Rift Valley fever: a review

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Rift Valley fever (RVF) is a mosquito-borne viral disease, principally of ruminants, that is endemic to Africa. The causative Phlebovirus, Rift Valley fever virus (RVFV), has a broad host range and, as such, also infects humans to cause primarily a self-limiting febrile illness. A small number of human cases will also develop severe complications, including haemorrhagic fever, encephalitis and visual impairment. In parts of Africa, it is a major disease of domestic ruminants, causing epidemics of abortion and mortality. It infects and can be transmitted by a broad range of mosquitos, with those of the genus *Aedes* and *Culex* thought to be the major vectors. Therefore, the virus has the potential to become established beyond Africa, including in Australia, where competent vector hosts are endemic. Vaccines for humans have not yet been developed to the commercial stage. This review examines the threat of this virus, with particular reference to Australia, and assesses gaps in our knowledge that may benefit from research focus.

Epidemiology and ecology

Epizootics of RVF occur at irregular intervals, with inter-epizootic periods often spanning years or decades. The survival and re-emergence of the virus after long periods of quiescence is thought to occur through transovarial transmission[1], but likely also by low-level transmission between mosquitoes and a wildlife reservoir[2]. Continuous low-level transmission also occurs within domestic livestock populations without noticeable disease or abortions[3]. RVF virus has been isolated from numerous mosquito species, but certain *Aedes* species associated with freshly flooded temporary water bodies are regarded as maintenance vectors, while *Culex* species associated with permanent fresh water are regarded as epidemic or amplifying vectors[4].

Originally confined to continental Africa since its first isolation in Kenya in 1930, RVFV has since spread to the Arabian Peninsula, Madagascar and islands in the Indian Ocean[5,6]. Molecular epidemiological studies further highlight the ability of the virus to be spread to distant geographical locations, with genetically related viruses found from distant regions of Africa[4]. Serological evidence of RVFV circulation in Turkey is concerning and serves as a warning for possible incursion into Europe[7]. However, serological surveys in Europe suggest absence of the virus[8,9] and modelling indicates that the risk of introduction and large scale spread is low[10]. Recent importations of human RVF cases into Europe and Asia from endemic African countries highlight the risk of intercontinental spread via acutely infected travellers[11–13]. Horizontal human-to-human transmission has never been documented, nevertheless, experimental infection studies have demonstrated that non-vector transmission can occur between animals[14].

RVF affects mainly domestic ruminant livestock species and the disease is particularly prominent in sensitive species such as sheep. Camelids, including dromedaries and alpacas, also appear to be sensitive to infection[15]. Because Australia has large populations of these species, the incursion of RVFV into the continent may be highly visible and may adversely affect livestock industries.

Vector competence

RVFV has been isolated from a wide range of mosquito species but laboratory vector competence studies on African mosquitoes support the epidemiological importance of only a few specific *Aedes* and *Culex* species[4]. Other species have been shown to be susceptible to infection but poor at transmitting the virus. A single study evaluated vector competence of Australian *Aedes* and *Culex* mosquitoes for RVFV, with high rates of infection noted, and the ability

to transmit the virus efficiently after intrathoracic inoculation or oral exposure[16].

Genome and taxonomy

Rift Valley fever virus is the only described member of the type species of the *Phlebovirus* genus, *Rift Valley fever phlebovirus*, classified in the family *Phenuiviridae*, order *Bunyavirales*[17]. The virus's relatively stable RNA genome, a result of alternating infection between arthropod and vertebrate hosts[18], consists of two negative-strand segments and a third segment utilising an ambisense coding strategy. The negative sense large and medium segments encode the polymerase and precursor glycoproteins respectively[19,20], while the small segment encodes the nucleoprotein in the negative sense and a non-structural protein in the positive sense[21]. This non-structural protein (NSs) is the major virulence factor of the virus due to its ability to counteract host innate immune responses by acting as an interferon antagonist[4]. Development of experimental live attenuated vaccines for RVF exploits this knowledge, following the discovery of a naturally attenuated avirulent isolate, clone 13, that has a large deletion in the NSs coding gene[22].

Diagnostics

Laboratory confirmation requires positive results from a combination of at least two different diagnostic test methods, which includes virus detection and serological assays[23]. Laboratory confirmatory testing is complicated by biocontainment requirements and potential use as a bioweapon, thereby limiting testing to a small number of reference laboratories in the world. Technically, however, laboratory testing is relatively simple due to the low genetic variability of the virus[4] and the existence of a single known serotype. Virus isolation in suckling mice or cell culture and demonstration of a neutralising antibody response by microneutralisation test or plaque-reduction neutralisation test remain the gold standard methods for virological and serological diagnosis respectively, but both require virus propagation, thus necessitating high biocontainment facilities. Safer alternatives have, however, been adapted by most laboratories and are used as first line assays. Molecular assays such as real-time RT-PCR or loop-amplification mediated PCR (LAMP) are mostly used for detecting acute infections[24,25], although antigen detection ELISAs have application for certain sample types[26]. Various ELISA platforms have been developed and shown to be sensitive and specific for detection of antibodies to the virus in various species[27,28], including some based on recombinant viral proteins that do not require biocontainment facilities for production[29]. Proper validation of assays using clinically relevant material in sufficient numbers remains a challenge and often depends on laboratory generated positive material. There is also no well established internationally available external quality assurance or proficiency testing scheme for either serological or molecular diagnosis of RVF, particularly in endemic African countries, apart from some *ad hoc* studies that are mostly opportunistic and dependent on funding availability[30,31].

Pathology and pathogenesis

Human infections, which are usually acquired from contact with infected animal tissues, and thus are an occupational risk for veterinarians, farm worker and abattoir workers[32], manifest as sub-clinical infection or mild febrile illness[33,34]. However, in a small number of cases the infection develops to cause severe disease, which may take the form of a haemorrhagic fever syndrome, encephalitis, retinal degeneration or other complications. The impact of these forms of the disease are usually severe with high mortality or long-term impairment of neurological function and sight. In the initial phase of the disease, 1–4 days after infection, there is a viraemia, which declines as antibody levels rise. Related to the viraemia is a vasculitis, which leads to thrombosis and other vascular complications, and these often manifest days to weeks after the initial infection. Infection of the liver is an important component of infection in highly susceptible species such as sheep and mice; this develops during the acute infection stage and may become the dominant pathological feature.

RVF haemorrhagic fever syndrome is characterised by haemorrhage and multi-organ failure and is caused by fulminant hepatic necrosis and vasculitis, two processes that lead to disseminated intravascular coagulopathy through non-renewal (hepatic necrosis) and depletion (vasculitis) of clotting factors. Clinical signs include vomiting, bleeding from the gums, conjunctivae and other mucous membranes, haematemesis, subcutaneous haemorrhages and jaundice[34,35]. Severity of disease has a strong correlation with viral load, cytokine responses and coagulation pathways[36,37].

Encephalitis may develop in a small proportion of cases some days or weeks after the initial febrile episode and its clinical presentation may depend on the localisation of infection foci in the brain[33,34]. On histopathological examination there is a focal necrosis with mononuclear cell perivascular cuffing[35]. Encephalitis usually occurs despite the presence of antibodies to RVFV, implying that the condition is due to immunologically mediated damage in response to residual infection. Recovery, like many viral encephalitides, can be long and of variable outcome.

Retinal degeneration is probably a sequel to local ocular vascular thrombosis, appearing during the initial febrile disease or up to

four weeks afterwards[34]. It can be associated with retinal detachment and uveitis. There is variable loss of vision, and this can be persistent and often permanent[33].

Sheep, and young lambs in particular, are highly sensitive to RVFV infection. Typically, the first sign of infection in a herd is signalled by abortions, and this can be very high with up to 100% of pregnant ewes losing their lambs[34]. Abortion is the outcome of infection of multiple foetal tissues, including the foetal–maternal interface of the placenta[38]. Infected lambs that survive to term are weak and usually do not survive longer than a few days. Viraemia in experimentally infected animals occurs from day 1–7 after inoculation, with peak viraemia around day 2 after inoculation[39]. While the frequency of severe illness and death in adult sheep is lower due to their relative resistance, adults may nevertheless often develop fatal illness, caused principally by hepatic necrosis, vasculitis and associated disorders. Clinical signs include abortion, lethargy and weakness, congested mucous membranes and bloody diarrhoea[34]. The principal lesions include hepatic necrosis, vasculitis, renal tubular necrosis and lymphoid necrosis[40].

The disease in other ruminants can be similar, but usually less severe, to that in sheep. Abortion in pregnant cattle, goats and camelids is the most common outcome of infection, while young animals tend to be highly susceptible[15,41]. Rodents and non-human primates are used as laboratory models to study infection and vaccination in humans[42].

Control

There are no registered human vaccines for RVF and the commercial prospects for such a vaccine remain unlikely unless the virus were to become more widespread and epidemics more frequent. Animal vaccines mainly consist of inactivated cell culture vaccines. The naturally attenuated clone 13 has been investigated as a potential safe vaccine candidate for livestock use, but a recent study found that although it is safe for use in lambs, the virus is able to cross the placental barrier and cause malformations and stillbirths, thereby excluding its use during the first trimester of gestation in sheep[43]. While they are commonly applied in those areas of Africa where the virus occurs, the long inter-epidemic periods frequently lead to complacency in their use. Therefore, there is a clear need for research into vaccine development. Research into the application of rapid scalable manufacture methods, for both human and animal vaccines, would be valuable to areas of the world that do not currently have the agent. For the African situation, there will also be value in more accurate epidemic forecasting, to assist farmers in planning their vaccination schedules prior to the beginning of outbreaks. Mixed vaccine formulations, adding RVF vaccine into vaccines targeting more common veterinary diseases, may help eliminate poor vaccination coverage due to complacency during inter-epizootic periods.

Concluding remarks

The competence of Australian mosquito vectors to become infected with and transmit RVFV indicates a potential risk if the virus were to be introduced. However, establishment of autochthonous transmission depends on more factors than vector competence, for example vector and susceptible host density and distribution, vector behaviour (zoophilic vs anthropophilic), climatic factors such as rainfall and temperature and agricultural practices. RVFV introduction into Australia would present a major challenge to both veterinary and public health authorities. Although RVF is listed as an arbovirus of importance by both the Departments of Agriculture and Health in Australia, very little if any research relevant to the Australian landscape has been published. Potential areas of importance could include an updated study on the competence of Australian mosquitoes for RVFV transmission, combined with detailed mapping of distribution and density of mosquitoes found to be potentially important in transmission. Such information would contribute to modelling disease transmission and thereby contribute to risk assessment and development of mitigation strategies. A multidisciplinary approach would enrich this data by including other factors shown to be important in the ecology of RVF, such as climate, vegetation and soil. To improve confidence in assay performance, baseline serological surveys in targeted areas of the country could be important, or at the very least provide panels of known negative sera to determine serological assay specificity estimates for specific Australian livestock populations. Susceptibility of common Australian livestock and wildlife species should be determined through experimental infection studies.

Conflicts of interest

The authors declare no conflicts of interest.

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Biographies

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Petrus Jansen van Vuren is a Research Scientist working on transboundary animal diseases at the CSIRO Australian Animal Health Laboratory since mid-2019. For 13 years prior to joining the CSIRO team, Petrus was a Medical Scientist at the National Institute for Communicable Diseases in Johannesburg, South Africa. During this time through his role as BSL-4 laboratory supervisor for eight years and head scientist of the Arbovirus Reference Laboratory for four years, his research focussed on development of diagnostic assays for viral zoonotic diseases, ecological and epidemiological studies of arthropod borne- and haemorrhagic fever viruses, pathogen discovery and mobile laboratory outbreak response capacity. Petrus obtained a PhD in Virology in 2011 from the University of the Witwatersrand in South Africa after completing research on diagnostic assay and vaccine development for Rift Valley fever. He has authored more than 50 peer-reviewed publications in international journals, two book chapters on haemorrhagic fever viruses, and contributed to the OIE Terrestrial Manual on Crimean-Congo haemorrhagic fever. Petrus has been actively involved in technical training on VHF and arbovirus laboratory diagnostic techniques at African institutes through programs offered by the World Health Organization, International Atomic Energy Agency and the FAO. Petrus contributed to the establishment and management of the first African institute-led mobile diagnostic laboratory in Freetown, Sierra Leone, during the peak of the Ebola haemorrhagic fever outbreak in West Africa between 2014 and 2016. Petrus holds a C2 researcher rating from the National Research Foundation of South Africa, as an established researcher enjoying international recognition of research contributions.