J.Natn.Sci.Foundation Sri Lanka 2014 42 (3): 273-277
DOI: http://dx.doi.org/10.4038/jnsfsr.v42i3.7401

RESEARCH ARTICLE

Analysis and mathematical modelling of possible inter-larval spread of the dengue virus

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Revised: 26 March 2014; Accepted: 18 July 2014

Abstract: The dengue virus continues its pathogenicity by horizontal transfer between humans and mosquitoes or vertical transfer through all metamorphic stages of infected female mosquitoes. A recent experiment has concluded the possibility of yet another mode of transmission, where the infected larvae in an aqueous habitat pass the virus to healthy ones. Although this mode of dengue virus transmission is not known to happen in nature, the virus adopting it as a survival strategy implicates a potential threat of more severe epidemics. A theoretical model constructed to study the spread of the virus suggests that when the larval population density exceeds a critical value the disease may quickly grow to epidemic proportions. The model also indicates that vertical transmission in the absence of human involvement is most unlikely to sustain the virus. Whereas in a densely larvae populated environment, inter-larval transmission could explosively generate infected mosquitoes without human mediation. The absolute necessity of eliminating mosquito breeding wet habitats and long term planning to avoid their creation is emphasized in light of this potential future threat. As evolution explores all the advantages and dengue virus evolves fast adaptively, virus resorting to inter-larval transmission should not be considered as an improbability.

Keywords: Dengue, inter-larval virus transmission, mathematical epidemiology, theoretical epidemiology, virus transmission.

INTRODUCTION

The epidemiology of dengue is complicated by the effects of varying weather patterns, anthropological factors in the environment and the reaction of the vector and virus to external conditions (Bartley *et al.*, 2002; Halstead, 2008; Whitehorn & Farrar, 2010). The virus also evolves responding to the immune feedback of the human host and different metamorphic stages of the mosquito (Rico-Hese, 2003). Presence of different serotypes of the virus further complicates the epidemiology and serotype-specific differences have been observed in major dengue outbreaks (Kanakaratne *et al*., 2009; Malavige *et al*., 2011). Responses of the vector and the virus manifest as new adaptations readily selected and enabled by their fast replication and mutation rates. Originally, dengue was believed to be transmitted only horizontally by mosquitoes biting human infectives. Now it is established that vertical transmission indeed occurs by the entry of virus into all metamorphic stages of the mosquito (Rosen *et al*., 1983; Adams & Boots, 2010). Consequently, as there are also infected male mosquitoes, sexual transmission adds to the persistence of the virus. Recent experimental evidence has suggested the possibility of the virus spreading among larvae in their aqueous habitat (Bara *et al*., 2013). Although inter-larval transfer of the dengue virus has not been detected under natural conditions, evolution of the virus in this direction could cause unexpected epidemic situations making control of the disease more difficult. In this note, a theoretical model of dengue epidemiology is presented. The model shows that beyond a critical larvae population density, the inter-larval spread of the virus, if it happens, may lead to explosive intermittent epidemics at times of adverse weather conditions. Emphasis on very strict mosquito larval control measures would be necessary to avoid the potential threat of the virus acquiring the capability of inter-larval transmission.

MATHEMATICAL MODEL

Theoretical epidemiological models (TEMs) are insightful and intellectually appealing exercises useful in understanding temporal development of an infectious disease (Estera & Vargas, 1998; Hethcote, 2000; Perera,

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2009). Despite their simplicity, TEMs have succeeded in determining effective control measures. The basis of TEMs is dynamical systems theory formulating coupled non-linear differential equations to describe the time evolution of the system, enabling elucidation of the stability criteria of complex systems involving several interacting components (Perko, 2000; Jones *et al*., 2009). A vector borne infectious disease whose progress depends on measurable variables such as population densities of susceptibles and infectives of the human host (N and N^*) and the vector (M and M^*), starts progressing because the absence of the disease or the origin of the dynamical system $N^* = 0$, $M^* = 0$ is a point of unstable equilibrium. Generally most infections pass the unstable equilibrium at the origin and reach a stable equilibrium at some point where the dynamical variables N^*, M^* take definite non-zero values. The existence of such equilibria maintains the disease making it endemic. Sometimes, because of external or internal causes, the equilibrium turns unstable resulting in sporadic epidemics.

The dynamical variables of the present model are defined as follows:

N = human population density
N^* = density of human infectives
M = population density of dengue transmitting mosquito types
M^* = population density of infected mosquitoes
L = population density of mosquito larvae
L^* = population density of infected mosquito larvae

Population densities are measured in the number of individuals of each category per unit area. The human population density N is assumed to be constant (an assumption valid for short duration infections of low mortality). Using mass action rules, the rate equations describing time evolution of the system can be written as follows,

$$dM/dt = kL - aM \quad ...(1)$$

$$dL/dt = bNM - hL - mL^2 \quad ...(2)$$

$$dM^*/dt = cMN^* + pL^* - qM^* \quad ...(3)$$

$$dL^*/dt = rM^* + eLL^* - sL^* \quad ...(4)$$

$$dN^*/dt = fNM^* - uN^* \quad ...(5)$$

Each equation takes into account the following processes.

(1) Generation of adult uninfected mosquitoes (at a rate kL) from larvae and the removal of mosquitoes (at a rate constant aM) due to their mortality and conversion into infected mosquitoes.
(2) Generation of uninfected larvae (at a rate bNM) by uninfected mosquitoes, their removal due to mortality and metamorphosis into adult mosquitoes (at a rate hL) and interspecific interaction (at a rate mL^2).
(3) Generation of infected mosquitoes by healthy ones feeding on human hosts, maturing infected larvae (at rates cMN^* *and* pL^*, respectively) and removal of infected mosquitoes due to their mortality (at a rate qM^*).
(4) Generation of infected larvae by infected mosquitoes (at a rate rM^*), infection of healthy larvae by infected larvae in the pool (at a rate eLL^*), their removal due to mortality and conversion into adult infected mosquitoes (sL^*).
(5) Generation of human infectives *via* infected mosquito biting (at a rate fNM^*) and their removal due to recovery (at a rate uN^*).

Effects due to virus serotypes and immunity have been ignored as they influence mainly the long term progression of the disease.

Parameters k, r and p are generation constants, whereas a, h, q, s and u are removal constants. Both sets of these parameters have dimensions T^{-1}. Remaining parameters b, m, c, e and f are interaction coefficients of dimensions L^2T^{-1}. All the parameters in equations (1) - (5) (defined positive) are biologically meaningful measurable quantities. They are intrinsic to the system but influenced by external conditions such as climate and anthropogenic factors in the environment.

MATHEMATICAL ANALYSIS

To arrive at biologically meaningful inferences, the above equations are analyzed as follows:

The dynamical systems (1) – (5) have an equilibrium point $M = 0, L = 0, M^* = 0, L^* = 0, N^* = 0$ and second equilibrium for set of non-zero values for M, L, M^*, L^* and N^*. The stability analysis of these points is complicated by the necessity of solving quantic equations, which cannot be solved analytically. However, the equations (1) – (5) can be used to understand how a dengue epidemic may be initiated when an inoculum of virus carrying mosquito eggs hatches in a larval habitat.

Equations (1) and (2) describing the breeding of uninfected mosquitoes de-coupled from infective sector have two equilibrium points,

$$L = 0, M = 0 \quad ...(6)$$

$L_o = 1/m\ (bNk/a\text{-}h),\ M_o = k/am\ (bNk/a - h)$ ...(7)

Clearly, physically meaningful solutions exist, provided $N > ha/bk$.

To examine the behaviour of the system at the equilibrium point $L = 0$, we substitute,

$L = 0 + \delta L;\ M = 0 + \delta M$, where δL and δM are small deviations of L and M from the equilibrium value in equations (1) and (2) to obtain the linearized equations.

$$d(\delta M)/dt = -a\delta M + k\delta L \quad ...(8)$$

$$d(\delta L)/dt = bN\delta M - h\delta L \quad ...(9)$$

Equations (8) and (9) have a solution of the form,

$$\delta M = a_1 \exp(\lambda_1 t) + b_1 \exp(\lambda_2 t),\ \delta L = a_2 \exp(\lambda_1 t) + b_2 \exp(\lambda_2 t) \quad ...(10)$$

where, $\lambda_1, \lambda_2 = \{-(a + h) \pm \sqrt{[(a+h)^2 + 4(bkN - ah)]}\}/2$ ...(11)

The condition $N > ha/bk$ ensures $\lambda_1 > 0$.

Thus the origin $M = 0, L = 0$ of the dynamical system described by the equations (1) and (2) is unstable as any deviation from the equilibrium tends to increase exponentially, indicating that complete eradication of mosquitoes and larvae and maintaining that situation is not realistic. Similarly to examine the mosquito-larvae system at the second equilibrium point (7), we insert $L = L_o + \Delta L\ ;\ M = M_o + \Delta M$ in equations (1) and (2) to obtain the linearized equations,

$$d(\Delta M)/dt = -a\Delta M + k\Delta L \quad ...(12)$$

$$d(\Delta L)/dt = bN\Delta M - (h + 2mL_o)\Delta L \quad ...(13)$$

Equations (12) and (13) have a solution of the form,

$$\Delta M = A_1 \exp(\Lambda_1 t) + B_1 \exp(\Lambda_2 t)\ ,\ \Delta L = A_2 \exp(\Lambda_1 t) + B_2 \exp(\Lambda_2 t) \quad ...(14)$$

where ,

$$\Lambda_1, \Lambda_2 = -(h+a + 2mL_o) \pm \sqrt{[(h+a + 2mL_o)^2 - 4(ah + 2maL_o - bNk)]} \quad ...(15)$$

Equation (7) and condition $N > ha/bk$ show that both Λ_1, Λ_2 are positive, confirming that the equilibrium point $M = M_o$, $L = L_o$ is unstable.

Suppose an inoculum of infected larvae is introduced into a larval habitat in a stabilized mosquito-larvae system, and then the time evolution of the infection could be described by the following equations, where we have replaced M and L in equations (2)–(5) by M_o and L_o, respectively.

$$dM^*/dt = c M_o N^* + pL^* - qM^* \quad ...(16)$$

$$dL^*/dt = rM^* + L_o L^* - sL^* \quad ...(17)$$

$$dN^*/dt = fNM^* - uN^* \quad ...(18)$$

When uninfected mosquitoes and larvae are in large excess, the initial growth of the infection is fairly well represented by equations (16) – (18), which assume that the population densities of healthy mosquitoes (M_o) and larvae (L_o) remain unaltered. The system defined by equations (16) – (18) has equilibrium,

$$M^* = N^* = L^* = 0 \quad ...(19)$$

and the solution of the equations (16) – (18) can be written in the form,

$$M^* = A^*_1 \exp(\lambda^*_1 t) + B^*_1 \exp(\lambda^*_2 t) + C^*_1 \exp(\lambda^*_3 t) \quad ...(20)$$

$$L^* = A^*_2 \exp(\lambda^*_1 t) + B^*_2 \exp(\lambda^*_2 t) + C^*_2 \exp(\lambda^*_3 t) \quad ...(21)$$

$$N^* = A^*_3 \exp(\lambda^*_1 t) + B^*_3 \exp(\lambda^*_2 t) + C^*_3 \exp(\lambda^*_3 t) \quad ...(22)$$

where, λ^*_1 , λ^*_2 , λ^*_3 are the roots of the cubic equation

$$(\lambda^* + u)[(\lambda^* + q)(\lambda^* - v) - rp] + fNcM_o(v - \lambda^*) \quad ...(23)$$

with $v = eL_o - s$

Consider the situation where the virus propagation is triggered only by infected eggs hatching to produce infected larvae and their maturation to adult mosquitoes. Arrestment of virus propagation by human host route is ensured if we set $c = 0$. Under this condition, the three roots of the cubic equation are,

$$\lambda^*_1 = -u \quad ...(24)$$

$$\lambda^*_2 = 1/2\{-(q - v) + \sqrt{[(q + v)^2 + 4rp]}\} \quad ...(25)$$

$$\lambda*_3 = 1/2 \{ -(q - v) - \sqrt{[(q + v)^2 + 4rp]} \} \quad ...(26)$$

The second root $\lambda*_2$ is a positive definite that provided,

$$qv + rp > 0 \quad ...(27)$$

Condition (27) is satisfied for all values of r and p, if $v > 0$, i.e.,

$$L_o > s/e \quad ...(28)$$

The first and the third roots ($\lambda*_1$ and $\lambda*_3$) are always negative and the existence of at least one positive root $\lambda*_3$ of equation (23) dictates instability to the system. Thus if the larval population density exceeds a critical value $L_c = s/e$, the seeds infected larvae introduced into a healthy larval habitat could initiate an exponentially growing population of infected mosquitoes. The time constant $1/\lambda*_2$ for this process could be relatively short as it decreases with the increase of the population density L_o of healthy larvae. The eggs of infected mosquitoes carry the virus and in dry weather the eggs survive in dormant condition for months. Spells of heavy rain transferring infected eggs to mosquito breeding sites could establish dengue infestation of epidemic proportions, if inter-larval virus transfer occurs. Infected larvae, which mature to female adult infected mosquitoes will also continue the main chain *via* transmission to the human host. When the environment is contaminated with dengue virus infected mosquito eggs, the occurrence of habitats densely populated with healthy larvae poses a serious threat, even if inter-larval virus transfer happens at rates slower than other transmission mechanisms. Short spells of rain of duration $1/\lambda*_2$ or more could generate significant populations of infected mosquitoes without the participation of infected humans. The virus evolving to acquire this capability as a viable strategy for survival is not ruled out. Prolonged incubation *of Aedes aegypti* (L.) eggs enhances vertical transmission of dengue possibly because the virus replicates within the egg. Consequently horizontal transmission of the virus among larvae in the aquatic habitat may also be enhanced during incubation in dry weather.

When $e = 0$, the condition (28) reduces to,

$$rp > qs \quad ...(29)$$

The parameter s is essentially greater than p, because s includes the removal of infected larvae due to their mortality as well as their metamorphosis into infected mosquitoes. Therefore, unless q (parameter determining mortality of infected mosquitoes) is sufficiently small the condition (30) cannot be readily satisfied, implying a negative value for $\lambda*_2$. An important conclusion inferred from the above argument is that, without human intervention (i.e. when $c = 0$), vertical transmission alone is most unlikely to sustain the dengue virus. The situation is different in the case of inter-larval transmission of the virus. Here, even without a human intervention in the cycle, an explosive population of infected mosquitoes could be generated if the larval population exceeds the threshold s/e. The explosion is triggered by the release of infected eggs into densely populated larval pools.

SUMMARY

Admittedly, the model is speculative in the sense that inter-larval transmission of the dengue virus has not been observed under natural conditions. However, recent laboratory experiments have presented evidence that the virus could spread among larvae in an aqueous habitat (Bara *et al*., 2013). The model demonstrates that without human involvement in the disease transmission cycle, vertical propagation alone is most unlikely to sustain the dengue virus. However, the situation is different if the inter-larval transmission of the virus also happens in the natural habitat. Here, even without a human intervention in the cycle, an explosive population of infected mosquitoes could be generated, if the larval population exceeds the threshold value (highly sensitive to external factors). The explosion is triggered by the release of infected eggs into densely populated larval pools. As infected mosquito eggs could survive in the environment (even under dry conditions), a heavy spell of rain could transport the disease to new locations.

CONCLUSION

The best known mode of dengue transmission is *via* virus mediating the vertebrate host and the adult mosquito horizontally. Recently, the occurrence of vertical or transovarial transmission has been confirmed and its importance in the epidemiology of the disease understood. It is not clear whether this is a subsequent evolutionary adaptation or had been in existence for 'ever'. Transovarial transmission assists the virus to survive under conditions of prolonged dry weather (Rohani *et al*., 2008). The present model indicates that this mode of virus transmission alone, without human intervention is unlikely to sustain the virus. A third possible mode of transmission is spread of the virus in the aqueous larvae habitat. A few infected larvae produced by the hatching of infected eggs could infect majority of the healthy larvae. Larvae-to-larvae dengue virus transmission has not been

shown to happen in nature, although recent laboratory experiments hint to this possibility. The present work, having examined the problem in a theoretical model, concludes that inter-larval virus migration could lead to more intense epidemics in situations where larval population density exceeds a critical limit. Furthermore, the model shows that inter-larval virus transmission could initiate explosive populations of infected mosquitoes without human involvement in the cycle. As virus evolving in this direction greatly favours their survival, its adoption of such an advantageous option cannot be ruled out. The precaution against this potential threat should be the planning of long term larval control measures. Surveillance of mosquito breeding pools for dengue virus infected larvae is also important.

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