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Rift Valley Fever

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SYNOPSIS

Rift Valley Fever (RVF) is a severe veterinary disease of livestock that also causes moderate to severe illness in people. The life cycle of RVF is complex and involves mosquitoes, livestock, people, and the environment. RVF virus (RVFV) is transmitted from either mosquitoes or farm animals to humans, but cannot be transmitted from person to person. People can develop different diseases following infection: febrile illness, ocular disease, hemorrhagic fever, or encephalitis. There is a significant risk for emergence of RVF into new locations, which would affect human health and livestock industries.

OVERVIEW

One Health is a concept that recognizes the inextricable linkages between human health, animal health, and the environment (Fig 1). Rift Valley Fever (RVF) is a long-recognized veterinary disease of livestock in Africa. Infection with RVF virus (RVFV) causes a highly lethal illness in domesticated livestock (sheep, cattle, and goats) that consequently has dire economic impacts in affected regions. RVF has been and remains on the World Organization for Animal Health (OIE)'s list of notifiable animal diseases of concern¹. Mosquitoes serve as both the reservoir and vector for RVFV. Since mosquito breeding is dependent upon rainfall, the occurrences of RVF outbreaks are linked to environmental conditions and thus are likely to be affected by climate change. Epizootic spillover to humans occurs by both mosquito bite and from directly handling of infected animal carcasses.

The geographic distribution of RVF has broadened since its discovery in 1931.² Initially a disease of the Rift Valley in eastern Africa, RVF has emerged throughout continental Africa as well as to Madagascar and the Saudi Arabian peninsula. Importantly, the insect vectors that transmit RVFV are found in Europe and the Americas, which opens the door to emergence in new locations and could cause considerable human morbidity and mortality as well as economic damage^{3–6}. The introduction and rapid spread of West Nile Virus into the U.S. in the last 17 years (and Chikungunya and Zika viruses more recently) serves as a good

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barometer for the impact of importation of another mosquito-borne virus such as RVFV. In addition to its potential as an emerging viral disease, RVFV is listed as a National Institute of Allergy and Infectious Disease (NIAID) Category A priority pathogen, is on the list of federal Select Agents and Toxins, and is considered a potential bioterror threat due to the ease of infection by inhalation.^{7,8}

In 2015, the World Health Organization (WHO)'s Workshop on Prioritization of Pathogens assigned RVF to the list of "severe emerging diseases with potential to generate a public health emergency, and for which no, or insufficient, preventive and curative solutions exist."⁹ This group of experts recommended urgent Research & Development (R&D) to address this need. At the same time, Science magazine listed RVF on the top-10 list of high priorities for research based on the need for vaccines and therapeutics.¹⁰ Thus, RVF is clearly a relevant emerging disease that could cause considerable economic damage and human morbidity and mortality if it emerged in new locations. This review article will examine the epidemiology and clinical profile of Rift Valley Fever.

MICROBIOLOGY

Rift Valley fever virus (RVFV) is one of the most important members of the large and diverse *Bunyaviridae* family. RVFV belongs to the *Phlebovirus* genus, which contains 9 other viral species including Punta Toro, Sandfly fever, and severe fever with thrombocytopenia syndrome (SFTS) virus. The name phlebovirus is derived from the fact that most of the viruses in this genus are transmitted by phlebotomine sandflies. RVFV is a notable exception because it is transmitted primarily by mosquitoes. All bunyaviruses, including RVFV, contain a tripartite genome consisting of 3 single-stranded, negative-polarity RNA segments. The genome segments are creatively named large (L), medium (M), and small (S). The L segment encodes the viral polymerase protein. The M segment encodes the glycoproteins (Gn and Gc), as well as a non-structural protein termed NSm. Both L and M segments use a negative-sense coding strategy. In contrast, phleboviruses use an ambisense coding strategy for the S segment. The nucleoprotein (N) is encoded with negative polarity on the S segment, while a second non-structural protein, NSs, is encoded with positive polarity. Nucleocapsids consist of the viral nucleoprotein (N) multiplexed with each RNA segment. Complementary nucleotide sequences at the 3' and 5' ends of each segment are thought to form circular RNAs.^{11,12}

Cells become infected with RVFV by receptor-mediated endocytosis, followed by pH-mediated fusion of virus-endosomal membranes to release nucleocapsids into the cell cytoplasm. Transcription, translation, and genome replication occur in the cytoplasm. A unique aspect to the life cycle of RVFV and other bunyaviruses is that mature viral particles assemble and bud from the Golgi apparatus in some cell types.¹³

Genomic sequence analysis of strains obtained between 1944 – 2007 reveal relatively low (5%) sequence divergence.^{14,15} There are at least seven genetic lineages, yet lineage does not correlate with geographic origin indicating that there is substantial regional movement of genotypes. Genetic evidence exists for the reassortment of viral segments in nature but no indication of recombination.^{15,16}

EPIDEMIOLOGY

The epidemiology of RVFV is complex and involves multiple players, including mosquitoes, wild animals, domesticated livestock, and humans (Fig 2).

Mosquitoes

RVFV has been isolated from a wide range of mosquito species spanning several genera (Table 1). *Aedes* mosquitoes are the primary reservoir and vector, while *Culex*, *Anopheles*, and *Mansonia* are important secondary vectors that contribute to amplification of epizootics and epidemics.^{17,18} Virus has also been isolated from other mosquito genera, as well as ticks, flies, and midges^{19–21}, but their role in biological transmission is unknown.

A unique aspect to the biology of RVFV is that the virus is maintained by transovarial transmission within *Aedes* mosquito eggs, meaning that live virus can be passed from parent mosquito to offspring by maintenance within eggs.²² (Fig. 2). During inter-epidemic periods, the virus remains infectious within dormant desiccated *Aedes* mosquito eggs in dry floodplains; infected mosquitoes will emerge during flooding. As would be expected, outbreaks are associated with unusually heavy rainfall, especially cyclical El Nino-Southern Oscillation (ENSO) weather patterns²³.

Mammals

Like most arboviruses, RVFV alternates between mosquitoes and vertebrate hosts. Evidence of RVFV infection (as determined by hemagglutinin inhibition or plaque-reducing neutralizing antibody titers) has been found in many wild mammalian species in Africa, including camels, bats, lions, and elephants (see Table 2).^{24–26} The virus causes mild or inapparent illness in these species. It is not known whether any of the wild animal species are amplifying hosts.

Unlike wild animals, RVFV is highly pathogenic in domesticated ruminants, which are the amplifying hosts, meaning they develop sufficient viremia to infect feeding mosquitoes and potentiate further transmission. The most severe disease occurs in developing fetuses and very young animals immediately after birth; older animals are somewhat more resistant. A description of disease in the three most common domestic animals (cattle, sheep, and goats) is summarized in Table 3. High titers of virus are found in the blood of infected animals for approximately a week after onset of illness. Direct animal-to-animal transmission of RVFV does not occur among herds nor experimentally in the laboratory. *Culex* and *Mansonia* mosquitoes are thought to be responsible for horizontal transmission between viremic animals and humans (Fig. 2).²⁷

Humans

Humans become infected with RVFV when there is widespread illness and death among domesticated livestock. People can be infected by the bite of a mosquito, but the primary means of transmission of the virus to people is thought to be through mucous membrane exposure or inhalation of viral particles during the handling of infected animals and carcasses. A number of retrospective studies suggest that touching/handling, living close to,

and consuming animal products are factors associated with increased likelihood of RVFV infection and possibly more severe outcomes.^{21,28–32} Between 1997–2010, there were 9 RVFV outbreaks, with 1,220 confirmed human deaths and >500,000 estimated human cases.³³ Most recently in March of 2016, human cases of RVF, associated with an outbreak in goats, occurred in Uganda³⁴. One of these patients was a butcher, and the other reported to have interacted with sick animals.³⁵ The virus has not shown direct human-to-human transmission, and there have been only a few documented cases of vertical transmission.^{36–38}

BIOSAFETY AND BIODEFENSE CONCERNS

Of note, a significant number of accidental infections with RVFV have occurred among people performing diagnostic testing or those working with the virus in animals or the laboratory.^{39–43} At least 25 accidental infections occurred through 1949,³⁹ with a total of 47 to date. Many of these infections were traced to aerosol (inhalational) exposure.^{39,40} These lab-acquired infections led to early knowledge about the disease course in humans.

The United States, Canada, Japan, the former Soviet Union, and potentially other nations performed research on RVFV within their offensive biological weapons programs during the height of the Cold War.^{44–51} Mention of RVFV dates back to the origin of the United States offensive program in 1941 with the establishment of the Bacteriological Warfare Committee.⁵²

Although much of the information concerning the United States' bioweapon program is still classified, records indicate that research on RVF was conducted under Operation Whitecoat, which was the primary US biodefense medical research program between 1954–1973.^{53,54} In 1968–69, a formalin-inactivated vaccine against RVF (termed NDBR 103 RVFV) was tested in volunteers under approved clinical protocols; the vaccine provided enough protection to receive investigational new drug (IND) status from the FDA. Volunteers were likely exposed to RVFV, presumably by aerosol, although further details about the specifics of the human testing with RVFV have not been declassified to date. This research concluded when President Richard M. Nixon ended the offensive biological weapon program in 1969 and the United States signed the Biological Weapons Convention in 1972. Despite its history, there are conflicting opinions on the current likelihood of the use of RVFV as a bioweapon.^{33,55}

Due to the fact that RVF can be acquired through inhalation, RVFV is classified as a Risk Group 3 agent, and biosafety level (BSL)-3 containment requirements are needed to work with the virus in the laboratory.⁵⁶ It is also a Select Agent that is regulated by both the CDC and USDA/APHIS.^{7,8}

CLINICAL PRESENTATION

Livestock

The clinical disease of RVF in domesticated animals is described in Table 3.^{2,57–59} At all stages of gestation, infection of pregnant domesticated animals will result in near 100%

death of the fetuses. Adult livestock are susceptible to peracute disease, which is defined as the occurrence of death before development of any clinical signs. Adult livestock can also develop acute disease characterized by weakness, anorexia, diarrhea, bloody nasal discharge, and jaundice. The mortality rate depends upon the species and age of the animal, with sheep and goats generally being more susceptible to death than cattle (Table 3). In livestock, the liver is the primary target of the virus, and characteristic lesions of RVF include widespread areas of necrosis and hemorrhage, giving the liver a mottled appearance. More extensive liver lesions are associated with more severe disease. Necrosis and hemorrhage is also seen in the splenic pulp. Hemorrhage and blood in the stomach and small intestine can lead to bloody diarrhea.

Humans

Most infected people develop uncomplicated RVF, which is characterized by non-specific flu-like symptoms with fever⁶⁰ (Table 4). In some patients, a biphasic fever occurs (3 days of fever, 1–2 days of remission, followed by another 2–3 days of fever)³¹. While this is not lethal, symptoms can be debilitating, and convalescence may take several weeks.

However, there are 3 additional more severe clinical outcomes that occur in some people infected with RVFV (Table 4). Ocular complications are the most frequently reported (up to 10% of infected people)^{31,61–64}. Patients have reduced vision (either bi-lateral or uni-lateral), blind or black spots, photophobia, and retro-orbital pain. Examination reveals inflammation of the retina and vessels of the eye, including retinal hemorrhage. Vision defects are not always permanent and may take weeks to months to resolve.

A severe hepatotropic disease (similar to that seen in sheep and other domesticated animals) occurs in people at an estimated frequency of about 1–2%. In addition to the non-specific symptoms described above, these patients also develop jaundice and hemorrhagic manifestations (blood in urine/feces, vomiting of blood, purple skin rash, gingival bleeding).⁶⁰ Evidence of liver necrosis is seen upon autopsy, and prolonged blood coagulation times are noted.^{21,65}

The third complication that can arise in RVF patients is neurological disease, typically with a delayed-onset. The delay can be anywhere from 5 – 30 days after the initial febrile illness. Clinical signs include severe headache, hallucination, disorientation, vertigo, excessive salivation, and weakness or partial paralysis.^{21,30,32} This form of RVF can be lethal (53% of patients with CNS complications died during the 2000 Saudi outbreak); in survivors, symptoms may be prolonged and even permanent.³⁰

Mechanisms determining the different disease outcomes in humans are not fully understood, but there is recent evidence that genetic polymorphisms, coinfections, and comorbidities may contribute to more severe disease outcomes.^{28,66,67} Even though isolated cases of vertical transmission have been documented,^{36–38} there appears to be no increase in apparent miscarriage in pregnant women. There is also no documented human-to-human transmission; infection of people appears to be limited to either mosquito bites or exposure to high titer animal tissues. Despite this, viral RNA was detected by PCR in urine and semen

from an immunosuppressed transplant recipient 4 months after illness.⁶⁸ It is not known what role (if any) this may play in transmission and spread.

DIAGNOSIS

In endemic regions, human illness soon follows in areas where there is concurrent RVF disease in animals, so monitoring of herds and efficient reporting is critical. Blood samples from acutely infected people can be tested for the presence of virus by either RT-PCR, antigen-detection ELISA, or isolation of live virus. After the cessation of viremia, IgM can be transiently detected. Recovered patients will have persistent IgG antibodies for years after infection, and thus can be useful for determining seropositivity and historical infection rates. While some rapid diagnostic tests are in development, none are yet commercially available. Currently, the availability of clinical testing is only through international reference laboratories such as the Centers for Disease Control and Prevention (CDC) in Atlanta, GA, the Kenya Medical Research Institute (KEMRI), and the Onderstepoort Veterinary Institute in South Africa, among others.⁶⁹

TREATMENT AND PREVENTION

There are no specific, FDA-approved treatments for Rift Valley Fever. Treatment of symptoms such as fever and body aches can be done with standard over-the-counter medications. Care of hospitalized patients is supportive, including fluid replacement. Drugs that affect the liver, kidney, or coagulation should be avoided.

Therapeutics

Historically, Ribavirin has been looked to as a potential antiviral therapeutic for Rift Valley Fever because of its demonstrated in vitro efficacy, and it has some limited in vivo efficacy against other emerging hemorrhagic fever viruses (Lassa fever, Crimean-Congo hemorrhagic fever)^{70–72}. However, intravenous administration of ribavirin to patients during the 2000 outbreak in Saudi Arabia was quickly stopped due the finding that it may increase the likelihood of neurological disease⁷³. Newer broad-spectrum antiviral drugs such as Favipiravir have shown some promise in rodent models⁷⁴.

Vaccines

RVF presents a unique opportunity to merge facets of both veterinary and human vaccination strategies under the One Health concept. Vaccination of livestock will not only help to control epizootics but also prevent the chain of transmission to humans (reviewed in⁷⁵). Since the 1960's, formalin inactivated vaccines have been used to protect lab workers from accidental exposure. The NDBR 103 vaccine was arguably one of the biggest successes of the Operation Whitecoat program. After the initial clinical trials, the vaccine was used for years to vaccinate and protect laboratory workers. The ultimate test came during the 1977 outbreak in Egypt where the highly virulent ZH501 strain emerged to cause lethal disease in people. U.S. naval soldiers working with the virus from patient samples at Naval Medical Research Unit No. 3 (NAMRU-3) off the coast of Egypt were given the NDBR 103 experimental vaccine. Since then, a next generation version of a formalin

inactivated vaccine, TSI GSD 200, has been used to vaccinate lab workers and high-risk personnel to this day through the Special Immunizations Program ⁷⁶.

A significant drawback of the formalin-inactivated vaccine is that development of an adequate immune response requires 3 inoculations, making this impractical for use in livestock ^{77–79}. To overcome this, several live-attenuated vaccines, such as MP-12 and Clone 13, were generated and tested in the 1980's and 1990's.⁸⁰ Protection of experimentally inoculated animals from virulent challenge was achieved, but there is a potential for teratogenic effects in pregnant animals.^{81–84} Another disadvantage is that use of live-attenuated RVF vaccines during epizootics have shown the potential for reversion to virulence and spread from animal to animal.⁸⁵ Despite these potential limitations, MP-12 is still being pursued as a human vaccine to this day.^{86–88}

More recently, reverse genetics has allowed generation of rationally-designed live attenuated vaccines. A recombinant virus with deletions in the NSs and NSm proteins (termed ZH501-NSs/ NSm or / virus) showed efficacy in rat and sheep models and had no apparent adverse effects on fetal animals.^{89,90} Other approaches have removed the NSm protein from the MP-12 virus (termed MP-12/ NSm).⁹¹ The advantage of both of these recombinant deletion-based vaccines is the ability to differentiate infected from vaccinated animals (DIVA) based on differential detection of antigen-based immune responses by ELISA.

Other vectored, replicon, and subunit vaccination strategies have been tested in lab animals ⁹². A replication-defective chimpanzee adenovirus-based vaccine expressing the RVFV glycoproteins provides protection in experimentally infected sheep, goats, cattle, and camels⁹³ and is effective in a thermostabilized form, making it attractive for field use.⁹⁴ Many of these next generation vaccine candidates could be used in both livestock and potentially humans; some are undergoing field testing to support veterinary approval⁹⁵, but significant financial investment from endemic countries is needed to enable veterinary use. The most likely scenario is that after a vaccine has demonstrated sufficient safety and efficacy in animals during outbreaks, the incentive may be there for testing and evaluation for human use in the event of a large-scale human outbreak.

PREVENTION OF ANIMAL AND HUMAN OUTBREAKS

The first step in the prevention of significant human disease is early detection of cases in animals through rigorous active surveillance and sentinel herd monitoring.⁹⁶ Once infected animals and/or herds are located, further spread can be prevented by mosquito control, animal movement control, ban on livestock slaughtering, or at least use of preventative measures (gloves, masks, and gowns) when handling carcasses or aborted fetuses. Public awareness and education as to the signs, symptoms, and risk factors are critical to prevent further animal disease and spread to people. Targeted vaccination of animals may be beneficial as a control measure in high-risk areas. Standard precautions prevent nosocomial transmission; risk to healthcare workers is low.⁹⁷

POTENTIAL FOR EMERGENCE

RVFV has spread throughout Africa, to the island of Madagascar, and into the Saudi Arabian peninsula. Most recently, endemic RVF was discovered in both Angola and Nigeria.⁹⁸ Notably, human cases have not yet been recognized in these areas, potentially due to focus on other diseases such as malaria, Yellow fever, and Dengue.

Concern over further spread of RVF outside of Africa or the Saudi Arabian peninsula stems from the unexpected expansion of other arboviruses, namely West Nile, Chikungunya, and most recently Zika. Infected mosquitoes or livestock from Africa or the Middle East could introduce the virus into new locations via natural (migration) or mechanical (air travel, cargo) mechanisms. Importation of viremic livestock is believed to be responsible for spreading the virus into the Arabian Peninsula.^{99,100} Travel-associated cases of human RVF have occurred numerous times, most recently to China from Angola, and to France from both Mali and Zimbabwe,^{101–103} without further transmission or establishment in the destination areas.

While the risk of sporadic introduction of RVFV to the U.S. or Europe is likely high, the confluence of conditions necessary to allow sustained transmission and subsequent endemicity are probably rare.¹⁰⁴ North American mosquito species have the capacity to become infected with and potentially transmit RVFV.^{105,106} Proximity of infected mosquito vectors and amplifying host animal populations, temperature, and rainfall conditions will all influence vector and virus survival, making accurate predictions of the likelihood of spread difficult.

Modeling studies are still unclear whether the virus would become enzootic in the United States if introduced via natural mechanisms.¹⁰⁷ By comparing the number of transmission days, livestock population, and proximity to potential entry points, the highest-risk states include Texas, California, Nebraska, Minnesota, and New York.⁶ Global warming may contribute to risk due to increased environmental temperatures that extend mosquito survival time. California is at particular risk due to a high density of both mosquitos and dairy cattle.¹⁰⁷

Experiments have not yet been performed on whether or not resident North American wildlife, such as deer and elk, are capable of becoming hosts and contributing to enzootic maintenance. However, since many different mosquito species are competent for virus replication (Table 1) and since a variety of wild animals in Africa are susceptible (Table 2), it is conceivable that North American wild animals could also serve as hosts. RVFV replicates readily to high titers in cell lines from white-tailed deer¹⁰⁸, although to date no experimental infections have been attempted in these animals.

Under the worst-case scenario, the US Department of Agriculture believes the virus would become endemic within the United States in just two years, and would result in over 50 billion dollars in damages and control efforts.¹⁰⁴ Immediate costs during or after an outbreak in terms of human illness, loss of animals, disruption of animal supply chains, and mitigation efforts would be massive. Further losses economically include control policies and international trade restrictions imposed on US livestock to other countries.⁵

CONCLUSIONS/SUMMARY

Rift Valley Fever is a One Health disease that highlights the need to consider climate, veterinary health, and human behavior in order to prevent future outbreaks. Prevention of significant epizootics and epidemics is important in endemic areas due to the severe economic impact. Also critical is prevention of spread to new areas.

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KEY POINTS

- Rift Valley Fever is an important human and veterinary pathogen that causes significant illness and death.
- The life cycle of RVF is complex and involves mosquitoes, livestock, climate, and humans.
- RVFV is transmitted from either mosquitoes or animals to humans, but cannot be transmitted from person to person.
- There is a significant risk of emergence of RVF into new locations, which would affect human health and livestock industries.
- There are no approved vaccines or therapeutics to treat human RVF.

Figure 1. Important players in the ecology of RVF

The dynamics of RVF depends upon the complex interplay between humans, mosquitoes, wild and domesticated animals, and the environment.

Figure 2. The complex life cycle of RVF

The enzootic cycle (also known as the sylvatic or cryptic cycle; green) occurs under normal rainfall conditions. Infected *Aedes* mosquitoes serve as both the reservoir and vector (#1). Infectious virus can survive for years in desiccated mosquito eggs (#2). Normal rainfall leads to formation of small floodplains (dambos), in which the infected mosquito eggs hatch. Infected adult mosquitoes will then feed on and infect wild ungulates (#3); their role in transmission cycle is not well understood. Heavy rainfall conditions, such as El Niño-southern oscillation events (ENSO), can lead to the epizootic cycle (also known as the domestic cycle; blue). Larger flood plains increase the likelihood of interaction between domesticated livestock and mosquitoes (#4,5), resulting in illness, abortion, and death. Other species of mosquito (*Culex*, *Anopheles*) can feed off of viremic animals and transfer the virus longer distances and to other herds (#6). Human epidemics occur when there are many infected and dying animals. People can be infected by mosquito or by handling infected animals (#7).

Table 1

Insect genera and potential role in life cycle of RVF

Genus	Type of vector
<i>Aedes</i>	primary enzootic reservoir and vector
<i>Culex</i>	secondary vector
<i>Mansonia</i>	secondary vector
<i>Anopheles</i>	secondary vector
<i>Coquillettidia</i>	secondary vector
<i>Eretmapodites</i>	secondary vector
<i>Culicoides</i> (biting midges)	role unknown
<i>Plebotomus</i> (sand flies)	role unknown
<i>Simulium</i> (other flies)	role unknown

Data from Refs 17–21.

Table 2

Wild and domesticated animals with evidence of RVF infection

Susceptible wild animals*	Domesticated animals[#]
springbok	cattle
wildabeest	sheep
impala	goats
lions	buffalo
gazelles	camels
African buffalo	horses
warthogs	donkeys
elephants	
bats	
rhinoceros	
murine rodents	

* based on detection of neutralizing antibodies or hemagglutinin inhibition

[#] susceptible to disease

Data from Refs 24–26, 109.

Table 3

RVF disease in domesticated animals

	Adult Sheep or Goats	Lambs or Kids	Adult Cattle	Calves
Peracute disease?	yes	no	yes	no
Acute clinical disease	fever, weakness, anorexia, diarrhea, bloody nasal discharge, jaundice, increased respiration; leukopenia, elevated liver enzymes, jaundice	high fever, listlessness, inactivity, anorexia; abdominal pain; increased respiration rate; bleeding and hemorrhage from the ruminant stomach; blood in intestine	weakness, anorexia, bloody diarrhea, hypersalivation, bloody nasal discharge	jaundice, fever, weakness, anorexia, bloody diarrhea
Macroscopic pathology	Liver appears mottled due to cell necrosis and hemorrhage; enlarged lymph nodes	enlarged, friable liver (mottled due to necrotic foci and hemorrhage); spleen: capsular hemorrhage with some enlargement; enlarged lymph nodes	Liver appears mottled due to cell necrosis and hemorrhage; enlarged lymph nodes	Enlarged, friable liver; enlarged spleen with some hemorrhage; enlarged lymph nodes
Microscopic pathology	hepatic and splenic necrosis (less severe and extensive than lambs)	hepatic necrosis; lung congestion; hemorrhage in mucosa of abomasum; necrosis of spleen; pyknotic/karyorrhexic kidney; sporadic necrosis in small intestine	hepatic and splenic necrosis (less severe and extensive than calves)	hepatic and splenic necrosis; lung congestion
Time frame	3 days	before 36 hours	2–3 days	2–8 days
Mortality rate	30–50%	90%	5–10%	20%
Fetal effects	frequent abortion (up to 100%)		Comparatively less frequent abortion (up to 85%)	

Data from Refs 2,58,59,96,110–112

Table 4

Human clinical symptoms of Rift Valley Fever

Uncomplicated	Ocular complications	Hemorrhagic complications	Meningoencephalitis
headache	vision reduction	jaundice	severe headache
body aches	blind spots	blood in urine/feces	hallucination
fever	photophobia	vomiting blood	disorientation
abdominal pain	retro-orbital pain	purple rash	vertigo
joint/muscle aches	uveitis	gingival bleeding	excessive salivation
vomiting	retinitis		weakness
anorexia			partial paralysis
weakenss			
nosebleeds			
sweating			
constipation			

Data from Refs^{21,30–32,60–65}