Predictive modelling of Ross River virus notifications in south-eastern Australia.

Z. Cutcher [a,b], E. Williamson [a,c], S. E. Lynch [d], S. Rowe [b], H. J. Clothier [a], S. M. Firestone [e *]

[a] Melbourne School of Population and Global Health, The University of Melbourne, Parkville, Victoria 3010, Australia.

[b] Victorian Department of Health and Human Services, Communicable Disease Epidemiology and Surveillance, Health Protection Branch, Melbourne, Victoria 3000, Australia.

[c] London School of Hygiene and Tropical Medicine, London, United Kingdom.

[d] Victorian Department of Economic Development, Jobs, Transport and Resources, Biosciences Research Division, AgriBio Centre, Bundoora, Victoria 3083, Australia.

[e] Asia-Pacific Centre for Animal Health, Faculty of Veterinary and Agricultural Sciences, The University of Melbourne, Parkville, Victoria 3010, Australia.

*Corresponding author: Tel: +61 3 9035 7891; Fax: +61 3 8344 7374;
E-mail: Simon.Firestone@unimelb.edu.au

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Summary

Ross River virus (RRV) is a mosquito-borne virus endemic to Australia. The disease, marked by arthritis, myalgia and rash, has a complex epidemiology involving several mosquito species and wildlife reservoirs. Outbreak years coincide with climatic conditions conducive to mosquito population growth.

We developed regression models for human RRV notifications in the Mildura Local Government Area, Victoria, Australia with the objective of increasing understanding of the relationships in this complex system, providing trigger points for intervention and developing a forecast model. Surveillance, climatic, environmental and entomological data for the period July 2000–June 2011 were used for model training then forecasts were validated for July 2011–June 2015.

Rainfall and vapour pressure were the key factors for forecasting RRV notifications. Validation of models showed they predicted RRV counts with an accuracy of 81%. Two major RRV mosquito vectors (*Culex annulirostris* and *Aedes camptorhynchus*) were important in the final estimation model at proximal lags.

The findings of this analysis advance understanding of the drivers of RRV in temperate climatic zones and the models will inform public health agencies of periods of increased risk.

1. Introduction

Ross River virus (RRV), Family *Togaviridae* Genus *Alphavirus*, is the most common mosquito-borne virus in Australia, with the largest burden occurring in the tropical north [1]. Symptoms in humans include debilitating fatigue, muscle and joint pain that persist between 3–6 months, and up to a year in some cases [2], leading to significant morbidity and economic loss [3]. However, 55–75% of cases are asymptomatic [4].

In the southeast State of Victoria, RRV is endemic with seasonal incidence. Most cases occur during the Southern hemisphere summer and early autumn, so reporting of arbovirus notifiable disease surveillance data typically refers to Australian financial years (1 July to 30 June the following calendar year) [1]. In the period July 2005–June 2010, a mean of 214 human cases were notified per year in Victoria (3.8 per 100,000 people per year), with the majority acquiring infection in either northern regions of the State (the Murray Valley) or southeast coastal regions [1]. Outbreaks have occurred in 1992/93, 1996/97, and more recently in 2010/11 when 1312 cases were notified across the State (23.3 per 100,000 people) [5].

The epidemiology of RRV is complex with the disease maintained in wildlife reservoirs and transmitted to humans by mosquitoes, with human-mosquito-human transmission potentially occurring during epidemics [4]. The virus has been isolated from over 40 different mosquito species however only a small number are thought to be competent vectors [6]. The predominant mosquito vector species vary by location and season. Macropods are thought to be the major wildlife reservoir, which also vary by ecological niche. Other marsupials, rodents and flying foxes may also be involved [6], particularly in urban areas [4]. Horses can also be clinically infected [7], however their role in amplifying the virus is unclear.

1.1. Arboviral surveillance and intervention in Victoria

Ross River virus is a notifiable human disease under the Public Health and Wellbeing Regulations (2009). In Victoria, doctors and/or pathology laboratories must notify all laboratory confirmed cases to the Department of Health and Human Services (DHHS) within five days of diagnosis. According to the nationally agreed case definition [1] laboratory definitive evidence confirming a case requires either:

- isolation of RRV, or
- detection of RRV nucleic acid, or
- immunoglobulin G (IgG) seroconversion or a significant increase in antibody level or a ≥fourfold rise in titre to RRV, or
- detection of RRV-specific IgM, in the absence of Barmah Forest virus IgM, unless Ross River virus IgG is also detected, or
- detection of RRV-specific IgM in the presence of Ross River virus IgG.

Control of arboviruses relies on early detection of increased levels of mosquitoes and/or virus activity, prompting public health interventions including vector control and public education for bite prevention [8]. Under the Victorian Arbovirus Disease Control Program (VADCP) local governments across Victoria implement surveillance and control strategies on vector mosquito populations during the peak season between November and April each year when most human arbovirus notifications are received [9]. This program has been providing standardized adult mosquito monitoring and sentinel chicken surveillance targeted at Murray Valley encephalitis (MVE) and other endemic arboviruses since 1991 in a One Health model of collaboration. The Victorian Department of Economic Development, Jobs, Transport and Resources (DEDJTR) provides virological and entomological support to the VADCP, funded equally by the DHHS and the local governments involved, overseen by a multidisciplinary Task Force. Surveillance involves weekly mosquito trapping using carbon dioxide and light-baited traps in eight local government areas across Victoria. Mosquitoes are counted and identified by species and viral isolation is attempted in an effort to detect the presence of RRV.

Before and during each peak season for arboviral activity, the VADCP analyses three broad environmental indicators [9-11] of conditions suitable for increased MVE virus activity in southeast Australia. Meteorological data (rainfall in the catchment basins of the four main river systems in Eastern Australia and proxy measures for the Southern Oscillation Index (SOI) and La Niña events) are considered by DHHS and councils to inform of likely disease occurrence and when to instigate interventions. No models are currently available to combine these data for RRV prediction, with public health interventions being informed by routine notifiable disease surveillance and mosquito monitoring through the VADCP.

1.2. Modelling and prediction

Due to the climatic dependence of wildlife and mosquito populations, models using climate and/or entomological variables to predict RRV incidence may be helpful for informing disease control activities and forecasting the impact of climate change. A detailed review [3] describes previous models for RRV. Most predictive models for RRV have used logistic regression to estimate the odds or probability of an outbreak within a season, using seasonal variables at fixed points in time [12-16]. Others have explored prediction of disease using time-series analysis techniques [12], such as seasonal autoregressive integrated moving average and polynomial distributed lag (PDL) time-series models [17], and also negative binomial regression [18], to predict rates of disease, rather than simply whether or not an outbreak might occur in a season. Models tailored to conditions at the local level have tended to have better predictive capacity than broader geographic models [13]. All previous models based on RRV surveillance data for Southern Australia have estimated associations with annual case counts, with only two incorporating both entomological and climatic variables (for the southwest region of Western Australia [13] and southern South Australia [15]). None of the models for RRV in southern Australia have attempted to model monthly counts and none have explicitly undertaken out-of-sample validation (forecasting), however their outputs have informed surveillance and control activities.

Models combining mosquito count and climate data have produced better results than models considering climatic variables alone [13, 17]. For example, Woodruff et al. (2006) developed early and late warning models for RRV outbreak years in 14 statistical local areas of Western Australia and found climate data alone had 64% sensitivity for an early warning model, and the addition of mosquito surveillance data increased the sensitivity to 85%. Previous models for predicting RRV in Victoria [16] have used only climatic data at one time point per season (total rainfall in July, maximum temperature in November) to estimate the probability of an outbreak during peak transmission season for two adjacent areas in the Murray Valley, achieving in-sample sensitivity (internal 'rotational' validation) of between 64–96% for predicting an outbreak season.

The aim of this analysis was to develop predictive models for monthly counts of human RRV notifications in a highly affected inland location. Specific objectives included estimating the association between notified case counts and explanatory climatic, environmental and entomological variables, evaluating the usefulness of mosquito count data for informing public health interventions by estimating trigger points for action and, lastly, developing a forecasting tool.

2. Methods

2.1. Data

Mildura Local Government Area (LGA), located inland in northwest Victoria (Figure 1) was selected for this analysis as it has the highest RRV disease burden in the State. RRV notifiable disease surveillance data for the period July 2000–June 2015 were provided by the DHHS including the following variables: estimated date of onset, 5 year age-group, sex and residential address (or exposure address where ascertained at interview by health officials). These data were geocoded utilising the Google Maps® application programming interface, aggregated by month of onset and divided by annual Australian Bureau of Statistics estimates of the resident LGA population.

Weekly mosquito trapping count data were provided by the Victorian Department of Economic Development, Jobs, Transport and Resources (DEDJTR) for the same time period, for four traps in the Mildura LGA. Six species of interest were investigated for predictive value, including two thought to play a major role in Victoria in RRV transmission [4] (*Aedes camptorhynchus* and *Culex annulirostris*), two mosquito species with possible roles in transmission (*Ae. notoscriptus*, *Coquillettidia linealis*) and two further species with unknown importance for RRV transmission (*Cx. australicus*, the principal vector for MVE, and *Cx. globicoxitus*). Mosquitoes are only counted for the months November to April of each year. The median, mean and maximum counts across the four traps located in the Mildura LGA were calculated each month and categorized as follows for each species: “no mosquitoes trapped” (the reference category), “1–9 mosquitoes”, “10–99 mosquitoes”, “100–999 mosquitoes”, “≥1000 mosquitoes”.

Climatic and environmental variables were selected following a review of previous models, and are summarized by source in Table 1. Weather station data were obtained from the Australian Bureau of Meteorology weather station with the most complete data in Mildura LGA (Mildura airport; Bureau of Meteorology Station Number: 076031; geo-coordinates 142.0867°E, -34.2358°S, see Figure 1).

2.2. Descriptive and univariable statistical analyses

The distribution of each variable was examined and described, using contingency tables for categorical variables, collapsing categories where appropriate. Summary statistics and histograms were inspected for continuous variables and these transformed as required.

Data for the period July 2000–June 2011 were used to train the model. Owing to over-dispersion, negative binomial regression models were constructed to predict the monthly count of notified RRV cases each month for Mildura LGA (y), of the form:

$$Y \sim Poisson(mu^*)$$

$$ln(mu^*) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p + \upsilon$$

$$exp(\upsilon) \sim Gamma(\frac{1}{alpha}, alpha)$$

where the p predictor variables $x_1, x_2, \ldots, x_p$ are given, and the population regression coefficients $\beta_0, \beta_1, \ldots, \beta_p$ are estimated, applying a dispersion parameter (α) to represent the ratio of the variance of the expected counts to their mean. The dispersion parameter affects the variance of the expected counts, not the expected counts themselves. Exponentiation allows expression of the coefficients as incidence rate ratios (IRR).

Climatic and entomologic variables were lagged by 1–12 months and screened for entry into multivariable modelling. For each putative predictor variable, the lag with the strongest statistical association was selected using Akaike's Information Criterion (AIC) [19] – as this criterion may be applied to non-nested models – and entered into multivariable models if they were crudely statistically associated with RRV case count based on a liberal *P*-value threshold ($P<0.25$). The linearity of the univariable relationship with the outcome variable was assessed graphically for each continuous variable and by comparing the AIC of univariable models including a linear term versus those with the variable categorized into quintiles. Where appropriate categorized variables were retained for further analyses and category levels collapsed.

All continuous covariates were tested for collinearity in pairs by calculating Spearman's correlation coefficient (ρ_s). Among pairs of highly correlated predictors ($\rho_s \geq |0.70|$), only the variable with the strongest statistical association with the outcome was retained for further analysis [20].

2.3. Multivariable analyses

Multivariable models were constructed including all retained variables and trimmed for parsimony using manual backwards-stepwise regression to $P<0.20$. Each removed variable was re-entered individually into the preliminary main effects model and retained if $P<0.15$. At this point, pairwise interactions were tested among all retained terms, categorising continuous variables as required, and the model was reconstructed as a generalized linear model to implement regression diagnostics (deviance-based goodness-of-fit to the training data, assessment of residuals, influence and leverage). Maximum likelihood R^2 was used as a robust measure of fit (no universally accepted adjusted-R^2 measure is available for negative binomial models [21]). The final 'estimation' model was checked for serial auto-correlation (AC) by including case counts in immediately preceding months [22] after testing for non-stationarity and trend in the time series following the Dickey-Fuller (DF) approach [23].

2.4. Prediction, validation and adjustment for over-fitting

The final estimation model was used to predict monthly notified human RRV case counts notified in each month in the 4 year validation dataset (July 2011–June 2015) for Mildura LGA, and 95% prediction intervals (PI) were estimated adapting the method of Farrington et al [24] to the negative binomial distribution. External ('out-of-sample') forecasts and their 95% PIs were then compared to observed data (not used in model development) using Pearson's correlation coefficient (ρ_p) [25], and models were tested for their proportional agreement with subjectively defined 'outbreak alerts' (months with >2 notified cases and where the count of cases exceeded the 5-year mean plus 1 SD for that month estimated excluding known outbreak years, i.e. 2010/11, assuming a negative binomial distribution) [26]. The final estimation model was pruned to account for over-fitting by removing variables sequentially, and the comparisons repeated, to arrive at the final 'prediction' model, selected based on its forecasting ability.

Analyses were undertaken using Stata (StataCorp Texas, version 14.0) and the R statistical package version 3.1.1 [27] using the libraries 'MASS' [28] and 'epiR' [29].

3. Results

There were 479 notified cases of RRV in Mildura LGA during the study period. The outbreak during the 2010/11 financial year accounted for 251 notifications (52.4%) (Figure 2). The mean notification rate (excluding 2010/11) was 63.9 per 100,000 person years (32.6 per 100,000). Cases were notified year-round however 87% had estimated dates of onset between November and April. There were 31 outbreak alerts in the study period, six of these in 2010/11 and sixteen in the model validation period.

Amongst those species investigated, the predominant mosquito species trapped in Mildura LGA during the study period were *Culex annulirostris* (n=142,638), *Aedes camptorhynchus* (n=24,349), *Cx. australicus* (n=6,768) and *Coquillettidia linealis* (n=5,249). Univariable associations between RRV incidence in Mildura LGA and lagged counts of the mosquito species and climatic and environmental variables are provided in supplementary material (Tables S1-2).

The final estimation model for Mildura LGA is presented in Table 2. A doubling of maximum vapour pressure was associated with a 3.5-fold rise in the rate of notifications in the following month (IRR=3.47; 95% CI: 1.57, 7.66). Mean trap counts of *Cx. annulirostris* ≥1000 were associated with a seven-fold increase in the rate of RRV notifications in the following month. When the mean *Ae. camptorhynchus* was ≥10, RRV notifications 2 months later were increased 55%. A doubling of precipitation and more rain days, were associated with 25% and 8% rises in RRV notifications, 4 and 6 months later, respectively. Two interaction terms were retained in the final model. The main effect of Murray River flows in the highest quintile (maximum daily flow in a month ≥16,268 ML) was an 85% reduction in RRV notifications 3 months later (IRR=0.15; 95% CI: 0.03, 0.81), whereas when the Southern Oscillation Index (measured 6 months prior) was greater than its median across the study period (≥1.7 units) Murray River flows in the highest quintile were associated with a 5.7-fold increase in the rate of RRV notifications 3 months later. The main effect of Pacific Ocean sea surface temperatures ≥26.8 °C was a 68% reduction in notifications 2 months later, whereas when minimum monthly sea levels (measured 7 months prior) were

$\geq$13.2 cm and sea surface temperatures $\geq$26.8 °C were associated with a 4-fold rise in RRV notifications 2 months later.

There was no long term trend in the time-series (P=0.14) and the null hypothesis of non-stationary was rejected (DF test statistic=-5.856, degrees of freedom=132, P<0.001). Moderate serial auto-correlation was detected (Lag 1, AC=0.61) with each case one month prior being associated with a 12% increase in RRV incidence the following month (IRR=1.12, 95% CI: 1.05, 1.19). An autocorrelation term was included then eliminated (owing to $P>0.20$) from the final estimation model.

Forecast ability of the model was improved by pruning to the final forecasting model (presented in Table 3 with a comparison of observed data and forecasts). Total observed annual counts were within forecast prediction intervals in all four validation years (Figure 2), and at a monthly resolution observed counts were within the forecast prediction intervals in 39 of 48 months in the validation period (81%), in comparison to 129 of 132 months in the model training period (98%). In two of the validation years (2011/2012 and 2013/2014) there was excellent agreement between forecast and observed case counts and outbreak alerts, proportional agreement of 0.92 and 0.83, respectively. The model under-predicted case counts in 2012/2013 and 2014/2015, all 9 months with observed counts above the forecast prediction interval occurred in these two years, resulting in poorer proportional agreement (0.50 in both cases) with observed outbreak alerts in these two years.

4. Discussion

Climate, environmental and entomologic variables were used to develop prediction models for monthly RRV incidence rates for the Victorian inland Local Government Area with the highest notification rates. To our knowledge, this study was the first to integrate mosquito count data into Victorian RRV predictive modelling and the first to attempt out-of-sample forecasting of monthly counts of RRV for a location in Southern Australia.

The most robust way to assess predictive model accuracy is to review a graphical representation of observed versus predicted events using external data [30], as adopted for assessing the current models. The final forecasting model performed extremely well at tracking the observed counts in the validation period, and clearly fit the data well (differentiating between the outbreak year 2010/11 and other years with relatively low counts). Forecast prediction intervals encompassed the observed monthly counts in 39 of 48 months in the validation period. Of the nine months with observed counts falling above the predicted interval, five in 2012/13 and two in 2014/15 had very low notified case counts (≤ 4) and raised outbreak alerts merely on the basis that these low counts were well outside the typical RRV activity season (when typically ≤ 1 case was observed in most other years). The subjectively defined outbreak alert threshold is likely to be oversensitive, so direct comparisons can only be interpreted cautiously. Raising the alert threshold to 2 SD greater than the long-term mean did not resolve the issue, as such a threshold was largely insensitive at detecting months that appeared to be clearly in excess of normal.

Statistical epidemiological modelling is often applied to address questions of causality (estimation and hypothesis testing) with fewer examples where the explicitly-stated aim is modelling for prediction of future observations [22]. When forecasting (predicting into the ‘out-of-sample’ future), a modified approach may be required, as was the case in this study, reducing the focus on the relationships between individual variables. While model fit remains important there is a trade-off, external validity is paramount (models constructed based on historical data must hold into the near future) and over-fitting to training data may well come at the expense of robust future prediction [22]. For this reason the final ‘estimating’ model, used for assessing the relationships between variables, was pruned to produce a more parsimonious ‘forecasting’ model.

Other models of RRV in Southern Australia have been restricted to providing early warning of outbreak years, rather than attempting to forecast monthly counts. As presented, the forecasting model will be utilized each year to provide forecasts to the DHHS. Further modelling will be required to refine the variable selection and improve the robustness of forecasts. Other more complex approaches may be required [25], perhaps following the PDL modelling approach that Hu et al. (2006) implemented for Brisbane, Queensland.

Rainfall and vapour pressure were key factors for forecasting RRV notifications in Mildura LGA. Rainfall has been included as an important predictor in all previous Ross River virus models for Southern Australia [12, 13, 15, 16], and underlies one of the broad early warning indicators [10] considered by DHHS for years of increased MVE activity. Vapour pressure is a measure of air humidity that depends on temperature and air pressure, similar variables have been included in all previous prediction models [12, 15, 16] developed for regions along the Murray River (that forms a natural border between the States of Victoria and New South Wales). It is biologically plausible that these variables are related to arbovirus transmission, as mosquitoes require a minimum temperature and moisture for breeding. The lags of these variables likely reflect effects of water, temperature and climatic conditions on local ecology, for example through their effects on vegetation and wildlife reservoir host populations along with their direct effect on mosquito populations. Whilst it is difficult to identify causal links between distally-lagged precipitation variables and the timescales of vector development and transmission of RRV, the main purpose of the models developed here was as predictive tools rather than to draw explicit conclusions regarding causation. Including rainfall parameters with lags between 4 and 6 months provided the model with the best predictive performance at a monthly resolution. When we evaluated rainfall variables over lags of 1 to 3 months (in univariable analysis), very similar estimates were obtained as those included in the final model (for total monthly precipitation lagged 4 months, and number of days with greater than 1 mm rainfall lagged 6 months). There were only low levels of temporal auto-correlation observed between these variables, so these were included in multivariable estimation and prediction models at shorter lags (as secondary effects of rainfall over different time-scales). However, these variables representing shorter lags of rainfall were subsequently eliminated. Owing to weak correlations between climatic variables (rainfall, vapour pressure, humidity and temperature) in our data, it is also likely that some of the proximal effect of rainfall is represented by other variables in the final models.

Culex annulirostris and *Ae. camptorhynchus* are the two major mosquito vectors for Ross River virus in Victoria [4]. Their inclusion in the final estimation model at proximal lags is consistent with their role in transmitting virus to humans from wildlife reservoirs and the time taken for mosquitoes to develop, the ~2 week extrinsic and 1-2 week intrinsic incubation periods of RRV [17]. The univariable associations presented in supplementary Table S1 represent useful trigger points for action by the local council (such as mosquito larvicidal treatments and public announcements about the risk and appropriate preventative actions). Risk of RRV is likely to be greatly increased in months subsequent to those when mean weekly trap counts of *Cx. annulirostris* and *Ae. camptorhynchus* exceed 100 and 10 mosquitoes, respectively. Contrary to the findings of previous modelling studies of RRV notifications in other Australian States [13, 17], we found that inclusion of variables representing mosquito numbers provided no improvement in model forecasting ability (although strongly statistically significant associations were observed between lagged mosquito count variables and RRV notifications in the final estimation model). Hu et al. (2006) noted the limitations of including mosquito count data in early warning forecasting models (cost of collection and proximal lags limiting the extent of early warning).

Two interesting interactions were present in the final estimation model, both of which appear indicative of periods of extreme climatic conditions. Elevated SOI (i.e. a La Niña event) 6 months earlier and maximum Murray River flow 3 months prior were associated with increased rates of notification for RRV. A severe flooding event affecting the Murray River valley occurred in the 2010/11 outbreak year. Interestingly, on its own, high maximum Murray River flows (indicative of low amounts of irrigation) were associated with substantially decreased rates of RRV notification.

Weather patterns in the study region are heavily influenced by the development and intensity of El Niño/La Niña events in the Pacific Ocean [31]. Across eastern Australia, El Niño events are often associated with drier than normal conditions while La Niña events are associated with wetter than normal conditions. Lower sea surface temperatures in the Niño 3.4 region (SST) are an indicator of La Niña events and in this analyses were associated with increased rates of RRV notification, which is biologically plausible as wetter conditions favour mosquito larval development. Sea surface temperature was considered as a potential model covariate, even for this inland study area, as it was identified by Woodruff et al [16] as a predictor in their model of RRV for the Murray region in Victoria, and for its role in the El Niño Southern Oscillation phenomenon that influence weather patterns across Australia.

Of interest, another biologically plausible and statistically significant interaction was detected, between SST and sea levels (when both were increased, rates of notification of RRV cases were also likely to be increased). Sea level changes are driven by complex processes including thermal expansion of water, input of water into the ocean from glaciers and ice sheets, and changed water storage on land [32]. Variables representing sea level were considered for inclusion in these models because sea levels are correlated with SST and the SOI [33]. Again, this interaction term may indicate periods of extreme climatic conditions, with extremes in sea levels and sea surface temperature being a feature of cyclones (as experienced in the 2010/11 outbreak year when cyclones in Queensland caused major flooding in the Murray-Darling river basin immediately preceding extremely high arbovirus activity). The DHHS utilizes another sea surface temperature measure, the Indian Ocean Dipole (IOP), which is based on the difference between sea surface temperature in the Western and Eastern tropical Indian Ocean, as a predictor for MVEV activity in south-eastern Australia [9]. Negative IOP events generally coincide with La Niña events.

The study was subject to a number of limitations: notification data may be undoubtedly understated and biased toward cases with typical clinical symptoms - those with less severe illness may not seek medical help or may be misdiagnosed. For this reason model outputs are interpreted as notification rates (rather than incidence rates). Residential location was accepted as a proxy for place of infection as this information was not available for a majority of cases. Misclassification of place of infection for some cases may have altered the measured associations between model covariates and disease, thus reducing predictive accuracy. The model did not account for mosquito control activities, as a reliable, consistent measure of these activities was unavailable. It is likely this omission has reduced the predictive accuracy of the models and ideally these should be accounted for in future research. Despite these limitations, the model presented appears a useful forecasting tool for RRV in region investigated with 81% of observed monthly counts in the validation period falling within forecast prediction intervals.

Changing climatic conditions over the coming decades are likely to alter the current patterns of arboviral disease in Australia [3, 34], although the nature of this change is controversial [35]. The effect on arbovirus transmission is likely to vary regionally. For example, the impact will differ in arid compared to temperate, and coastal versus inland regions, reflecting variation in the effect of climate change on local ecological conditions [34]. Advanced tools, such as the models presented here, will be required to monitoring the changing relationship between notified cases and local conditions, and to provide early warning of periods of high arbovirus activity.

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6. Conflict of interest statement

The authors have no competing interests to declare.

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9. Figure captions

Figure 1: Study extent of predictive modelling of Ross River virus cases in the Mildura Local Government Area (shaded grey), Victoria, Australia, for the period 1 July 2000 to 30 Jun 2015. Black circle represents the location of the Mildura airport weather station. The Murray River forms the northern border of Mildura local government area.

Figure 2: Monthly time-series, predictions and forecasts of notified Ross River virus cases in the Mildura Local Government Area, Victoria, Australia, for the period 1 July 2000 to 30 Jun 2015. Data for the Australian financial year 2010/11 have been rescaled by a factor of 3. Dotted lines represent upper 95% prediction intervals.