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The forecasting of dynamical Ross River virus outbreaks: Victoria, Australia

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ABSTRACT

Ross River virus (RRV) is Australia's most epidemiologically important mosquito-borne disease. During RRV epidemics in the State of Victoria (such as 2010/11 and 2016/17) notifications can account for up to 30% of national RRV notifications. However, little is known about factors which can forecast RRV transmission in Victoria. We aimed to understand factors associated with RRV transmission in epidemiologically important regions of Victoria and establish an early warning forecast system. We developed negative binomial regression models to forecast human RRV notifications across 11 Local Government Areas (LGAs) using climatic, environmental, and oceanographic variables. Data were collected from July 2008 to June 2018. Data from July 2008 to June 2012 were used as a training data set, while July 2012 to June 2018 were used as a testing data set. Evapotranspiration and precipitation were found to be common factors for forecasting RRV notifications across sites. Several site-specific factors were also important in forecasting RRV notifications which varied between LGA. From the 11 LGAs examined, nine experienced an outbreak in 2011/12 of which the models for these sites were a good fit. All 11 LGAs experienced an outbreak in 2016/17, however only six LGAs could predict the outbreak using the same model. We document similarities and differences in factors useful for forecasting RRV notifications across Victoria and demonstrate that readily available and inexpensive climate and environmental data can be used to predict epidemic periods in some areas. Furthermore, we highlight in certain regions the complexity of RRV transmission where additional epidemiological information is needed to accurately predict RRV activity. Our findings have been applied to produce a Ross River virus Outbreak Surveillance System (ROSS) to aid in public health decision making in Victoria.

1. Introduction

Mosquito-borne diseases are a significant burden to human health worldwide, with approximately 700 million infections and one million deaths per year (World Health Organisation, 2016). The distribution and occurrence of mosquito-borne diseases are dependent on environmental and climatic factors, as well as biological factors including host animal populations and vector mosquitos. Thus, understanding the transmission dynamics of mosquito-borne diseases can be complex. Using readily available environmental data, statistical models can be developed to begin to account for this complexity, enabling early warning forecast systems to be developed to aid in the monitoring of disease and the action of early intervention programs.

Ross River virus (RRV) (family Togaviridae, genus Alphavirus) is Australia's most epidemiologically important mosquito-borne disease with 1451–9551 notifications per year (annual incidence > 40/100,000 population) (Australian Government Department of Health, 2016) with an estimated annual health care and lost productivity cost of approximately $15 million (Harley et al., 2001; Aaskov et al., 2012; Australian Government Department of Health, 2016). RRV is endemic to Australia and parts of Papua New Guinea, where it is transmitted by multiple mosquito species and where several species of vertebrates act

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as amplifying reservoir hosts (Russell, 2002; Koolhof and Carver, 2017; Stephenson et al., 2018). Recent serological studies have also shown the silent circulation of RRV into regions in French Polynesia and in American Samoa in the Pacific Islands (Aubry et al., 2017; Lau et al., 2017). The tropical northern regions of Australia commonly report higher rates of RRV notifications with an annual epidemic cycle of RRV transmission owing to seasonal mosquito habitat and climate (Yu et al., 2014; Australian Government Department of Health, 2016). RRV outbreaks in the southern temperate regions of Australia, such as Victoria, occur periodically when environmental conditions are conducive to mosquito breeding (Cutcher et al., 2017). Improvements are needed in forecasting RRV disease occurrence across local scales to allow timely and geographically targeted public health interventions to prevent human RRV infection (Australian Government Department of Health, 2016; Cutcher et al., 2017).

In Australia, RRV is a nationally notifiable disease, with laboratories and/or clinicians required to notify their jurisdictional health department. Cases are classified as 'confirmed' or 'probable' based on the national surveillance case definition (Australian Government Department of Health, 2019b). Cases are reported according to their area of residence, although at times additional public health follow-up is undertaken to determine place of likely acquisition of RRV if the case resides in a non-endemic area.

The southeastern Australian State of Victoria spans temperate and semi-arid climatic regions, with most cases of RRV occurring during summer and autumn periods (Knope et al., 2013; Australian Government Department of Health, 2016). RRV epidemics were recorded during summers of 2010/11 and 2016/17, preceded by heavy rainfall and flooding that led to a prolonged breeding period for vector mosquitos and the reservoir host species. There are two primary mosquito species which play a major role in RRV transmission in Victoria these include: Aedes camptorhynchus and Culex annulirostris (Harley et al., 2001; Cutcher et al., 2017). Few studies have focused on key host reservoirs in Victoria, however, macropod marsupials are generally regarded as key reservoir species, making Eastern Grey kangaroos (Macropus giganteus) and possums (Trichosurus vulpecula) likely reservoirs (Campbell et al., 1989; Koolhof and Carver, 2017; Stephenson et al., 2018). Herd immunity, spatial distribution, and movement patterns of hosts play an important role in disease dynamics. The transmission of RRV is primarily maintained by host breeding and herd immunity, whereby juvenile susceptible hosts amplify transmission more so than high mosquito populations (Carver et al., 2009, 2010; Ng et al., 2014). A combination of environmental and biological factors led to Victoria having the highest notification rates of RRV in Australia during the 2010/11 and 2016/17 epidemics (Australian Government Department of Health, 2019a; Cutcher et al., 2017), in contrast to most years where Victoria contributes around five percent to the total national notifications for RRV (Australian Government Department of Health, 2016).

These environmental and climatic drivers for the transmission of RRV across Australia have been well documented over the past three decades, with studies linking the importance of precipitation, temperature, tides and floods, and humidity with notifications of RRV (Tong et al., 2008; Yu et al., 2014; Flies et al., 2017; Koolhof et al., 2017). Where available, mosquito surveillance can also significantly improve upon our understanding of transmission cycles and the forecasting of outbreaks of RRV (Woodruff et al., 2006; Cutcher et al., 2017). However, due to the economic cost of mosquito surveillance, monitoring of mosquito populations is generally only targeted to known high-risk areas for RRV and other high-consequence arboviral diseases (e.g. Murray Valley encephalitis, West Nile virus (Kunjin) and dengue). Environmental determinants used in early warning forecast systems for RRV are not equal across regions (Tong et al., 2002; Tall et al., 2014; Yu et al., 2014; Koolhof et al., 2017), resulting in predictive models that are often region specific, suited to the local spatial and temporal ecology and transmission dynamics. There are over 30 potential species of mosquitos capable of transmitting RRV and multiple hosts with different ecological life history traits creating complexity which limits the adaptability of disease predictive techniques across regions (Harley et al., 2001; Russell, 2002; Tong et al., 2008; Koolhof and Carver, 2017). Although mosquitos play a large ecological role in the transmission of RRV, in forecasting RRV transmission the inclusion of mosquito surveillance data with environmental and climatic modelling does not always lead to improved forecasting accuracy (Cutcher et al., 2017). When using environmental determinants, the epidemiological and biological relationships affecting the transmission of RRV, including the life cycles of the virus and mosquito, RRV incubation periods, and host reservoir population dynamics, are accounted for by introducing time lags in environmental predictors (Jacups et al., 2008a; Yu et al., 2014; Koolhof et al., 2017).

Victoria, in comparison to other States and Territories around Australia, has had few studies investigating the transmission and prediction of notifications of RRV. The aim of this study is to develop predictive early warning forecast models for monthly notifications of RRV across epidemiologically important areas in Victoria. By comparing time-lagged environmental predictors of the notifications of RRV across 11 LGAs within the State, we evaluated broad, common and site-specific environmental drivers of RRV transmission in Victoria. Furthermore, the development of these models may provide a stepping stone for further development and integration of future notifications of RRV for nearby LGAs where predictive models are not available, to form an expanded and valuable forecasting tool to inform public health intervention programs.

2. Material and methods

2.1. Data

Notifications of RRV and environmental data were collected from 11 of 79 LGAs located across Victoria, Australia. Sites were selected due to the regularity of high numbers of notifications of RRV; being and based on a distinct epidemic season. The 11 LGAs included in this study were Ballarat, Benalla, Greater Bendigo, Campaspe, East Gippsland, Greater Geelong, Horsham, Mildura, Shepparton, Surf Coast, and Swan Hill covering most geographic regions of the State (Fig. 1). RRV notification data were extracted from the Public Health Event Surveillance System (PHESS) held within the Victorian Department of Health and Human Services for cases notified between July 2005 to June 2018. Data obtained included the estimated month and year of RRV symptom onset, LGA where the RRV patient resided at the time of notification, and results of serological testing for RRV. Notifications of RRV were included if they met the most recent national surveillance case definition for confirmed or probable RRV (effective 1st January 2016), specifically detection of RRV by PCR or demonstration of RRV-IgG seroconversion for confirmed RRV, or detection of both RRV-IgM and RRV-IgG within the same specimen for probable RRV (Australian Government Department of Health, 2019b). Population statistics for each LGA were collected from the Australian Bureau of Statistics and used as a denominator in our models (Australian Government, 2019).

Environmental and climatic variables were obtained from multiple government departments (Table 1). All data were summarized into monthly observations by LGA. Climatic and environmental variables were collected from Australian Bureau of Meteorology weather stations (See Appendix in Supplementary Material). Due to discontinuous monitoring from weather stations, for each LGA, a single weather station was used which was in proximity with the LGAs population centre where the major of RRV notifications were being reported.

2.2. Statistical analyses

A systematic approach was followed during the construction of our LGA based forecast models and each LGA was modelled independently

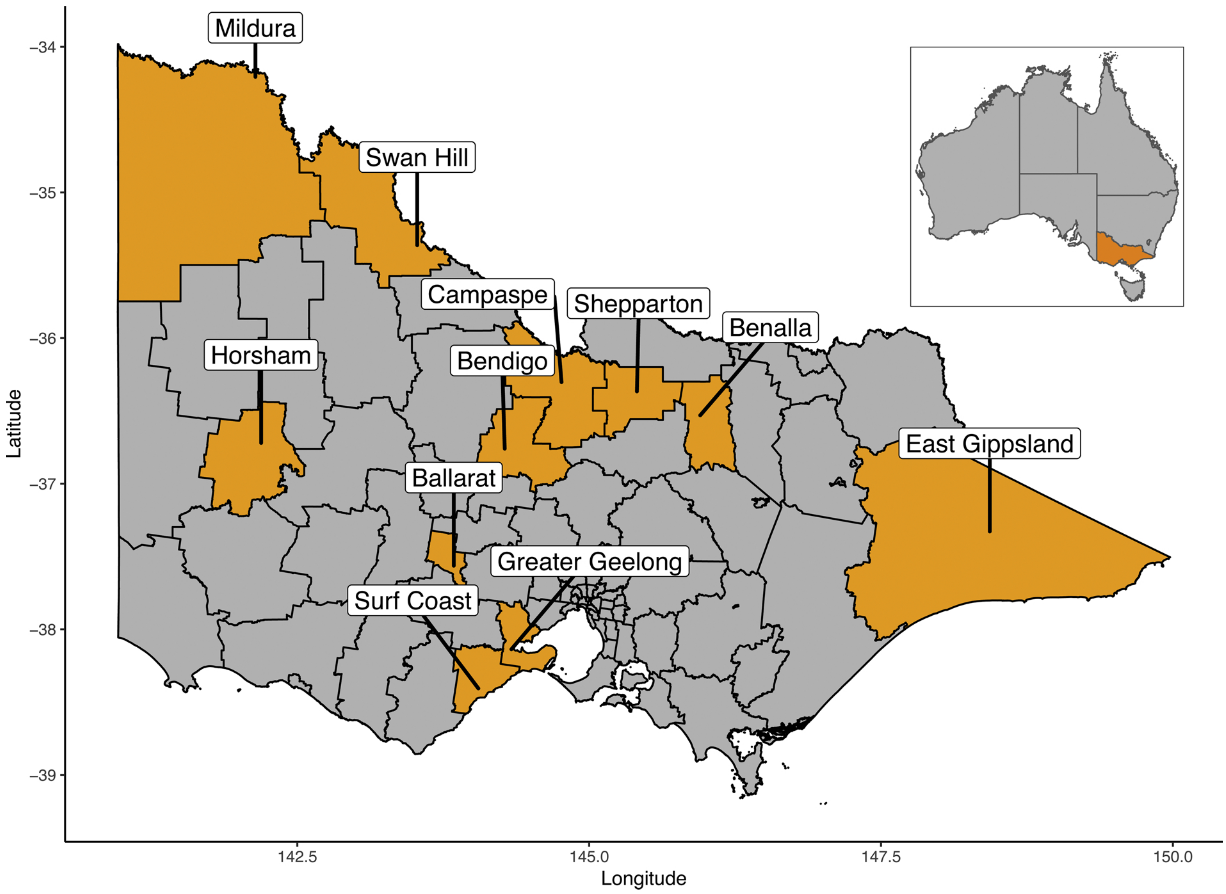

Fig. 1. Local Government Areas used in forecasting Ross River virus notifications across the State of Victoria, Australia.

from the others. First, summary statistics and distributions were examined; severely skewed variables, which have non-normal distributions, were transformed using either a logarithm or square root transformation to achieve as close to a normal distribution as possible for each independent variable. Transformations are beneficial in seasonally driven transmission systems, such as in the transmission of RRV, allowing for seasonal variables to be assessed as a stationary effect that improves forecasting accuracy (Hu et al., 2004, 2006; Cutcher et al., 2017). Further, the use of transformations limits the ability to generalise findings and interpret disease rates on the original unit of measurement. Second, variables had a maximum, mean, or minimum value which were ranked using Akaike's Information Criterion (AIC), the variable with the best AIC score was retained for use in the later stepwise multivariate model (Akaike, 1998). Third, a lag of 1–12

Table 1
Descriptions of climatic and environmental variables used in the construction of negative binomial models of forecasting monthly Ross River virus notifications in Local Government Areas across Victoria.

Variable	Description	Unit	Source
SOI	Southern Oscillation Index (monthly)	–	Australian Bureau of Meteorology (BOM)
RAIN	Total monthly precipitation	mm	BOM
RDAYS	Number of days with > 1 mm precipitation per month	days	BOM
RDTOT	Estimated monthly total rainfall within the local government area	mm	BOM
$TMIN^{max/min/mean}$	The absolute maximum and minimum lowest temperature within month, and average minimum temperature per month	°C	BOM
$TMAX^{max/min/mean}$	The absolute maximum and minimum highest temperature within month, and average maximum temperature per month	°C	BOM
$HM_{9/15}$	Humidity at 9 a.m. & 3 p.m. on the day with the maximum temperature per month	%	BOM
$VAP_{9/15}{}^{max/min/mean}$	Maximum, minimum, & mean vapour pressure at 9 a.m. & 3 p.m. per month	hPa	BOM
$VAPS_{9/15}{}^{max/min/mean}$	Maximum, minimum, & mean saturated vapour pressure at 9 a.m. & 3 p.m. per month	hPa	BOM
$MSLP_{9/15}{}^{max/min/mean}$	Maximum, minimum, & mean sea level pressure at 9 a.m. & 3 p.m. per month	hPa	BOM
EVPA	Evapotranspiration actual	mm	BOM
EVPP	Evapotranspiration potential	mm	BOM
SST	Monthly sea surface temperature (SST) measured at Niño 3·4 (a standardized region for sea surface temperature measurement in the Pacific Ocean)	°C	National Oceanic and Atmospheric Administration
$SEA^{max/min/mean}$	Monthly maximum, minimum, & mean sea level measured by tide height at Lorne, Victoria, Australia (GDA94: Latitude 38° 33'S, Longitude 143° 59' E)	m	National Tidal Centre
$RIVER_{C/T/H}{}^{max/min/mean}$	Maximum, minimum, & mean monthly river flow (-F) & level (-L) for the Murray River at Colignan and Tocumwal, or the tributary river at Hinnomunjie (Mitta Mitta River) (indicative of irrigation)	ML & m	Victorian Water Resources data warehouse

months was introduced for possible climate and environmental variables after examining cross-correlations of independent with dependant variables. These temporal lags were used to account for the biological processes in the virus, mosquito, and host reservoir population dynamics, as well as the RRV incubation periods, prior to onset of symptoms of RRV cases (Jacups et al., 2008a; Yu et al., 2014; Koolhof et al., 2017). Last, data from July 2005 to June 2012 were considered a training data set for the development of the models and data from July 2012 to June 2018 were used to test the model predictions. Negative binomial regression models were constructed to predict the monthly counts of notifications of RRV, as inspection of our dependent variables showed that there was significant over dispersion and negative binomials are generally a good fit to such data. A dispersion parameter (α) was included in the models to represent the ratio of the variance to mean of notifications of RRV. During model training, forward and backwards stepwise AIC variable selection (Cutcher et al., 2017) was used on the multivariable model to determine a parsimonious set of variables to be included in the final predictive model for forecasting and validation testing. All variables in the multivariable model, prior to the stepwise selection, were examined for collinearity using the Spearman correlation coefficient ρ (with high correlation considered where $|\rho| > 0.8$), similar to that of other RRV predictive modelling (Cutcher et al., 2017; Koolhof et al., 2017). If variables were found to be highly correlated, we selected the variable with the strongest statistical association with our dependant variable and discarded the other(s). Human population data were used for each LGA as a denominator in the models, and incidence rate ratios (IRR) calculated via exponentiation of output model coefficients.

To assess the predictive performance of our models, we used Pearson's correlation coefficient to determine the correlation between our predicted notifications of RRV and the observed monthly notifications of RRV in the testing data set. Model predictive performance also examined how well predicted notifications of RRV matched those of observed notifications of RRV in-relation to outbreaks of RRV. Here we classified an outbreak of RRV to be above the preceding the monthly mean of five years plus one standard deviation (Cutcher et al., 2017), substituting for any years deemed a priori as 'outbreak years' a consecutive earlier 'non-outbreak' year.

All statistical analyses were undertaken in R (Version 3.5.3, www.r.project.org), using packages 'MASS' and 'stats'.

3. Results

There were a total of 1957 notified human cases of RRV across all sites for the entire study period, with Mildura having the most cases and Benalla the fewest (Table 2). RRV notifications were generally recorded year-round; however, two major outbreaks of RRV were documented during the 2010/11 and 2016/17 financial years (Fig. 2). The large RRV outbreak in 2010/11 affected all LGAs we examined except for Benalla, Shepparton, and Surf Coast.

Table 2
The number of RRV notifications from July 2005 to June 2018 across 11 LGAs from Victoria.

LGA	RRV notifications
Mildura	381
Campaspe	262
Shepparton	236
Horsham	214
Bendigo	190
East Gippsland	176
Swan Hill	147
Geelong	107
Surf Coast	103
Ballarat	76
Benalla	65

4. Predictors of monthly RRV notifications

The analyses were performed for each LGA using environmental and climatic variables from weather stations within that LGA to determine the variables most likely to be predictors for RRV notifications. A range of environmental and climatic variables were important in predicting the incidence of RRV across different LGAs. However, there were notable commonalities among some LGAs, with two groups of positively predictors found to be predictive of RRV notifications, with at least one of the two included in each final model across all eleven LGAs analysed (Tables 3 and 4). The two common groups of predictors included variables related to precipitation and evapotranspiration (whereby water transfers from the land to the atmosphere via evaporation). Both precipitation and evapotranspiration were included in six of the 11 final forecasting models (Table 3), all with a positive association with notifications of RRV, however, both variables were not necessarily associated with the same LGAs.

Among the oceanic determinants examined, sea level, sea surface temperature (SST), and maximum sea level pressure (MSLP) were found to have associations across five LGAs (Tables 3 and 4). Across these LGA models, sea level was included in four of the LGAs (Table 3). SST was included in the models for two LGAs, having a positive, albeit not statistically significant association in East Gippsland, and a negative association in Horsham. Sea surface pressure was included in three LGAs, having a negative association with RRV notifications in Greater Bendigo, East Gippsland, and Swan Hill.

River-related variables, including water level and flow rate for the Murray River (Mildura) and of the tributary Mitta Mitta River for Campaspe and East Gippsland were included in the three LGA models each at different locations along the rivers (Tables 3 and 4).

There were site-specific predictors in our models that were only seen in a small number of the LGA models. Campaspe, Mildura, and Swan Hill were found to have the mean vapour pressure at 9am as a positive predictor in their models. The minimum monthly temperature had a positive association with RRV notifications in Shepparton, while lower monthly maximum temperatures were negatively associated with RRV notifications in Surf Coast and Swan Hill. Mean humidity at 9am was negatively associated with notifications of RRV in Shepparton (Tables 3 and 4).

5. Temporal trends and forecasts

The forecasting models for Greater Bendigo, Campaspe, Greater Geelong, Horsham, and Mildura, had Pearson's correlation coefficients ≥ 0.6 (Table 5). Forecasts made for these LGAs predicted increases in the notifications of RRV during months of observed RRV activity, and in most cases, capturing the onset and magnitude of the 2016/17 outbreak (Fig. 2). In contrast, the 2016/2017 outbreak was not well predicted by the models for sites with a Pearson's correlation coefficient of < 0.6, excluding Swan Hill (Table 5, Fig. 2). Other than for those LGAs which experienced an RRV outbreak in 2010/2011 (included in the 'training' dataset), forecasts rarely predicted the magnitude of the 2016/17 outbreak (Fig. 2).

6. Discussion

This study identifies unique and previously unrecognised predictors of Ross River virus (RRV) activity for forecasting notifications of RRV disease across several Local Government Areas (LGA) in Victoria, Australia. This has enabled the consideration of environmental and climatic determinants that are important across multiple regions in predicting notifications of RRV. We highlight the complexity in mosquito-borne disease transmission which is required in forecasting disease outbreaks of RRV. From the 11 LGAs investigated here, six LGA models were able to predict the most recent outbreak of RRV in Victoria. Using environmental and climate driven models developed

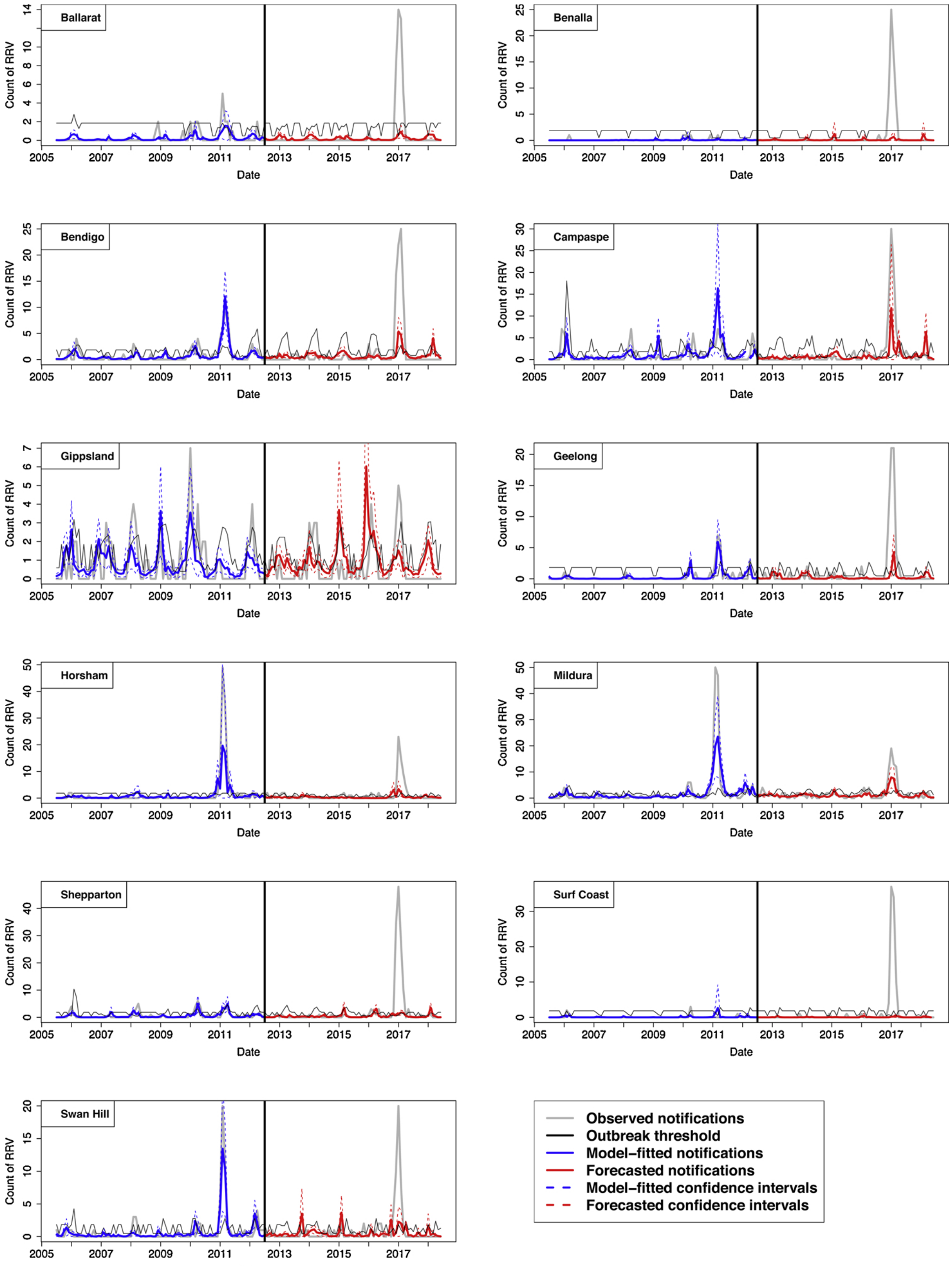

Fig. 2. Negative Binomial logistic regression model predictions of notifications of Ross River virus (RRV) per month for 11 Local Government Areas in Victoria, Australia. Legend: solid grey line: observed monthly notifications of RRV; solid black line: outbreak threshold; solid blue line (left of vertical black line at June 2012): model-fitted RRV notifications; solid red line (right of vertical black line): forecasted RRV notifications; and dotted blue and red line: 95% confidence interval. The black vertical line divides the dataset into training and testing sets (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

here, an in-depth understanding of epidemiological and ecological factors useful for predicting mosquito-borne diseases can provide public health systems with information that can inform disease prevention and control programs. The transmission of RRV spans a wide range of vectors and hosts, which may be mediated by environmental factors. Previous predictive modelling has shown in some areas vector and host surveillance can improve the predictive ability of models (Woodruff et al., 2006; Ng et al., 2014; Yu et al., 2014). Due to do logistical costs of vector and host surveillance, these activities often aren't feasible for remote communities. Thus, having simple environmental predictive models can be of public health use where mosquito surveillance isn't currently being conducted. Our findings suggest for some epidemiologically important regions RRV transmission can be readily predicted by environmental and climatic factors. However, for the remaining areas where predictions were not as accurate, additional epidemiological variables (such as vector and host surveillance) may be needed to support forecasting methods. Whilst environmental determinants of RRV have been well documented, we have examined climatic and environmental variables previously neglected in forecasting approaches and developed a much more comprehensive approach in evaluating multi-site forecasting RRV disease in Victoria.

Among the 11 Victorian LGAs examined, we found several sites with similar environmental and oceanic-related (sea level, sea surface temperature, sea level pressure), and hydrological determinants, as well as unique site-specific factors for predicting RRV disease. There were two common important environmental determinants: evapotranspiration and precipitation, with either one or both found to be positively associated with RRV incidence in all LGAs examined. We evaluated actual and potential evapotranspiration, which are derived by the Bureau of Meteorology and Australian Water Resource Assessment modelling system (Australian Government, 2019d). Actual evapotranspiration is the total water removed from surfaces via evaporation, while potential evapotranspiration is the amount of evaporation which would occur if there were no limit on water (Australian Government, 2019d). Actual

Table 3
Environmental variables used in the final models predicting notifications of RRV in Victoria. For abbreviations, please see Table 1. The columns: Lags in months; IRR represents the incidence rate ratio per a one unit increase in the predictor variable with the upper and lower confidence intervals in brackets; p represents the variable p-value. Variable transformations are included as a lower subscript in brackets.

Variable	Lag (months)	IRR	p	Relationship	Variable	Lag (months)	IRR	p	Relationship
Ballarat					Horsham				
EVPA(log)	3	11.51 (3.63–46.44)	< 0.001	Positive	$RDTOT_{(sqrt)}$	4	1.35 (1.09–1.71)	0.004	Positive
Benalla					SST	3	0.43 (0.28–0.66)	< 0.001	Negative
$RDAYS_{(sqrt)}$	7	6.80 (1.77–35.18)	0.010	Positive	$RAIN_{(sqrt)}$	1	1.20 (1.01–1.45)	0.045	Positive
Greater Bendigo					Mildura				
EVPA(log)	3	1.02 (1.02–1.03)	< 0.001	Positive	$RDTOT_{(sqrt)}$	3	1.15 (1.00–1.32)	0.043	Positive
SEA^{min}	8	18.58 (1.90–201.60)	0.014	Positive	VP_9^{mean}(log)	1	32.63 (10.46–107.6)	< 0.001	Positive
$MSLP_9^{max}$	2	0.92 (0.87–0.7)	0.004	Negative	RIVER-L_C^{max}(log)	2	2.99 (1.74–5.20)	< 0.001	Positive
Campaspe					Shepparton				
$EVPA_{(sqrt)}$	3	1.72 (1.36–2.22)	< 0.001	Positive	EVPA(log)	2	5.01 (2.82–9.49)	< 0.001	Positive
VP_9^{mean}	1	1.23 (1.04–1.46)	0.011	Positive	$TMIN^{min}$	1	1.41 (1.27–1.58)	< 0.001	Positive
RIVER-F_T^{max}(log)	4	0.62 (0.36–1.05)	0.061	Negative	HM_9^{mean}	7	0.93 (0.90–0.96)	< 0.001	Negative
East Gippsland					Surf Coast				
$EVPA_{(sqrt)}$	1	1.62 (1.19–2.24)	0.003	Positive	$TMAX^{min}$	1	1.82 (1.21 – 3.59)	0.024	Positive
SEA^{min}	2	0.25 (0.03–1.80)	0.165	Negative	$RDTOT_{(sqrt)}$	1	1.59 (0.96– 3.22)	0.034	Positive
$MSLP_9^{max}$	1	0.93 (0.87–0.99)	0.037	Negative	Swan Hill				
SST	1	1.28 (0.99–1.65)	0.069	Positive	$RDTOT_{(sqrt)}$	4	1.19 (1.02–1.40)	0.037	Positive
RIVER-L_H^{mean}(log)	5	0.34 (0.08–1.34)	0.121	Negative	SEA^{min}	8	63.84 (1.98–2606)	0.022	Positive
Geelong					$MSLP_9^{mean}$	1	0.81 (0.71–0.91)	< 0.001	Negative
$EVPA_{(sqrt)}$	4	2.43 (1.74–3.54)	< 0.001	Positive	VP_9^{mean}(log)	1	240.8 (18.48–3933)	< 0.001	Positive
SEA^{min}	8	30.84 (1.10–1359)	0.058	Positive	$TMAX^{min}$	1	0.80 (0.70–0.90)	< 0.001	Negative
$RDAYS_{(sqrt)}$	7	1.95 (0.94–4.07)	0.074	Positive					

Table 4
Each type of variable included in each LGA model indicated by an 'X'. Variables included in each group include Oceanographic: SOI, MSLP, SST, and SEA; Precipitation: RAIN, RDAYS, and RTOT; evapotranspiration: EVPA and EVPP; River related: RIVER; Temperature: TMIN and TMAX; Vapour pressure: VP; and Humidity: HM (refer to Table 1 for abbreviations).

Variable	Ballarat	Benalla	Bendigo	Campaspe	East Gippsland	Geelong	Horsham	Mildura	Shepparton	Surf Coast	Swan Hill
Oceanographic			X		X	X	X				X
Precipitation		X				X	X	X		X	X
Evapotranspiration	X		X	X	X	X			X		
River related				X	X			X			
Temperature									X	X	X
Vapour pressure				X				X			X
Humidity									X		

evapotranspiration was included in the predictive models for RRV notifications in six LGAs, while potential evapotranspiration was not included in any of the final models (perhaps unsurprisingly). To the best of our knowledge, we are the first to examine the role of evapotranspiration in forecasting RRV and to identify evapotranspiration as a better predictor than previously recognised determinants such as rainfall, temperature and vapour pressure. Evapotranspiration has been found to influence the breeding habitats of Anopheles and Culex species outside of Australia, but the direct relationship to Australian species is yet to be fully explored (Koenraadt et al., 2004; Dale et al., 2013; Roiz et al., 2014). Evapotranspiration may provide a useful predictor in inland areas where rainfall drives mosquito breeding that may lead to increases in RRV transmission. The importance of evapotranspiration in our models may reflect a biological pathway not previously considered as it can be indicative of soil moisture content, the longevity of pooling water, and possible available cool vegetation necessary for breeding and harbourage, possibly contributing to the observed associations (Koenraadt et al., 2004; Paaijmans et al., 2008). Evapotranspiration likely captures a different temporal dynamic in RRV transmission compared with precipitation. Precipitation typically has a longer lagged

Table 5
Predictive performance of the forecast models for RRV notifications in Victoria. The number of observed and predicted notifications and outbreaks of RRV, whether the 2011 and 2017 outbreak of RRV were seen in the models, and the Peason's correlation coefficient of the observed and predicted RRV notifications.

LGA	Observed Cases	Predicted Cases (Confidence interval)	Pearson's Correlation	Observed outbreaks	Predicted Outbreak	2011 Outbreak predicted	2017 Outbreak predicted
Ballarat	41	12 (4–21)	0.34	5	2	Yes	No
Benalla	59	7 (0–16)	0.27	4	2	NA	No
Greater Bendigo	92	49 (27–71)	0.71	10	8	Yes	Yes
Campaspe	107	60 (16–103)	0.71	14	16	Yes	Yes
East Gippsland	43	60 (19–101)	0.19	14	20	Yes	No
Greater Geelong	71	17 (5–29)	0.71	10	4	Yes	Yes
Horsham	69	26 (6–46)	0.63	14	7	Yes	Yes
Mildura	107	78 (43–112)	0.88	13	8	Yes	Yes
Shepparton	144	34 (15–52)	0.25	13	9	NA	No
Surf Coast	90	4 (0–10)	0.35	5	0	NA	No
Swan Hill	60	35 (6–65)	0.34	14	11	Yes	Yes

effects whereby extreme events happen over shorter periods which may not reflect the mosquito reproductive time span as accurately.

Precipitation has been regularly identified as a predictor for RRV, with large amounts of rainfall creating flooding that may lead to transient water bodies, which can act as breeding habitats for mosquitos (Hu et al., 2006; Carver et al., 2015; Cutcher et al., 2017; Koolhof et al., 2017). Precipitation-related determinants were found to be important in areas where inland flooding was seen during the 2010/11 and 2016/17 RRV epidemics in Victoria and is regularly used as an indicator for early warnings of mosquito-borne diseases and mosquito breeding (Cutcher et al., 2017).

There were important differences between the LGAs for the remaining predictors included in our models. There were several environmental, oceanic, and hydrological determinants which included: sea level, sea surface temperatures, sea level pressure, and the flow and level, temperatures, and vapour pressure of the Murray River and its tributaries. Interestingly, coastal sites were not the only LGAs to include oceanic predictors in their models. Sea level, sea surface temperature, and atmospheric pressure at sea level are typically found to be important factors for transmission of RRV in coastal areas, however less is known about their role in inland areas (Jacups et al., 2008a; Tong et al., 2008; Cutcher et al., 2017; Koolhof et al., 2017). We found these oceanic factors to be important predictors for notifications of RRV in some inland LGAs. This may suggest an indirect link with other environmental conditions, such as lagged pressure systems from marine areas moving inland, which may subsequently impact mosquito breeding. In support of this, we observed longer lags between oceanic factors in inland compared with coastal sites. It is unclear the precise mechanism tide height has on inland sites, however, high pressure systems can depress sea levels which can often be indicative of clearer sunny weather while higher tides can cause low-pressure systems to carry rain further inland prior to releasing rainfall creating mosquito development habitat (National Oceanic and Atmospgeric Administration, 2019). Tide heights are likely to impact ground temperatures, that may also lead to faster larval development time in inland waterways. Lower sea level pressure and sea surface temperatures were associated with greater RRV notifications, except for one LGA, East Gippsland, where there was a statistically non-significant association. Atmospheric pressure at sea level has, to the best of our knowledge, not been investigated as a predictor for RRV, though similar variables such as air and vapor pressure have been examined in temperate regions (Woodruff et al., 2002, 2006; Cutcher et al., 2017). In other regions of Australia sea surface temperature has been observed to have a positive association with RRV notifications (Woodruff et al., 2002, 2006), contrary to that in the present analysis. However, in our models, one LGA examined, Horsham, suggest a negative association between RRV notifications and sea surface temperature, supporting a previous study's findings that showed that sea surface temperatures of ≥26·8 °C led to a 68% reduction in RRV notifications two months later (Cutcher et al., 2017). Given Horsham's inland location, it is likely that the association of sea surface temperature and notifications of RRV represents the biological pathway of La Niña. La Niña have previously been associated with warmer and wetter conditions ideal for mosquito breeding and potential increase in RRV transmission as suspected by other forecasting using similar approaches (Woodruff et al., 2002; Cutcher et al., 2017).

In most studies that have sought to understand RRV transmission and develop forecasting methods, air temperature has been found to be a common predictor across regions in Australia (Tong and Hu, 2002; Woodruff et al., 2002, 2006; Yu et al., 2014; Koolhof et al., 2017). However, across LGAs in Victoria, only three of 11 sites were found to benefit from temperature as a predictor of RRV transmission in the models. Hotter minimum monthly temperatures were associated with increases in RRV notifications, fitting with the known understanding of accelerated larval development in Ae. camptorhynchus, a known RRV vector in Victoria, when introduced to more favourable temperatures for growth (Carver et al., 2015). Furthermore, increases in temperature are known to speed up not only immature stages of mosquito development, but also RRV viral replication, and to create conditions ideal for host breeding, potentially extending RRV epidemic seasons (Russell, 2002; Dale et al., 2013). Two different associations were found between LGAs with colder maximum monthly temperatures, with the inland LGA of Swan Hill having a negative association and the coastal LGA of Surf Coast having a positive association. The difference in association between these two LGA models could be attributed to the difference in their spatial location, local weather conditions and non-climatic factors (Parham et al., 2015), with these temperatures impacting mosquito breeding and development times differently. Warmer temperatures have been shown to be closely linked to mosquito and disease biology, ecology and transmission, creating ideal conditions when coupled with suitable habitats (Russell, 1994, 2002; Ewing et al., 2016). Extreme high and low temperatures are known to inhibit the development and dispersal of mosquitoes and potentially limit disease transmission (Dhileepan et al., 1997; Russell, 2002), with recent findings also suggesting sustained higher temperatures decrease the reproductive ratio of RRV(Shocket et al., 2018). RRV transmission is seen to have an optimal temperature of 26.4 °C, with thermal limits of 17–31.5 °C (Shocket et al., 2018). These optimal temperatures may explain difference seen in our LGAs, whereby Swan Hill is seen to reach colder temperatures than Surf Coast which may explain why temperature is seen to decrease notifications of RRV (Australian Government, 2019c). Oceanic-related predictors underpin many of these changes in environmental conditions, including temperature (Woodruff et al., 2002; Lombard et al., 2005; Cutcher et al., 2017), which may explain why many of our LGAs did not include temperature in the final forecasting model, while SST and SLP were found to be predictive. Furthermore, the lack of inclusion of temperature-related variables may also be explained by the positive role of evapotranspiration found for several LGA models tested.

Humidity has been shown to have a significant association with the incidence of RRV in other parts of Australia; however, this relationship varies between regions and seasons (Tong and Hu, 2002; Woodruff et al., 2002; Bi et al., 2009; Yu et al., 2014). Humidity was found to be of significance in the forecasting of RRV in Shepparton only. Vapour pressure and its association to the transmission of RRV has not received much attention, despite its suggested role in increased mosquito breeding and activity (Woodruff et al., 2002; McMichael et al., 2006; Woodruff et al., 2006; Parham et al., 2015; Cutcher et al., 2017). We found vapour pressure to be a predictor in three LGAs including Campaspe, Mildura, and Swan Hill, however the size of its effect is smaller. Vapour pressure has previously been used in forecasting epidemic events of RRV in Australia (Woodruff et al., 2002) and as a predictor of monthly RRV notifications in one Victorian LGA (Mildura) (Cutcher et al., 2017).

The Murray River flows through several of the included LGAs and is prone to flooding during extreme rainfall events. The Murray River and its tributaries are known to contribute to the transmission of RRV, with mosquito breeding commonly being found along the Murray River in Victoria and South Australia (Johnston et al., 2014; Cutcher et al., 2017). The Murray River has important implications for mosquito breeding both from flooding and irrigation use, creating high risk areas for mosquito breeding and the transmission of mosquito-borne diseases (Tall et al., 2014; Flies et al., 2016). The LGAs of Campaspe and Mildura were found to have positive associations between Murray River flow and level and notifications of RRV. The Mitta Mitta River level, a tributary river system of the Murray River (Murray-Darling Basin Authority, 2019) in East Gippsland, also had a positive association with increased notifications of RRV.

Interestingly models for five of the eleven LGAs were unable to predict the RRV outbreak in 2016/2017. For three of these LGAs; Benalla, Shepparton, and Surf Coast, the RRV outbreak during 2011/2012 observed in other LGAs was not observed in the portion of the data used to train the models for these LGAs. Models for Ballarat and

East Gippsland also were not able to predict the 2016/2017 outbreak, despite the 2011/2012 outbreak being observed in their training data. For LGAs such as Ballarat, Benalla, and Surf Coast this discrepancy could be due to the low number of RRV notifications when constructing the models which is a known issue in forecasting RRV (Koolhof et al., 2017). However, this is not the case for East Gippsland and Shepparton, having much higher RRV notifications, comparable to the LGAs which successfully predicted the later outbreak in the testing portion of the timeseries. The Surf Coast LGA had very few RRV notifications within the data used to train the models, with a large proportion of the cases occurring in the testing dataset in the 2016/2017 outbreak. This is seen to have impacted predictive forecasting of RRV in other areas in Australia (Koolhof et al., 2017). Another possible explanation for this poor ability for the models to predict outbreaks could be the complexity in RRV transmission, with many vector and host dynamics not being adequately expressed through lagged environmental variables. Recent mechanistic modelling of the transmission of RRV through mosquito and kangaroo reservoirs has demonstrated that seasonally forced vector mosquito and kangaroo hosts populations may help to explain some of the unpredictability in RRV epidemics (Denholm et al., 2017). Vector and host RRV transmission dynamics vary across Australia. An example of this can be seen in northern Australia, where RRV epidemics consistently occur on an annual basis owing to the combined effect of seasonal vector dynamics and non-seasonal host population dynamics. This is in contrast to southern more temperate latitudes of Australia, where epidemics shift to being multi-annual and both the vector and host populations are seasonally driven and complex. Vector and host communities are also likely to vary at broad and fine spatial scales. The differences in vector and host species between sites may also help explain poor forecasting using environmental and climatic predictors (Carver et al., 2009; Koolhof and Carver, 2017). Differences in host communities may affect an area's herd immunity and the general host contributions to transmission impacting upon human spill-over epidemics of RRV. Previous modelling has indicated that the inclusion of host factors within RRV predictive modelling has been beneficial in model forecasting (Ng et al., 2014). Multiple studies have also found the inclusion of mosquito surveillance data to be an important factor within epidemiological models for understanding RRV transmission in some regions of Australia (Yu et al., 2014). However, this is not the case for some areas, where mosquito surveillance information does not significantly contribute to improving our understanding RRV transmission more than using environmental and climatic predictors alone (Williams et al., 2009; Cutcher et al., 2017). Thus, it is likely that for our two LGAs which had a similar number of RRV notifications used in training the models but poor predictive ability, the addition of vector and host information may improve model performance.

The results of the current study indicate that several environmental and climatic variables are important in predicting of notifications of RRV across multiple regions of Victoria. However, results also indicate site-specific variables that are important for forecasting RRV. This is likely to be related to the spatial distribution of LGAs across Victoria used in the study that influenced the impact of these variables on the types of mosquito species present, the type of breeding habitats and the development time that determines mosquito abundance. For instance, the inland LGA of Mildura commonly has Cx. annulirostris and Ae. camptorhynchus related to RRV transmission, while East Gippsland is dominated by Ae. camptorhynchus and Culex globocoxitus (Dhileepan et al., 1997; Cutcher et al., 2017). Breeding of mosquitos in Mildura is dependent on precipitation and stagnant water bodies; in contrast to East Gippsland mosquito breeding, the latter is also influenced by precipitation and maintained by the estuarine environment and mediated by tidal interactions with halotolerant mosquito species. Furthermore, differences also occur in host species community structures and their response to the environment and climate. Victoria spans temperate and semi-arid climatic regions, with host community structures varying across these LGAs. For example, aerial surveys indicate that the Western Grey and Eastern Grey kangaroo populations (the likely primary host reservoirs for RRV in Victoria), have drastically different abundance across Victoria (Moloney et al., 2017). RRV transmission has cryptic dynamics in host and vector populations which are specific to different regions. Examples of these include: changes in host populations, host reproductive timing that introduce susceptible hosts to host communities, environmental conditions for emerging mosquito populations, differences in local host contribution to transmission dynamics, and unknown contributions of secondary hosts to the amplification of RRV transmission (Poole, 1983; Koolhof and Carver, 2017; Stephenson et al., 2018).

Central to the development of RRV forecast models has been the use of time-lagged environmental variables. The inclusion of time lags allows for representation of biological and ecological events in disease transmission. The timing of environmental events and increases in RRV activity vary greatly by region often reflecting abiotic and biotic dynamics specific to an area's local transmission ecology (Russell, 2002; Jacups et al., 2008a; Yu et al., 2014; Koolhof et al., 2017). Environmental lags investigated here were congruent with these differences, where in some instances lags for the same environmental variable differing between LGAs. A likely explanation for these differences is potential biotic and abiotic aspects to each LGA involved in RRV transmission. For example, host communities are likely to vary greatly between sites, effecting the local herd immunity of the host communities, and hosts reproductive activity and movement in relation to environmental events (Harley et al., 2001; Carver et al., 2009; Koolhof and Carver, 2017). The precise role a host movement has in the mechanism for RRV transmission remains unclear, a recent study on likely RRV hosts has highlighted the capacity for RRV to be a multi-host reservoir pathogen (Stephenson et al., 2018). Hosts respond differently to environmental stimuli. For instance, possum abundance in the central highlands of Victoria was found to be correlated with vegetation structure and composition which in turn are likely influenced by (lagged) seasonal and environmental conditions (Lindenmayer et al., 1990) (such as evapotranspiration and precipitation), while both Red and Western Grey kangaroo (Macropus fuliginosus) population abundances in New South Wales are seen to have a lagged effect with rainfall events (Bayliss, 1985). Interactions between environmental changes and host dynamics help provide pathways for RRV to enter human populations. In the Northern Territory, the Agile Wallaby (Macropus agilis) and the Dusky Rat (Rattus colletti) are thought to be the reservoirs for RRV at different seasons of the year (Jacups et al., 2008a). The Agile Wallaby and the Dusky Rat feed and reproduce on floodplains during the dry season, but during the wet season the floodplains become inundated, forcing them to migrate to areas closer to human settlements resulting in their increased involvement in RRV transmission and potential outbreaks in human populations (Hu et al., 2004). Inland areas of Victoria are likely to get similar situations whereby flooding of host habitat forces hosts into closer proximity to human populations.

6.1. Summary

The Pearson correlation coefficient was used to assess our predictive models performance, with the models having a higher correlation (≥ 0.6) seen to be able to predict the 2016/2017 RRV outbreak in our testing data with reasonable success. Among the 11 LGAs examined, models for six LGAs were able to successfully predict the 2016/2017 outbreaks. Forecast models often underperform if there are an insufficient number of observations in the outcome variable (in this instance notifications of RRV in the data used to train the model). While this could explain why the models underperformed in Ballarat, Benalla, and Surf Coast, the remaining LGAs for which our models underperformed (East Gippsland and Shepparton) had a similar number of RRV notifications as the LGAs in which the models performed well. This may indicate there are other biotic and abiotic predictors needing consideration in refining our models further. The epidemiology of RRV is complex with host and vector ecological mechanisms varying between regions. Thus, for the sites were the models underperformed, there may be biotic factors (such as vector and host dynamics) which may not be represented or respond to the environmental and climatic variables investigated here. For example, the inclusion for mosquito numbers in forecasting models in some regions of Australia can improve RRV forecasting, while in other regions it may not provide improvements in a model's forecasting ability (Woodruff et al., 2002; Jacups et al., 2008b; Cutcher et al., 2017). Other such forecasting methods have investigated environmental, vector, and host variables in predicting RRV transmission across four distinct bioclimatic regions, which suggests that reservoir host data can improve ecological understanding of disease and predicting transmission of RRV (Ng et al., 2014). For several of the forecast models developed herein, the number of predicted outbreaks closely matched the observed number of outbreaks. This suggests, while some models may not accurately predict the precise number of monthly notifications of RRV, they can reasonably predict the months likely to have outbreaks, with future predictions being made one month or more in advance. Most notable is East Gippsland, since, while the model fails to precisely capture observed notifications of RRV, it clearly indicates the seasonality of transmission of RRV. For public health programs, understanding the temporal activity of RRV transmission in seasonally-driven areas compared with precisely predicting the severity of a season is potentially of equal or greater importance, as it allows for timely public health interventions.

A considerable strength to this study has been the number of LGAs investigated and the number of environmental and climatic predictors considered in constructing the early warning RRV forecasting models. A regional study in New South Wales provided the first insights into large spatial RRV predictive forecasting, with forecasts spanning multiple government jurisdictions and utilizing host and mosquito information (Ng et al., 2014). While useful for broad scale decision making, adapting these approaches may not be able to determine fine spatial outbreaks of RRV needed to guide local council disease and mosquito control programs. This was clearly demonstrated in our study, with specific environmental and climatic conditions found to be positively related to RRV within specific LGAs. The drivers for transmission of RRV at differing spatial resolutions are complex and a single spatial analysis can only create an incomplete picture of factors in RRV disease ecology (Flies et al., 2017). For instance, climatic and environmental factors are often found to be strong predictors in larger spatial analysis, as seen here, while at fine spatial scales studies indicate biotic factors (e.g., neighbourhood socio-economic status) to be of more importance (Flies et al., 2017). Thus, when developing public health interventions, the spatial disease ecology must be considered. This study is the first to examine and forecast RRV across multiple LGAs in Victoria and to give a broad view on the types and variation of predictors for RRV notifications.

6.2. Caveats

In this study we were unable to make direct comparisons between coastal and inland LGAs. Most notably, measurements for our oceanic related factors are from a single monitoring station. Tide related sea level for coastal regions has been shown to increase transmission of RRV owing to the availability of water sources for mosquito breeding (Woodruff et al., 2006; Tall et al., 2014; Koolhof et al., 2017). Victoria has a limited number of tide monitoring stations that provide continuous data, limiting the investigation of site-specific associations of sea level with the transmission of RRV. Because of this limited information, our associations seen with changes in sea level were imprecise and often non-significant in the models. Another limitation to the models developed here is that the variables included in the models were based on the AIC at a lag of zero before investigating larger lags. This may have caused premature exclusions of variables. However, this process was necessary to reduce the initial number of variables considered and to reduce the number of comparisons being made. Furthermore, as with many other RRV forecasting attempts, notification data is often incomplete, missing asymptomatic and other unreported infections. However, we would argue that non-reported and asymptomatic infections do not subtract from the epidemic signal observed in RRV notification data when developing outbreak surveillance forecasts.

Many of the predictor variables included in the models underwent either a logarithmic or square-root transformation and as a result we are at risk of overfitting the models and may be limited in our ability to interpret the increase in RRV in relation to the original unit of measurement of the transformed predictor variable. However, our aim was to develop reliable forecast models and was less focused on the broader epidemiological implications for RRV transmission outside of the LGAs investigated here.

Several sites investigated here were not able to accurately predict the outbreak present in the testing portion of our time series data. While we speculate on some of these sites having insufficient human notifications in the training portion of the time series, this was not the case for two of the LGAs, which had relatively high RRV notifications. An inherent limitation of environmental and climatic predictive disease models is the dependence on strong biological and ecological pathways which these factors contribute to in disease transmission. Lack of vector and host information was not assessed, and we could not determine if models could be improved in their predictive ability with its inclusion.

6.3. Closing

This work presents a network of early warning forecasting tools which spans across several Local Government Areas the State of Victoria, that is being adopted and integrated into the Victorian Department of Health and Human Services' arbovirus surveillance systems to aid in decision making processes and potential early intervention to reduce mosquito numbers through mosquito control and possibly human case notifications. Earlier modelling within Victoria have previously been used to advise councils to conduct mosquito control through larvae spraying and adulticide treatments and through public engagement with general practitioners and media releases to help raise awareness and preventative action by residents. As climate conditions continue to change, epidemics may become more frequent in temperate and southern latitudes. The control of RRV and other mosquito-borne diseases in Australia is typically managed through the reduction of larval mosquito population prior to pupation through habitat modification and chemical control (de Little et al., 2012). Having a forecast system in-place to predict increases in notifications of RRV disease in epidemiologically important regions is critical to ensure that public health authorities are provided with early warning systems that allow appropriate, targeted and timely interventions to be deployed.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.epidem.2019.100377.

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