EPIDEMIC DYNAMICS OF A VECTOR-BORNE DISEASE ON A VILLAGES-AND-CITY STAR NETWORK WITH COMMUTERS

MPOLYA, Emmanuel Abraham

Doctor of Philosophy (PhD)

Department of Evolutionary Studies of Bio-systems (ESB),
School of Advanced Sciences,
The Graduate University for Advanced Studies (SOKENDAI),
Japan

March, 2014

A thesis submitted to the

Department of Evolutionary Studies of Bio-systems (ESB),

School of Advanced Sciences,

The Graduate University for Advanced Studies (SOKENDAI) in

partial fulfillment of the requirements for the degree of Doctor of

Philosophy

PhD advisory committee members:

Dr. IWASA, Yoh	Kyushu University
Dr. NISHIURA, Hiroshi	The University of Tokyo
Dr. SASAKI, Akira	SOKENDAI
Dr. INNAN, Hideki	SOKENDAI
Dr. OHTSUKI, Hisashi	SOKENDAI

Table of Contents

(i)   List of Publications

1) **Mpolya E.A**., Yashima K., Ohtsuki H., Sasaki A., Epidemic dynamics of a vector-borne disease on a villages-and-city star network with commuters. *Journal of Theoretical Biology* (in press), 2013, http://dx.doi.org/10.1016/j.jtbi.2013.11.024.

2) Furuse Y., Suzuki A., Kamigaki T., **Mpolya E.A**., Khandaker I., Oshitani H., Viruses That Cross Borders: Factors Responsible for Global Dissemination of Viral Infections, *Intervirology* ; 54(5): 246–252, 2011, http://dx.doi.org/10.1159/000320967.

3) **Mpolya E.A**., Furuse Y., Nukiwa N., Suzuki A., Kamigaki T., Oshitani H., Pandemic (H1N1) 2009 virus viewed from an epidemiological triangle model. *Romanian Journal of Infectious Diseases*, 13(1): 25-33, 2010. [*Reprint*]

4) **Mpolya E.A**., Furuse Y., Nukiwa N., Suzuki A., Kamigaki T., Oshitani H., Pandemic (H1N1) 2009 virus viewed from an epidemiological triangle model. *Journal of Disaster Research*, 4(5): 356-364, 2009.

(ii) Acknowledgements

(iii) Abstract

We develop a star-network of connections between a central city and peripheral villages and analyze the epidemic dynamics of a vector-borne disease as influenced by daily commuters. We obtain an analytical solution for the global basic reproductive number R_0 and investigate its dependence on key parameters for disease control. We find that in a star-network topology the central hub is not always the best place to focus disease intervention strategies. Disease control decision is sensitive to the number of commuters from villages to the city as well as the relative densities of mosquitoes between villages and city. With more commuters it becomes important to focus on the surrounding villages. Commuting to the city paradoxically reduces the disease burden even when the bulk of infections are in the city because of the resulting diluting effects of transmissions with more commuters. This effect decreases with heterogeneity in host and vector population sizes in the villages due to the formation of peripheral epicenters of infection. We suggest that to ensure effective control of vector-borne diseases in star networks of village and cities it is also important to focus on the commuters and where they come from.

1. Chapter One: Introduction

Thanks to the development of the concept of metapopulation in ecology, our understanding of epidemic dynamics of infectious diseases in connected populations has increased immensely. Metapopulations are groups of interconnected populations that are subject to semi-independent local dynamics(Adams and Kapan, 2009). Classical ecological assumptions of metapopulations are; that space is discrete with some patches suitable for habitation by a focal species and some patches not; that habitat patches have equal areas and isolation; that local populations in the metapopulation have entirely independent (uncorrelated) dynamics; and that the exchange rate of individuals among local populations is so low that migration has no real effect on local dynamics in the existing populations. In addition, it is said that the classical hallmarks of a true metapopulation are; population turnover (births and deaths), local extinctions and colonization(Hanski, 1998; Hanski and Gaggiotti, 2004; Hanski et al., 1997).

These classical ideas from ecology have been imported into the realm of epidemiology of infectious diseases. For example, for microparasitic infections such as viruses and bacteria, each susceptible host is a potential patch of a favorable habitat. Propagules from infected patches can colonize (infect) others (susceptible hosts), followed by parasitic multiplication and local growth of a parasite population(Keeling et al., 2004). More importantly, hosts are usually structured into communities of local populations within which contacts among hosts are more frequent than between such communities. We therefore have two scales for the spatio-temporal dynamics and

persistence of parasites; infrapopulation scale (a local population scale; parasite within host) and the metapopulation scale (spatial and/or social aggregation within hosts) (Keeling et al., 2004).

Therefore metapopulation concepts help us understand behaviors of disease dynamics at a higher spatial scale. Through determination of key metapopulation characteristics relevant to disease dynamics a deeper and better understanding of disease behavior and consequent potential disease control strategies can be achieved.

At the infrapopulation scale (at a host-parasite level) we have different modes of transmission of parasites. Infectious diseases can be transmitted either directly, such as influenza, or indirectly, such as vector-borne diseases like malaria. From a modeling perspective the dynamics of directly transmitted diseases are simpler than those of vector-borne diseases because of the presence of an intermediate host in the later. At a metapopulation scale dynamics of vector-borne diseases will be sensitive to the different ways we assume about the agent of connectivity. Some studies have considered static hosts connected by mobile zoonotic vectors as in the epidemic dynamics of outbreaks of bubonic plague in which rat movements resulted in very weakly connected human subpopulations (Keeling and Gilligan, 2000). Other commentators have assumed static vector populations connected by mobile hosts as in the epidemic dynamics of dengue (Adams and Kapan, 2009; Luz et al., 2003). These considerations are based on different biological facts of vectors such as life span and physiology; for instance in the case of bubonic plague it was assumed that the plague is driven by the dynamics of disease in the rat populations, considering the fact that rats

are mammals, it makes sense to use this assumption. While when the vectors are much weaker like mosquitoes, dynamics of diseases among mobile hosts is usually assumed to drive dengue and malaria epidemics.

In my study we consider a specific structure of the metapopulation, specifically as a star network. In my network a centrally located city is connected to arbitrary number of surrounding villages. Focusing specifically on malaria we investigate how movements of hosts between the city and surrounding villages determine the epidemic dynamics of malaria and consequent control strategies. In the next section we give an overview of the mathematical theory of disease dynamics and control. We argue that the development of the theory in infectious diseases was essentially a search for a threshold parameter similar to what was done in ecology and demography. In chapter two the main research is presented which will include the model, its analysis, results, discussion and conclusion

Mathematical theory for vector-borne disease control: search for R_0

In this section I review the literature to trace the development of the mathematical theory of infectious diseases. The focus will be on vector-borne diseases as much as possible. The main argument in this section is that the history of mathematical theory of infectious diseases is simply the history of the search for a threshold parameter in epidemiology, the so-called basic reproductive number, R_0.

The first recorded application of mathematical methods to inform decisions of public health importance was undertaken by Daniel Bernoulli in 1760. He investigated

theoretically whether inoculation against smallpox should be encouraged even if it was sometimes a deadly operation (Bacaer, 2011; Dietz and Heesterbeek, 2002). While Bernoulli's analysis did not produce explicitly a concrete concept of a threshold parameter it laid a foundation for application of mathematical concepts in understanding infectious diseases dynamics.

After Bernoulli and his contemporaries' pioneer attempts at using mathematics to investigate dynamics of infectious diseases in the early 18th century, about one hundred years would pass before another recorded attempt would be undertaken. This came in the 1900s with the works of Sir. Ronald Ross. Ronald Ross worked with malaria. Not only did Ross prove experimentally that malaria was transmitted by Anopheline mosquitoes through their bites of hosts, but also he went on to suggest that in order to eliminate malaria in a given area it was important to kill only a certain amount of mosquitoes, the critical density, and not necessarily all of them. This claim, that it was possible to eliminate malaria by attacking mosquitoes, was met with skepticism. In 1911 Ross built a mathematical model of transmission for malaria in order to support his claim (Heesterbeek, 2002; Ross, 1911). Ross was the first to introduce the concept of a threshold density of mosquitoes above which the disease becomes endemic and below which the disease dies out. It was with this result that he backed up his claim that it was not necessary to exterminate all mosquitoes in an area in order to eliminate malaria. While Ross defined a concept of a threshold in terms of population density of mosquitoes, he did not generalize it to directly transmitted diseases.

Around the time of Ross's work, another analyst by the name of Alfred J. Lotka was defining threshold concepts in demography, ecology and epidemiology. Notably in demography, Lotka defined "net fertility" as the expected number of female offsprings born to one female during her entire life (Heesterbeek, 2002; Smith et al., 2012). However, despite the fact that Lotka worked in all three interrelated fields of ecology, demography and epidemiology, he did not substantively define the threshold concept that was specifically addressing epidemiology at the time. The closest he could come to linking demography with epidemiology was to remark that growth of population and spread of diseases are very similar from a mathematical point of view.

After Ross and Lotka, a duo of modelers interested in presenting a mathematically coherent theory of infection dynamics came into the scene. These were Anderson Gray McKendrick and William Ogilvy Kermack (Kermack and McKendrick, 1933; Kermack and McKendrick, 1939; Kermack and McKendrick, 1932; Kermark and Mckendrick, 1927; M'Kendrick, 1925). Kermack and McKendrick made up for Ross' omission of generalizing the threshold property beyond vector-borne diseases. They proved the threshold theorem, which states that in order for an infectious agent to be sustained in a population, the population density N has to exceed a certain critical density $N_c = 1/A$, where $A = \int_0^\infty \phi_t B_t \, dt$: (B_t is the probability that a newly infected individual is still infected at infection-age t, and ϕ_t is the infectivity at infection-age t) (Heesterbeek, 2002). This is a more general formulation of the threshold property formerly derived by Ross.

The idea of a threshold property in epidemiology was therefore more rigorously

presented by Kermack and McKendrick. It was more formalized in the 1950s

particularly with respect to vector-borne diseases through the works of George

MacDonald. In 1952 George MacDonald published a paper titled; "The analysis of

equilibrium in malaria" (Macdonald, 1952), in which he formally coined the term "basic

reproductive rate" and defined it as the number of infections distributed in a community

as the result of the presence in it of a single primary non-immune case. He also assigned

a symbol z_0 to this quantity.

After this flurry of activities in the 1950s a period of inactivity would follow

during which the threshold concept in epidemiology was hardly addressed in the

literature. Some commentators attribute this trend to the failure of the Global Malaria

Eradication Program which had relied heavily on the threshold concept (Heesterbeek,

2002). However, things would change for better beginning from mid 1970s to 1980s.

During this era several scientists endeavored to establish practical applications of the

threshold concept in epidemiology for control of epidemics. They established the basic

reproductive number as an important parameter for both theoretical and practical

epidemiology. Notable actors during this time include Hethcote and Dietz and later on

in the 1980s to early 1990s, Robert May and Roy Anderson (Heesterbeek, 2002).

The 1990s witnessed the establishment of mathematical tools for calculating the

basic reproductive number in heterogeneous populations (Diekmann et al., 1990) after

which this threshold quantity became a core ingredient of most mathematical works in

epidemiology. The development in computing powers since mid-1990s enabled analysts

to incorporate high-dimensions in their analytical structures with the consideration of networks and metapopulations in the dynamics of infections diseases (Hanski et al., 1997; Keeling et al., 2004). The behaviors of the basic reproductive number could be studied using more realistic models.

From the review presented, I argue that the maturity of the mathematical theory of infectious diseases epidemiology came with the establishment of the basic reproductive number. This is because the basic reproductive number provides us with several pieces of information such as; measure of the possibility of an epidemic in a totally susceptible population, measure of a disease burden in an ongoing epidemic, and measure of the amount of effort required to stop an epidemic (Smith et al., 2007). Therefore, defining this parameter in any infectious disease epidemic system gives the analyst immense opportunities to inform on various practical and theoretical possibilities related to disease spread and control.

In the sections that follow I describe my research in detail. My research is about the spread of vector-borne disease in a metapopulation with a shape of a star network. At the time of conception of this research there was no analyst who had ever analyzed epidemic dynamics of a vector-borne disease in a metapopulation shaped as a star network. I define the basic reproductive number of this system and extract vital information key to control of the vector borne disease.

2 Chapter Two: Human mobility and the epidemiology of vector-borne diseases

The role of host mobility in the epidemic dynamics of vector-borne diseases was not taken into consideration during the malaria eradication programs of the 1950s and 1960s. This was cited as one of the reasons for failure of that program (Bruce-Chwatt, 1968; Prothero, 1977). Since then there has been a substantial increase in the human population size, revolutions in transportation technologies and a sharp rise in urbanization. Poor levels of hygiene in most tropical cities has led to a rise in incidence of vector-borne diseases such as malaria and dengue (Knudsen and Slooff, 1992; Robert et al., 2003; Sharma, 1996).

Concentration of most economic and social activities in cities has led to the formation of mobility patterns of hosts between these central hubs and the surrounding villages. When hosts move between the central city and peripheral villages they form a network structure of contact between themselves and the vector populations of the two spatial places. Since malarial vectors have short maximum flight distances, such as about 691 metres per life time for *Anopheles funestus* and *Anopheles gambiae* (Midega et al., 2007), it is effectively the host movements and their contact with stationary vectors that determine epidemic dynamics between two spatially separate localities.

Commuters move back and forth between two subpopulations forming a connecting link that couples the epidemic dynamics of those subpopulations (Barrat et al., 2008; Colizza and Vespignani, 2008). This coupling forms a system of populations

with semi-independent local dynamics, called meta-populations (Adams and Kapan, 2009). An infection event at one spatial point could trigger a full-blown outbreak at another spatial point in this meta-population structure making the study of the role of connectivity important for disease control (Hanski and Gaggiotti, 2004; Hanski et al., 1997; Keeling et al., 2004).

Theoretical studies on vector-borne disease dynamics in interconnected populations have produced several useful results. For example, in meta-populations mobility leads to disease occurrence among connected patches and speeds up the time for disease to reach equilibrium in the system (Cosner et al., 2009; Hsieh et al., 2007; Torres-Sorando and Rodri'guez, 1997). Besides, for heterogeneous vector densities among patches the disease burden is determined by the patch with the largest vector subpopulation and decreased with a greater degree of mixing of hosts (Adams and Kapan, 2009). While most studies do not elicit specific network structure, we believe that geographical relationships between villages and cities are approximately structured as a star-network in most tropical cities (Briggs and Mwamfupe, 2000) and that host commute patterns are not random (Gonzalez et al., 2008). We construct a simple star-network in which daily commuters connect an arbitrary number of villages to a central city, and incorporate a vector-borne disease transmission epidemic model to understand the influence of meta-population parameters on the epidemic dynamics.

The most important parameter in epidemiology is the basic reproductive number, defined as the total number of secondary infections resulting from a single infectious agent after its introduction into a totally susceptible population throughout

16

the agent's infectious period (Anderson and May, 1992; Arino and Van Den Driessche, 2003; Diekmann et al., 1990; Dietz, 1993; May and Anderson, 1991; Shao, 1999). Because of the importance of the basic reproductive number in understanding infectious diseases epidemiology and guiding their public health interventions (Ferguson et al., 2006; Ferguson et al., 2003; Ferguson et al., 2005), we derive this quantity explicitly and investigate how it can inform disease control decisions as well as the behavior of the epidemic.

3   Chapter Three: The Model

Epidemiological dynamics in a homogeneous star network

Network structure of the host population assumed here is a star with daily
commuters between the central node (city) and each of m peripheral nodes (or villages)
(Figure 1).

For mathematical simplicity we assume that all peripheral populations have
identical numbers of residents, mosquitoes and commuters to the city. This assumption
is relaxed later. We also assume that infection dynamics of all peripheral populations are
synchronized. The rate of movement of hosts is not affected by their disease statuses.

We adopt frequency-dependent transmission in a susceptible-infectious-
susceptible (SIS) epidemic model for hosts (Anderson and May, 1992; Macdonald,
1956; May and Anderson, 1991; Ross, 1911). We adopt a susceptible-infectious (SI)
epidemic model for mosquito vectors because once infected they do not recover from
infection. There is no vertical transmission within the mosquito population; that is,
newborns do not acquire infection from their parents. Susceptible mosquitoes are
supplied by newborns. In this construction an infection of a susceptible host occurs
through a bite by an infected mosquito, and an infection of a susceptible mosquito
occurs through its bite of an infected host. There is no direct transmission between hosts
or between mosquitoes.

The variables describing epidemic dynamics of the SIS model among hosts and the SI model among mosquitoes are as follows (see also Table 1). The number of susceptible and infected mosquitoes is denoted respectively by x_u and y_u *in the central city* (or urban area, and hence the subscript *u*), and by x_r and y_r *in a peripheral village* (or rural area, and hence the subscript *r*). On the other hand, the number of susceptible and infected hosts is denoted respectively by X_u and Y_u *in the central city*; by X_c and Y_c in those hosts commuting (and hence the subscript *c*) from a peripheral village to the central city every day and staying in the city only during daytime; and by X_r and Y_r for resident hosts who stay in a *peripheral village* for the whole day.

During daytime in the city, there are $X_u + mX_c$ susceptible hosts and $Y_u + mY_c$ infected hosts (where m stands for the number of peripheral villages as noted before), and x_u susceptible mosquitoes and y_u infected mosquitoes. During nighttime, $m(X_c + Y_c)$ people go back to their own villages, leaving only $X_u + Y_u$ in the city.

In a frequency-dependent transmission we assume that mosquitoes bite hosts at a constant rate. Transmission is therefore sensitive to the number of hosts available to receive the bites. Infection dynamics are separated into daytime and nighttime dynamics. The people who commute to the city can be infected when being bitten by an infected mosquito in the city during daytime and when being bitten by an infected mosquito in the village during nighttime. Writing only dynamics for infected components (see the Appendix for full ODEs) we have the following expressions for dynamics at any arbitrary point in daytime (time is measured in units of days) $k \leq t < k + 0.5$ $(k = 0,1,2...)$:

$$\frac{dY_u}{dt} = \frac{b_d \tau X_u}{N_u + mN_c} y_u - \gamma Y_u, \tag{1}$$

$$\frac{dy_u}{dt} = \frac{b_d \tau'(Y_u + mY_c)}{N_u + mN_c} x_u - Dy_u, \tag{2}$$

$$\frac{dY_c}{dt} = \frac{b_d \tau X_c}{N_u + mN_c} y_u - \gamma Y_c, \tag{3}$$

$$\frac{dy_r}{dt} = \frac{b_d \tau' Y_r}{N_r} x_r - Dy_r, \tag{4}$$

$$\frac{dY_r}{dt} = \frac{b_d \tau X_r}{N_r} y_r - \gamma Y_r, \tag{5}$$

where b_d is the rate at which a mosquito bites a host in daytime, τ is the per bite probability that the disease is transmitted from an infected mosquito to a susceptible host and τ' is the per bite probability that the disease is transmitted from an infected host to a susceptible mosquito. γ is the rate at which an infected host recovers (and becomes susceptible again) and D is the mortality rate of adult mosquitoes. Also, N_u, N_c and N_r are the respective numbers of host residents in the city, commuters from a village and daytime village residents. M_u and M_r are the respective numbers of mosquitoes in the city and in a single village. Therefore $X_u(t) = N_u - Y_u(t)$, $X_c(t) = N_c - Y_c(t)$, $X_r(t) = N_r - Y_r(t)$, $x_u(t) = M_u - y_u(t)$ and $x_r(t) = M_r - y_r(t)$ are the numbers of susceptible hosts and mosquitoes in each compartment. The rate at which a particular host is bitten by a particular mosquito during the day in the city is $b_d/(N_u + mN_c)$ and is b_d/N_r in one village.

Nighttime epidemiological dynamics are derived similarly for any time point

$k+0.5 \leq t < k+1 \ (k=0,1,2,....)$ as

$$\frac{dY_u}{dt} = \frac{b_n \tau X_u}{N_u} y_u - \gamma Y_u \tag{6}$$

$$\frac{dy_u}{dt} = \frac{b_n \tau' Y_u}{N_u} x_u - D y_u \tag{7}$$

$$\frac{dY_c}{dt} = \frac{b_n \tau X_c}{N_r + N_c} y_r - \gamma Y_c \tag{8}$$

$$\frac{dy_r}{dt} = \frac{b_n \tau' \left(Y_r + Y_c\right)}{N_r + N_c} x_r - D y_r \tag{9}$$

$$\frac{dY_r}{dt} = \frac{b_n \tau X_r}{N_r + N_c} y_r - \gamma Y_r \tag{10}$$

where b_n is the mosquito biting rate at night.

In the following sections we derive an analytical solution for the global basic

reproductive number R_0 of the star network and investigate its sensitivity to key

population and networks parameters relevant to disease control.

4 Chapter Four: Results

Basic reproductive number R_0 for the meta-population

Linearization of epidemic dynamics (1)-(10) by assuming that infected densities are small near the disease-free equilibrium results into a system;

$$\frac{d\mathbf{y}}{dt} = \begin{cases} A_d\mathbf{y}(t), & \text{for } t \text{ at daytime } (k \le t < k+0.5; \quad k = 0,1,2,\cdots), \\ A_n\mathbf{y}(t), & \text{for } t \text{ at nighttime } (k+0.5 \le t < k+1; \quad k = 0,1,2,\cdots), \end{cases} \quad (13)$$

where $\mathbf{y} = (Y_u, y_u, Y_c, y_r, Y_r)^T$ with T denoting transposition of vector $\mathbf{y}$, and

$$A_d = \begin{pmatrix} -\gamma & \beta_1\tau N_u & 0 & 0 & 0 \\ \beta_1\tau' M_u & -D & \beta_1\tau' M_u m & 0 & 0 \\ 0 & \beta_1\tau N_c & -\gamma & 0 & 0 \\ 0 & 0 & 0 & -D & \beta_2\tau' M_r \\ 0 & 0 & 0 & \beta_2\tau N_r & -\gamma \end{pmatrix}, \quad (14a)$$

$$A_n = \begin{pmatrix} -\gamma & \beta_3\tau N_u & 0 & 0 & 0 \\ \beta_3\tau' M_u & -D & 0 & 0 & 0 \\ 0 & 0 & -\gamma & \beta_4\tau N_c & 0 \\ 0 & 0 & \beta_4\tau' N_r & -D & \beta_4\tau' M_r \\ 0 & 0 & 0 & \beta_4\tau N_r & -\gamma \end{pmatrix}, \quad (14b)$$

where

$$\beta_1 = \frac{b_d}{N_u + mN_c}, \; \beta_2 = \frac{b_d}{N_r}, \; \beta_3 = \frac{b_n}{N_u}, \text{ and } \beta_4 = \frac{b_n}{N_r + N_c} \; . \quad (15)$$

The solution to equation (13) for $t = k$ (integer) is given by

$$y(k) = y(0)e^{\frac{k}{2}(A_d + A_n)} = y(0)^{k\overline{A}}, \text{ where}$$

$$\overline{A} = \frac{A_d + A_n}{2}. \tag{16}$$

In the Appendix an equation for non-integer time point ($t \neq k$) is shown, which is a bit more complicated but it does not affect the subsequent calculations of the basic reproductive number by assuming that infection starts at $t = 0$, as in the next generation matrix method we count the cumulative number of secondary infections toward $t \to \infty$.

Equation (16) is the averaged matrix for daytime dynamics and nighttime dynamics. This calculation is possible because of linearization around the disease-free equilibrium. In the Appendix the basic reproductive number is calculated using the method of next-generation matrix (Diekmann et al., 1990; Diekmann et al., 2010; Diekmann et al., 2012; Heesterbeek, 2000; Heesterbeek, 2002), which after rearrangement gives the expression for the basic reproductive number R_0 for the whole system as

$$R_0 = \sqrt{\frac{\rho_1 + \rho_2 + \rho_3 + \rho_4}{2} + \sqrt{\frac{(\rho_1 + \rho_2 + \rho_3 + \rho_4)^2}{4} - (\rho_1\rho_3 + \rho_1\rho_4 + \rho_2\rho_4)}}, \tag{17}$$

where

23

$$\rho_1 = \frac{1}{D\gamma}\left(\frac{\beta_1+\beta_3}{2}\right)^2 \tau\tau' N_u M_u = \frac{\tau\tau' N_u M_u}{4D\gamma}\left(\frac{b_d}{N_u+mN_c}+\frac{b_n}{N_u}\right)^2,$$

$$\rho_2 = \frac{1}{D\gamma}\left(\frac{\beta_1}{2}\right)^2 \tau\tau' mN_c M_u = \frac{\tau\tau' mN_c M_u}{4D\gamma}\left(\frac{b_d}{N_u+mN_c}\right)^2,$$

$$\rho_3 = \frac{1}{D\gamma}\left(\frac{\beta_4}{2}\right)^2 \tau\tau' N_c M_r = \frac{\tau\tau' N_c M_r}{4D\gamma}\left(\frac{b_n}{N_r+N_c}\right)^2,$$

$$\rho_4 = \frac{1}{D\gamma}\left(\frac{\beta_3+\beta_4}{2}\right)^2 \tau\tau' N_r M_r = \frac{\tau\tau' N_r M_r}{4D\gamma}\left(\frac{b_d}{N_r}+\frac{b_n}{N_r+N_c}\right)^2,$$

(18)

are the basic reproductive numbers of infection cycles for: city residents and city mosquitoes (ρ_1), daytime commuters and city mosquitoes (ρ_2), returning nighttime commuters and village mosquitoes (ρ_3), and non-commuting village residents and village mosquitoes (ρ_4) (see Figure 2). See Appendix for the derivation of (17)-(18). More important applications of the explicit formula (17) for the whole system basic reproductive number is seen in sensitivity analyses discussed in next sections.

Sensitivity analysis of parameters to system basic reproductive number

Where should mosquito control be focused between the city and surrounding villages?

In this section we show how the analytical results for the basic reproductive number obtained in the last section (equation 17) can be used to design the control strategy. This is based on the derivation of the dependence of the global basic reproductive number R_0 on a given epidemiological or network parameters shown in details in the Appendix. Here we choose the number of mosquitoes in a village and the

city, M_r and M_u respectively as the target parameters for control of the vector-borne disease. We consider the relative impact on R_0 of proportional changes in the mosquito populations of city or villages. Since R_0 also estimates the effort required to control a disease (Smith et al., 2007), we are hereby answering the question of where to focus control effort for a certain predetermined fractional reduction in R_0 given a distribution of mosquitoes between the city and villages (see Appendix for full derivation). We obtain conditions when intervening in city will lead to more prevention of disease as

$$\frac{\partial R_0}{\partial(\log M_u)} > \frac{\partial R_0}{\partial(\log M_r)} \Leftrightarrow \frac{\rho_1 + \rho_2}{\rho_3 + \rho_4} > 1. \tag{20}$$

From equation (20) we see that focusing control efforts in the city is more effective when $\rho_1 + \rho_2 > \rho_3 + \rho_4$. But if it becomes such that $\rho_3 + \rho_4 > \rho_1 + \rho_2$ then focusing control efforts in villages becomes more effective. Substituting equation (18) into equation (20) results into an expression for a critical value, denoted hereby by θ_c which is related to the ratio of mosquito densities in the city and villages as

$$\frac{\partial R_0}{\partial(\log M_u)} > \frac{\partial R_0}{\partial(\log M_r)} \quad \text{if and only if} \quad \frac{M_u}{M_r} > \theta_c, \tag{21}$$

where

$$\left(\frac{M_u}{M_r}\right)_c = \theta_c = \frac{N_c\left(\dfrac{b_n}{N_r + N_c}\right)^2 + N_r\left(\dfrac{b_d}{N_r} + \dfrac{b_n}{N_r + N_c}\right)^2}{N_u\left(\dfrac{b_d}{N_u + mN_c} + \dfrac{b_n}{N_u}\right)^2 + mN_c\left(\dfrac{b_d}{N_u + mN_c}\right)^2}. \tag{22a}$$

25

or, since the total host population is $N = N_u + m\left(N_r + N_c\right)$ we define the proportions

of city residents as $p_u = N_u / N$, commuters as $p_c = mN_c / N$, and village residents as

$p_r = mN_r / N$, and write 22a as,

$$\left(\frac{M_u}{M_r}\right)_c = \theta_c = \frac{m\left[p_c\left(\dfrac{b_n}{p_r + p_c}\right)^2 + p_r\left(\dfrac{b_d}{p_r} + \dfrac{b_n}{p_r + p_c}\right)^2\right]}{p_u\left(\dfrac{b_d}{p_u + p_c} + \dfrac{b_n}{p_u}\right)^2 + p_c\left(\dfrac{b_d}{p_u + p_c}\right)^2}. \tag{22b}$$

To see how the strength of connections between city and village through

commuting affects the effective mosquito control in city and villages, we here fix the

proportion of city host population, p_u, and the number of villages, m in (22b), and

allow the proportion of commuters, p_c (and hence village hosts, $p_r = 1 - p_u - p_c$), to

vary so we can observe how θ_c varies with the proportion of commuters, p_c. Since θ_c

is a threshold value, it divides the region into two, each with different implications to

the focus of disease control as shown in Figure 3. In the region under the curve which

corresponds to $(M_u/M_r) < \theta_c$, reducing mosquito density in the surrounding villages by

a fixed factor is more effective in reducing R_0 than doing so in the city. The region

above the curve corresponds to $(M_u/M_r) > \theta_c$ when focusing on the central city is more

effective than focusing on the surrounding villages. From Figure 3 we observe that an

increase in commuters to the central city makes infections more likely to occur in the

surrounding villages making focus of mosquito control there more effective. This is

because in frequency-dependent transmission the efficiency of transmission depends on

the possibility of one person being bitten by a mosquito in succession; one to receive an

infection and the second to pass it on (Keeling and Rohani, 2011). When more

commuters move to the city, they leave a smaller number of people in the villages

making vector-borne disease transmissions more efficient there than in the city. Since

people in the city do not move, any increase in the number of hosts because of the

incoming commuters serves to make the possibility of a mosquito biting a host in two

successions less likely, lowering the infection risk.

Epidemic occurrence with intensity of village-to-city connections

(a) Homogeneous case

The host and vector meta-population structure we assume in this paper is quite

simple: a star network with the central city and m surrounding villages (Figure 1).

However, we can ask several important questions about the effects of host population

structure within this framework.

For subsequent analyses, we assume that the total nighttime population of city

residents, N_u, and the total nighttime villages residents, $m(N_c + N_r)$, are constant when

we vary the host population structure. Consequently, the total host population, denoted

by $N = N_u + m(N_c + N_r)$, is also kept constant. The total mosquito population

$M = M_u + mM_r$ is also kept constant. In numerical examples in this section we

assume, for simplicity, that the biting rates during day and night are the same:

$\left(\text{i.e., } b_d = b_n = b\right)$. The more general case of heterogeneous bite rates between day and

night ($b_d \neq b_n$) was also analyzed (see section 4 in Appendix) and yielded qualitatively

similar results to the homogeneous case reported in this section. Moreover, in addition to fractions of city residents, p_u, commuters, p_c, and village residents, p_r defined in equation 22b we define proportions of mosquitoes in the city as $q_u = M_u / M$ and in all villages as $q_r = mM_r / M$. For example, we can change the fraction of commuters by increasing the number N_c of daytime commuters while keeping the nighttime total population $m(N_c + N_r)$ constant, and ask how this changes the global basic reproductive number R_0.

We here examine whether or not increasing connectivity would increase R_0 when metapopulation is nearly isolated. This could be answered by looking at the partial derivative of R_0 with respect to p_c, $(\partial R_0 / \partial p_c)$, as $p_c \to 0$ while keeping $p_c + p_r = 1 - p_u$ constant. We find a paradoxical case where increasing connectivity (i.e., number of commuters) in the network decreases the basic reproductive number, lowering the possibility of disease occurrence (see full derivation in the Appendix). This happens if the following condition is true,

$$\frac{q_u}{q_r} > \frac{p_u}{1 - p_u} \ , \tag{23}$$

or simply if $q_u > p_u$ (as $q_r = 1 - q_u$), i.e. when mosquitoes are more concentrated in the city than their hosts. This simple condition remains the same even when daytime and nighttime biting rates are different (i.e., $b_d \neq b_n$).

Equation (23) shows that a paradoxical region in which there is decreasing possibility of disease occurrence with increasing connectivity exists when the ratio of mosquitoes to hosts in the city exceeds the ratio of mosquitoes to hosts in the villages.

This condition is shown graphically for homogeneous assumptions in Figure 4 (dark lines) showing the dependence of the basic reproductive number R_0 on the whole range of proportion of commuters p_c, and not just for $p_c \to 0$. The paradoxical region is observed in panels *b-d* (dark line). The reverse is true when hosts are more concentrated in the city than mosquitoes ($q_u > p_u$). This condition holds in panel *a* of Figure 4.

The paradoxical region of decreasing basic reproductive number with increasing number of commuters to the city occurs because movement of hosts acts to reduce the efficiency of infections in the city by decreasing the mosquitoes-to-hosts ratio while at the same time the increased efficiency of transmissions in the villages being not enough to compensate the decrease in the city. This paradoxical region becomes more pronounced with increasing mosquito density in the city (Figure 4d) as more commuters are needed before the epidemic can start increasing again. The sharp rise in the basic reproductive number at very high proportions of commuters is a direct artifact of frequency-dependency assumptions. That is when there are extremely small numbers of hosts left in the villages relative to the number of mosquitoes, making transmissions extremely efficient, leading to the observed sharp rise in the values of the basic reproductive number.

(b) Heterogeneous case

Furthermore, we investigated the influence of heterogeneity in the number of hosts and mosquitoes in the villages on the behavior of the paradoxical region. We fixed the number of city hosts at 20% of the total population and assumed that all villages had

the same proportion of commuters to the city. Keeping total host and total vector

populations in villages constant, heterogeneity was introduced through random

assignments of host and vector population sizes among a fixed number of villages using

a uniform distribution in a simplex (a space formed by possible values of proportions

allotted to villages) (see Appendix section 5 for details). While in the homogeneous

case all villages had the same numbers of hosts and vector populations, the

randomization in the heterogeneous case produced villages with various sizes of human

and vector populations. Field evidence suggests a high degree of clustering in mosquito

populations among villages (Keating et al., 2005; Mbogo et al., 2003) and our purpose

here was to imitate this heterogeneity using a simple probability distribution. Results

are shown in Figure 4 with grey lines.

Firstly, we observe that depending on the ratio of mosquitoes to hosts,

heterogeneity can increases the basic reproductive number even for lower values of the

proportion of commuters as seen in Fig 4a and 4b. With more mosquitoes in the city this

increase only occurs for higher proportions of commuters as seen in Fig 4c and 4d.

Random heterogeneity can result into some villages having higher numbers of

mosquitoes than that of humans leading to a formation of peripheral epicenters with

higher transmissions than in the homogeneous case. Also heterogeneity could result in

some mosquito to host ratios becoming smaller in some villages than in the

corresponding homogeneous case, but the existence of epicenters in villages with higher

mosquito to host ratios outweighs in the net effect. This result has direct implications

for surveillance systems, it is important to try to understand the demographic

30

characteristics of surrounding villages both in terms of their host and mosquito densities.

Secondly we observe that heterogeneity tends to narrow the paradoxical region. The paradoxical region depends on the relative densities of hosts and mosquitoes in an area. Heterogeneity in host and vector populations in villages leads to formation of peripheral epicenters with extremely efficient infections making the dilution effect of commuters in the city less important unless mosquito-to-human ratio is extremely high in the city as well, thereby narrowing the paradoxical region.

5   Chapter Five: Discussion

We constructed a simple star network model of connections between a central city and an arbitrary number of surrounding villages. Then we incorporated a classic epidemic model for vector-borne diseases in order to understand the effects of connectivity as effected by daily commuters on the epidemic dynamics and disease control decisions.

Through the method of next generation matrix we obtained an explicit expression for the basic reproductive number R_0 of the system. A basic reproductive number is an important quantity in epidemiology because it has implications in planning of public health interventions against infectious diseases by aiming to maintain its value below the threshold, which is unity (Anderson and May, 1992; Ferguson et al., 2006; Ferguson et al., 2003; Ferguson et al., 2005; Scherer and McLean, 2002). The behavior of the basic reproductive number can be more complicated at the threshold value; such as disease-free state being unstable even for $R_0 < 1$ (Hadeler and Van den Driessche, 1997; Van den Driessche and Watmough, 2000; Van den Driessche and Watmough, 2002) or the threshold vanishing altogether as in complex networks (Barrat et al., 2008). However, it provides a good theoretical approximation for most practical purposes of disease control (Anderson and May, 1992).

The primary goal of this research was to investigate explicitly the role that commuters play in affecting the behavior of an epidemic and the implications to disease

control in a defined network structure. Based on the basic reproductive number, two questions were asked and answered; first one was on effects of commuters on the decision of where to direct disease control efforts between the city and villages when we aim to reduce the basic reproductive number R_0 and the second one was on the effects of commuters on the overall behavior of the epidemic.

In a meta-population it is not always obvious where to focus disease control strategies because of the unknown influence of commuters as well as relative densities of mosquitoes to hosts. Besides, the disease control decision is normally a function of many factors such as economic, humanitarian, clinical and even political factors. Different points of view can give different prescriptions for disease control. For example, from an optimal control perspective some studies suggest focusing on subpopulations with the lowest number of infected hosts (Mbah and Gilligan, 2011; Rowthorn et al., 2009). Our study prescribes from the perspective of effectiveness of infections as influenced by commuters. We find that the decision of where to focus control efforts is sensitive to the proportion of commuters and the relative mosquito densities in the city and villages but an increase in the number of commuters from the villages to the city makes focusing on the surrounding villages more effective in vector-borne diseases. This is because when more and more people commute they make infections in the villages more effective thereby increasing chances of an epidemic in the whole meta-population.

We found that commuters can influence the epidemic dynamics by lowering the basic reproductive number in certain conditions. In frequency-dependent transmissions

the effective ratio of mosquitoes to hosts is key in determining the occurrence of an epidemic. When this ratio is high in the city (and therefore higher basic reproductive number) any increase in the commuters to the city lowers the basic reproductive number leading to a paradoxical region. On the other hand, when this ratio becomes higher in the surrounding villages than in the city the paradoxical regions narrows down as commuting has weaker effect in this case. Particularly, for higher mosquito to host population ratios in the city heterogeneity in host and vector populations in villages increases the basic reproductive number and narrows the paradoxical region because of formation of peripheral epicenters with highly efficient transmissions. Therefore, understanding the demographic dynamics of villages in terms of its hosts and vectors is important for planning disease control.

Our two results can be combined to inform disease control strategies. The first result emphasizes focusing control in the surrounding villages after determining key parameters which are commuters and the mosquito densities in city and villages; the second results emphasizes on the surveillance of the surrounding villages in order to capture those epicenters of infections. It is well known that rural tropical Africa has more vector borne disease transmissions than the urban Africa because of the presence of large vector populations and ubiquity of breeding sites in the former (Walker, 2002). Recent theoretical and empirical studies have shown that movements of hosts between two spatial points such as from villages to central cities is responsible for persistence of vector-borne diseases in cities despite control strategies (Adams and Kapan, 2009; Le Menach et al., 2011; Wesolowski et al., 2012). Our study has pinpointed one possible

way of how such movements affect disease control decisions and the behavior of the

epidemic dynamics of vector-borne diseases.

6. Chapter Six: Bibliography

Adams, B., Kapan, D. D., 2009. Man bites mosquito: understanding the contribution of human movement to vector-borne disease dynamics. *PloS one* 4, e6763.

Anderson, R. M., May, R. M., 1992. Infectious diseases of humans: dynamics and control. Oxford; Oxford University Press.

Arino, J., Van Den Driessche, P., 2003. The basic reproduction number in a multi-city compartmental epidemic model. *Positive Systems*, Springer, pp. 135-142.

Bacaer, N., 2011. A short history of mathematical population dynamics. London; Springer.

Barrat, A., Barthlemy, M., Vespignani, A., 2008. Dynamical processes on complex networks. Cambridge; Cambridge University Press.

Briggs, J., Mwamfupe, D., 2000. Peri-urban development in an era of structural adjustment in Africa: the city of Dar es Salaam, Tanzania. *Urban Studies* 37, 797.

Bruce-Chwatt, L., 1968. Movements of populations in relation to communicable disease in Africa. *East African Medical Journal* 45, 266.

Colizza, V., Vespignani, A., 2008. Epidemic modeling in metapopulation systems with heterogeneous coupling pattern: Theory and simulations. *Journal of Theoretical Biology* 251, 450-467.

Cosner, C., Beier, J. C., Cantrell, R. S., Impoinvil, D., Kapitanski, L., Potts, M. D., Troyo, A., Ruan, S., 2009. The effects of human movement on the persistence of

vector-borne diseases. *Journal of Theoretical Biology* 258, 550-60, http://dx.doi.org/10.1016/j.jtbi.2009.02.016 (S0022-5193(09)00075-7 [pii])].

Diekmann, O., Heesterbeek, J., Metz, J., 1990. On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biology* 28, 365-382.

Diekmann, O., Heesterbeek, J., Roberts, M., 2010. The construction of next-generation matrices for compartmental epidemic models. *Journal of The Royal Society Interface* 7, 873-885.

Diekmann, O., Heesterbeek, H., Britton, T., 2012. Mathematical Tools for Understanding Infectious Disease Dynamics. Princeton; Princeton University Press.

Dietz, K., 1993. The estimation of the basic reproduction number for infectious diseases. *Statistical Methods in Medical Research* 2, 23.

Dietz, K., Heesterbeek, J., 2002. Daniel Bernoulli's epidemiological model revisited. *Mathematical Biosciences* 180, 1-21.

Ferguson, N., Cummings, D., Fraser, C., Cajka, J., Cooley, P., Burke, D., 2006. Strategies for mitigating an influenza pandemic. *Nature* 442, 448-52, http://dx.doi.org/10.1038/nature04795 (nature04795 [pii]).

Ferguson, N. M., Keeling, M. J., Edmunds, W. J., Gani, R., Grenfell, B. T., Anderson, R. M., Leach, S., 2003. Planning for smallpox outbreaks. *Nature* 425, 681-685.

Ferguson, N. M., Cummings, D. A. T., Cauchemez, S., Fraser, C., Riley, S., Meeyai, A., Iamsirithaworn, S., Burke, D. S., 2005. Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature* 437, 209-214.

Gonzalez, M. C., Hidalgo, C. A., Barabasi, A. L., 2008. Understanding individual human mobility patterns. *Nature* 453, 779-782.

Hadeler, K., Van den Driessche, P., 1997. Backward bifurcation in epidemic control. *Mathematical Biosciences* 146, 15-35.

Hanski, I., 1998. Metapopulation dynamics. *Nature* 396, 41-49.

Hanski, I., Gaggiotti, O. E., 2004. Ecology, genetics, and evolution of metapopulations. *Recherche* 67, 02.

Hanski, I., Gilpin, M. E., ScienceDirect, 1997. Metapopulation biology: ecology, genetics, and evolution. San Diego, Academic Press .

Heesterbeek, J., 2000. Mathematical epidemiology of infectious diseases: model building, analysis, and interpretation. New York; John Wiley & Sons.

Heesterbeek, J., 2002. A brief history of R_0 and a recipe for its calculation. *Acta Biotheoretica* 50, 189-204.

Hsieh, Y. H., van den Driessche, P., Wang, L., 2007. Impact of travel between patches for spatial spread of disease. *Bulletin of Mathematical Biology* 69, 1355-75, http://dx.doi.org/10.1007/s11538-006-9169-6.

Keating, J., Mbogo, C. M., Mwangangi, J., Nzovu, J. G., Gu, W., Regens, J. L., Yan, G., Githure, J. I., Beier, J. C., 2005. Anopheles gambiae sl and Anopheles funestus

mosquito distributions at 30 villages along the Kenyan coast. *Journal of Medical Entomology* 42, 241.

Keeling, M., Gilligan, C., 2000. Metapopulation dynamics of bubonic plague. *Nature* 407, 903-906.

Keeling, M., Bjornstad, O., Grenfell, B., 2004. Metapopulation dynamics of infectious diseases. Ecology, evolution and genetics of metapopulations. Elsevier, Amsterdam, pp. 415-446.

Keeling, M. J., Rohani, P., 2011. Modeling Infectious Diseases in Humans and Animals. Princeton; Princeton University Press.

Kermack, W., McKendrick, A., 1933. Contributions to the mathematical theory of epidemics. III. Further studies of the problem of endemicity. *Proceedings of the Royal society of London Series A* 141, 94-122.

Kermack, W., McKendrick, A., 1939. Contributions to the mathematical theory of epidemics: V. Analysis of experimental epidemics of mouse-typhoid; a bacterial disease conferring incomplete immunity. *Epidemiology and Infection* 39, 271-288.

Kermack, W. O., McKendrick, A. G., 1932. Contributions to the mathematical theory of epidemics. II. The problem of endemicity. *Proceedings of the Royal society of London Series A* 138, 55-83.

Kermark, M., Mckendrick, A., 1927. Contributions to the mathematical theory of epidemics. Part I. *Proceedings of the Royal Society Series A*, Vol. 115, pp. 700-721.

Knudsen, A. B., Slooff, R., 1992. Vector-borne disease problems in rapid urbanization: new approaches to vector control. *Bulletin of the World Health Organization* 70, 1.

Le Menach, A., Tatem, A. J., Cohen, J. M., Hay, S. I., Randell, H., Patil, A. P., Smith, D. L., 2011. Travel risk, malaria importation and malaria transmission in Zanzibar. *Scientific reports* 1: 93, http://dx.doi.org/10.1038/srep00093.

Luz, P. M., Codeco, C. u. T., Massad, E., Struchiner, C. J., 2003. Uncertainties regarding dengue modeling in Rio de Janeiro, Brazil. *Memorias do Instituto Oswaldo Cruz* 98, 871-878.

McKendrick, A., 1925. Applications of mathematics to medical problems. *Proceedings of the Edinburgh Mathematical Society* 44, 98-130.

Macdonald, G., 1952. The analysis of equilibrium in malaria. *Tropical Diseases Bulletin* 49, 813.

Macdonald, G., 1956. Epidemiological basis of malaria control. *Bulletin of the World Health Organization* 15, 613.

May, R., Anderson, R. M., 1991. Infectious diseases of humans: dynamics and control. Oxford; Oxford University Press.

Mbah, M. L. N., Gilligan, C. A., 2011. Resource allocation for epidemic control in metapopulations. *PloS One* 6, e24577.

Mbogo, C. M., Mwangangi, J. M., Nzovu, J., Gu, W., Yan, G., Gunter, J. T., Swalm, C., Keating, J., Regens, J. L., Shililu, J. I., 2003. Spatial and temporal heterogeneity of Anopheles mosquitoes and Plasmodium falciparum transmission along the

Kenyan coast. *American Journal of Tropical Medicine and Hygiene* 68, 734-742.

Midega, J. T., Mbogo, C. M., Mwambi, H., Wilson, M. D., Ojwang, G., Mwangangi, J. M., Nzovu, J. G., Githure, J. I., Yan, G., Beier, J. C., 2007. Estimating dispersal and survival of Anopheles gambiae and Anopheles funestus along the Kenyan Coast by using mark-release-recapture methods. *Journal of Medical Entomology* 44, 923.

Prothero, R. M., 1977. Disease and mobility: a neglected factor in epidemiology. *International Journal of Epidemiology* 6, 259-267.

Robert, V., MacIntyre, K., Keating, J., Trape, J.-F., Duchemin, J.-B., Warren, M., Beier, J. C., 2003. Malaria transmission in urban sub-Saharan Africa. *The American Journal of Tropical Medicine and Hygiene* 68, 169-176.

Ross, R., 1911. The Prevention of Malaria. John Murray, London.

Rowthorn, R. E., Laxminarayan, R., Gilligan, C. A., 2009. Optimal control of epidemics in metapopulations. *Journal of The Royal Society Interface* 6, 1135-1144, http://dx.doi.or/10.1098/rsif.2008.0402.

Scherer, A., McLean, A., 2002. Mathematical models of vaccination. *British Medical Bulletin* 62, 187-199.

Shao, Q. X., 1999. Some properties of an estimator for the basic reproduction number of the general epidemic model. *Mathematical Biosciences* 159, 79-96.

Sharma, V., 1996. Re-emergence of malaria in India. *The Indian Journal of Medical Research* 103, 26.

Smith, D. L., McKenzie, F. E., Snow, R. W., Hay, S. I., 2007. Revisiting the basic
reproductive number for malaria and its implications for malaria control. *PLoS Biology* 5, e42.

Smith, D. L., Battle, K. E., Hay, S. I., Barker, C. M., Scott, T. W., McKenzie, F. E.,
2012. Ross, Macdonald, and a theory for the dynamics and control of mosquito-transmitted pathogens. *PLoS Pathogens* 8, e1002588.

Torres-Sorando, L., Rodri'guez, D. J., 1997. Models of spatio-temporal dynamics in
malaria1. *Ecological Modelling* 104, 231-240.

Van den Driessche, P., Watmough, J., 2000. A simple SIS epidemic model with a
backward bifurcation. *Journal of Mathematical Biology* 40, 525-540.

Van den Driessche, P., Watmough, J., 2002. Reproduction numbers and sub-threshold
endemic equilibria for compartmental models of disease transmission.
Mathematical Biosciences 180, 29-48.

Walker, K., 2002. A review of control methods for African malaria vectors. Washington
(DC), *Environmental Health Project (USAID)*, 54p; Report No 108; Contract
No: HRN-I-00-99-00011-00.

Wesolowski, A., Eagle, N., Tatem, A. J., Smith, D. L., Noor, A. M., Snow, R. W.,
Buckee, C. O., 2012. Quantifying the impact of human mobility on malaria.
Science 338, 267-270.

Table 1: Meaning of symbols used

Symbol	Meaning
x_u	Number of susceptible mosquitoes in the central city
y_u	Number of infected mosquitoes in the central city
x_r	Number of susceptible mosquitoes in the peripheral village
y_r	Number of infected mosquitoes in the peripheral village
X_u	Number of susceptible hosts in the central city
Y_u	Number of infected hosts in the central city
X_c	Number of susceptible commuting hosts
Y_c	Number of infected commuting hosts
X_r	Number of susceptible hosts who stay in the village the whole day
Y_r	Number of infected hosts who stay in the village the whole day
m	Number of peripheral villages
b_d	Daytime mosquito bite rate
b_n	Nighttime mosquito bite rate
τ	Per bite probability of transmission from mosquito to host
τ'	Per bite probability of transmission from host to mosquito
γ	Recovery rate of hosts
D	Death rate of mosquitoes
$N_u = X_u + Y_u$	Total number of residents in the city
$N_c = X_c + Y_c$	Total number of commuters from one of the villages
$N_r = X_r + Y_r$	Total numbers of residents remaining in one village
$N = N_u + m(N_c$	Total number of hosts in the entire system

$M_u = x_u + y_u$ Total number of mosquitoes in the central city

$M_r = x_r + y_r$ Total number of mosquitoes in one peripheral village

$M = M_u + mM_r$ Total equilibrium density of mosquitoes in the whole system

ρ_1 Basic reproductive number for the infection cycle in the city (between hosts and mosquitoes in the city)

ρ_2 Basic reproductive number for the daytime commuters and mosquitoes in the city

ρ_3 Basic reproductive number for the nighttime commuters and mosquitoes in one village

ρ_4 Basic reproductive number for the infection cycle in a village (between hosts and mosquitoes in a village)

R_0 Basic reproductive number for the entire system (a central city and m villages)

p_u Proportion of hosts in the city

p_c Proportion of commuting host

p_r Proportion of hosts in a village

q_u Proportion of mosquitoes in the city

q_r Proportion of mosquitoes in a village

θ_c Critical value for ratio of mosquitoes in the city to mosquitoes in the villages

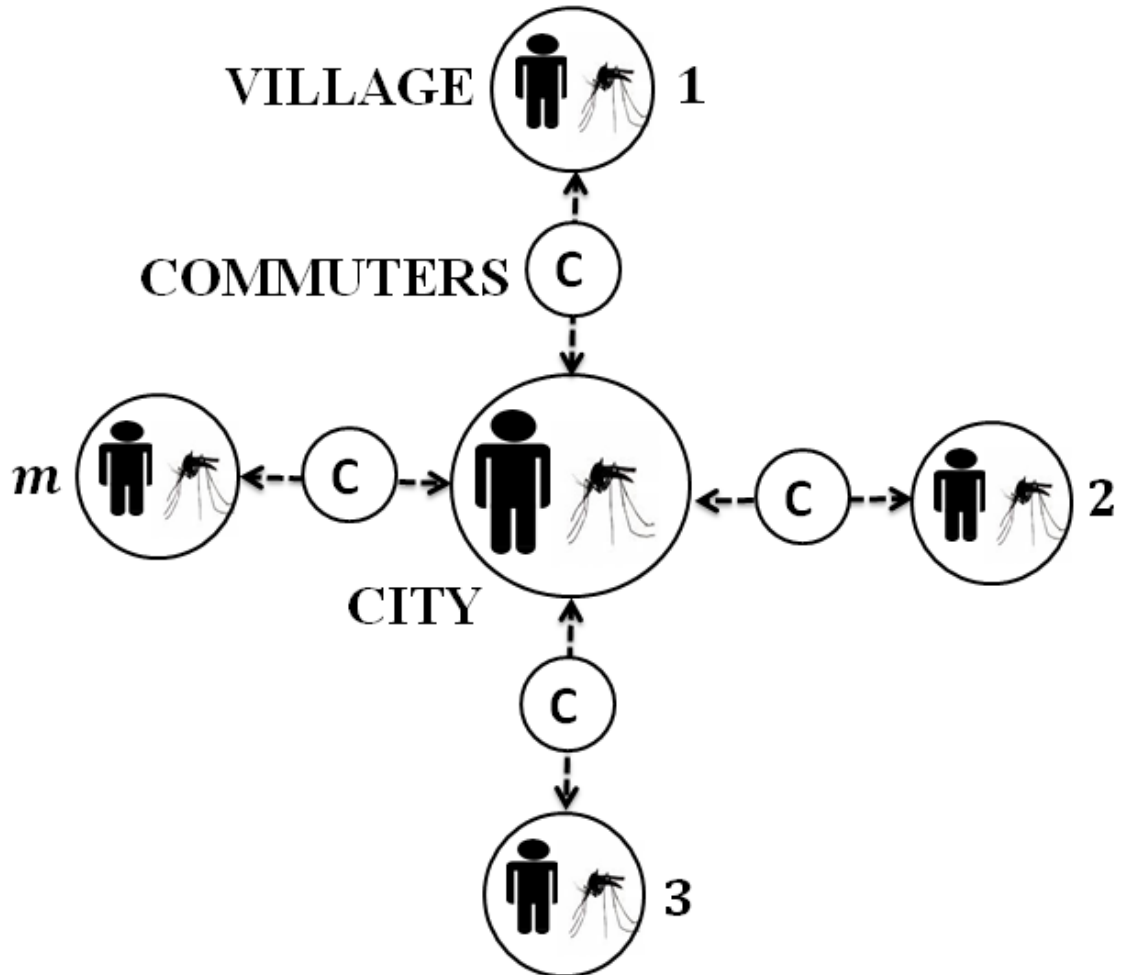**Figure 1: A star-network with a central city and surrounding villages**

Figure 1. A star-network with a central city and m peripheral villages. Mobility patterns in the homogeneous assumption is such that daily commuters (shown by C in the figure) from surrounding villages connect the infection dynamics of all populations of villages with each other as well as with the city. Mosquitoes don't move between city and village or between villages.

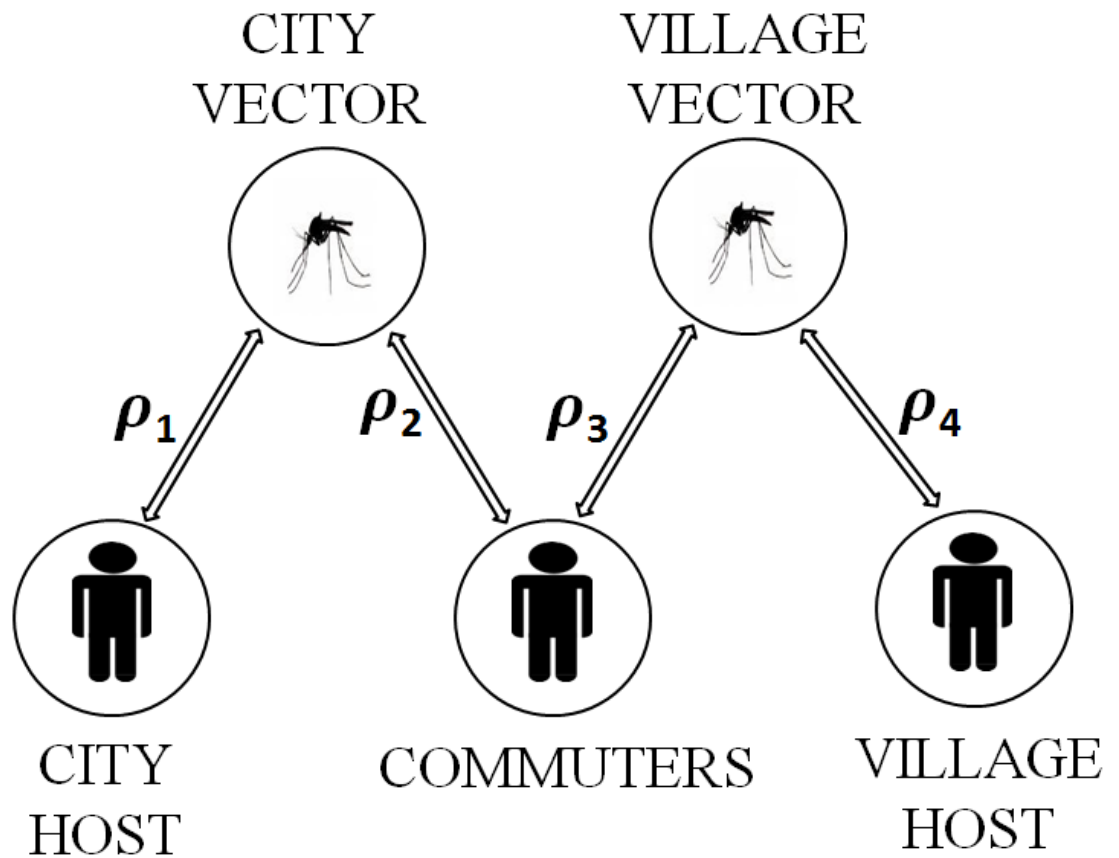**Figure 2: Basic reproductive numbers for various infection cycles**

Figure 2. Basic reproductive numbers for various infection cycles: In homogeneous assumption that m village populations in the star network are identical in their resident and commuter host and mosquito population sizes, we derive individual basic reproductive numbers (ρ_i's) for four infection cycles in the network as shown: city hosts and city mosquitoes infection cycle (ρ_1), daytime commuters and city mosquitoes infection cycles (ρ_2), nighttime commuters and village mosquitoes infection cycle (ρ_3), and village hosts and village mosquitoes infection cycle (ρ_4).

Figure 3: Dependence of control decision on the mosquito densities and proportion of commuters to the city
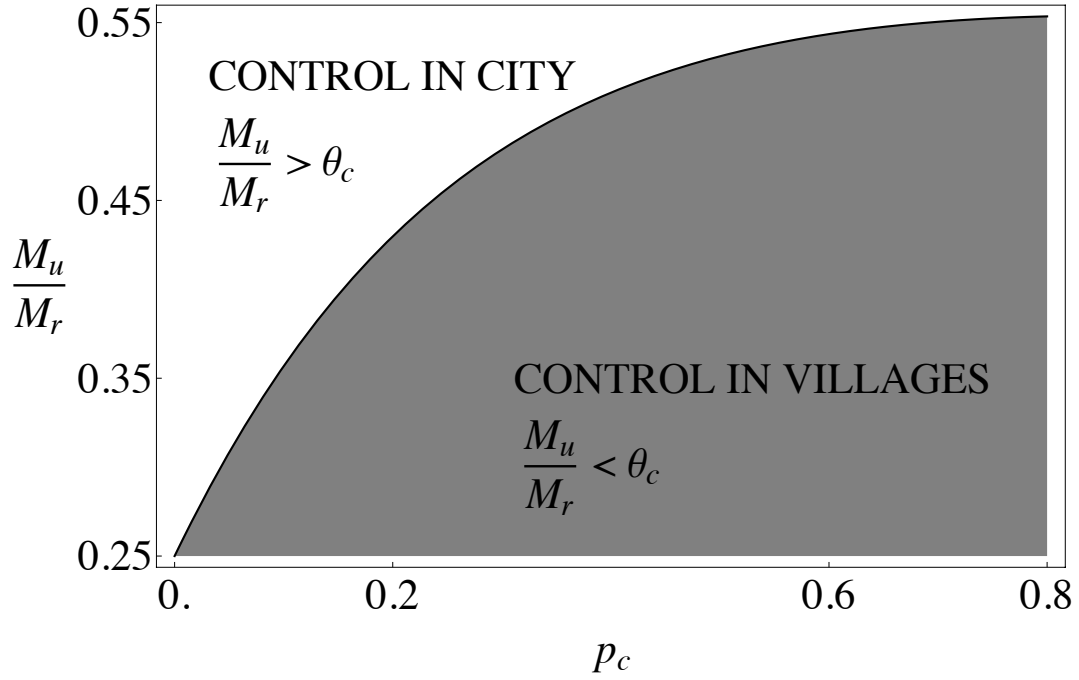

Figure 3: Ratio of city-to-villages mosquito densities (M_u / M_r) as a function of the proportion of commuters, p_c from villages. When we change p_c, the total nighttime populations are kept constant; the proportion of city residents $p_u = 0.2$ remains unchanged while the proportion of village residents, p_r changes with p_c as

$p_r = 1 - p_u - p_c = 0.8 - p_c$. (Parameters: $\gamma = 1/30$, $D = 1/7$, $m = 5$, $b_d = b_n = 0.15$)

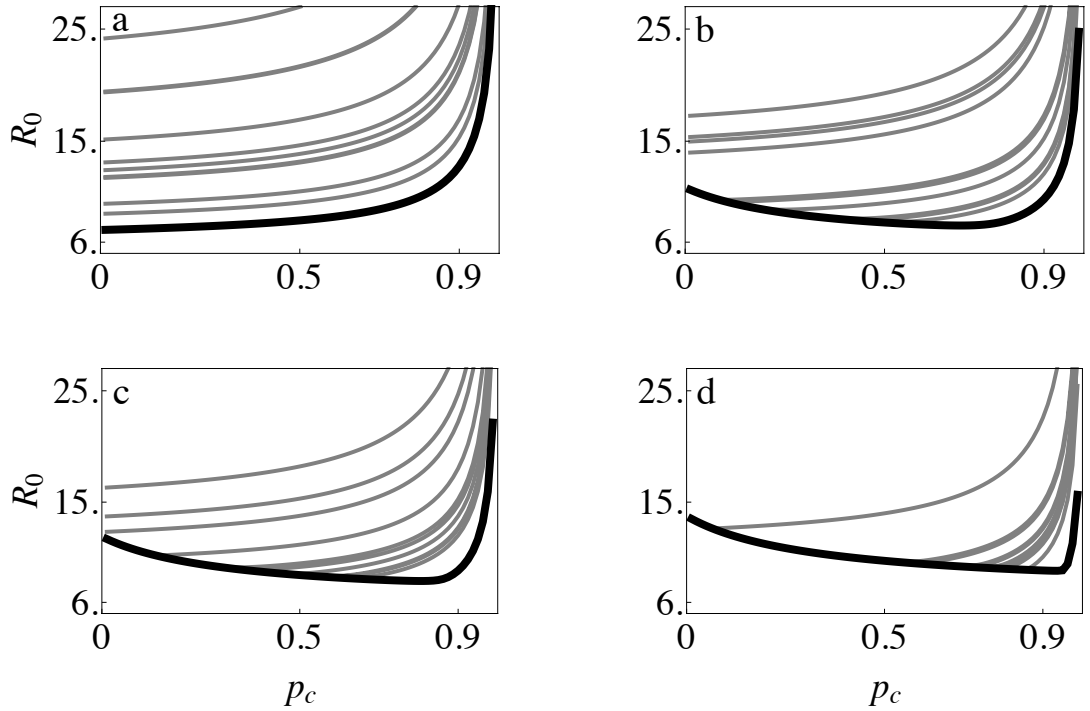# Figure 4: Behavior of basic reproductive number with respect to commuters and behavior of village populations

Figure 4. Dependence of basic reproductive number R_0 on the proportion of commuters p_c that move to the city everyday in homogeneous assumption *(solid black curves)* and heterogeneous assumption *(gray curves)*. The proportion of mosquitoes in villages q_r differs for each panel such that in 4a, ($q_r = 0.85$); in 4b, ($q_r = 0.50$); in 4c, ($q_r = 0.40$); and in 4d, ($q_r = 0.20$). Corresponding city mosquito densities can be obtained using the assumption that $q_r + q_u = 1$. The proportion of city residents is fixed at $p_u = 0.2$ and the proportion of commuters, p_c, as well as that of village residents,

$p_r = 1 - p_u - p_c = 0.8 - p_c$, are changed simultaneously along the horizontal axis.

(Parameters are: $b_n = b_d = 0.15$, $m = 5$, $D = 1/7$, and $\gamma = 1/30$.)

Appendix

1. Full ODEs for epidemic dynamics

We here consider frequency dependent transmission of malaria in a city-and-villages star network with commuters. Full ODEs for host susceptible-infected-susceptible (SIS) model for susceptible and infected city residents (X_u and Y_u), susceptible and infected commuters from a village (X_c and Y_c), susceptible and infected resident of a village (X_r and Y_r), together with the vector susceptible-infected (SI) models for susceptible city mosquitoes (x_u and y_u), and susceptible and infected mosquitoes in a village (x_r and y_r) are as follows.

(i). Daytime infection dynamics for hosts and vectors:

$$\frac{dX_u}{dt} = -\frac{b_d \tau X_u}{N_u + mN_c} y_u + \gamma Y_u, \tag{A1}$$

$$\frac{dY_u}{dt} = \frac{b_d \tau X_u}{N_u + mN_c} y_u - \gamma Y_u, \tag{A2}$$

$$\frac{dx_u}{dt} = -\frac{b_d \tau'\left(Y_u + mY_c\right)}{N_u + mN_c} x_u - Dx_u + r\left(1 - \frac{x_u + y_u}{K_u}\right)(x_u + y_u), \tag{A3}$$

$$\frac{dy_u}{dt} = \frac{b_d \tau'\left(Y_u + mY_c\right)}{N_u + mN_c} x_u - Dy_u, \tag{A4}$$

$$\frac{dX_c}{dt} = -\frac{b_d \tau X_c}{N_u + mN_c} y_u + \gamma Y_c, \tag{A5}$$

$$\frac{dY_c}{dt} = \frac{b_d \tau X_c}{N_u + mN_c} y_u - \gamma Y_c, \tag{A6}$$

$$\frac{dx_r}{dt} = -\frac{b_d \tau' Y_r}{N_r} x_r - Dx_r + r\left(1 - \frac{x_r + y_r}{K_r}\right)(x_r + y_r),$$ (A7)

$$\frac{dy_r}{dt} = \frac{b_d \tau' Y_r}{N_r} x_r - Dy_r,$$ (A8)

$$\frac{dX_r}{dt} = -\frac{b_d \tau X_r}{N_r} y_r + \gamma Y_r,$$ (A9)

$$\frac{dY_r}{dt} = \frac{b_d \tau X_r}{N_r} y_r - \gamma Y_r.$$ (A10)

All symbols are as defined in the main text except for the demographic parameters for mosquitoes: r, the intrinsic growth rate of mosquito, and K_u and K_r, the mosquito carrying capacity in city and a village, respectively.

(ii) Nighttime infection dynamics for hosts and vectors

$$\frac{dX_u}{dt} = -\frac{b_n \tau X_u}{N_u} y_u + \gamma Y_u,$$ (A11)

$$\frac{dY_u}{dt} = \frac{b_n \tau X_u}{N_u} y_u - \gamma Y_u,$$ (A12)

$$\frac{dx_u}{dt} = -\frac{b_n \tau' Y_u}{N_u} x_u - Dx_u + r\left(1 - \frac{x_u + y_u}{K_u}\right)(x_u + y_u),$$ (A13)

$$\frac{dy_u}{dt} = \frac{b_n \tau' Y_u}{N_u} x_u - Dy_u,$$ (A14)

$$\frac{dX_c}{dt} = -\frac{b_n \tau X_c}{N_r + N_c} y_r + \gamma Y_c,$$ (A15)

$$\frac{dY_c}{dt} = \frac{b_n \tau X_c}{N_r + N_c} y_r - \gamma Y_c,$$ (A16)

$$\frac{dx_r}{dt} = -\frac{b_n \tau'(Y_r + Y_c)}{N_r + N_c} x_r - Dx_r + r\left(1 - \frac{x_r + y_r}{K_r}\right)(x_r + y_r), \tag{A17}$$

$$\frac{dy_r}{dt} = \frac{b_n \tau'(Y_r + Y_c)}{N_r + N_c} x_r - Dy_r, \tag{A18}$$

$$\frac{dX_r}{dt} = -\frac{b_n \tau X_r}{N_r + N_c} y_r + \gamma Y_r, \tag{A19}$$

$$\frac{dY_r}{dt} = \frac{b_n \tau X_r}{N_r + N_c} y_r - \gamma Y_r. \tag{A20}$$

Note that, from (A1)-(A20), we first see that the total number of city resident

$N_u = X_u + Y_u$, that of commuters from a village, $N_c = X_c + Y_c$, and that of residents in

a village, $N_r = X_r + Y_r$, remain constant. Note also that the total numbers of

mosquitoes in the city, $M_u = x_u + y_u$, and that in a village, $M_r = x_r + y_r$, change with

time, irrespective of whether it is in day time or in nighttime, and independent of the

epidemiological state of populations, as

$$\frac{dM_i}{dt} = r\left(1 - \frac{M_i}{K_i}\right)M_i - DM_i, \quad (i = r, u), \tag{A21}$$

where K_i is the mosquito carrying capacity in either village or city which yields the

equilibrium number of mosquitoes as

$$M_i = K_i\left(1 - \frac{D}{r}\right), \quad (i = r, u). \tag{A22}$$

Hereafter we assume that mosquito total densities in city and a village are kept constant

defined as (A22).

2. Basic reproductive number

Using (A1)-(A20), noting that the total human densities, N_u, N_c, and N_r, remain constant, and assuming that the total mosquito densities, M_u and M_r, are kept at their equilibrium values (A22), the density of infected humans in urban resident (Y_u), commuters (Y_c), rural resident (Y_r) and those in infected mosquitoes in urban (y_u) area and rural area (y_r) change during daytime when commuters resides in the urban place as

$$\frac{dY_u}{dt} = \frac{b_d \tau X_u}{N_u + m N_c} y_u - \gamma Y_u,$$

$$\frac{dy_u}{dt} = \frac{b_d \tau' (Y_u + m Y_c)}{N_u + m N_c} x_u - D y_u,$$

$$\frac{dY_c}{dt} = \frac{b_d \tau X_c}{N_u + m N_c} y_u - \gamma Y_c, \tag{A23}$$

$$\frac{dy_r}{dt} = \frac{b_d \tau' Y_r}{N_r} x_r - D y_r,$$

$$\frac{dY_r}{dt} = \frac{b_d \tau X_r}{N_r} y_r - \gamma Y_r,$$

for $k < t < k + 0.5$ ($k = 0,1,2,\cdots$). Note that we measure time in units of days, and divide a day into half for daytime and nighttime. Here, b_d is the rate at which a mosquito bites a human in daytime, τ is the per bite probability that the disease is transmitted from infected mosquito to susceptible human, τ' is the corresponding quantity from infected human to susceptible mosquito. Unlike under density dependent

transmission (or mass action rule), the biting rate is independent of human density. Therefore the probability that a particular human is bitten by a particular mosquito is $b_d / (N_u + mN_c)$ in city and b_d / N_r in a village during daytime. The nighttime epidemiological dynamics are derived similarly as

$$\frac{dY_u}{dt} = \frac{b_n \tau X_u}{N_u} y_u - \gamma Y_u,$$

$$\frac{dy_u}{dt} = \frac{b_n \tau' Y_u}{N_u} x_u - D y_u,$$

$$\frac{dY_c}{dt} = \frac{b_n \tau X_c}{N_r + N_c} y_u - \gamma Y_c, \qquad (A24)$$

$$\frac{dy_r}{dt} = \frac{b_n \tau' (Y_r + Y_c)}{N_r + N_c} x_r - D y_r,$$

$$\frac{dY_r}{dt} = \frac{b_n \tau X_r}{N_r + N_c} y_r - \gamma Y_r,$$

for $k + 0.5 < t < k + 1$ ($k = 0, 1, 2, \cdots$), where b_n is the mosquito biting rate at night.

We then linearize the epidemiological dynamics by assuming that infected densities are small to have

$$\frac{d\boldsymbol{y}(t)}{dt} = \begin{cases} A_d \boldsymbol{y}(t), & \text{for } t \text{ in daytime} \\ A_n \boldsymbol{y}(t), & \text{for } t \text{ in nighttime} \end{cases} \qquad (A25)$$

where $\boldsymbol{y} = (Y_u, y_u, Y_c, y_r, Y_r)^T$, with superscript T denoting vector transform, and

$$A_d = \begin{pmatrix} -\gamma & \beta_1\tau N_u & 0 & 0 & 0 \\ \beta_1\tau' M_u & -D & \beta_1\tau' M_u m & 0 & 0 \\ 0 & \beta_1\tau N_c & -\gamma & 0 & 0 \\ 0 & 0 & 0 & -D & \beta_2\tau' M_r \\ 0 & 0 & 0 & \beta_2\tau N_r & -\gamma \end{pmatrix}, \tag{A26}$$

$$A_n = \begin{pmatrix} -\gamma & \beta_3\tau N_u & 0 & 0 & 0 \\ \beta_3\tau' M_u & -D & 0 & 0 & 0 \\ 0 & 0 & -\gamma & \beta_4\tau N_c & 0 \\ 0 & 0 & \beta_4\tau' N_r & -D & \beta_4\tau' M_r \\ 0 & 0 & 0 & \beta_4\tau N_r & -\gamma \end{pmatrix}, \tag{A27}$$

where

$$\beta_1 = \frac{b_d}{N_u + m N_c}, \quad \beta_2 = \frac{b_d}{N_r}, \quad \beta_3 = \frac{b_n}{N_u}, \text{ and } \beta_4 = \frac{b_n}{N_r + N_c}. \tag{A28}$$

The solution to (A25) for $t = k$ is given simply by

$$y(k) = y(0) e^{\sum_{j=0}^{k-1} \left\{ \int_j^{j+1/2} A_d\, dt + \int_{j+1/2}^{j+1} A_n\, dt \right\}} = y(0) e^{\frac{k}{2}(A_d + A_n)} = y(0) e^{k\bar{A}}.$$

where $\bar{A} = (A_d + A_n)/2$ is the mean of the daytime matrix (A26) and the nighttime matrix (A27). For t not exactly at an integer value, $y(t)$ is expressed in a slightly complicated form:

$$y(t) = \begin{cases} y(0) e^{k\bar{A} + (t-k)A_d}, & (k < t < k+1/2), \\ y(0) e^{k\bar{A} + \frac{A_d}{2} + (t-k-1/2)A_n}, & (k+1/2 < t < k+1), \end{cases}$$

but this complication does not affect the subsequent calculations of the basic reproductive number, if we assume that initial infected agents are introduced at $t = 0$

55

(at an integer point). If the initial infected agents are introduced in another hour in a day (not at the beginning of daytime), we would have a very minor difference in the basic reproductive numbers, but we ignore such a technical trivia in this paper.

Now we define the next generation matrix and obtain the basic reproductive number. At first, we decompose the averaged matrix $\bar{A}$ into transmission part F and transition part V as

$$
\bar{A} = \frac{A_d + A_n}{2}
$$

$$
= \begin{pmatrix}
0 & \frac{\beta_1+\beta_3}{2}\tau N_u & 0 & 0 & 0 \\
\frac{\beta_1+\beta_3}{2}\tau' M_u & 0 & \frac{\beta_1}{2}\tau' M_u m & 0 & 0 \\
0 & \frac{\beta_1}{2}\tau N_c & 0 & \frac{\beta_4}{2}\tau N_c & 0 \\
0 & 0 & \frac{\beta_4}{2}\tau' M_r & 0 & \frac{\beta_2+\beta_4}{2}\tau' M_r \\
0 & 0 & 0 & \frac{\beta_2+\beta_4}{2}\tau N_c & 0
\end{pmatrix}
- \begin{pmatrix}
\gamma & 0 & 0 & 0 & 0 \\
0 & D & 0 & 0 & 0 \\
0 & 0 & \gamma & 0 & 0 \\
0 & 0 & 0 & D & 0 \\
0 & 0 & 0 & 0 & \gamma
\end{pmatrix} \quad \text{(A29)}
$$

$$
\equiv F - V,
$$

We then define a next generation matrix G as in (Diekmann et al., 2010; Diekmann et al., 2012)

$$
G = FV^{-1} = \begin{pmatrix}
0 & \frac{\beta_1+\beta_3}{2D}\tau N_u & 0 & 0 & 0 \\
\frac{\beta_1+\beta_3}{2\gamma}\tau' M_u & 0 & \frac{\beta_1}{2\gamma}\tau' M_u m & 0 & 0 \\
0 & \frac{\beta_1}{2D}\tau N_c & 0 & \frac{\beta_4}{2D}\tau N_c & 0 \\
0 & 0 & \frac{\beta_4}{2\gamma}\tau' M_r & 0 & \frac{\beta_2+\beta_4}{2\gamma}\tau' M_r \\
0 & 0 & 0 & \frac{\beta_2+\beta_4}{2D}\tau N_c & 0
\end{pmatrix}, \text{(A30)}
$$

We can obtain all the eigenvalues of the next generation matrix G from the

characteristic equation

$$|\lambda I - G| = \lambda \left\{ \lambda^4 - (\rho_1 + \rho_2 + \rho_3 + \rho_4)\lambda^2 + (\rho_1\rho_3 + \rho_1\rho_4 + \rho_2\rho_4) \right\} = 0, \quad \text{(A31)}$$

where ρ_i ($i = 1,2,3,4$) is the product of $(i,i+1)$ and $(i+1,i)$ components of the next

generation matrix G, and are the individual cycles' basic reproductive numbers. The

whole system basic reproductive number is given by the largest eigenvalue of the next

generation matrix G and is obtained as

$$R_0 = \sqrt{\frac{\rho_1 + \rho_2 + \rho_3 + \rho_4}{2} + \sqrt{\left(\frac{\rho_1 + \rho_2 + \rho_3 + \rho_4}{2}\right)^2 - (\rho_1\rho_3 + \rho_1\rho_4 + \rho_2\rho_4)}}, \text{(A32)}$$

where

$$\begin{aligned}
\rho_1 &= \frac{1}{D\gamma}\left(\frac{\beta_1 + \beta_3}{2}\right)^2 \tau\tau' N_u M_u = \frac{\tau\tau' N_u M_u}{4D\gamma}\left(\frac{b_d}{N_u + mN_c} + \frac{b_n}{N_u}\right)^2, \\
\rho_2 &= \frac{1}{D\gamma}\left(\frac{\beta_1}{2}\right)^2 \tau\tau' mN_c M_u = \frac{\tau\tau' mN_c M_u}{4D\gamma}\left(\frac{b_d}{N_u + mN_c}\right)^2, \\
\rho_3 &= \frac{1}{D\gamma}\left(\frac{\beta_4}{2}\right)^2 \tau\tau' N_c M_r = \frac{\tau\tau' N_c M_r}{4D\gamma}\left(\frac{b_n}{N_r + N_c}\right)^2, \\
\rho_4 &= \frac{1}{D\gamma}\left(\frac{\beta_3 + \beta_4}{2}\right)^2 \tau\tau' N_r M_r = \frac{\tau\tau' N_r M_r}{4D\gamma}\left(\frac{b_d}{N_r} + \frac{b_n}{N_r + N_c}\right)^2.
\end{aligned}$$
(A33)

This completes the derivation of basic reproductive number (17) in the text.

3. Sensitivity of basic reproductive number on urban/rural mosquito densities

The basic reproductive number has a form $R_0 = \sqrt{A + \sqrt{B}}$ where

$A = (\rho_1 + \rho_2 + \rho_3 + \rho_4)/2$ and $B = A^2 - (\rho_1\rho_3 + \rho_1\rho_4 + \rho_2\rho_4)$. It then follows that

$$\frac{\partial R_0}{\partial \rho_1} = \frac{1}{8R_0\sqrt{B}}\left\{2\sqrt{B} + \rho_1 + \rho_2 - \rho_3 - \rho_4\right\}$$

$$\frac{\partial R_0}{\partial \rho_2} = \frac{1}{8R_0\sqrt{B}}\left\{2\sqrt{B} + \rho_1 + \rho_2 + \rho_3 - \rho_4\right\}$$

$$\frac{\partial R_0}{\partial \rho_3} = \frac{1}{8R_0\sqrt{B}}\left\{2\sqrt{B} - \rho_1 + \rho_2 + \rho_3 + \rho_4\right\}$$

$$\frac{\partial R_0}{\partial \rho_4} = \frac{1}{8R_0\sqrt{B}}\left\{2\sqrt{B} - \rho_1 - \rho_2 + \rho_3 + \rho_4\right\}$$

(A34)

with which the sensitivity of the basic reproductive number on an arbitrary parameter w

is expressed as

$$\frac{\partial R_0}{\partial w} = \sum_{i=1}^{4} \frac{\partial R_0}{\partial \rho_i}\frac{\partial \rho_i}{\partial w} \tag{A35}$$

As for the sensitivity on urban mosquito density ($w = M_u$), we have, from

$$\frac{\partial \rho_1}{\partial M_u} = \frac{\rho_1}{M_u}, \quad \frac{\partial \rho_2}{\partial M_u} = \frac{\rho_2}{M_u}, \quad \frac{\partial \rho_3}{\partial M_u} = \frac{\partial \rho_4}{\partial M_u} = 0 \tag{A36}$$

and (A33)-(A34),

$$\frac{\partial R_0}{\partial M_u} = \frac{\partial R_0}{\partial \rho_1}\frac{\rho_1}{M_u} + \frac{\partial R_0}{\partial \rho_2}\frac{\rho_2}{M_u}$$

$$= \frac{1}{M_u 8R_0\sqrt{B}}\left[2\sqrt{B}(\rho_1 + \rho_2) + (\rho_1 + \rho_2)^2 - \rho_3(\rho_1 - \rho_2) - \rho_4(\rho_1 + \rho_2)\right]$$

(A37)

Likewise, as

$$\frac{\partial \rho_1}{\partial M_r} = \frac{\partial \rho_2}{\partial M_r} = 0, \quad \frac{\partial \rho_3}{\partial M_r} = \frac{\rho_3}{M_r}, \quad \frac{\partial \rho_4}{\partial M_r} = \frac{\rho_4}{M_r}, \tag{A38}$$

we have

$$\begin{aligned}
\frac{\partial R_0}{\partial M_r} &= \frac{\partial R_0}{\partial \rho_3}\frac{\rho_3}{M_r} + \frac{\partial R_0}{\partial \rho_4}\frac{\rho_4}{M_r} \\
&= \frac{1}{M_r 8 R_0 \sqrt{B}}\left[2\sqrt{B}(\rho_3+\rho_4) - \rho_1(\rho_3+\rho_4) + \rho_2(\rho_3-\rho_4) + (\rho_3+\rho_4)^2\right]
\end{aligned} \tag{A39}$$

From (A37) and (A39), we have

$$\begin{aligned}
&\frac{\partial R_0}{\partial(\log M_u)} - \frac{\partial R_0}{\partial(\log M_r)} \\
&= \frac{1}{8R_0\sqrt{B}}\left[2\sqrt{B}\{(\rho_1+\rho_2)-(\rho_3+\rho_4)\} + (\rho_1+\rho_2)^2 - (\rho_3+\rho_4)^2\right] \\
&= \frac{1}{8R_0\sqrt{B}}\left\{2\sqrt{B}+\rho_1+\rho_2+\rho_3+\rho_4\right\}\{(\rho_1+\rho_2)-(\rho_3+\rho_4)\}
\end{aligned}$$

and therefore decreasing urban mosquito density is more effective in reducing basic reproductive number if

$$\frac{\partial R_0}{\partial(\log M_u)} > \frac{\partial R_0}{\partial(\log M_r)} \quad \Leftrightarrow \quad \frac{\rho_1+\rho_2}{\rho_3+\rho_4} > 1. \tag{A40}$$

Substituting (A33) into the second inequality of (A40), we see that the condition for that controlling urban mosquitoes is more effective than controlling rural mosquitoes if

$$\frac{M_u}{M_r}\frac{\left(\dfrac{b_d}{N_u+mN_c}+\dfrac{b_n}{N_u}\right)^2 N_u + \left(\dfrac{b_d}{N_u+mN_c}\right)^2 mN_c}{\left(\dfrac{b_n}{N_r+N_c}\right)^2 N_c + \left(\dfrac{b_d}{N_r}+\dfrac{b_n}{N_r+N_c}\right)^2 N_r} > 1. \tag{A41}$$

This completes the derivation of equation (22) in the text.

4. Sensitivity of basic reproductive number on the fraction of commuters in rural area

For what follows, we assume that the biting rates in day and night can be different: $b_d \neq b_n$. For homogeneous daytime and nighttime bite rates similar results are obtained by setting $b_d = b_n = b$. The definitions of ρ_is are

$$\rho_1 = \frac{1}{4}\left(\frac{b_d}{N_u + mN_c} + \frac{b_n}{N_u}\right)^2 \frac{\tau\tau' N_u M_u}{D\gamma},$$

$$\rho_2 = \frac{1}{4}\left(\frac{b_d}{N_u + mN_c}\right)^2 \frac{\tau\tau' mN_c M_u}{D\gamma},$$

$$\rho_3 = \frac{1}{4}\left(\frac{b_n}{N_u + N_c}\right)^2 \frac{\tau\tau' N_c M_r}{D\gamma},$$

$$\rho_4 = \frac{1}{4}\left(\frac{b_d}{N_r} + \frac{b_n}{N_r + N_c}\right)^2 \frac{\tau\tau' N_r M_r}{D\gamma}.$$

(A42)

We now introduce the fractions

$$p_u = N_u / N, \quad p_c = mN_c / N, \quad p_r = mN_r / N,$$
$$q_u = M_u / M, \quad q_r = mM_r / M,$$

(A43)

where $N = N_u + m\left(N_c + N_r\right)$ is the total number of humans and $M = M_u + mM_r$ is the total number of mosquitoes.

We then ask how the basic reproductive ratio

60

$$R_0 = \sqrt{\frac{\rho_1 + \rho_2 + \rho_3 + \rho_4}{2} + \sqrt{\left(\frac{\rho_1 + \rho_2 + \rho_3 + \rho_4}{2}\right)^2 - \left(\rho_1\rho_3 + \rho_1\rho_4 + \rho_2\rho_4\right)}} \quad \text{(A44)}$$

depends on the fraction of commuters p_c in rural area when the fraction of urban

human population p_u is kept constant.

To see this we first substitute (A43) into (A42)

$$\rho_1 = \frac{1}{4}\left(\frac{b_d}{Np_u + Np_c} + \frac{b_n}{Np_u}\right)^2 \frac{\tau\tau'}{D\gamma} Np_u Mq_u = r_0\left(\frac{b_d}{p_u + p_c} + \frac{b_n}{p_u}\right)^2 p_u q_u,$$

$$\rho_2 = \frac{1}{4}\left(\frac{b_d}{Np_u + Np_c}\right)^2 \frac{\tau\tau'}{D\gamma} Np_c Mq_u = r_0\left(\frac{b_d}{p_u + p_c}\right) p_c q_u,$$

$$\rho_3 = \frac{1}{4}\left(\frac{b_n}{\dfrac{Np_c}{m} + \dfrac{Np_r}{m}}\right)^2 \frac{\tau\tau'}{D\gamma} \frac{Np_c}{m} \frac{Mq_r}{m} = r_0\left(\frac{b_n}{p_c + p_r}\right)^2 p_c q_r, \qquad \text{(A45)}$$

$$\rho_4 = \frac{1}{4}\left(\frac{b_d}{\dfrac{Np_r}{m}} + \frac{b_n}{\dfrac{Np_r}{m} + \dfrac{Np_c}{m}}\right)^2 \frac{\tau\tau'}{D\gamma} \frac{Np_r}{m} \frac{Mq_r}{m} = r_0\left(\frac{b_d}{p_r} + \frac{b_n}{p_r + p_c}\right) p_r q_r,$$

where

$$r_0 = \frac{\tau\tau'}{4D\gamma} \frac{M}{N}. \qquad \text{(A46)}$$

In what follows, we assume that the fraction of urban human population p_u

remains constant, and change the fraction of commuters p_c. The fraction of rural

daytime resident p_r changes accordingly by changing p_c (i.e., $p_r = 1 - p_u - p_c$). Under

this assumption, we differentiate each ρ_i by p_c and take the limit of $p_c \to 0$ to find the

condition under which introduction of nonzero fraction of commuters decreases R_0.

We first eliminate p_r by substituting $p_r = 1 - p_u - p_c$ into (A45) and then see

the derivative by p_c evaluated at $p_c = 0$,

$$\left.\frac{\partial \rho_1}{\partial p_c}\right|_{p_c=0} = r_0 \frac{\partial}{\partial p_c}\left.\left(\left(\frac{b_d}{p_u+p_c}+\frac{b_n}{p_u}\right)^2 p_u q_u\right)\right|_{p_c=0} = -2r_0\left(b_d+b_n\right)b_d\frac{q_u}{p_u^{\,2}}$$

$$\left.\frac{\partial \rho_2}{\partial p_c}\right|_{p_c=0} = r_0 q_u \frac{\partial}{\partial p_c}\left.\left(\left(\frac{b_d}{p_u+p_c}\right)^2 p_c\right)\right|_{p_c=0} = r_0 b_d^{\,2}\frac{q_u}{p_u^{\,2}}$$

$$\left.\frac{\partial \rho_3}{\partial p_c}\right|_{p_c=0} = r_0 q_r \frac{\partial}{\partial p_c}\left.\left(\left(\frac{b_n}{1-p_u}\right)^2 p_c\right)\right|_{p_c=0} = r_0 b_n^{\,2}\frac{q_r}{\left(1-p_u\right)^2} \tag{A47}$$

$$\left.\frac{\partial \rho_4}{\partial p_c}\right|_{p_c=0} = r_0 q_r \frac{\partial}{\partial p_c}\left.\left(\left(\frac{b_d}{p_r}+\frac{b_n}{1-p_u}\right)^2 p_r\right)\right|_{p_c=0} = 0,$$

and

$$\left.\rho_1\right|_{p_c=0} = r_0\left(b_d+b_n\right)^2\frac{q_u}{p_u},$$

$$\left.\rho_2\right|_{p_c=0} = \left.\rho_3\right|_{p_c=0} = 0, \tag{A48}$$

$$\left.\rho_4\right|_{p_c=0} = r_0\left(b_d+b_n\right)^2\frac{q_r}{p_r}$$

As for the partial derivatives of $R_0 = \sqrt{A+\sqrt{B}}$ by ρ_i's, evaluated at $p_c = 0$,

where $A = \left(\rho_1+\rho_2+\rho_3+\rho_4\right)/2$ and $B = A^2 - \left(\rho_1\rho_3+\rho_1\rho_4+\rho_2\rho_4\right)$, we have

$$\frac{\partial R_0}{\partial \rho_1}\bigg|_{p_c=0} = \frac{\frac{\partial A}{\partial \rho_1} + \frac{1}{2\sqrt{B}}\frac{\partial B}{\partial \rho_1}}{2\sqrt{A+\sqrt{B}}}\bigg|_{p_c=0} = \frac{2\sqrt{B}\frac{\partial A}{\partial \rho_1} + 2A\frac{\partial A}{\partial \rho_1} - (\rho_3+\rho_4)}{4R_0\sqrt{B}}\bigg|_{p_c=0}$$

$$= \frac{2\sqrt{B}/2 + (\rho_1+\rho_2+\rho_3+\rho_4)/2 - (\rho_3+\rho_4)}{4R_0\sqrt{B}}\bigg|_{p_c=0} \tag{A49}$$

$$= \frac{2\sqrt{B}+\rho_1+\rho_2-\rho_3-\rho_4}{8R_0\sqrt{B}}\bigg|_{p_c=0} = \frac{1}{4R_0}\left(1 + \frac{\rho_1-\rho_4}{|\rho_1-\rho_4|}\right)\bigg|_{p_c=0}$$

where we used

$$B\big|_{p_c=0} = \left(\frac{\rho_1-\rho_4}{2}\right)^2\bigg|_{p_c=0} = \frac{r_0^2(b_d+b_n)^4}{4}\left(\frac{q_u}{p_u} - \frac{q_r}{p_r}\right)^2 . \tag{A50}$$

Similarly,

$$\frac{\partial R_0}{\partial \rho_2}\bigg|_{p_c=0} = \frac{2\sqrt{B}+\rho_1+\rho_2+\rho_3-\rho_4}{8R_0\sqrt{B}}\bigg|_{p_c=0} = \frac{1}{4R_0}\left(1 + \frac{\rho_1-\rho_4}{|\rho_1-\rho_4|}\right)\bigg|_{p_c=0} \tag{A51}$$

$$\frac{\partial R_0}{\partial \rho_3}\bigg|_{p_c=0} = \frac{2\sqrt{B}-\rho_1+\rho_2+\rho_3+\rho_4}{8R_0\sqrt{B}}\bigg|_{p_c=0} = \frac{1}{4R_0}\left(1 - \frac{\rho_1-\rho_4}{|\rho_1-\rho_4|}\right)\bigg|_{p_c=0} \tag{A52}$$

$$\frac{\partial R_0}{\partial \rho_4}\bigg|_{p_c=0} = \frac{2\sqrt{B}-\rho_1-\rho_2+\rho_3+\rho_4}{8R_0\sqrt{B}}\bigg|_{p_c=0} = \frac{1}{4R_0}\left(1 - \frac{\rho_1-\rho_4}{|\rho_1-\rho_4|}\right)\bigg|_{p_c=0} \tag{A53}$$

and hence

$$\frac{\partial R_0}{\partial \rho_1}\bigg|_{p_c=0} = \frac{\partial R_0}{\partial \rho_2}\bigg|_{p_c=0} = \begin{cases} 1/2R_0, & \text{if } (\rho_1-\rho_4)_{p_c=0} \geq 0, \\ 0, & \text{if otherwise.} \end{cases} \tag{A54}$$

$$\frac{\partial R_0}{\partial \rho_3}\bigg|_{p_c=0} = \frac{\partial R_0}{\partial \rho_4}\bigg|_{p_c=0} = \begin{cases} 0, & \text{if } (\rho_1 - \rho_4)_{p_c=0} \geq 0, \\ 1/2R_0, & \text{if otherwise.} \end{cases} \tag{A55}$$

Using these evaluations, we see the following. Suppose first that $(\rho_1 - \rho_4)_{p_c=0} > 0$ or

$$\frac{q_u}{p_u} > \frac{q_r}{p_r}. \tag{A56}$$

Then it follows that

$$\frac{\partial R_0}{\partial p_c}\bigg|_{p_c=0} = \sum_{i=1}^{4} \frac{\partial R_0}{\partial \rho_i} \frac{\partial \rho_i}{\partial p_c}\bigg|_{p_c=0} = \frac{1}{2R_0}\left(\frac{\partial \rho_1}{\partial p_c} + \frac{\partial \rho_2}{\partial p_c}\right)\bigg|_{p_c=0}$$
$$= -\frac{r_0 b_d \left(b_d + 2b_n\right)}{2R_0} \frac{q_u}{p_u^2} < 0 \tag{A57}$$

Thus (A56) gives the condition for the existence of the paradoxical region.

If the reverse inequality holds $(q_u/p_u < q_r/p_r)$, we have

$$\frac{\partial R_0}{\partial p_c}\bigg|_{p_c=0} = \sum_{i=1}^{4} \frac{\partial R_0}{\partial \rho_i} \frac{\partial \rho_i}{\partial p_c}\bigg|_{p_c=0} = \frac{1}{2R_0}\left(\frac{\partial \rho_3}{\partial p_c} + \frac{\partial \rho_4}{\partial p_c}\right)\bigg|_{p_c=0}$$
$$= \frac{r_0 b_n^2}{2R_0} \frac{q_r}{(1-p_u)^2} > 0 \tag{A58}$$

and hence R_0 increases as p_c is increased from 0.

Similar result holds for the homogenous bite rates obtained by setting $b_n = b_d$. This conclusion holds no matter how large is the difference between daytime and nighttime mosquito bite rates. This completes the derivation of the condition (23) in the text for paradoxical dependence of R_0 on connectivity.

5. Incorporating heterogeneity

We define a parameter h that assigns different levels of heterogeneity and homogeneity in the host and vector population sizes. When $h=1$ we only recover the heterogeneous component and when $0<h<1$ there is a nonzero homogeneous component.

The heterogeneous component is obtained by sampling host and vector populations using a uniform distribution in the simplex whose dimension equals the number of villages (see example in Figure A1 below for 3 villages).

We sample a vector of uniform random real numbers between 0 and 1; $u_i \in U(0,1]$, $(i=1,2...m)$ where m is the number of villages. The normalized negative logarithm of this vector produces a uniform distribution in a simplex (Devroye, 1986; Tanizaki, 2004), also see **Fig A1** below. If H_i represents the size of host population in one village among villages containing a total of N_r hosts then:

$$H_i = \frac{-\log(u_i)}{\sum_{i=1}^{m}\left(-\log(u_i)\right)} hN_r + \left(1-h\right)\frac{N_r}{m} \tag{A59}$$

Where the first part of the right-hand side of (A59) represents a random population size component weighted by the homogeneity parameter h such that $0 \leq h \leq 1$ and the second part represents a uniform population size component.

Similarly, if V_i represents the size of vector population in one village among villages containing a total of M_r vectors, then:

$$V_i = \frac{-\log(u_i)}{\sum\limits_{i=1}^{m}\left(-\log(u_i)\right)} h M_r + \left(1-h\right)\frac{M_r}{m} \ . \qquad \text{(A60)}$$

Note that those u_i's used in (A60) are different from those used in (A59); therefore the human population size and the mosquito population size are not necessarily synchronized. For each realization of (A59) and (A60) a dominant eigenvalue of the resulting $(3m+2)$ by $(3m+2)$ dimensional next-generation matrix (NGM) is calculated numerically. Note that for m villages we have one urban infected human population and m infected commuters and m infected rural human populations as well as one infected rural mosquito population and m infected rural mosquitoes, giving the aforementioned dimension of the next-generation matrix.
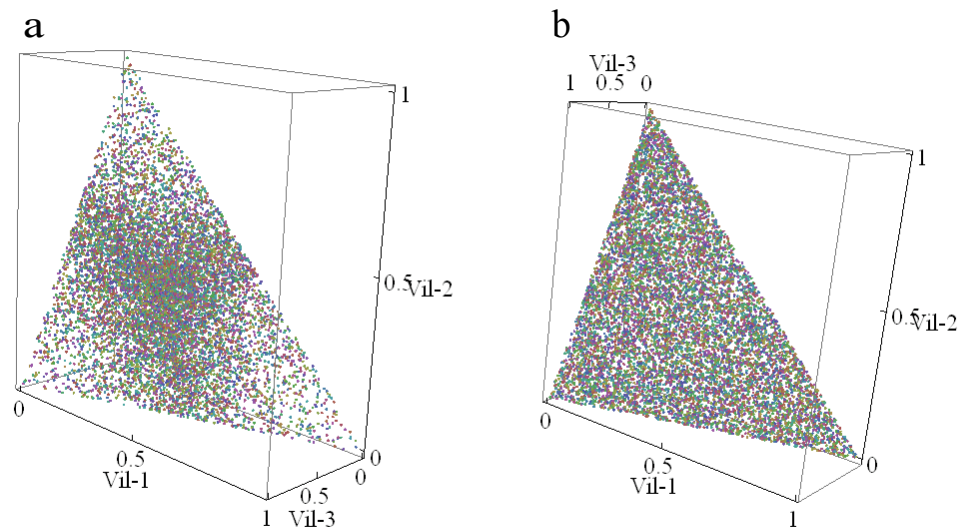
Figure A1. Comparison of sampling results among three villages between (a) normalized random real numbers between 0 and 1 and (b) normalized negative logarithms of random real numbers between 0 and 1. In both (a) and (b) 10,000 samples were plotted.

References used in Appendix

Diekmann, O., Heesterbeek, J., Roberts, M., 2010. The construction of next-generation matrices for compartmental epidemic models. Journal of The Royal Society Interface 7, 873-885.

Diekmann, O., Heesterbeek, H., Britton, T., 2012. Mathematical Tools for Understanding Infectious Disease Dynamics. Princeton University Press.

Devroye, L., 1986. Sample-based non-uniform random variate generation. Proceedings of the 18th conference on Winter simulation. ACM, pp. 260-265.

Tanizaki, H., 2004. Computational methods in statistics and econometrics. CRC Press.