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Source: Journal of Medical Entomology, 48(2):453-460. 2011.
Published By: Entomological Society of America
DOI: http://dx.doi.org/10.1603/ME10193
URL: http://www.bioone.org/doi/full/10.1603/ME10193

Arbovirus Models to Provide Practical Management Tools for Mosquito Control and Disease Prevention in the Northern Territory, Australia

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J. Med. Entomol. 48(2): 453–460 (2011); DOI: 10.1603/ME10193

ABSTRACT Ross River virus (RRV) causes the most common human arbovirus disease in Australia. Although the disease is nonfatal, the associated arthritis and postinfection fatigue can be debilitating for many months, impacting on workforce participation. We sought to create an early-warning system to notify of approaching RRV disease outbreak conditions for major townships in the Northern Territory. By applying a logistic regression model to meteorologic factors, including rainfall, a postestimation analysis of sensitivity and specificity can create rainfall cut-points. These rainfall cut-points indicate the rainfall level above which previous epidemic conditions have occurred. Furthermore, rainfall cut-points indirectly adjust for vertebrate host data from the agile wallaby (*Macropus agilis*) as the life cycle of the agile wallaby is intricately meshed with the wet season. Once generated, cut-points can thus be used prospectively to allow timely implementation of larval survey and control measures and public health warnings to preemptively reduce RRV disease incidence. Cut-points are location specific and have the capacity to replace previously used models, which require data management and input, and rarely provide timely notification for vector control requirements and public health warnings. These methods can be adapted for use elsewhere.

KEY WORDS mosquito control, arbovirus, Ross River virus, mosquito-borne disease, modeling

Ross River virus (RRV) is a mosquito-borne virus that requires a vertebrate host to complete its life cycle, and so by definition is a zoonosis. The primary vectors in the Northern Territory (NT) of Australia are the northern salt-marsh mosquito *Aedes vigilax* (Skuse) and the common banded mosquito *Culex annulirostris* (Skuse) (Whelan 1987, 1989; Russell 2002; Whelan et al. 2006; Kurucz et al. 2009a). The virus is thought to be maintained primarily by enzootic cycles, although it may be maintained in some localities by transovarial transmission (Lindsay et al. 1993, Russell 2002). The most commonly implicated reservoir hosts are marsupials (Kay et al. 1982, Russell 1994). Marsupials provide the best disease amplification, with humans considered poor amplifiers, and are usually regarded as dead-end hosts in the cycle (Kay et al. 1982, Russell 1994). It has been speculated that RRV and Barmah Forest virus are evolutionally linked with marsupials. This explains the restriction of these viruses to Australia and Papua New Guinea, where there are many endemic marsupial species (Kay et al. 1982, Lindsay et al. 1995). Serological studies indicate that marsupials are commonly infected with RRV, and macropods (kangaroos and wallabies) are known to be major reservoirs (Doherty et al. 1971). This link between marsupials and RRV is consistent with the failure of RRV to establish outside this region after the 1979 Western Pacific epidemic (Mackenzie et al. 1998).

RRV disease is the most geographically widespread and frequently occurring arboviral disease in Australia, with up to 4,800 cases reported in some years (Communicable Diseases Australia 2006). In humans RRV disease is nonfatal, with minor symptoms such as the following: rash, fever, arthritis, arthralgia, myalgia, general weakness, and fatigue (Flexman et al. 1998, Harley et al. 2002, Jacups et al. 2008a). Although the symptoms of RRV infection are mild, the arthritis and fatigue can be debilitating for 3–6 mo, with postinfection fatigue further affecting a minority of cases (12%) (Hickie et al. 2006). This disease is of economic concern because RRV infections occur most commonly in 30–34 yr olds, a critical age group for workforce participation (Jacups et al. 2008b). Financial costing from a 1997–1999 Australian cohort estimated $1,018 (Australian currency) per patient averaged across all severity levels. Calculations by others indicate that annual costs to the Australian health system amount to more than $10 million (United States currency) in direct medical costs, with millions more spent on mosquito control (Aaskov et al. 1998, Harley et al. 2001). Mechanisms for surveillance and control of RRV transmission include surveillance of human cases, monitoring of mosquito vectors, surveillance of meteorological conditions, timely and targeted vector

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control, and public health warnings, sometimes with the aid of predictive models (Whelan et al. 1997, Jacups et al. 2008a).

Predictive early-warning models have been produced for RRV infections for different regions in Australia, including locations in the wet-dry tropics such as Darwin, NT (Jacups et al. 2008a). The creation of a regionally-specific predictive model for RRV epidemics can guide public health interventions, such as the timing of media releases, which notify the public to minimize vector attack by the use of protective clothing and repellents and the avoidance of high mosquito-density habitats. However, models require maintenance, collecting, cleaning, and imputing of data, as well as staff training. The South Australian-based RRForcastor requires the input of the predicted rainfall using Bureau of Meteorology three monthly outlooks for the preceding 3 mo as a proportion of the historic mean for each region (Williams et al. 2007, 2009). Queensland Health has introduced the Vector-Borne Disease Early Detection and Surveillance System, designed to provide public health officials (secure log-in required) with decision-support tool to assist with the management of mosquito-borne disease. By mapping weekly counts of RRV infection by Local Government Area against a threshold (algorithm not given), it provides public health officials with access to disease data for RRV and Barmah Forest virus in Queensland (Queensland Institute of Medical Research 2010). The model for Darwin requires counts of three mosquito species, plus total rainfall from the preceding month and the average minimum monthly temperature from the preceding 3 mo (Jacups et al. 2008b). Moreover, the timeliness of predictive models is usually limited; as such early-warning systems notify the public to avoid mosquito attack, but rarely can models provide timely notification for mosquito control. Conditions for RRV disease epidemics are commonly signaled by peak numbers of adult vector mosquitoes or disease cases, by which time mosquito larval control efforts are redundant. Broad area vector adulticiding is not considered practical or effective in the Darwin area because of the short duration of effective control, the potential impact on non-target organisms, and the inability of aerosol fogs to penetrate thick vegetation. Once adult mosquitoes are abundant, larviciding is no longer practical or effective. Public health professionals are then left with media releases and public warnings as the only preventative measures to reduce the infection rate from this debilitating disease.

Meteorological factors, especially rainfall and temperature, are established drivers of arboviral epidemics (Tong and Hu 2001, Day and Shaman 2008). For instance, exceptionally high rainfall coincided with all major regional Rift Valley fever epidemics in Kenya since 1951 (Linthicum et al. 1999). Summer rainfall is associated with Murray Valley encephalitis seroconversion in chickens, with a cut-point (threshold) of >100 mm rain for Alice Springs, and >400 mm for Tennant Creek (Whelan et al. 2003). Furthermore, the analysis of Australian RRV epidemics between 1886 and 1998 showed above average rainfall commonly preceded RRV epidemics (Kelly-Hope et al. 2004, Williams et al. 2009). Epstein reports the importance of weather parameters in projecting conditions conducive to disease epidemics (Epstein 1999). Knowledge of disease/environmental associations is essential for predicting and responding to weather-related increases in RRV incidence.

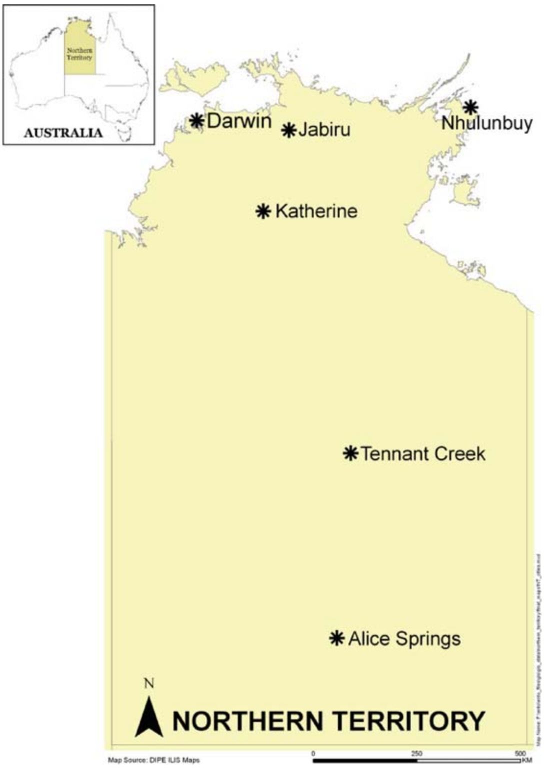

Fig. 1. Major townships in the NT with adult mosquito monitoring programs. (Online figure in color.)

The Medical Entomology (ME) unit of the Department of Health and Families, NT, currently monitors vector mosquito populations in the major NT towns (Fig. 1) using adult mosquito encephalitis vector surveillance traps (Rohe and Fall 1979). To reduce the risk of arboviral disease transmission and nuisance mosquito biting to Darwin residents, helicopter-assisted larval surveys guide ME mosquito larval control efforts, specifically for *Ae. vigilax* and *Cx. annulirostris* (Whelan 1987, 1989; Russell 2002; Whelan et al. 2006; Kurucz et al. 2009a). Aerial surveys and control operations are expensive and labor intensive, usually conducted by three ME staff who survey pooled water and indicator sites by helicopter, landing frequently to sample mosquito larvae (Kurucz et al. 2009a). Aerial larval control operations are rarely performed outside the Darwin urban area proximity, although ground operations (on quad bikes) and control are routinely performed, sometimes in cooperation with other landholders in the urban and peri-urban areas where helicopter operations are impractical.

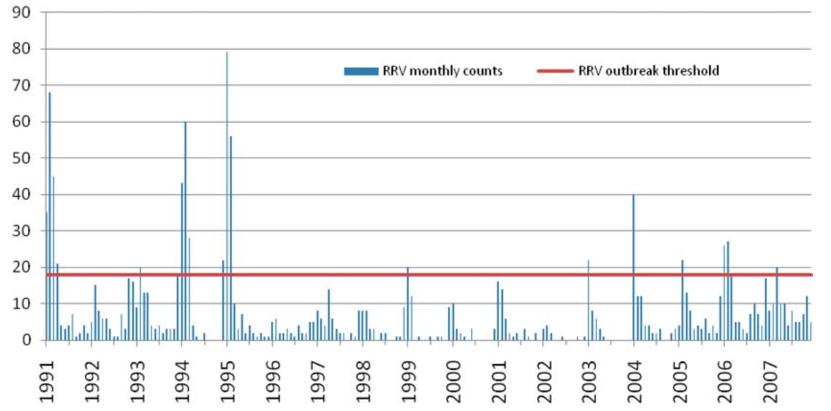

Fig. 2. Monthly Darwin RRV counts with RRV outbreak threshold. (Online figure in color.)

We sought to create a management tool, not just an early-warning system, to improve ME's intensive mosquito larval operations by providing timely advisories for vector control. We have addressed this problem by applying sensitivity and specificity cut-points from logistic regression postestimation methods. This method has previously been used as an epidemiological tool for health risks (Bruzzi et al. 1985) and to generate malaria parasitemia cut-points for diagnosing clinical malaria (Smith et al. 1994, Tjitra 2001). Applying these methods to a logistic regression for RRV epidemic conditions, including the variable "total cumulative rainfall during the preceding month," allows a sensitivity and specificity analysis that determines the rainfall cut-point above which previous RRV epidemics have occurred, specific to each township in the NT. These rainfall cut-points can then prospectively act as simple early-warning systems that notify of potential RRV epidemic conditions across the NT. When used in Darwin, these cut-points provide ME with a management tool to deliver an earlier indicator or RRV outbreaks than previously used models, and to indicate timing for priority vector control to decrease the risk of RRV disease epidemics. For the other major townships in the NT where vector control measures are rarely undertaken, cut-points provide early notification of disease risk to assist public health warnings.

Woodruff et al. (2006) found that preconditions for an epidemic in temperate Western Australia were established by November; meteorologic conditions after November did not determine the occurrence of epidemics, although conditions in later months influenced epidemic scale. In the NT and Queensland, January and February are peak months for RRV notifications (Gatton et al. 2005), whereas the critical months for establishing ecological epidemic conditions are just before the start of the RRV disease season in the September to November period (Whelan et al. 1997). Furthermore, larval control is less relevant later in the wet season (December–April) when the tidally influenced wetlands become seasonally flooded, creating the opportunity for larval predation by fish, and offering fewer sites for salt-marsh mosquito oviposition. We thus assessed December and January rainfall, as these months have historically been associated with establishing epidemic conditions (Whelan et al. 1997).

Materials and Methods

Case Data. Laboratory-confirmed cases of RRV infections notified to the arbovirus disease surveillance program of the Northern Territory Centre for Disease Control during the 17 yr between 1 January 1991 and 31 December 2007 (204 mo) were included. Data were provided by NT Centre for Disease Control as monthly counts for all six major towns in the NT. Woodruff et al. (2002) defined "RRV outbreak" or "RRV epidemic" as any financial year in which the number of cases exceeded the mean plus 1 standard deviation during the study period (Fig. 2). We analyzed climatic and disease variables at a monthly time scale and thus defined an epidemic month as a calendar month in which the number of cases exceeded the monthly mean plus 1 standard deviation (rounded to the nearest integer) for the 17-yr study period. This study was approved by the Joint Human Ethics Committee of the Northern Territory Department of Health and Families, and Menzies School of Health Research, approval number 06/28.

Meteorologic Data. Daily rainfall, daily temperature (minimum, maximum, mean daily), humidity (minimum, maximum, mean daily), and tidal (sea level) data were provided by the Australian Bureau of Meteorology for each of the relevant NT townships throughout the study period. To identify the most strongly associated variables for each predictive model, meteorological data were cumulated or averaged, with lag times applied for up to 3 mo (Jacups et al. 2008b). Tide was only included in models of coastal or subcoastal townships (Jabiru has tidally influenced river systems within salt-marsh mosquito flight range).

Statistics. Correlations were used to examine meteorological associations with RRV epidemics for each of the major townships in the NT. The best fit of each meteorological variable (or derivative) most strongly associated with RRV epidemics was then included in multivariate logistic regression models,

Table 1. The association of rainfall and RRV epidemics, NT

Exposure	Disease epidemic		Totals
	RRV epidemic month	RRV nonepidemic month	
Rainfall > c	$n_c\lambda_c$	$n_c(1-\lambda_c)$	n_c
Rainfall ≤ c	$N\lambda - n_c\lambda_c$	$N(1-\lambda) - n_c(1-\lambda_c)$	$N - n_c$
Totals	$N\lambda$	$N(1-\lambda)$	N

fitted for parsimony. Coefficients with errors and 95% confidence intervals (Smith et al. 1994, Woodruff et al. 2002) were generated as previously verified, using a multivariate logistic regression model in the form of the following:

$$\text{Log}\ (P/[1-P]) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n \quad [1]$$

Where P is the probability of an epidemic, x_1 are meteorological variables specific to each township, and $\alpha, \beta_{1\ldots n}$ are constants estimated from the data. As previously verified and published, the following formulae were used to estimate sensitivity and specificity of RRV epidemic definition (Table 1) (Smith et al. 1994, Tjitra 2001):

$$\text{Sensitivity} = (n_c\lambda_c)/(N\lambda) \quad [2]$$

$$\text{Specificity} = 1 - n_c(1-\lambda_c)/N(1-\lambda) \quad [3]$$

$$\text{Positive predictive value (PPV)} = n_c\lambda_c/n_c = \lambda_c \quad [4]$$

Where c represents the rainfall cut-point, n_c represents the number of months with rainfall cut-points in excess of c for each township, and λ_c represents the proportion of true positives (PPV) (5). The symbol $n_c\lambda_c$ represents the number of RRV epidemic months correctly predicted; $n_c(1-\lambda_c)$ represents the number of months incorrectly predicted as RRV epidemic months. N represents the total number of months for the study, and λ is the proportion of months that are RRV epidemic months (Smith et al. 1994, Tjitra 2001). The crossover point between sensitivity and specificity creates the threshold, as previously described (Smith et al. 1994, Tjitra 2001). χ^2 tests were used to compare outbreak months below and above cut-points for each of the NT townships. Statistical analyses were performed using Intercooled Stata 11.0 (Stata, College Station, TX) and R freeware (R Development Core Team 2010).

Results

The best-fit logistic regression models are shown for each of the NT townships as determined by Akaike information criterion, with only biologically plausible combinations retained (Table 2). All final models included rainfall, with 1-mo lag, whereas some also contained variables for minimum monthly temperature, average minimum humidity or tide, with various lag times. Darwin urban sensitivity, specificity, and positive predicted value with rainfall cut-point are provided (Fig. 3). The highest cumulative rainfall cut-point was for Darwin urban at 279 mm, with the lowest for Alice Springs at 41 mm (Table 2). These results approach average December rainfall as provided by Bureau of Meteorology (Table 3), indicating that some years will require additional larvicidal control in December, whereas most years will require additional January control. These rainfall cut-points have been cross-tabulated against RRV outbreak months for each of the NT townships (Table 4).

Table 2. Logistic regression models with postestimation-generated cumulative rainfall cut-offs for NT townships

Likelihood of RRV outbreak	Independent variables	Beta	SE	*p*	95% CI	AIC	Sensitivity/ Specificity crossover (%)	Monthly rainfall cut-points (mm)
Darwin	Rainfall (1-mo lag)	0.005	0.001	<0.001	0.003–0.009	78.5	77	279
	+ Avg min. monthly temp (3-mo lag)	1.28	0.30	<0.001	0.49–1.6			
	+ Max tide (3-mo lag)	−7.83	2.31	0.001	−12.4–−3.3			
Jabiru	Rainfall (1-mo lag)	0.005	0.001	<0.001	0.003–0.008	187.3	77.7	181
	+ Max tide	−0.91	0.481	0.058	−1.85–−0.032			
Katherine	Rainfall (1-mo lag)	0.009	0.002	<0.001	0.005–0.014	84.7	75.8	207
	Avg min. monthly temp (3-mo lag)	0.772	0.263	0.003	0.26–1.28			
	Average humidity (2-mo lag)	−0.17	0.047	<0.001	−0.27–−0.08			
Nhulunbuy	Rainfall (1-mo lag)	0.004	0.001	0.003	0.002–0.008	103.8	78	270
	+ Max tide (2-mo lag)	−2.66	1.44	0.65	−5.49–−0.17			
Tennant Creek	Rainfall (1-mo lag)	0.01	0.003	0.001	0.005–0.018	44.3	88.5	74
	Avg min. monthly humidity (2-mo lag)	0.11	0.037	0.001	0.045–0.19			
Alice Springs	Rainfall (1-mo lag)	0.01	0.004	0.012	0.002–0.019	136.2	83	41
	Avg min. monthly temp (1-mo lag)	0.19	0.050	<0.001	0.19–0.29			

AIC, Akaike information criterion; CI, confidence interval; SE, standard error.

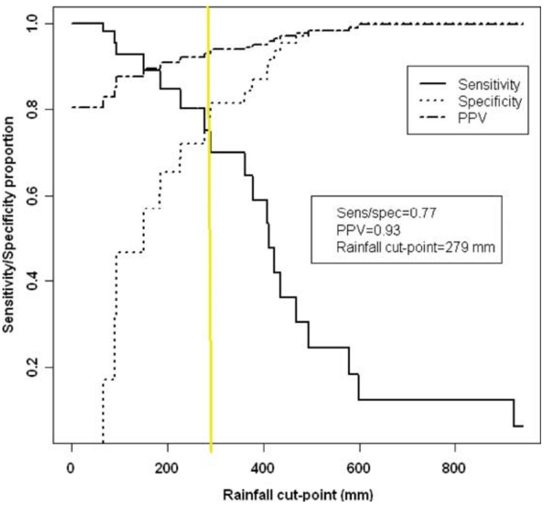

Fig. 3. Sensitivity, specificity, and PPV fraction-RRV outbreak months for Darwin, NT. (Online figure in color.)

Table 4. RRV outbreak months for major NT townships (1991–2007)

Township	Months above cut-points	Months below cut-points	Significance $(p)\ \chi^2$
Darwin			
Outbreak month	13	7	
Non-outbreak month	30	154	<0.001
Jabiru			
Outbreak month	20	19	
Non-outbreak month	45	120	0.004
Katherine			
Outbreak month	19	8	
Non-outbreak month	20	157	<0.001
Nhulunbuy			
Outbreak month	8	7	
Non-outbreak month	28	161	<0.001
Tennant Creek			
Outbreak month	6	3	
Non-outbreak month	31	164	<0.001
Alice Springs			
Outbreak month	8	20	
Non-outbreak month	21	155	0.019

Discussion

We have produced accurate meteorologic-only models for predicting RRV epidemics across the NT. The models differ across NT townships, highlighting the variability of local meteorologic factors influencing RRV epidemics. This is consistent with findings that conditions for RRV disease outbreaks are locally specific and should not be generalized across states or territories (Tong and Hu 2002, Gatton et al. 2005, Jacups et al. 2008a). Using the postestimations from these models has extended their application to the creation of practical rainfall cut-points that guide Darwin larval control regimes and facilitate timely public health warnings for major NT towns. This is the first time the statistical methods previously used to create malaria parasitemia cut-points have been used to predict epidemics of an arbovirus using meteorological inputs. The cut-points are simple indicators of the cumulative threshold of rainfall required to commence epidemic conditions for December and January, the months in which RRV preepidemic conditions are established.

The start of RRV transmission in Darwin usually coincides with a rise in numbers of *Ae. vigilax* during buildup months (September–November), with most transmission taking place in the December to January period when both *Ae. vigilax* and *Cx. annulirostris* are present. Presently, ME conducts surveys for salt-marsh mosquito larvae in Darwin's tidally influenced wetlands after high tides (>7.4 m) and/or >25 mm rain (Whelan 2007). Initial rainfall on the wetland occurring at the end of the dry season is quickly absorbed and has little impact on salt-marsh mosquito numbers (Kurucz et al. 2009b). Later rain of 10–25 mm or more may cause pooling in the drains or wetlands, and result in flooding areas of habitat containing drought-resistant eggs, leading to an increase of adult salt-marsh mosquitoes.

Table 3. Rainfall averages for major NT townships (1941–2008) (Australian Bureau of Meteorology 2008a) compared with generated monthly rainfall cut-points from Table 2

Township	Average annual rainfall (mm)	Average Dec. rainfall (mm)	Average Jan. rainfall (mm)	Monthly rainfall cut-points[a] (mm)
Darwin	1,706	246	420	279
Jabiru	1,583	224	356	181
Katherine	1,118	211	270	207
Nhulunbuy	1,447	174	284	270
Tennant Creek	452	68	107	74
Alice Springs	278	37	35	41

[a] Generated cut-points from Table 2.

The provision of a cumulative rainfall threshold that is specific for each NT town adjusts for heavy downpours in a short period or small amounts of rainfall over longer periods of time. For the Darwin coastal wetlands, larvae of the salt-marsh mosquito can best be controlled 3–4 d after salt or fresh water inundation (Whelan et al. 1997). Salt-marsh mosquitoes initiate RRV disease outbreaks and also assist in the maintenance of enzootic viral endemicity and transmission, as well as possibly enabling virus survival via drought-resistant eggs over the dry season (Kay 1982, Whelan et al. 1997, Glass 2005). Targeting rainfall also enables timely control of *Cx. annulirostris*, the major vector of RRV disease epidemics in the NT later in the wet season (Whelan et al. 1997, Glass 2005, Jacups et al. 2008b). The cumulative rainfall cut-point is a practical management tool that has the capacity to guide ME larval surveys and enable timely aerial and ground-level larval control responses (Woodruff et al. 2006), hence reducing labor-intensive larval sampling in Darwin's wetlands. The method may be applicable to other areas where rainfall is an important determinant for RRV epidemics.

Throughout Australia, RRV epidemics have been linked to increases in rainfall, temperature, and the Southern Oscillation Index (Maelzer et al. 1999, Woodruff et al. 2002, Kelly-Hope et al. 2004). Although most RRV infections occur in the tropical regions, little has been published on the relation between RRV epidemics and environmental factors in northern Australia (Gatton et al. 2005). Gatton et al. (2005) found that rainfall was the most important predictor of RRV disease epidemics for central and northern regions of Queensland. Additionally, the majority of epidemics in Queensland commenced in January or February, indicating that meteorologic factors leading to RRV disease epidemics occur early in the RRV season, namely December and January. Thus, preconditions of rainfall or other meteorological and environmental variables responsible for commencing the epidemic are of paramount importance in predicting or preventing epidemics (Gatton et al. 2005). Furthermore, extreme weather rainfall events are increasing in frequency as the world's climate changes (Epstein 2002, Intergovernmental Panel on Climate Change 2007), and extreme summer rainfall further increases the likelihood of large RRV disease epidemics (Epstein 2002, Woodruff et al. 2002, Whelan et al. 2003). Our results add to the growing body of data exploring the impact of weather and meteorologic factors on infectious disease (Epstein 2002).

One limitation of this study is the classification of cases based on residential address or post office, as identified on diagnostic blood sample. This address may not reflect the true location of disease acquisition. However, for most cases, this address is the likely location of acquisition (Whelan et al. 1997). The models created high PPVs, and these are best explained by relatively low numbers of false positives, as RRV outbreak months in the NT only occur in wet season months; thus, the Woodruff definition detected fewer outbreak months than would have occurred if environmental variables other than rainfall were strongly at play. In contrast, South Australian RRV epidemics are strongly associated with Murray River height rather than rainfall (Williams et al. 2009).

We recognize that vertebrate hosts play a vital role in the maintenance and amplification of this virus (Russell 1998, Jacups et al. 2008b). Agile wallabies (*Macropus agilis*) living at East Point Reserve, Darwin, reproduce throughout the year, with greater numbers of large pouch young observed during wet season months (Stirrat 2008). Moreover, there is a peak of RRV naive wallabies emerging from the pouch in December, which coincides with the establishment of outbreak conditions for RRV disease (Stirrat 2008). Our created cut-points for December and January indirectly incorporate vertebrate host data, as the life cycle of the agile wallaby appears to be intricately meshed with the environment of the Australian wet-dry tropics (Stirrat 2008).

Whereas this tool is yet to be validated by ME, there are indications of its applicability in the approach to the next RRV disease season. Darwin recently received unseasonal rainfall in September 2010 of 40 mm (historical average 15.4 mm) and October 2010 of 157.8 mm (historical average 68.7 mm) (Australian Bureau of Meteorology 2008b). This rainfall was accompanied by unusually high tides of >7.7 m from August to October, which, combined with this rainfall, resulted in extremely high and sustained numbers of *Ae. vigilax* over a 6-wk period that has been unprecedented in >30 yr. The ME responded to the environmental events with routine aerial and ground larval control, but by the end of October there was no outbreak of RRV and, indeed, very few RRV cases reported from the Darwin area. Moreover, agile wallabies (which live in close proximity to Darwin residential areas) have the greatest number of large pouch young during wet season months (December–April), confirming the intricate connection between vertebrate host life cycle, rainfall, and vector numbers. These recent peaks of vectors, in the absence of a subsequent rise in RRV disease cases, indicate that vector numbers alone are not necessarily precursors for RRV outbreaks or epidemics. This is consistent with results in this study that hold December and January as the months in which RRV outbreak conditions are set.

We have produced accurate meteorologic-only models for RRV disease epidemics for each of the major NT towns. Additionally, we have created cumulative rainfall cut-points that provide useful management tools for mosquito control and disease prevention programs. This rainfall threshold has the capacity to reduce the need for expensive helicopter-assisted or ground-based labor-intensive field sampling time. Additionally, these cut-points have superseded predictive models, which require more complex data collection and maintenance, but do not provide timely notification of approaching RRV epidemic conditions. This method may be used to generate meteorological cut-points for other areas in Australia and, indeed, globally for other mosquito-borne diseases.

Acknowledgments

We thank Peter Markey, Centre for Disease Control, Darwin, for providing RRV disease notifications; Joseph McDonnell from Menzies School of Health Research for statistical advice; and all Medical Entomology staff, past and present, for tirelessly surveying, monitoring, and managing mosquito populations across the Northern Territory. Raelene Whitters is thanked for providing Fig. 1. We also thank Sam Cleland and James Turnbull from the Northern Territory Regional Office, Bureau of Meteorology, who cheerfully provided weather data. This work was supported by an Australian Research Council Linkage Grant and a National Health and Medical Research Council and Sidney Myer Foundation postgraduate scholarship.

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Received 10 August 2010; accepted 28 November 2010.