

ROSS RIVER VIRUS IS A MOSQUITO-TRANSMITTED ALPHAVIRUS: IS IT THREATENED TO ARAB COUNTRIES INCLUDING EGYPT?

By

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Abstract

Ross River virus (RRV) is mosquito-borne arboviral infection that causes fever, polyarthritis, and rash. First described in northern Australia and then, widely throughout Australia and many western South Pacific islands. It is common in the tropical coastal regions of northern Australia. RRV can be transmitted by, *Aedes aegypti*, *Ae. camptorhynchus*, *Ae. vigilax*, and *Culex annulirostris*. Kangaroos, wallabies and horses are principal vertebrate hosts. Symptoms frequently occur together but may occur in single. Arthritis in wrists, knees, ankles, and finger joints is common and frequently symmetric. Rash is usually maculopapular involving limbs and trunk. Arthralgia may persist for up to 3 months. Fatigue is the commonest symptom. Diagnosis is by hemagglutination inhibition (HI) antibody and ELISA. A fourfold rise in HI titer is diagnostic; $\geq 1:1280$ levels is recent infection. RRV-specific IgM persists for months after acute infection.

Treatment is supportive care, analgesics, and non-steroidal anti-inflammatory drugs. Feasible preventive measure is avoidance of mosquito bites. Helpful interventions include use of window and door screens, mosquito repellants, and light colored clothing. Over the long-term, drainage of mosquito breeding areas in endemic areas may be helpful to control infection.

Introduction

Ross River virus (RRV) is an arbovirus group transmitted by mosquitoes that causes a fev-erish disease manifest by polyarthritis and rash. The illness was first described in northern Australia in 1928 and subsequently has been observed widely through Australia and many islands of the western South Pacific. It is most the most prevalent vector borne disease in Australia. The virus can be transmitted by many mosquito species and survives in mosquito eggs in arid environments (Kelly-Hope *et al*, 2004). Therefore, it has capacity to spread to other geographic areas worldwide (Toivanen, A, 2008).

Epidemiology: RRV infection was described in mainland Australia, Papua New Guinea (Fraser *et al*, 1988), the Solomon Islands, the islands of eastern Indonesia, and western South Pacific (Fauran *et al*, 1984), Fiji (Rosen *et al*, 1981), and American Samoa (Tesh *et al*, 1981). As many as 500,000 people were infected in Fiji when the disease first appeared in 1979 (Aaskov *et al*, 1981). Outbreaks have been described in American Samoa, New Caledonia, French Polynesia, the Cook Islands, and most states of Austral-

lia (Lindsay *et al*, 1996).

In Australia, about 6000 people were infected annually (Bi *et al*, 2009). The highest infection rates were in the Northern Territory (Quinn *et al*, 2005). Endemic foci occur in more temperate eastern Australia. Infection was seen in outskirts of Sydney since 1997 (Amin *et al*, 1998). Epidemics increased in frequency, size, via Australia European settlements (Weinstein *et al*, 2011), expanded in Queensland (Tong *et al*, 2004) and South Australia (Selden and Cameron, 1996).

RRV occurs most frequently in tropical coastal regions with salt marsh habitats suitable for the principal mosquito vector species (Mackenzie and Smith, 1996). Infection is commonest in spring, after summer rains, or after salt marshes inundation by rain or tides. Virus persists in arid areas of inland Australia within desiccation-resistant mosquito eggs. Outbreaks occur after rain, when mosquitoes hatch (Lindsay *et al*, 1993),

Climate influences: Predicting disease activity differed among regions; relationships between climate, social, and environmental factors are complex. In the River Murray Valley in Southern Australia, important fact-

ors include river height, rainfall, and mosquito abundance (Williams *et al*, 2009). In a Tasmanian study, a combination of high spring tides and excessive summer rainfall produced a salt marsh habitat with a high density of mosquitoes (Robertson *et al*, 2004). Isolation of RRV from these mosquitoes coincided with the onset of the first human cases of RRV infection. In Western Australia, climate data were moderately sensitive in predicting epidemics of 64%; the addition of mosquito surveillance data improved sensitivity of an early warning model for epidemics of 90% (Woodruff *et al*, 2006).

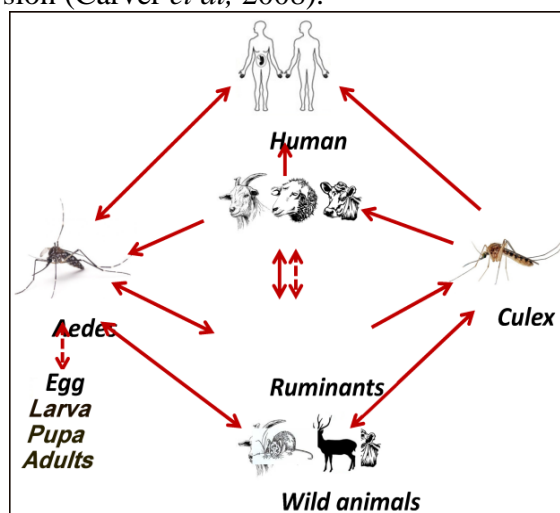
Dry-land salinity, a substantial and expanding problem in the wheat belt of South-western Australia, is associated with an abundance of *Aedes camptorhynchus* and increased potential for zoonotic transmission (Carver *et al*, 2009), although increased human seroprevalence was not yet been demonstrated (Jardine *et al*, 2008). Important factors for infection in the Darwin region of tropical Northern Australia include rainfall, minimum temperature, and abundance of 3 mosquito species (Jacups *et al*, 2008). The relative importance of these environmental factors differs according to region, but rainfall was associated with increased disease activity (Suhriebier and La Linn, 2004).

Who is at risk?: People who are in contact with known mosquito habitats and who live in warm, humid climates near bodies of water are at risk of infection. Ross River virus infections are the most common mosquito-borne infection in Australia and infections occurs in many rural areas in NSW. Infections are uncommon in the major cities and towns. Outbreaks can occur when local conditions of rainfall, tides and temperature promote mosquito breeding.

Vectors and hosts: Mosquito species that serve as vectors for RRV vary by region. In Australian coast *Aedes vigilax* (salt marsh mosquito) and *Ae. camptorhynchus* were major vectors; both are day feeding species. Except Tasmania in inland areas, a night feeding *Cx. annulirostris* predominates (Wols-

tenholme, 1992). Other vectors include *Aedes aegypti*, *Ae. tremulus*, *Ae. polynesiensis*, and many others (Harley *et al*, 2000), with the *Ae. aegypti* has the potentiality of RRV extend distribution.

Native macropods (kangaroos and wallabies) are the principal vertebrate hosts (Mylonas *et al*, 2002), infection occurs among other wild animals and livestock. In urban areas possums and horses are potential reservoirs (Kay *et al*, 2007). Vertical transmission occurs in mosquitoes, and man-mosquito-man transmission may occur. RRV in northwest Victoria showed that density of short-lived, highly fecund hosts, as domestic mice also influence rural disease transmission (Carver *et al*, 2008).



Pathogenesis: Ross River virus (RRV) is an enveloped RNA virus; distinct genetic types have been found in Eastern and Western Australia, with a mix in northern Australia. The membrane bilayer, which surrounds the nucleocapsid, is penetrated by spikes, each of which consists of glycoproteins E1 and E2 (Cheng *et al*, 1995). E2 is thought to be involved in recognition of the cellular receptor in the host (Smith *et al*, 1995). Relapse or persistence of symptoms in many patients may be related to persistent replication within synovial macrophages despite neutralizing antibodies and antiviral cytokine responses (Boyd *et al*, 2001). This process may be initiated by an initial IgG anti-RRV antibody response, which enhanc-

es infection in macrophages and monocytes (Linn *et al*, 1996).

Functional polymorphisms in immune response genes, contribute to individual susceptibility and outcome. Polymorphisms in the IFN-gamma and IL10 loci influence cytokine production and the severity and duration of illness after infection with RRV (Vollmer-Conna *et al*, 2008). These risk-associated cytokine genotypes may act in combination to potentiate their impact on illness severity. IL10 is a potent inhibitor of IL-1 beta and TNF-alpha production by macrophages, and these cytokines often have synergistic activities in induction of inflammation in the acute sickness response. In vitro models showed that cellular antiviral response can direct selective pressure for viral sequence evolution that impacts on viral fitness and sensitivity to alpha/beta interferon (Lidbury *et al*, 2011). Arthritis of RRV infection is mediated by local cell-mediated immune responses. In the majority of patients, inflammation is present in the absence of detectable virus, although RRV/DNA was identified in inflamed synovium of some patients more than a month after symptoms onset (Soden *et al*, 2000).

Rash of RRV infection may be a manifestation of a cell-mediated immune response to viral antigen in the basal epidermal and eccrine duct epithelial cells. Circulating immune complexes have not been found in patients with persistent symptoms (Fraser *et al*, 1988). In a mouse model, macrophages have been shown to be the primary mediators of muscle damage (Lidbury *et al*, 2000)

Clinical manifestations: Ross River virus (RRV) infection has been observed in individuals between 4 and 85 years of age; the disease occurs more commonly in women. The incubation period for acute presentations is usually 3 to 9 days, but may be as long as 21 days. The subclinical infection is common (Harley *et al*, 2001)

Symptomatic RRV presents in one of the three ways: a- Acute febrile illness with arthritis and rash, b- Acute fever, rash, or ar-

thritis alone, and c- Chronic polyarthritis or polyarthralgia (Fraser *et al*, 1983).

There are no specific laboratory tests for RRV-infection. Leukocyte count is usually normal; atypical lymphocytes or a mild neutrophilia may be in some patients, serum C-reactive protein concentration usually normal, but modest elevations in the erythrocyte sedimentation rate may be observed.

Arthritis: The most dramatic clinical features of RRV infection are marked arthralgia and myalgia. Joint pains are present in more than 95% of patients. True arthritis occurs in 40 percent of patients. The joints of the extremities are most frequently involved, especially the wrists, knees, ankles, and the metacarpophalangeal and interphalangeal joints of the fingers. Joint involvement is usually symmetric, but the severity of inflammation may be asymmetric. The intensity of the pain and inflammation may resemble that of gout. Effusions are often present in joints and tendon sheaths, and Achilles tendinitis and plantar fasciitis may occur. Back pain is also common; no association between HLA-B27, or another HLA allele has been detected. Synovial fluid analysis early in the disease may suggest viral arthritis. The fluid is viscous with entirely or predominantly mononuclear cells; neutrophils may comprise up to 12% of cells (Fraser, 1986). Kivity *et al*. (2011) stated that travel returnees might complain of protracted rheumatic symptoms, but there are sparse data regarding their causes. In a retrospective analysis of Israeli travelers who were referred to the Sheba Medical Center from January 2005 to January 2010 with prolonged (>4 weeks) non-traumatic arthralgia or arthritis. They found that 14 patients (7 men & 7 women) with post-travel arthritis/arthralgia were seen, 5 patients were diagnosed with reactive arthritis, and 9 were diagnosed with rheumatic symptoms related to infection with Alphaviruses: Chikungunya virus or RRV. Some disability remained for several months in most cases, but only one case of reactive arthritis eventually evolved to a chronic spon-

dyloarthropathy. They concluded that travel-related arthritis persisted several months after the exposure, and assessing patients' travel history may help in evaluation of some cases with rheumatic manifestations.

Rash and fever: Rash and fever are observed in about one-half of patients with RRV infection. Rash and arthritis usually develop within two days of one another, but may be separated by up to two weeks. The rash may occur before or after the arthritis. It is typically short-lived (1 to 10 days) but may persist for several months. The palms, soles of the feet, face, and mucous membranes of the mouth may be involved. The rash usually consists of 1-5mm maculopapular lesions on the limbs and trunk; it is often sparse, although in some cases it is dense and can include purpuric areas or small vesicles. Fever up to 39°C, present early in RRV infection in about 20% and usually dropped within 3 days. Chills and delirium occurred; but rigors unusual (Aaskov *et al*, 1981).

Other clinical features: Fatigue is the most frequent constitutional symptom, occurring in 90% of patients. It may be prominent, even in the absence of fever, and may persist after other symptoms resolve (Bennett *et al*, 1998). Anorexia and headache (50% patients) are common. Other symptoms and signs include diarrhea, neck stiffness, photophobia, splenomegaly, aseptic meningitis (Penna and Irving, 1993), hematuria and glomerulonephritis (Anstey *et al*, 1981), and superficial lymphadenopathy (usually mild; occasionally tender). Several patients with encephalitis have been described (Scrimgeour, 1999), one case of fatal encephalitis was attributed to RRV infection (Scrimgeour *et al*, 1987). RRV was not associated with congenital abnormalities, although transplacental viral transmission was described (Aaskov *et al*, 1991).

Clinical course: The average duration of symptoms differs considerably in different reports. Some arthralgias persist for more than three months in two-thirds of patients, but it usually steadily diminishes in severity

over that time (Harley *et al*, 2002). For example, non-steroidal anti-inflammatory drug use decreased from 63% at one month to 15% at three months. Early studies suggested patients can have persistent arthralgia, myalgia, and fatigue for more than a year after infection; more recent evidence suggests that symptoms usually resolve within three to six months (Westley-Wise *et al*, 1996). Many patients with longer duration of symptoms had other underlying comorbidities such as rheumatic disease or depression. But, degenerative joint changes did not occur and relapses were infrequent (Doggett *et al*, 1999).

In a prospective cohort study of patients with RRV, Epstein Barr virus, or Q fever infection, 12% of patients had prolonged illness with disabling fatigue, musculoskeletal pains, neurocognitive difficulties, and mood disturbance at six months following initial infection. Out-come was predicted by severity of acute illness rather than the underlying microbiologic diagnosis (Hickie *et al*, 2006).

Diagnosis: Ross River virus (RRV) infection should be suspected in the setting of acute polyarthritis and rash with a history of travel or residence in endemic or epidemic areas.

Differential diagnosis: Differential diagnosis includes rubella, infectious mononucleosis, parvovirus B19, Henoch-Schönlein purpura (IgA vasculitis), serum sickness, a drug reaction, erythema multiforme, and systemic lupus erythematosus. It also includes other arboviral infections, mainly Barmah Forest virus infection and Chikungunya fever.

Other causes of arthritis and/or arthralgia are Hepatitis A, B & C, Parvovirus, Rubella and Rubella vaccine, Chikungunya, Diffuse infiltrative lymphocytosis syndrome, Dengue virus, Mumps virus, Cocksackie virus and Echovirus, Adenovirus infection, Herpes virus, Varicella, Epstein-Barr virus, Herpes simplex, Cytomegalovirus, HIV & HIV-associated arthritis, reactive, septic and psoriatic arthritis and others (Daily *et al*, 2016).

Barmah Forest virus: Barmah Forest virus

(BFV) is an alphavirus transmitted by mosquitoes that causes polyarthrititis. BFV causes approximately 10% of epidemic polyarthrititis in north-eastern Australia. It was first recognized as a cause of human infection in 1988 and has been increasingly reported in Australia (Lindsay *et al*, 1995). Epidemics were recognized in the Northern Territory (1992), Western Australia in (1992 to 1993) after (Tong *et al*, 2001), coastal New South Wales (1995), Victoria (2002) and Queensland (2002 to 2003) after Passmore *et al*. (2002)

Transmission of BFV is determined by a number of environmental factors. Transmission peak occurs in summer and autumn. Endemic activity is believed to be restricted to northern Australia (Naish *et al*, 2009). Exotic vector mosquitoes involved in past epidemics include *Aedes camptorhynchus* (1993), *Ae. vigilax* (1995) and *Ochlerotatus camptorhynchus* (2002). High rates of infection among brushtail possums suggested that they may play a role in transmission of urban human infection (Russell, 2002).

The BFV clinical manifestations are similar to those of RRV although, in general, BFV tends to cause milder disease. Rash is more common with BFV infection, but arthritis is more prominent in RRV infection, although these diseases cannot be distinguished based on symptoms alone. Among BFV 84 patients, the commonest symptoms and signs were lethargy (89%), joint pain (82%), and rash (68%). Dermatologic pictures include urticated erythema and widespread vesiculopapular, macular, or purpuric eruptions (Beard *et al*, 1997). Ross River virus can result in debilitating arthritis and other symptoms (as muscle ache and lethargy), sometimes recurred over many years. How the virus causes these symptoms is still not well understood. Ross River Virus discovery may also have implications to other disease-causing viruses such as HIV, respiratory viruses and the virus that causes dengue fever.

BFV diagnosis is confirmed by a virus-specific-IgM response (Cashman *et al*, 2008).

Laboratory evaluation: Diagnosis of RRV

infection is generally established by serology; the most common serologic methods are the hemagglutination inhibition (HI) antibody test and the ELISA test. A fourfold rise in HI titer is diagnostic; levels of $\geq 1:1280$ indicate recent infection. RRV-specific IgM persists for months after acute infection. Thus, acute infection should be confirmed by rising IgM titers if patients live in endemic areas. Testing for a specific IgA response can demonstrate acute infection in patients with persistent high levels of anti-IgM and IgG antibodies although this test is rarely necessary (Carter *et al*, 1987).

Viral culture and polymerase chain reaction (PCR) are less widely used diagnostic tools. RRV can be isolated from blood taken early in the course of infection. RRV was not been cultured from joint fluid, but viral antigen was detected by the immunofluorescence in joint fluid specimens collected early in the disease. A nested PCR is being developed for RRV infection, but it remains a research tool currently (Sellner *et al*, 1994).

Treatment of RRV consists of supportive care; no specific antiviral therapy is available. Treatment of arthralgias and myalgias with analgesics and non-steroidal anti-inflammatory drugs may be helpful. Some may benefit from swimming, hydrotherapy, physiotherapy, or massage; others gain relief only with rest. Basic studies may lead to better therapy in place of current ad hoc approach to treatment.

Prevention: The most important preventive measure is avoidance of mosquito bites. In a case-controlled study, mosquito coils, repellants, and citronella candles were shown to decrease the risk of infection at least two-fold; light colored clothing decreased risk threefold (Harley *et al*, 2005). In contrast, camping increased the risk of Ross River virus (RRV) eightfold. Screens must be fitted to windows and doors in high risk areas. Drainage of mosquito breeding areas in endemic areas may also be helpful over the long-term to control the infection. Mosquito control programs affect RRV disease rates

(Tomerini *et al*, 2011) Preemptive surveillance based on knowledge of disease habitats was associated with lower RRV rates.

RRV & Barmah Forest virus are theoretically transmissible by blood products transfusion; consideration of blood product screening may be warranted. There was no documented transmission of RRV by transfusion; asymptomatic viremia was documented (Dunstan *et al*, 2008). Theoretical possibility is that transmission may occur with donors from high risk areas, especially at outbreaks time (even if symptomatic patients are excluded from blood donation).

No vaccine is yet available, though experimental vaccines are under investigation (Jones *et al*, 2010). An inactivated whole virus vaccine that proved effective in mice may a promising candidate for human trials (Holzer *et al*, 2011).

Conclusion

Alphaviruses that cause arthritis/arthralgias are globally distributed mosquito-borne RNA viruses causing epidemics of polyarthritis/arthralgia, with disease emerging or re-emerging and increasingly being reported in travelers. They are maintained in nature by continuous cycles of transmission between hematophagous arthropods (usually mosquitoes) and enzootic vertebrate hosts (mammals or birds). Bites by infected mosquitoes can result in epizootic infections of humans, with most cases occurring after seasonal rains when mosquito numbers are high.

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