

Rift Valley fever

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Summary

Rift Valley fever (RVF) is a mosquito-borne zoonotic viral disease affecting domestic and wild ruminants, camels and humans. The causative agent of RVF, the RVF virus (RVFV), has the capacity to cause large and severe outbreaks in animal and human populations and to cross significant natural geographic barriers. Rift Valley fever is usually inapparent in non-pregnant adult animals, but pregnant animals and newborns can be severely affected; outbreaks are characterised by a sudden onset of abortions and high neonatal mortality. The majority of human infections are subclinical or associated with moderate to severe, non-fatal, febrile illness, but some patients may develop a haemorrhagic syndrome and/or ocular and neurological lesions. In both animals and humans, the primary site of RVFV replication and tissue pathology is the liver. Outbreaks of RVF are associated with persistent high rainfalls leading to massive flooding and the emergence of large numbers of competent mosquito vectors that transmit the virus to a wide range of susceptible vertebrate species. Outbreaks of RVF have devastating economic effects on countries for which animal trade constitutes the main source of national revenue. The propensity of the virus to spread into new territories and re-emerge in traditionally endemic regions, where it causes large outbreaks in human and animal populations, presents a formidable challenge for public and veterinary health authorities. The presence of competent mosquito vectors in RVF-free countries, the wide range of mammals susceptible to the virus, altering land use, the global changes in climate, and increased animal trade and travel are some of the factors which might contribute to international spread of RVF.

Keywords

Control – Ecology – Mosquito – Pathogenesis – Prevention – Rift Valley fever – Transmission – Zoonosis.

Introduction and background history

Rift Valley fever virus (RVFV) is a zoonotic RNA arthropod-borne virus of the genus *Phlebovirus* in the family *Bunyaviridae* affecting primarily domestic ruminants and humans (1). The virus was first discovered in 1930, during an outbreak associated with high rates of abortion among pregnant ewes and acute deaths of newborn lambs on a sheep farm in the Rift Valley of Kenya (2). Subsequently, epizootics occurred in Kenya (3) followed by the first major outbreak in South Africa in 1950–1951, which caused an estimated 500,000 abortions and the death of 100,000 sheep. Similar heavy livestock losses occurred in cattle in Zambia and Zimbabwe. Further epizootics were then reported from Namibia, Mozambique, Sudan, and other East African

countries. Between 1974 and 1976, South Africa experienced a second major and even more widespread outbreak of RVF. It was during this outbreak that the potential lethality of the virus for humans, associated with encephalitis and/or haemorrhagic fever, was first recognised (4).

By the late 1980s, the geographic distribution of RVFV had further extended, with outbreaks of the disease or evidence of virus activity reported in many countries of sub-Saharan and Central Africa (4). The virus emerged for the first time outside continental Africa in 1979 in Madagascar (5). Up to 1977, RVF had been largely regarded as a veterinary problem. This perception drastically changed after the first outbreaks of RVF in North and West Africa. The Egyptian outbreak of 1977 to 1978 resulted in an estimated 200,000 human infections and some 18,000 cases of illness, of which at least 598 were fatal, due to encephalitis, liver necrosis and/or haemorrhagic fever. Retinitis was present

in a large proportion of infected individuals (6). In West Africa, severe outbreaks of the disease among livestock and humans were first recorded in Mauritania and Senegal in 1987 and 1988 (7, 8).

Climate change and anthropogenic factors may contribute to the emergence of the disease (9, 10, 11). In addition to flooding, changing land use is one of the major factors contributing to the emergence of RVF. The RVF outbreak of 1977 in Egypt occurred six years after completion of the Aswan dam, which had created large floodlands and increased the breeding habitat of competent mosquito species. Likewise, there was a second dam-linked emergence of RVF in 1987 in Senegal and Mauritania, where an outbreak occurred just one year after the construction of the Diama dam along the Senegal River (4).

Large outbreaks of RVF occurred among livestock and humans in the Horn of Africa countries following the El Niño floods of 1997 and 1998. The greater than normal rainfall resulted in the flooding of two rivers in Somalia, and further flooding in Kenya, creating a large inland lake and setting up suitable conditions for an outbreak that affected an estimated 89,000 people, 478 of whom died (12). Three years later, in 2000–2001, RVFV spread across the Red Sea into the Arabian Peninsula (13) and resulted in an estimated 20,000 human infections and 886 reported cases of illness, of which 123 were fatal. Given the proximity of the Saudi and Somali port cities and the increased livestock trade which takes place before the Hajj festive season, it is likely that the virus was introduced into the Arabian Peninsula through the importation of viraemic animals (14). Between 2006 and 2011, resurgence of severe outbreaks of RVF was reported from East Africa (15, 16, 17), Madagascar (18), South Africa (19, 20) and, for the first time, from the Archipelago of Comoros, on the French island of Mayotte (21). Of the total of 2,842 RVF cases reported in East Africa, West Africa, Madagascar and South Africa between 2006 and 2010, 613 (21.57%) were fatal (12).

The recent reoccurrence of large outbreaks in historically endemic areas, the emergence of the disease in previously disease-free regions and the presence of competent mosquito vectors outside known endemic regions (22, 23, 24, 25) have led to renewed interest in RVF as a significant veterinary and public health threat. This is evidenced by significant progress made in our knowledge of the epidemiology, pathogenesis, control and prevention of the disease; the development of diagnostics, therapeutics and vaccines (26, 27, 28); the implementation of new surveillance, prediction and control strategies (29); and our increased understanding of the molecular biology and genetic diversity of the disease (30, 31). Identification of RVFV virulence factors and host defence mechanisms (32, 33) has stimulated the development of new-generation vaccines (34, 35, 36, 37, 38, 39) and antivirals (40, 41). Despite this considerable progress, there are no RVF vaccines

or specific therapies approved for general public use. There are also no safe, efficacious and affordable vaccines licensed for veterinary applications outside Africa.

Rift Valley fever: an emerging animal and public health challenge

The capacity of the virus to spread into new territories and re-emerge in endemic regions after long periods of silence to cause large outbreaks in human and animal populations constitutes a fearsome test for public and veterinary health authorities. The presence of competent mosquito vectors in RVF-free countries, the wide range of mammals susceptible to the virus, the global changes in climate, and increased animal trade and travel are some of the factors which might contribute to international spread (42).

Rift Valley fever virus belongs to a group of agents causing viral haemorrhagic fevers (VHFs), namely, the taxonomically diverse RNA viruses of the *Arenaviridae*, *Bunyaviridae*, *Flaviviridae*, and *Filoviridae* families. Outbreaks of VHFs have severe implications, such as public panic, disruption of social life and commerce, restrictions on the trade of animals and animal products, and fear of wider and uncontrolled spread (43).

As one of the most important emerging zoonotic pathogens, RVFV poses a particular threat to vulnerable African communities with low resilience to economic and environmental challenges. Outbreaks of RVF prompt strict international restrictions on the movement of livestock and the export of livestock products, which has severe socio-economic effects on countries for which animal trade constitutes the major source of national revenue. Also, a high death rate among pregnant and newborn ruminants affects the survival of pastoral nomads and local herders, who are economically and physically dependent on milk and meat. Large outbreaks in livestock are associated with high numbers of human infections whose clinical management poses a challenge in resource-constrained healthcare settings (44).

There are no licensed vaccines or chemotherapeutics available for RVF prevention and treatment in humans. Therefore, there is increasing international concern that, were the virus to be introduced to naive populations of humans and both domestic and wild ruminants in non-endemic regions, it may potentially cause dramatic health and socioeconomic consequences. As a zoonotic agent with the potential to be used as a bioweapon, RVFV is of great concern for biosecurity authorities worldwide (45,

46). Within the framework of the International Health Regulations, members of the World Health Organization and members of the World Organisation for Animal Health are accountable for early detection and reporting of RVF outbreaks, together with evaluation of the risk of spread to new areas. Observance and execution of this international commitment are essential for timely implementation of effective control measures.

Classification and molecular biology

Rift Valley fever virus is a member of the genus *Phlebovirus* in the family *Bunyaviridae*. It is an enveloped spherical virus with a diameter of 90–110 nm (Fig. 1). The envelope is composed of a lipid bilayer containing two glycoproteins. The genome consists of three single-stranded RNA segments designated large (L), medium (M) and small (S). The L and M segments are of negative polarity. The L segment encodes the viral RNA-dependent RNA polymerase (L protein). The M segment encodes the precursor to the glycoproteins Gn and Gc, and two non-structural proteins, designated NSm1 and NSm2. The S segment utilises an ambisense strategy to code for two proteins, the nucleoprotein N and a non-structural protein NSs (10). The RVFV virion composition and transcription strategy is illustrated in Fig. 2.

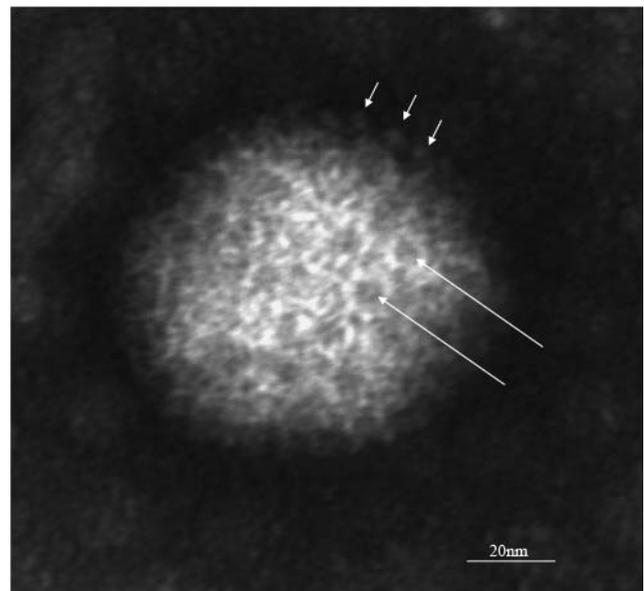


Fig. 1
Rift Valley fever virus particle
Regularly spaced envelope spikes (short arrows) and distinct central cavities (long arrows)

The RVFV glycoproteins are involved in the host cell attachment, penetration, the virion assembly and escape from infected cells. They induce the production of neutralising antibodies, which play an important role in

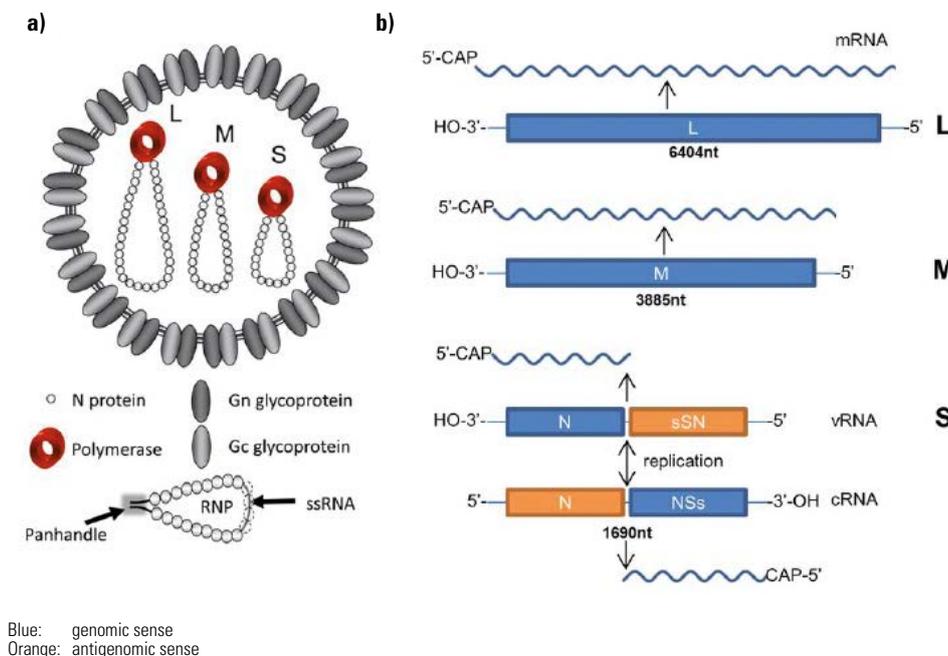


Fig. 2
Rift Valley fever virus virion and transcription strategy

a) Rift Valley fever (RVF) virus particle with the Gn and Gc glycoproteins anchored in the viral envelope. RVF virus genome consists of three single-stranded RNA segments S, M, and L, which are encapsidated by the nucleoprotein (N) into ribonucleoproteins and associate with the viral polymerase. The terminal ends of the genomic RNA segments are complementary, permitting the ends of the RNAs to base-pair with a panhandle structure
b) L and M segments are of negative and the S segment of ambisense polarity

protection. The N protein is essential for virion capsid formation, transcription and replication (31). The N protein does not elicit neutralising antibodies, but it was shown to induce partial immune protection (47, 48). The M-segment-encoded NSm proteins suppress virus-induced apoptosis (49). The S-segment-encoded NSs protein is a major factor of virulence because it inhibits the host's innate viral defences (31). Removal of the NSs gene results in attenuation of the virus (34). Host alternation is important as it helps to maintain stability of the NSs gene, thereby promoting RVFV capacity to evade the innate immune response (50). The NSs and NSm proteins play an important role in RVFV replication in mosquito vectors (51).

Although RVFV is dispersed over an extensive geographic area and infects a wide range of arthropod vectors and vertebrate hosts, it displays low genetic diversity (52, 53). The existence of only one serotype of RVFV and the high degree of conservation of genes encoding the surface glycoproteins indicate that a single vaccine would protect against all circulating genetic variants. The high preservation of the RNA-dependent RNA polymerase gene sequence implies that antiviral drugs will inhibit replication of all known genetic lineages of the virus.

Host range

A wide range of animal species (42) are susceptible to RVFV infection (Table I). Domesticated ruminants are the primary species affected and likely the major amplifiers of the virus. Humans are highly susceptible to RVFV infection and develop sufficient viraemia to be a source of infection for mosquitoes and a means of introducing the disease into uninfected areas (1).

Many African wildlife species tested positive for antibody against RVFV, including: topi (*Damaliscus korrigum*); red-

fronted gazelle (*Eudorcas rufifrons*); dama gazelle (*Nanger dama*); scimitar-horned oryx (*Oryx dammah*); common reedbuck (*Redunca redunca*); African buffalo (*Syncerus caffer*); Dorcas gazelle (*Gazella dorcas*); Thomson's gazelle (*Gazella thomsonii*); gerenuk (*Litocranius walleri*); lesser kudu (*Tragelaphus strepsiceros*); impala (*Aepyceros melampus*); sable antelope (*Hippotragus niger*); waterbuck (*Kobus ellipsiprymnus*); warthog (*Phacochoerus aethiopicus*); African bush elephant (*Loxodonta africana*); giraffe (*Giraffa camelopardalis*); Burchell's zebra (*Equus burchellii*); and black rhinoceros (*Diceros bicornis*). Although serological evidence suggests that a large number of African wildlife species might play a role in the epidemiology of RVF, their possible role in the cryptic maintenance of the virus is poorly understood (42, 54, 55).

Epidemiology and transmission cycles

The most important mosquito vectors of RVFV are members of the subgenera *Neomelanicion* (genus *Aedes*) and *Culex* (genus *Culex*) (28). Biting flies such as midges, phlebotomids, stomoxids and simuliids might serve as mechanical transmitters of infection (1).

In eastern and southern Africa, large outbreaks of RVF occur at irregular intervals of up to 15 years and are strongly associated with heavy rainfall and floods (4, 56). The fate of the virus during long interepizootic periods (IEP) is, however, not well understood. Cryptic maintenance and transmission cycles have been postulated following isolation of RVFV from the floodwater *Ae. mcintoshi* mosquitoes collected during IEP in Kenya (57). Based on these findings, aedine mosquitoes are generally accepted as being capable of maintaining the virus in nature by transovarial transmission. It is believed that the virus can

Table I
Rift Valley fever virus: host range and disease severity

High (~100%) mortality	Severe illness, abortion, mortality	Severe illness, abortion, viraemia	Infection, viraemia	Refractory to infection
Lambs	Sheep	Monkeys	Horses	Guinea pigs
Calves	Cattle	Camels	Cats	Rabbits
Kids	Goats	Rats	Dogs	Pigs
Puppies	Water buffalo	Grey squirrels	Monkeys	Hedgehogs
Kittens	Humans			Frogs
White mice				Chickens
Hamster				Canaries
Field voles				Pigeons
Field mice				Parakeets
Door mice				

survive in dried aedine mosquito eggs for a long period of time. However, as yet, RVFV has never been isolated from the eggs of aedine mosquitoes and the mechanism through which the virus could survive for long periods is not understood. Of potential epidemiological importance is the finding that the larvae of *Cx. pipiens*, *Ae. mcintoshi* and *Ae. circumluteolus* become infected with RVF after feeding on liver homogenates from experimentally infected animals (58).

Flooding is one of the major factors contributing to the emergence of RVF (Fig. 3). After flooding of aedine mosquito breeding habitats (grasslands with shallow depressions called dambos or pens), the floodwater aedine mosquitoes are responsible for the primary cycle of RVFV transmission and the virus is then carried further afield in a secondary transmission cycle by culicine mosquitoes. While aedine mosquitoes tend to remain in the immediate vicinity of their breeding sites, *Culex* mosquitoes disperse widely to feed on vertebrate hosts (28, 59). Epidemics do not occur as a result of lateral spread from a single source, but rather as a result of the intensification of vector activity following their massive and multiple emergences over large endemic areas. This would explain why localised heavy rainfall does not precipitate an epidemic (14). Flooding also increases the concentration of animals and humans on areas of dry land, thus further increasing the potential for virus transmission.

The RVF outbreaks in North and West Africa are associated with mosquito vectors breeding in rivers and dams. The construction of large dam systems in North (Aswan dam) and West Africa (Diama dam) significantly increased mosquito breeding sites and also led to a high concentration of people and livestock in the proximity of the dams during severe drought conditions. In this region, breeding conditions are more suited for flood-breeding aedine mosquitoes of the subgenera *Aedimorphus*, including *Ae. vexans*, *Ae. ochraceus*, *Ae. dalzieli*, and *Ae. cumminsii* (60). During the second large outbreak of RVF in this region in 1998–1999, there



Fig. 3
Flooded area in Garissa District, North Eastern Province of Kenya: the epicentre of the Rift Valley fever outbreak in Kenya, 2006–2007

was apparently a shift in the dominant species towards *Mansonia uniformis* and *Cx. poicilipes* (61). Irrigation for agriculture in the Tihama regions of Yemen and Saudi Arabia and the proximity of the Jizan Dam provide suitable breeding grounds for *Ae. vexans* and *Cx. tritaeniorhynchus* (13). Although mosquito bites are the principal infection mechanism of RVF in animals, during large epidemics other transmission mechanisms also play a role, including active vector dispersal, movements of infectious animals, and passive vector dispersal (20).

In countries where RVFV activity was not previously detected, outbreaks of the disease in animal and human populations resulted from the spread of a single lineage of the virus (52, 53). Results of molecular epidemiology studies in East Africa indicate ongoing RVFV activity and evolution during the IEP and highlight the importance of a cryptic enzootic transmission cycle that allows for the establishment of RVFV endemicity (62, 63). In endemic areas, a decrease in the herd immunity of livestock populations to levels that enable the virus to spread widely eventually leads to explosive outbreaks in which massive flooding precipitates the emergence of large numbers of competent mosquito vectors (56).

A retrospective study on spatial and temporal patterns of RVF outbreaks in Tanzania over the past 80 years demonstrated that epidemics grew larger and larger during that time and steadily covered more and more parts of the country. Moreover, whenever infection was introduced into an area, it was usually involved in later outbreaks. During the 2006/2007 RVF outbreak wave in Tanzania, cases were more likely to be reported from the eastern Rift Valley than the western Rift Valley ecosystem and in areas with clay and loam soil than in areas with soil of a sandy texture. The findings demonstrate the value of retrospective spatio-temporal analysis for informing the planning and implementation of strategic control measures (64).

There have been reports that the RVF virus has been transmitted during IEP without causing noticeable outbreaks or clinical cases (e.g. African wildlife [54, 65, 66, 67], cattle [21], sheep and goats [68], and humans [69, 70, 71, 72]). However, it remains unclear why a low level of virus circulation during IEP does not result in clinical manifestations in livestock and people. One possible explanation could be that sporadic clinical cases occurring during IEP are underreported and/or misdiagnosed.

Source of human infection

There are two different types of secondary cycles by which RVFV can be transmitted to humans: the sylvatic cycle and the urban peridomestic cycle. The mosquito vectors

of RVFV in sub-Saharan Africa tend to be zoophilic and sylvatic; consequently, the virus is generally transmitted in a sylvatic cycle in which humans become infected mostly from direct or indirect contact with the blood or organs of infected animals to which the virus has been transmitted by zoophilic mosquitoes. The virus is transmitted to humans through the handling of animal tissues and body fluids during slaughtering or butchering, assisting with animal births, conducting veterinary procedures, or from the disposal of carcasses or fetuses. The virus infects humans through inoculation, e.g. via a wound from an infected knife or through contact with broken skin, or through inhalation of aerosols produced during the slaughter of infected animals or obstetric procedures. There is some evidence that humans may become infected with RVFV by ingesting the unpasteurised or uncooked milk of infected animals (Fig. 4).

The second type of secondary cycle is the urban peridomestic cycle, in which humans become infected through the bites of mosquitoes (1). The main vector in the Egyptian epizootic of 1977–1978, *Cx. pipiens*, is known to be peridomestic and anthropophilic, implying that large numbers of humans can be infected by mosquito bites and subsequently serve as amplifying hosts for the infection of mosquitoes. Human infections can also result from bites by other blood-feeding insects, such as midges, phlebotomids, stomoxids and simuliids, which might serve as mechanical transmitters of infection.

To date, no human-to-human transmission of the virus has been documented. There are also no reports of RVFV transmission to healthcare workers and no evidence of outbreaks of RVF in urban areas (1). Urban consumers of animal products are not affected by the sylvatic cycle, as the virus is rapidly inactivated when the pH of meat falls below 6 during processing (4).



Fig. 4

Settlement of nomadic pastoralists in Kenya

Infections with Rift Valley fever virus are often diagnosed in pastoralists who have handled infected animals, their tissues or products

Clinical manifestations in humans

Infection with RVFV results in several different disease syndromes in humans. The majority of infections are inapparent or associated with moderate to severe, non-fatal, flu-like febrile illness with headache, nausea, myalgia and arthralgia. Less than 1% of human patients develop the haemorrhagic and/or encephalitic forms of the disease. The overall case fatality rate (CFR) is estimated to range from 0.5% to 2%, but it appears to have been higher in recent outbreaks (15, 16, 19). The onset of the meningo-encephalitic form of the disease usually occurs one to four weeks after disease onset. Haemorrhagic symptoms of RVF appear two to four days after the onset of illness and usually begin with evidence of severe liver impairment followed by bleeding manifestations. The CFR for patients developing the haemorrhagic form of the disease can be as high as 50%. In a minority of patients the disease is complicated by the development of ocular lesions at the time of the initial illness or up to four weeks later. Estimates for the incidence of ocular complications in human infections range from less than 1% to 20%. The ocular disease usually presents as a loss of acuity of central vision, sometimes with development of scotomas. The lesions and the loss of visual acuity generally resolve over a period of months, with variable residual scarring of the retina, but in instances of severe haemorrhage and detachment of the retina there may be permanent uni- or bilateral blindness. Human patients with jaundice, neurological disease or haemorrhagic complications are at increased risk of fatality. Hepatorenal failure, shock, and severe anaemia are the major factors associated with patient death (1, 43).

Clinical manifestations in animals

There are marked differences in the patterns of RVF in domestic animals, varying from moderate to serious clinical disease. Newborn lambs and kids are extremely susceptible to RVFV infection, with mortality exceeding 90% two days after the onset of illness in animals less than a week old. Lambs and kids older than two weeks and mature sheep and goats are less susceptible to the disease but some animals may die peracutely. Most develop an acute disease with high fever, anorexia, weakness, listlessness and hyperpnoea. Some animals may develop melaena or foetid diarrhoea and a blood-tinged, mucopurulent nasal discharge. Most adult sheep and goats undergo subclinical infection. The disease in calves resembles that in lambs and sheep, but a higher proportion of calves may develop icterus. Death generally occurs two to eight days after infection, and mortality is usually less than 10%. Infection is frequently inapparent in adult cattle, but some animals develop acute disease.

Abortion is an almost inevitable outcome of infection in pregnant sheep, goats and cattle. Animals may abort at any stage of gestation. However, abortion rates vary with epidemiological circumstances, and have ranged from 15% to 100% in different outbreaks, or in separate herds and flocks in a single outbreak. Frequently, abortion may be the only overt manifestation of disease in a herd or flock (1, 4).

Pathogenesis

In both animals and humans, the primary site of RVFV replication and the major site of tissue pathology is the liver (Fig. 5, Fig. 6a). However, during severe infections, the virus can be found in virtually all tissues (Fig. 6b, Fig. 6c) and cell types. Hepatic necrosis and increased liver enzymes are early markers for fatal RVF in humans (1). In the mouse model the pathogenesis of the virus in the liver and brain is mostly driven by chemokine and pro-inflammatory cytokine responses (73). A single nucleotide mutation of the M segment affects the RVFV virulence in mice (74). Results of molecular study (53) suggest that the pathogenicity of the virus to humans might be influenced by massive vaccination of ruminants in Africa with the live attenuated RVFV Smithburn neurotropic strain (SNS). The SNS vaccine virus was intensively passed by intracranial inoculation of mice, and is only partially attenuated, as evidenced by its abortogenic and teratogenic effects in ruminants (75, 76). Viruses attenuated through intracranial passage in mice may acquire new tissue tropism and pathogenic properties (43). Aerosol exposure to RVFV causes earlier and more severe neuropathology in the mouse model (77).

Diagnosis

Epidemics of RVF have a number of concurrent and interrelated features, which allow for a fairly accurate tentative diagnosis. They include:

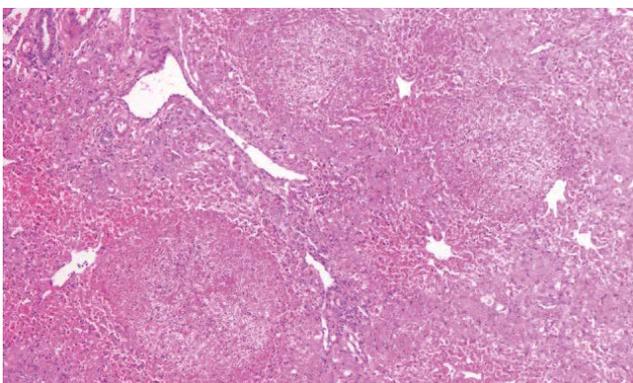


Fig. 5
Histopathology of the liver of a calf infected with Rift Valley fever virus: multifocal hepatic necrosis

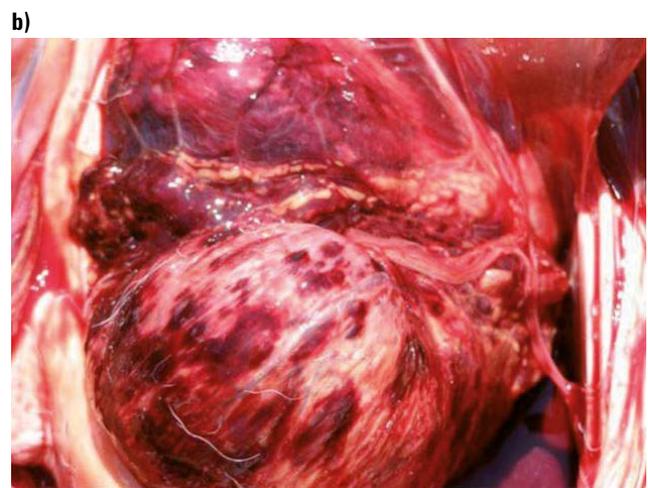


Fig. 6
Rift Valley fever gross pathology

- a) Liver of a calf with diffuse hepatic necrosis and cholestasis, which give the liver a yellow/gold appearance, and widespread capsular and parenchymal haemorrhages
- b) Abomasums of a calf with large paint-brush haemorrhages (sugillations) on the serosal surface
- c) Kidney of a calf with diffuse congestion and widespread haemorrhage

- unusually heavy and persistent rainfall resulting in flooding over a wide area and subsequent abundance of mosquitoes
- sudden and simultaneous onset of abortions among domestic ruminants or camels and a high mortality rate, particularly in newborn lambs, kids and calves
- other severe, often haemorrhagic, clinical signs and gross and histological lesions, especially in the livers of young animals or aborted fetuses
- the presence of usually benign febrile illness among people involved in handling the blood, tissues, secretions or excretions of infected animals (especially after abortion) or involved in the slaughtering and autopsying of infected animals.

There are health and safety issues to be addressed when considering the clinical and laboratory diagnosis of RVF. The virus presents a high bio-hazard risk for laboratory personnel, veterinarians and others engaged in the livestock industry.

Acute RVF can be diagnosed using several different methods. Serological tests such as enzyme-linked immunosorbent assay (ELISA) may confirm the presence of specific immunoglobulin M (IgM) antibodies to the virus. The virus itself may be detected in blood during the early phase of illness or in post-mortem tissues using a variety of techniques, including virus propagation (in cell cultures or inoculated animals), antigen detection by antigen ELISA, immunohistochemistry, and detection of specific nucleic acid by polymerase chain reaction assays (28). Immunoglobulin G (IgG) and IgM antibodies are produced early in an infection. The dynamics of virological, IgM and IgG responses in a sheep experimentally infected

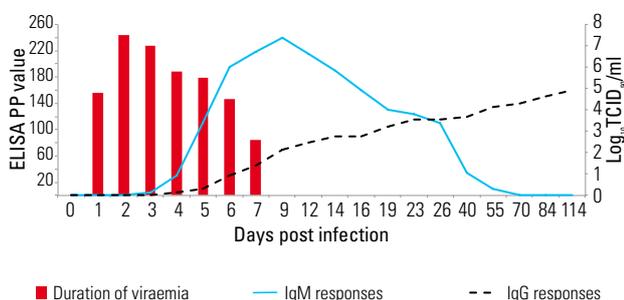


Fig. 7
Duration of viraemia, and IgM and IgG responses in a sheep experimentally infected with a wild strain of Rift Valley fever virus

Enzyme-linked immunosorbent assay (ELISA) readings are measured as percent positivity of internal positive control serum. Concentration of the virus in blood is given as median tissue culture infectious dose ($\log_{10} \text{TCID}_{50}$) per ml of blood

with a wild strain of RVFV (J.T. Paweska, unpublished data) are shown in Fig. 7.

Single cases of RVF may be confused with many viral diseases of small ruminants causing sudden death associated with generalised lymphadenopathy and haemorrhages. However, RVF should always be considered when there is a sudden onset of abortions and acute death in young animals, associated with necrotic lesions in the liver in all cases. Liver necrotic lesions are pathognomonic for RVF, but laboratory confirmation is advisable (14).

Diseases to be taken into consideration in the differential diagnosis of RVF in animals (4) include: Wesselsbron disease, bluetongue, ephemeral fever, Nairobi sheep disease, rinderpest, peste des petits ruminants, Thogoto, Simbu and Palyam virus infections, Q fever, toxoplasmosis, brucellosis, salmonellosis, pasteurellosis, leptospirosis, chlamydiosis and anthrax. It is also worth considering whether or not the animal may have ingested poisonous plants (causing hepatic lesions, haemorrhages, and/or icterus).

In the differential diagnosis of RVF in humans, several agents causing VHF syndrome should be considered. These pathogens have worldwide distribution, but a specific agent is usually restricted to a known endemic region, where its existence depends on the presence of natural reservoirs and/or competent arthropod vectors. As for most VHFs, the nonspecific presentation of RVF in humans makes it difficult to diagnose clinically. Therefore, the differential diagnosis concerns a broad array of conditions, especially when first cases are encountered during yet unrecognised outbreaks. These include malaria, rickettsial infections, Q fever, typhoid fever, dysentery, plague, brucellosis, leptospirosis, meningitis, other sepsis from bacterial infections, viral hepatitis, other viral haemorrhagic fevers, non-infectious causes of disseminated intravascular coagulopathy, and acute leukaemia. The cause can be tentatively assumed based on a history of recent travel and exposure in endemic regions (43).

Treatment

No specific treatment is available for humans. Treatment is symptomatic and, in more severe cases, general supportive therapy is provided. Considering the high burden of malaria and tick-borne rickettsial disease in Africa, patients should be experimentally treated with broad-spectrum antibacterial and/or antiparasitic drugs until a diagnosis of RVF can be confirmed. Due to high viraemia in severely ill patients, strict barrier and isolation nursing should be implemented, especially where intravenous transfusion of fresh frozen plasma, blood, and albumin is performed. Haemodialysis for patients with severe acute renal failure and other intensive care and supportive measures, such as mechanical ventilation, are provided as necessary (43).

In some studies, the antiviral drug ribavirin was shown to have a therapeutic efficacy against RVFV in mice (78, 79), various cell cultures, hamsters and rhesus monkeys (80). However, in another study, mice infected with RVFV by aerosol exposure and treated with ribavirin were not protected and developed severe neuropathology (77). Ribavirin did not prevent the late occurrence of encephalitis in patients in Saudi Arabia, and its use is now contraindicated in humans (1).

Preventive control measures

The most effective way of protecting animals and humans against RVF would be vaccination. However, there are no safe, efficacious, and affordable vaccines licensed for veterinary applications, except in Africa, where inactivated vaccines and the live attenuated Smithburn vaccine are in use, although only to a limited extent. An animal immunisation programme based on the use of a naturally occurring RVFV mutant (Clone-13) was recently introduced in South Africa (83). Immunisation of professionals at high risk of infection is implemented on a voluntary basis through the use of an experimental inactivated RVF vaccine (84).

Restricting or prohibiting the movement of livestock may be useful in slowing the spread of the virus from infected to uninfected areas. As outbreaks of RVF in animals usually precede human cases, an active animal health surveillance system to detect new cases is essential in providing early warning for public health authorities. Detecting animal cases during the early stages of an outbreak and sharing information about the cases with public health sectors is critical for implementation of timely control measures. Forecasting models and early warning systems using satellite images and weather/climate prediction data are useful for signalling increased risk of RVF outbreaks (1, 4, 14).

During an outbreak of RVF, close contact with animals, particularly with their tissues and body fluids, either directly or indirectly, is the most important risk factor. Therefore, in the absence of specific treatment and vaccine, raising awareness of the risk factors of RVF infection is the only practical way to reduce human infection and deaths. Public health messages should focus on reducing the risk of animal-to-human transmission as a result of unsafe animal husbandry and slaughtering practices. Appropriate protective clothing should be worn and care taken when handling sick animals or their tissues or when slaughtering animals. In the epizootic regions, all animal products should be heat processed before eating (1).

In affected areas, there should be a strong emphasis on the importance of personal and community protection against mosquito bites. People can protect themselves using impregnated mosquito nets and personal insect repellent,

wearing light-coloured clothing, long-sleeved shirts and trousers, and avoiding outdoor activity, especially at peak biting times of mosquitoes. Although no human-to-human transmission of RVF has been demonstrated, there is still a potential risk of transmission of the virus from infected patients to healthcare workers through contact with infected blood or tissues. Healthcare workers caring for patients with suspected or confirmed RVF should implement standard precautions thoroughly. Samples taken from suspected human and animal cases of RVF for diagnosis should be handled by trained staff and processed in suitably equipped laboratories.

Conclusion

Severe outbreaks of RVF continue to reoccur in historically endemic areas, affecting the survival of pastoral nomads and local herders who are economically and physically dependent on animal food products. Large outbreaks in livestock are associated with high numbers of human infections whose management poses a significant challenge in resource-limited healthcare settings.

There is global concern about the unpredictable and sudden emergence of the virus outside its traditional geographic boundaries in areas where competent vectors are present. There is also concern about how the virus may be affected by changing land use, global climate change and the intensification of international livestock and wildlife trade, and about the potentially dramatic health and socioeconomic consequences of its deliberate release or accidental introduction into RVF-free countries.

Despite the development of new diagnostic tools and vaccines and recent progress in studies on virus pathogenesis, there are, as yet, no safe and efficient commercial vaccines available for animal and human use in RVF-free countries. There is also a general lack of effective antiviral drugs for human use.

Recent advances in molecular epidemiology help to unravel the natural history of the virus and trace its movements. However, we still have only a limited understanding of the complexity of interactions between the virus and the vectorial, host, ecological, climatic and anthropogenic factors governing the cryptic transmission of the virus during long inter-epidemic periods and the emergence of massive RVF outbreaks.

Given these challenges and, particularly, the general lack of biologicals for immunisation and treatment, RVFV remains a significant zoonotic viral threat to public and veterinary health.

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Fièvre de la vallée du Rift

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Résumé

La fièvre de la vallée du Rift est une maladie zoonotique virale transmise par les moustiques, affectant les ruminants domestiques et sauvages, les chameaux et l'être humain. Elle est causée par le virus de la fièvre de la vallée du Rift (RVFV) qui provoque de graves foyers épidémiques dans les populations animales et humaines sans que les barrières géographiques naturelles lui fassent barrage. La fièvre de la vallée du Rift passe généralement inaperçue chez les femelles adultes non gestantes ; en revanche, les femelles gestantes peuvent être gravement atteintes ; les foyers se caractérisent par le déclenchement soudain d'avortements et par une néomortalité élevée. La plupart des infections humaines se présentent sous forme infra-clinique ou sont associées à une atteinte fébrile modérée à sévère et non mortelle ; néanmoins, quelques patients développent parfois un syndrome hémorragique et/ou des lésions oculaires ou neurologiques. La réplication du virus de la fièvre de la vallée du Rift et les premières lésions tissulaires ont lieu dans les tissus hépatiques, aussi bien chez l'homme que chez l'animal. Les foyers de fièvre de la vallée du Rift sont associés à de fortes précipitations entraînant des inondations massives et l'émergence d'un grand nombre de moustiques compétents qui transmettent le virus à un large éventail d'espèces de vertébrés sensibles. Les foyers de fièvre de la vallée du Rift ont des effets économiques dévastateurs dans les pays pour lesquels les exportations d'animaux et de produits d'origine animale constituent la principale source de revenus. La tendance naturelle du virus à conquérir de nouveaux territoires et à réapparaître dans des régions où il avait déjà sévi à l'état endémique, en occasionnant des foyers de très grande envergure dans les populations humaines et animales constitue un défi majeur pour les autorités en charge de la santé publique et de la santé animale. La présence des moustiques compétents en tant que vecteurs dans des pays indemnes de fièvre de la vallée du Rift, la grande diversité des mammifères sensibles au virus, les modifications de l'utilisation des sols, le changement climatique planétaire et l'intensification des échanges et des mouvements d'animaux comptent parmi les facteurs de propagation internationale de la fièvre de la vallée du Rift.

Mots-clés

Contrôle – Écologie – Fièvre de la vallée du Rift – Moustique – Pathogénie – Prévention – Transmission – Zoonose.

Fiebre del Valle del Rift

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Resumen

La fiebre del Valle del Rift (FVR) es una enfermedad vírica zoonótica transmitida por mosquitos, que afecta a rumiantes domésticos y salvajes, camellos y humanos. Su agente causal es un virus capaz de provocar vastos y graves brotes en poblaciones animales y humanas y de superar importantes barreras geográficas naturales. La enfermedad suele ser asintomática en el adulto, pero las hembras embarazadas y los neonatos pueden resultar gravemente afectados. Los brotes se caracterizan por la súbita aparición de abortos y una elevada mortalidad neonatal. En el hombre la mayoría de las infecciones son latentes o se acompañan de un cuadro febril entre leve y moderado, no letal, aunque ciertos pacientes pueden sufrir un síndrome hemorrágico y/o lesiones oculares y neurológicas. Tanto en animales como en el ser humano, el hígado es el principal centro de replicación del virus de la FVR, y el tejido más afectado es el hepático. Los brotes de FVR están correlacionados con episodios de pluviosidad elevada y persistente, que provocan grandes inundaciones e inducen la aparición de un ingente número de mosquitos competentes para actuar de vectores y transmitir el virus a muy diversas especies de vertebrados sensibles. Esos brotes tienen consecuencias económicas devastadoras para los países cuya principal fuente de ingresos es el comercio de animales. La propensión del virus a extenderse a nuevos territorios y a reemerger en regiones tradicionalmente endémicas, donde causa grandes brotes en las poblaciones animales y humanas, plantea un espinoso problema a las autoridades de salud pública y veterinaria. La presencia de mosquitos competentes como vector en países libres de la enfermedad, el amplio elenco de mamíferos sensibles al virus, la modificación de los usos del suelo, el cambio climático planetario y la intensificación del comercio y los desplazamientos de animales son otros tantos factores que podrían contribuir a la propagación internacional de la FVR.

Palabras clave

Control – Ecología – Fiebre del Valle del Rift – Mosquito – Patogénesis – Prevención – Transmisión – Zoonosis.



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