Rift Valley fever

Introduction

Rift Valley fever (RVF) is an acute hepatic and sometimes haemorrhagic disease of domestic ruminants and humans, caused by a mosquito-borne virus. Epidemics occur when particularly heavy rains favour the breeding of mosquito vectors.

An acute and highly fatal disease of lambs accompanied by reports of illness in humans was first recognized in the Rift Valley in Kenya in the early 1900s but the causative agent was not isolated until 1930. Since then all outbreaks except one have been confined to countries in Africa. In 2000-2001 RVFV escaped from the African continent to cause a major outbreak of disease in Saudi Arabia and Yemen on the Arabian Peninsula. The disease was first recorded in southern Africa late in 1950 when an estimated 100 000 sheep died and 500 000 ewes aborted in South Africa alone. A second severe epidemic occurred in southern Africa in 1974 and 1975 during which more severe losses than in the 1950 epidemic were reported. In 1977 and 1978, a major epidemic occurred in the Nile delta and along the Nile in Egypt, causing an unprecedented number of human infections (more than 200 000) and deaths (about 600 humans died), as well as numerous deaths and abortions in sheep and cattle and some losses in goats, water buffaloes and camels. Other noteworthy outbreaks in which high mortality in animals and deaths in humans were reported include the outbreaks in South Africa (1975), Mauritania (1987), Senegal (1987) and Kenya and neighbouring countries (1997-1998). Since RVFV can be transmitted by an unusually wide range of mosquitoes and livestock circulate sufficiently high levels of virus to infect mosquitoes, many parts of the world would probably be receptive to the virus.

Aetiology

Rift Valley fever is caused by a *Phlebovirus* of the family *Bunyaviridae*.

No significant antigenic differences have been detected between RVFV isolates and laboratory passaged strains from many countries, but differences in pathogenicity have been demonstrated.

Wilde-type RVFV, which is hepatotropic, has been attenuated to produce vaccine by serial passage in highly permissive systems such as suckling mice or tissue culture, by selection of small plaque variants and by chemical mutagenesis. The Smithburn vaccine, which has been used extensively to control outbreaks, was developed by 105 serial intracerebral passages in suckling mice until it lost its tropism for the liver and became neuroadapted.

Two *Phlebovirus* virions

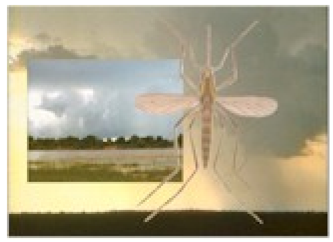
Epidemiology
Distribution

With the exception of the 2000-2001 outbreak on the Arabian Peninsula all other outbreaks or serological evidence of RVF have been limited to the African continent and Madagascar.

Apart from the more recent outbreaks in Sudan, Egypt, Senegal and Mauritania, epidemics, associated with above average rainfall, have tended to occur in eastern, central and southern African countries usually at irregular intervals of 5 to 15 years or longer.

The recent outbreaks of RVF in countries in North and West Africa occurred independently of rainfall in dry countries, apparently in association with vectors which breed in large rivers and dams.

A flooded area in northern Kenia



Periods of above average rainfall favour mosquito vectors

Hosts/Reservoirs

The central enigma in the epidemiology of RVF has always concerned the fate of the virus during the inter-epidemic periods. For decades it was widely accepted that the virus is endemic in indigenous forests, where it circulated in mosquitoes and unknown vertebrates, and that it spread to livestock-rearing areas when heavy rains favoured the breeding of epidemic mosquito vectors. However, there is no proof that the virus is maintained in transmission cycles in birds, monkeys, baboons or other wild vertebrates.

Vectors transmit the virus to domestic ruminants and wildlife

It is currently postulated that RVFV in sub-Saharan Africa is maintained in inter-epidemic periods principally by transovarial transmission in aedine mosquitoes particularly in areas where there are dambos or broad vleis, with a low level of transmission to livestock. Pans, dambos and vleis retain water for months or even years, and constitute an ideal environment for the breeding of mosquitoes, particularly floodwater-breeding aedines of the subgenera *Aedimorphus* and *Neomelaniconion*, which attach their eggs to vegetation such as grasses, sedges and rushes at the water's edge. In contrast to culicine mosquitoes, the eggs of aedines have to be subjected to a period of drying as the water recedes in order to hatch on being wetted again when next the pan, dambo or vlei floods. Thus, aedine mosquitoes overwinter as eggs. The eggs can survive for long periods in dried mud possibly for several seasons if pans, dambos or vleis remain dry.


Dambo: Ideal breeding sites of vector mosquitoes

Maintenance of virus through the dry winter is possible by means of vertical (transovarial) transmission by *Aedes* spp. or by overwintering adult *Culex* mosquitoes. It is thought that epidemics are precipitated by abnormally heavy rains which lead to an explosive increase in vector populations and spread of the disease from these endemic foci.

Serological surveys in cattle and wildlife indicate that varying amounts of virus activity occur each year in certain areas in eastern and southern Africa without epidemics occurring. In southern Africa the onset of epidemics tends to be recognized late in summer following an initial increase in vector populations.

Although a wide variety of domestic and wild ruminants are susceptible to RVF, the disease is mainly of economic importance in sheep, goats and cattle with new-born animals being most susceptible. Antibodies to RVF have been found in a range of African antelopes, camels, and African and Asian buffalo sometimes accompanied by abortion.


Sheep and cattle in East Africa where outbreaks have occurred

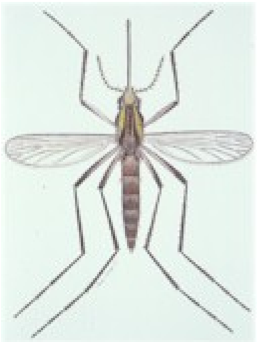
In North Africa mortality in young camels, and abortion has been reported

Water buffaloes

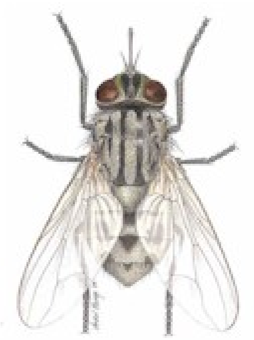
African buffaloes

Transmission

The flooding of dambos or vleis and the humid weather conditions prevailing in epidemics favour the breeding not only of the aedine maintenance vectors such as *Aedes mcintoshi, Aedes unidentatus* and *Aedes juppi* and the non-aedine mosquitoes such as *Culex* and *Anopheles* species which serve as epidemic vectors, but also of other biting insects such as midges, phlebotomids, stomoxids and simulids which are all potential mechanical transmitters of RVFV because of the high level of viraemia in infected livestock. Contagion is not considered to be important in livestock, as opposed to the case in humans.



Aedes mcintoshi - an important vector



Stomoxys calcitrans

Biting midges (*Simulium* sp.)

Humans usually become infected when performing necropsies on infected animals as a result of contact of blood or body fluids with abrasions or wounds in the skin or mucous membranes but aerosol infections is also possible. Consumption of raw milk has been associated with infection in humans. Mosquito-borne transmission may occur.

Contact transmission is important in humans

Milking a cow in East Africa

Socio-economic importance

Epidemics occur at irregular intervals of 5-15 years following higher than average rainfall. Affects mainly domestic ruminants and may result in:

- A mortality rate of higher than 90% in new-born lambs and kids.
- A mortality rate of 15–30% or higher in adult sheep and goats.
- An abortion rate of 40-60% or higher in pregnant sheep.
- A mortality rate of 0-5% in adult cattle and of about 10% in calves.
- Abortion in up to 40% of pregnant cows.

The cost of control measures as a result of vaccination and other control measures and trade embargoes on animals and their products such as those that were imposed by Saudi Arabia and Yemen on countries in the Horn of Africa (e.g. Somalia and Sudan) during the recent outbreaks (2000-2001) should also be taken into account.


High mortality rate in sheep


Death in cattle and aborted fetuses

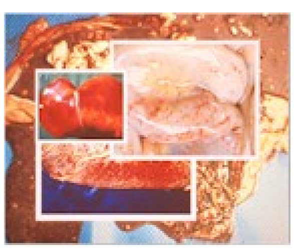

Numerous aborted foetuses in sheep

Pathogenesis

The pathogenesis of RVF encompasses the spread of virus from the initial site of replication to target organs such as the spleen and the liver. Intense viraemia results from the release of virus following replication in target organs.

Hepatic disease occurs in all species but it is most severe in extremely susceptible hosts, such as new-born lambs and kids. In these hosts hepatic lesions rapidly progress to a massive necrotic hepatitis just before death. In less susceptible animals such as adult sheep and goats the hepatic lesions tend to be more focal in nature.

The haemostatic derangement which manifests as a viral haemorrhagic fever with a bleeding tendency and disseminated intravascular coagulopathy is most severe in the fatal hepatic syndrome in animals and humans. It is postulated that the critical lesions in the development of the haemorrhagic state are thrombocytopenia, vasculitis, hepatic necrosis and a reduction in certain clotting factors which result in widespread haemorrhage.


Disseminated intravascular coagulopathy
is responsible for many of the lesions

Clinical signs

In new-born lambs and kids the incubation period is usually 24-36 hours. The onset of the disease is marked by fever, listlessness, disinclination to move or feed, evidence of abdominal pain, and rapid respiration.

New-born lambs are highly susceptible

The course of the disease is usually peracute and lambs rarely survive more than 24-36 hours after the onset of the first signs of illness; many are simply found dead. In animals less than a week old mortality is 90 % or more.

Lambs and kids older than two weeks and mature sheep and goats are significantly less susceptible than are new-borns. Most of these animals develop the acute disease. Affected animals show fever, anorexia, listlessness and an increased respiratory rate. Some animals may develop a bloody or foetid diarrhoea and a blood-tinged, mucopurulent nasal discharge. A few animals may be icteric.

Ewe aborting

Pregnant sheep and goats may abort at any stage of gestation as a result of the febrile reaction and/or infection of the foetus. Aborted foetuses are usually autolysed. Retained placenta and purulent metritis may occur as complications of abortion. In sheep mortality rates varying from 5 to 30% and abortion rates of 40 to 100% have been reported in outbreaks. Goats are said to be more resistant to the disease than sheep, but in some outbreaks similar mortality and abortion rates to those in sheep have been occurred.

In adult cattle it is usually an inapparent infection, but some develop peracute or acute disease. Icterus may be marked. In calves the disease is usually acute: icterus and diarrhoea (sometimes bloody) often occur. The mortality rate is 0-5% and about 10% in adult cattle and calves respectively. An abortion rate of up to 40% may occur in pregnant cows.

The majority of RVF infections in humans are inapparent or are associated with moderate to severe, non-fatal, influenza-like illness, but a minority, probably less than 1%, develop ocular lesions, encephalitis or severe fatal hepatic disease with haemorrhagic manifestations.

After an incubation period of 2-6 days, the onset of the more benign illness is usually very sudden. The disease is characterized by rigor, fever that persists for several days and is often biphasic, headache with retro-orbital pain and photophobia, weakness, and muscle and joint pains. Sometimes there is nausea and vomiting, abdominal pain, vertigo, epistaxis and a petechial rash.

Signs of encephalitis (e.g. headaches, confusion, tremors, convulsions) may occur 1-4 weeks after the acute febrile illness in a small percentage of human patients. It has been suggested that the encephalitic and ocular syndromes may have an immuno-pathological basis because of the late onset.

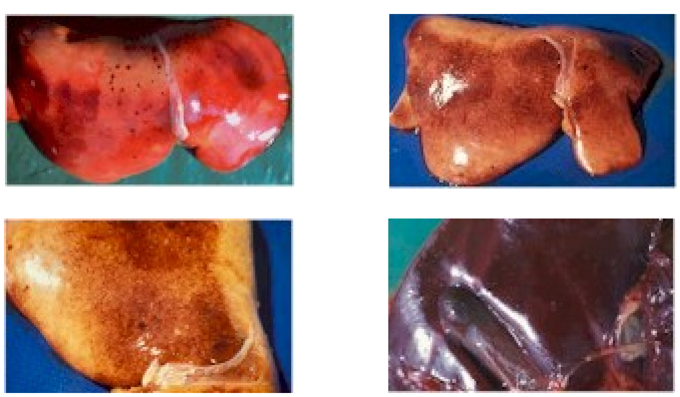
In a minority of humans the disease is complicated by the development of ocular lesions during the acute disease or up to 4 weeks later. The ocular disease usually presents as a loss of acuity of central vision, sometimes with development of scotomas as a result of ischaemic lesions in the macular and paramacular areas of the retina. The loss of visual acuity generally resolves over a period of months with variable residual scarring of the retina, but in cases in which there is severe haemorrhage and detachment of the retina there may be permanent uni- or bilateral blindness.

Collecting blood samples for antibody detection

Macropathology

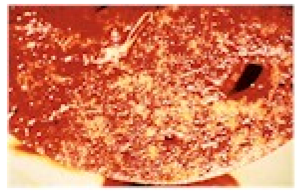
The hepatic lesions of RVF are essentially similar in all domestic animals and humans, varying mainly with the age of the affected individual.

The most severe lesions occur in aborted sheep foetuses and new-born lambs in which the liver is usually moderately to greatly enlarged, soft, friable and yellowish-brown to dark reddish-brown in colour with irregular congested patches and sometimes haemorrhages of varying size scattered throughout the parenchyma. Numerous greyish-white necrotic foci, 0,5 to 1,0mm in diameter, are invariably present in the parenchyma, but they may not be clearly discernible because of the discolouration of the organ. There may be oedema and haemorrhages in the wall of the gall bladder and hepatic lymph node. Mild icterus is evident in only about 10% of affected lambs because of the peracute course of the disease.



New-born lamb liver

The hepatic lesions in adult sheep are generally not as severe or as widespread as in new-born lambs. Pin-point reddish to greyish-white necrotic foci may be distributed throughout the parenchyma, and in a small proportion of sheep there are larger centrilobular haemorrhages and necrotic lesions which impart a mottled appearance to the organ.



Adult sheep liver

Haemorrhages and oedema of the wall of the gall bladder are common, and the lumen may contain a blood coagulum or blood-tinged bile.

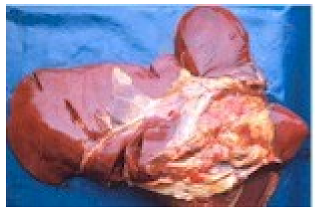
Adult sheep. Blood coagulum in gall bladder

Adult sheep.
Haemorrhagic and oedematous gall bladder wall

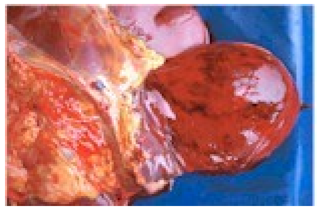
Adult sheep.
Gall bladder with blood-tinged bile

The livers of aborted calf foetuses, calves and adult cattle resemble those of adult sheep. The wall of the gall bladder is frequently oedematous and haemorrhagic.

Rift Valley fever is often a very haemorrhagic disease in cattle characterized by numerous haemorrhages in the serosal surfaces and tissues. The lumen of the abomasum and small and large intestines may contain copious amounts of free blood.



Adult bovine



Adult bovine.
Oedema and haemorrhage of gall bladder wall

Adult bovine.
Splenomegaly with numerous haemorrhages in capsule

Adult bovine.
Haemorrhages in mucosa of abomasum

Adult bovine.
Numerous haemorrhages in serosa of intestine

The hepatic lesions in new-born lambs are almost invariably accompanied by numerous petechiae and ecchymoses in the mucosa of the abomasum, and its contents are dark chocolate-brown as a result of the presence of partially-digested blood. The contents of the small intestine may be similar in appearance.

New-born lamb abomasum.
Chocolate-brown partially digested blood

New-born lamb abomasum.
Numerous mucosal haemorrhages

Most mature sheep and cattle have haemorrhages and oedema in the abomasal folds, and sometimes copious amounts of free blood in the lumen of the intestines.

Adult sheep abomasum.
Mucosal oedema and haemorrhages

Adult sheep abomasum.
Oedema and petechiation of mucosal folds

In domestic ruminants the spleen is slightly to moderately enlarged, with haemorrhages in the capsule.

In domestic ruminants the peripheral and visceral lymph nodes are enlarged, oedematous, and may contain petechiae. Other changes include widespread subcutaneous, serosal and visceral haemorrhages, mild to moderate effusion of fluid, often blood-tinged, into body cavities, and congestion and oedema of the lungs.

Diagnosis

One should suspect RVF when heavy rains are followed by the occurrence of abortions in sheep, goats and cattle together with fatal disease, particularly in young animals, which is marked by necrotic hepatitis and haemorrhages in the abomasum and serosal surfaces. Frequently there is also an influenza-like illness in farm workers.

Specimens

Specimens to be submitted for laboratory confirmation of the diagnosis include heparinized or clotted blood, plasma or serum of live affected animals, or tissue samples, including liver, spleen, kidney, lymph nodes and heart blood of dead animals.

Samples from aborted foetuses should include brain since this is usually less autolysed or putrefied than viscera.

Specimens should be securely packaged and submitted on ice to a suitable laboratory for isolation of virus or demonstration of antibody. Where delay in getting specimens to the laboratory is unavoidable or where material has to be transported at ambient temperature, tissue samples can be preserved in glycerol-saline solution.

Virus isolation

Virus can be isolated readily in a variety of cell cultures, or in suckling and weaned mice or hamsters inoculated intracerebrally or intraperitoneally.

Virus/antigen detection

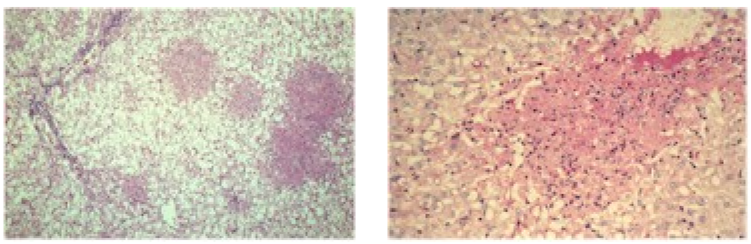
This is rapidly done in impression smears of infected tissues by immunofluorescence, in tissue suspensions by complement fixation (CF) and immunodiffusion (ID), in tissue sections by immunoperoxidase staining and in serum by ELISA. Viral nucleic acid can readily be detected in serum and other tissues of infected livestock and humans, as well as mosquitoes, by the reverse transcription polymerase chain reaction.

Serology

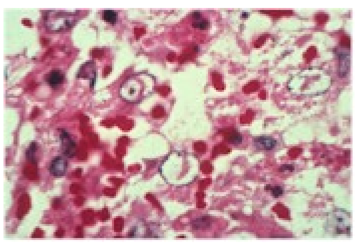
In animals that survive the disease, paired serum samples, one taken during the acute illness and the other 2 - 3 weeks later, should be submitted for antibody tests by tests such as CF, ID, serum neutralization or ELISA.

Microscopic pathology

Tissue specimens from the liver, spleen, and lymph nodes should also be collected in 10% buffered-formalin for histopathological examination. Histopathological liver lesions are pathognomonic and, in particular, the hepatic lesions of new-born lambs leave little room for doubt about the diagnosis of RVF.



New-born lamb liver



Sheep liver

Differential diagnosis

Rift Valley fever, Wesselsbron disease and other arthropod-borne virus diseases tend to occur under the same climatic conditions. Rift Valley fever should be differentiated from Wesselsbron disease as both diseases can cause mortality in new-born lambs and kids and abortion in ewes. However, RFV is associated with much higher mortality and abortion rates than Wesselsbron disease.

Wesselsbron disease.
Severe icterus in a new-born lamb

Wesselsbron disease. Orange-brown discoloured liver
with congested patches in a new-born lamb

Agents causing mortality associated with hepatic lesions, haemorrhages and/or icterus which may superficially resemble RVF in domestic ruminants include poisonings by plants such as *Senecio, Crotalaria* and *Cestrum* spp. and an alga, *Microcystis aeruginosa* as well as bacterial septicaemias such as pasteurellosis, salmonellosis and anthrax. Nairobi sheep disease could also be confused with RVF.

A high percentage of pregnant sheep, goats or cattle may abort and diseases which must be eliminated by appropriate laboratory investigations include brucellosis, leptospirosis, chlamydiosis, salmonellosis, bovine viral diarrhoea, Simbu-group virus infections and Palyam virus infections.

Control

Vector control

A major factor contributing to the abatement of epidemics is the onset of cold weather which suppresses vector activity.

In southern Africa outbreaks tend to terminate abruptly soon after the first frosts of winter.
In contrast, virus activity may persist in those parts of Africa which experience warmer winters.
Vector control is of limited or no use in the control of RVF and immunization remains the only effective way to protect livestock.

Vaccination

Although the use of vaccine is beneficial in reducing losses, it is generally applied too late to avert epidemics or to prevent considerable losses from occurring.

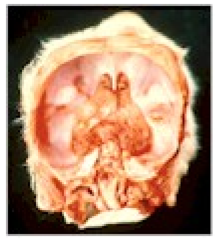
Epidemics of RVF tend to occur at irregular intervals of many years and it is usually difficult to persuade farmers to vaccinate livestock during long inter-epidemic periods. The occurrence of epidemics is difficult to predict and they usually have a very sudden onset. Hence it is advisable in African countries with large sheep and goat populations to immunize the offspring of vaccinated ewes and nannies on a regular basis at 6 months of age, when colostral immunity has waned, with a single dose of the modified live Smithburn vaccine. This should afford life-long protection. Lambs and kids of susceptible dams can be immunized at any age.

A range of anomalies of the central nervous system, including porencephaly, hydranencephaly and micrencephaly, as well as arthrogryposis and other defects in foetuses and hydrops amnii and prolonged gestation, may occur if ewes are inoculated with the modified live Smithburn strain vaccine between about 5 and 10 weeks of gestation. Its use in pregnant animals should only be contemplated in the face of an epidemic when its adverse effects may be outweighed by the dangers of allowing the disease to take its natural course. It is advised that only inactivated vaccines should be used when it is considered necessary to immunize animals in countries where the presence of RVF has not been proven.

In contrast to the live Smithburn vaccine, formalin-inactivated vaccines are safe for use even in pregnant animals, but they are expensive to produce and induce short-lived immunity, so that the administration of regular booster doses is necessary to ensure adequate protection.

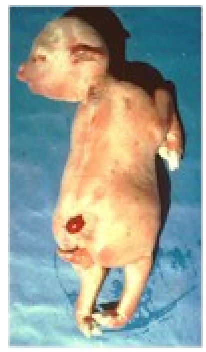
Hydrops amnii following inoculation with Smithburn vaccine

Ewe. Hydrops amnii. There may be up to 20 litres of fluid



Hydranencephaly
(mid-brain and medulla partially developed)

Arthrogryposis and anasarca



Arthrogryposis, anasarca and spina bifida

The live Smithburn RVF vaccine induces poor antibody response in cattle, and they should preferably be immunized with formalin-inactivated vaccine to ensure that cows are able to confer colostral immunity to their offspring. Cattle should receive a booster dose 1-2 months after initial vaccination, followed by annual boosters before the rains are due as immunity only lasts about one year.

Veterinarians and others engaged in the livestock industry should be made aware of the potential dangers of exposure to zoonotic agents in handling tissues of diseased animals, and precautions should be increased during RVF epidemics. Protective clothing such as gloves and masks should be used when doing necropsies on suspected cases of RVF or handling infected tissues. A formalin-inactivated cell culture vaccine produced in the USA has been used on an experimental basis to immunize persons such as laboratory and field workers who are regularly exposed to RVF infection.