Infections by viruses of the families
Bunyaviridae and Filoviridae

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Summary

Rift Valley fever is the most important bunyaviral disease of animals in Africa. The virus, transmitted by mosquitoes, causes abortions and mortality in young animals in addition to haemorrhagic fevers in humans. Although vaccines against this virus are available, the uses of these vaccines are limited because of deleterious effects or incomplete protection, justifying further studies to improve the existing vaccines or to develop others. Nairobi sheep disease is transmitted by ticks. The disease is endemic in East Africa and sporadic cases are reported in India and Sri Lanka. Other viruses transmitted by mosquitoes or midges are teratogenic in cattle or sheep, these include Akabane and related viruses in Asia, Australia and the Middle East, and Cache Valley in North America. The Marburg and Ebola viruses of the genus Filovirus are associated with epidemics in Central Africa with high fatality rates in humans; some outbreaks were related to contact with monkeys. Another subtype of Ebola virus was first described in a quarantine facility in the United States of America among cynomolgus monkeys (Macaca fascicularis) from the Philippines. The reservoir of these viruses remains unknown.

Keywords


Introduction

The Bunyaviridae family comprises more than 300 members grouped into five genera named Bunyavirus, Hantavirus, Nairovirus, Phlebovirus and Tospovirus, the latter is composed of viruses infecting plants only (32). With the exception of hantaviruses, a genus of viruses which is transmitted by rodents and which is described in a separate paper in this volume (14), members of the family Bunyaviridae are transmitted by arthropods, more specifically by mosquitoes, ticks, phlebotomines and biting midges (24) (Table I). Although most of these viruses infect a variety of vertebrate hosts, including laboratory animals (mice, hamsters and rats), which are widely used for virus isolation, only a few are responsible for zoonoses. The most important of these is Rift Valley fever (RVF) virus which is transmitted by mosquitoes to livestock in Africa. Most of the other viruses have a common tropism for foetal tissues and cause embryonic and foetal death, stillbirths and multiple congenital malformations. These viruses belong to different genera and serogroups and are widely distributed. Among members of the genus Bunyavirus, Akabane from the Simbu serogroup is found in Australia, Asia and the Middle East, and Cache Valley from the Bunyamwera virus serogroup is present in North America. Among members of the genus Nairovirus, Nairobi sheep disease circulates in East Africa and India. In addition to these viruses, Crimean-Congo haemorrhagic fever virus was reported to infect domestic animals which became a source of contamination for humans (52). This virus is widely distributed throughout Africa, the Middle East, southern Europe and Asia, and is transmitted by ticks to livestock and birds such as ostriches. The infection is asymptomatic in animals but the virus is highly pathogenic in humans, resulting in haemorrhagic fevers with possible nosocomial infections. The main sources of human contamination are infected tick bites or infectious aerosols produced by viraemic animals in slaughterhouses (49, 52).

Rift Valley fever and Crimean-Congo haemorrhagic fever viruses are highly pathogenic, causing lethal haemorrhagic fevers in humans, thus generating serious public health problems. Viruses belonging to other families are responsible
for similar haemorrhagic manifestations, for example, yellow fever and dengue viruses in the family Flaviviridae, Lassa and South American haemorrhagic fever viruses in the family Arenaviridae, and Marburg and Ebola viruses in the family Filoviridae. In common with hantaviruses, arenaviruses are transmitted by rodents which are chronic carriers of these viruses and represent an excellent reservoir. The host reservoir for filoviruses is still undetermined, although filovirus-infected monkeys have been documented. Zoonoses associated with these viruses will be presented in the last section of this paper.

**Bunyaviridae**

**Rift Valley fever**

Introduction and history

Rift Valley fever was first described near Naivasha in the Rift Valley of Kenya in 1931 by Daubney et al. (9), who isolated the causative viral agent which was classified later as a member of the genus Phlebovirus of the family Bunyaviridae. Major outbreaks were recorded in Kenya in 1968, 1978-1979 and 1997-1998, in addition to southern Africa, South Africa, Zimbabwe, Zambia and Madagascar (30, 36, 47). The RVF virus was isolated for the first time in 1974, in West Africa, from *Aedes* mosquitoes. Later, the virus was also detected in Mauritania, Mali and Guinea. Circulation beyond the sub-Saharan countries was not reported before 1977, when a sudden and dramatic outbreak occurred in Egypt; the virus reappeared in the same region in 1993. Manifestations of the virus were observed in Madagascar in 1990-1991, in Kenya, Tanzania and Somalia in 1997-1998, and in Mauritania in 1998. A recent study indicated that the viruses circulating in Madagascar in 1990 and in Kenya in 1997 were closely related (42).

**Importance for animal and public health**

The disease was first described as an enzootic hepatitis with extensive necrosis, leading to the rapid death of new-born lambs. During a notable epizootic of RVF in South Africa in 1950 and 1951, 100,000 sheep died and 500,000 aborted. Before the epidemic in Egypt in 1977, RVF was essentially known as a disease which affected domestic animals, especially sheep, cattle and goats, producing high mortality in new-born animals and abortions in pregnant animals, with only a few fatal human cases reported. However, since 1977, outbreaks have not only caused great economic losses in livestock, but humans have also been affected by the disease. Infections in humans occur after contact with infected animals or mosquito bites. The disease has a wide variety of clinical manifestations, generally beginning as an influenza-like illness which is usually without sequelae, however in some cases, severe complications, such as meningitis, encephalitis and fatal haemorrhagic fevers, are observed. In 1977, between 18,000 and 200,000 human cases were estimated to occur in Egypt, with 600 recorded deaths from encephalitis and/or haemorrhagic fevers. In 1987, 224 people died from RVF virus in Mauritania. An estimation of the number of human and animal cases of RVF in 1997-1998 in East Africa was difficult due to the circulation of numerous pathogens, however, more than 89,000 humans were infected, indicating that this was probably the most important epidemic recorded (3).

**Aetiological agent and classification**

Rift Valley fever virus was classified as a member of the family Bunyaviridae and the genus Phlebovirus (19, 45). Negative staining revealed enveloped particles, measuring 90 nm to 110 nm in diameter, which are composed of a tripartite single-stranded ribonucleic acid (RNA) genome and four structural proteins consisting of two glycoproteins, G1 and...
G2, a nucleoprotein, N, and an RNA-dependent RNA polymerase, called the L (large) protein (Fig. 1). The three segments of the genome which are associated with multiple copies of the N protein and a few copies of the L protein form the inner circular and helical ribonucleoproteins. In common with all the enveloped viruses, RVF virus is sensitive to ionic and non-ionic detergents, hypochlorite and common disinfectants. The N protein appears as the major antigen during infection. The envelope glycoproteins G1 and G2 carry epitopes which induce neutralising antibodies which were shown to play an important protective role against infection.

The complete genome of RVF virus has been sequenced, indicating that the L (large) and M (medium) segments are of negative polarity and the S (small) segment utilises an ambisense strategy, expressing the N protein and the non-structural protein coded by the S segment (NSs) proteins from the antigenomic and genomic stranded RNA, respectively. As is the case for all the viruses of this family, the viral particles mature by budding through the membranes of the Golgi apparatus. Exceptions to this rule were reported in infected rat hepatocytes and in epithelial cells of the midgut of infected mosquitoes, where budding from the plasma membrane was observed (2).

**Epidemiology**

In addition to contamination by contact with infected tissues, RVF virus is generally transmitted by mosquito bites. Numerous strains of RVF virus have been isolated from various species of mosquitoes, including Aedes, Culex and Mansonia, in addition to Culicoides, and occasionally from ticks. The occurrence of epidemics or epizootics following periods of heavy rains or in association with the building of dams, for example, in Aswan in 1977, or on the Senegal River in 1987, appears to be related to particularly dense populations of mosquitoes (Fig. 2). Analysis of records of rainfall and vegetation index data, coupled with satellite observations demonstrated that outbreaks could be predicted up to five months in advance in East Africa (27). During inter-epidemic periods, the virus is maintained in nature via transovarial transmission in mosquitoes, as shown in Aedes lineatopennis in Kenya and in Ae. vexans in Senegal (54). Recently, infection of Aethomys namaquensis rodents by RVF virus has been reported; these rodents were able to propagate the virus and might be involved in a vertebrate-mosquito cycle, thereby constituting a possible reservoir for the virus in South Africa (38).

Phylogenetic analysis of strains of various geographical origins isolated from different hosts (humans, animals and mosquitoes) which was performed during epidemics/epizootics or during endemic/enzootic periods, indicated the existence of three lineages, namely: Egyptian, West African and East-Central African (43). Extended analyses performed by sequencing regions in the three genomic segments, strongly suggested that some of the strains were generated by genomic reassortment between phylogenetically different viruses, indicating that RVF viruses of different origins were present at the same time and location and had co-infected mosquito or vertebrate hosts.

**Biology of infection**

In new-born lambs of less than one week of age, the mortality rate is 90%. The incubation period may be as short as twelve hours, but usually lasts from 24 h to 36 h, after which the animal develops a high fever, exhibits abdominal pain and dies within 24 h to 36 h of the onset of the first clinical signs. Older animals exhibit various clinical signs, from inapparent to peracute or acute infection; the latter form is the most frequent under field conditions. Sick animals exhibit fever, anorexia, nasal discharge, bloody or foetid diarrhoea and, in
Enzootic  Epidemic

Fig. 2
Rift Valley fever virus cycle involving mosquitoes, animals and direct transmission to humans

some cases, a severe icterus. For pregnant animals, abortion may occur at any stage of pregnancy. Abortion rates are usually very high, ranging from 40% to 100% in southern Africa, or 80% to 100% in Egypt in 1977. Mortality rates of 10% to 30% or higher, have been recorded in adult cattle and sheep, depending on the nutritional state of the animal.

In humans, RVF is usually benign, resulting in fever, headache and myalgia, followed by a complete recovery. However, in some cases infection progresses to severe and sometimes fatal complications, such as retinitis, encephalitis and haemorrhagic fever with acute hepatitis. The latter was observed in 1% of the cases in Egypt in 1977.

Pathogenesis
The disease affects primarily the liver, with rapid hepatocellular changes progressing to massive necrosis. In some animals, haemorrhages are observed in the liver. Experimental infections of susceptible animals have helped to understand RVF pathogenesis more fully. Infections of mice, hamsters and some strains of rats, by peripheral routes with virulent strains, lead to a transient viraemia followed by an acute hepatitis and death. In other strains of rats, RVF virus infection provokes encephalitis. Some other strains are completely resistant with asymptomatic infection (1). Resistance was shown to be governed by a dominant Mendelian gene. Rhesus monkeys (Macaca mulatta) represent an excellent model for human infection. These animals exhibit a variety of clinical symptoms, including haemorrhagic forms with disseminated intravascular coagulation.

Diagnosis and surveillance
Since epizootics or epidemics of RVF are usually preceded by heavy rains, a high density of mosquitoes and frequent abortions in sheep and cattle, these criteria should be considered as an indication of the possible circulation of the virus. Liver lesions found by histopathological examinations provide a good indication of RVF infection. When infected liver sections are observed under electron microscope, many hepatic cells appear disorganised with nuclei containing rod or fibre-like structures composed of NSs protein. During an outbreak, a clear demonstration of the presence of the RVF virus must be obtained by virological and serological methods. Isolation of the virus after inoculation of suckling mice, or in Vero cells, is considered to be the method of choice. Diagnosis can also be performed by detection of RVF virus-specific immunoglobulin M (IgM) or IgG in animal or human sera as the presence of IgM indicates a recent infection. The enzyme-linked immunosorbent assay (ELISA) is widely used in reference laboratories and preferred to the previously established methods of complement fixation, inhibition hemagglutination and plaque-reduction neutralisation. More recently, detection of the viral genome by reverse transcriptase polymerase chain reaction (RT-PCR) amplification has been developed and was found to be very useful for rapid diagnosis. This technique could be followed by sequencing to characterise the strains further.

Prophylaxis and treatment
On account of the economic importance of the disease in sheep and cattle, efforts have been made to produce a veterinary vaccine. The Smithburn neurotropic strain was...
obtained by intracerebral passages of the virulent strain, Entebbe, in suckling mice and embryonated eggs (46). However, the strain was not attenuated completely since this live attenuated vaccine is still neurotropic and provokes a range of anomalies of the central nervous system in foetuses, such as porencephaly, hydranencephaly and microencephaly. Vaccination of ewes may also result in abortion and still birth. Teratogenic effects associated with vaccination have been reported in up to 15% of pregnant ewes. For this reason, other attenuated strains have been produced or isolated. One of these, the mutagenised strain MP12, which was derived from a virulent strain isolated in Egypt in 1977, appeared to be a good candidate because of the presence of attenuating mutations in each of the three segments of the genome (6, 44). However, although this virus was an efficient immunogen in adult and young animals, deleterious effects were observed after vaccination of pregnant ewes in the first three months (B. Erasmus and D.H.L. Bishop, personal communication). Recently, a naturally attenuated strain, clone 13, which was isolated from a benign human case, was found to be highly immunogenic for mice. Interestingly, this RVF virus possesses a large deletion in the gene coding for the non-structural NSs which seems to be an important determinant for attenuation (51).

In terms of treatment, administration of antibodies, interferon, interferon inducer or ribavirin in mice, rats or monkeys which had been experimentally infected with RVF virus, was demonstrated to be efficient in protecting against the disease (35).

Perspectives
Recent epidemics in East and West Africa have emphasised the importance of irrigation and rainfall in the re-emergence of the virus, in addition to a risk of importation from Africa. Since mosquitoes play an important role in viral transmission and propagation, means for mosquito eradication should be implemented. Of utmost importance is the control of the circulation of the virus during entomological or serological surveys or virus isolation from captured mosquitoes or sentinel herds. To this end, methods for rapid detection of the virus by immunocapture-ELISA or RT-PCR amplification have been, or are in the process of being, developed. Vaccination of at least the most susceptible animals, i.e. sheep, cattle and goats, would also prevent or reduce circulation of the virus and contamination of humans.

Akabane and related teratogenic viruses
Introduction and history
Akabane is the major cause of epizootics of congenital malformations in ruminants in Japan and Australia. The virus has also been identified in the Republic of Korea, Taipei China and the Middle East (Israel and Oman), and sporadic outbreaks have been suspected in other countries. Biting midges and other blood-sucking arthropods transmit the virus to vertebrates (41). Akabane was first isolated from mosquitoes in Japan in 1959, but association of the virus with disease was recognised during epizootics from 1972 to 1974 in Japan, when 42,000 calves out of a population of 3.6 million were premature, stillborn or deformed. Another large outbreak was recorded in 1974 in Australia, when 3,000 calves died. In the 1950s and 1960s, epizootics with similar pathology were reported in Japan and Australia, but the aetiological agent was unknown. Other viruses related to Akabane in Japan or Australia are involved in teratogenic disease, namely: Aino, Tinaroo, Douglas and Peaton. Antigenic and genetic comparisons of some of these viruses suggest evidence of natural virus reassortants. Antigenic and genetic comparisons of some of these viruses suggest evidence of natural virus reassortants (4). Molecular studies have not shown variations between strains with different virulence.

Epidemiology
Cattle, sheep, goats, buffalo and horses appear to be infected by the Akabane, Aino and other related viruses. Antibodies to Akabane virus were reported in pigs in Taipei China, Indonesia and the Philippines, and in horses in Thailand. Other serological surveys have demonstrated antibodies to Akabane virus in domestic animals in Malaysia, the Republic of Korea, Japan, South Africa, Kenya, the Sudan, Cyprus, Syria and Turkey. In Kenya, a wide range of wild ruminants were found to be carriers of Akabane antibodies (waterbuck, impala, wildebeest and zebra). Pigs appear to be infected by Peaton virus in Australia, but not by the other four viruses. These viruses do not cause disease in humans.

Akabane and related viruses have been isolated in healthy domestic ruminants in several countries, but rarely from aborted foetuses or affected animals, as reported in Japan, Australia and Taipei China. The virus is eliminated from the mother and foetus long before the results of damage are detected. In non-pregnant animals, the infection is hardly noticeable. Although the disease also occurs naturally in sheep, the true economic impact has not yet been evaluated.

Several months after the period of viral transmission, epizootics of disease are revealed when calves or lambs are close to term. Shorter gestation in sheep (five months), compared with the gestation period in cattle (nine months), could restrict the vulnerability of sheep.

Akabane and related viruses have been recovered from mosquitoes such as Culex tritaeniorhynchus and Ae. vexans in Japan, or Anopheles funestus in Kenya, and from biting midges, principally Culicoides brevitarsis, in Australia, C. oxystoma in Japan and C. imicola in South Africa and Oman. In Australia, the presence of Akabane and the other teratogenic viruses is related to the area of distribution of C. brevitarsis in the north and east of the country. Climatic factors influence the seasonal activity and geographic range of the vector population. In addition, the presence of C. brevitarsis has been reported from Papua New Guinea, the Solomon Islands, New Caledonia and Fiji.
The destruction of neuronal cells appears to be a significant feature of the pathogenesis of central nervous system lesions due to viral infection. The disease has been reproduced in ruminants in Japan and Australia. Inoculated animals seroconvert rapidly after a short subclinical viraemia. Infection is of consequence only if ruminants are pregnant and are not protected by previous specific neutralising antibodies. Akabane, Aino, Douglas and Tinaroo viruses have been shown to cross the placenta. Experimentally-infected ewes became viraemic, with virus replication in the trophoblastic cells of the placenta. Subsequently, foetal membranes and tissues were infected with a tropism for immature cells of the foetal central nervous system and skeletal muscle, inducing necrotising encephalomyelitis and polymyositis. In surviving foetuses, multiple abnormalities may be described as arthrogryposis, hydranencephaly, microencephaly, cerebellar hypoplasia, irregular neuromuscular development with atrophy and neural degeneration of muscles and deformed skeleton. The severity of brain damage can range from microscopic to severe cavitation atrophy and eventually a complete absence of the cerebrum. Spinal cord lesions are always present. Late gestational infections cause inflammation in the brain and spinal cord, premature birth, or foetal death with stillbirth or abortion. Without assistance, females unable to deliver deformed full-term foetuses may die. Many calves with little more than the brain stem intact may be born alive. Affected neonates are non-viable (7).

A correlation was found between the gestational age of the infection and birth defects. The earlier foetal infection occurs in gestation, the more severe the lesions, reflecting the lack of foetal immunocompetency in the earlier stages of pregnancy. Infection from week eleven to fourteen after conception caused hydrencephaly or microencephaly, from week fifteen to twenty-four, arthrogryposis, and from week twenty-five to thirty-three, polioencephalomyelitis. The infection of embryonated chicken eggs is also used as a convenient model for experimental studies. Induced lesions are very similar to those found in congenital abnormalities in calves with a variety of malformations (26).

Diagnosis
Diagnosis is performed by serology, viral isolation and antigen detection. The damaged foetus or neonate does not normally contain virus. Viruses are isolated from the blood of healthy cattle, and rarely from affected cattle or foetuses (50). The blood is inoculated to mosquito cells, or via the intracerebral route, into suckling mice. The virus may be adapted to various mammalian cell cultures including Vero or baby hamster kidney (BHK)-21 cells. An ELISA can be used for specific identification of viruses (5). Virus-specific neutralising tests are necessary to establish the specific aetiology.

Prevention
The only risk factor relevant to disease is pregnancy. Killed vaccine against Akabane virus has been produced and has been used to prevent disease by protecting susceptible cows during pregnancy in areas at great risk. However, this is not always justified economically.

Nairobi sheep disease
Nairobi sheep disease (NSD) is a viral disease which is one of the most pathogenic for sheep in East Africa. In 1910, the cause was identified from sheep in quarantine in Nairobi, Kenya, as a filterable agent. The virus is transmitted trans-stadially and transovarially by *Rhipicephalus appendiculatus* ticks. The infection in sheep, and to a lesser extent in goats, causes an acute haemorrhagic gastroenteritis resulting in mortality rates exceeding 90% in susceptible populations. The disease has been observed in Kenya, Uganda, Somalia, Rwanda and Tanzania (10). Outbreaks are often related to movements of non-immune herds in endemic areas. The virus belongs to the genus *Nairovirus* and is now recognised to be indistinguishable from *Ganjam*, a virus isolated from *Haemaphysalis intermedia* ticks in India and Sri Lanka, which causes a similar disease in sheep and goats (34). Occasional cases of human disease, with pyrexia, headache and abdominal pains, have been described in laboratory workers.

Pathology
The disease in sheep is characterised by a febrile illness with peak temperature reaching 41°C two to three days after onset, and persisting for up to eight days. Animals stand with the head down and are disinclined to move. Symptoms include anorexia, injection or cyanosis of the conjunctiva, a rapid respiratory rhythm, and sometimes a nasal discharge. Mucous and blood-tinged diarrhoea appear one to three days after onset, with abdominal pain. Death can occur at any stage after the onset of the disease. In postmortem examination of early deaths, unspecific congestion of most organs and petechial and ecchymotic haemorrhages have been described (11).

Epidemiology
Sheep and goats are the principal hosts of the disease. In areas of Kenya, Tanzania and Uganda where *R. appendiculatus* is common, several clinical forms have been observed, and NSD antibodies have been detected in sheep sera. In enzootic areas, rapid immunisation of young animals may occur while the animal is protected by maternal antibody and challenged by tick exposure. Movements of susceptible animals in endemic areas result in clinical cases and death. In experimental infections, susceptibility differed according to the animal species. East African hair sheep are highly susceptible with mortality reaching 75% compared to 30%-40% for some imported sheep. Cattle and other domestic animals are not susceptible to the virus. No clinical cases of NSD have been identified in wildlife, and no antibodies have been recorded in wild ruminants.
The true range of NSD remains to be established. The geographic distribution of the disease includes Kenya (highland plateau and coastal regions), Uganda, Rwanda (Lake Kivu), Ogaden in Somalia, and northern Tanzania. The disease may also exist in the south-east of Ethiopia. Some serological NSD cross-reactions in sheep sera from Namibia and Botswana have been observed. The distribution of *R. appendiculatus* tick populations is influenced by the climate, in particular the temperature and the intensity and duration of the rainfall. Variations in *R. appendiculatus* tick populations with a seasonal breeding cycle, as observed in south Tanzania, Zambia and Mozambique, could act as a biological barrier to NSD virus transmission. A temperature range of 19°C-30°C and humidity over 45% are necessary for tick maturation (10). The distribution also includes India and Sri Lanka where the virus was recovered from *H. intermedia* ticks and, in sporadic cases, from animals. Introduction of the disease from India to East Africa, via sheep and goats, has been suggested.

The persistence of the virus in tick populations has been demonstrated. Vertically infected *R. appendiculatus* larvae remained infective 245 days after hatching, nymphs 348 days after molting, and adults 81 days after incubation (10). The virus was also isolated from *Amblyomma variegatum*. This species is capable of transmitting the virus trans-stadially, but is a far less efficient vector. Another tick species, *R. pulchellus*, may occasionally transmit the virus.

**Diagnosis**

The virus can be isolated from the plasma of infected animals during the febrile phase and from the spleen and mesenteric lymph nodes after death. The virus may be recovered by inoculating BHK-21 clone 13 cells, which produces a cytopathogenic effect within two to four days. Viral antigen can be detected by immunofluorescence 12 h-24 h post inoculation. Vero cells are reported to be less sensitive to viral infection. The virus can also be isolated in suckling mice following inoculation by the intracerebral or intraperitoneal route. Other techniques are available, such as the direct detection of viral antigen in tissues, amplification of fragments of the viral genome using suitable primers and amplification by RT-PCR.

**Prevention**

Epidemics of NSD are caused by the introduction of a non-immune population into endemic areas, the introduction of infected ticks into a receptive area, or ecological changes which extend the tick vector distribution into non-endemic areas. Tick control has been attempted, but is difficult to maintain and is very costly.

**Other bunyaviruses of animal importance**

In 1987, Cache Valley virus, a bunyavirus member of the Bunyamwera serogroup, was described as a causative agent of disease in sheep in Texas, United States of America (USA) (12). The clinical, pathological and immunological features were similar to those reported for Akabane virus infection. The virus is endemic in North America (Canada, USA and Mexico) and has been isolated from several mosquito species, including *Culicoides inornata*, *A. quadrimaculatus*, *Ae. sollicitans* and *Ae. albopictus*.

Experimental infections in sheep and goats provide signs of central nervous system disturbances. Cache Valley virus causes embryonic and foetal death, stillbirth and congenital malformations, arthrogryposis and hydranencephaly. The disease has been reproduced by experimental infection (8). Human infections are not uncommon although the effect on pregnancy is unknown.

In experimentally infected ewes, other bunyaviruses, for example, Main Drain from the Kari serogroup, and San Angelo and La Crosse from the California serogroup, have been shown to induce teratogenic effects identical to those described in ovine infections by Cache Valley and Akabane viruses (13). Main Drain is also associated with encephalomyelitis in horses. Viruses from the California group are transmitted by mosquitoes and are distributed primarily in North America. These viruses generally produce subclinical or mild infection associated with central nervous system involvement in humans. La Crosse virus, transmitted mainly by *Ae. triseriatus*, induces classical acute encephalitis in children, sometimes with sequelae, such as epilepsy, occasionally leading to death during the acute phase (20). In chipmunks and squirrels, the natural hosts of La Crosse virus, the virus produces non-symptomatic infection with a viraemia, thereby allowing blood-sucking mosquitoes to be infected. Domestic rabbits are used as sentinels for surveillance (33). San Angelo virus, which was primarily isolated from *Anopheles* mosquitoes in 1958 in Texas, has not been associated with clinical illness in humans and the natural host remains unknown. Large gaps of knowledge remain with regard to the real importance of these diseases in local livestock.

Other bunyaviruses have some importance for human public health, although natural infections of wild and domestic animals have not been associated with disease. Wild rodents and marsupials are implicated as the main vertebrate hosts of Group C bunyaviruses which induce benign febrile illness in humans and are mostly distributed in the Amazon region of South America. In Africa, bunyaviral fevers with headache and arthralgia have been reported in humans but no natural disease has been demonstrated in animals.

**Filoviridae**

**Introduction**

Filoviridae are the causative agents of diseases with high mortality in primates. Two biochemically and genetically distinguishable types exist, namely: Marburg and Ebola. Marburg virus was first isolated during an outbreak in Europe in 1967, and Ebola virus in 1976 as the causative agent of two.
different outbreaks in the Sudan and the Democratic Republic of the Congo. Transmission by intimate contact between individuals seems to be a major route of infection. Another Ebola subtype was identified in 1989, in a quarantine facility in Reston, USA, among dying monkeys imported from the Philippines. The natural reservoir of these viruses remains a mystery (29).

**Aetiological agents**

The virions of filoviruses have a particular bacilliform morphology with filamentous particles of 800 nm to 1,000 nm in length and a uniform diameter of 80 nm, hence the name of the viral family. The virus possesses a helicoidal capsid, an envelope and seven major structural proteins. The genome is composed of a single negative strand of linear RNA which requires a polymerase for transcription before replication (15).

**Epidemiology**

In 1967, in Marburg, Germany, and in Belgrade, Yugoslavia, epidemics resulted in thirty-one cases of infection with Marburg virus, including six secondary cases and seven deaths, among laboratory workers in contact with African green monkeys (*Cercopithecus aethiops*) from Uganda, or with monkey primary cell culture suspensions. Sporadic cases were reported in humans from Zimbabwe in 1975, and Kenya in 1980 and 1987 (29). A main focus of Marburg disease was confirmed in May 1999, in the north-eastern province of the Democratic Republic of the Congo, with tens of deaths, mainly among miners working in a gold mine in the Durba area.

Ebola virus was first described in Central Africa in 1976. An outbreak occurred in July 1976 in south-western Sudan (Nzara, Maudi) and two months later in Yambuku, in the northern region of the Democratic Republic of the Congo, with very high mortality (318 cases, 280 deaths) (25). The origins of primary contamination remained unknown, but poor sanitary conditions in the local hospitals led to the spread of the virus. In 1994, in Côte d'Ivoire, an ethologist working in the Tai National Park noted several deaths in a troop of chimpanzees. She contracted the disease and symptoms commenced with fever, progressing to diarrhoea and rash, eight days after performing an autopsy on a chimpanzee. High mortality in chimpanzee colonies of the surveyed area was reported in November 1992, and in November 1994 when 25% of a group of forty-three wild chimpanzees died or disappeared (17). Ebola infection was identified in one of these animals (33). In 1995, in Kikwit, in the Bandundu Province of the Democratic Republic of the Congo, a large outbreak was recorded in the local hospital, resulting in 244 human deaths among 315 cases. Two separate epidemics were also recorded in Gabon in 1996 (23). Following transportation, preparation and cooking for consumption of a dead chimpanzee from the forest, thirty-seven people from Mayibout village were infected, twenty-one of whom died (57%). Twenty-one of the patients had direct contact with the dead animal or organs, and sixteen cases occurred through person-to-person transmission. Another epidemic was reported a few months later in the Makokou area. The index case was a hunter who died in hospital.

In November 1989, an epizootic was reported in a primate import quarantine facility in Reston (Virginia, USA) involving numerous deaths in cynomolgus monkeys (*Macaca fascicularis*). The monkeys had been imported from the Philippines, directly or via Amsterdam, before reaching the USA. A virus closely related to Ebola was isolated from monkeys and named Ebola subtype Reston. All the monkeys in the facility were euthanised. From January to March 1990, a new epizootic occurred among monkeys of the same origin. Animals were not euthanised and the virus propagated from room to room, probably by droplet contact. Four human infections were recorded among workers from the facility without any clinical symptoms, suggesting an absence of virulence in humans (25). A single holding company was the source of these different shipments of monkeys from the Philippines. Evidence was found of an epizootic among monkeys in 1990, in the facility in the Philippines, with filoviral antigen detected in 52.8% of monkeys which died during a surveillance period of 2.5 months (22). A further outbreak was reported in 1992 in Siena, Italy. The virus was isolated from three monkeys from the same holding company in the Philippines; no human infections were recorded. The animals from the Philippines were caught in the wild, hence the virus could be reintroduced into the facility at any time. Other monkeys imported to the USA in 1993 had Ebola Reston antibodies but no viral infection. For transportation and importation of non-human primates, a mandatory disease control requirement was necessary. In 1994, the Philippines banned the export of monkeys caught in the wild and instituted a forty-five-day quarantine period prior to the export of animals. However, in March 1996, a monkey imported from the Philippines died in a quarantine facility in Texas and this animal and one other were found to be positive for Ebola Reston. All animals from the same quarantine cohort were destroyed (39). In the Philippines, surveillance was initiated among five monkey-breeding and export facilities. In one facility, one animal was reported to be acutely infected, and three monkeys and one animal handler tested positive for Ebola Reston antibodies (28).

**Pathology**

In African green monkeys experimentally infected with Ebola subtype Zaire or Marburg virus, the incubation period is four to sixteen days. During the incubation period, the virus replicates primarily in monocytes and macrophages, then in the liver, spleen, lymph nodes and lungs. With the onset of the disease, the severity of damage increases with diffuse necrosis in the parenchyma, and is directly correlated with the presence of large numbers of virions (16, 23, 37). Little inflammatory response is observed in lesion sites. Thrombocytopenia and microcirculatory disturbances are
described as capillary stasis and formation of small thrombi. Dystrophic changes in endothelial and epithelial cells of the lungs and extensive destruction in the liver, spleen and adrenals are reported. Moderate elevation of alanine aminotransferase and high elevation of aspartate aminotransferase in serum indicates other target sites besides hepatocellular dysfunction. Some features, such as the responses of blood clotting and vascular permeability appear to be species-specific in the monkey (40). The subtypes Ebola Sudan and Ebola Reston are less virulent and cause a self-limiting infection in monkeys (16, 18, 23).

The reservoir of filoviruses

The distribution of Marburg virus appears to be limited principally to one region of Africa, comprising Kenya, Uganda and the north-east of the Democratic Republic of the Congo. Ebola virus has been recovered in the Democratic Republic of the Congo, southern Sudan, Gabon and Côte d'Ivoire, from infected dying monkeys in two outbreaks. In addition, the Reston episode indicated the presence of filoviruses in monkeys in Asia. The epizootics of Ebola Reston and the epidemics of Ebola and Marburg raise the question of whether non-human primates might be the primary reservoir. Persistence of filoviruses in monkeys has never been demonstrated and the high mortality rate among monkeys suggests that these animals could not act as a reservoir of the filoviruses. Furthermore, Marburg virus has never been isolated from wild monkeys, and all monkeys which have been experimentally inoculated with Marburg virus died (21).

Chronic infection of a mammal is nevertheless the likely mechanism for survival of these viruses in nature. In Kikwit in 1995, the putative index case was a farmer who had recently excavated a local charcoal pit. An extensive search to reveal a potential reservoir or vector in the area was unsuccessful. In a hypothetical transmission cycle, bats are considered the most likely vertebrate hosts of viruses (29). Few studies have been undertaken in this particular field. Some fruit and insectivorous bats supported replication of the virus without clinical symptoms (48). A recent publication identified filoviral RNA by genetic amplification in some rodents in the Central African Republic. If such findings are confirmed, this would be the first evidence of a naturally infected rodent (31).

Diagnosis

In the case of suspected filoviral disease in primates, handling and autopsy must be conducted following strict guidelines. Specimens (blood, skin biopsy and tissues) must be sent for diagnosis to a laboratory with biosafety level 4 facilities, following the recommendations of the World Health Organization. Viral isolation or identification are necessary for epidemiological investigations. As an alternative, formalin specimens are suitable as non-infectious material and are simple to transport.

Prevention and control

Risk of exposure to filoviruses mainly concerns people in contact with monkeys caught in the wild, or workers in quarantine facilities. Transmission by aerosol has been demonstrated for Ebola Reston and Marburg viruses. Filoviruses have been shown to survive for a few days on contaminated surfaces at room temperature. Infectious virions can be inactivated by heating at 60°C for 30 minutes or by using an appropriate amount of lipid solvent, or disinfectants such as formaldehyde or hypochlorite (15). A reduction in the use of monkeys in the pharmaceutical industry for vaccine production and controls is encouraged. For transportation and importation of non-human primates, a mandatory disease control requirement is necessary in some countries. Given that, in 1994, the Philippines banned the export of monkeys caught in the wild and instituted a forty-five-day quarantine requirement prior to exporting animals, the 1996 episode suggests poor sanitary and containment conditions in the export facilities. Further investigations on the pathology, virulence and ecology of filoviruses are necessary to improve understanding of the cycle and to provide adequate preventive measures.

Conclusion

Many aspects of bunyaviral diseases are misunderstood, or unknown. No reliable small rodent model exists to study the pathogenesis of viruses causing teratogenic or abortogenic effects. La Crosse, Main Drain and San Angelo viruses were found to induce teratogenic effects in experimental infections of sheep. However, whether such pathogenicity occurs in wild or domestic animals in nature is not known. Rift Valley fever remains an emerging disease in Africa and is related to ecological changes. On account of the substantial economic losses when an outbreak occurs, active research on vaccine is needed to prevent disease in animals and frequent transmission to humans. In contrast to RVF, NSD virus is restricted to a specific population of ticks in East Africa and does not lead to disease in humans. Although Akabane and related viruses have a wide geographic distribution, the economic impact of the disease is not known and requires further study. The recent epidemics of Ebola virus in Africa and Ebola Reston in monkeys from the Philippines have attracted attention. Extensive studies have been undertaken to understand more fully the ecology and the transmission of filoviruses and to avoid infections; however, the reservoir remains to be determined.
Infections dues aux virus appartenant aux familles des *Bunyaviridae* et des *Filoviridae*

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**Résumé**

La fièvre de la Vallée du Rift est la principale maladie animale due à des bunyaviridés en Afrique. Transmis par les moustiques, le virus est à l'origine, chez l'animal, d'avortements et d'une mortalité élevée des jeunes, et chez l'homme, de fièvre hémorragique. Il existe des vaccins contre ce virus mais leur utilisation est limitée en raison de leurs effets secondaires ou de l'insuffisance de la protection qu'ils confèrent ; les recherches doivent donc être poursuivies pour améliorer la qualité de ces vaccins ou pour mettre au point de nouveaux vaccins plus efficaces. La maladie de Nairobi est transmise par les tiques. La maladie est endémique en Afrique de l'Est et des cas sporadiques sont signalés en Inde et au Sri Lanka. D'autres virus, transmis par les moustiques et les mouches *Culicoides* spp., sont tératogènes pour les bovins et les ovins, notamment le virus d'Akabane et d'autres virus apparentés qui sévissent en Asie, en Australie et au Moyen-Orient et le virus de la Vallée Cache en Amérique du Nord. Le virus de Marburg et le virus Ebola, du genre *Filovirus*, sont à l'origine d'épidémies très meurtrières en Afrique centrale ; certains cas ont été attribués à des contacts avec des singes. Un autre virus appartenant au sous-type Ebola a été décrit pour la première fois dans un établissement de quarantaine aux États-Unis d'Amérique chez des singes cynomolgus (*Macaca fascicularis*) en provenance des Philippines. Le réservoir de ces virus demeure inconnu.

**Mots-clés**


Infecciones por virus de las familias *Bunyaviridae* y *Filoviridae*

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**Resumen**

La fiebre del Valle del Rift es la principal enfermedad causada por bunyavirus que afecta a los animales africanos. El virus, transmitido por mosquitos, provoca abortos y la muerte de animales jóvenes, así como fiebres hemorrágicas en el ser humano. Pese a que existen vacunas contra este virus, su utilización no está muy extendida a causa de los deletéreos efectos que a veces conllevan y de la insuficiente protección que confieren, lo cual justifica nuevas investigaciones que intanten mejorar las vacunas existentes o crear otras nuevas. La enfermedad de Nairobi, transmitida por garrapatas, es endémica en África Oriental, y esporádicamente se declaran también casos en la India y Sri Lanka. Otros virus transmitidos por mosquitos o moscas *Culicoides* spp. son teratógenos en bovinos y ovinos, como es el caso del virus Akabane y otros virus afines en Asia, Australia y Oriente Medio y del virus del Valle Cache en Norteamérica. Los virus Marburg y Ebola, del género *Filovirus*, han dado lugar a epidemias en África Central, acompañadas de elevadas tasas de mortalidad en el hombre. Algunos casos han sido relacionados con el contacto con monos. En una instalación de
cuarentena en Estados Unidos de América se describió por primera vez la presencia de otro virus del subtipo Ebola en monos cynomolgus (Macaca fascicularis) procedentes de las Filipinas. El reservorio de esos virus constituye por ahora un enigma.

**Palabras clave**

**References**


