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Recognizing Rift Valley Fever

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Introduction

Rift Valley Fever (RVF) is an acute arthropod-borne virus infection with a wide range of vertebrate disease hosts. This is a zoonotic disease problem. Until relatively recently, the range of RVF had been confined to the Ethiopian faunal region of Africa, but the disease was identified in Egypt in 1977 and in the Arabian Peninsula in 2000. The virus is a member of the Phlebovirus genus of the Bunyaviridae family. It is an RNA virus, which is related to some other members of the group by haemagglutination or by indirect fluorescent antibody tests at low titres and from which it may be readily distinguished by virus-serum neutralization tests. The virus is transmitted by mosquitoes of at least six genera and probably over 30 different species. It is transmitted transovarially by some of the Aedes spp. of the Neomelaniconium group of mosquitoes. These are floodwater breeding species, which emerge in enormous numbers in floodplains and other habitats where they oviposit.

The disease was first recognized and characterized in the Great Rift Valley in Kenya in 1931 - hence its name - although it may have occurred earlier. Several thousand ewes aborted and there was 90 percent mortality in young lambs. While the problem was first identified in sheep, cattle were also affected, although the abortion rates and mortality in calves were much lower. The affected animals were of breeds that had been imported from Europe or elsewhere into Africa to improve livestock production. Indigenous breeds on adjacent farms were unaffected. A further point of some interest was that humans associated with the affected animals suffered an influenza-like disease with fever, headaches and muscle and joint pains. The investigations carried out during this outbreak showed that the disease was being transmitted by mosquitoes. The movement of livestock to the top of the escarpment above the Rift Valley resulted in a cessation of transmission and no new cases of the disease since the location is at a much greater

The Rift Valley

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altitude with few insect vectors present.
Subsequently the disease has been recognized in an enzootic or epizootic form in many tropical and subtropical African countries, and in Madagascar. However, the absence of any livestock disease problems has resulted in few searches for RVF virus activity in many other countries in Africa. In some of these countries, clinical RVF has not been encountered, either in humans or animals, and yet there is evidence of the existence of a cryptic cycle for RVF virus maintenance involving mosquitoes and various vertebrate hosts. Sporadic human cases have sometimes been encountered.
Subsequent RVF epizootics were experienced in South Africa in the 1950s, when huge losses were sustained in the wool sheep populations, and subsequently in most of the neighbouring southern African countries. Epizootic RVF has been seen in the Sudan, at the Gezira irrigation scheme in 1973-74 and in Egypt in 1977-79 and 1993-94, where hundreds of thousands of human cases were reported, with at least 600 deaths. A highly fatal haemorrhagic syndrome was described in Egypt and also an ocular syndrome with macular degeneration, in some cases leading to blindness. There were enormous losses in sheep, goat and cattle populations, with abortion in camels. In Mauritania and Senegal, there was an epizootic associated with the creation of a barrage on the Senegal River in 1987-88. Both humans and animals were affected and, in this instance, neurological signs were detected in humans. In 1997-98, a major epizootic of RVF occurred, which affected countries in the Horn of Africa. There were hundreds of human cases, with some mortality, and abortion storms and neonatal deaths in domestic animals, including camels. This was probably the most dramatic episode of RVF ever encountered.

In 2000, RVF was recognized in humans and animals in the Arabian Peninsula. Both Yemen and Saudi Arabia simultaneously experienced an epizootic, which principally involved the Tihama region of the country, adjacent to the Red Sea. The Red Sea forms the floor of the Rift Valley in this region and the Tihama is the floor of the Rift in the east with an escarpment running from north to south 40-70 km inland. There were some 100 human fatalities and many thousands

Saudi Arabia: typical swamp area susceptible to mosquito breeding during the epidemic

of deaths and abortions in domestic animals.
RVF is one of the most significant zoonotic disease problems in Africa. The occurrence of the highly fatal haemorrhagic human disease syndrome, similar to Ebola and other haemorrhagic fevers, generates a degree of panic among the human populations at risk. RVF is highly contagious for humans if animals are viraemic at the time of slaughtering. However, one of RVF's greatest impacts is upon trade in livestock. Even if the disease tends to disappear after epizootics, livestock bans may last for several years, severely affecting the livelihood of pastoralists. Indeed, viraemic animals constitute

Trade of livestock between the Horn of Africa and the Arabian Peninsula (Port of Berbera, northern Somalia)

a serious hazard during epizootic periods and all trade in livestock from the affected countries and their neighbours ceases. In the pastoral regions of eastern Africa, incomes are almost entirely derived from the sale of mature male sheep and goats for the religious festivals in Mecca. Cessation of this trade has had disastrous effects upon the livelihood of highly vulnerable population groups.

RVF also has the potential to extend its range to other receptive regions to the north and northeast outside Africa, such as the Tigris/Euphrates Delta zone, which would be receptive for RVF virus transmission. Delta areas such as the Indus in the Indian subcontinent are also at risk. Aerial transport of vectors and increased animal movements facilitate the introduction of the disease.

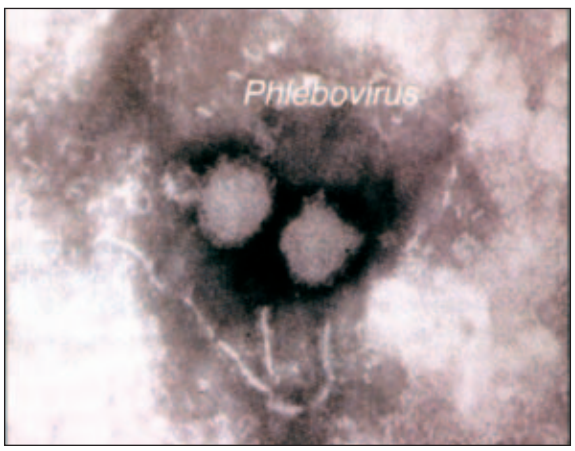
Nature of the disease

Rift Valley fever is a zoonotic disease, which affects humans, ruminants and camels. It may manifest itself as a fatal haemorrhagic disease syndrome in humans, either as sporadic cases or during a major epizootic involving animals.

There may also be many severe influenza/malaria-like cases, some with ocular or neurological lesions. Hepatitis is a feature of both human and animal RVF cases. In animals, RVF manifests itself with a sudden onset of abortion in a large proportion of the herd/flock,

CAUSES

- **An arbovirus**
- **Phlebovirus**
- **Bunyaviridae**
- **RNA virus**



RVF virus

associated with high neonatal mortality. Clinical examination of individual animals reveals a biphasic febrile reaction with severe prostration and collapse in young animals, agalactia in milk animals, lymphadenitis, debility with jaundice and deaths in older age groups.

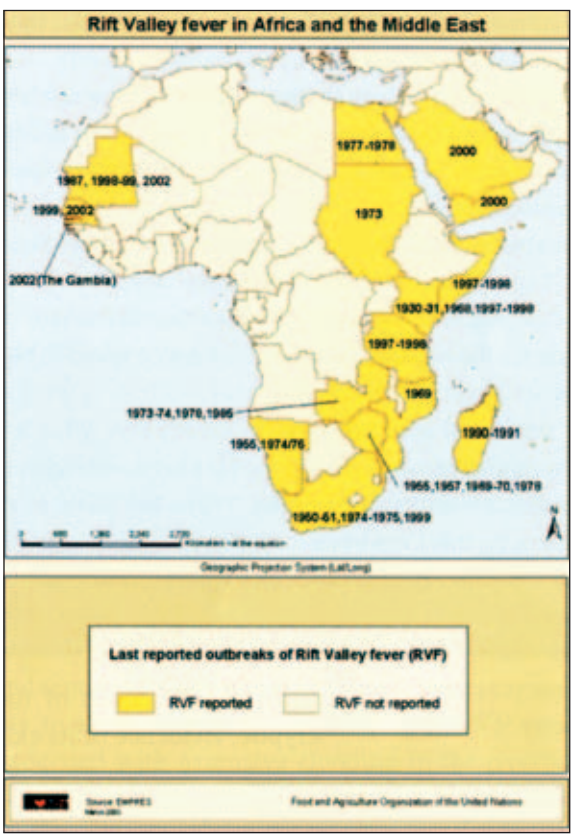
RVF is caused by an arbovirus of the genus *Phlebovirus* of the Bunyaviridae family. The virus replicates in mosquitoes and in vertebrates. It has a lipid envelope and two surface glycoproteins G1 and G2; the genome has three segments L, M and S. Genetic characterization suggests that all strains are closely related but there are some regional differences, suggesting two or three regional virus types. The RVF virus is serologically

resistant to RVF compared with cattle.
Human disease has frequently been the indicator system signalling epizootic RVF virus activity in many African countries. This is particularly the case in semi-arid and arid zones such as the Horn of Africa, Sahelian West Africa and the Arabian Peninsula.
Horses experience an infection that is inapparent with RVF. There is a brief period of viraemia and the antibody develops. Pigs are relatively non-susceptible, but do respond with a viraemia after a high titre parenteral inoculation with RVF virus. Poultry and wild birds are non-susceptible to RVF.

Geographic Distribution

Rift Valley fever has occurred in:

- the sub-Saharan region of Africa
- Egypt



Typical ecosystem close to the mountains where RVF was prevalent in Saudi Arabia in 2000

- the Arabian Peninsula - Yemen and Saudi Arabia
- Madagascar

The natural distribution of RVF is throughout the Ethiopian faunal region of sub-Saharan Africa. In Saudi Arabia and Yemen, the ecology of the RVF-affected Tihama regions (eastern Rift Valley zone) is identical with those of the west floor of the Rift Valley in Ethiopia and Eritrea, across the Red Sea. The occurrence of RVF in Egypt in 1977 was thought to result from movement of the infection from RVF enzootic areas in Africa to the south. This may or may not be the case. There are descriptions in the Bible of a plague in Egypt, which clinically appears very similar to RVF.
Throughout much of its range, RVF virus infection remains cryptic. Evidence of its existence may be found in sporadic cases of human disease, virus isolation from mosquito pools or serum antibody prevalence to RVF of 2-15 percent or more in domestic animals. Such virus activity takes place with no manifestation of clinical disease in these animals.

ANIMALS AFFECTED

- **Sheep, goats and cattle**
- **Camels**
- **Buffaloes (mild)**
- **Carnivores (dogs, cats) and rodents (viraemic)**
- **Other primates - usually subclinical**
- **Horses (inapparent)**

1977 outbreak in Egypt: petechial haemorrhages and hyphema in a woman's face

related, by Immunofluorescence Assay Test (IFAT) and inhibition of haemagglutination (IHA), to some other Phleboviruses from South America, but can be readily distinguished from these by virus-serum neutralization tests, which are specific. There is only one serological and immunological type of RVF virus.

Sheep, goats, cattle and camels are the domestic animal species most affected by RVF. However, there is considerable variation in the levels of susceptibility of the different breeds to the virus, from infections that are inapparent and have no sickness or febrile reactions, to high temperatures, severe prostration and death in animals that are most susceptible. In general, breeds that are non-susceptible are those indigenous to the tropical and subtropical zones in Africa, while those highly susceptible are the European or imported genotypes exotic to the continent. Birds and pigs are not affected.

The small ruminants in the arid and semi-arid ecozones, where RVF virus activity only occurs after long intervals, appear to be more susceptible than the sheep and goats in the Guinean and Sudanese zones of Africa. RVF virus activity occurs more frequently in the Sudan.

The indigenous cattle breeds show a marked resistance to RVF, compared with imported breeds. There may be no abortions in pregnant cattle in indigenous herds while there are high abortion rates in exotic breeds on the same farm.

RVF infection in adult camels can manifest itself as a clinical disease, with abortion rates that may reach 100 percent of pregnant animals. Some neonatal mortality may occur in camel foals.

Primates, rodents and carnivores are susceptible to experimental infections with some deaths, but no mortality has been observed in the wild.

The many wild ruminant species in Africa sustain a brief period of viraemia and abortions have been reported. The African buffalo (*Syncerus caffer*), for example, develops a transient viraemia and may abort. Many wild ruminant species have antibodies to RVF virus and show evidence of contact with the virus. The Asian water buffalo, *Bubalis bubalis*, appears to be relatively resistant to RVF, but specific antibodies to RVF have been documented. Buffalo herds mixing with cattle that evidence high abortion rates caused by RVF, have a much lower number of abortions. Some neonatal mortality and abortions in buffaloes were attributed to RVF during the Egyptian RVF outbreak. Although this may have been true, buffaloes still appear to be relatively

RVF manifests itself as a serious disease problem for livestock production systems in those countries where exotic breeds of sheep, goats and cattle have been imported. Such highly susceptible animals then act as an indicator host system for RVF virus activity, since they show obvious signs of disease. Regions such as East Africa (Kenya, the United Republic of Tanzania and Uganda) and southern Africa (Zambia, Zimbabwe and South Africa) have introduced such bloodlines and have been most severely affected. Many other neighbouring countries have also imported

ECOLOGICAL CONSIDERATIONS
THE WADI BIOTOPE IN THE ARABIAN PENINSULA

The Tihama describes the whole of the coastal plain in the Arabian Peninsula in the west and southwest of Saudi Arabia and Yemen. It consists of low hillocks bordering the north-south mountain chain. Wadis or river valleys occur in the Tihama and constitute the alluvial floodplains of the rivers as they emerge from the mountains. These soils are sands, loamy silts and clays, of very low salt content, with little humus or nitrogen. The first ecozone is of *Panicum* and *Cyperus* grasslands, which are seasonally flooded. In many areas, terraced catchments have improved the utilization of water from the rivers at these points. The second and larger zone borders the rivers as they proceed to the sea, and consists of *Acacia zizyphispina* and *Dobera* spp., with some grasses and bare earth. The riverine zones are characterized by the presence of *Dactyloctenium* grasses and are altered in some wadis by lateral canal systems extending north and south of the rivers. The rivers are seasonal in flow, largely fed by the mountain catchment areas, and are dry for much of the year. Towards the sea is a belt of land with a high salt content, planted with Salsola spp.

The Tihama biotope has been the focus of extensive agricultural development over the last 20 to 30 years as greater use is made of the available water resources for cultivation. These changes have a direct impact upon the environment, creating a more extensive habitat for RVF virus mosquito vectors. In Yemen, for example, the largest wadi (Wadi Mawr) covers some 18 000 hectares watered by the canal systems.

The methods used for the utilization of the spate flow in the wadis are very similar in Saudi Arabia and Yemen. Agriculture is practised in the riverine alluvial deposits and surrounding sandy soils. Water flow is directed by channel systems into field units, and new areas are flooded sequentially. Together with the rainfall, this results in many large and small water pools suitable as breeding sites for certain mosquito species.ù

The changes in the wadi systems, which have been made to ensure more effective use of the available water, are also those that favour the development of more extensive breeding sites for the mosquito species that are believed to be of greatest importance in amplifying and transmitting the RVF virus.

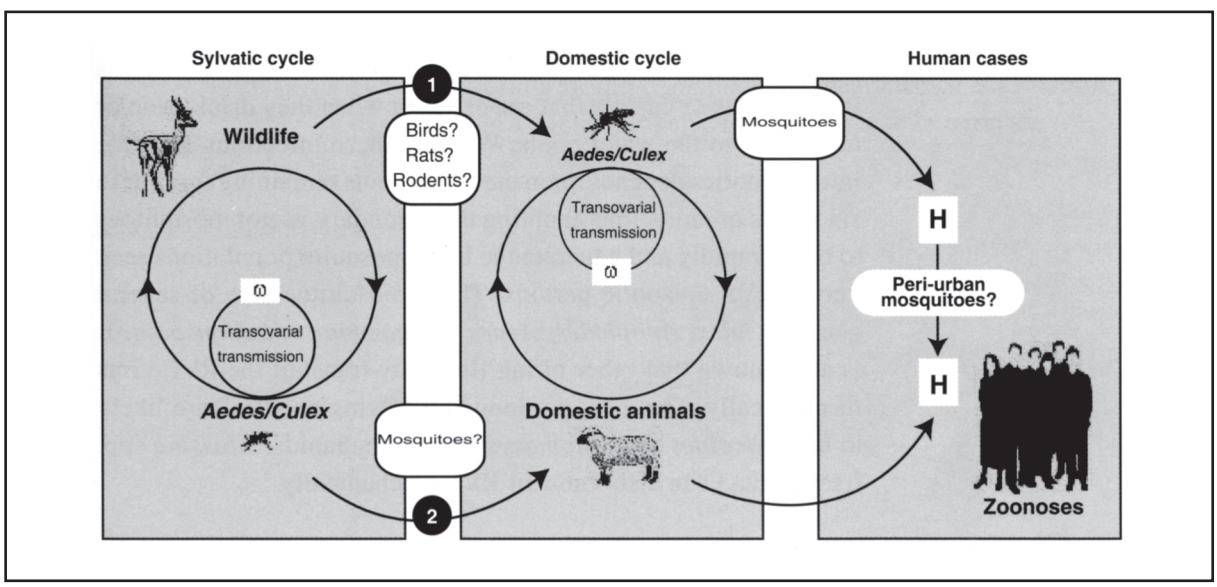
Additional ecozones where primary RVF virus amplification may take place following the emergence of *Aedes* mosquitoes are in the wet highland plateau grasslands planted with *Acacia combretum* and allied species. These are found in Thaiz and Ibb Governorates and possibly also in Sa'dah. The virus may also be expected to occur along the wadi river beds far up into the mountain zones, especially where these broaden out into alluvial plains with pockets of clay soil.

exotic ruminants at different times and have experienced RVF problems. Epizootic RVF disease also occurs in domestic animals in the arid and semi-arid Sahelian zones in the north and south of the continent; they appear to be more susceptible than those in bushed and wooded grasslands and forest zones. Animals, particularly sheep, goats and camels have been affected in the Sudan, Mauritania and Senegal. They suffer abortion storms but at lower levels than the exotic breeds - usually 5-40 percent abortion rates in small ruminants and low levels or no abortions in cattle. Some neonatal mortality may also occur.

Camels are probably the best animal indicator host system for RVF in the arid and semi-arid zones of Africa. Virtually all pregnant females are likely to abort if there is a high level of RVF virus amplification associated with extensive flooding in the riverine floodplains. Surveillance for RVF should be established in areas to the north of the existing epizootic range for the disease. Areas considered to be at high risk for the extension of RVF are the Tigris/Euphrates Delta in Iraq/Islamic Republic of Iran and all irrigation project zones in Arabian countries, whether wellhead, oasis or catchment systems for water conservation are utilized. Further east, the riverine delta systems in Pakistan and India may be considered potential extension zones for RVF, although at a lower level of risk than those mentioned above because of their greater distance from the enzootic areas and the prevailing wind currents and trade in animals.

CAUSES OF TRANSMISSION

- **By mosquitoes**
- **Primary vectors - *Aedes* spp. of the Neomelaniconium group**
- **Many secondary vectors - *Culex, Anopheles, Aedes (Stegomyia), Mansonia, Eretmopodites* species**
- **Some mechanical spread - *Culicoides* spp. and other biting flies**
- **Not spread by animal to animal contact**
- **Aerosol of blood from infected tissues such as foetuses/slaughtered infected animals, to humans**
- **Meat at time of slaughter**



Theoretical cycle of RVF virus transmission

Flooded dambo in Kenya

Transmission and spread

As stated previously, RVF is an arbovirus, transmitted transovarially by *Aedes* mosquitoes of the Neomelaniconium group. These mosquitoes breed in the temporary floodwater pools and floodplains that occur throughout the range of the Rift Valley. They are found in tropical forest, Guinean and Sudanese zones and out into the semi-arid and arid zones wherever these are associated with alluvial riverine floodplains. Flooding is clearly dependent upon rainfall patterns and occurs frequently in the moist high rainfall zones and infrequently in the arid and semi-arid zones. However, forest zones where annual or biannual emergence of RVF virus infected vectors may occur, do not have susceptible disease hosts to act as indicators of RVF virus activity. These are found principally in the bushed and wooded grasslands and semi-arid zones, which occur throughout the African continent to the north and south.

It is in the latter zones that RVF is an epizootic disease problem. Epizootic virus activity has been associated with periods of more than average persistent heavy rainfall. This raises the water table to a level where the water pans, *dambo, walo* or *dieri*, as they are called in different parts of the continent, are flooded. These floods last for several weeks. Riverine floodplains may be flooded as a result of distant rainfall in their catchment areas and not as a result of local rains. This flooding results in the emergence of a single generation of *Aedes* (Neomelaniconium) mosquitoes, such as A. *lineatopennis*, *macintoshi* and *vexans*. A proportion of these mosquitoes may be infected with the RVF virus and seed the virus in ruminants or camels that are exposed when they drink from or feed close to the water pools. Whether these infections generate into epizootics depends upon the water pools remaining for four to six weeks or more, thus enabling the secondary vector mosquitoes to breed rapidly and generate the huge mosquito populations seen during RVF epizootic periods. These mosquitoes are of several genera: *Culex*, *Anopheles*, *Aedes* (*Stegomyia*) and *Mansonia*. It is also known that other biting flies may transmit the RVF virus mechanically. The most predominant "flying needles" are likely to be *Culicoides* spp., *Stomoxys* spp. and tabanids. *Glossina* spp. (tsetse flies) can also transmit RVF mechanically.

Spread of RVF

The climatic conditions that predispose major RVF epizootics are likely to be of a regional nature. Determinants of climate such as the intertropical convergence zone (ITCZ) are continental features. This explains the simultaneous multifocal origin of RVF during the early days of an epizootic. The disease does not spread in the manner of classical contagious diseases. It occurs in several countries in a region at one and the same time. Some local spread may occur from the initial foci through the

movement of infected vectors, but epizootic RVF virus activity requires the presence of huge numbers of vectors and the potential for this to occur is clearly limited.

The disease persists for periods of 8-16 weeks, when the infection rate may decline and disappear. The full epidemic curve is often completed in 16-20 weeks in semi-arid and arid situations but cases may continue to occur for one to two years in more temperate coastal or moist highland areas.

RVF has not been known to spread by the movement of infected animals from infected to uninfected areas. However, in theory this could happen and has in fact been put forward as the mechanism for the occurrence of the disease in Egypt and the Arabian Peninsula, although there is no evidence to support this idea. The globalization of trade and the reduction in transportation times have also created new possibilities of disease spread that must be taken into consideration in the epidemiology of transboundary animal diseases.

Direct animal to animal or contact transmission of RVF has been difficult to demonstrate. There is no evidence from the field that this transmission route is significant in epizootics. Movement of a flock of infected and susceptible sheep away from the mosquito challenge results in the complete disappearance of RVF within days. RVF is a vector-propagated virus disease in animals.

Signs of Rift Valley Fever

RVF epizootics may develop after the climatic changes described in the previous chapter, usually associated with persistent heavy rainfall and flooding and subsequent occurrence of huge mosquito populations. The onset of disease is sudden and dramatic. The initial signs will depend upon the breed and genotype of the target animals. However, a sudden onset of abortions among sheep, goats, cattle or camels over a wide area is probably the most significant sign. There will also probably be sudden deaths and disease with many fatalities in all species, especially in the early post-natal period. Nearly 100 percent of young lambs of susceptible breeds may die. Older animals at one to four months may suffer an acute febrile disease with prostration and 10-40 percent fatalities. Adult animals in a milking herd show a febrile disease with agalactia. Some deaths occur, however, in all age groups. Young adult exotic sheep, for

CLINICAL SIGNS OF RVF

- **Sudden onset of abortion storms**
- **Up to 100 percent mortality in lambs under five to six days old**
- **High fever, lymphadenitis, nasal and ocular discharges in mature animals**
- **Profuse fetid diarrhoea (often haemorrhagic)**
- **Vomiting, abdominal colic**
- **Severe prostration, dysgalactia, jaundice**
- **Epizootic period of 8-16 weeks**

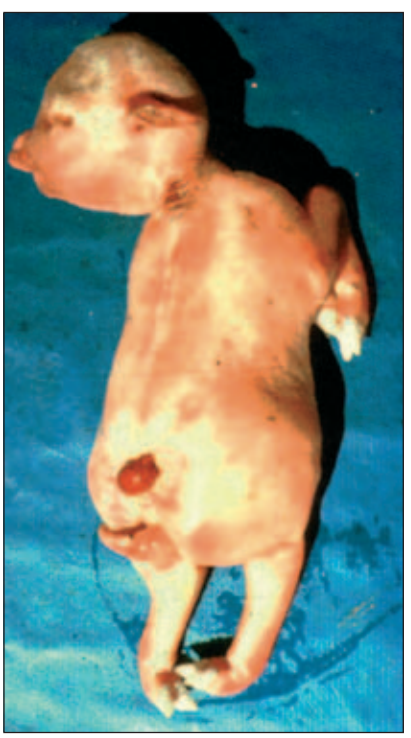
Ewe aborting as a result of RVF

example, may die with acute hepatitis and jaundice. The simultaneous occurrence of an influenza-like disease among people working with livestock is an additional feature of RVF epizootics.

It should be noted that resistant genotypes of indigenous African cattle and sheep often show no clinical signs of illness, despite having a brief period of viraemia. However, in some situations the cattle or sheep will have abortions that may be wrongly diagnosed. The abortion rate may reach 30 percent of the flock in small ruminant species, but is rarely more than this in indigenous breeds.

RVF in sheep and goats

The clinical signs of RVF in sheep and goats have been classified into four groups according to the severity of the disease. These are hyperacute, acute, subacute and inapparent. Each group is considered separately. In general, goats are less severely affected than sheep, with much lower morbidity and mortality, with fewer abortions and less severe clinical signs.



Abortion resulting from RVF infection

Hyperacute RVF

Susceptible sheep breeds may suffer 90-100 percent abortion during periods of intense RVF virus transmission in epizootic situations. Some 80-100 percent of lambs under ten days of age, which are born during such periods, die from RVF. Most deaths are sudden and occur within 12 hours after the onset of a pyrexia (40-42°C). Collapse and death are all that may be seen. Other lambs may be depressed, too weak to suckle or stand, and die within 24-48 hours, without showing clinical disease other than fever, an elevated respiratory rate and prostration.

Acute RVF

Older lambs, from two to three weeks of age and all susceptible breeds, may show severe clinical signs with high fever and an elevated respiratory rate, mucopurulent or sero-sanguineous nasal discharges, injected conjunctivae, vomiting and often abdominal pain.

A generalized lymphadenitis and gait abnormalities may be detected. Animals are disinclined to move, become recumbent and often develop a haemorrhagic diarrhoea, and abortion. Deaths occur after 24-48 hours and may continue throughout the flock for up to ten days. Mortality rates may be from 10 to 60 percent. Sick and recovering animals generally show moderate to severe signs of jaundice.

Subacute RVF

This is more frequent in adult animals. A febrile reaction develops of 40.5- 42°C and persists for one to five days. Anorexia, injected conjunctivae, nasal discharges, vomiting and other signs are seen but are generally less severe than in young animals. Abortion is a feature, as is diarrhoea. The colic may be less obvious, there may be

some lack of coordination of movement, animals are weak or recumbent for several days but most recover. Many will be jaundiced and may remain unthrifty and weak for several months. The mortality rates are of the order of 5-20 percent.

Inapparent RVF

This occurs in older or resistant animals. There may be transient periods of fever, which are not detected. The fever may be accompanied by depression or a brief period of inappetence, which are unremarkable. These infections are only detected by subsequent serological testing. Abortions may, however, follow such infections.

RVF in cattle

Hyperacute RVF

Calves under ten days of age may suffer from this form of the disease and die within 20-24 hours with few, if any, premonitory signs. Signs that may be observed are sero-sanguineous nasal and lachrymal discharges, an elevated respiratory rate and a temperature of 41.5-42°C. Total prostration occurs with the animal lying on its side, with opisthotomus and progressively greater respiratory distress. The course of the disease is rapid and death occurs within 48 hours. Up to 70 percent mortality has been experienced in genetically susceptible breeds.

Acute RVF

Older calves, yearlings and even adult animals show a high febrile reaction of 41.5-42°C, nasal and lachrymal discharges that may be blood-tinged, partial or total anorexia, some depression and possibly prostration. The animals may have colic with a profuse fetid haemorrhagic diarrhoea that persists for several days. A moist cough may develop with evidence of respiratory distress and rhales. The superficial lymph nodes generally become enlarged and there is a dysgalactia in milking animals. Animals may haemorrhage from the mouth or nose. Abortion commonly occurs. The temperature reaction and sickness may persist for three to ten days during which many animals die. Jaundice develops subsequently and, if this is severe, further mortality occurs.

Animals of any age, from three months to mature adults, may show all or some of the above signs and experience mortality, most commonly in the younger age groups. Mortality varies from 10 to 40 percent, depending on the age groups exposed. From 5 to 10 percent mortality has been experienced among older cattle of susceptible genotypes.

Subacute RVF

Older cattle generally show a less obvious response to RVF, which may be manifest as a brief period of temperature rise, with nasal and lachrymal discharges and a dysgalactia of three to seven days duration. There may be a brief period of profuse watery diarrhoea, often accompanied by colic. Some respiratory signs may be noticed, a raised rate and a moist cough with some rhales. Abortion is perhaps the most common consequence and this may occur during the acute phase of the disease or up to six to eight weeks later. Some deaths may occur. A persistent ill thrift may follow such mild infections, which is usually associated with moderate to severe jaundice and liver damage. Photosensitization is a common sequel to RVF virus infections.

Inapparent RVF

RVF is usually inapparent in the majority of the adult susceptible and indigenous bovids in Africa, which are relatively resistant to RVF. Abortion may follow this infection in the susceptible genotypes but is rare in the indigenous animals in the classical RVF enzootic zones of the continent. This is the most common

presentation of RVF in epizootics, where only a retrospectively noted fall in milk production, abortions and serological testing reveal the true extent of the infections.

RVF in camels

Camels do not normally show any clinical signs following RVF infections and fall into the inapparent infection group. They have a brief period of viraemia. Abortion is a common consequence of the infection, however, and pastoralists complain of "all their camels aborting". The infections can be confirmed serologically. Deaths do occur in the early post-natal period in camel foals born during RVF epizootic periods, probably as a result of RVF.

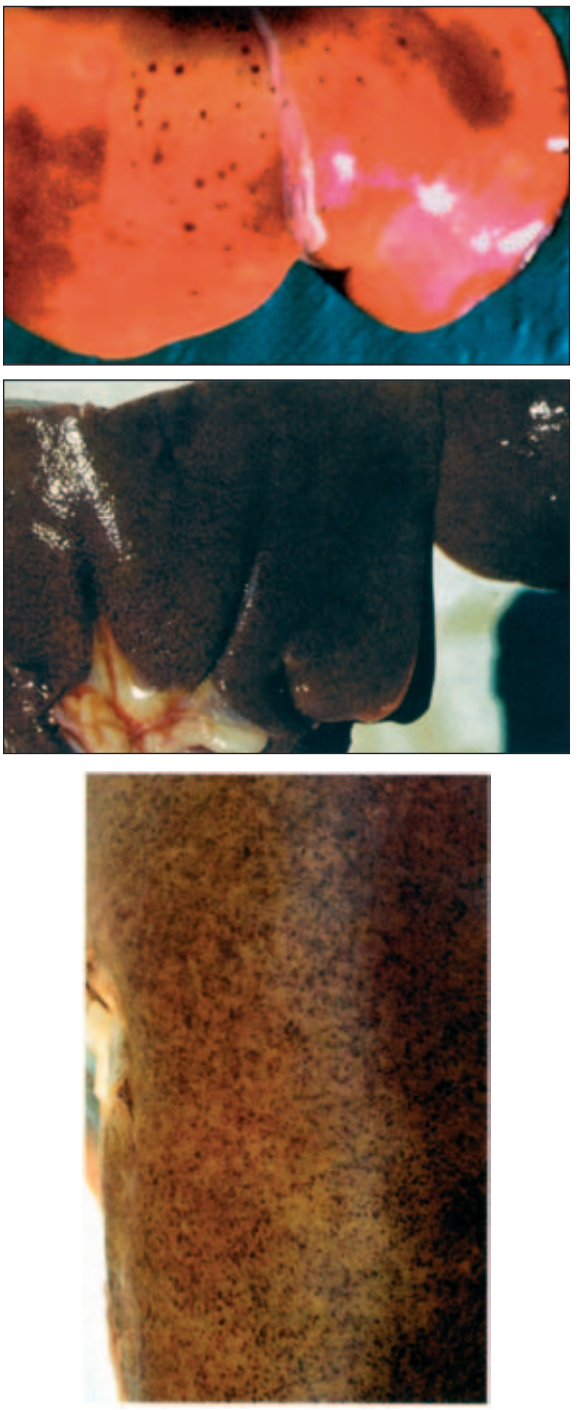
RVF in wild ruminants

Wild ruminants do not manifest any clinical signs of RVF during epizootics of the disease, which may be affecting domestic animals in shared grasslands. However, they develop antibodies to the virus and may even abort, following inapparent infections, yet this is difficult to demonstrate in the field. The African buffalo, Syncerus caffer, has a viraemia for two days following experimental inoculation, and buffaloes may abort if pregnant.

Clinical pathology

- Leucopenia
- High blood levels of enzymes associated with liver damage
- Thrombocytopenia

A viraemia persists over the period of the biphasic temperature reaction and possibly also after this has declined. There is a profound leucopenia associated with RVF infection, which is most obvious in the early period of the infection. Severe liver damage results in high serum levels



Hepatic syndrome, vasculitis and necrosis of the liver. Gross lesions of acute RVF in mouse liver specimens. Similar lesions are seen in other species

of the enzymes associated with this pathology, e.g. glutamic dehydrogenase (GLDH).

Postmortem signs of RVF

- Liver enlargement and necrosis, initially focal then often pannecrosis
- Liver congestion, then later a bronze to yellow colour
- Petechial and ecchymotic haemorrhages throughout the carcass
- Often severe haemorrhagic gastroenteritis
- Generalized lymphadenopathy
- Pulmonary oedema and emphysema
- Similar pathology in foetus, with autolysis

Haemorrhage and bloody discharge from nostrils

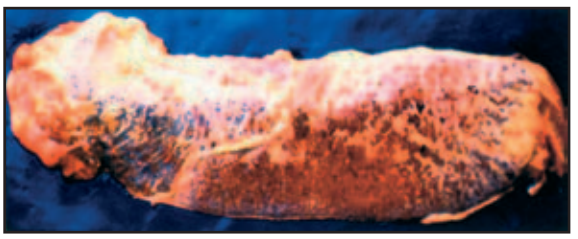
Intestine showing petechial haemorrhages on the serosal surface

Mucosal haemorrhages in the abomasum

Haemorrhagic and oedematous lymph node

The most important pathological changes are to be found in the liver. The severity of the lesions that develop will depend upon the age group and susceptibility of the animals affected. They are likely to be more severe in young lambs and less severe in older animals.

Hepatic necrosis is present in all RVF carcasses, for the lesions develop early in the course of the disease. In the early stages the liver is congested, swollen and engorged with rounded edges and many scattered petechial haemorrhages. Later, the necrosis may be evident as small 1-3 mm foci, which coalesce to form larger areas of necrosis and these changes involve



Varying levels of liver necrosis produced by RVF infection

the whole of the liver.

There may be widespread petechial and ecchymotic haemorrhages throughout the parenchyma and visible in subcapsular tissues. The necrotic changes induce jaundice and a stage is reached when the liver has a bronze appearance as the congestion, necrotic areas and icterus develop. At later stages the liver will be completely yellow with jaundice.

Petechial and ecchymotic haemorrhages may be found throughout the carcass in lambs. They are especially noticeable on the serosal and pleural surfaces of the body cavities, and on the heart, gall bladder, kidneys, bladder and other organs. There may be some bloodstained ascitic fluid.

The alimentary tract usually shows some level of inflammation from catarrhal to haemorrhagic and necrotic. The serosal surfaces may have haemorrhages and also the mucosal lining of the bowel, particularly of the abomasum and small intestine and ileo-caecal areas.

The lungs may be congested with oedema and emphysema and subpleural haemorrhages are commonly found. The heart will show subepicardial and endocardial haemorrhages. There is a generalized lymphadenopathy involving the superficial and visceral lymph nodes. These are oedematous with petechial haemorrhages.

The spleen may or may not be enlarged with subcapsular haemorrhages.

Similar changes will be found in the foetuses, particularly of the liver where various levels of necrosis will be seen. There is also a necrotic placentitis.

Differential diagnosis

- **Nairobi sheep disease - no hepatitis, not in newborn lambs**
- **Bluetongue - mouth and foot lesions (coronitis)**
- **Heartwater - serous fluids in body cavities; neurological signs**
- **Ephemeral fever - recumbency and rapid recovery**
- **Wesselbron - rare viral disease, less severe than RVF**
- **Toxoplasmosis, leptospirosis, brucellosis, Q fever, salmonellosis - basic diagnostic methods for differentiation**
- **Peste des petits ruminants - high mortality in lambs**
- **Foot-and-mouth disease - neonatal mortality and abortions in small ruminants**

Single cases of RVF can be confused with many viral diseases, which cause sudden death in sheep and produce generalized lymphadenopathy and petechial and ecchymotic haemorrhages throughout the carcass. However, RVF manifests itself in a dramatic fashion with the following:

- a sudden onset of many abortions at all stages of pregnancy; these may affect an extensive area or be countrywide
- an acute febrile disease with high fatality rates in young animals
- liver lesions are present in all cases
- associated with high mosquito populations and/or flooding of grasslands

- may be associated with an influenza-like disease in humans.

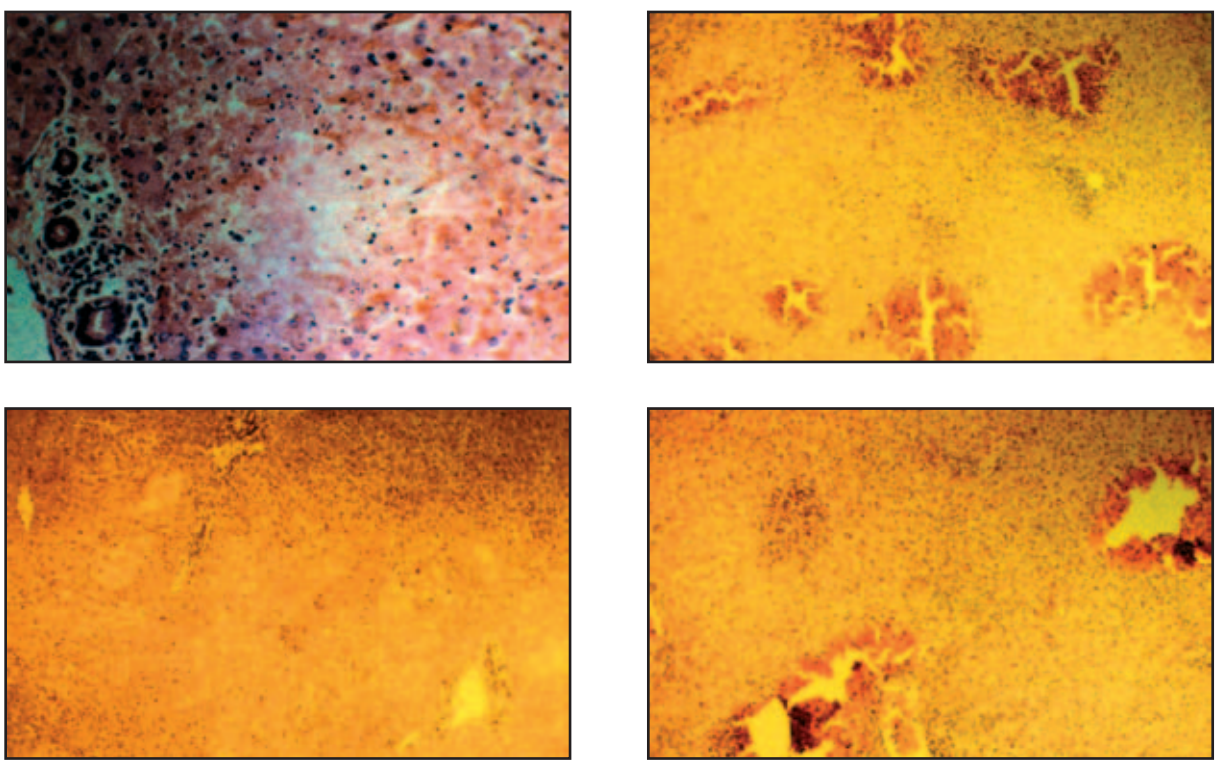
The diseases that may be manifested in this manner are described below.

Nairobi sheep disease causes abortions, high fatality rates and produces gastroenteritis in sheep and goats. This does not show a higher pathogenicity for neonates, however, which is a feature of RVF, and while it does cause abortions, these and the clinical disease are of a more sporadic nature. Deaths are usually in older animal age groups, and the carcasses have similar haemorrhages, but there is no hepatitis.

Bluetongue causes a febrile disease often with diarrhoea, but also causes muzzle oedema and mouth lesions, which will be obvious in some cases. Hyperaemia and erosion of the buccal mucosae, lameness and coronitis with skin hyperaemia will assist in making a clinical differentiation. Sudden deaths at the viraemic stage produce generalized petechial and ecchymotic haemorrhages, which on postmortem appear similar to RVF. There is no hepatitis.

Heartwater can cause sudden death with lymphadenopathy and generalized haemorrhages throughout the carcass. There is no hepatitis and usually the fluid in the serous cavities will be excessive and obvious. Neurological signs can be seen. Brain smears can be prepared to make a definitive diagnosis.

Ephemeral fever produces a clinical syndrome in dairy cattle that is very similar to RVF. There is a sudden onset of fever of a similar nature to RVF but generally more severe. The dysgalactia that occurs is the same, together with nasal and ocular discharges. However, the muscle weakness and recumbency, which are a feature of ephemeral



Varying levels of liver necrosis produced by RVF infection

fever cases, do not occur with RVF. Ephemeral fever does not produce any disease in sheep, goats or young cattle.

Wesselbron virus has been confused with RVF in South Africa, where it appeared to produce similar lesions and occurred in similar circumstances. This has not presented a problem elsewhere in Africa, nor in subsequent epizootics in South Africa.

Toxoplasmosis, leptospirosis, brucellosis, Q fever and **salmonellosis** all feature as possible differential diagnosis for RVF. However, they are not present in such an explosive manner over large areas simultaneously. They are not associated with rainfall, nor do they produce such high neonatal mortality. Good supportive laboratory competency is required to make a diagnosis.

Diagnosis of RVF

RVF antigen detection

- Agar gel diffusion test
- Virus isolation in mice/hamsters/tissue culture
- RT-PCR identification of RVF virus
- Capture ELISA test
- Immunochemical staining of fixed tissues

RVF antibody detection

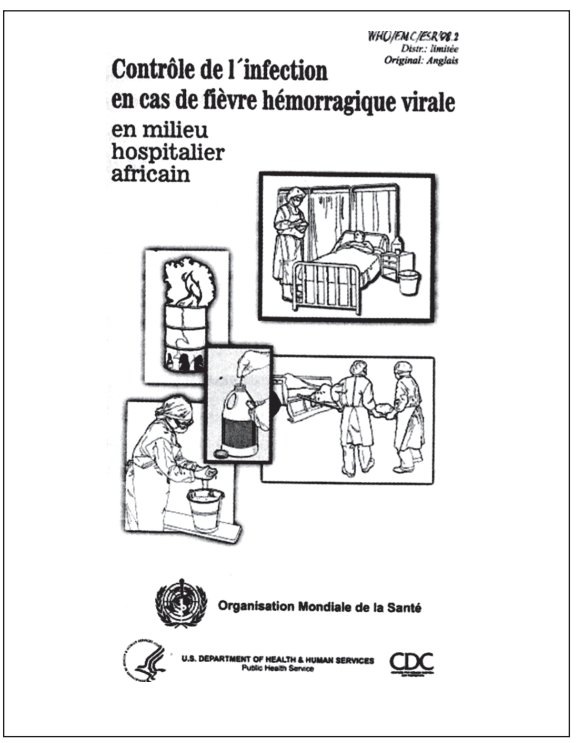
- ELISA tests for IgM/IgG
- Indirect immunofluorescent/peroxidase tests
- Microtitre virus-serum neutralization tests
- Indirect haemagglutination tests
- Plaque reduction assays

The International Office of Epizootics (OIE) *Manual of standards for diagnostic tests and vaccines* contains guidelines on the collection of samples and the diagnostic techniques for diagnosis of RVF infection.

RVF should be suspected if there is a sudden onset of large numbers of abortions in cattle, sheep, goat or camel populations associated with a high neonatal mortality and the presence of liver lesions. Cases of disease in people associated with the affected animals also assist in making a tentative diagnosis. A provisional diagnosis may be based upon the clinical picture, climatic and ecological factors such as the presence of huge mosquito populations, together with the explosive nature and onset of the disease.

Laboratory confirmation of RVF

RVF is a member of the human haemorrhagic fever group of viruses, such as Ebola and Crimean Congo haemorrhagic fevers. These viruses present a serious hazard to all personnel handling infected carcasses, blood and other tissues both in the field abattoir and in the laboratory. For this reason it is recommended that field veterinarians and laboratory personnel be vaccinated against RVF, if this is possible. The handling of RVF infected material should only



Control of infection in case of haemorrhagic fever in African hospitals

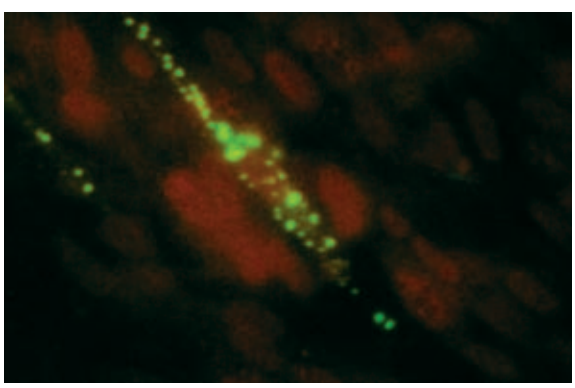
be carried out under P-2/P-3 conditions or with type II biosafety cabinets and HEPA filtered respirators, where the security of the staff can be assured. For this reason, the appropriate diagnostic procedures are dependent upon the facilities available.

Diagnostic tests

There are two types of test. The first is to identify or isolate the RVF virus or antigen and the second to demonstrate the presence of rising titres of RVF specific antibody or IgM. The test system chosen will depend upon the facilities available that can be safely used.

Detection of RVF virus/antigen

- A simple agar gel double diffusion test, with test tissue (liver or spleen) and with RVF positive and negative control antigens and immune sera
- Antigen capture ELISA test systems are available for the RVF virus antigen
- RT-PCR (reverse transcription-polymerase chain reaction) identification of the RVF virus
- Virus isolation in suckling or weaned mice, or hamsters by intraperitoneal inoculation (mice and hamsters die within three to four days)
- Virus identification in tissue culture - the RVF virus may be identified in culture within 12-36 hours by immunofluorescent or peroxidase staining of the fixed cells
- Cryostat sections of formalin fixed tissues and staining for RVF by immuno-histochemical methods
- Histopathology of the liver showing characteristic RVF hepatic necrosis with intracytoplasmic and intranuclear inclusion bodies.



RVF virus antigen in cell cultures 24 hours post inoculation with specimens for diagnosis

Detection of specific antibody to the RVF virus

- ELISA system for IgM antibody
- ELISA system for IgG antibody
- Microtitre virus-serum neutralization tests in tissue culture
- Plaque reduction tests in tissue culture
- *Indirect immunofluorescent test
- *Indirect haemagglutination test

(*These tests may detect low titre cross-relationships with other Phleboviruses, but high titre positives will be specific, i.e. 1/160 to 1/320 or greater).

Specimen collection for RVF diagnosis

Refrigerate but do not freeze.

- Blood in EDTA or heparin
- Aliquots of liver, spleen or lymph nodes on ice
- Similar tissue specimens in buffered formalin
- Foetal liver and spleen on ice
- Clotted blood for serum for serological testing (decant serum or remove clot before sending)

All tissue samples should be transported preferably in a phosphate buffered saline/glycerol suspension. Samples in buffered formolin may be transported in unfavourable conditions for many days without any deterioration. See the OIE *Manual of standards for diagnostic tests and vaccines* for further details.

What samples should be collected in an outbreak?

At an outbreak site, where sheep, cattle or camels are aborting and there are deaths in neonates, it
is suggested that the following samples be collected:

- at least 10-20 serum samples from animals that have recently aborted
- 10-20 samples from animals that have not aborted
- blood in anticoagulant from any animals with a fever of 40.5-42°C
- liver and spleen from any freshly dead animals, on ice, in glycerol buffered saline and/or in buffered formalin
- liver, spleen and brain from fresh foetuses

What information is required?

The following basic information should be collected:

- sampling site with map reference or full address
- owner's name, contact address, telephone, etc.
- herds/flocks/breeds/strains affected, numbers and age groups
- date of first case/date sampling
- no affected/no dead/no abortions/age groups
- full clinical history
- presence/absence of febrile human disease
- basic ecological characteristics of affected area

Prevention and control of Rift Valley Fever

Early detection of RVF is a prerequisite to effective control of the disease. Sentinel herd monitoring has been used in different parts of Africa to monitor viral circulation in susceptible populations. It can be enhanced by the additional monitoring of climatic parameters (see: *Towards early warning for RVF prevention: satellite imagery*, p. 35).

Sentinel herd monitoring

Activities should be directed towards active disease surveillance in order to build up baseline information on inter-epidemic virus transmission patterns, areas at risk and early warning of any increased virus activity or buildup in vector mosquito populations. This surveillance should be carried out by regular field visits and contact with livestock farmers and communities and

Sentinel herd monitoring in Mali

should include periodic purposefully designed and geographically representative serological surveys and participatory epidemiological techniques. The detection of RVF virus activity by serology is usually too late to be of any relevance for control.

Sentinel herds are an important means of obtaining baseline epidemiological information on RVF. These are small ruminant herds located in geographically representative areas. Locations where mosquito breeding activity is likely to

be greatest, e.g. near rivers, swamps and dams, should be selected. Such mosquito breeding sites are typically shallow depressions that are flooded during prolonged periods of rainfall and along irrigation channels.

In order to be effective and more reliable, sentinel herds should be monitored in conjunction with the monitoring of other risk indicators such as climatic parameters (see paragraphs below).

Once herds have been identified, livestock owners are informed about the background and the importance of the study and asked for their cooperation. Incentives such as free antiparasitic drugs for internal parasites should be provided during each visit to ensure the owner's cooperation. If possible, no acaricides, pour-on or insecticides should be provided since their application will influence the attack rate of the animals from potential arthropod vectors.

About 30 young female sheep or goats (with two permanent incisors) are identified and permanently marked. Choosing young females reduces the probability that these animals are slaughtered or sold between visits. The animals should be at least one year old, ideally between 12 and 15 months. At the first visit, blood samples are collected from the animals and tested for IgG antibodies and IgM antibodies to the RVF virus. Only antibody negative animals should be included in the sentinel herd. If some of the animals are seropositive they should be excluded from the monitoring exercise and replaced by seronegative animals.

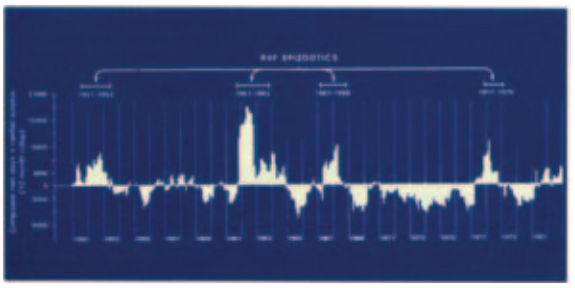
Sentinel herd monitoring in Mauritania

The sentinel herds should be visited at regular intervals. Ideally, animals should be sampled at the beginning of the rainy season and thereafter every four to six weeks up to the end of the rainy season. In a typical year this would involve four or five visits to each herd. At each visit some basic information is obtained and blood is collected from all the sentinel animals. Samples should be forwarded to the National Central Veterinary Laboratory and tested within two days of arrival for the presence of IgM and IgG antibodies.

Attempts should be made to keep the size of the sentinel herd above 20 animals at each location. This means that during most visits it will probably be necessary to identify new animals since some animals of the established herd may have died or have been removed for other reasons. If animals have seroconverted they will also be excluded during the next visit and replaced by new fully susceptible animals. The principle here is to maintain at any time a basic number of animals (sheep and goats) that are well identified and fully susceptible to RVF infection at the locations prone to the emergence of RVF epidemics, and to follow these animals closely through clinical and serological investigations to detect the emergence of RVF epidemics in time.

Towards early warning for RVF prevention: Satellite imagery

The three essential prerequisites for an epidemic to occur are a susceptible livestock population, a massive buildup in the populations of vector



Correlazione tra epizoozie di RVF e persistenza delle piogge

mosquitoes and the presence of the RVF virus. Assuming the continuing presence or at least the close proximity of the virus in regions where the disease has occurred previously, the first two factors become the key to early forecasting of likely RVF activity.

Early work on forecasting was centred at a study site in Kenya where ground truth data for RVF virus activity had been generated for many years. Periodic outbreaks of RVF over a 40-year period were found to correlate with the positive value of a statistic based upon the number of rain days and the quantity of rainfall.

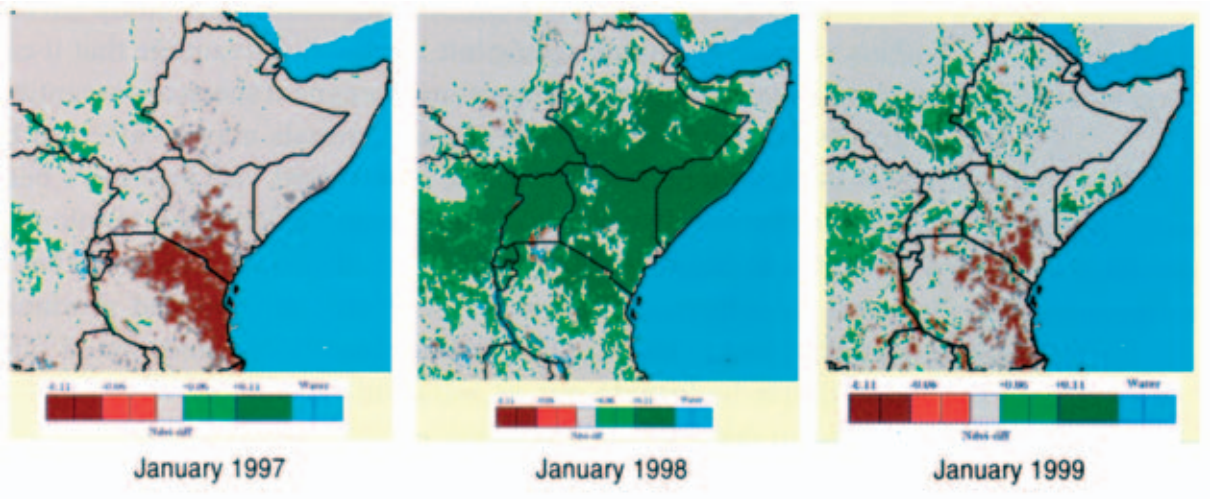
Correlation of RVF epizootics with the persistence of rainfall

The three-month rolling mean value formed a positive spike when RVF virus activity occurred and this was a function of cumulative persistent rainfall, rather than heavy precipitation over a short period. Data were based upon longitudinal rainfall data generated and recorded in the old-fashioned manner. The characteristics of the intertropical convergence zone were also important as a determinant of prevailing conditions conducive to RVF virus activity. These data allowed forecasting of RVF outbreaks with a four to ten week period during which vaccination could be carried out before cases occurred.

More sophisticated studies were possible when remote sensing satellite data (RSSD) became available. These data enabled national and regional monitoring of rainfall and climatic patterns and their effects upon the environment. Cold cloud density (CCD) measurements are closely correlated with rainfall and have replaced the laborious daily collection of rainfall data from many stations. Climatic patterns are regional in East Africa and the Horn of Africa and may be studied on this basis. A detailed analysis was made with virus isolation data over a 25-year period and the normalized differentiated vegetation index (NDVI) for the study areas. NDVI data are derived from probes measuring relative "greenness" and "brownness" of the vegetation. As the water table rises to the point where flooding may occur, the ratio approaches 0.43 to 0.45. This point was reached at each of the epizootic periods in the study period.

More recent retrospective studies using the same ground truth data have included the surface sea temperatures (SST) for the Indian and Pacific Oceans. When these were combined with NDVI data, they approached 100 percent accuracy in predicting periods of RVF virus activity during the study period. This has a pre-epizootic predictive period of two to five months before virus activity occurs.

New statistics have been derived from satellite data, known as basin excess rainfall monitoring systems (BERMS). These measure rainfall in the catchment areas of river/wadi systems and are based upon digital maps of basin and river networks. They can predict periods when flooding might occur, which is particularly valuable for the floodplain zones in the Horn of Africa countries and the Arabian Peninsula. Early data suggest that BERMS might be able to predict virus activity five months before its occurrence.



Maps representing NDVI difference in January 1997, 1998 and 1999

The advantages of RSSD for RVF predictive epidemiology are in the relatively low costs of the systems used for analysis. These are readily available on a country and regional basis and give time for preventive measures such as the vaccination of susceptible stock and mosquito larval control methods, wherever possible.

International agencies are best placed to analyse satellite and other data and to provide risk countries with early warning about likely weather patterns conducive to increased RVF activity. FAO, through its Global Information and Early Warning System on Food and Agriculture (GIEWS) and the Emergency Prevention System for Transboundary Animal and Plant Pests and Diseases (EMPRES)/Livestock Programme intends to take a central role in generating these data on a continuing basis, thus providing an early warning/risk assessment service.

It must be recorded that little work has been done in other parts of Africa to validate the RSSD systems because the ground truth data have not been available and it takes many years of dedicated work to generate such data. Recent outbreaks in Somalia and northeast Kenya in 1997-98 showed retrospectively that the foci of RVF virus activity in these countries could be correlated with high NDVI values. However, more validation work is needed before the use of such techniques becomes an operational early warning system (see maps representing NDVI difference in January 1997, 1998 and 1999).

Control strategies

Preventive vaccination

This is the most effective means to control RVF. Early warning of high-risk periods for the disease is possible and this information should drive strategic vaccination campaigns. The most effective vaccine is the modified live Smithburn neurotropic strain (SNS). This vaccine is immunogenic but has the disadvantage that it can cause foetal pathology and abortion in pregnant sheep of susceptible genotypes. Up to 30 percent of such animals may be affected by abortion or foetal abnormalities. Inactivated vaccines have been prepared but are often poorly immunogenic. Onderstepoort Biological Products in South Africa produce an inactivated vaccine that is based on a bovine virulent RVF isolate,

adapted and produced in cell culture. The vaccine is then inactivated and mixed with aluminium hydroxide gel as adjuvant. It has the advantage of being suitable for use in pregnant ewes. Given the poor antibody response in cattle, the inactivated vaccine is recommended even in cows so that they can confer colostral immunity to their offspring. A booster three to six months after initial vaccination is required, followed by annual boosters.

Routine vaccination when animals are not pregnant is recommended. The SNS vaccine is perfectly safe and protective in cattle. Vaccination is NOT recommended once evidence of epizootic virus activity has been confirmed. Apart from being too late, needle propagation of the virus is a real danger.

Vaccine development

Other modified live virus and molecular derived RVF antigens are being developed, but are not currently available for field use.

- The MP 12 strain was developed by mutagen induced changes in the ZH 548 strain of the RVF virus and Clone-13 is a cloned population, obtained from a field strain isolated from a mild human case in the Central African Republic. Both have been shown to be good immunogens in mice, and produce antibodies detectable by ELISA and plaque reduction neutralization assays. The Protective Dose (50 percent) (PD 50) for Clone 13 was 100.1 TCID50 and for MP 12 was 103. The S segment of the RVF virus determines virulence/loss of virulence and the NSs deletion results in attenuation. The role of NSs has been elucidated: it is an antagonist of type I interferon production. Indeed, infection of mice with strains that possess an efficient NSs does not lead to any production of interferon, whereas high levels of interferon were observed in mice infected with the NSs defective Clone 13 virus. Clone 13 is of interest because of the low risk of reversion in this virulence/attenuation marker. However, the L and M segments do not contain markers for attenuation. If animals are vaccinated when virulent strains are circulating, there is a possibility that reassortment may occur; in this case Clone 13 would induce a viraemia (which is not observed in mice). The majority of reassortants could become virulent.
- An R566 strain has been derived from Clone 13 and MP 12 by reassortment in Vero cells: it contains the S segment of Clone 13 and the L and M segments of MP12, which contain seven and nine point mutations compared with their virulent parent. Some of them induce attenuation and thermosensitivity. Thus R566 is safe, because of its attenuation in the three segments of the genome. R566 has been shown to protect mice in the laboratory.

Vector control

Strategic larvicidal treatment of mosquito breeding habitats is recommended. Both hormonal inhibitors such as methoprene and larvical toxins such as those produced by *Bacillus thurigiensis* give excellent results and both are commercially available. However, they may be difficult to use in some places with floods of wide distribution. The widespread use of vehicle or aerial mounted ultra low volume insecticide sprays appears to have limited effect upon RVF transmission rates or the target adult mosquito species.

Movement controls

These do not appear to have any effect upon the course of an outbreak within an infected country. They may, however, be relevant to the movement of animals for trade from

enzootic/epizootic areas, where RVF virus transmission is occurring. In this situation, viraemic animals could arrive in an uninfected country within the incubation period for the disease. If this should happen and there were large numbers of mosquito vectors present, capable of RVF virus transmission, then the possibility of introduction of RVF is very real. For this reason, all export of livestock should be banned during RVF epizootic periods.