Chapter 17

Statistical Tools for the Interpretation of Enzootic West Nile virus Transmission Dynamics

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Abstract

Interpretation of enzootic *West Nile virus* (WNV) surveillance indicators requires little advanced mathematical skill, but greatly enhances the ability of public health officials to prescribe effective WNV management tactics. Stepwise procedures for the calculation of mosquito infection rates (IR) and vector index (VI) are presented alongside statistical tools that require additional computation. A brief review of advantages and important considerations for each statistic's use is provided.

Key words *West Nile virus*, Mosquito surveillance, Surveillance indicators, Mosquito infection rate, Vector index

1 Introduction

Public health officials must continuously monitor various *West Nile virus* (WNV) surveillance indicators to make informed decisions to attempt to minimize human infection risk. Ideally, effective surveillance indicators provide geographically sensitive and specific advanced warnings of imminent increases in human WNV risk. Since human infection risk is preceded by pathogen amplification within animal reservoirs, environmental WNV surveillance attempts to measure pathogen presence or intensity of the enzootic (animal–mosquito–animal) transmission cycle. Mosquito-transmitted pathogen surveillance should be sufficiently spatially and temporally resolved to provide disease management officials the necessary information to direct control efforts to specific areas prior to the elevation in human infection risk. At a minimum surveillance should indicate areas that are experiencing increased human risk to potentially prevent additional human infections. The sensitivity and specificity of surveillance systems must be balanced with fixed financial, labor, and equipment resources. Many of these indicators have been more extensively reviewed in Chaps. 14–16 of this book and elsewhere [1]. Table 1 lists surveillance indicators for WNV

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Table 1
Enzootic *West Nile virus* surveillance indicators

Category	Surveillance indicator	Advanced warning of human infections	Usefulness	Cost	Primary disadvantages
Sentinel animals	Antibody seroconversion	++	++	$$$	Requires phlebotomy and antibody testing, logistically difficult
Reservoir hosts	Dead bird presence/ abundance	++	+	$$	Requires pathogen testing, population dependent reporting
	Antibody or pathogen prevalence	+/−	+	$$$$	Requires phlebotomy and antibody testing, logistically difficult; low sample size
	Host species presence	+/−	+	$$	Requires species identification skills; logistically difficult across space
	Host community index	++	+++	$$	Requires species identification skills and computation; logistically difficult across space
Vectors	Species presence	+	++	$	Requires species identification skills
	Species abundance	+	+++	$	Requires species identification skills
	Pathogen presence	+++	++++	$$$	Requires species identification skills and pathogen testing capability
	Mosquito infection rate (MIR)	+++	+++++	$$$	Requires species identification skills, pathogen testing capability, and computation
	Vector index (VI)	+++	++++++	$$$	Requires species identification skills, pathogen testing capability, and computation

and includes information on their relative cost and usefulness as advanced warning of elevated human WNV risk. Though monitoring elements of both hosts and vectors can be useful in environmental WNV surveillance, most widely used indicators focus on vector-specific factors for three reasons: (1) they are relatively inexpensive and can be scaled easily to achieve moderate spatial resolution across wide areas; (2) they often provide advanced warning (1–3 weeks) of pending human infections [2]; and (3) due to the lack of an effective human vaccine, management of human exposure to vector populations is currently the only option for WNV risk reduction [1]. Mosquito-centric WNV surveillance indicators include monitoring vector presence, vector abundance, pathogen presence in vectors, pathogen prevalence (infection rate) in vectors, and abundance of infected vectors. Traditional entomologic measures of describing transmission dynamics for pathogens such as malaria including the entomologic inoculation rate, vectorial capacity, and the basic reproductive rate are not commonly used in WNV surveillance. New or novel applications of existing calculations such as the WNV host community index and force of infection give insight into vector–host interactions that are difficult to observe, but particularly important in the transmission of zoonotic arboviruses. Each of these indicators require increasing levels of skill, cost, and computation, but the additional information gained usually is accompanied by increasing level of correlation with human infection risk.

Relatively few statistical tools have been developed to aid in the estimation of human WNV infection risk. Some of these tools, such as the Centers for Disease Control and Prevention's Pooled Infection Rate calculator (Fig. 1) [3], are available at no

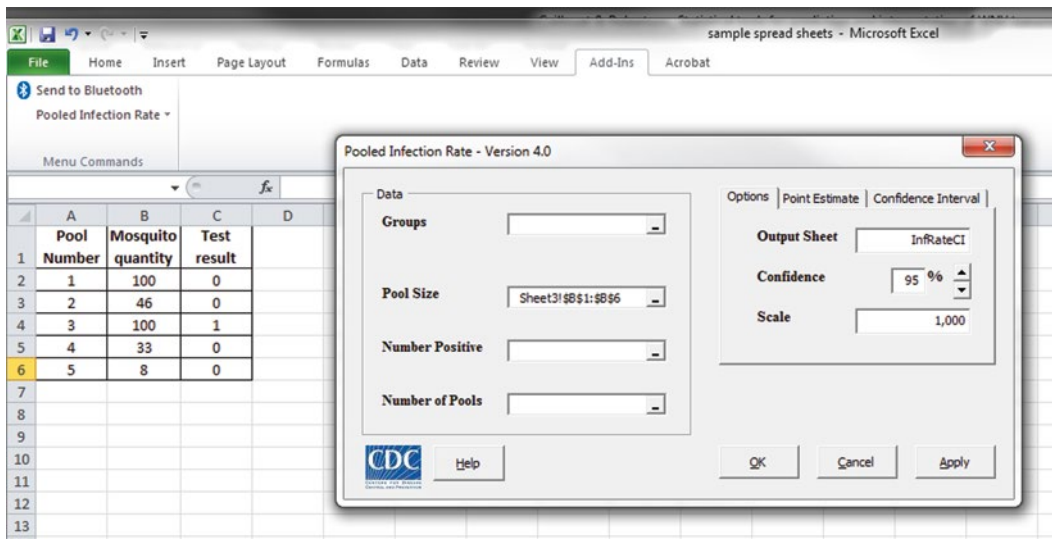

Fig. 1 Designating fields in the Pooled Infection Rate calculator Microsoft Excel Add-in

cost, in user-friendly software formats. All WNV surveillance indicators, regardless of the complexity of computation, require basic knowledge of how they are generated and how they may be biased in order to appropriately apply their estimation to the practice of WNV risk management. This chapter reviews the statistical tools and processes currently available for the estimation and interpretation of WNV infection risk to humans using enzootic transmission indicators.

2 Materials

2.1 Surveillance Data Storage

Chapters 14 and 15 outlined tools and mosquito collection devices for WNV surveillance. Once mosquitoes are collected using any type of collection device, at a minimum they should be enumerated and recorded with corresponding information regarding how they were collected (i.e., collection method), where they were collected (i.e., site identification), and when they were collected (i.e., date). If possible, mosquitoes should be identified to species using morphological taxonomic keys (such as [4]) or molecular methods. Species information should also be stored along with the collection information (*see* Tables 2 and 3). It is also a good practice to enumerate male mosquito specimens and to note the abdominal status of individual female mosquitoes (e.g., whether the female mosquito's abdomen is filled with eggs (gravid), blood, or empty). The storage and retrieval of mosquito surveillance data is greatly aided by the use of a digital database or spreadsheet software. Digital storage of surveillance data in a database file can be easily integrated into mapping software to create a geographic information system (GIS) to enable easier visualization and communication of the data.

2.2 Software to Calculate Mosquito Infection Rates

The Centers for Disease Control and Prevention has developed freely available software for the calculation of mosquito infection rates for pooled specimens. The infection rate calculator, Pooled Infection Rate 4.0 [3], is available for download at http://www.cdc.gov/westnile/resourcepages/mosqsurvsoft.html. The software operates as an "add-in" in Microsoft Excel. Follow the accompanying documentation for installation of the software. *See* also Fig. 2.

3 Methods

3.1 Vector Species Presence and Abundance

Though the monitoring of vector species abundance is a critical element of WNV control, it is not always directly correlated with WNV intensity or even pathogen presence. In other words, locations that have relatively higher vector populations may not have WNV present or may not have the highest intensity of WNV transmission [5].

Table 2
A sample mosquito surveillance data table

Pool number	Species	Date	Site	Collection method	Sex	Mosquito quantity			
						Empty	Gravid	Bloodfed	Half blood-fed/ half gravid
	Culex salinarius	7/1/2015	5th St.	Gravid Trap	Male	3			
1	*Culex salinarius*	7/1/2015	5th St.	Gravid Trap	Female	91	5	1	3
	Culex salinarius	7/1/2015	5th St.	Gravid Trap	Male	1			
2	*Culex salinarius*	7/1/2015	5th St.	Gravid Trap	Female	43	2		1
	Culex quinquefasciatus	7/3/2015	Joan St.	CDC-Light Trap	Male	5			
3	*Culex quinquefasciatus*	7/3/2015	Joan St.	CDC-Light Trap	Female	98	2		
4	*Culex restuans*	7/3/2015	Joan St.	CDC-Light Trap	Female	31	2		
	Culex restuans	7/5/2015	Bluebird St.	CDC-Light Trap	Male	11			
5	*Culex restuans*	7/5/2015	Bluebird St.	CDC-Light Trap	Female	6	2		

Specimens that are pooled for WNV testing are noted by their pool number. In this example male mosquitoes are quantified and the abdominal status of female mosquitoes is also recorded

Table 3
Sample mosquito pool data displaying the minimum required data to calculate the mosquito infection rate (MIR)

Pool number	Mosquito quantity	Test result
1	100	0
2	46	0
3	100	1
4	33	0
5	8	0

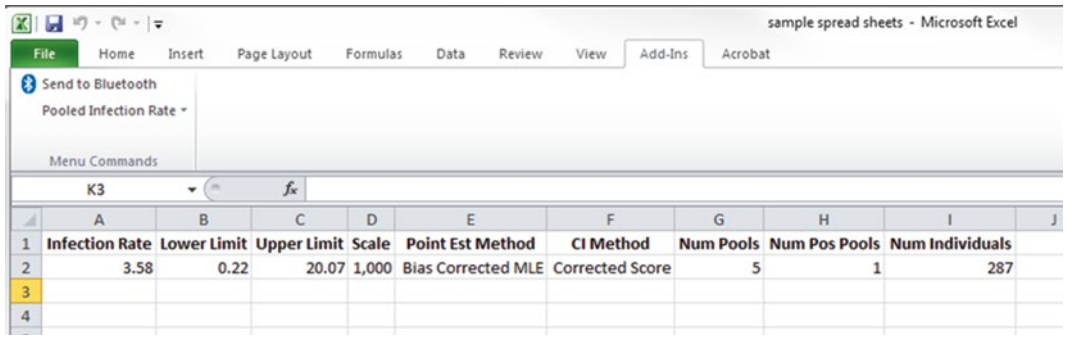

Fig. 2 Sample mosquito infection rate output. *Column A* displays the estimated mosquito infection rate (IR). *Column B* and *C* display the 95 % confidence intervals. *Columns D–I* present summary information for the estimation methods and the pooled data summary

This is due largely to the complexity of the animal host community and selectivity of mosquito vectors for certain host groups across geography [6, 7]. For this reason the presence and abundance of vector species populations alone provide a poor indication of imminent increases in human WNV infection risk.

3.2 Calculation of the Mosquito Infection Rate (IR)

The molecular detection of WNV in mosquito vectors was described in Chaps. 14 and 15. Though mosquitoes can be tested individually for the presence of WNV, they are often tested in groups or "pools" of multiple mosquitoes due to the relative rarity of the pathogen in mosquitoes in the wild. Subsampling from individual pools of specimens into "super" pools has also been shown to sensitively diagnose WNV infection in mosquitoes [8]. For individually tested specimens the mosquito infection rate (IR; number infected mosquitoes per 1000) is simply the number of infected mosquitoes divided by the number of mosquitoes tested scaled by 1000:

$$\mathrm{IR} = 1000\frac{x}{y}$$

Where x is the number of mosquitoes in which WNV was detected and y is the total number of individual mosquitoes tested.

When mosquitoes are tested in pools of multiple specimens the mosquito infection rate is based on an estimate of the number of infected individuals within the pool. The IR estimate varies with the number of individuals within the pool and with certain assumptions regarding the number of infected specimens within the pool.

The minimum infection rate (MIR) assumes that only one mosquito is infected in each pool that tests positive. The MIR can be calculated as the number of infected pools divided by the total number of mosquitoes tested:

$$\text{MIR} = \frac{\text{\# pools testing positive}}{\text{total number of mosquitoes tested}}$$

The MIR gives a lower bound on mosquito infection rates and is a poor estimator when infection rates are high or pool sizes are large [9].

The maximum likelihood estimate (MLE) of the IR estimates the actual infection rate as well as confidence intervals, without requiring any additional data beyond the pool sizes and infection status of each pool [9]. The MLE takes pool size into account and is more accurate than the MIR when infection rates are high. While variable pool sizes lead to calculations requiring numerical tools, they may also lead to improved MLE estimates [10].

3.3 Calculation of Basic Mosquito Infection Rates

Here we present the step by step procedure for calculating mosquito infection rates:

1. Open or create the mosquito pooling data table (*see* Table 3). At a minimum this table must have individual mosquito pools listed as rows and include a column indicating the number of mosquitoes per pool and the test result (usually stored as a binary 1 = infected and 0 = uninfected). Additional information such as mosquito species designations, date collected, and site information are useful to create specific infection rates based on that information.
2. In the Add-Ins Tab on the MS Excel File bar click on Pooled Infection Rate and select "One-sample". A pop-up window will appear.
3. In the window for "Pool Size" select the column indicating the quantity of mosquitoes in each pool (*see* Fig. 1).
4. Next, designate the column that includes the binary (1 or 0) test result in the "Number Positive" window.
5. Leaving the default options checked for the bias-corrected MLE is recommended.
6. Clicking OK will produce a report of the infection rate that includes an estimate of the mosquito infection rate in column A, the lower 95 % Confidence Interval (CI) in column B, upper

95 % CI in column C, scale (per 1000 mosquitoes) in column D, the method used to calculate the estimates in columns E and F, and a summary of the pools in columns G–I.

3.4 Calculate Mosquito Infection Rates by Group

To stratify mosquito infection rates across sites, dates, species, or other group requires the storage of this information along with the mosquito pooling data and selecting this information as a grouping criterion for infection rate calculations (Table 4). The Pooled Infection Rate 4.0 calculator only allows you to group infection rates by a single field. If you wish to create infection rates by two or more groups you must first stratify your dataset by these categories. For example, you may wish to stratify infection rates by species and by week—IR for *Culex pipiens* and (separately) *Culex salinarius* by week of the year. In MS Excel or other spreadsheet software this is easily accomplished by using either the data filtering or pivot table functions. Note that groups must have identical spelling and spacing—extra leading or trailing spaces or misspellings will be treated as separate groups. To illustrate the procedure for creating IR by groups we will create IRs for each calendar week in the dataset (Table 4):

1. Perform actions 1–4 in the above Subheading 3.2.
2. Designate a grouping criterion in the "Groups" window to calculate infection rates that are specific to that criterion. For instance, if you are interested in weekly trends of WNV infection rates, select the column storing the week number. TIP: To quickly calculate week numbers use the MS Excel WEEKNUM function = (WEEKNUM(specify cell with date, 1)). The number "1" in this function specifies the week to start on Sundays; a number "2" would specify the week to start on Mondays.
3. Leaving the default options checked for the bias-corrected MLE is recommended.

Table 4
A sample of a mosquito pooling data table with additional descriptive information

Pool number	Species	Sex	Mosquito quantity	Site	Collection method	Date collected	Week number	Test result
1	*Culex salinarius*	Female	100	5th St.	Gravid	7/1/2015	27	0
2	*Culex salinarius*	Female	46	5th St.	Gravid	7/1/2015	27	0
3	*Culex quinquefasciatus*	Female	100	Joan St.	CDC-light	7/3/2015	27	1
4	*Culex restuans*	Female	33	Joan St.	CDC-light	7/3/2015	27	0
5	*Culex restuans*	Female	8	Bluebird St.	CDC-light	7/5/2015	28	0

4. Click "Ok".
5. An information pop-up or error message may appear to inform you that corrections of estimates are not defined for samples that are <= 0. This occurs because some of the groups you selected do not have any infected mosquito pools. Click through these messages by selecting "Ok".

3.5 Vector Index (VI)

Though the IR is widely used and is an easily calculated WNV entomologic surveillance indicator, in certain instances it may not be well correlated with human risk. This is primarily due to the fact IRs may be high when vector abundances are low. In these situations the actual number of infected mosquitoes is often quite low, though the proportion of infected mosquitoes is high (Fig. 3). The Vector Index (VI), an estimate of the number of WNV infected mosquitoes derived from the IR and average mosquito abundance, has been shown to be more closely linked to imminent human WNV risk [11, 12]. The individual species VI can be calculated with the equation:

$$\mathrm{VI} = x\frac{y}{1000}$$

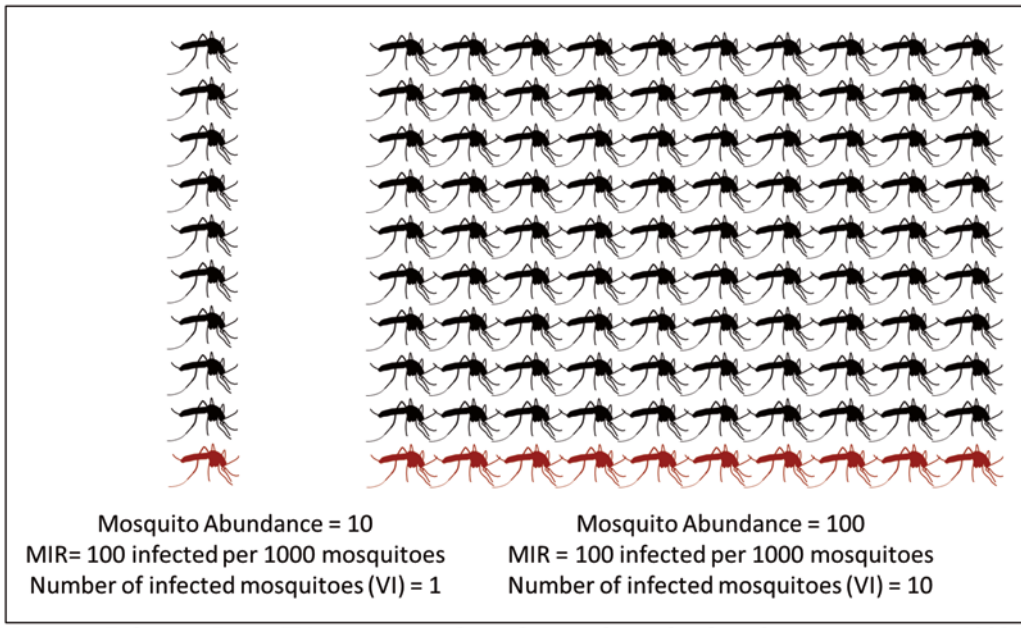

Fig. 3 A graphic demonstration of the effect of mosquito abundance on the interpretation of the mosquito infection rate (IR) and Vector Index (VI). At low mosquito abundances IR may be high, but the actual number of infected mosquitoes is low. Vector Index estimates the number of infected mosquitoes from the IR and the average mosquito abundance

where x is the IR and y is the abundance of the species. Created by Nasci et al. [13] as an indicator of human WNV risk, the VI was originally intended as an estimate of the number of infected mosquitoes (NIM) across multiple key vector mosquito species in an area. The VI calculation has been applied to describe the single species estimate of the number of infected mosquitoes [14–17] as well as the estimate of NIM across species within a genus [2, 13, 18]. Setting threshold triggers for mosquito control interventions based on VI is the current best practice for epidemic WNV management.

3.6 Calculation of the Species Vector Index and Multiple Species Vector Index Across Groups Such as Weeks or Sites

1. To calculate the species VI you must first compile the vector species abundance information. If you are calculating the VI for each individual trap location and for each night collected at this location, the mosquito abundance data is the raw number of female mosquitoes (regardless of abdominal status) collected in each trap for each night of collection. If you are creating an aggregated VI that represents data averaged from multiple collection nights at the same site or multiple sites during the same time period, you must first create the average abundance for the group.
2. Divide the IR for the group of interest or the individual trap by 1000 and multiply the product by the group average (multiple traps or time periods) or raw mosquito species count (individual trap).

3.7 Spatial Applications of the Vector Index

There have been relatively few reported geographic applications of the VI. Some studies report a single VI calculated for the entire area under surveillance (e.g., municipality or county) [2, 14]. Though VI estimates representing relatively large geographic areas, whether from individual trap sites or averaged from aggregated sites, may obscure the intensity of transmission in certain focal areas, the VI has been shown to be correlated with human WNV cases [2, 12, 17]. Jones et al. [19] created weekly and biweekly IR and VI values at the census tract level to provide a geographic and temporal illustration of entomologic WNV risk in order to guide preventative mosquito control activities. In their demonstration, Jones et al. [19] calculated IR and VI from individual mosquito traps. When mosquito abundance per trap is low, the few mosquitoes that are collected are often pooled into one pool resulting in high estimates of IRs (with large confidence intervals). By multiplying IR by mosquito abundance, the VI per individual trap night does to some extent account for the exaggeration of the IR, but care should be taken to include the 95 % confidence intervals of each IR.

3.8 Additional Measures of West Nile virus Transmission

Other indices and statistics have been created to give insight into the enzootic WNV transmission and resultant human WNV risk, but require computation that is beyond the scope of the methodology

presented in this chapter. We include a brief description of each the WNV host community index, force of infection, entomological inoculation rate (EIR), vectorial capacity (VC), and the basic reproduction number (R_0).

3.8.1 West Nile virus Host Community Competence Index and Force of Infection

The composition of reservoir hosts and vectors in a community is very important for determining levels of enzootic WNV transmission [5, 20–22]. Reservoir species are highly variable in their competence, or ability to transmit WNV [23]. Competence is a function of a host's susceptibility, infectivity, and duration of the infectious period. Competence (C) is defined as follows [23]:

$$C = SID$$

where S is the fraction of hosts susceptible to infection when challenged with WNV, I is the proportion of mosquitoes infected with WNV after feeding on the infected host, and D is the duration (in days) of viremia in the host at a sufficient level to infect mosquitoes feeding upon it. Some animal hosts never become infectious and therefore have a competence value of zero and are referred to as non competent or dead-end hosts [23]. Note the factors determining competence may be vector dependent as well as host dependent. Host diversity is frequently associated with an increased presence of non-competent hosts in a community. These hosts serve as sinks for WNV transmission as they absorb bites that might otherwise result in transmission of WNV if another competent host were bitten.

The host community competence index (CCI) is a measure of overall competence for an area [5]:

$$\mathrm{CCI} = \sum_j a_j C_j$$

where a_j is the abundance of species j and C_j is the laboratory derived competence value of species j [23]. The CCI for a community will decrease with the addition of non-competent species or species exhibiting lower WNV competence.

Vectors do not always bite hosts in proportion to their abundance; some species may be preferred hosts. Increased feeding on moderate or highly competent species will amplify transmission while preferential biting of noncompetent or low-competence species will result in the dilution of transmission [24]. A feeding preference index (P_j) can be calculated for each species as follows to quantify the heterogeneity in vector biting rates [6]:

$$P_j = \frac{f_j}{a_j}$$

Where f_j represents the proportion of total blood meals from species j and a_j is the proportion of the population abundance comprised by species j. If a species is bitten in proportion to its abundance, then the feeding preference index will be 1. A value of P_j significantly different from 1 indicates a feeding preference for or against that species.

Kilpatrick et al. [6] used the product of the feeding preference index, host abundance, and competence measures to calculate the relative contribution of a single infected individual of each species to the total infectious mosquitoes in an area (F_j) as: $F_j = a_j P_j C_j$.

Hamer et al. [25] defined a similar measure, called the amplification fraction, to estimate the fraction of WNV infectious mosquitoes that were infected by feeding upon a single individual of a certain host species. They modify the above measure by multiplying by P_j to account for the likelihood the host species has been infected:

$$F_j = a_j P_j^2 C_j.$$

Since $P_j a_j = f_j$ this simplifies to

$$F_j = f_j P_j C_j.$$

Multiplying by the abundance of species j gives the fraction of infected mosquitoes infected by all individuals of that species [26]:

$$F_j = f_j^2 C_j.$$

Summing F_j over all species gives the community force of infection [7].

3.8.2 Entomological Inoculation Rate (EIR)

The Entomological Inoculation Rate (EIR), the number of infectious bites per human per day, provides a measure of human WNV risk. The EIR will depend not only on the number of infectious mosquitoes and overall vector biting rate, but also the proportion of bites going to human hosts, as opposed to avian or other hosts. For some important vector species, such as *Culex pipiens*, this proportion is not constant but can vary throughout the season [27].

3.8.3 Vectorial Capacity and R_0

The vectorial capacity (VC) is the total number of infectious bites resulting from vectors infected by one infectious host in 1 day [28].

$$\mathrm{VC} = \frac{V/H\, b a^2 p^n}{-\ln p}$$

where V is the number of vectors, H is the number of hosts, a is the per capita per day biting rate, b is the probability per bite of transmission from vertebrate host to mosquito (we note this term

is not always included), p is the daily survival rate, and n is the length of the extrinsic incubation period of the disease. The number of bites per day per host is aV/H. The number of mosquitoes infected in one day from biting the original infected host is baV/H. These infected mosquitoes survive the incubation period of the disease to become infectious with probability p^n, then bite a times per day for the duration of their infectious period.

The basic reproduction number, denoted by R_0, is defined as the expected number of secondary infections produced by a typical infected individual over the course of its lifetime in a completely susceptible population. It is used to measure transmission at the start of an outbreak; if R_0 is greater than 1, an outbreak will occur, whereas if R_0 is less than 1 the disease will die out in the population. R_0 can be calculated by multiplying the vectorial capacity (VC) by the probability an infectious bite results in vector to host transmission (c) and the length of the infectious period of the host ($1/r$) [29]:

$$R_0 = \frac{c\mathrm{VC}}{r}.$$

Heterogeneity in vector biting rates can increase R_0 [30]. The presence of preferred hosts or host groups can result in increased levels of infection in the vector population and may even result in fewer overall infected hosts [29]. For vector-borne diseases like WNV, the amplification of the virus in the vector population still increases human risk due to increasing the EIR.

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