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Short Communication

First evidence of concurrent enzootic and endemic transmission of Ross River virus in the absence of marsupial reservoirs in Fiji

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ABSTRACT

Background: Ross River virus (RRV) is a zoonotic alphavirus transmitted by several mosquito species. Until recently, endemic transmission was only considered possible in the presence of marsupial reservoirs.
Methods: RRV seroprevalence was investigated in placental mammals (including horses, cows, goats, pigs, dogs, rats, and mice) in Fiji, where there are no marsupials. A total of 302 vertebrate serum samples were collected from 86 households from 10 communities in Western Fiji.
Results: Neutralizing antibodies against RRV were detected in 28% to 100% of sera depending on the species, and neutralization was strong even at high dilutions.
Conclusions: These results are unlikely to be due to cross-reactions. Chikungunya is the only other alphavirus known to be present in the Pacific Islands, but it rarely spills over into non-humans, even during epidemics. The study findings, together with a recent report of high RRV seroprevalence in humans, strongly suggest that RRV is circulating in Fiji in the absence of marsupial reservoirs. Considering that all non-human vertebrates present in Fiji are pan-global in distribution, RRV has the potential to further expand its geographic range. Further surveillance of RRV and access to RRV diagnostics will be critical for the early detection of emergence and outbreaks.

Ross River virus (RRV, an *Alphavirus* of the family *Togaviridae*) is closely related to chikungunya virus (CHIKV), and can be transmitted by various *Culex* and *Aedes* mosquitoes (Harley et al., 2001). Marsupials, including macropods (kangaroos and wallabies), possums, and bandicoots, are competent amplifiers under experimental conditions (Harley et al., 2001). The possible role of placental mammals and birds is poorly understood (Stephenson et al., 2018). During epidemics, when there are many viremic humans, direct human–mosquito–human transmission (urban transmission cycle) can also occur (Harley et al., 2001). RRV is endemic and enzootic in Australia, resulting in approximately 5000 reported human cases and economic losses of 5.7 million Australian dollars every year (Australian Department of Health, 2019; Harley et al., 2001); symptoms include polyarthritis, lethargy, and rash.

During the years 1979–1980, RRV caused large outbreaks in humans across the South Pacific, with >500 000 cases reported (Harley et al., 2001). The outbreak was thought to have been seeded by an Australian who travelled to Fiji, where post-epidemic seroprevalence reached 90% in some communities (Harley et al., 2001; Aaskov et al., 1981). The outbreak was presumed to be predominantly driven by an urban transmission cycle, and once it had subsided, it was assumed that RRV transmission would cease

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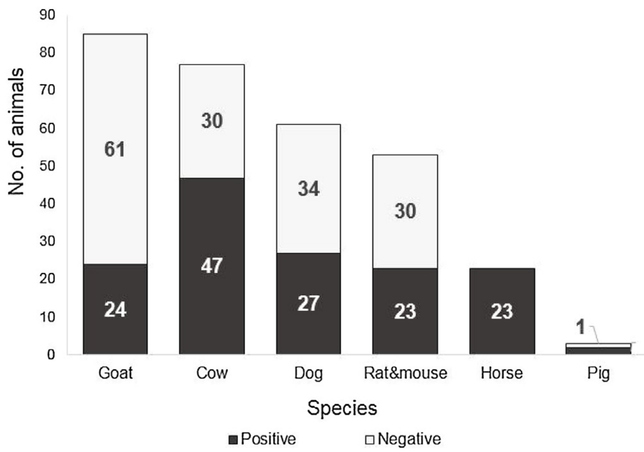

Figure 1. Ross River virus seropositivity in non-human vertebrates in Ba, Western Fiji, sampled from September to November 2015.

because marsupials were absent (Harley et al., 2001). However, reports of RRV infections in travelers returning from Fiji (Lau et al., 2012) and recent human seroprevalence studies in Fiji (Aubry et al., 2019), American Samoa (Lau et al., 2017), and French Polynesia (Aubry et al., 2017) suggest ongoing endemic transmission. In 2013, human samples from Fiji tested for anti-RRV antibodies using a validated recombinant antigen-based microsphere immunoassay (Aubry et al., 2019; Aubry et al., 2017), showed overall seropositivity of 59% in the greater Western Division, and seroconversion patterns suggested ongoing endemic circulation in Fiji (Aubry et al., 2019). These findings suggest endemic RRV transmission is possible without marsupials, which has important implications for the risk of global spread.

To investigate the role of non-marsupials in RRV transmission, we studied the serological status of seven placental mammal species for neutralizing antibodies of RRV in Fiji.

In September to November 2015, sera were collected from cows, horses, goats, pigs, dogs, rats, and mice in Ba, Western Fiji (Figure 1). Sera were tested for anti-RRV antibodies using a plaque reduction neutralization test, as described previously (Gyawali et al., 2019); the test was considered positive if plaque numbers were reduced by >50%. In total, 302 non-human vertebrates were sampled from 86 households (mean 3.5/household, range 1–13) across 10 communities (mean 30.2/community, range 5–69). Overall, 48% (146/302) were seropositive for RRV, including 100% of horses (23/23), 62% of cows (47/76), 67% of pigs (2/3), 28% of goats (24/85), 44% of dogs (27/61), 43% of rats (22/51), and 50% of mice (1/2). Seropositive vertebrates were identified in all 10 communities in 74% (64/86) of households (Figure 2). These findings support previous hypotheses (Aubry et al., 2019; Lau et al., 2017) that enzootic RRV transmission can be maintained by non-marsupial vertebrates.

The study findings are unlikely to be the result of cross-reactivity with other alphaviruses. Ten percent of the positive s-
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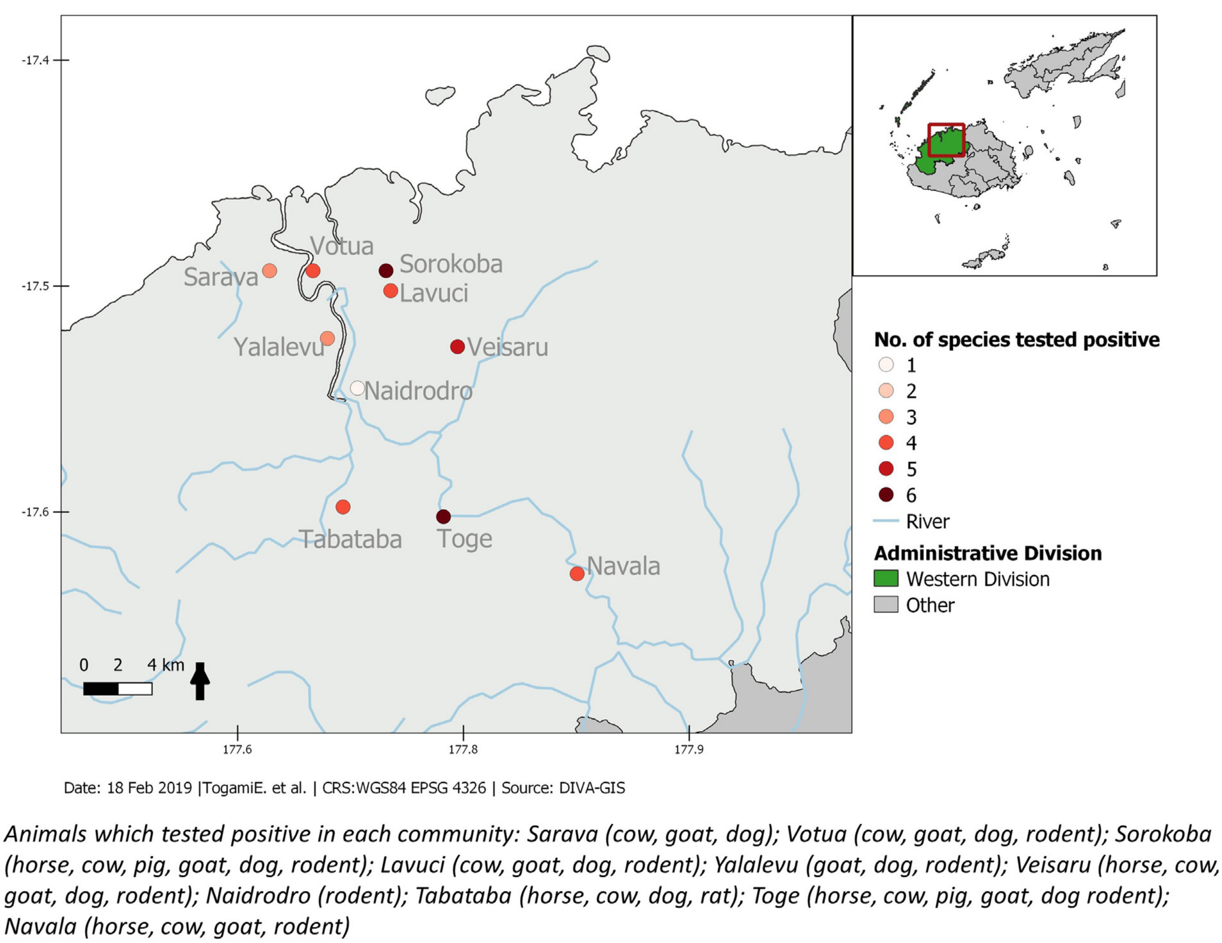

Figure 2. Ten communities from which human and non-human vertebrate samples were collected from households in Ba, Western Fiji from September to December 2013 (human) and September to November 2015 (non-human vertebrate). A 'household' is defined as a unit of individuals occupying one house, in many instances a family, which comprise a community in Fiji. A 'community' is defined as a traditional Fijian (iTaukei) village, settlement, or a suburban group of households, which comprise a subdivision in Fiji.

mples were re-tested at dilution rates of >160-fold and these continued to neutralize RRV, suggesting strong and specific antibody binding (Gyawali et al., 2019). Although endemic circulation of an unidentified alphavirus that cross-reacts with RRV cannot be ruled out, we can exclude the majority, because alphaviruses are classified by serological cross-reactivity (Calisher et al., 1980). Sindbis virus belongs to a different alphavirus group and does not cross-react with RRV. Of the Semliki Forest group, only CHIKV has been reported in the Pacific Islands. CHIKV rarely spills over into non-humans, even during epidemics. Barmah Forest virus is not a good antigenic match with RRV and has never been described outside of Australia. In the context of recent seroprevalence results in humans in Fiji, RRV is by far the most likely explanation for our findings.

Serological surveys cannot determine which reservoirs facilitate sufficient virus replication to sustain transmission. However, high seroprevalence in all tested species, including short-lived rodents, strongly suggests endemic transmission. Considering that humans can sustain epidemic but not endemic transmission (Flies et al., 2018), the only possible explanation for long-term endemic circulation of RRV in Fiji is enzootic transmission in one or more non-human vertebrate species. Although RRV transmission in non-marsupials is poorly understood, horses are known to exhibit high, long-lasting viremia with proven capacity to infect mosquitoes (Stephenson et al., 2018). In our small sample of horses, all were antibody-positive. Conversely, dogs do not appear to be efficient reservoirs (Harley et al., 2001).

Given the extensive travel between Fiji and Australia, it is possible that RRV was reintroduced into Fiji after 1980. Alternatively, transmission might have continued at low levels after 1980, but not recognized due to low clinical suspicion, limited diagnostic capacity, and non-specific symptoms that overlap with those of other diseases. All species tested are common, peridomestic, and pan-global. Regardless of which species is the primary reservoir or amplifying host(s), the study findings suggest RRV could potentially become established in other areas with competent vectors. In immunologically naïve populations, there is a risk of virgin soil outbreaks such as those experienced in the Pacific Islands. Future studies should focus on pathogen isolation to unequivocally confirm RRV transmission and on the identification of competent reservoirs and vectors. Laboratory diagnosis is crucial for surveillance and the early detection of emergence and outbreaks.

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Ethical approval

Ethical approval was granted by the Ministry of Health and Medical Services, and the Ministry of Agriculture in Fiji prior to the beginning of field work. The ethics approval granted for the human seroprevalence study was extended and expanded to this study by the Fiji National Research Ethics Review Committee (2013 03). The procedures performed on live animals were approved by the Massey University Animal Ethics Committee (Reference #15/70).

Conflict of interest

None.

Author contributions

CLL, ET, JMCE, GJD, and PW conceived the research and designed the study. ET and CLL collected the specimens. NG, OO, and GJD conducted the laboratory testing of samples. ET conducted the data analysis. ET, CLL, PW, GJD, NG, and OO developed the manuscript. NG, OO, MK, VMCL, MA, AIK, EJN, JMCE, GJD, and PW provided input in the development stage of the manuscript and provided feedback to revise and finalize the manuscript. CLL provided oversight of the research.

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