Barmah Forest virus (BFV)

Pathogen

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Overview

BFV is considered theoretically transfusion-transmissible as transfusion-transmission has not been reported. Reported Australian outbreaks are geographically restricted and it is considered a very low severity agent in the context of potential transfusion-transmitted disease. It is a low risk to blood safety and additional mitigations are therefore unlikely to be implemented, even in an outbreak.

Classification and morphology

BFV is a member of the *Togaviridae* family and *Alphavirus* genus and, like all alphaviruses, it is an arbovirus (arthropod-borne virus). BFV is an enveloped virion with icosahedral symmetry and 60-70 nm in diameter. The genome is a single-stranded positive sense RNA molecule of approximately 11.5 kb. Phylogenetically BFV belongs to the Semliki virus clade. Immune sera against BFV do not cross-neutralise, or inhibit haemagglutination of, other alphaviruses and therefore BFV is classified as a distinct antigenic group within the genus.

BFV was first isolated from *Culex annulirostris* mosquitoes in the Barmah Forest of northern Victoria (south eastern Australia) in 1974. Human infection was first diagnosed in 1986 in a patient in NSW and the virus was first cultured in 1988 from a patient in far north Queensland. The first reported outbreak of BFV was in 1992 in the Northern Territory. BFV has now been reported from every state and territory in Australia, although very few cases have been reported in Tasmania, indicating that it is not endemic on the island.

[1-4]

Associated disease

Similar to Ross River virus (RRV) infection, BFV infection is characterised by a high subclinical rate of infection which is highest in children. Clinical cases of BFV infection (BFV disease) show similar incubation times and symptoms, although typically milder and of shorter duration, as RRV disease. Following infection with BFV the incubation period is 7–9 days (can vary between 3–11 days) and patients typically present with a 12- to 24-hour history of apathy and malaise, followed by non-itchy diffuse maculopapular erythematous rash on the limbs and trunk lasting 2–10 days. Symmetrical joint pains may precede or follow the rash, usually in the wrists and small joints of the hands and feet. True arthritis with joint swelling, heat and tenderness often occurs and may fluctuate for some weeks. Fever is usually mild and short, and may be accompanied by headaches. Recovery usually occurs within several weeks but lethargy, arthralgia and myalgia persist for over six months in about 10% of cases. Infection with BFV confers life-long immunity.

[1,2,5-8]

Blood phase

Along with the related alphaviruses, chikungunya virus (CHIKV) and RRV, the BFV viraemic period is considered to be brief, typically about seven days. A study using the mouse model reported a detectable murine viraemic period of approximately five days following subcutaneous infection with BFV. The immune response involves the

production of both IgM and IgG antibodies, the latter conferring immunity.

[5,9,10]

Chronic carriage

Chronic BFV infection has not been reported. A small proportion of infected people develop persistent arthritis, probably arising from direct cellular and tissue damage caused by virus replication and inflammatory responses stimulated by the virus persisting in joint tissues, given that persistence of the related RRV has been reported in human synovial cells and mouse macrophage cell lines *in vitro* for up to 180 days. However, a BFV murine model has indicated that compared to RRV, BFV has reduced tropism for muscle tissue, slower disease onset, faster recovery and milder inflammation. The authors of the study also noted that BFV replicated poorly in both human muscle cell lines and primary human myoblast compared to RRV.

[10-14]

Human exposure routes

BFV is transmitted to humans by the bite of infected mosquitoes in certain geographical ranges, particularly after heavy rains which encourage breeding of mosquito vectors. BFV does not appear to be spread directly from human-to-human or animal-to-human.

[5-8]

Vector and reservoir

BFV has been isolated from at least 15 species of mosquito, but vector competence has not been demonstrated for most of them. Mosquito species for which there is some evidence of vector competency include *Aedes notoscriptus*, *Ae. procax*, *Ae. vigilax*, *Ae. annulirostris*, *Ae. normanesis* and *Verrallina funereal*.

Based on detection of BFV antibodies, implicated reservoirs, at least in NSW and Queensland, include horses, brushtail possums and kangaroos. However, there remains some uncertainty regarding the natural reservoirs of BFV in Australia.

Following experimental infection of kangaroos, wallabies, possums, horses, cats and dogs, the detected viraemia is considered too low for an insect vector to acquire the virus. The genetic similarity of BFV strains across Australia, as well as the pace at which they spread, suggests an avian or bat host.

[2,3,10,15,16]

At risk populations

The first reported outbreak of BFV infection occurred in 1992 in the Northern Territory and appeared to be a dual outbreak of BFV and RRV. Subsequent outbreaks have been reported from southwest Western Australia in 1993-1994, NSW in 1995 and Victoria 2002. The largest epidemic to date occurred in 2005-2006 with 1,895 notifications nationwide. BFV disease is the second most common mosquito-borne disease in Australia after RRV disease with Queensland reporting the highest number of cases.

Outbreaks are mostly confined to coastal regions and water recreation areas, and the important environmental factors are warm temperatures, above average rainfall, humidity, low tides and a non-immune population. Non-immune people in outbreak areas engaged in outdoor activities are

most at risk. In particular, people living within 3–5 kilometres of saltmarshes or brackish wetlands (i.e. estuaries and tidal rivers) and freshwater wetlands are at greater risk of contracting RRV and BFV diseases than people living in other areas.

[2,7,17-20]

Transfusion-transmissibility

There have been no reported cases of transfusion-transmitted BFV infection. However, as the course of BFV infection includes an asymptomatic viraemic period, transfusion-transmission cannot be excluded.

The potential for transfusion-transmission of BFV is also indicated by the related alphaviruses CHIKV and RRV. Although transfusion-transmission of CHIKV has not been reported, modelling has indicated there is a risk of transfusion-transmission of CHIKV during outbreaks. In addition, a probable case of transfusion-transmitted RRV has been reported in Australia.

[21-23]

Treatment and efficacy

Treatment of BFV infection is limited to the management of symptoms as there is no specific treatment. There is no vaccine for BFV.

[5-8]

Assay and algorithm options for screening and confirmatory / diagnostic testing

There are no TGA-approved BFV serological or NAT assays for blood donor screening.

BFV IgG and IgM antibodies can be detected using enzyme-linked immunosorbent assays (ELISAs), and a neutralisation assay, while in-house nucleic acid testing (NAT) assays are available for detecting BFV RNA.

A confirmed case of BFV infection is defined as (i) isolation of BFV, or (ii) detection of BFV by NAT or (iii) IgG seroconversion or a significant increase in IgG antibody level (e.g. fourfold or greater rise in titre) to BFV. A probable case of BFV infection is defined as detection of BFV virus IgM AND BFV IgG EXCEPT if BFV IgG is known to have been detected in a specimen collected greater than three months earlier.

[9,24]

Lifeblood risk assessment: blood components

During the 10-year period from 2007 to 2016, the number of BFV notifications in Australia varied annually between 323 (2016) and 4,237 (2013). The record high annual number of notifications nationally in 2013 was due to record high numbers in Queensland and Western Australia. However, the Western Australian Department of Health reported that the unexpected increase in BFV cases in 2012/2013 had been attributed to an increase in false positive laboratory test results. From 1 January 2016 the case definition for BFV infection was changed so that a single IgM positive result would no longer meet the confirmed or probable case definition.

In 2014 the number of notifications nationally declined to 742 followed by 629 in 2015, 232 in 2016 and 438 in 2017. Nationally, reported case numbers for the periods 19/01/2018 to 18/01/2019, 18/01/2019 to 17/01/2020, 18/01/2020 to 17/01/2021

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there were 337, 254, 744 and 274 cases, respectively. In 2021 there have been 274 cases to 29 August. The highest number of notifications is reported in Queensland while the highest notification rate (per 100,000 population) is typically reported in the Northern Territory.

In the future, climate change is expected to have an impact on the risk of BFV infection in humans. However, modelling has indicated that predicting the nature and extent of the impact of climate variation on BFV disease risk is difficult due to the number of factors that affect BFV outbreaks which include temperature, rainfall, tidal conditions, proximity to coast and human immunity. Therefore, climate change conditions (particularly increased temperatures and rainfall) may potentially result in a future increase in areas at high risk of BFV infection due to increased density of mosquito vectors.

In 2011, a study in relatively higher BFV risk areas in Queensland reported an overall IgM seroprevalence rate in blood donors of 1.21% (95% CI: 0.91-1.51%). Risk modelling based on these results estimated the risk of collecting an infectious donation from 'higher-risk' regions over a 6-month period was 1 in 7,333 (range 2,497–58,284) for BFV and the authors noted this was of a similar magnitude to previous estimates for RRV and dengue virus (DENV) during respective outbreaks. The authors noted the geographical focus of BFV infections and that most infections in recipients would be asymptomatic, with mild symptoms in symptomatic cases.

Given these considerations, it was suggested that if additional risk mitigation strategies were required during a BFV outbreak, a similar approach to DENV may be the most feasible i.e. restriction of donations in outbreak areas to fractionated plasma products during the outbreak period. However, this conclusion is not supported by subsequent risk assessment of the similar Ross River virus (RRV) and is therefore unlikely to be supported based on risk and severity

Given the geographical focus of BFV outbreaks, the absence of reported transfusion-transmitted cases and the availability of appropriate risk mitigation strategies if required, at present BFV represents a low risk to blood safety in Australia.

[25-31]

Current Lifeblood risk management strategy for blood safety

Donor deferrals exist for allogeneic/therapeutic donors with current or recurrent infection, past infection and contacts with infectious disease. These deferrals are regularly reviewed and any outbreaks or new developments are constantly monitored.

Proposed strategy should local outbreak occur

Based on BFV being a very low severity impact and comparison with RRV, it is unlikely that additional risk strategies are required. In the event of an unprecedented outbreak, Lifeblood may perform a risk assessment to determine whether additional risk mitigation measures are required. Potential strategies for mosquito-borne viruses that are potentially transfusion-transmitted include the implementation of a supplementary question to identify donors visiting/residing in risk areas and restriction to plasma for fractionation for those donors.

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Leucoreduction efficacy

No specific data is available. However, the lack of a documented association with blood cells would suggest that leucodepletion would have limited, if any, efficacy for the removal of BFV.

Pathogen reduction efficacy (fresh components)

There is no licensed pathogen reduction technology (PRT) in Australia. PRT is a possible future option if an effective RBC technology becomes available.

The Mirasol Pathogen Reduction System (CaridianBCT Biotechnologies) has been demonstrated to reduce the level of infectious BFV by almost 2 logs. Specific data for BFV has not been reported for other PRT systems. However, the INTERCEPT Blood System (Cerus Corporation) is effective against the related alphavirus CHIKV and the Theraflux UV Platelet System (MacoPharma) effectively inactivates another alphavirus, RRV. Therefore, these two systems may also effectively inactivate BFV.

[32-34]

Pathogen reduction efficacy (plasma derivatives)

All of CSL Behring (CSLB)'s plasma-derived products include specific virus inactivation or virus removal steps designed to ensure viral safety.

[35]

Further information available on the CSL Behring website:

https://www.cslbehring.com/products/safety-and-manufacturing

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