RIFT VALLEY FEVER

AETIOLOGY

Classification of the causative agent

Rift Valley fever (RVF) virus is a negative-sense, tri-segmented RNA virus of the within the order *Bunyavirales*, family *Phenuiviridae*, genus *Phlebovirus*. Only one serotype is recognised but strains exist of variable virulence.

Resistance to physical and chemical action

Temperature:	Virus is destroyed by heat treatment of serum for 120 minutes at 56°C
pH:	Resistant in alkaline environments but inactivated at pH <6.8
Chemicals/Disinfectants:	Inactivated by lipid solvents (i.e. ether, chloroform, sodium deoxycholate), low concentrations of formalin and by strong solutions of sodium or calcium hypochlorite (residual chlorine should exceed 5000 ppm)
Survival:	Survives in freeze dried form and aerosols at 23°C and 50–85% humidity. Virus maintained in the eggs of certain arthropod vectors during inter-epidemic periods. Can survive contact with 0.5% phenol at 4°C for 6 months

EPIDEMIOLOGY

RVF is an acute or peracute disease of wild and domestic ruminants and humans caused by a *Phlebovirus* and transmitted by insect vectors or direct contact with organs or fluids of infected animals.

The disease usually presents in an epizootic form over large areas of a country following heavy rains and sustained flooding or linked to the construction of irrigation schemes and hydrological dams, which present a suitable breeding sites for vector populations. The disease is characterised by high rates of abortion and neonatal mortality in domestic ruminants. In humans, the disease mainly develops as an influenza-like illness, sometimes with ophthalmic sequelae

Hosts

- Cattle, sheep, goats, several rodents
- Wild ruminants, buffaloes, antelopes, wildebeest, etc.
- Humans are highly susceptible to infection but represent dead end hosts. No human-to-human infection has been reported
- African monkeys and domestic carnivores present a transitory viraemia
- Camelids do not play a relevant role in hosting or transmitting the virus

Transmission

- RVF virus regularly circulates in endemic areas between wild ruminants and haematophagous mosquitoes; disease is usually inapparent in wild species of animals due to their lower susceptibility
- Certain *Aedes* species act as reservoirs for RVF virus during inter-epidemic periods. Increased precipitation or flooding in dry areas leads to an explosive hatching of mosquito eggs, many of which harbour RVF virus
- The longer the period between heavy precipitation events (usually from 5 to 25 years), the more individuals within the population will be naïve to infection, leading to explosive outbreaks of disease
    - Satellite imaging has been used to confirm historic importance of precipitation in RVF outbreaks and in forecasting high-risk areas for future outbreaks. It has been proved that heavy precipitation events are predictable up to 4 months and adequate prophylactic measures can be taken in order to avoid greater outbreaks

- Infected *Aedes* feed preferentially on domestic ruminants which act as an amplifier of RVF
  - broad vector range of mosquitoes (*Aedes*, *Anopheles, Culex, Eretmapodites, Mansonia,* etc.) coupled with increased circulating virus lead to expansion of disease
  - extrinsic incubation occurs in vectors
- Sylvatic cycle and inter-epidemic maintenance occur in some areas
- The duration of epizootic and inter-epizootic periods depends on the particularities of the area and animals concerned
- Direct contamination: occurs in humans when handling infected animals and meat
- Mechanical transmission by various vectors has been demonstrated in laboratory studies

Sources of virus

- For animals: infected animals and vectors
- For humans: animal fluids such as nasal discharge, blood, vaginal secretions after abortion; mosquito bites; infected meat; also by aerosols and possibly consumption of unpasteurised milk
- *Aedes* mosquitoes may vertically transmit the virus to their offspring via eggs
- RVFV does not cause persistent infection (carrier state)

Occurrence

Historically, the disease has occurred in parts of the African continent, Madagascar, some other Indian Ocean Islands and the Arabian Peninsula. However, vector distribution, climatic changes and land usage dynamics may modify the temporal and spatial distribution of the infection. Epizootic outbreaks in Africa among peri-endemic countries have been associated with above average rain fall and climatic conditions favourable for competent vectors. Important outbreaks of RVF have been recorded in Egypt (1977–78 and 1993), Mauritania (1987), Madagascar (1990–91), Kenya and Somalia (1997). RVF was recognised for the first time outside of the African continent in 2000 with outbreaks reported in Saudi Arabia and Yemen. The most recent reports happened in Botswana, Mauritania and Mozambique in 2014, and Comoros and Saudi Arabia in 2015 (and previous years). There are a few other African countries which reporter not suspected cases of RVF.

For more recent, detailed information on the occurrence of this disease worldwide, see the *OIE World Animal Health Information Database* (WAHID) interface [http://www.oie.int/wahis/public.php?page=home]

DIAGNOSIS

Incubation period varies from 1 to 6 days; 12–36 hours in lambs. For the purposes of the *Terrestrial Code,* the infective period for RVF is considered to be 14 days.

Clinical diagnosis

Severity of clinical disease varies by species:

- lambs, kids, puppies, kittens, mice and hamsters are considered “extremely susceptible” with mortalities of 70–100%
- sheep and calves are categorised as “highly susceptible” with mortality rates between 20–70%
- in the “moderately susceptible” category are cattle, goats, African buffalo, domestic buffalo, Asian monkeys and humans with mortalities less than 10%
- camels, equids, pigs, dogs, cats, African monkeys, baboons, rabbits, and guinea-pigs are considered “resistant” with infection being inapparent
- Birds, reptiles and amphibians are not susceptible to RVF

Signs of the disease tend to be non-specific; however, the presentation of numerous abortions and mortalities among young animals, together with influenza-like disease in humans, is indicative. Humans tend to be infected far later during the onset of an outbreak, due to direct contact with bodily fluids from infected animals or mosquito bites. However, if the outbreak happens in remote areas, humans may act as sentinels of infection with RVF virus.

Cattle

- Calves (highly susceptible)
  - fever (40–41°C)
  - inappetence
  - weakness and depression
  - bloody or fetid diarrhoea
  - more icterus than in lambs
- Adults (moderately susceptible):
  - often inapparent infection but some acute disease
  - fever lasting 24–96 hours
  - dry and/or dull coat
  - lacrimation, nasal discharge and excessive salivation
  - anorexia
  - weakness
  - bloody/fetid diarrhoea
  - fall in milk yield
  - abortion rate may reach 85% in the herd

Sheep

- Newborn lambs or under 2 weeks of age (extremely susceptible):
  - biphasic fever (40–42°C); fever subsides just prior to death
  - anorexia; in part due to disinclination to move
  - weakness, listless
  - abdominal pain
  - rapid, abdominal respiration prior to death
  - death within 24–36 hours
- Lambs over 2 weeks of age (highly susceptible) and adult sheep
  - peracute disease: sudden death with no appreciable signs
  - acute disease more often in adult sheep
  - fever (41–42°C) lasting 24–96 hours
  - anorexia
  - weakness, listlessness and depression
  - increased respiratory rate
  - vomiting
  - bloody/fetid diarrhoea
  - mucopurulent nasal discharge
  - icterus may be evident in a few animals
  - in pregnant ewes, ‘Abortion storms’ with rates approaching 100%

Goat

- Similar to adult sheep (see above)

Humans

- Influenza-like syndrome: fever (38–40°C), headache, muscular pain, weakness, nausea and epigastric discomfort, photophobia
- Recovery occurs within 4–7 days
- Complications: retinopathy, blindness, meningo-encephalitis, hemorrhagic syndrome with jaundice, petechiae and death

Lesions

- Focal or generalised hepatic necrosis (white necrotic foci of about 1 mm in diameter)
- Congestion, enlargement, and discoloration of liver with subcapsular haemorrhages
- Brown-yellowish colour of liver in aborted fetuses
- Widespread cutaneous haemorrhages, petechial to ecchymotic haemorrhages on parietal and visceral serosal membranes
- Enlargement, oedema, haemorrhages and necrosis of lymph nodes

- Congestion and cortical haemorrhages of kidneys and multifocal petechiation advancing to diffuse haemorrhages associated with gallbladder
- Marked mesenteric and serosal inflammation and oedema of digestive tract; multifocal hemorrhagic enteritis
- Icterus (low percentage except in calves)

Differential diagnosis

- Bluetongue
- Wesselsbron disease
- Enterotoxemia of sheep
- Ephemeral fever
- Brucellosis
- Vibriosis
- Trichomonosis
- Nairobi sheep disease
- Heartwater
- Ovine enzootic abortion
- Toxic plants
- Bacterial septicaemias
- Rinderpest and Peste des petits ruminants
- Anthrax

Laboratory diagnosis

Samples

- Heparinised or clotted blood
- Plasma or serum
- Tissue samples of liver, spleen, kidney, lymph node, heart blood and brain from dead animals or aborted fetuses
    - specimens should be submitted preserved in 10% buffered formalin and in glycerol/saline and transported at 4°C
    - liver or other tissue for histological examination may be placed in formol saline in the field for diagnostic purposes; facilitates handling and transport in remote areas

Procedures

Identification of the agent

<u>Virus Isolation</u>

- In cell culture – Vero, BHK and AP61 mosquito cells may be used
- In sucking mice – for ethical and welfare reasons, should be avoided
- Confirmation of virus isolation should be performed preferably by immunostaining or polymerase chain reaction (PCR)

<u>Reverse-transcription PCR</u>

- Able to make a rapid diagnosis by detection of viral RNA

<u>Antigen detection (through enzyme-linked immunosorbent assay [ELISA])</u>

- The antigen detection ELISA is an immunocapture test
- Samples are tested at different dilutions with appropriate positive and negative controls
- This test has been used for human and animal samples during outbreaks in Saudi Arabia and Kenya

Histopathology with immunohistochemistry

- Histopathological examination of the liver of affected animals will reveal characteristic cytopathology, and immunostaining will allow the specific identification of RVF viral antigen in tissue
- This is an important diagnostic tool because liver or other tissue placed in neutral buffered formaldehyde in the field is inactivated and does not require a cold chain, which facilitates handling and transport from remote areas

Serological tests

Immunofluorescence assays are still used, although cross-reactions may occur between RVFV and other phleboviruses. Techniques such as the agar gel immunodiffusion (AGID), radioimmunoassays, haemagglutination inhibition (HI), and complement fixation are no longer used.

Virus neutralisation – microneutralisation, plaque reduction neutralisation (PRN) and neutralisation in mice

- The test is highly specific and can be used to test serum of any species
- It is generally used to measure vaccine efficiency
- Cannot differentiate presence of antibodies of naturally infected animals from animals vaccinated with RVF vaccine; detects antibodies against RVF virus in the serum of a variety of species
- Highly specific and will record the earliest response
- These tests can only be performed with live virus, and are thus not recommended for use outside endemic areas or in laboratories without appropriate biosecurity facilities and vaccinated personnel

Enzyme-linked immunosorbent assay

- Represents the currently most widely used technique
- It is a reliable and sensitive test to detect antibodies against RVFV
- Both IgG and IgM ELISAs are available for most species
- Can be performed with inactivated antigen and can therefore be used in RVF-free countries
- Cross-reactions may occur between RVF virus and other phleboviruses
- Commercially available kits
- indirect ELISA with pre-coated plates using a nucleocapsid protein (N) recombinant antigen and Protein G peroxidase conjugate is described in OIE *Terrestrial Manual*
- IgM-capture ELISA allows diagnosis of a recent infection

The use of one of the above-mentioned serological tests is sufficient to confirm the disease status of the animal. These tests are appropriate for using within eradication programmes.

For more detailed information regarding laboratory diagnostic methodologies, please refer to Chapter 3.1.18 Rift Valley fever in the latest edition of the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* under the heading "Diagnostic Techniques".

PREVENTION AND CONTROL

- There is not any specific treatment for RVF
- Hides, skins, wool and fibre are safe commodities
- Meat from animals slaughtered in an approved slaughterhouse/abattoir, subject to ante- and post-mortem inspection and which has undergone maturation process poses no risk if transmission of RVF virus. However, meat from animals which come from endemic areas must be accompanied by a veterinary certificate when exported, to attest the above-mentioned conditions

Sanitary prophylaxis

- Control of animal movements (extension of disease)
- Controls at slaughterhouses (exposure to disease)
- Draining of standing water to eliminate or reduce vectors
    - Disinfestations of low depression accumulations of water where mosquitoes may reproduce (in Africa known as 'dambos')
        - use of methoprene spraying or controlled burning
- It is possible to forecast high precipitation events, up to 4 months, that may lead to explosive outbreaks of RVF that are related to the increase in hatching of mosquito eggs. Thus, prophylactic measures such as monitoring risk factors and vector populations and assessment of livestock vaccination opportunity must be considered
- During widespread outbreaks, the focus should be on: coordinating the efforts of stakeholders regarding human and animal health; promotion of education of personnel; control of animal movements and clinical management of RVF cases

Medical prophylaxis

- Attenuated virus vaccine (Smithburn strain)
    - one inoculation confers immunity lasting 3 years
    - Safe for all breeds of cattle, sheep and goats
    - May cause fetal abnormalities or abortion in pregnant animals
    - pathogenic for humans
- Clone-13 live attenuated virus vaccine
    - Natural attenuated strain
    - No abortion or side effects seen in experimental trials
    - Single injection regimen
- Inactivated virus vaccine
    - Needs a booster 3-6 months after initial vaccination, followed by yearly boosters.
    - Used in outbreak situations and pregnant animals
- TSI-GSD-200 inactivated human vaccine (presently not available)

Neither of the mentioned vaccines allows for the differentiation of infected and vaccinated animals.

For more detailed information regarding vaccines, please refer to Chapter 3.1.18 Rift Valley fever in the latest edition of the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* under the heading "Requirements for Vaccines".

For more detailed information regarding safe international trade in terrestrial animals and their products, please refer to the latest edition of the OIE *Terrestrial Animal Health Code*.

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The OIE will periodically update the OIE Technical Disease Cards. Please send relevant new references and proposed modifications to the OIE Scientific and Technical Department (scientific.dept@oie.int). Last updated December 2019