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Considerations for Cellular Therapy Products

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ORIGINAL RESEARCH

TRANSFUSION

Viral agents (2nd section)

1 | MISCELLANEOUS ARBOVIRUSES

1.1 | Disease agents

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

1.2 | Disease agent characteristics

- Family: *Flaviviridae*; Genus: *Flavivirus* (MVEV and KUNV).
- Family: *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: 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 has four and KUNV a single genotype and evolved slowly and uniformly in geographically separate areas of Australia. They are members of the Japanese encephalitis serocomplex; KUNV is a variant (member of lineage 1) of West Nile virus and thus has been expressed as: WNV_{KUN}.
- RRV belongs to the same *Alphavirus* antigenic group as chikungunya and Barmah Forest viruses.

1.3 | Disease names

- MVE disease
- KUNV disease
- RRV disease

1.4 | 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 United States and Canada.
- Public concern regarding disease agent: Absent in nonendemic areas; high in endemic areas and during epidemics.

1.5 | Background

- MVEV occurs naturally throughout the northern half of Australia, Papua New Guinea and possibly eastern Indonesia. MVEV is the most pathogenic of the endemic arboviruses in Australia and responsible for outbreaks of encephalitis in southeastern Australia with the last large event in 1974. MVE usually occurs in remote northwestern Australia where there have been five fatalities in the Northern Territories in the past two decades.
- In Australia, MVE is seen when heavy rainfall, flooding and hot weather favor bird and mosquito breeding. In Australia, the pattern of disease over the last century has been outbreaks occurring decades apart, with no or very few cases identified in between. For example, Victoria (SE Australia) recorded its first fatality (February 2023) since 1974.
- 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 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 human disease attributed to MVEV infection 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 waterfowl 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 isolated in 1963 from *Aedes vigilax* in Northern Queensland collected 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 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.

1.6 | Common human exposure routes

- Vector-borne; transmission occurs through a mosquito-human or wild water birds-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 giving rise to human-mosquito-human transmission.

1.7 | Likelihood of secondary transmission

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

1.8 | 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 KUNV/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.

1.9 | 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. tritaeniorhyncus* and *C. pipiens* may also transmit. *Aedes vigilax*, *A. camptorhynchus* and *A. notoscriptus* are also common vectors for RRV.
- Waterfowl 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, pelecaniforms (pelicans and cormorants), and placental and marsupial mammals.
- RRV is enzootic in Australian native mammals (kangaroos, wallabies, and the dusky rat, *Rattus colletti*). There is evidence that humans act as reservoir hosts in epidemic situations and may also distribute the virus geographically.

1.10 | 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.

1.11 | Survival/persistence in blood products

- Unknown

1.12 | Transmission by blood transfusion

- There has been a single case of possible transfusion transmission of RRV, which was reported in Australia (none for MVEV or KUNV). Given the asymptomatic viremic period for all of these agents, the potential for transfusion transmission exists.
- A 2018 study of 7500 Australian donors using RRV PCR from high-risk areas of the country during an active transmission season found no infected donors for a risk point estimate of zero (with an upper bound of the 95% CI of 1/2019). The study was designed to measure the occurrence of RRV viremia among donors who donated at Australian collection centers. However, regions with the highest rates of RRV transmission have few donors and donor centers. The risk of RRV transfusion transmission in Australia is considered acceptably low and well managed with existing measures, including donation restrictions and recall policies.

1.13 | 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. The Australian Department of Health has been reporting MVEV infections since 2001. Between 2001 and 2022, the annual number of reported human cases has varied from 0 to 6 cases, except for 2011 when 17 possible cases were reported.
- There is a lower incidence of KUNV infections, although some cases were identified during the MVEV epidemics.
- An average of 4426 cases of RRV are reported annually (has varied from 1481 in 2002 to 9535 in 2015). These tend to cluster in areas with relatively few blood donors.

1.14 | Incubation period

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

1.15 | Likelihood of clinical disease

- The ratio of clinical to subclinical cases ranges from 1:150 to 1:1000 for MVEV and 1:1.2 to 1:3 for RRV; no reliable estimates are available for KUNV.

1.16 | Primary disease symptoms

- Most cases of MVE and Kunjin disease are asymptomatic or mild with nonspecific symptoms including 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 and more similar to WNV infection. KUNV infection can result in rare cases of nonfatal 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.

1.17 | 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.

1.18 | Mortality

- There is 15%–31% mortality for those with clinically significant MVEV disease.
- RRV and KUNV infections are rarely, if ever, fatal.

1.19 | 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.

1.20 | Treatment available/efficacious

- Supportive treatment only

1.21 | Agent-specific screening question(s)

- None

1.22 | 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 enzyme immunoassays can be used to distinguish MVEV from KUNV.
- Both serological (IgG and IgM-specific immunoassays) and PCR are available for RRV.

1.23 | Currently recommended donor deferral period

- No US FDA Guidance or AABB Standard exists.
- Australia has more detailed policies
  - A flavivirus deferral is in force whereby allogeneic donors with a current infection are deferred for 4 months from date of recovery.
  - For RRV and Barmah Virus, alphaviruses, allogeneic donors with a current/reoccurrence infection are deferred for 4 weeks from date of recovery based viral kinetics.
- Donors with CHIKV infection are deferred for 4 months after recovery, while those potentially exposed in countries experiencing outbreaks are restricted to donating plasma for further manufacture for 4 weeks.

1.24 | Impact on blood availability

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

1.25 | Impact on blood safety

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

1.26 | Leukoreduction efficacy

- No data available

1.27 | Pathogen reduction efficacy for plasma derivatives

- Expected to be effective.

1.28 | Other prevention measures

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

1.29 | 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.

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