

## Miscellaneous Arboviruses

### Disease Agents:

- Murray Valley Encephalitis virus (MVEV)
- Kunjin virus (KUNV)
- Ross River virus (RRV)

### Disease Agent Characteristics:

- Family: *Flaviviridae*; Genus: *Flavivirus* (MVEV and KUNV)  
*Togaviridae*; Genus: *Alphavirus* (RRV)
- Virion morphology and size: All are enveloped, spherical particles, with icosahedral nucleocapsid symmetry; RRV diameter ~ 60-70 nm, MVEV and KUNV ~ 40-65 nm.
- Nucleic acid: Linear, positive-sense, single-stranded RNA (~11 kb in length)
- Physicochemical properties: Alphaviruses and flaviviruses are labile in the environment and rapidly inactivated by lipid solvents, such as ether or chloroform, and by formaldehyde, heat and low pH as well as by common lab disinfectants (70% ethanol, 1% sodium hypochlorite, 2% glutaraldehyde and quaternary ammonium compounds).
- MVEV and KUNV each has a single genetic type and evolved slowly and uniformly in geographically separate areas of Australia. They are closely related antigenically and genetically to Japanese encephalitis virus; KUNV is a variant (member of lineage 1) of West Nile virus.
- RRV belongs to the same alphavirus antigenic group as Chikungunya and Barmah Forest viruses.

### Disease Names:

- Murray Valley Encephalitis (MVE)
- KUNV disease
- RRV disease

### Priority Level:

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical; other flaviviruses and alphaviruses are known to be transmitted via blood.
- Public perception and/or regulatory concern regarding blood safety: Absent in nonendemic areas including the US and Canada
- Public concern regarding disease agent: Absent in nonendemic areas; high in endemic areas and during epidemics

### Background:

- MVEV occurs naturally throughout the northern half of Australia, Papua New Guinea and eastern Indonesia. MVEV usually occurs in remote northwestern Australia. In southeastern Australia, MVEV is seen when heavy rainfall, flooding and hot weather favor bird and mosquito breeding. In New South Wales, the pattern of disease over the last century has been outbreaks occurring decades apart, with no or very few cases identified in between.

- While the geographic distribution of KUNV and MVEV overlap, the latter is more widely distributed.
- The term "Australian encephalitis" (AE) has been used to indicate encephalitis induced by infection with either MVEV and/or KUNV. However, because these are different viruses, with slightly different clinical symptoms, it is more accurate to specify the diseases in terms of the causative virus.
- The first reports of disease potentially attributed to MVEV infection in humans in Australia occurred in southeastern Australia in 1917, 1918 and 1925 (114, 67 and 10 cases, respectively) and were described under the title of "Australian 'X' disease". The virus, designated as MVEV, was later isolated from fatal cases during an epidemic in 1951, when there were 48 cases (19 fatalities); MVEV has been accepted as the causal agent of the earlier Australian 'X' disease outbreaks or outbreaks previously referred to as "Australian encephalitis."
- MVEV has a natural endemic cycle, which involves water fowl as the vertebrate host and *Culex annulirostris* (which breeds in freshwater environments) as the major vector in northern regions of Australia. Epidemic activity in the southeast has been associated with excessive rainfall which increases bird and mosquito populations and leads to a virus overflow infecting humans.
- KUNV was first isolated from *C. annulirostris* in Northern Queensland in 1960.
- RRV was first isolated from *Aedes vigilax* in Northern Queensland in 1959. Prior to the introduction of serological blood testing, RRV was inseparable from Barmah Forest virus (the latter only known in Australia where it was first described in 1974).
- RRV infection is responsible for most arboviral disease in Australia. The largest epidemic on record occurred in the 1979-1980 when an RRV epidemic in Fiji spread to Samoa, the Cook Islands and New Caledonia. RRV cases continue to be reported from Fiji, and the virus remains endemic in Australia and Papua New Guinea.

### Common Human Exposure Routes:

- Vector-borne; transmission occurs through a mosquito-human or other vertebrate host -mosquito cycle.
  - MVEV and KUNV can infect animals such as horses, kangaroos and non-water birds; however, they are not thought to play a role in the transmission cycle.
  - RRV infects Australian native mammals, particularly kangaroos and wallabies; humans can also act as vertebrate reservoir hosts.

### Likelihood of Secondary Transmission:

- MVEV, KUNV and RRV are not transmitted person-to-person.
- MVEV, KUNV and RRV infection results in long-lasting immunity that is probably life-long.

**At-Risk Populations:**

- Many people who have lived for a long time in affected areas will be immune due to previous infections. Those at highest risk are individuals who have not had previous exposure, including:
  - Infants and young children
  - Those who visit or have recently moved to MVEV/RRV-affected areas.
- The aboriginal population in northern Australia has the highest exposure rate. Others at risk are those who bush-walk, camp, boat, fish and bird-watch in MVEV/RRV-affected areas.

**Vectors and Reservoir Involved:**

- *Culex annulirostris* is the major vector in Australia for all three viruses and feeds on a variety of vertebrate species. *C. tritaeniorhynchus* and *C. pipiens* may also transmit. *Aedes vigilax*, *A. camptorhynchus* and *A. notoscriptus* are also common vectors for RRV.
- Water fowl are the major vertebrate hosts for MVEV and KUNV, especially ciconiiforms (herons and egrets). Antibodies to MVEV have been detected in many vertebrate species, including ciconiiforms, pelecaniiforms (pelicans and cormorants), and placental and marsupial mammals.
- RRV is enzootic in Australian native mammals (kangaroos, wallabies, and the dusky rat, *Rattus collettii*). There is evidence that humans act as reservoir hosts in epidemic situations and may also distribute the virus geographically.

**Blood Phase:**

- The blood phase for MVEV and KUNV is not well characterized. The viremic period is believed to be short and the virus is cleared from the blood by the time symptoms appear. In a single case report, MVEV RNA was detected in serum 3 days after the onset of illness and 4 days before the appearance of MVEV-specific IgM.
- Skeletal muscle in humans is the primary site of RRV replication. The virus enters the blood where IgM can be detected in acute infection and may persist for months to years. IgG can usually be detected within 10-14 days of IgM, peaks within 4 weeks and persists indefinitely. The duration of viremia in humans is not well characterized but most likely has a short duration. In mice, the viremic period is typically 5 days with low-level viremia extending up to 9 days.

**Survival/Persistence in Blood Products:**

- Unknown

**Transmission by Blood Transfusion:**

- In Australia, there have been no documented cases of transfusion transmission for any of the three arboviruses. Given the asymptomatic viremic period, the potential for transfusion transmission exists.

- Using the data from the 2004 RRV outbreak in Cairns, Queensland, the risk of transfusion transmission (assuming that RRV is transfusion transmissible) has been estimated at 1:13,500 (range of 1:4800-1:48,000).

**Cases/Frequency in Population:**

- The last major epidemic of MVEV in Australia was in 1974 (58 cases/13 fatalities). Sporadic cases occur in non-epidemic years.
- There is a lower incidence of KUNV infections, although some cases were implicated during the MVEV epidemics.
- An estimated 4,800 cases of RRV are reported annually.

**Incubation Period:**

- 5-28 days for MVEV and KUNV
- 2-21 days for RRV (usually 7-9 days)

**Likelihood of Clinical Disease:**

- Most human MVEV infections are subclinical, but clinical cases can be fatal. The ratio of clinical to subclinical cases ranges from 1:500 to 1:5000 for MVEV and KUNV and 1:1.2 to 1:3 for RRV.

**Primary Disease Symptoms:**

- Most common symptoms of mild MVEV and KUNV diseases are nonspecific and include fever, headache, nausea, vomiting and loss of appetite, diarrhea, and muscle aches.
  - Severe symptoms include convulsions, brainstem disease or respiratory failure in severe and fatal cases, and involvement of the spinal cord, cranial nerves, or cerebellum in moderate cases.
  - This can progress to trouble with coordination and speech, seizures, loss of consciousness, coma and death. Some individuals who recover from MVE are left with permanent neurological complications.
  - KUNV is similar clinically, but with usually milder disease than MVEV or closely-related WNV. KUNV infection can result in rare cases of non-fatal encephalitis.
- Common symptoms of RRV are fever, polyarthritis and rash; other symptoms include lymphadenopathy, lethargy, headache, myalgias, photophobia and glomerulonephritis. The length of time that symptoms persist varies, but usually several weeks.

**Severity of Clinical Disease:**

- Those with clinical MVE demonstrate 25-50% permanent neurological sequelae.
- Generalized malaise and polyarthritis RRV infection may persist for a year or more.

**Mortality:**

- There is 15-31% mortality for those with clinically significant MVEV disease.
- RRV and KUNV infections are not known to be fatal.

**Chronic Carriage:**

- Chronic carriage is not reported; however, for RRV, the virus may persist in synovial cells and in cell lines of mouse macrophages for months.

**Treatment Available/Efficacious:**

- Supportive treatment only

**Agent-Specific Screening Question(s):**

- None

**Laboratory Test(s) available:**

- No licensed tests are available.
- For MVEV and KUNV, infection is usually diagnosed from measuring levels of antibody in samples of blood or cerebrospinal fluid, or from detecting viral nucleic acids in these samples. It can sometimes be difficult to distinguish recent infections from prior infections by testing one specimen. Two samples of blood taken a week apart usually need to be tested to see if there has been an increase in antibody levels. Testing includes:
  - Detection of antigens or antibody, including IgG seroconversion with exclusion of related viruses
  - Detection of virus-specific IgM in serum or cerebrospinal fluid with exclusion of related viruses
  - Culture of the virus from clinical samples
  - Detection of viral RNA in clinical samples
- Neutralization or epitope blocking EIAs can be used to distinguish MVEV from KUNV.
- Both serological (IgG and IgM-specific immunoassays) and PCR are available for RRV.

**Currently Recommended Donor Deferral Period:**

- No FDA Guidance or AABB Standard exists.
- Australia: 2 weeks after RRV recovery, then plasma for fractionation is the only component utilized for the next 12 months; N/A for MVEV or KUNV.
  - The 12-month interval for fractionated plasma use is based on operational considerations; the apparent short duration of viremia suggests that deferral periods substantially less than 12 months for other blood components would be adequate and would not compromise patient safety.

**Impact on Blood Availability:**

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

**Impact on Blood Safety:**

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

**Leukoreduction Efficacy:**

- No data available

**Pathogen Reduction Efficacy for Plasma Derivatives:**

- Expected to be effective.

**Other Prevention Measures:**

- No vaccines are available.
- RRV vaccine is in development.

**Other Comments:**

- A May 2011 report describes a fatal case of a 19-year old Canadian that returned to Canada from extended travel in the northern territory of Australia infected with MVEV. This is the first lab-confirmed Canadian case.

We would like to acknowledge the contributions from the Australian Red Cross Blood Services in sharing their "Infectious Disease Agent Templates for MVEV and RRV, May 2011."

**Suggested Reading:**

1. Broom AK, Lindsay MD, Wright AE, Smith DW, Mackenzie JS. Epizootic activity of Murray valley Encephalitis and Kunjin Viruses in an aboriginal community in the Southeast Kimberly region of Western Australia: Results of mosquito fauna and virus isolation studies. *AM J Trop Med Hyg* 2003;69:277-83.
2. Carver S, Bestall A, Jardine A, Ostfeld RS. Influence of hosts on the ecology of arboviral transmission: Potential mechanisms influencing Dengue, Murray Valley Encephalitis, and Ross River Virus in Australia. *Vector Borne Zoonotic Dis* 2009;9:51-64.
3. CBW Factsheets on Chemical and Biological Warfare Agents. Murray valley Encephalitis: essential data. <http://www.cbwinfo.com/Biological/Pathogens/MVEV.html>.
4. Department of Health, Government of Western Australia. Murray Valley Encephalitis. *Environmental Health Guide* March 2010.
5. Jacups SP, Whelan PI, Currie BJ. Ross River Virus and Barham Forest Virus Infections: A Review of History, Ecology, and Predictive Models, with Implications of Tropical Northern Australia. *Vector-Borne Zoo Diseases* 2008;8:283-97.
6. Johansen CA, Susai V, Hall RA, Mackenzie JS, Clark DC, May FJ, Hemmerter S, Smith DW, Broom AK. Genetic and phenotypic differences between isolates of Murray Valley encephalitis virus in Western Australia, 1972-2003. *Virus Genes* 2007;35:147-54.
7. Klapsing P, MacLean JD, Glaze S, McClean KL, Drebot MA, Lanciotti RS, Campbell GL. Ross River virus disease reemergence, Fiji, 2003-2004. *Emerg Infect Dis* <http://wwwnc.cdc.gov/eid/article/11/4/04-1070.htm>.
8. Mackenzie JS, Poidinger M, Lindsay MD, Hall RA, Samuels LM. Molecular epidemiology and evolution of mosquito-borne flaviviruses and alphaviruses enzootic in Australia. *Virus Genes* 1996;11(2/3):225-37.
9. McMinn PC, Carman PG, Smith DW. Early diagnosis of Murray Valley Encephalitis by reverse transcriptase-polymerase chain reaction. *Pathol* 2000;32:49-51.

10. Murray Valley Encephalitis Factsheet. NSW Health Department [http://www.health.nsw.gov.au/factsheets/infectious/murray\\_valley\\_enceph.html](http://www.health.nsw.gov.au/factsheets/infectious/murray_valley_enceph.html).
11. ProMed-mail. Murray valley encephalitis—Australia (07): Canada ex Australia (Northern Territory); ProMed mail 2011; 25 May 2011. <http://www.promedmail.org/pls/pm/pm?an=20110526.1610>. Accessed 08 October 2011.
12. Russell RC, Dwyer DE. Arboviruses associates with human disease in Australia. *Microbes Infect* 2000;2:1693-704.
13. Scherret JH, Poidinger M, Mackenzie JS, Broom AK, Deubel V, Lipkin WI, Briese T, Gould EA, Hall RA. The relationships between West Nile and Kunjin viruses. *Emerg Infect Dis* 2001;7:697-705.
14. Shang G, Seed CR, Rolph MS, Mahalingam S. Duration of Ross River viraemia in a mouse model—implications for transfusion transmission. *Vox Sang* DOI:10.1111/j.1423-0410.2011.01536.x.
15. Williams DT, Daniels PW, Lunt RA, Wang LF, Newberry KM, Mackenzie JS. Experimental infection of pigs with Japanese encephalitis virus and closely related Australian flaviviruses. *Am J Trop Med Hyg* 2001;65:379-87.