Host-vector interaction in dengue: a simple mathematical model

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(Index words: dengue, dengue model, dengue Sri Lanka, endemic equilibrium, dengue virus diversity)

Abstract

Introduction Dengue is a mosquito-borne viral infection endemic in tropical and subtropical regions,now spreading at epidemic proportions causing a major health issue in Sri Lanka and elsewhere. No effective vaccine or a curative antiviral drug is available to prevent or treat the disease. The only way of mitigating dengue at present, is through mosquito eradication and educating the public on preventive measures which can minimize the cycle of transfer.

Objectives A theoretical model of dengue with simple mathematics is presented to gain a quantitative understanding of the pattern of dengue outbreaks in Sri Lanka and suggest control measures.

Method The statistics on incidence of the disease reported by the Epidemiology Unit is analyzed using the model. Despite simplicity, the model possesses explanatory and predictive capacity, enabling determination of crucial parameters. The model shows that the "infectives" increase exponentially in an outbreak, provided the number of vectors per human exceeds a threshold, illustrating not only vector eradication but measures which minimize their biting frequency and preventing prolonged survival are effective safeguards.

Results In a population consisting of 75% who are susceptible, the threshold is estimated to be 20 mosquitos per person.

Conclusions The model showed that the endemic equilibrium of the system can occur at any level. As demographic changes escalate mosquito breeding, they infect more and more susceptible people. The consequent increase in virus replication induces new strains broadening the genetic diversity of the virus and helping it to overcome the human immune response. The increasing endemicity of dengue due to this is demonstrated by the model.

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Introduction

The evolving pattern of dengue transmission leading to sporadic epidemics is a major health issue in Sri Lanka and many other tropical and subtropical countries. In the absence of an effective vaccine or a curative antiviral drug, the only way of mitigating the spread of this disease is mosquito eradication and adoption of precautionary measures to minimize the cyclical transfer of the virus [1,2]. Such programs, carefully designed, based on the epidemiology of infection have been successful in combatting the spread of mosquito borne diseases [3-5]. In this context, mathematical models that quantitatively depict the epidemiology of the system, insightfully assist the optimization of control strategies [6-8]. Unfortunately, most models of dengue reported in literature are too mathematical and cannot be used by non-specialist health care workers, medical professionals, students or educated laymen [8-14]. Mathematical epidemiological models are intellectually appealing, have a high pedagogic value, motivate deeper study and suggest control strategies. It is important to recollect the contributions by Ross and Macdonald in malaria eradication. They modeled the epidemic mathematically following the findings of Manson and these three malaria pioneers exhaustively studied malaria epidemics in Sri Lanka [6, 15,16]. This paper introduces a simple model of dengue that requires only a high school background in mathematics. The data on distribution of dengue cases reported by the Epidemiology Unit, Ministry of Health, Sri Lanka is used to test the model predictions and suggest disease control strategies based on the analysis [17].

The mathematical model

Dengue fever is caused by a virus transmitted by the Aedes aegypti mosquito which is mainly active during day time. However, mosquitoes which bite at night may also act as dengue vectors. Increased human population density, effect of climate on mosquito breeding and presence of several stereotypes of the virus and human reservoirs with marginal to severe clinical manifestations

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complicate the epidemiology of the disease [18-20]. The simple model presented here examines the development of dengue infection in an environment of constant human and mosquito populations. Nevertheless, the contribution of these parameters on temporal progression of the disease can be inferred from the analysis.

When a mosquito x bites a dengue infected human subject X^*, there is a high probability of the virus being transmitted to the mosquito and it acquiring the infection after an incubation period of 4-10 days, to reach the stage of an infected mosquito denoted x^*. During its life time, x^* is capable of transferring the virus to the human subjects it bites. The host X bitten by x^* could develop the infection after 4-14 days of incubation.

Some humans do not get infected even if they are bitten by virus carrying mosquitoes but those who are susceptible acquire the infection. If S and S^* denote the population densities of healthy and infected human "susceptibles" in a population of density N and n and n^* the densities of healthy and infected mosquitoes, the time evolution of the infection can be described by the following rate equations,

$$\frac{d}{dt}\left(S^*\right) = an^*(S/N) - kS^* \qquad (1)$$

$$\frac{d}{dt}\left(n^*\right) = b(S^*/N)n - hn^* \qquad (2)$$

where k, h, a and b are constants. The first term in (1) accounts for the interaction between healthy humans and infected mosquitoes in transmitting the infection. The rate of biting of infected mosquitoes described by the first term of (1) is assumed to be proportionate to the density of infected mosquitoes and the fraction of human "susceptibles" in the population. The constant a measures the rate of biting per unit time per infected mosquito with a weightage for the probability of virus transmission. Similarly, the first term of (2) accounts for the interaction between infected humans and healthy mosquitoes in transferring the infection to the mosquitoes and b is the biting rate of infected persons by healthy mosquitoes per unit time, per mosquito with weightage for mosquito acquiring the infection. The second term in (1) accounts for recovery of infected humans and the parameter k^{-1} which has the dimension of time, measures the median recovery time. Analogously, infected mosquitoes are eliminated due to their senescence, and the inverse of h in the equation (2) is their mean life time. Even in the case of an intense dengue outbreak, $S^* << S$ and the death rate is relatively low. Unlike in more detailed models of dengue, approximate but reasonable assumption $S^* << S$ avoids the necessity of writing a separate equation for the time evolution of S. The model assumes these conditions and does not explicitly consider the immunities originating from presence of more than one stereotype of the virus or different strains of the same stereotype. The model does not explicitly take into account inputs from control programs such as fogging, elimination of stagnant water or adoption measures to reduce the mosquito biting rate, instead the relative importance of these are assessed.

The system described by the equations (1) and (2) has an equilibrium when $S^* = S_0^*$, $n^* = n_0^*$, corresponding to the condition.

$$an_0^*(S/N) - kS_0^* = 0 \quad b(S_0^*/N)n - hn_0^* = 0 \qquad (3)$$

Clearly (3) imply that the equilibrium occurs when,

$$\frac{n}{N} = \frac{kh}{ab}(N/S) \qquad (4)$$

To examine the behavior of the system near the equilibrium, we set,

$$S^* = S_0^* + (\delta S^*) \qquad n^* = n_0^* + (\delta n^*) \qquad (5)$$

where S and n^* the deviations of S^* and n^* from the equilibrium values. Inserting (5) in (1) and (2) subject to the condition (3), we obtain the equations,

$$\frac{d}{dt}\left(\delta S^*\right) = a(\delta n^*)(S/N) - k(\delta S^*) \qquad (6)$$

$$\frac{d}{dt}\left(\delta n^*\right) = b[(\delta S^*)/N]n - h(\delta n^*) \qquad (7)$$

Equations (6) and (7) can be easily solved as follows: Differentiate (6) with respect t and eliminate n^* and $\frac{dn^*}{dt}$ using (7) to obtain the equation (8) given below.

$$\frac{d^2}{dt^2}\left(\delta S^*\right) + (k+h)\frac{d}{dt}\left(\delta S^*\right) + [kh - ab(n/N)(S/N)](\delta S^*) = 0 \qquad (8)$$

Solutions of (8) have terms of the form, $S^* = Ke^{t}$ where K is constant and the possible values of is λ are being given by the quadratic equation,

$$\lambda^2 + (k+h)\lambda + [kh - ab\,(n/N)(S/N)] = 0 \qquad (9)$$

Thus the solution of (1) and (2) can be expressed as,

$$S^* = S_0 + Ae^{\lambda_1 t} + Be^{\lambda_2 t} \qquad (10)$$

$$n^* = n_0 + Ce^{\lambda_1 t} + De^{\lambda_2 t} \qquad (11)$$

where A, B, C, D are arbitrary constants and

$$\lambda_1 = -\frac{1}{2}(k+h) + \frac{1}{2}\sqrt{(k+h)^2 - 4[kh - ab(n/N)(S/N)]} \qquad (12)$$

$$\lambda_2 = -\frac{1}{2}(k+h) - \frac{1}{2}\sqrt{[(k+h)^2 - 4[kh - ab(n/N)(S/N)]]} \qquad (12)$$

The quantity λ_2 is essentially real and negative, implying that the second term in (10) and (11) vanishes as $t \rightarrow \infty$ whereas λ_1 can be positive or negative, depending on whether (n/N) is greater or less than a threshold value $(n/N)_c = (kh/ab)(N/S)$. The former condition is indicative of the onset of an epidemic and in the latter case any sudden increase in number of infectives above the equilibrium, decays off without expanding into epidemic proportions.

The parameter can be approximated and written as,

$$\lambda_1 = [\frac{ab}{k+h}][\frac{n}{N} - \frac{kh}{ab}(N/S)] \qquad (14)$$

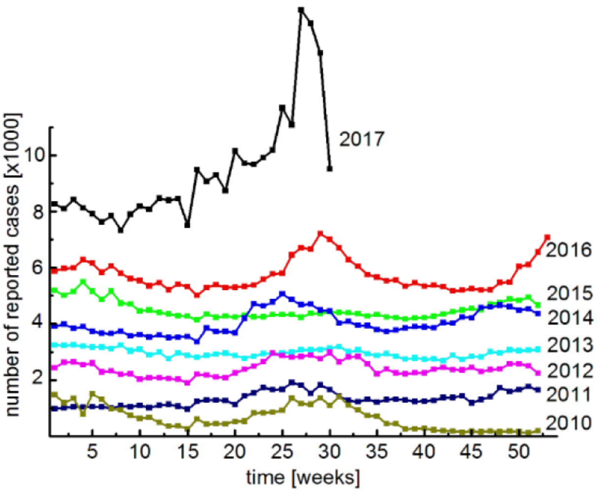

Figure 1a. **Yearly dengue cases distribution from 2010 to 2017 plotted using data reported by Epidemiology Unit, Sri Lanka** [17].

so that the progression of infection is described approximately, by the expression,

$$S^* \approx S_0^* + A\exp(\lambda_1 t) \qquad (15)$$

Equilibrium becomes unstable and an epidemic situation develops when the number of mosquitoes per person (n/N) exceeds the threshold value. Otherwise the equilibrium remainss table without growing to an outbreak. The model does not fix the value of S_0^*, implying that the endemic equilibrium can be at any level. An alternative way of understanding this issue is as follows: The general solution of equations (1) and (2) can be written as

$$S^* = Ae^{\lambda_1 t} + Be^{\lambda_2 t} \qquad (16)$$

When $n/N < (kh/ab)(N/S)$ is satisfied, $S^* \rightarrow 0$ as $t \rightarrow \infty$, implying that the above condition leads to an natural elimination of the disease. However, if $n/N = (kh/ab)(N/S)$, (16) reduces to

$$S^* = A + Be^{-(k+h)t} \qquad (17)$$

Here the system approaches an equilibrium $S^* = A$ which is not essentially zero.

An analysis of extensive data on dengue cases reported by the Epidemiology Unit of the Ministry of Health, indicates that the pattern of development of an outbreak follows the trend of the equation (15) to a significant level of confidence [18]. The distribution of dengue cases in Sri Lanka from 2010 to 2017 are plotted in Figure1a. It is seen that the annual incidence of the disease shows two peaks, occurring around June-July and October-December, correlating with South-Western and North-Eastern monsoon periods. The October-December peak of the previous year wanes during the February-March dry season and signs of a more pronounced June-July peak begins around the 15th week (March/April) of the year.

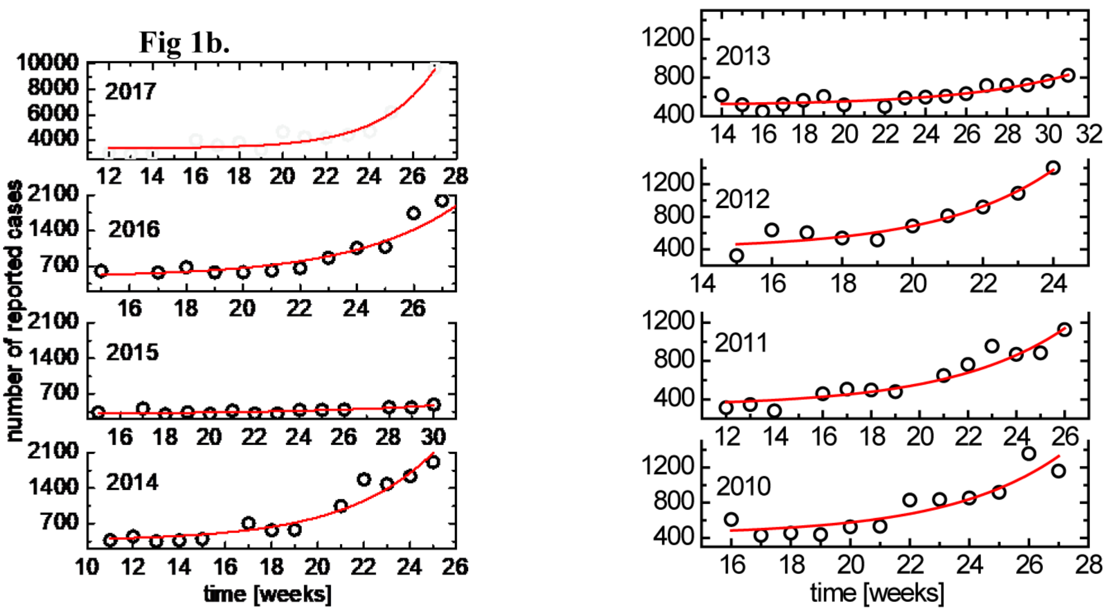

Figure 1b. **Fitting of midyear dengue cases distribution 2010 to 2017 according to the equation** [15].

Figure 1b. Shows the regression analysis fitting of the data for each year from around 15th week (March/April) and up to the June/July peak to the equation (14). The fitting parameters S_0^*, A, λ_1, $\tau = \lambda_I^{-1}$ and R-squared confidence levels are given in Table.1.

Table 1. Parameters extracted from curve fitting process for each year

Year	*Weeks*	S^*_O	*A*	τ *[months]*	λ *[months^{-1}]*	*R-squared %*
2017	12 - 28	3355	0.11	0.63	1.06	94
2016	15 - 29	482	0.77	0.93	1.08	95
2015	15 - 30	313	0.72	1.43	0.70	67
2014	11 - 25	362	2.4	0.95	1.05	92
2013	13 - 31	512	0.95	1.33	0.75	82
2012	15 - 25	401	0.6	0.8	1.25	93
2011	12 - 27	328	3.4	1.18	0.85	91
2010	15 - 27	435	0.72	0.95	1.05	83

It is seen that data fits the expression (15) more significantly when the outbreak has been large (in 2015 the June/July dengue peak was almost absent and here the R-squared value is 67%). The parameter λ_I varies from 1.59 - 0.7 months^{-1} (equivalently τ varying from 0.63 -1.43 months), clearly larger epidemics corresponds to larger values of λ_I (smaller values of τ). The year 2017 epidemic had the highest value of λ_I or equivalently the smallest value of the time constant τ. Another peculiarity of 2017 distribution is the large value of S_0^* (= 3355), whereas in all the other years this parameter had varied in the range 300-500. The larger value of S_0^* in 2017 implicates a situation where pervious outbreak (October-December 2016) has equilibrated at an unusually high ground level. The parameters of the expression (15) obtained by regression analysis of dengue cases reported on district basis for the 2017 mid-year outbreak are presented in Table 2. Here the correlation of the time evolution of the epidemic with expression (15) is highly significant (except in some districts, mostly in the Northern and Eastern Province). Presumably, district statistics correspond to localities of uniform conditions, notably the characteristic parameters of λ_I. In the district based data, λ_I is seen to vary between 0.5 and 2 month^{-1} ($\tau \sim 2$ - 0.5 months). Most significantly variable factors in the expression for λ_I given by (14) are the number of mosquitoes per person (*n/N*), the fraction of "susceptibles" *(S/N)* and the survival time of infected mosquitoes (same order as that of uninfected ones) $\sim h^{-1}$.

The above analysis implies that interventions for preventing an epidemic should be aimed at controlling the mosquito population per person ratio (*n*/*N*) to a level below a critical value $(n/N)_c = (kh/a)(N/S)$. According to the model (*n*/*N*) is dependent only upon parameters *k, h, a, b* defining the dynamics of the system as well as the fraction *(S/N)*. A higher value for $(n/N)_c$, implies that the system could maintain its resistance to an epidemic during adverse weather conditions causing an increase of the mosquito population. It is important to realize, that not only mosquito eradication but measures elevating $(n/N)_c$ are also important in controlling dengue. An increase of *k* and/or *h* and decrease of *a* and/or *b* will raise the magnitude of $(n/N)_c$. As the inverse of *h* is the mean life time of infected mosquitoes, decreasing mosquito survival time will increase $(n/N)_c$. The life time of Aedes aegypti is about two weeks to one month depending on environmental conditions. There is no evidence that acquiring the virus has a significant influence on longevity of Aedes aegypti. The effect of climatic conditions on survival of Aedes aegypti has been studied [21-22]. Extreme temperatures and torrential rains lower mosquito survival [23-24]. Nature of the microenvironment seems to play an important role in longevity of mosquitoes. It has been observed that longevity of Aedes aegypti is significantly higher in disorganized and thickly populated urban areas compared to more organized and planned urban dwellings [25]. Presence of moist shady resting and hiding places enhance mosquito breeding and survival. Consequently, according to the model, the critical mosquito population per person $(n/N)_c$ sufficient to initiate a dengue out-break in congested urban area is relatively low.

It is interesting to estimate the threshold value $(n/N)_c$ for reasonable values of the parameters of the theory. The average values of *k* and *h* are the order of 0.1 and 0.05 days^{-1} respectively. Biting rates of Aedes aegypti under varying conditions have been studied, we choose $a \approx b = 0.02$ days^{-1} based on average of a range reported in literature [26]. If we assume a situation where the population consists of 75% who are susceptible, the equation (4) yields $(n/N)_c = 17$. Thus persistence of a dengue vector population of around 20 per person for a period of the order of the time constant ($\tau = \lambda_I^{-1} \sim 1$ month) would turn an endemic situation to an epidemic.

Table 2. Parameters extracted from curve fitting process for different districts (cases reported 2017). The total cases reported until July is also given. In districts marked X data does not fit into the equation (15)**. District population density is denoted *N***

District	*Total cases*	*Population density (N)*	N_0	*A*	τ*[months]*	λ*[months^{-1}]*	R^2
Colombo	25847	3438	2325	3.20	0.87	1.15	99.8
Gampaha	22465	1719	2158	0.82	0.8	1.25	93.5
Kalutara	6930	775	831	0.067	0.7	1.43	98.2
Kandy	7237	716	400	0.35	0.7	1.43	99.6
Matale	1660	248	114	0.085	0.6	1.67	98.9
Nuwara Eliya	606	132	38	0.008	0.7	1.43	99.9
Galle	3916	658	226	1.8	1.2	0.83	94.6
Hambantota	2366	240	333	0.02	0.8	1.25	99.8
Matara	4158	641	375	0.001	0.5	2.00	98.8
Jaffna	3404	629	X	X	X	X	X
Kilinochchi	348	94	X	X	X	X	X
Mannar	498	53	X	X	X	X	X
Vavuniya	605	92	X	X	X	X	X
Mulativu	229	38	X	X	X	X	X
Batticaloa	4255	202	X	X	X	X	X
Ampara	620	154	54	0.11	0.97	1.03	99.1
Trincomalee	4496	150	323	12	0.6	1.67	100
Kurunegala	6958	350	391	1.7	0.8	1.25	99.5
Puttalam	3555	265	207	6	1.3	0.77	96.8
Anuradhapura	1900	129	109	0.13	1	1	96.5
Polonnaruwa	954	132	59	6	1.9	0.53	81.3
Badulla	2261	288	127	0.17	0.8	1.25	99.9
Moneragala	1556	82	106	0.011	0.58	1.72	98.2
Ratnapura	7094	336	376	4	1	1	96.7
Kegalle	6020	499	210	0.33	0.7	1.43	98.9
Colombo Municipality	4223		545	0.004	0.6	1.67	98.9
Other areas of Colombo	21624		2760	2	0.9	1.11	94

The rate constant *a* defining the extent to which humans are infected when bitten by infected mosquitos, occur in the denominator of the expression (14), therefore decrease of *a* will increase $(n/N)_c$. Use of mosquito nets, meshing the windows, wearing cloths to cover body extremities, application and spraying of mosquito repellants, could effectively lower the value of *a*. Such personal preventive care not only lessen the probability of an individual contracting dengue, but also greatly helps to increase the critical mosquito population needed to initiate an explosive infection.

The dengue virus occurs as four antigenically distinct stereotypes. When a person contracts dengue of one type and recovers, he or she acquires life-time immunity to that virus and immunity to other three types happens to be temporary and last only for two to three months. Consequently, sometime after an epidemic of one type, the propensity of an outbreak of an infection of another type is greatly increased. In this situation the "susceptibles" are excessive, which decrease fraction (N/S) and therefore $(n/N)_c$ decreases, implying that even a relatively small population density of mosquitoes could trigger an epidemic. Generally, when a dengue outbreak dwindles, mosquito control activities and other precautionary measures also become less. This can lead to more severe epidemics in the future.

Although people consciously take precautions to avoid contracting dengue, there is often ignorance about the need to prevent mosquitos acquiring dengue from humans. Generally, dengue patients' beds are not covered with mosquito nets during the day, nor do they apply mosquito repellents. Reducing the constant *b* by adopting safeguards to minimize passing of the infection to mosquitos is equally important to maintain $(n/N)_c$ at a level sufficiently high to escape the onset of an epidemic.

A feature of the yearly distribution of dengue cases in Sri Lanka is a progressive increase in the number of reported cases in the lull period of the outbreak approximately between 10th and 20th weeks (Figure1a). Presumably the yearly endemic equilibrium (the lull period) has continued to increase from 2010 to 2017. The situation appears to be parallel to the increase in the value of *A* in equation (17). The important question is what causes this behavior? The following may be a plausible explanation.

Demographic changes make the environment more conducive to breeding of mosquitoes increasing the number of "infectives". More "infectives" result in more virus replications and therefore a higher probability of creating genetic variations in the virus. This process progressively increases the genetic diversity of the virus (a wide spectrum genetic strains within each stereotype). The diversity of the virus enables it to overcome the immune response in the human host.

Discussion

The main finding of the model is demonstration of the existence of a threshold for the number of mosquitos per $(n/N)_c$ above which a community could become susceptible to an outbreak of dengue. The threshold depends on dynamic constants of the system and the fraction of "susceptibles" in the human population. As complete extermination of mosquitos is a very difficult task, a more practical dengue control strategy would be the adoption of measures to maintain the value of $(n/N)_c$ as high as possible. This precautionary measure will ensure that even if there is a sudden introduction of an infestation, it will decay, without developing into an epidemic.

Mosquito mediated diseases, malaria and filaria have been eradicated in Sri Lanka and elsewhere. It is important to realize that these successes are not entirely the result of effective mosquito control programs. Emptying of human pathogen reservoir by drug treatment of infected humans has played a crucial role. Similarly, for vaccination suppressed yellow fever in Africa. In controlling dengue, more emphasis should be placed on measures that reduce the human reservoir of the virus in situations where mosquitoes cannot be adequately eliminated. In the absence of drugs and vaccines, promoting methods of minimizing mosquito-human contact may be an option. In terms of the model such efforts will lower the values of the parameters a and b raising the threshold number of mosquitoes per person necessary to initiate an epidemic. The model reinforces the warning that mosquito control efforts should not be neglected as October-December peak of dengue incidence in Sri Lanka subsides. Control programs during this period will curtail rising of the mosquito population up to threshold and beyond.

Historically, Sri Lanka has been successful in controlling and also eliminating infectious diseases [3-5]. In the challenging case of dengue, attacking the problem from every angle is essential. Here mathematical models and analysis of data on incidence of dengue in relation to climate, demographic factors and eradication programs will play a vital role. The following section summarizes important factors which should be considered by the dengue control programme. These factors were identified by the model.

The model demonstrates the effectiveness of the National Dengue Control Programs in reducing the mosquito population. To prevent the onset of an epidemic, the mosquito eradication work needs to be initiated at the first sign of an increasing trend in the cases of dengue, which is more effective than escalation of these activities during an epidemic. The main component of this effort is insecticide spraying and work geared towards elimination of mosquito breeding stagnant water. The model clearly indicates that the threshold value $(n/N)_c$ is inversely proportional to the mean life time of the mosquito (k^{-1}). The longevity of mosquitos is significantly higher in damp shady environments. Thus the dengue control program should also make a concerted effort to educate the general public and conduct activities to clear shrubs and shady locations in close vicinity of living areas. Not only stagnation, wetness and shade also greatly contribute to spread of dengue via reduction of the threshold mosquito population needed to initiate an epidemic situation. It is also important to pay more attention to measures which minimise the passing of the infection from humans to mosquitoes. We need to highlight the importance of dengue patients using mosquito nets during day time and the provision of such facilities to hospitals, will reduce the parameter b in the expression $(n/N)_c = (kh/ab)(N/S)$, increasing the threshold. Urban and suburban congestion will also reduce the threshold (i.e. by increasing N). National housing construction and planning programs should keep this in mind when implementing developmental work. Frequently, schools are found to be foci of dengue, this can be understood as they are places of potentially low threshold (because of large N). Extra precautions need to be adopted in a situation with low potential threshold.

Conflicts of Interest

There are no conflicts of interests.

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