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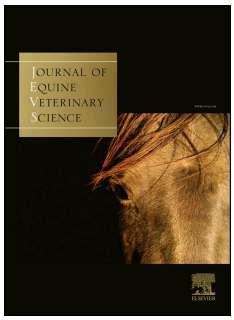

Clinical presentation, progression and management of 5 cases of Ross River virus infection in performance horses located in southeast Queensland: A longitudinal case series

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Clinical presentation, progression and management of 5 cases of Ross River virus infection in performance horses located in southeast Queensland: A longitudinal case series

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Ross River virus; horse; arbovirus; arthritis; febrile illness; lethargy

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Abstract

Background: Ross River virus (RRV), a mosquito-transmitted alphavirus prevalent in Australia, is believed to cause poor performance, lethargy and muscle stiffness in Australian horses. However, disease progression and management is poorly documented. A better understanding of disease presentation, acute therapy and long-term management is required.

Objectives: To describe clinical presentation, diagnosis, acute treatment and long term management of RRV-infection in horses

Study design: Retrospective case series

Methods: Clinical and diagnostic data were obtained from both veterinary records and owner interviews for 5 performance horses that presented with acute poor performance coupled with serological evidence of RRV exposure. Clinical and owner reports were evaluated from the time of presentation until the horses appeared asymptomatic and had returned to normal performance.

Results: RRV was suspected to be the cause of generalized muscle stiffness and poor performance in 5 performance horses located in southeast Queensland between 2011 and 2015. Clinical symptoms included pyrexia, tachypnoea, exercise intolerance, generalized muscle stiffness, synovial effusion, and oedema of the lower limbs. Serological investigations (ELISA and/or virus neutralization assay) detected antibody responses to RRV. Horses were treated with non-steroidal anti-inflammatory drugs (n=5) and disease-modifying osteoarthritis drugs (n=2). Most horses returned to previous athletic capabilities between 7 and 12 months after onset of symptoms.

Main limitations: Not all horses in the study had pre-clinical serology or submitted paired blood samples for serology, meaning assumption of acute infection in those horses was made based on clinical signs coupled with positive serology

Conclusion: RRV is a significant but poorly understood cause of poor performance in Australian horses. This report is the only one to document longitudinal management of performance horses affected by RRV infection. Much more research is needed to gain a better understanding of this infection in horses.

Abbreviations

AID, Australian Infectious Diseases Research Center; AST, aspartate aminotransferase; BFV, Barmah Forest virus; CHIKV, Chikungunya virus; CK, creatinine kinase; DMOAD, disease-modifying osteoarthritis drug; ELISA, enzyme-linked immunosorbent assay; JEV, Japanese Encephalitis virus; KUNV, kunjin virus; MAYV, Mayaro virus; MVEV, Murray Valley Encephalitis virus; NSAID, non-steroidal anti-inflammatory drugs; ONNV, O'nyong-nyong virus; RT-PCR, real-time polymerase chain reaction; RRF, Ross River fever; RRV, Ross River virus; SINV, Sindbis virus; VADCP, Victorian Arbovirus Disease Program; VNT, virus-neutralising antibody titre

Introduction

Ross River virus (RRV) is an arthropod-borne Alphavirus in the family *Togaviridae* found in Australia and Papua New Guinea, and is suspected to occur epidemically in the Solomon Islands [1; 2]. The primary vertebrate reservoir host for RRV may vary regionally and seasonally, but includes possums, macropods, such as kangaroos and wallabies, and humans [3-5]. Although birds commonly feature as reservoir hosts for many other arboviruses, RRV antibody prevalence in birds is generally low, and avian species are generally not considered important in transmission of RRV [4]. The major arthropod vector for RRV is believed to be *Aedes vigilax* in coastal regions of northern and eastern Australia, *Aedes camptorhynchus* in southern and southwestern Australia, and *Culex annulirostris* in tropical and temperate inland areas, although the virus has been isolated from over 30 different species of mosquito Australia-wide [6]. Even though serological surveys have detected RRV-specific antibodies in a range of wild and domestic species, such as marsupials, livestock and domestic pets, it is unknown if animals other than marsupials play a role in amplification and transmission of the virus, or if RRV is capable of causing symptomatic disease in animal species other than horses and humans [2; 7; 8]. Speculation exists about whether horses function as a reservoir host for RRV, and if they play a role in disease transmission to humans. It appears that in most cases viraemia is transient in horses and humans, and they are generally unable to amplify the virus sufficiently to extend transmission to mosquitoes. Nevertheless, some evidence exists that in unique circumstances human viraemia may be high enough to perpetuate the transmission cycle, and it is possible this could occur in horses also [3; 4; 9; 10]. A recent documented case of transfusion-transmission of RRV has also proven that, in exceptional circumstances, human to human transmission of the virus is possible [11].

RRV is responsible for debilitating illness in both humans and horses characterised by severe arthralgia, myalgia, fever and fatigue and known as ‘epidemic polyarthritis’ or Ross River

fever. Clinical disease in humans presents as severe joint pain and lethargy, in some cases preceded by a transient fever (~30% of cases), and may be accompanied by a transient rash [2; 12]. Arthritis and arthralgia typically affect the knees, ankles, wrists and small joints in the fingers. Fatigue and arthralgia in humans has been reported to persist for as long as six to twelve months [12-14]. Relapses of clinical signs following periods of illness or stress have been suspected but not definitively documented.

Very few studies document the effects of RRV infection in horses [15; 16], despite it being suspected of causing poor performance and musculoskeletal disease in the Australian equine population for more than 25 years [17; 18]. Reports to date suggest horses experience a transient fever and often present acutely with non-specific viral vasculitis of hind or fore limbs resulting in 'filling' or oedema of the limb between the fetlock and carpus or hock. Swelling of joints, ataxia, submandibular lymphadenopathy, oral petechiae and high serum fibrinogen and globulin levels have also been reported [15; 16].

This case series documents clinical presentation and progression during 12 or more months in 5 performance horses located in southeast Queensland and suspected of having RRV-induced disease. Diagnosis was made based on clinical symptoms coupled with seroconversion to the virus. Cases were presented between 2011 and 2015. Four of the five horses were located within the Lockyer Valley region.

Case reports

Table 1.

Insert Table 1

Case study 1

A 6-year-old warmblood gelding dressage horse located in the Lockyer Valley, Southeast Queensland, presented in February 2011 for acute onset inappetence, depression, marked reluctance to move and stiffness in his gait at walk. Rectal temperature was 40.0°C. The owner reported no limb swelling at this time. Hematology examination revealed mild neutropenia (N-), anaemia (An) and lymphocytosis (Ly+). Serological test for RRV 6 weeks later revealed elevated IgM (1:20480) and IgG (1:20480) in ELISA performed at IDEXX Laboratories, Brisbane. The horse was treated acutely with non-steroidal anti-inflammatory drugs (NSAIDs) (Phenylbutazone 3mg/kg initially, followed by 2mg/kg orally BID for 10 days). Temperature and appetite returned to normal within 24 hours of commencing NSAIDs. The horse was rested in paddock and the owner reported an obvious stiffness to gait and on flexion of limbs for about 2 months after first presenting, with a gradual improvement over the following month. Three months after presenting the horse was placed into light exercise, but was reported to remain subtly stiff through his limbs, and was spelled in the paddock for a further 3 months. At this time the horse returned to training with apparent resolution of all clinical signs.

As the owner was satisfied of the diagnosis, a follow-up blood test to monitor changes in RRV antibody levels was not made.

Case study 2

A 12-year-old Clydesdale gelding dressage horse located in the Lockyer Valley, Southeast Queensland, presented in May 2012 with a history of transient low-grade pyrexia (39.4°C recorded on one occasion), oedema of both hindlimbs from the fetlock to hock of less than 24hrs duration, and persistent synovial effusion of the hind fetlocks that lasted 4 months. The horse was treated acutely with NSAIDs (Phenylbutazone 3mg/kg initially, followed by 2mg/kg orally BID for 5 days) and given two weeks' rest from exercise. On returning to

exercise the rider observed the horse to have a slight exercise intolerance characterized by an inability to sustain activity, increased sweating and a delayed recovery in respiratory rate. Blood was collected at this point and tested for routine hematology and biochemistry and arbovirus isolation. Hematology and biochemistry results were unremarkable. An ELISA screening for RRV, performed at the Australian Infectious Diseases Research Center (AID), University of Queensland, was negative. A virus-neutralising antibody test, also performed at the AID using the RRV prototype strain T48 [19-21] gave a titre of 1:320 for RRV and was negative for Murray Valley Encephalitis virus (MVEV) and Kunjin virus (KUNV). Samples taken from this horse 7 months prior to illness as part of a research survey had returned a negative virus-neutralizing titre (VNT) to RRV [20]. The horse was rested for 6 months in the paddock and treated with the disease-modifying osteoarthritis drug (DMOAD) pentosan polysulphate 3mg/kg IM monthly. Seven months after initial presentation the horse returned to training with apparent resolution of exercise intolerance. Follow-up samples taken 3 years later and submitted to the AID as part of continued arbovirus surveillance reported a VNT of >1:2880.

Case study 3

An 8-year-old warmblood stallion dressage horse located in East Brisbane, Southeast Queensland, presented in February 2013 with a history of exercise intolerance and dyspnoea during exercise. The horse developed anhydrosis and displayed a markedly increased respiratory rate, around 100bpm, for up to 3 hours following exercise. The owner reported swelling of the hind limbs from fetlock to hock of 7 days' duration that did not go down following exercise or icing. The horse became progressively inappetant and continued to show tachypnoea even once he was placed on stable rest. At no time did the owner detect an elevation in rectal temperature. On clinical exam, the horse was depressed, moderately dehydrated and had an elevated respiratory rate (45bpm). Clinical examination and thoracic auscultation were unremarkable. The stallion was admitted for endoscopic examination,

blood and urine tests and placed on IV fluids. No abnormalities were detected on endoscopic examination or urinalysis. Plasma biochemistry showed an increase above normal reference range in creatinine kinase (CK) (621u/l; normal 113-375u/l) and aspartate aminotransferase (AST) (463u/l; normal 194-440u/l), both indicators of muscular damage. Hematology was unremarkable. An ELISA test performed at IDEXX Laboratories, Brisbane for RRV revealed an elevated IgM (1:20480) and IgG (1:20480). A paired sample was not submitted. The stallion was treated with NSAIDs (Phenylbutazone 3mg/kg initially, followed by 2mg/kg orally BID for 21 days), an iron supplement and sodium acid citrate 7.93g SID to aid in muscle damage repair. He was rested from exercise for three months and hand walked twice daily during this time. He then commenced a month of short walks under saddle, followed by a further two months of gradual increase in workload. The owner reported the horse as still having exercise intolerance, anhydrosis and fatiguing quickly with exercise. The horse had a further six months of rest from exercise and a change in diet to reduce the levels of starch and sugar. The owner reported an improvement in both the anhydrosis and demeanor. Tachypnoea resolved one month after commencing the iron supplement.

Case study 4

A 10-year-old warmblood mare dressage horse located in the Lockyer Valley, Southeast Queensland, presented in February 2015 with 3-month history of neck stiffness to lateral bending during exercise, a low-grade intermittent cough both in the paddock and on commencement of exercise, and mild loss of performance characterized by lethargy and delayed response to rider's aids during work. The owner had observed no joint swelling or oedema of the limbs. No pyretic episodes had been detected during the preceding 3 months. The mare had been screened for RRV 24 months prior when an in-contact horse had been conclusively diagnosed with RRV, and her VNT at that time was zero. The mare was admitted for cervical radiographs and endoscopic examination of the upper airways. Blood

was collected for general hematology, biochemistry and VNT for RRV. Cervical radiographs detected no evidence of bone disease, and mild hyperemia of the pharyngeal region was observed on endoscopy. Routine hematology and biochemistry results were unremarkable. RRV-specific neutralization titre performed at the AID was 1:160. A follow-up VNT to the same laboratory 2 months later was 1:2880. The mare was treated with rest, a short course of NSAIDs (phenylbutazone 2mg/kg orally BID for 5 days), and a combination of DMOADs (Pentosan polysulphate 3mg/kg IM fortnightly and hyaluronic acid 60mg IV weekly for 5 weeks). Two months after presenting to the clinician the mare returned to training and the owner reported an improvement in all clinical signs except for an intermittent cough at the beginning of each training session. The cough appeared to resolve after 3 months back into work (9 months after the suspected date of virus infection). The owner also felt the mare seemed to have increased susceptibility to respiratory infections following attendance at organised performance events, which resulted in a temporary relapse in stiffness and lethargy. Periods of 'relapse' lasted around 2 weeks in each instance (4 episodes over a 6 months' period), accompanied by a mild increase in rectal temperature. The owner also reported some low-grade intermittent irregularity in gait, when the horse was asked to trot on a firm surface, that had not been present prior to contracting RRV infection. The reason for the irregularity remained undiagnosed and appeared to improve with anti-concussive corrective shoeing.

Case study 5

A 10-year-old warmblood gelding dressage horse located in the Lockyer Valley, Southeast Queensland presented in March 2015 with acute onset of intermittent low-grade lameness on commencement of exercise, neck stiffness to lateral bending during exercise, a loss of performance characterized by reluctance to work, reduced responsiveness to riders' aids and rapid fatigue, and an elevated respiratory rate at rest. The owner reported enlarged

fetlocks and generalized malaise in the paddock. A month after onset of clinical signs the owner observed laminar rings on the proximal hoof capsule that had not been there previously. No evidence of distal phalangeal rotation was observed radiographically. An initial serum sample was taken 6 weeks after the onset of clinical signs. A paired sample was taken four weeks later. Both samples were submitted for serology. The initial RRV-specific neutralization titre was 1/1440, the follow-up VNT one month later was 1:2880. The horse was treated with rest and NSAIDs (phenylbutazone 2mg/kg orally BID for 5 days). Ten months after initial presentation the horse returned to training with mild residual stiffness. The owner reported an improvement in stiffness 12 months after initial clinical signs.

Discussion

RRV is an arthritogenic mosquito-borne disease endemic to Australia that is known to cause clinical disease in horses and humans, however, very little is known about the disease in horses.

Clinical signs

The clinical symptoms observed in the documented horses were consistent with previously reported cases [15; 16]. The consistent findings among all the cases were poor performance and generalized muscle stiffness. However, poor performance reports can be very non-specific ranging from exercise intolerance and reluctance to work, stiffness to lateral bending exercises, to severe resistance and complete unwillingness to perform their regular work. Many other symptoms, such as pyrexia and oedema of limbs were reported by the owners to be transient, and may often be missed, precluding early detection of infection. It is likely that many cases of RRV in horses are overlooked due to owners blaming the symptoms on behavioral anomalies or training-related setbacks rather than suspecting viral disease. Some researchers still debate whether the virus is responsible for clinical disease in horses, due to limited published investigations, low reporting of clinical disease despite high

serological surveillance rates [9, 10, 14, 35], and poor understanding of the disease process in horses, but front-line astute veterinarians often correlate acute muscle stiffness and reluctance to perform in horses undertaking athletic pursuits with seroconversion to RRV.

Serological surveillance of horses often detects prevalence rates of RRV as high as 65% [16; 22]. Between 2010 and 2013 the Victorian Arbovirus Disease Program (VADCP), Agribio, Bundoora, recorded an incidence rate of approximately 30% in commercial samples from suspect horses submitted for arbovirus investigation, increasing to around 45% between 2013 and 2015. It is difficult to obtain similar data from Queensland and New South Wales, as these states primarily test for Flavivirus and do not routinely check for RRV as is done in Victoria. However, a limited survey of horses entering race meetings in Brisbane in late 2012 and early 2013 found that 20/70 (28%) and 22/47 (47%), respectively, were seropositive for RRV in a highly specific virus neutralization assays (Bielefeldt-Ohmann, Prow, Wright & Hall, unpublished data). Additional testing in the Summer of 2015-16 also revealed RRV-neutralizing antibodies in ~50% or racehorses and horses admitted to the University of Queensland Equine Hospital for non-arthritic morbidities (Bielefeldt-Ohmann & Wiseman, unpublished data). Blood samples evaluated for routine hematology and biochemistry in horses with seroconversion to RRV often show no abnormalities, making screening for changes in inflammatory markers suggestive of a viral infection (neutrophilia/neutropenia, lymphocytosis, monocytosis) unreliable as a precursor to deciding whether or not to investigate for RRV. Infection must be suspected based primarily on clinical examination, and a decision to perform serology must be made independent of other laboratory investigation, as demonstrated in this case series.

Management of RRV in horses and humans

Currently, there are no specific treatments, such as antivirals, or commercially available vaccines for alphavirus infection. There are also no reported clinical trials for therapeutic management of horses or humans affected by RRV. Surveillance of human patients affected by RRV found that one half of affected people surveyed reported pain relief to be the most effective management of joint pain (36.4% reported NSAIDs provided the most relief, while 16.4% reported aspirin or paracetamol as providing the most effective relief) [14]. Rest was cited by 24.1% of human patients as their main source of relief. One study also reported a reduction in duration of clinical signs in human patients receiving corticosteroids [23], but to date all recommendations for therapeutic management of RRF in humans are based on subjective and anecdotal responses. Management of horses affected by RRV should include NSAIDs in the acute stages to control pyrexia, arthalgia and myalgia, and an extended period of rest from imposed exercise, such as ridden activities. The minimum anecdotal recommendation for rest based on duration of clinical symptoms in humans is 4 to 6 months, and certainly in this investigation we observed most horses did not return to normal performance until between 7 and 12 months after onset of clinical symptoms. Chondroprotective agents, such as sodium hyaluronan or polysulphated glycosaminoglycans, may be of assistance in reducing arthralgia and arthritis [24; 25]. Responses from human surveys also indicate alternative therapies such as hydrotherapy and massage may provide relief to clinical symptoms,[14] and the use of these therapies could be adopted in the management of clinically affected horses. The potential for low-grade laminitis due to either pyrexia or systemic cytokine release [26; 27] should not be ruled out, and horses affected by RRV should be closely monitored during acute illness and convalescence for signs of pain within the hoof capsule.

Diagnostic testing for RRV

Diagnosis of RRV is commonly made based on serological testing for IgM (acute phase) and IgG antibodies. Paired serum samples taken 2 to 4 weeks apart assist in making a more accurate diagnosis of recent infection. An IgM response is generally detectable 7 to 10 days after infection and peaks within 2 to 3 weeks before declining as antibody class switching occurs and IgG becomes the predominant antibody detected. Since IgG antibodies to RRV are believed to be life-long, detection of IgG in horses or humans can only demonstrate prior exposure to RRV. Certainly in this investigation, a very high antibody titre was detected in a horse 3 years after his initial infection. The detection of IgM, either alone or in combination with IgG enables an estimate of the time of infection. However, it should be noted that 1% of horses may maintain a detectable IgM titre for at least 18 months [15]. Diagnosis of a recent infection depends on showing an IgG seroconversion or a rising IgG titre. Where IgM is detected in the absence of IgG it is important to demonstrate IgG seroconversion on a convalescent sample. Cross reactivity with serological testing is documented and false positives have been reported with EIA IgM tests. Virus isolation can be performed using inoculation of tissue cultures or reverse transcription-polymerase chain reaction (RT-PCR). RT-PCR for viral RNA (i.e., nucleic material) is a very specific and sensitive tool for diagnosing current/recent infection, and has been validated for use on equine blood and synovial fluid [28]. VNT are commonly used in research as they are more specific, but require PC2 laboratory certification for handling of live virus and are time consuming. Cross reactivity with related alphaviruses and low neutralizing titres can affect this approach to diagnosis.

Conclusion

RRV is an arthritogenic mosquito-borne disease endemic to Australia that is known to cause clinical disease in horses and humans, however, very little is known about the disease in horses. Serological surveillance have detected infection rates as high as 65% in horses [16; 22]. Clinical symptoms in horses are non-specific, and include exercise intolerance, joint

swelling, vascultis and oedema of the lower limbs, generalized musculoskeletal stiffness and transient pyrexia. It is likely that many cases are overlooked due to owners blaming the symptoms on behavioral anomalies or training-related setbacks rather than suspecting viral disease. Diagnosis of RRV in horses is best achieved by submitting paired serum samples 2 to 4 weeks apart to a diagnostic laboratory and demonstration of either an isotype switch from virus-specific IgM to IgG antibodies, or a rising IgG titre. IgM antibodies may persist for as long as 18 months in the horse.[15] Recommendations on treatment for RRV are not based on clinical trials, but rather extrapolated from retrospective human surveillance and subjective feedback.

The long-term sequelae of RRV infection in horses are not known. Horses are economically highly valuable animals, dependent on their athletic capabilities, and information regarding the inflammation and possible degradation of articular cartilage and subchondral bone is essential to provide information to trainers and riders about the crucial nature of appropriate rest and management of horses affected by RRV. More research is needed into clinical manifestations of RRV in horses, particularly the effects on joints, bone and hoof lamellae, as well as the affect of exercise on inflamed joints. Response of horses to treatment, such as NSAIDs or judicious use of corticosteroids, should also be assessed for any benefit in reducing severity of clinical signs or duration of illness. Given the considerable morbidity of this disease in both horses and humans, much more research needs to be conducted to provide a more evidence-based approach to therapeutics and management.

This investigation is the only one to document clinical progression and management of RRV in horses over a longitudinal period.

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Conflict of Interest

The authors have no conflicts of interest.

Table 1. Summary of clinical findings and treatment in horses suspected to be infected with Ross River virus. N- = Neutrophilia; An = Anaemia; Ly+ = Lymphocytosis; CK = creatinine kinase; AST = Aspartate Aminotransferase

	Horse 1	Horse 2	Horse 3	Horse 4	Horse 5
Pyrexia	+	+	-	-	-
Tachypnoea	-	+	+	-	+
Synovial effusion	-	+	+	-	+
Limb oedema	-	+	+	-	-
Muscle pain/stiffness	+	+	+	+	+
Lameness	-	-	-	+	+
Poor performance/lethargy	+	+	+	+	+
Inappetance/colic	+	-	+	-	-
Hematology changes	N-, An, Ly+	-	-	-	-
Biochemistry changes	-	-	CK +, AST +	-	-
IgM titre					
Sample 1	1:20480	-	1:20480	-	-
Sample 2	-	-	-	-	-
IgG titre					
Sample 1	1:20480	-	1:20480	-	-
Sample 2	-	-	-	-	-
VNT					
Sample 1	-	0 titre 7 months prior to illness	-	0 titre 2 years prior to illness	1:1440
Sample 2	-	1:320	-	1:160	1:2880
Sample 3	-	>1:2880	-	1:2880	-
Treatment					
NSAID	+	+	+	+	+
DMOAD	-	+	-	+	-
Other	-	-	Iron & sodium citrate	-	-

Time to return to work	3 months	7 months	5 months	6 months	10 months
Time to return to normal performance	6 months	7 months	11 months	9 months	12 months

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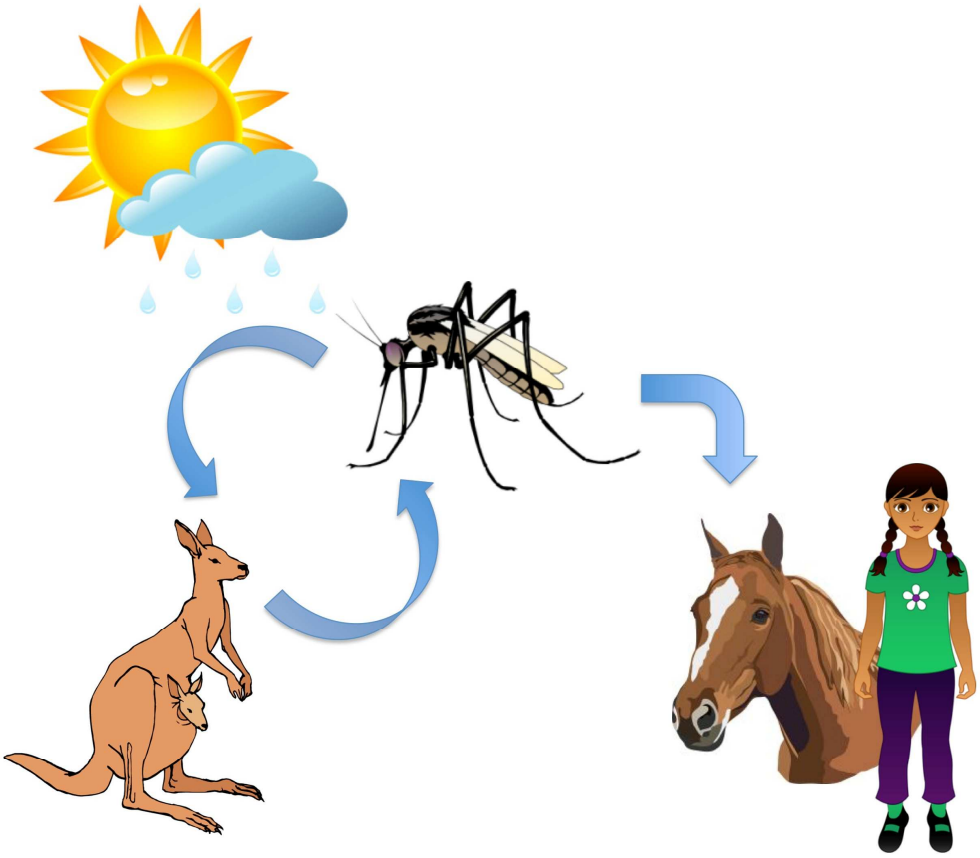

Highlights:

- Ross River virus is an arthitogenic mosquito-borne Alphavirus endemic to Australia and Papua New Guinea
- The virus causes debilitating disease in horses and humans known as Ross River Fever, characterised by joint pain, fatigue and fever that can last up to a year
- Ross River fever in horses is poorly understood and often underdiagnosed
- Management of Ross River Fever in horses and humans is symptomatic and based more on anecdotal reports rather than evidence-based medicine