific information on human demographics, herd immunity, and the breeding habitat of *Ae. aegypti* and related mosquitoes. Descriptions and validation studies of these models have been presented earlier.[5-7] CIMSiM is used to integrate a host of factors pertaining to vector dynamics and provides the entomological inputs to DENSiM. Site parameterization of CIMSiM requires conducting a pupal and demographic survey described below. Whereas CIMSiM is essentially an accounting program of vector dynamics, DENSiM is the corresponding account of the dynamics of human population and virus transmission between hosts and vectors. Both models are weather-driven and stochastic with a daily time step.

Specifically, the models take into account the following aspects of the dengue system: the development rates and survival rates of *Ae. aegypti* eggs, larvae, pupae, and adults are functions of temperature and atmospheric moisture (saturation deficit); the extrinsic incubation period of the virus within the mosquito is a function of temperature and the titre of virus within the host, the titre being a characteristic of the particular type of virus circulating; human age structure and density are dynamic, reflecting country-specific demographic patterns in age-specific birth, fecundity, and death rates; the type-specific immune status of individuals is maintained with maternally-acquired antibody of newborns reflecting the mother's immune status; age-specific and type-specific ratios of cases to infections or of DHF/DSS to cases, if known, can be used to model incidence of clinical illness in addition to infection.

Transmission thresholds

We begin with a brief discussion of transmission thresholds as they pertain to the *Ae. aegypti*/dengue system because they will be a useful measure in subsequent sections; a fuller description was published earlier.[8] The phenomenon of thresholds is based on two concepts: *the mass action principal*—the course of an epidemic is dependent on the rate of contact between susceptible hosts and infectious vectors, and *threshold theory*—the introduction of a few infectious individuals into a community of susceptibles will not give rise to an outbreak unless the density of vectors exceeds a certain critical level. In practice, both of these concepts require knowing the ratio of humans to vectors in absolute numbers. In contrast to other mosquito-borne systems such as malaria where it is essentially impossible to quantify adult production or density, the strict preference of *Ae. aegypti* for artificial containers in the domestic and peridomestic environment allows estimation of the required ratio with a high degree of accuracy. Before presenting estimates of dengue thresholds, we need to

look at the quantification tool, the pupal and demographic survey, and at a definition of what constitutes an epidemic.

Pupal and demographic survey

Dengue control programmes today are most commonly based on the suppression of *Ae. aegypti* and not on eradication. With the trend away from a strict reliance on insecticides, current efforts largely focus on reducing the number of larval breeding habitats.[9-10] Several authors have recently made the case that the traditional *Stegomyia* indices, as epidemiologic indicators of dengue transmission risk, should be abandoned as they have a number of serious shortcomings.[11] These authors instead argue that a pupal and demographic survey, providing an estimate of the number of pupae per person in a community by type of container, e.g. drums, flower vases, pots, cisterns, discarded tyres, is more appropriate for assessing risk and directing control operations.[11] This method uses the ratio of pupae per person for several reasons: 1) unlike any of the other life stages, it is possible to actually count the absolute number of *Ae. aegypti* pupae in most domestic environments; 2) container-inhabiting *Stegomyia* pupae are easily and inexpensively separated from other genera and identified to species as emerged adults or pupae; 3) because pupal mortality is slight and well-characterized, the number of pupae is highly correlated with the number of adults; 4) the statistic of pupae per person can be related to transmission risk and provide target levels of reduction required in control efforts.

In practice, conducting the pupal and demographic survey involves visiting 50 or more residences, usually with a pair of inspectors equipped with nothing more than a few litres of clean water, a sieve,* some large-mouth pipettes, a white enamel pan, and small shell vials. The inspectors request permission to examine the water-holding containers and enquire as to the number of people living at the house (or sleeping there the previous night). With permission, they proceed to strain each container at the location, re-suspending the sieved contents in a small amount of clean water in the enamel pan, from where the container's pupae are pipetted into a labelled vial. If there are other container-inhabiting species in the area besides *Ae. aegypti*, the contents of each vial are transferred to small cups covered with bridal veil secured with a rubber band; these are held in the lab (or hotel room) until adult emergence occurs and identification can be made.[11] A key for identification of container-inhabiting mosquito pupae from South-East Asia has recently been published.[12] Data are usually summarized by container type in a spreadsheet.

Definition of epidemics

A definition of an epidemic that was arbitrary but useful from a public health point of view was used in defining transmission thresholds: any single year where seroprevalence rises by at least 10% was to be considered to be an epidemic year. Ten per cent was selected because any disease involving that proportion of the population would be considered an epidemic and this level of transmission would result in slightly more than 1% of the population being infected during the peak of the epidemic – a minimum value that has been suggested as sufficient for the detection of transmission.[13] Just how many mosquitoes per person are required to support this level of transmission is a function of many factors, but the ones considered key determinants are seroprevalence of dengue antibody and temperature.[8] In these assessments, several important assumptions that are likely to be true in most tropical locations were made: 1) vector competence is adequate; 2) blood feeding by *Ae. aegypti* occurs primarily (>90%) on humans; 3) essentially all hosts are at risk of being bitten. The conditions

* USA Standard Sieve Series Number 30 sieve (equivalent to ASTM designation E11, 600 μm (0.0243") opening)

in the southeastern United States are an obvious exception to these assumptions. The catholic feeding preferences of some of the other *Aedes* dengue vectors, e.g. *Aedes albopictus*, would preclude using the thresholds developed specifically for *Ae. aegypti* presented here.

Transmission thresholds

The dengue models were used to estimate thresholds as a function of pre-existing antibody levels in human populations, ambient air temperatures, and size and frequency of viral introduction (table 1). [8] Because the dengue system (both models and biology) is stochastic, at threshold, as defined above, the probability of a viral introduction leading to an epidemic is 50%. And obviously, therefore, 50% of introductions would lead to situations ranging from the complete loss of virus to situations where there was less than a 10% rise in seroprevalence. In other words, the threshold is the break or tipping point. Threshold levels were estimated to range between about 0.5 and 1.5 *Ae. aegypti* pupae per person for ambient air temperatures of 28°C and initial seroprevalences ranging between 0% to 67%. The size of the viral introduction used in these studies, ranging between 1 and 12 infectious individuals per year, was not seen to significantly influence the magnitude of the threshold. The development of transmission thresholds has given us a new and important tool for monitoring targets for source reduction/control efforts. Moreover, in terms of risk assessment, transmission thresholds provide estimates of the level of elimination or control that are necessary to preclude transmission (table 2).

Table 1. Transmission thresholds in terms of *Ae. aegypti* pupae per person as a function of ambient temperature and prevalence of dengue antibody. Specifically, this table contains the estimated number of *Ae. aegypti* pupae per person required to result in a 50% probability of a 10% or greater rise in seroprevalence of dengue antibody during the course of a year resulting from 12 monthly viral introductions of a single viraemic individual.[8]

Temperature (°C)	Transmission threshold by initial seroprevalence of antibody		
	0%	33%	67%
22	7.13	10.70	23.32
24	2.20	3.47	7.11
26	1.05	1.55	3.41
28	0.42	0.61	1.27
30	0.10	0.15	0.30
32	0.06	0.09	0.16

Table 2. Comparison of observed numbers of *Ae. aegypti* pupae per person in various dengue-endemic or dengue-receptive locations with estimated transmission thresholds based on average summertime temperatures and an initial seroprevalence of 33%.[8]

Location	Temp (°C) [a]	Pupae per person [b]	Threshold [c]	Ratio [d]	% Control [e]
Reynosa, Mexico [f]	29.4	2.75	0.26	10.4	90
Mayaguez, Puerto Rico [f]	26.6	1.73	1.05	1.7	40
Trinidad (20 sites) [11]	27.0	22.7 [g]	0.86	26.4	96
El Progreso, Honduras[7]	29.1	0.34	0.31	1.1	10
San Juan, Puerto Rico [f]	27.8	2.75	0.58	4.7	79
Bangkok, Thailand [6,20]	29.2	1.69	0.29	5.8	83

[a] *Temp* refers to average temperature during the months of June–August or December–February in locations above and below the equator, respectively.

[b] *Pupae per person* refers to the average number of *Ae. aegypti* pupae per person observed in survey.

[c] *Threshold* refers to the estimated transmission threshold for 12 monthly introductions, assuming an initial seroprevalence of 33%.

[d] *Ratio* is the ratio of observed pupae per person and the estimated temperature and seroprevalence-specific threshold.

[e] *% Control* is the degree of reduction in pupae per person necessary to reduce observed field level to that of the threshold.

[f] Unpublished studies conducted by Focks in collaboration with others. Surveys in Puerto Rico and Mexico were limited and preliminary.

[g] Observed range: 1.4–63.4 pupae per person; the island-wide average is used for calculation.[11]

It should go without saying that we see exceeding threshold as being a necessary but not sufficient cause of transmission. Using a table of transmission thresholds (table 1) takes into account the degree of susceptibility in the human population (and can give you an appreciation of the possible consequences of inadequately knowing herd immunity levels), but there is obviously no statement about the presence or type of viruses that may or may not be circulating or introduced. As presented below, transmission thresholds are useful for risk assessment and risk reduction. In the absence of virus and a control programme, they speak of receptivity to virus; in the endemic state, they provide targets and end points for targeted source reduction/control programmes. Because for a given level of herd immunity transmission thresholds are so strongly influenced by temperature (table 1), there is the possibility of developing early warning systems for dengue in regions such as parts of South-East Asia where predictable El Niño/Southern Oscillation (ENSO) events are associated with known temperature anomalies.

Immature habitat

The primary habitat of immature *Ae. aegypti* in the domestic and peridomestic environment is man-made containers. Breeding in natural containers such as leaf axils in the domestic environment is thought possible only in so far as adults from nearby artificial containers can supply oviposition. For surveillance and control programmes, containers have been classified by a number of schemes: indoors/outdoors, essential/non-essential, presence of active immatures, etc. However, the notion of

using the product of productivity and abundance of each type of container has been shown to more useful from the perspective of adult dynamics, risk assessment and control.[8,11]

Productivity

Initial efforts based on counting positive containers

During the initial efforts to control urban yellow fever in South America, control specialists discovered that a substantial reduction in the number Ae. aegypti breeding sites would often eliminate transmission. This observation became the basis of efforts, organized in 1923 by the Rockefeller Foundation, to eradicate yellow fever in coastal cities of northern Brazil.[14] Improved methods developed subsequently under Fred Soper resulted, quite unexpectedly, in the eradication of Ae. aegypti in several cities in 1933. The goal of vector eradication arose later in Brazil, not as a requirement for yellow fever eradication but rather from a desire to protect Ae. aegypti-free zones from re-infestation.[15] To monitor vector control progress and to determine if prophylactic levels had been achieved, Stegomyia indices were developed.[16-17] The initial indices, described in 1923, were the House (Premises) Index (HI) – the percentage of houses infested with larvae and/or pupae, and the Container Index (CI) – the percentage of water-holding containers infested with active immatures; 30 years later, the Breteau Index (BI) – the number of positive containers per 100 houses – became a common measure.

Inadequacy of traditional measures

Today, most dengue control efforts are based on suppression of Ae. aegypti and not eradication. [18-19] The Stegomyia indices, as epidemiologic indicators of dengue transmission, have recently been shown to be inadequate. The traditional indices have a number of serious shortcomings. The CI is probably the poorest since it reflects only the proportion of containers positive in an area and does not take into account the number of containers per area, per house, or per person. The HI is perhaps better, but this index fails to give the number of positive containers per positive house or person. Of the indices, the BI is arguably the best, combining information on containers and houses. Ostensibly these measures are, in some undefined sense, related to risk of transmission; surprisingly, however, the statistics HI, CI, and BI do not correlate well with one another.[11] Moreover, all three indices fail to take into account the fact that containers vary in the production of adult Ae. aegypti. For example, two very different containers, an indoor flower vase, commonly found with larvae but seldom producing an adult because of frequent water changes and, say, an uncovered, outdoor 55-gallon (207-litre) drum under a fig tree which supports a standing crop of 10 or 20 or 50 pupae, are for the purposes of calculating the indices, equally positive. Field observations bear this out: Southwood et al. reported, for a temple area in Bangkok, about a 23-fold difference in the most and the least productive types of container.[20] A six-fold difference was seen in Honduras.[8] Connor and Monroe, in their original paper on indices, recognized these shortcomings and, in 1923, pointed out that herd immunity was an additional and important epidemiologic factor not considered by the Stegomyia indices.[16] We would add an additional shortcoming – the indices fail to adequately provide information about Ae. aegypti density on a per area or, more importantly, a per person basis. This latter statistic, Ae. aegypti pupae per person, can be used to estimate, for each type of container (drum, tyre, vase, etc.), what proportion of the transmission threshold it accounts for. Pupae per person, through the use of the table of transmission thresholds (table 1), permits specifying the epidemiological significance if that particular type is eliminated or controlled (table 3).

Table 3. An example of pupal/demographic survey results from urban sites in St. George County of Trinidad conducted during the rainy season of 1995 and incorporating a transmission threshold estimate of 0.71 pupae per person.[11] The threshold estimate is based on interpolating values in table 1 using an average June temperature of 27.7ºC and an overall seroprevalence of 33%. *Pupae per ha* is the product of *containers per ha* and *pupae per container*. *Pupae per person* is the ratio of *pupae per hectare* and the average human density of 160 per ha. *Portion of threshold* is the ratio of *pupae per person* and the threshold estimate. *Relative importance* is the ratio of *pupae per person* for each container type and the total number of pupae per person, 1.307. In the dry season, the rain-filled containers dry out and cease to produce adult mosquitoes.[a]

Container type[a]	Containers per hectare	Pupae per container	Pupae per hectare	Pupae per person	Portion of threshold	Relative importance
Saucer	3.9	0.20	0.8	0.005	0.007	0.004
Tyre	0.8	1.00	0.8	0.005	0.007	0.004
Small miscellaneous	1.2	1.10	1.3	0.008	0.012	0.006
Indoor vase	40.0	0.05	2.0	0.013	0.018	0.010
Tank	9.5	0.40	3.8	0.024	0.034	0.018
Bucket	1.1	10.90	12.0	0.075	0.106	0.057
Tub	13.5	3.80	51.3	0.321	0.452	0.245
Outdoor drum	8.3	6.70	55.6	0.348	0.490	0.266
Indoor drum	19.4	4.20	81.5	0.509	0.719	0.390
Totals	97.7	-	209.1	1.307	1.844	1.000

[a] Container names in bold indicate rain-filled containers.

Threshold estimates in risk assessment and targeted source control programmes

The underlying notion of targeted source reduction is one of selectively attacking the most important types of container. Field observations cited above suggest the rationale is sound in that containers vary significantly in their production of Ae. aegypti. The actual epidemiologic significance of any particular type of container, say discarded tyres, is a function of the average standing crop of pupae found in that type and the abundance of that container. Table 3 is an example of how transmission thresholds and the pupal and demographic survey could provide guidance to a targeted source reduction effort. The estimate of the transmission threshold provides an overall target, an upper limit to the number of pupae per person for the environment that ensures viral introductions would result in very little or no transmission. The survey permits estimating the contribution of each type of container and allows, using nothing more than a spreadsheet, conducting what-if analyses of various strategies designed to selectively attack different types of containers at various rates of elimination or control based on their epidemiologic importance and how amenable they are to elimination and/or control.

Our example is based on surveys conducted during June 1995 in urban areas of central St. George County in northern Trinidad. [11] Based on average temperatures for this period (27.8ºC) and assuming a seroprevalence rate of 33%, the estimate of the transmission threshold is ca. 0.71 pupae per person (interpolation of table 1). The surveys estimated human densities to be ca. 160 per hectare and provided data on the nine major types of breeding container, their abundance and average standing crop of Ae. aegypti pupae (table 3). In this environment, there was an average of ca. 98 water-filled containers and 209 pupae per hectare; the number of pupae per person was 1.31 or 184% of the threshold. Numerically, the two most common types were indoor containers, the flower vase and water storage drum. Notice, however, that because these types differed significantly in

productivity, the epidemiologic significance of the indoor drum, based on contribution to the number of pupae per hectare or per person, is some 40-times that of the vase. Dividing the estimate of pupae per person for each type by the threshold of 0.71 yields an estimate of what proportion of the threshold is contributed by each; this indicates the vases contribute <2% of the threshold whereas the indoor drum accounts for >70%. Obviously, as eradication is not in mind, targeting the more important types based on this logic would suggest a focus on indoor and outdoor drums and perhaps on tubs. If table 3 is put into a spreadsheet, evaluating various targeted strategies becomes easy. We see that an overall reduction of ca. 50% of all containers, the control or elimination of about 50 of the 100 containers, would result in the number of pupae per person being about 92% of the threshold. We also can see that a targeted approach that eliminated about 55% of the three most important types, the drums and the tubs, would put the population at about 93% of threshold, and would require the control or elimination of only about 23 containers per hectare. This approach would also take into account specific container types for the required reduction in pupae, given some types were uncontrollable by virtue of their location, ownership, use, etc. Below, we return to this site, and will look at the consequences of lack of rain during the dry period of March–May.

Weather

Daily, seasonal, and interannual variability in temperature, atmospheric moisture, and rainfall all influence the dengue system in a variety of ways. Whether a particular aspect of weather can exert a controlling influence depends on the state of the system.

Rainfall and the immature habitat

The response to seasonal and interannual variation in amount of rainfall is a function of the proportion of the transmission threshold that arises from rain-filled containers. The following examples illustrate the role of rainfall in the dynamics of vector and transmission, and how precipitation seasonality can interact with other parameters.

Bangkok, Thailand

In response to the emerging problem of epidemic dengue haemorrhagic fever (DHF) in South-East Asia in the late 1950s, the World Health Organization, at the request of the government of Thailand, set up the Aedes Research Unit (ARU) to study the ecology and control of Ae. aegypti. At the time it was fairly well established that dengue viruses were responsible for DHF and that Ae. aegypti was the epidemic vector.[21] Moreover, the initial hypothesis was that seasonal changes in the density of the vector and the incidence of DHF were correlated, primarily because the disease was associated strongly with the wet season, when rainfall would presumably increase the number of breeding sites and/or increase adult survival.[22-23] In light of these conjectured relationships, a series of year-long studies was conducted between 1966 and 1968 on the larval habitat,[23] survival, density, and dynamics of immature[20] and adult populations,[24] and on the gonotrophic cycle of Ae. aegypti.[25]

With one exception, these studies were conducted in the residential compound of a Buddhist temple, the Wat Samphaya. The Wat was chosen because of its convenient size and because the type of housing and human density were representative of much of Bangkok. Also typical was the water supply of standpipes and the types of water-filled containers present, primarily large 100–200-litre water-storage jars, flower pot plates, and ant traps located under the legs of food cupboards, tables, etc.[24] Southwood et al. and Tonn et al. reported finding that in the Wat, as in the rest of Bangkok, Ae. aegypti was the only mosquito breeding in the great majority of containers.[20,23] Throughout the

study period there were ca. 100 jars, 50 flower plates, and 50 ant traps present in the Wat and ca. 53% of these were occupied by Ae. aegypti; the number of water-filled containers and the proportion with mosquitoes were remarkably constant, and with the exception of a portion of the ant traps, all containers were filled manually and not influenced by rainfall.[20,23] The initial conclusion from the larval studies was that the key factor(s) responsible for the seasonality of DHF in Bangkok was not fluctuation in adult production and density in response to rainfall. The models demonstrate this as well: in 20-year runs, there is only a slight, and not statistically significant, variation in the number of Ae. aegypti females per person and this and its lags going back several months do not correlate with cases. The initial field results led to the next hypothesis, that seasonality in transmission was due to seasonality in adult survival due to temperature and/or atmospheric dryness associated with the hot season. We will come back to the Bangkok story when the role of these variables is discussed.

South-western Puerto Rico

In contrast with Bangkok, longitudinal studies in southwestern Puerto Rico show a positive correlation between rainfall and vector abundance, with the correlation being strongest in the dry, south coastal portions of the island. [26] Also in marked contrast with Bangkok is the fact that most breeding occurs outdoors and in rain-filled containers, the primary ones being animal watering dishes and discarded tyres. Moore describes the relationship between rainfall, vector abundance, and transmission as follows: "At least in southern Puerto Rico, Ae. aegypti densities rise quickly with the onset of rains in July and August. This relationship further leads to a rather close correspondence between seasonal rainfall and dengue fever incidence, the peak of which occurs about six or eight weeks after the peak in rainfall. In 1973 the rains began in June, and dengue therefore also appeared earlier than usual. In 1974, however, when the rains began later than usual, the peak dengue fever incidence did not occur until December 1974 and January 1975". [26] The authors concluded under their conditions of principally outdoor breeding that "rainfall patterns seem to be a reasonably effective predictor of time of peak dengue transmission." That is not to say that they understood only rainfall to be necessary, as they certainly appreciated the need for viruses and susceptible human populations. So here we have an example, especially in the south coastal areas, of where rainfall is the key factor influencing temporal and spatial patterns of transmission.

St. George County of Trinidad

To put the influence of seasonal variation in rainfall into a more quantitative context, that of pupae per person, contrast the total number of pupae per person in table 3 (wet season) with that of table 4 representing the dry season. Note that the rain-filled containers (tyres, small miscellaneous, and outdoor drums) cease to support breeding and the total number of pupae per person falls from 1.31 to 0.95; in the uncontrolled situation, the respective proportions of the transmission threshold are 1.84 and 1.33 respectively. Note also that in the dry season when the populations are a bit lower, only a single class of container, either the tub or the indoor drum, would have to be controlled or eliminated to bring the community below threshold.

Container type[a]	Containers per hectare	Pupae per container	Pupae per hectare	Pupae per person	Portion of threshold	Relative importance
Saucer	3.9	0.20	0.8	0.005	0.007	0.005
Tyre	-	-	-	-	-	-
Small miscellaneous	-	-	-	-	-	-
Indoor vase	40.0	0.05	2.0	0.013	0.018	0.013
Tank	9.5	0.40	3.8	0.024	0.033	0.025
Bucket	1.1	10.90	12.0	0.075	0.106	0.079
Tub	13.5	3.80	51.3	0.321	0.452	0.339
Outdoor drum	-	-	-	-	-	-
Indoor drum	19.4	4.20	81.5	0.509	0.717	0.538
Totals	87.4	-	151.4	0.946	1.332	1.000

Table 4. Pupal/demographic survey results from urban sites in St. George County of Trinidad, conducted during the dry season (March–May) and incorporating a transmission threshold estimate of 0.71 pupae per person. [11]

[a] Container names in bold indicate rain-filled containers.

Atmospheric moisture

The drying power of the atmosphere, as measured in saturation deficit (mBars pressure), reflects the combined influence of temperature and relative humidity. The dengue system (and models) are influenced by saturation deficit in several ways. In CIMSiM, atmospheric moisture influences evaporation rates from containers along with certain characteristics of the container, including their size, shape, and exposure to direct sunlight. Also, deficits greater than ca. 10 mBars progressively reduce survival of newly-laid eggs and adults. The impact on egg survival under very dry conditions is minimal and, with the possible rare exception of breeding in exposed lime rock solution holes adjacent to beaches, is easily compensated by subsequent density-dependent larval survival. Based on CIMSiM, only at particularly hot and dry continental locations such as Ouahigouya, Burkina Faso, are conditions such that adult survival is reduced by excessive temperatures and high saturation deficits. Here, the dynamics and abundance of adults and immatures would not be materially different under milder conditions, again, primarily due to resilience in the entomological system from density-dependent larval survival. However, the shortened adult lifespan significantly reduces transmission in simulation studies (not shown).

Temperature

Vector dynamics

In temperate locations, *Ae. aegypti* overwinters in the immature stages, and seasonal variation in adult abundance clearly reflects the key role of temperature on the development of immature stages. However, under tropical conditions, adult abundance varies not with temperature but with variation in the abundance and productivity of water-holding containers; container productivity is limited, not by temperature or oviposition, but by density-dependent larval survival which is ultimately driven by the amount of food falling into or formed photosynthetically within the container. This is consistent with

both CIMSiM's rather constant estimates of adult abundance from manually-filled containers under conditions of constant temperatures of 22ϒC to 32ϒC (not shown). In light of this, going back to the Bangkok story of the investigation into the cause(s) of seasonal variation in incidence of dengue, we should not be surprised to read that the field work of Sheppard et al. indicated no seasonal trends in adult survival.[24].

The influence of temperature-driven variation on the extrinsic incubation period and gonotrophic cycle length

Under moist, tropical field conditions, for example Bangkok, where the major mortality sources are accidents such as encountering a spider's web, the probability of surviving a single day (Sa) is constant and independent of temperature. Experiments to measure this parameter in the field are notoriously noisy but a consensus value is somewhere between 0.87 and 0.91 per day under conditions without temperature or moisture deficit extremes such as for most locations in dengue-endemic regions, e.g. South-East Asia.[5] The integral of Sa^t provides the average lifespan of the female; for Sa = 0.89, the average lifespan is ca. 8.6 days. Keeping in mind that the resulting age distribution declines exponentially with age, it is easy to see that numerically, while most emerging females die at an early age, the tail of this age distribution contains the rather rare but older individuals with the potential to transmit.* The length of time required for a newly infected female to become infectious, the extrinsic incubation period (EIP), is a non-linear function of temperature; the same can be said regarding the length of the gonotrophic cycle (table 5). Notice that if a female takes an infectious bite on her first day of life, the length of time required for her to have a disseminated infection is EIP plus one day—a substantial portion of the average lifespan, so most will not pass on virus before death. Moreover, once disseminated, the probability of transmitting virus will vary with how often the mosquito bites, which is related to the duration of gonotrophic development. Figure 1 presents an estimate of the average number of potentially infectious replete feeds per newly-emerged female as a function of temperature and daily survival probability. This figure makes, for the purpose of comparisons, the unrealistic assumption that all mosquitoes take an infectious blood at one day of age. The actual number of potentially infectious bites per replete feed is unknown and may be as high 2 or 3 or more interrupted feeding attempts with resumption on the same or different host.[7][7] From an epidemiological perspective, it is important to realize that a temperature-related doubling of expected number of potentially-replete feeds, the consequence of 2 or 3 degrees warmer temperatures, is equivalent to a doubling of the density of Ae. aegypti. While temperature plays a role in most facets of transmission dynamics, its influence on the speed of viral dissemination and frequency of biting is a key regulating force entraining seasonal variability. And indeed, the field work of Pant et al. allowed them to conclude that the source of the seasonality seen in dengue in Bangkok was due not to rainfall variability leading to adult abundance seasonality, nor to excessively high temperatures and/or dryness leading to reduced adult survival, but to temperature-related variability in the infectiousness of Ae. aegypti females through the agency of EIP and gonotrophic development rates.[25] This is the same conclusion reached through an analysis of the Bangkok situation made with CIMSiM/DENSiM.[6].

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* $\int_{t=1}^{t=\bullet} Sa^t \, dt$

Temperature	Extrinsic incubation period		Gonotrophic cycle	
	Rate per day[a]	Days	Rate per day[a]	Days
22	0.04	24.0	0.14	7.3
24	0.05	20.0	0.17	6.1
26	0.07	14.0	0.24	4.2
28	0.08	11.8	0.29	3.5
30	0.10	9.9	0.34	2.9
32	0.12	8.4	0.41	2.4

Table 5. Lengths and daily rates of the extrinsic incubation period of virus within *Ae. aegypti* and the gonotrophic development cycle.[5]

[a] The 'daily rate' is that proportion of total development occurring on a particular day at the specified temperature

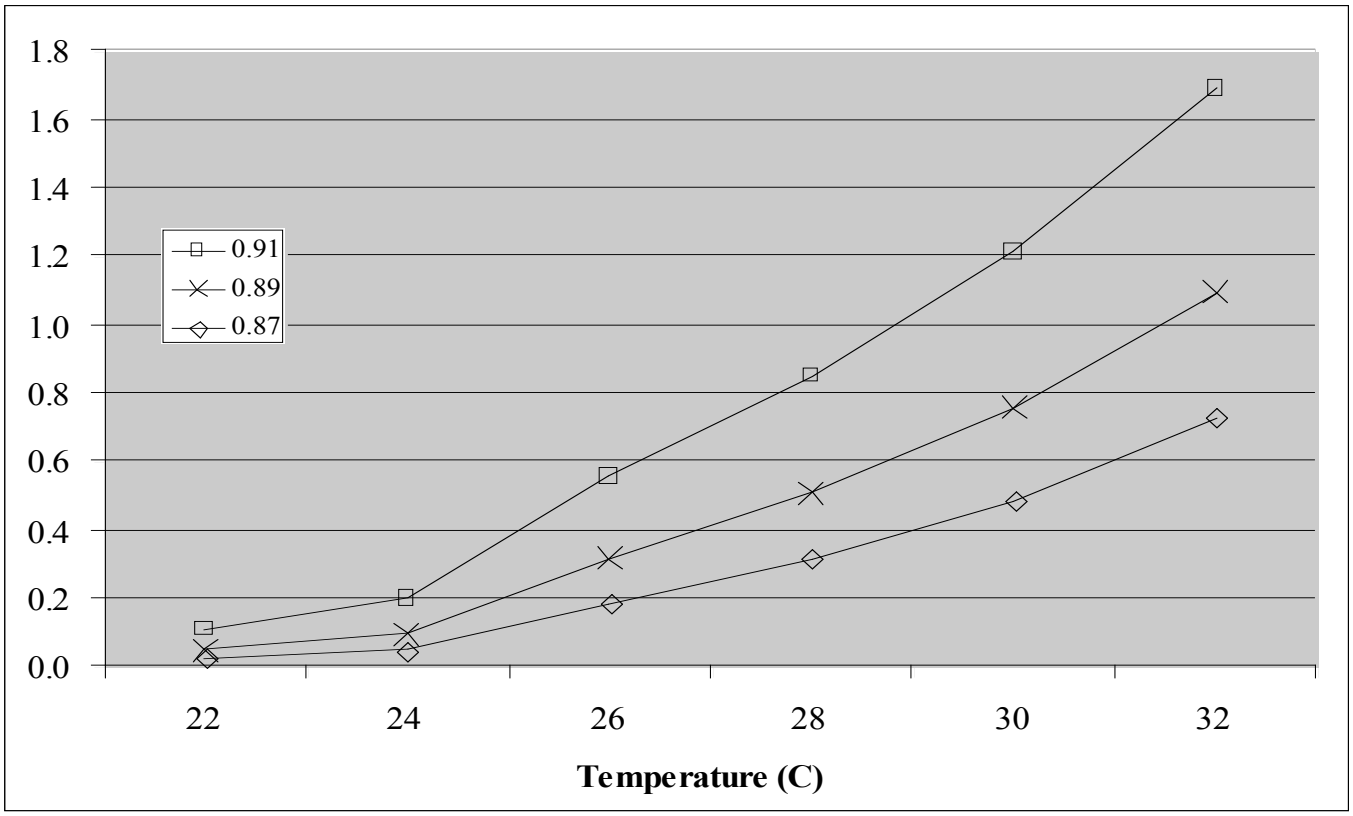

Figure 1. Average number of potentially infectious replete feeds per newly-emerged female as a function of temperature and daily survival probability. This figure makes, for the purpose of comparisons, the unrealistic assumption that all mosquitoes take an infectious blood meal at one day of age. The actual number of potentially infectious bites per replete feed is unknown and may be as high 2 or 3 or more interrupted feeding attempts with resumption on the same or different host.[7]

The influence of interannual climate variation

The El Niño Southern Oscillation (ENSO) is an atmosphere–ocean coupled system which produces quasi-periodic short-term climate and sea surface temperature changes over the Pacific region with impacts on weather worldwide including many countries in the Americas, Africa, and Asia. The system oscillates between two extremes known as El Niño and La Niña, which are associated with approximately opposite disturbances to climate worldwide. A chief phenomenon of an El Niño phase is eastward extension of warm surface waters situated off northwestern Australia towards the west coast of equatorial South America. During the cool phase, La Niña, equatorial westerlies result in an upwelling of cold abyssal water which is transported to the west creating a tongue of abnormally cool surface waters extending towards Indonesia. Because convection rainfall in this region is limited to sea surface temperatures greater than ca. 26–27ϒC, the spatial distribution of rainfall is associated with equatorial sea surface temperature anomalies associated with ENSO state. The 'Southern Oscillation' refers to the oscillation of atmospheric pressures between the eastern and western Pacific. One of the summary or indicator statistics of ENSO state is the southern oscillation index (SOI), the normalized difference in pressure between Darwin and Tahiti. El Niño and La Niña are associated with negative and positive values of the SOI respectively. It is not surprising that much innerannual variability in climate in the central Pacific is attributable to the state and intensity of ENSO.

Because many infectious disease systems are influenced by weather, ENSO state and associated anomalies in rainfall, atmospheric moisture, and temperature have become topics of considerable interest. An excellent review of ENSO and health has been provided by Menno Bouma and others.[27] Largely through the use of numerical simulation models of the ocean and atmosphere, forecasts of anticipated ENSO state are increasingly skilful, such that it is reasonable to expect that useful early warning systems (EWSs) will be developed.[28] Initial efforts involved nothing more that simple attempts to demonstrate correlations between ENSO state and outbreaks. More sophisticated development of ENSO-based EWSs will require addressing two related problems. The first of these is that, while skill in forecasting an ENSO event is currently adequate, predicting the strength of the oscillation is problematic and leads to lack of skill in predicting regional weather anomalies. The second area in need of much attention is elucidation of the mechanisms whereby weather anomalies lead to anomalies in the disease system.[29] Several recent studies have shown temporal correlations between malaria epidemics and various indices of ENSO state.[30-32]

Given that dengue incidence is a function of interaction of the many factors outlined above, it is not surprising that dengue activity has been correlated with ENSO state or one of its statistics, SOI, in regions (most clearly in the South Pacific) where ENSO or SOI is correlated with temperature and/or rainfall anomalies.[28,33] Unfortunately this study does not identify the environmental risk factors unequivocally.

At a recent World Health Organization dengue workshop in the South-East Asian region, directors of national anti-dengue programmes in Thailand, Vietnam, and Indonesia expressed the operational need for an early warning system (EWS) that would provide sufficient lead time (one to three months) to permit mobilization of control operations. In response, Focks et al. have attempted to develop practical EWSs for Yogyakarta, on the island of Java in Indonesia, and Bangkok, Thailand, based on logistic regression.[34] The predictor variables are sea surface temperature (SST) anomalies (a five-month running mean of spatially averaged SST anomalies over the tropical Pacific: 4°S–4°N, 150°W–90°W as measured by the Japanese Meteorological Association) and past monthly cases of dengue in each city. Previous incidence of anomalously high or low cases is an indication of interaction between the types of virus currently circulating and the nature of the immune status of the human population. SST

anomalies are highly correlated with subsequent surface air temperature anomalies and may be correlated with atmospheric moisture as well. The predicted variable is the probability of an epidemic year forecast one to three months before peak transmission season. The skill level for three-month predictions for Bangkok were inadequate for an operational system (6 errors in 35 years); the two and one-month forecasts had error rates of 3 and 2 per 35 years, respectively. The Java EWS, however, was sufficiently skilful to be put into use in Yogyakarta, Indonesia; one, two and three-month forecasts were without error for the 14-year period of record. Note that this system does not use ENSO state directly, but rather, one of its indicators, sea surface temperature anomalies.

A recent National Research Council report on the subject of early warning systems is cautiously optimistic but concludes that substantially more research is needed to understand the relationships between climate, human behaviour, and infectious diseases. The report states that one goal of such research should be to support a transition from the current practice of "surveillance and response towards a more proactive 'prediction and prevention' strategy."[29]

Lags between factors favouring transmission and cases

Dengue epidemics obviously involve one person's infection leading to another's; the number of infections resulting in the next cycle from a single individual is commonly referred to as R_0. As long as R_0 is greater than one, the epidemic grows exponentially at a rate proportional to this ratio. The magnitude of R_0 is dynamic, reflecting integration of the host of factors influencing dengue dynamics. Higher temperatures shorten EIP and the gonotrophic cycle and are thus a factor tending to increase R_0, as would rainfall lead to more *Ae. aegypti* in the case of southwestern Puerto Rico. High levels of herd immunity, effective spraying that shortens adult survival, or window screens limiting host access would favour reductions in R_0. Dynamically accounting for the influences of the various factors through time is a chief activity of accounting software such as CIMSiM/DENSiM. Table 6 and figure 2 present three examples of how increasingly high initial values of R_0 in the months preceding an epidemic can result in substantially more infections in the subsequent epidemic phase when conditions may have actually moderated and R_0 values are lower. This produces a *lag* between conditions promoting transmission and the subsequent realization of the epidemic when the number of infections is high.

Cycle	*Days*	*Months*	Example 1		Example 2		Example 3	
			Ro	*Infections (1.5, 1.5)*	*Ro*	*Infections (2.0, 1.5)*	*Ro*	*Infections (2.5, 1.5)*
1	1	0.03	1.5	1	2.0	2	2.5	3
2	17	0.56	1.5	2	2.0	4	2.5	8
3	33	1.08	1.5	2	2.0	8	2.5	19
4	49	1.61	1.5	3	2.0	16	2.5	47
5	65	2.14	1.5	5	2.0	32	2.5	117
6	81	2.66	1.5	8	1.5	48	1.5	176
7	97	3.19	1.5	11	1.5	72	1.5	264
8	113	3.72	1.5	17	1.5	108	1.5	396
9	129	4.24	1.5	26	1.5	162	1.5	593
10	145	4.77	1.5	38	1.5	243	1.5	890

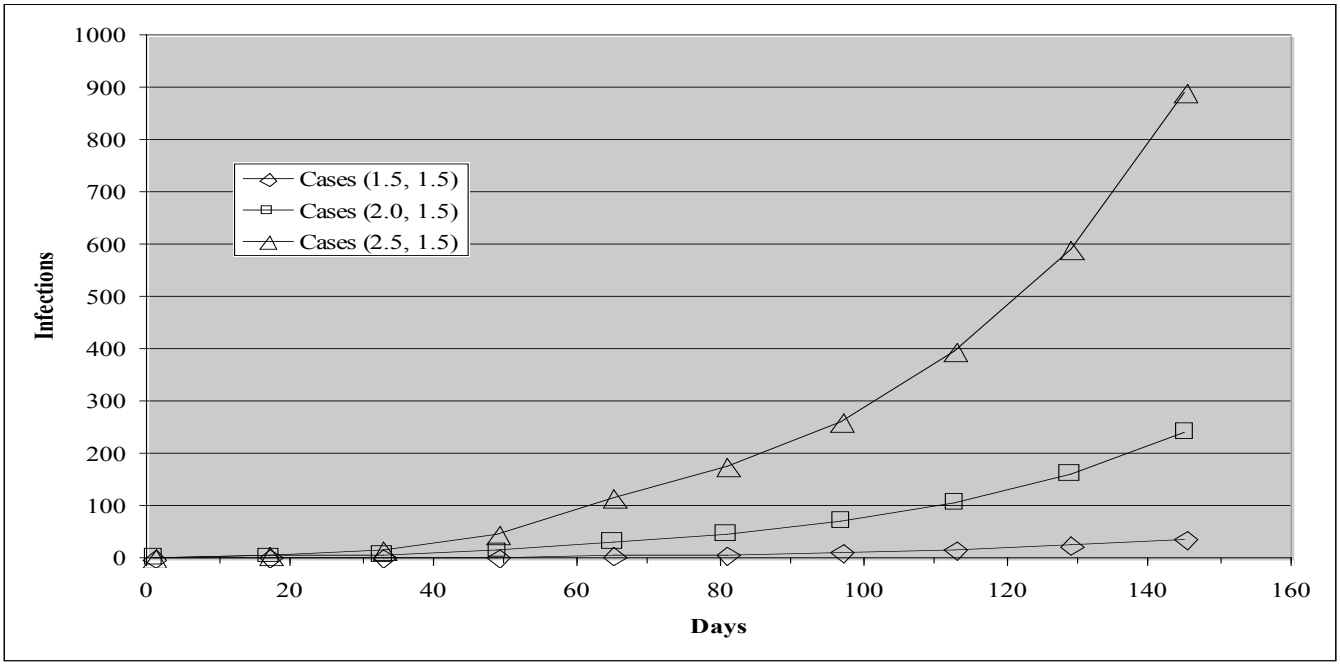

Table 6 and Figure 2. Projected numbers of infections over time as a function of R_o. For illustration, we assume the periods of time between the onset of viraemia in the first and subsequent infection cycles are multiples of 17 days. In each example, the epidemic is initiated with a single viraemic individual. During the first four cycles, the pre-epidemic period (up to day 81), R_o is set to a constant value of 1.5, 2.0, or 2.5 for lines labelled infections *(1.5, 1.5)*, infections *(2.0, 1.5)*, and infections *(2.5, 1.5)*, respectively. For cycles 5–10, R_o is set to a constant 1.5 in each case. The purpose of this illustration is to demonstrate that conditions several months before the appearance of a large number of cases (the epidemic) significantly affect the magnitude of the event. Note in each example that the ratio of new infections in each cycle after day 81 is the same, 1.5, but the *absolute* numbers of infections after additional cycles in the epidemic phase is larger as a function of the number of infected in the pre-epidemic period. This then is a mechanism whereby environmental conditions that promote increased intensity of transmission but before there are large numbers of infections can become manifest months later as an epidemic under conditions that are less conducive to transmission.

Table 7 provides correlation coefficients between monthly cases and lagged monthly cases, average temperature, rainfall, length of gonotrophic cycle, and EIP for dengue in Bangkok, Thailand, 1966–1994. It is not surprising that cases are highly auto-correlated going back at least four months; anomalously high (or low) prevalence this month reflects unusually large (or small) prevalence last month through the agency of *Ae. aegypti* giving rise to subsequent cases. The lack of substantive correlation between current cases and current weather, temperature and rainfall and their lags going back one, two or three months may come as a bit of a surprise to people who are not acquainted with dengue data. This phenomenon reflects the fact that epidemics take several months to develop to a level where they are recognized to be a result of antecedent conditions as described above.[13,35] To be truthful, there are some non-trivial correlations between cases and the preceding two months' rainfall, suggesting that, in contrast to the Wat Samphaya temple area, not all containers are manually-filled in the metropolitan area.[20] With regard to collaborating the story of antecedent conditions being key determinants of epidemics, the peaks in correlations between cases and temperature, gonotrophic cycle length, and EIP (as estimated with CIMSiM and DENSiM using historical weather data) three and four months earlier, are important. Epidemics, under these conditions of constantly endemic virus, are entrained by environmental determinants at play months before the health community is aware that a nascent epidemic is building. And, epidemics can and do occur under weather conditions less than optimal for intense transmission.

Lag (months)	Correlations between current and past monthly averages				
	Cases	Temperature	Rain	Gonotrophic cycle	EIP
0	1.00	0.07	0.22	-0.06	-0.09
1	**0.91**	0.18	0.28	-0.16	-0.20
2	**0.74**	0.29	0.24	-0.25	-0.29
3	**0.57**	**0.37**	0.09	**-0.32**	**-0.36**
4	**0.41**	**0.37**	-0.04	**-0.31**	**-0.35**
5	0.27	0.26	-0.14	-0.21	-0.25
6	0.17	0.08	-0.22	-0.05	-0.07

Table 7. Correlations between monthly cases and lagged cases, monthly average temperature (ϒC), rainfall, length of gonotrophic cycle (Gono) and extrinsic incubation period (EIP) for dengue in Bangkok, Thailand, from 1966–1994. The length of the gonotrophic cycle and EIP were estimated using CIMSiM and DENSiM with historical weather data from metropolitan Bangkok. Correlations greater than ± 0.30 are highlighted.

Viral factors

Virus titre and variation in viraemic periods

The size of the virus inoculum, that is, the product of viral titre and quantity of blood, influences the probability of the vector subsequently developing a disseminated infection with virus in the salivary glands.[7] It has been suggested, and there is some evidence to support the notion, that the titre of virus in the blood meal alone could influence the probability of subsequent infection. [36-38] Moreover, duration of the dissemination period, EIP, can vary with titre. Watts et al. reported that the EIP for dengue in *Ae. aegypti* at 30ϒC was 12 and 25 days for mosquitoes infected with *high* and *low* doses

respectively.[39] Provision has been made in DENSiM to allow evaluation of the consequences of these relationships.

Simulation studies regarding the nature of epidemic and endemic transmission

Studies comparing the consequences of viral titre on the dynamics of endemic dengue suggest that titre, through the agency of probability of dissemination and EIP, does indeed play a role. In studies by Focks et al,[7] the titres evaluated were 10^5 (low) and 10^6 (high) median infective dose (MID_{50}), the human population was low, and the number of *Ae. aegypti* pupae per person was ca. 150% of threshold. Using 10^5 MID virus, the initial virgin soil epidemic was acute leaving only 20% of the population uninfected. For the next five or six years after the initial epidemic, additional introductions resulted in few locally-contracted infections due to herd immunity and the relatively low abundance of vector. As the immune population aged, the younger age classes progressively became more susceptible and, as a consequence, most of the subsequent infections occurred primarily in these classes. If this scenario is run for decades, the age-specific distribution of seroprevalence settles down to one of rising prevalence with age, with only small epidemics involving at most a few hundred (primarily young) individuals, and with the overall prevalence of antibody averaging ca. 70%. If this scenario is run again with the titre of the introduced virus increased from 10^5 to 10^6 $MID_{50,}$ the initial epidemic is more acute and shorter in duration and involves ca. 95% of the population. The nature of transmission following the primary is different as well, with transmission being more intense, the small ensuing epidemics sporadic and more frequent, and with fewer people involved but producing higher levels of immunity than those associated with the lower-titre virus.

Simulation studies evaluating combinations of titres and viraemic periods clearly indicate that combinations favouring transmission, e.g. higher titres and longer periods, lead to more acute initial epidemics followed by more frequent smaller epidemics that ultimately involve a larger portion of the population and higher seroprevalences.

Simulation studies on the role of stochastic events

The dengue models have been used to estimate the probability of an epidemic following a single introduction.[7] Obviously, any number of factors combine to determine the fate of introduced virus – temperature, herd immunity, virus and vector characteristics, to name a few. However, under conditions near transmission threshold, the outcome of an introduction is highly unpredictable for stochastic reasons. An interesting question could be: how receptive is a small village to a single introduction occurring at various times of the year? Would this be modified by titre of the virus, given the influence of titre on the probability of infection and EIP in the mosquito? Less ambitiously, we could frame the questions in terms of parameter sensitivity – if conditions are near threshold, would factors such as seasonality in mosquito abundance, size, and temperature be sufficiently influential against the backdrop of other factors to significantly alter the probability of an epidemic, and would we expect this to be substantially modified by the titre of introduced virus?

Simulation results for the eastern coastal region of Honduras indicate that, at a low titre (10^5 MID_{50}), seasonal changes in weather result in an almost three-fold difference in probability of an epidemic resulting from a single introduction (30%–35% in December and January vs. 80% in April–May). That is to say, a wintertime introduction is about one-third as likely to cause an epidemic as one occurring in the spring or summer. The results, while suggesting that many introductions into a naive population would be lost and not produce an epidemic, also indicate that a single introduction is capable of producing an epidemic at any time of the year. Simulations also indicate that introductions of high-titre virus more frequently lead to epidemics than introductions of the lower-titre type. Associated with the

higher-titre virus is a reduction in magnitude of the role played by seasonal influences – summer introductions are only ca. 1.5 times more likely to cause an epidemic than wintertime introductions of the same virus. The difference between the ability of the two viruses to cause an epidemic is most pronounced during the cooler months when the high-titre virus is about two times more likely to result in an epidemic than introduction of the lower-titre type. These results are typical of others (unpublished), where different factors or combinations of factors become key regulatory factors under different conditions of weather, antibody presence, demographics, and mosquito characteristics.

Co-circulation of multiple serotypes

The current pandemic of dengue and DHF/DSS originated in the Pacific and South-East Asia in the 1940s, and has subsequently spread to the Americas and Africa. Today, most urban centres of South-East Asia and many in Central and South America are hyperendemic for dengue, frequently with all four serotypes circulating simultaneously.[40] Given the significance of sequential infections in developing serious illness via antibody-dependent enhancement, factors regulating or influencing the spatial and temporal distributions of dengue serotypes may be important in regulating or influencing the age-specific dynamics of infection and illness.[41]

An example of spatial and temporal variation in serotype abundance

Figures 3 and 4 are presented as examples of serotype variability on a country scale; the figures are based on ca. 1200 virus isolations from human sera in North and South Viet Nam between 1990 and 1999.[42] The data provide an indication of the relative frequency and dynamics of dengue serotypes in circulation over a ten-year period. These estimates are not necessarily unbiased or highly correlated with the real picture, considering the possible differences in virulence among serotypes and low number (<30–40) of isolations in several years. Keeping in mind the nature of the data, and that dengue activity is usually confined to roughly June–November in the North and is continuous but seasonal in the South,[43] what can be said regarding some of the possible factors influencing the dynamics of serotypes spatially and temporally?

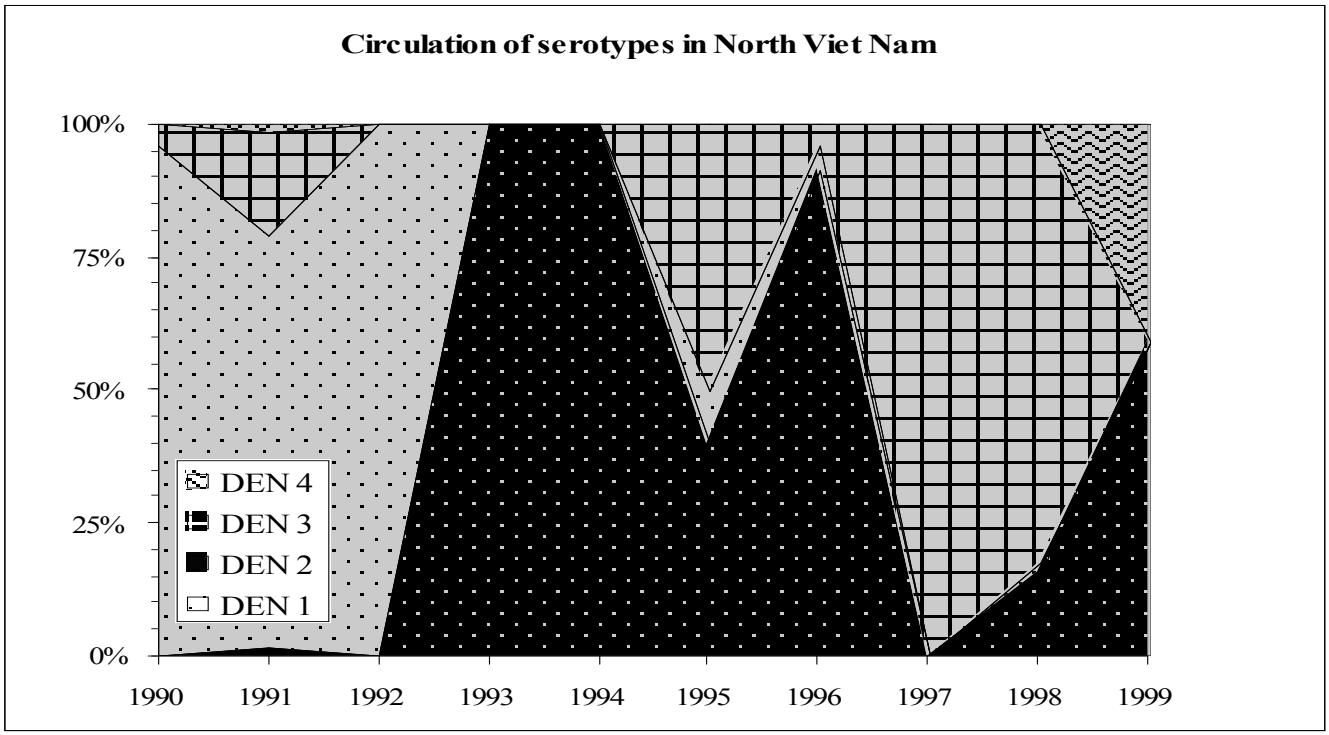

Figure 3. Circulation of dengue serotypes in North Viet Nam between 1990 and 1999 based on virus isolation from febrile patients.[42]

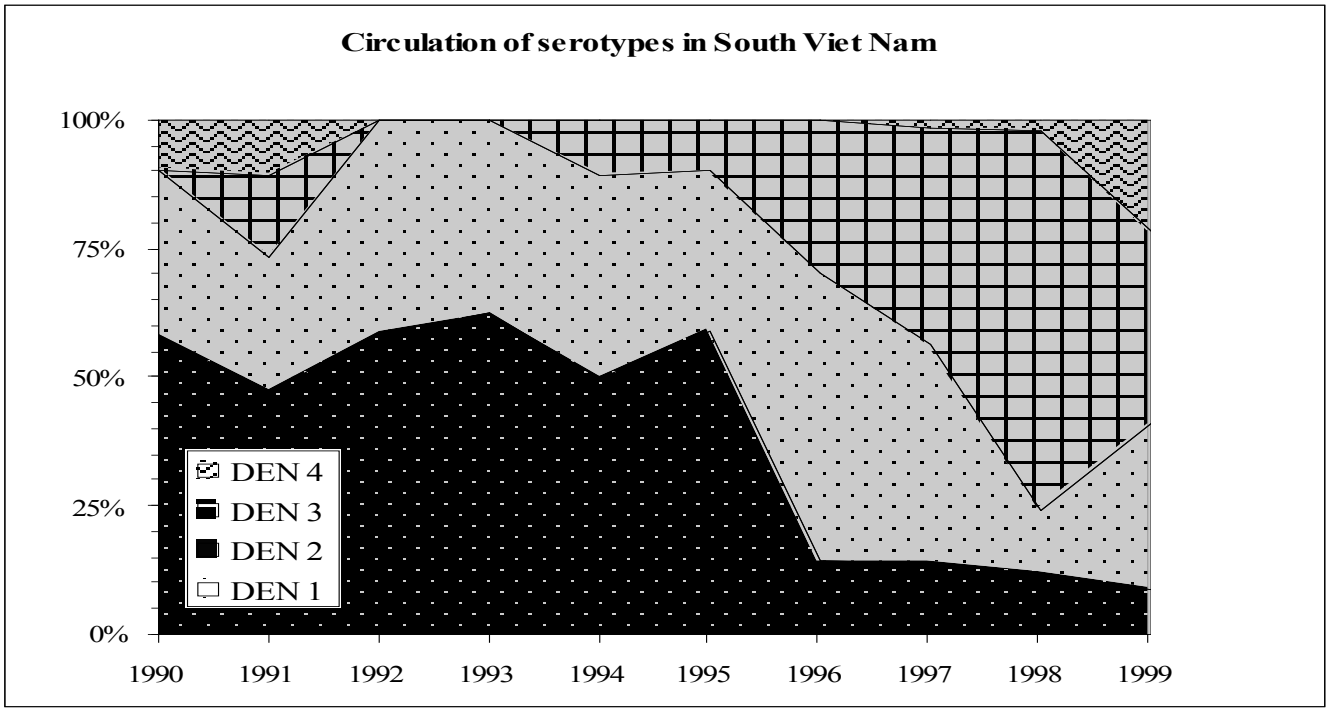

Figure 4. Circulation of dengue serotypes in South Viet Nam between 1990 and 1999 based on virus isolation from febrile patients.[42].

Founder or stochastic effect

In some regions, the mix of serotypes found each year simply reflects the mix in other endemic areas. It is likely that dengue virus is lost during the cool season in the North and is annually reintroduced from more southerly locations each year;[39] hence it is not unexpected that the mix of serotypes circulating in the North bares some correspondence to those in the South. A similar situation is reported for small relatively isolated Pacific islands that are too small to remain endemic; when virus does arrive, the introduced strain was usually active earlier on other larger islands.[33]

The influence of herd immunity on serotype abundance

Another factor influencing the distribution of serotypes is the nature of herd immunity. During the course of an epidemic not influenced by control efforts or cooling temperatures, R_o ultimately falls to less than one as a function of the rising proportion of immunes – increasingly, potentially infectious bites fall on refractory individuals and the epidemic dies out. The notion of herd immunity, the proportion of individuals immune to a particular serotype of virus, therefore is a useful concept. In acute, virgin soil epidemics, such as the DEN-1 outbreak in Cuba of 1977–1979 where some 44.5% of the urban population experienced infection in a single year, the level of herd immunity was roughly identical with the prevalence of antibody in each age class.[44] However, in endemic areas where the norm is ongoing circulation of multiple serotypes, there is a general trend of increasing seropositivity with age. As a result, not only is the nature of illness and the age-specific distribution of serious illness a function of current and previous dengue activity, but the dynamics in abundance of dengue serotypes is a function of previous dengue activity through the proxy of herd immunity. Here past activity (or lack of it) can influence the innate R_o of the same serotype through the agency of herd immunity.

Figure 5 is a plot of output from DENSiM for a hypothetical site where dengue has historically been endemic and seroprevalence to all four serotypes is high. During the 20 years displayed, virus was not introduced from the outside but remained endemic in the ca. 150 000 people in the simulation. The ca. 3–4 year periodicity of epidemics is driven by waxing and waning herd immunity in the 0–9 year age classes. The volatility in prevalence of antibody in the 1–4 year age class, and to a lesser extent among the 5–9 year age class, reflects two sources. Reductions in prevalence through time come about by children moving from the 1–4 year class to the 5–9 year class, with replenishment from predominantly uninfected infants from the 0–1 year age class during years of low transmission. Prevalence in the 1–4 year age class goes up sharply in epidemic years because infection occurs in the age class and the recruits from the infants' class are more likely to already be positive in epidemic years. In this example of hyper-endemicity, the variability in seroprevalence directly influences abundance of the associated virus serotype. Note that in this example it is ultimately the human birth rate that entrains the 3–4 year epidemic cycle.

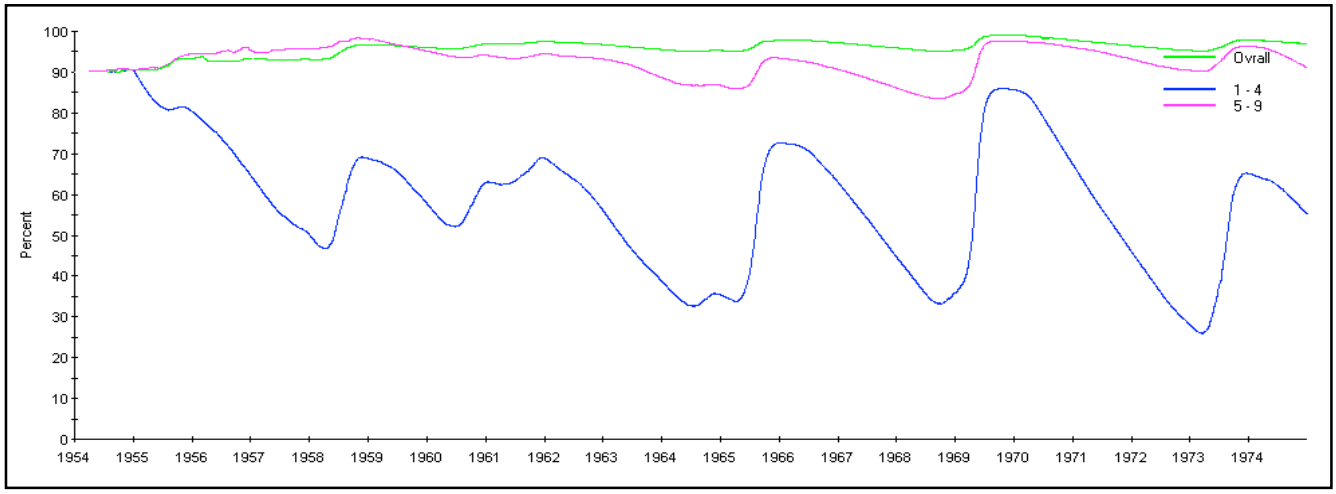

Figure 5. Output from DENSiM for a hypothetical site where dengue is endemic (see text for explanation). The green line is overall prevalence and mirrors the different age classes closely except for those of 1–4 and 5–9 years.

The interaction of different serotypes through the mechanism of heterologous immunity

On the basis of simulation studies with DENSiM, abundances of the different serotypes can influence each other through the phenomenon of short-lived heterologous immunity following infection. In essence, an ongoing epidemic of a particular serotype temporally raises the effective herd immunity to the other three serotypes by producing heterologous and cross-reacting titres in those recently infected; once one epidemic is under way, it is somewhat less probable that a second epidemic (with similar force of infection) will begin. This is a factor in the commonly observed phenomenon of asynchrony of epidemics of different serotypes (figure 6). But regarding the question of relative abundance by serotype for any particular month, the proximate determinant of abundance of each virus type in mosquitoes is simply a linear function of the frequency of human infection of that type.

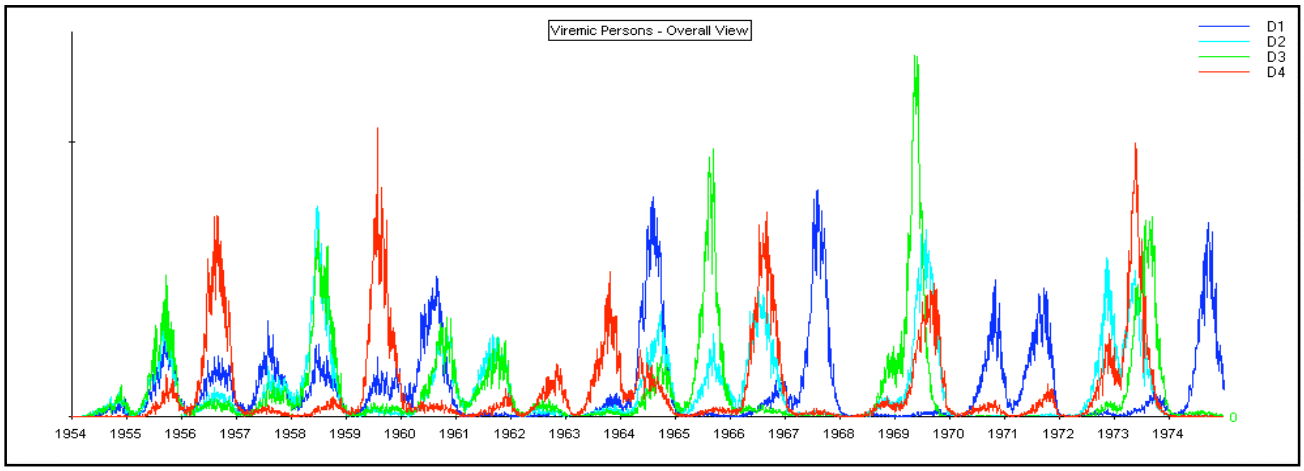

Figure 6. Output from DENSiM for hypothetical site where dengue has historically been endemic for all four serotypes. Simulation begins with all age classes being 90% positive for antibody and an initial human population of 100 000; the annual population growth is ca. 3.2%. Virus was introduced only during the year preceding the results shown here, i.e. the results depict a situation where the viruses are not lost between epidemics.

The potential influence of antibody-dependent enhancement on the dynamics and persistence of multiple serotypes of virus

Recently, another interesting hypothesis regarding the interaction of serotypes was made by Ferguson et al. [45] The authors note that antibody-dependent enhancement (ADE) of dengue infection involves cross-reactive antibodies from a previous infection that serve to facilitate virus replication within the host. They posit that the phenomenon of 'enhanced' infections in a subset of cells can result in a higher probability of transmission of the virus causing the secondary infection. Using a simple set of differential equations, they demonstrate that this linkage between serotypes via ADE can result in persistent and complex cyclical patterns in the relative abundance of serotypes of virus given the assumption regarding ADE leading to a change in transmission probabilities. The results of this study suggest that this phenomenon of linkage via ADE theoretically makes possible the co-existence of multiple serotypes, whereas without such linkages, one or more serotypes would be expected to be lost due to drift.

The recent work by Vaughn et al. has clearly demonstrated that peak viraemia is increased in at least some secondary infections in humans.[46] Given that virus titre is thought to influence both the probability of disseminated infection and the duration of EIP within the female mosquito, a hypothesis linking ADE and increased probability of transmission seems plausible.

Acknowledgement

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