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Review Article

A Short Review on Etiopathogenesis and Management of Rift Valley Fever

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Abstract: Rift Valley fever (RVF) is an acute arthropod-borne viral disease that can cause severe disease in domestic animals, such as buffalo, camels, cattle, goats, and sheep. Rift Valley fever is also an important zoonosis that can cause severe disease in humans. This article will provide complete information regarding the historical background, mode of transmission, clinical signs and symptoms, clinical complications and new insights including pathogenesis, differential diagnosis, treatment & prevention.

Keywords: Rift Valley fever (RVF), pathogenesis, differential diagnosis, treatment, prevention.

INTRODUCTION

Rift valley fever (RVF) is veterinary disease of livestock in Africa, as such it exemplifies the one health concept, in which animal and human health is inextricably intertwined. Infection of domesticated livestock (sheep, cattle, and goats) with RVF virus (RVFV) causes a highly lethal illness that result in dire economic consequences in affected regions. Initially a disease of the Rift Valley in eastern Africa, RVFV has spread through continental Africa as well as to Madagascar and the Arabian Peninsula. The World Health Organization (WHO)'s first 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 of the changing recognition of human disease over time. The clinical presentations of human RVF disease and the potential mechanisms underlying different disease exist". RVF remains on the World Organization for Animal Health (WOAH)'s list of notifiable animal diseases of concern. Veterinary and human vaccination strategies and development of therapeutic interventions is the key to limiting spread and alleviating disease burden. Both have recently been comprehensively reviewed and are not discussed here. Instead, this review article is designed to assist laboratory researchers, clinicians, and public health practitioners in understanding the manifold aspects of RVF disease in animals and humans. We first provide a historical perspective on the disease; including a discussion manifestations are then addressed. We then review evidence supporting exposure and transmission potential. In the concluding section, we discuss the historical and current role of RVF as a biological weapon [3].

Historical Background

- **In Kenya**

In 1930, R. Daubney and J.R Hudson working within the Division of Veterinary Research in Kenya were alerted to an unusually high mortality in lambs on a farm near freshwater Lake Naivasha in the Rift Valley .Their initial investigation determined that these deaths were caused by a previously unrecognized disease of sheep and cattle. Illness in the lambs was abrupt; mortality often occurred within 24 hours of disease onset. As Daubney described, the disease might entirely escape observation during life and the animal would simply be found dead in the morning. Mortality of lambs was age-dependent; the highest mortality rates (up to 95%) occurred in 3–7 day old lambs. Signs of disease in adult animals included vomiting, diarrhea, and

listlessness. In pregnant ewes, often the only sign of illness was abortion of the fetus, while the ewes themselves displayed few symptoms prior to being found dead. The high mortality in pregnant animals gave rise to the characteristic (and eerily descriptive) term 'abortion storms' used to describe the massive fetal mortality the accompany epizootic outbreaks of RVF the liver is the organ most affected in infected livestock. Upon gross examination, the liver was mottled in appearance and friable, with extensive necrotic lesions.

Daubney and colleagues demonstrated that blood transferred from a sick to a healthy animal could transmit the disease; however, they could detect no evidence, either naturally or experimentally, that the illness was naturally transmitted between animals. In an effort to control the epizootic, farmers transported sheep from the affected farm (at an altitude of 5,500-6,000 feet) to one located at a higher altitude (at 7,000-8,000 feet). This led to the subsidence of disease, which suggested that an intermediate vector was needed and that animals did not readily transmit the disease amongst themselves .In addition, field exposure experiments performed by Daubney and colleagues determined that mosquitoes or other insects that can be excluded by a common mosquito net were likely the cause of disease transmission, as housing sheep covered with a net prevented infection, whereas uncovered sheep were still susceptible. Furthermore, they determined that these vectors seemingly feed primarily at night, as cattle restricted to a day-time feeding did not become ill. Finally, an unusually large amount of rainfall that year (twice the normal annual precipitation level) coincided with the animal deaths. Collectively, these early observations pointed towards mosquitos as the likely vector. Later studies by others were able to isolate RVFV from a variety of mosquito species and demonstrate experimental transmission by mosquitoes.

In hindsight, RVF likely existed in the Rift valley of Kenya for at least 20 years prior to its identification as a distinct disease in 1931. In 1913, for example, R.J Stordy, then the Chief Veterinary Officer in the Department of Agriculture for British East Africa (present-day Kenya), submitted a report detailing the occurrences of known livestock diseases during the previous year. The known diseases included rinderpest, East Coast fever, scabies, variola, and anthrax, among others. Stordy includes an intriguing section describing unnamed mortality among lambs.

"A mortality of 90 percent was recorded among lambs. In some cases the symptoms were very acute, and death occurred within a few hours. In others, the disease ran a more sub-acute or chronic course. In the acute form, the only symptoms shown were dullness, rapid respirations, collapse, and death within four hours. In post-mortem, the liver was found to be soft and friable and the kidneys congested. In the sub-acute or chronic form, the umbilicus was incompletely closed and swelling of the joints occurred. Investigation pointed to the disease resulting from the infection gaining entrance through the umbilicus."

The first description of human disease was of illness among the scientists and veterinarians involved in the investigation of the 1931 epizootic, and then it was retrospectively identified among the local farmers of the affected herds during the outbreak. Human disease was confirmed by injection of a malaria patient at Native Hospital in Nairobi with filtered blood from a sick lamb. The disease that developed in this patient and the other initial cases was described as 'dengue-like fever' or similar to influenza. One patient described "pains that developed in or near the joints extending from the base of the skull to the extremities. Other common symptoms include fever, headache, abdominal pains, joint and muscle pains, photophobia, retro-orbital pain, vomiting, nosebleeds, and sweating. The disease was first named 'enzootic hepatitis' due to the hepatic disease in animals, however it was quickly renamed 'Rift Valley fever' as a more accurate description of the febrile illness observed in humans.

After the 1931 recognition of RVF as a new disease, Daubney and colleagues transported infectious blood samples to the Welcome Bureau of Scientific Research in London where G.M. Findlay experimentally inoculated an assortment of animal species to examine the range of susceptibility. Mice, rats, and hamsters were as susceptible as lambs, while other species (rhesus monkeys, cats, and rabbits) were less [3].

- **In European Union:-**

RVF virus (RVFV) is an enveloped RNA virus characterized by a genome composed of three segments, designated L, M, and S, of negative or ambisense polarity. Like many bunya viruses, RVFV produces a non-structural protein encoded by the segment, the NSs protein, which acts as a virulence factors. It is transmitted from ruminants to ruminants by mosquito bites, mainly from the genera Aedes and Culex, but also from the genera Anopheles and Mansonia, as recently suggested in Madagascar and Kenya. Direct transmission between ruminants through contact with viraemic fluids, i.e. blood or fetal liquid, is also strongly suspected. Humans are mostly contaminated after contact with aborted fetal material, i.e. placental membranes from infected ruminants, which contain large numbers of virus particles and blood. Furthermore, RVFV was observed or experimentally demonstrated to persist for long periods in different biotic or a biotic settings. A laboratory assistant was infected in a laboratory 4 months after the virus was handled in this laboratory; the virus may be isolated from carcase tissues such as spleen or liver between 36 and 72 h after death; and infected sheep plasma retained RVFV infectivity after 8 years of storage and shipment under a variety of refrigeration conditions. Consequently, veterinarians and laboratory, agricultural

and slaughter house workers may be at risk. If it exists, the viral load in raw milk is assumed to be low.

The presence of virus in nasal and lachrymal secretions and the health and economic consequences of RVF outbreaks are severe. Besides losses resulting from animal trade controurine and faeces of infected animals has not been demonstrated to date, no human-to-human transmission of RVF has been documented.

RVF infection causes abortion storms in pregnant ruminants and acute deaths in newborns. However, the severity of clinical signs depends on the species: sheep are more susceptible than goats, which are themselves more susceptible than cattle and camels. In adults, one may observe non-specific signs such as vomiting, diarrhoea, respiratory disease, fever, lethargy, and anorexia. Although, in the majority of human cases, RVFV causes a mild illness with fever, headache, myalgia, and liver abnormalities, a minority of human cases of infection may lead to either retinitis with permanent vision loss, encephalitis, or haemorrhagic forms that may lead to death. During the2000 Saudi Arabia outbreak, the major clinical characteristics reported among 165 consecutive patients included a high frequency (75%) of hepatocellular failure, acute renal failure for42% of patients, and haemorrhagic manifestations for approximately 19% of patients. A total of 56 patients died (33.9%). There is no etiological treatment, for either animals or humans. Several vaccines are under development, but, to date there are no licensed and commercially available vaccines to protect humans. Regarding ruminants, the Smith burn vaccine, a live attenuated vaccine, has been used for years in Africa. It cheaply and efficiently protects sheep and cattle with a single inoculation, but it may cause abortion or teratogenic effects in fetuses, and may present a risk of reversion to virulence: its use is thus reduced to endemic areas. A new promising live attenuated vaccine candidate clone 13 was obtained from a strain isolated from a mild human case in the Central African Republic. This vaccine was recently registered and marketed in South Africa. Owing to its severity, RVFV is considered to be a major zoonotic threat to the USA, and is number 3 on the list of the 17 most dangerous animal threats, behind highly pathogenic avian influenza and food and mouth disease. Early detection and implementation of appropriate measures, which are essential to minimize the consequences of outbreaks, require a deep understanding of transmission spread and persistence mechanisms. However, the epidemiology of RVF is complex. The disease is enzootic in many African countries and Madagascar, with outbreaks occurring every 5–15 years. However, the factors triggering outbreaks and the way in which the virus persists during inter-epizootic periods remain mostly unknown [4].

- **In USA and European Union:-**

Rift Valley fever [RVFV] is responsible for wide spread outbreaks in both humans and ruminants. Epizootics are characterized by mass abortions and high mortality in ruminants, resulting in high economic burden. High mortality rates have also been observed in humans and severe complications developing a small proportion of people, including hemorrhagic fever, blindness and residual neurological deficits. First identified in Kenya in1930, the geographical range of RVFV has been largely constrained to the African continent. However, over the past 50 years, RVFV has spread outside of its traditional endemic region and has been identified in over 30 countries, including parts of western Africa, Egypt, Madagascar and the Comoros. Recently, RVFV spread to the Arabian Peninsula in 2000, marking the first epidemic ever identified outside of the African continent.

Concerns over the potential for further spread and transmission of RVFV have been heightened by the significant spread and establishment of vector-borne diseases worldwide such as West Nile Virus (WNV), Crimean-Congo hemorrhagic fever and Japanese encephalitis. Crimean-Congo hemorrhagic fever has spread to over 30 countries in a range of ecological conditions. Similarly, Japanese encephalitis unexpectedly emerged in Australia, extending 3000 km from the previous known outbreak in Indonesia. Most notably the widespread establishment of WNV demonstrated the vulnerability of western nations to the introduction of arbo viruses.

RVFV can be spread by a range of mosquito vector species as well as other arthropods, many of which are currently present in North America and Europe.19–22 RVFV is considered to have high colonization capacity and has been identified as a potential emergent risk in western nations, both as a natural exotic pathogen and an intentionally introduced biological weapon. RVFV is, for example classified as a category a priority pathogen by the National Institute of Allergy and Infectious Diseases—indicating the potential to cause social disruption and requiring public health preparedness a high-consequence pathogen by the World Organization for Animal Health and the third most dangerous animal threat by the United States Department of Agriculture Animal and Plant Health Inspection Service after an influenza and foot-and-mouth disease.

The mobility of RVFV and its ability to survive in a range of bioclimatic environments has raised concern among both the human and animal health communities regarding the probability of its introduction into western regions, including North America and Europe. Despite this, there has been no comprehensive and systematic review of the literature to evaluate the state of knowledge regarding the risk of RVFV introduction and establishment in these regions. We present a systematic scoping review of existing literature and knowledge of RVFV to assess the feasibility of emergence and establishment of the virus in the United

States (US) and European Union (EU). The objectives herein include:

1 Review and characterize the epidemiological characteristics of RVFV that affect transmission potential.
2 Identify and evaluate the feasibility of potential pathways for the introduction of RVFV.
3 Assess the viability of the establishment of RVFV into the US and EU based on current knowledge [5]

Taxonomical classification of RVF:-

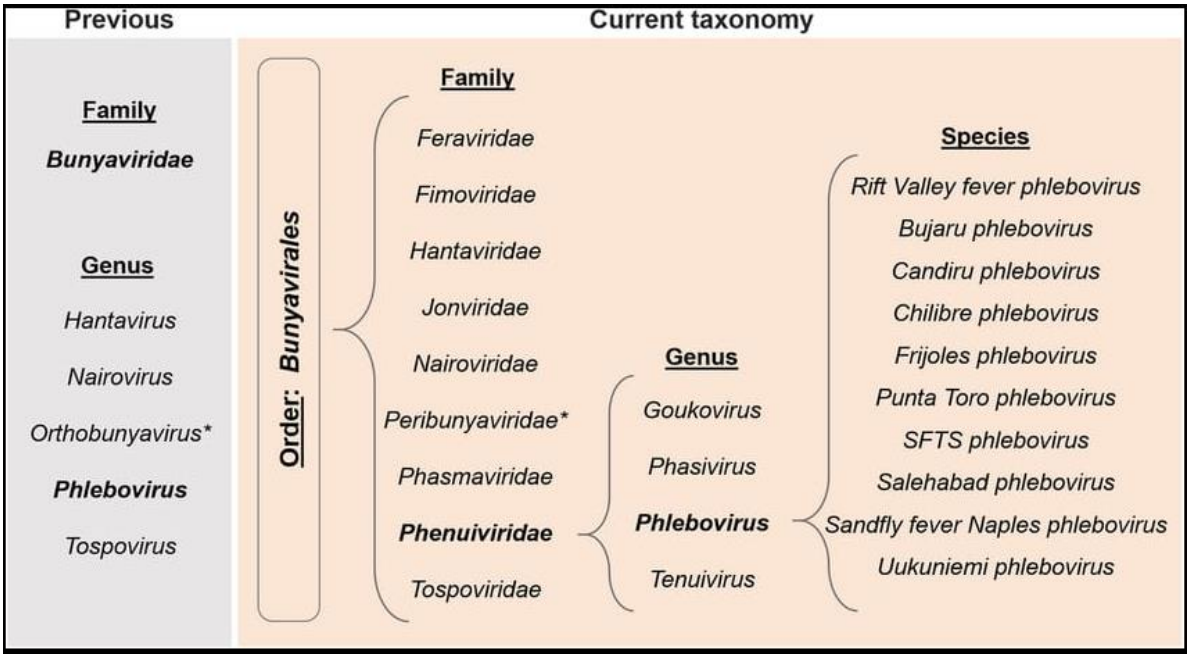

Figure-1: Classification of Rift valley fever [6]

Structure of RVF:-

Like all bunya viruses, RVFV is an enveloped RNA virus characterized by a genome composed of the segments designated L, M and S of negative or ambisense polarity. All the replication steps occur in the cytoplasm of infected cells and virions mature by budding in the Golgi compartment.

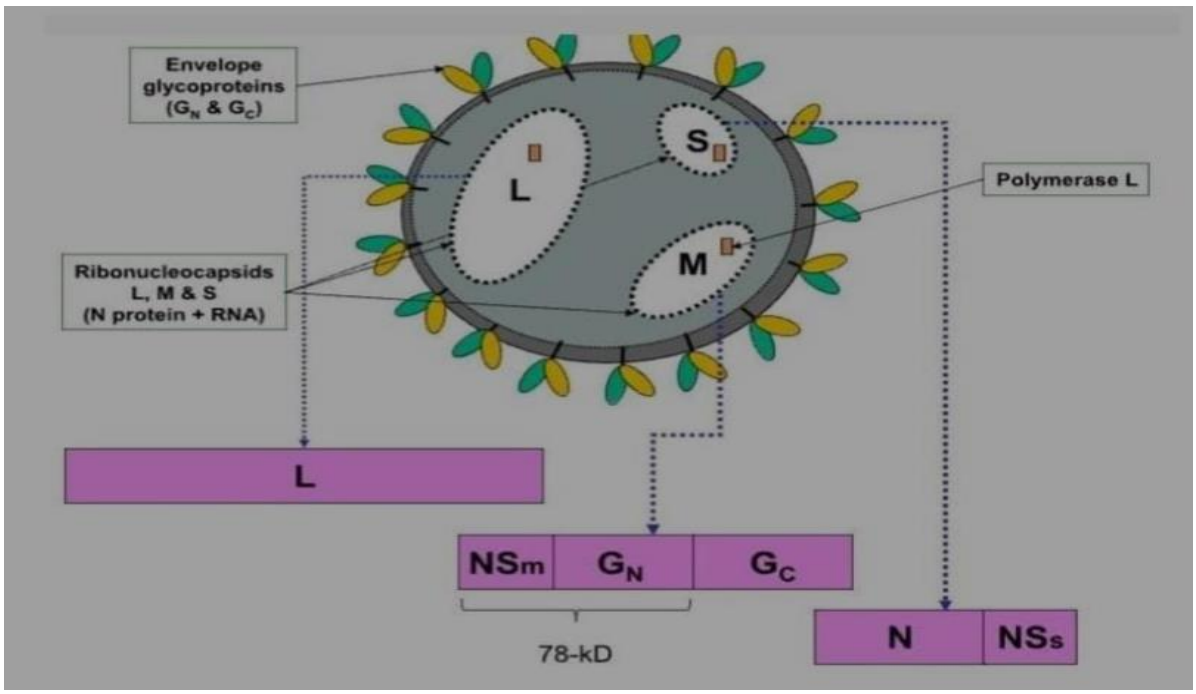

Figure-2: Schematic diagram of Rift valley Fever virus [7]

Transmission:-

RVFV Transmission in Natural Environments

Multiple studies have been conducted on the epidemiology of RVFV among vectors, hosts, and reservoirs in its endemic range, in particular to understand environmental links with vector life cycles that may underlie the episodic nature of large epizootics and epidemics.

Primary Mosquito Vectors, Endemic Cycles, and the Environment

Sero surveys conducted in a number of areas in the absence of epizootic circulation detected RVFV-neutralizing antibodies, indicating an endemic maintenance cycle independent of epizootic. Linthicum *et al*., isolated RVFV during inter epizootic periods from male and female *Aedes mcintoshi* reared to adult from larvae collected in the field after artificial flooding. These findings led to the hypothesis that RVFV is maintained during inter epizootic periods in an endemic cycle that depends on intermittent periods of heavy rainfall and periodic short-term flooding of low-lying habitats, known as *dambos* in East African and *pans* ad *vleis* in South Africa , and on the vertical transmission of the virus (i.e., transovarial inheritance of the virus from female mosquitoes to offspring) by floodwater *Aedes* mosquitoes.

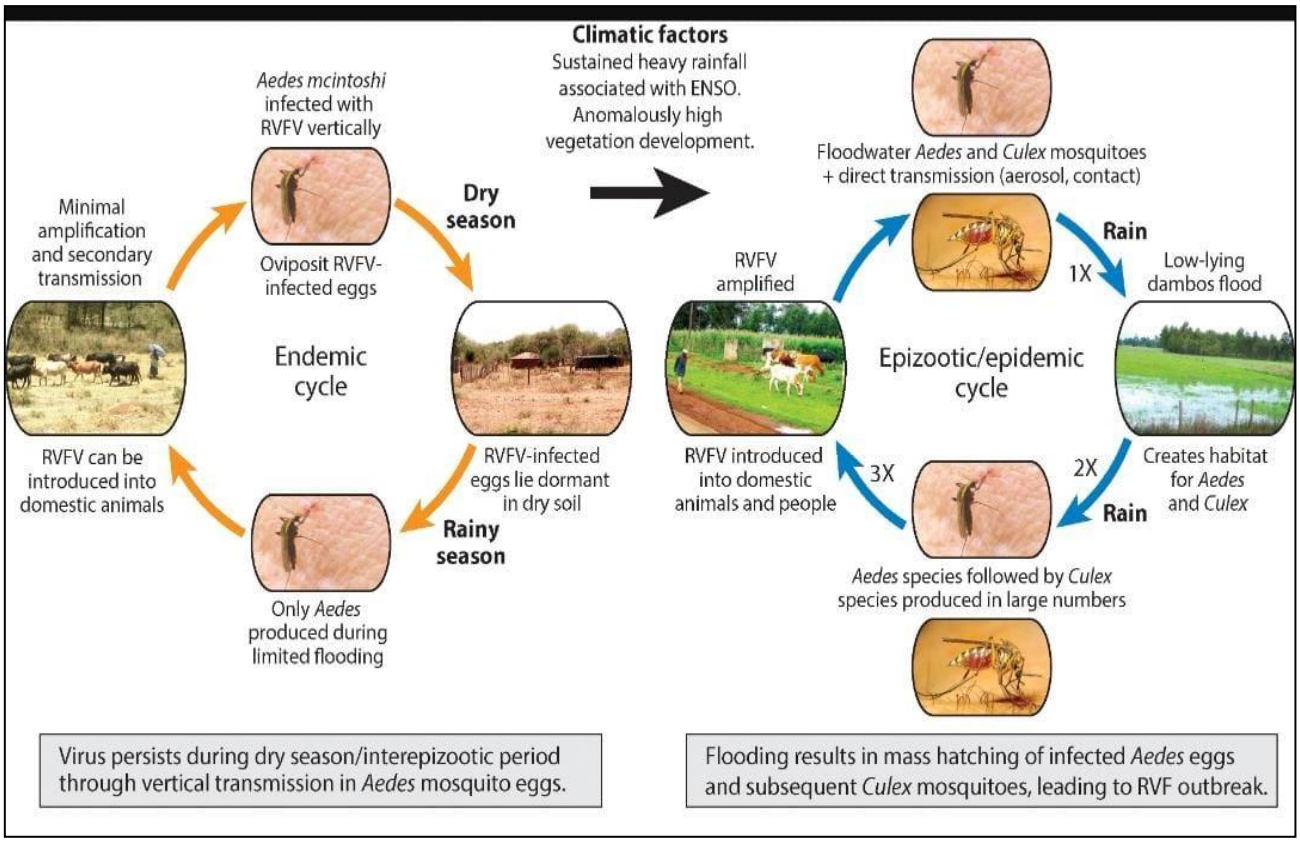

Figure-3: Schematic of the Rift valley fever virus (RVFV) life cycle depicting the endemic (left)and epizootic(right) phases, depending on the temporal and spatial extent of excessive rainfall

- **RVFV Transmission in Experimental Infection Studies:-**

Given the recent movement of RVFV out of its endemic range and the potential for the virus to further expand its range, experimental infection studies have been conducted to identify possible vectors and hosts in emerging regions.

➢ **Vectors**

Laboratory studies have identified many European, African, and North American mosquito species as potential competent vectors of RVFV. The ability of mosquitoes to become infected with RVFV and transmit the virus varies widely. More extensive laboratory investigations are needed to quantify these differences, particularly in different geographic populations of the same species, and in other vectors that might transmit RVF in different geographical regions of sub-Saharan Africa.

➢ **Vertebrate hosts**

RVFV circulates in the blood of experimentally infected domestic livestock for 1 to 4 days and has been found in the liver and spleen of sheep for up to several weeks. The persistence of RVFV in sheep could contribute to the transmission cycle by permitting the virus to be introduced into new geographic areas through the movement of infected animals. Additional information on the historical background of RVFV (geographic groupings, role of land-use change, climate

and weather links to RVF epizootic periods, social and economic impact, and movement and trade restrictions) and on the virus in general (strain variation, antigenic relationships, evolution, reassortment, and geography; host range; diagnostic procedures; disease association; and effects of virus on vectors) can be found in the Supplemental Material [8].

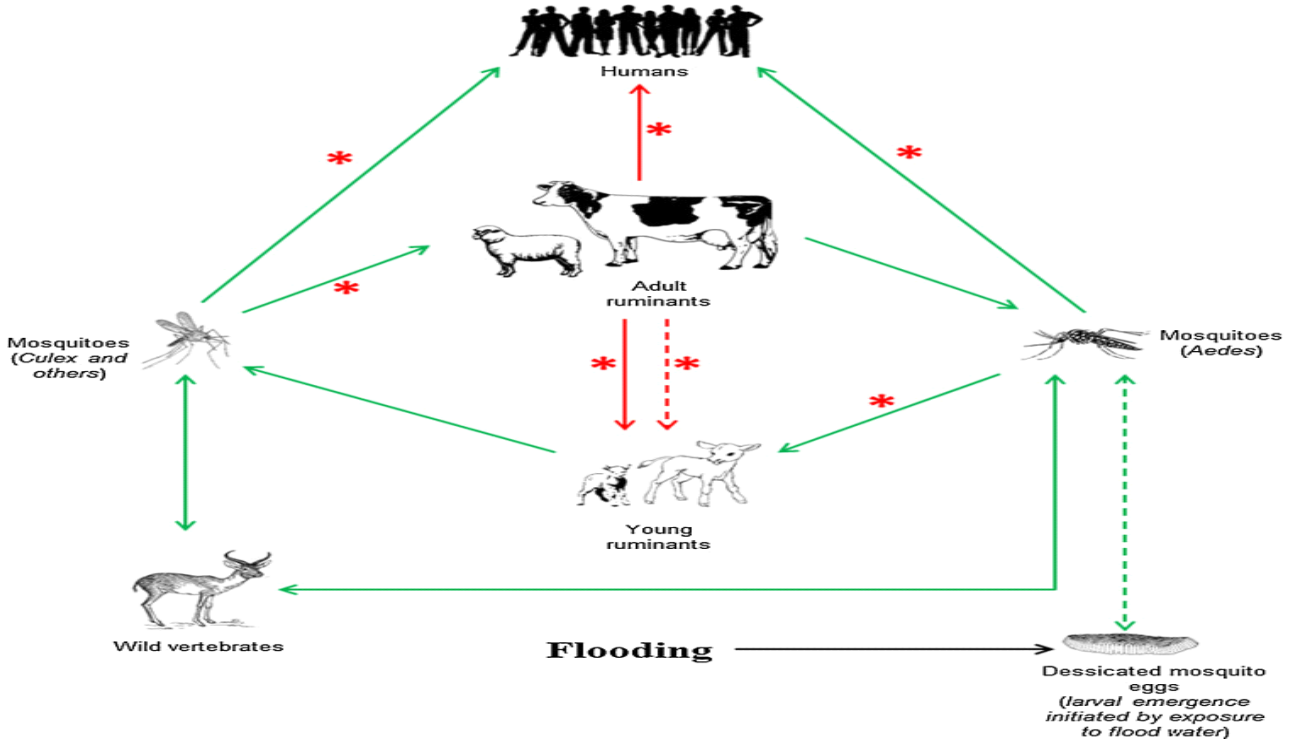

Figure-4: Schematic detailing the vectorial (red), direct (dashed arrow) transmission cycle of RVFV [21]

Etiology:-

RVF is caused by RVF virus which belongs to the family Bunyaviridae and the genus Phlebovirus. These are spherical virions with diameter of 80-120 nanometers and a host cell derived, bi lipid layer envelop through which virus coded glycoprotein spikes project. This single stranded Ribose Nucleic Acid (RNA) virus has a lipid envelope and two surface glycoprotein, G1 and G2. The genome has three segments: L (Large), M (Medium) and S (Small). RVF virus replicates in the mosquitoes and in the vertebrate animals. The liver, spleen and brain are the major sites of viral replication. The Virus is resistant in alkaline environments but inactivated at pH <6.8.The virus can be inactivated by disinfectants such as calcium hypochlorite, sodium hypochlorite and acetic acid; and be maintained for 8 years when stored below 0°C [9].

Risk Factors:-

- Livestock such as goats, sheep, camels and cattle can become infected with RVF virus (RVFV) when bitten byan infected mosquito, typically of the Aedes genus. In more susceptible breeds, pregnant goats, sheep and cattle infected with RVFV experience.
- High rates of spontaneous abortions, and there are high case fatality rates for young animals. Indigenous breeds of livestock appear to be less susceptible than imported breeds.
- Most infected humans are asymptomatic or experience a mild febrile illness, but ocular damage, meningoencephalitis, haemorrhagic fever or death may occur in a minority of cases. This possibility of severe complications from infection makes identification of human RVF risk factors a public health priority in affected areas.
- Most of the likely risk factors relate to modes of transmission of RVFV, Humans are thought to become infected with RVFV when they handle the blood or tissues of infected animals or inhale the aerosolized body fluids of infected animals during slaughter or veterinary procedures.
- Humans may also contract RVFV from infected mosquitoes, and some studies suggest that raw milk from infected animals and bites from infected haematophagous (blood-consuming) flies may also be transmission routes (World Health Organization 2008) [10].
- Rift Valley fever virus (RVFV) was first isolated in Kenya as a virus with the capacity to infect live stock herds of sheep and cattle, as well as humans.
- Since its initial discovery, RVFV has been primarily contained within the African continent, with the exception of movement of the eastern coast of African to the island of

Madagascar in 1990.

- Significant emergence into neighboring regions occurred in the early 2000s when outbreaks were reported in Saudi Arabia and Yemen .To this day, much of sub-Saharan Africa and Egypt is endemic for RVFV or has been affected by sporadic outbreaks.
- Wild animals have been suspected to contribute to maintenance of RVFV evidence driving such speculation is limited to the presence of antibodies in certain wildlife species. Amplification of the virus in mosquitoes is linked to mosquito abundance and breeding behaviors that are expanded by periods of heavy rainfall following extreme drought.
- Of the many competent vector species, infected females of some mosquito species may transmit the virus to their offspring during or transovarial transmission (TOT), readily allowing future generations of mosquitoes to transmit RVFV.
- Transmission in livestock is initiated by mosquito bite and amplified within herds by direct contact with infected bodily fluids, yet there has been little evidence of transmission between animals by way of respiratory droplets and nasal discharge that are characteristic of common respiratory infections.
- There is Significant evidence to suggest that vertical transmission may be possible in pregnant animals that are not viremical though findings are limited to laboratory studies and cannot conform aviable offspring following in utero exposure, as infection of pregnant animals typically results in abortion storms that eliminate any viable offspring.

❖ **Humans can be exposed by mosquito bite or through contact with infected fluids and tissues**.

- Many studies suggest vector-borne transmission is less likely for humans. Zoonotic exposures are driven by many of the occupational and homestead behaviors that are performed with regularity such as herding, milking, slaughtering animals, and tending to animal health neesds in both veterinary and animal health worker capacities.
- An exposure has been shown to elicit a higher incidence than individuals having close contact with or caring for animals at the homestead and is likely related to contact with a higher volume of animals and their fluids.
- Aerosolization Occupational is also a possible, although unlikely route of transmission, and has been correlated with a higher likelihood of severe disease in laboratory experiments.
- Despite the presence of RVFV in Africa and the Middle East, emergence of the virus has the potential to cause catastrophic damage to naïve populations of animals and humans.
- Competent vector species have been identified in many regions that are currently unaffected by RVFV providing the ecological support for amplification by mosquito breeding and varial transmission (TOT).
- Rift Valley fever (RVF) causes mild to severe disease in many animal species, with aninverse relationship between the age of the animal and morbidity and mortality, where the younger the animal, the higher the likelihood that the infection will be fatal.
- Infection in older animals usually produces mild, self-limiting febrile and respiratory symptoms, with a mortality rate ranging from 10%to 30%.
- Disease severity is also dependent on the species of the animal, and may be specifically virulent in sheep, followed by other commonly domesticated animals such as goats, cattle, buffalo and camels.
- While initial symptoms in animals tend to be non-specific, such as diarrhea, vomiting and respiratory disease, more notable signs of RVFV infection in animals include epitaxis, wasting spontaneous abortion by pregnant animals and animal fatalities.
- In humans, RVF disease presentation varies widely, and factors contributing to disease severity are widely unknown. Many experience mild, non-specific, and self-limiting febrile illness that may occasionally present as a biphasic fever with an intermittent remission period of 1–2 days between febrile events.
- More severe symptoms, typically occurring in up to 8–10% of cases, include ocular scarring, central nervous system (CNS) involvement, hemorrhagic fever, organ failure and death. RVF can also cause human abortions, still births, and congenital infections.
- Approximately 1–2% of cases experience hemorrhagic fever symptoms, wherein up to 50% of hemorrhagic cases are fatal.
- The increased risk of fatality with hemorrhagic presentation maybe due to a loss of fluids and multisystem shock, organ failure related to loss of blood volume and fluids, or lack of or mismanagement of symptomatic treatment.
- In vitro studies have suggested that hemorrhage resulting from RVFV infection may be linked to transcription factor IIH (TFIIH) expression levels, yet there have yet to be effective treatments for viral hemorrhagic fevers (VHF) beyond basic symptomatic treatment and monitoring. It has been suggested that hemorrhagic cases of RVFV infection may increase the risk of nosocomial transmission for healthcare workers and other individuals providing care, yet human-to-human transmission by nasocornial routes of exposure have yet to be documented.
- Despite RVF commonly being presented as a

mild, self-resolving febrile illness, disease severity has varied by region in epidemiological reports.

- Publications from Yemen from January 2014 to August 2016reported hemorrhagic fever in 9% of their anti-RVFV IgM positive hospitalized patients; whereas estimates for hemorrhagic symptoms are often limited to 1–2% of cases.
- Early outbreaks in Saudi Arabia experienced approximately double the amount of fatal cases than neighboring Yemen, which is likely due to insufficient immunity in the previously naïve community, or increased pathogenicity and disease severity as a result of genomic mutations and reassortments.
- Variability in disease severity is also seen in neighboring regions, such as countries in East Africa, or intercontinental differences seen in Egypt versus in countries in sub-Saharan Africa and the horn of Africa that are affected by RVFV.
- Ocular scarring is often reported in 10% of patients, while some outbreaks have been associated with more than 40% of patients experiencing loss of vision. Patient's experiencing ocular symptoms typically report blurred or loss of vision and posterior eye pain, possibly caused by the development of lesions, edema at the optic disc, or retinal vasculitis or hemorrhaging.
- Loss of vision as a result of RVFV infection may be temporary or permanent, depending on the location and severity of the lesions within the ocular tunics. Reports have not distinguished a unilateral or bilateral effect specifically associated with RVFV infection, as confirmed RVFV-positive patients have been documented to suffer retinal scars both unilaterally and bilaterally.
- Multisystem effects of acute RVF are illustrated by involvement of the liver and kidneys, occasionally leading to the onset of hepatitis and nephropathy. Jaundice and splenomegaly are commonly found in patients during physical exams for diagnosis, and should be monitored carefully to avoid progression to multiple organ failure.
- Many studies have attempted to identify mechanisms of neurological complications from RVF, yet clear pathways, even those suggesting immune-mediation, have yet to be identified.CNS involvement may superficially appear as dizziness or vertigo, confusion and disorientation, and intense headaches, yet may suggest severe underlying manifestations.
- Meningo encephalopathy can occur in 1–2% of cases and may lead to convulsions, coma, or death. Psychological evaluations of such symptoms suggest CNS involvement may elicit the onset of mental health syndromes, with diagnoses similar to schizophrenia, and should be taken into consideration when considering immediate treatment and care options.
- Patients with progression of such syndromes should be evaluated for long term sequelae, as the persistence of psychological syndromes related to RVFV infection has yet to be fully described.
- Inconsistent prevalence and incidence of RVFV infection reported is possibly linked to untimely reporting or underreporting of cases or lack of laboratory confirmation in cases of suspected diagnosis.
- Acute cases are best confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) but facilities equipped with the resources, such as skills and instrumentation, required for thorough diagnosis using PCR may be sparse in many endemic regions.
- Epidemiological studies for assessing RVF burden are often limited to community surveys based on serological analysis of retrospective infection, represented by the presence of immunoglobulin G (IgE) antibodies.
- Detection of immunoglobulin M (IgM) antibodies may be possible yet assays designed for IgM detection are notoriously problematic, with potential cross-reactivity and interfering factors (such as rheumatoid factor) leading to inconsistent results, and are therefore not as reliable as PCR diagnostics for acute cases.
- These analyses may not describe the true burden of RVF in a given population, as acute infections are rarely detected and clinical factors cannot be monitored in real time.
- Underreporting may also be due to stigma associated with reporting cases of RVF in animals and humans, which is a phenomenon that is not limited to RVF, but described broadly with infectious diseases throughout history.
- Stigma against RVF survivors has not been reported, yet both internal and societal stigmas borne from restrictions with livestock trade and sales may influenced own stream behaviors.
- Trade restrictions for three years are implemented when animal cases are reported and confirmed which may have a major impact on local economies and personal incomes. Additionally, animal infections can trigger a loss of revenue from a reduction in herd size from livestock deaths, and delayed production of sellable animal products due to illness and costly quarantine procedures.
- Spontaneous abortion in pregnant animals also reduces future product generation capacity with the loss of offspring influencing further financial burden.
- Community beliefs about processing animal carcasses and use of specific animal parts after death drive personal behaviors that are

negligent of the estimated risk of disease exposure, leading individuals to continue engaging in behaviors to avoid bad luck or cultural stigma despite increased risk of personal exposure or continued exposure of other animals, such as skinning animal carcasses before disposal, or harvesting and are consuming specific organs.

- Appropriate risk-mitigating behaviors may not be engaged if the perceived risk of exposure is low or not well understood.
- Travel and tourism catalyzes new opportunities for infections in international populations, with the ease of air travel allowing for acutely infected individuals to rapidly reach new destination.
- Traveler-acquired cases of RVF continue to occur, and the public health implications of such cases continue to stress the importance of accurate incidence and prevalence reporting, rapid diagnostic availability and affordability and the need for a vaccine for human use [11].

Pathogenesis of RVF:-

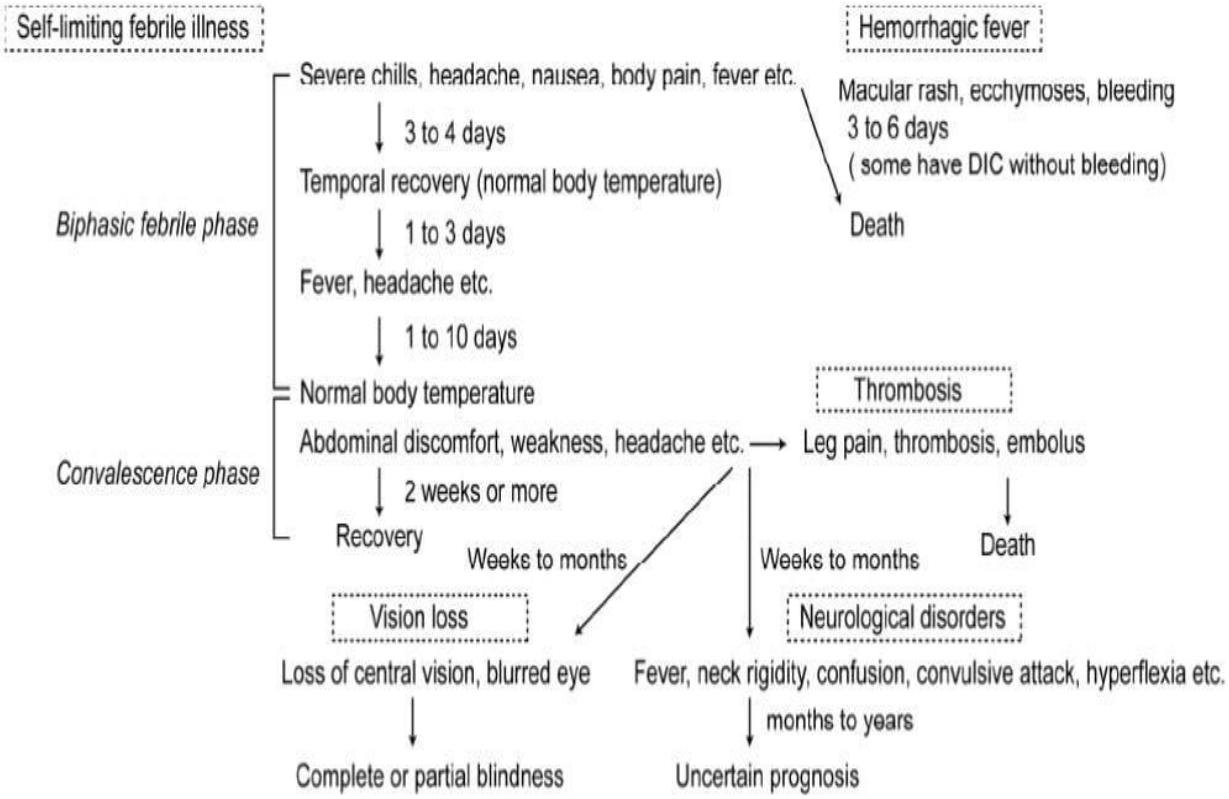

Figure-5: The pathological forms of Rift valley fever in Humans [12]

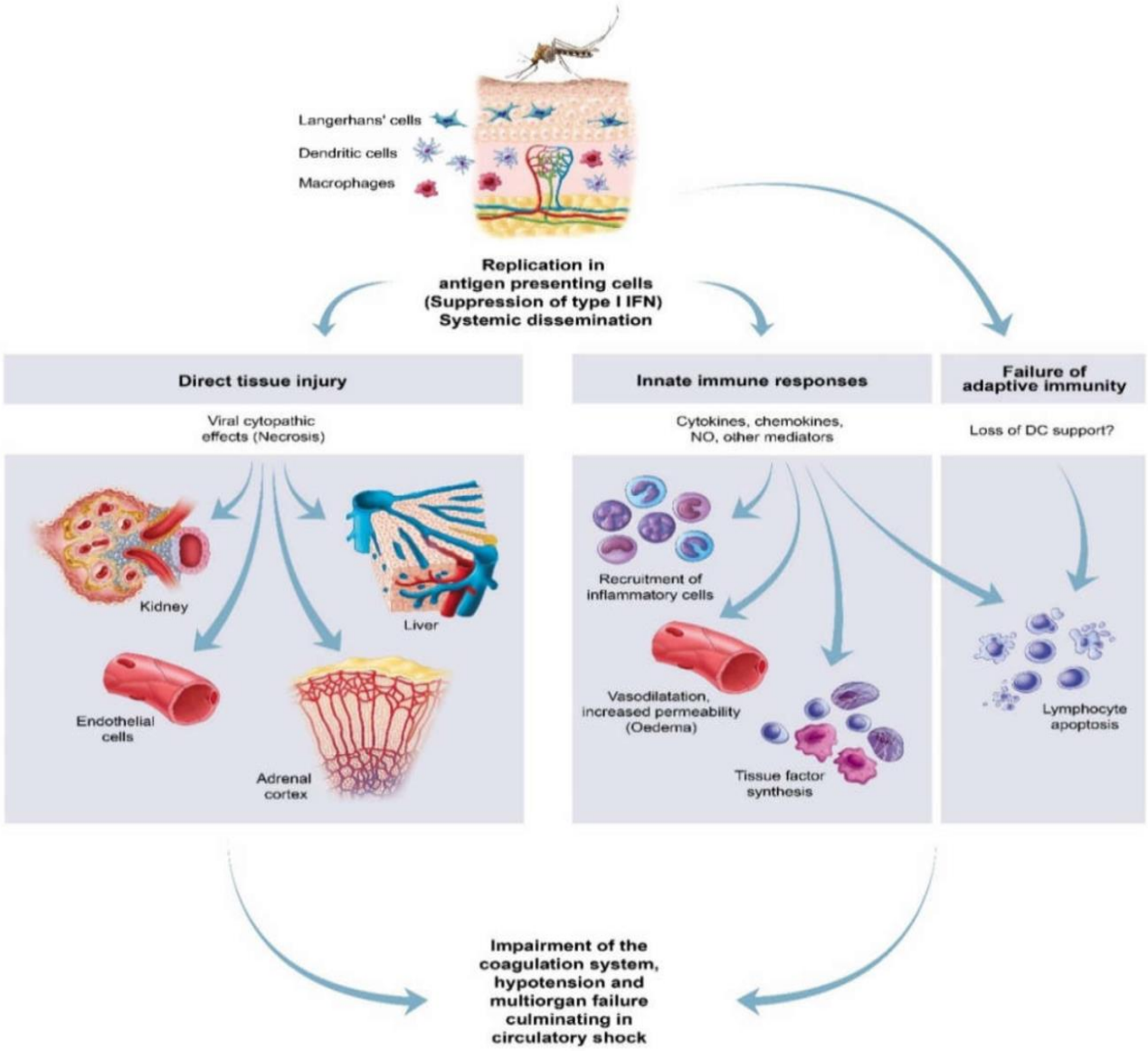

Figure-6: Model of the Pathogenic mechanism underlying RVFV infection [13]

Clinical signs and symptoms of RVF

➢ **Mild form of RVF in humans**

The following are clinical features of the mild form of RVF in humans:

- ✓ The incubation period (the interval from infection to onset of symptoms) for RVF varies from 2 to 6 days.
- ✓ Those infected either experience no detectable symptoms or develop a mild form of the disease characterized by a feverish syndrome with sudden onset of flu-like fever, muscle pain, joint pain and headache. Some patients develop neck stiffness, sensitivity to light, loss of appetite and vomiting; in these patients the disease, in its early stages, may be mistaken for meningitis.
- ✓ The symptoms of RVF usually last from 4 to 7 days, after which time the immune response becomes detectable with the appearance of antibodies and the virus disappears from the blood.

➢ **Severe form of RVF in humans**

While most human cases are relatively mild, a small percentage of patients develop a much more severe form of the disease. This usually appears as 1 or more of 3 distinct syndromes: ocular (eye) disease (0.5–2% of patients), meningoencephalitis (less than 1% of patients) or haemorrhagic fever (less than 1% of patients).

The following are clinical features of the severe form of RVF in humans:

➢ **Ocular form:-**

In this form of the disease, the usual symptoms associated with the mild form of the disease are accompanied by retinal lesions. The onset of the lesions in the eyes is usually 1 to 3 weeks after appearance of the first symptoms. Patients usually report blurred or decreased vision. The disease may resolve itself with no

lasting effects within 10 to 12 weeks. However, when the lesions occur in the macula, 50% of patients will experience a permanent loss of vision. Death in patients with only the ocular form of the disease is uncommon.

- **Meningoencephalitis form:-**

The onset of the meningoencephalitis form of the disease usually occurs 1 to 4 weeks after the first symptoms of RVF appear. Clinical features include intense headache, loss of memory, hallucinations, confusion, disorientation, vertigo, convulsions, lethargy and coma. Neurological complications can appear later (after more than 60 days). The death rate in patients who experience only this form of the disease is low, although residual neurological deficit, which may be severe, is common.

- **Haemorrhagic fever form:**

The symptoms of this form of the disease appear 2–4 days after the onset of illness, and begin with evidence of severe liver impairment, such as jaundice. Subsequently signs of hemorrhage then appear such as vomiting blood, passing blood in the faeces, a purpuric rash or ecchymosed (caused by bleeding in the skin), bleeding from the nose or gums, menorrhagia and bleeding from vene puncture sites. The case-fatality ratio for patients developing the haemorrhagic form of the disease is high at approximately 50%. Death usually occurs 3 to 6 days after the onset of symptoms. The virus may be detectable in the blood for up to 10 days, in patients with the hemorrhagic icterus form of RVF.

The total case fatality rate has varied widely between different epidemics but, overall, has been less than 1% in those documented. Most fatalities occur in patients who develop the haemorrhagic icterus form [14].

Clinical Complications arising in different countries

- **Ocular complications of RVF in Saudi Arabia**

Patients suspected of having RVF were identified through an elaborate preexisting system of primary health centers that refer acutely ill persons to district hospitals for assessment of criteria for admission as RVF case patients.

Only those patients who had symptoms and signs consistent with RVF and who were serologically positive for RVF were diagnosed as RVF cases and were included in this study. The patient's were studied in 2 groups. The patients in group 1 (n 206 inpatients) were consecutively seen patients who were admitted to the RVF unit of the King had Central Hospital from September through November 2000 for the management of moderately severe illness. Group 2 consisted of ambulant patients (outpatients) who were referred to the ophthalmology outpatient department for an assessment of visual symptoms. They had mild symptoms consistent with RVF and were serologically positive for RVF but did not require admission into the hospital. They were followed up in the clinics at regular intervals.

Information such as medical history and demographic data, risk factors of RVF virus infection, clinical manifestations, and laboratory results were obtained from each patient, as well as the onset of ocular and systemic symptoms. Complete ophthalmologic examination, laterality, localization of uveitis, and ocular finding were undertaken. It included baseline and final best-corrected visual acuity on a Snellen scale, slit-lamp bio microscopy, tonometry, and detailed funduscopy by indirect ophthalmoscopy with a20-diopter (D) or 90-D lens, or both. Color fundus photography and fluoresce in angiography were performed in selected patients when media opacities allowed visualization of the fundus. Out patients were reexamined at 3-, 6-, and 9-month intervals.

Patients who experienced only anterior inflammatory reactions were classified as having anterior uveitis. Those who had vitreitis sheathing of retinal vessels, retinitis, retinal hemorrhage, or optic disc edema were classified as having posterior segment inflammation. Ocular complications were defined as irreversible structural changes caused by intraocular inflammation [15].

- **RVF as a possible cause of human abortions**

A retrospective serological survey was designed to common are the mevalence of antibodies to RVF virus in-three groups of people treated at two clinics in villages in the centre of the epidemic area in Sharqiya Governorate, 70 km north-east of Cairo. The first group consisted of 45 women who had aborted during the first three months of 1977, before the RVF outbreak. The second group included 51 women who aborted during the neak of the epidemic in October, November-and early December of 1977. The last group consisted of 115 males and females randomly sampled from the villages. All blood samples were collected in May and $.me, 1978, and were examined for antibodies to RVF virus by the haemaealutination-inhibition (HI) test following the processes Of CASALS (1967).

RVF was not endemic in this area before October,

Consequently, any increased prevalence of antibodies in women who aborted during the epidemic, as compared to that in the other two groups (which should reflect a base-line antibody rate for the villages), would suggest that these women had aborted due to RVF virus infection.

- **Hemoglobin in west Africa**

During a recent survey in northern Liberia we found several "fast" haemoglobins with the mobility of HbN.* Electro phoretic mobility alone is not final proof of identity but our samples seem to behave as the "Liberian I" of ROBINSON *et al.*, (1956). This variant was investigated by AGAR & LEHMANN (1958) and renamed HbN. They found it to be similar to the two "fast" haemoglobins from Nigeria and Ghana mentioned by Facer & Brown. Thus HbN appears to be widely

scattered in West Africa. In Liberia, with one exception, all individuals with HbN trait hitherto discovered come from tribes speaking a Mande tongue (Mano, Kpelle, Lorma, etc.). Further, in our study we found the haemoglobin electrophoretic pattern A + S in 117 samples (3 *Q'$) and A + C in 12 (0.4%) suggesting that in this lmguistic group HbN is at about the same prevalence as HbC [16].

- **RVF Virus Infection with Miscarriage in Sudanese Women**

Miscarriage was the chief outcome variable. Categorical data such as pregnancy outcome, clinical symptoms in Rift Valley fever virus or chikungunya virus positive compared with negative patients, and if haemorrhagic disease was correlated with miscarriage, were analyzed using Pearson's χ^2 test. Fisher's exact test was used in analyzing the timing of miscarriages (early vs. late) between patients positive and negative for Rift Valley fever virus. Analysis of the relation of scale variables (age, total white blood cell counts, platelets, haemoglobin, and haematocrit) to Rift Valley fever virus or chikungunya virus infection was done with independent-samples t tests. Multiple logistic regressions was used to calculate the odds ratio (OR) for risk of miscarriage depending on Rift Valley fever virus infection with adjustment for age, haemorrhagic disease, and chikungunya virus infection. To test if chikungunya virus infection affected the association between Rift Valley fever virus infection and risk of miscarriage, the chikungunya virus by Rift Valley fever virus interaction was added to the model. CIs were set at 95% and statistical significance was 0·05.

In this study we found that infection of pregnant women with Rift Valley fever virus was significantly associated with miscarriage. The results were conclusive and they have not been described before. Acute infection was detected using complementary methods; the presence of Rift Valley fever virus RNA was detected by RT-PCR and anti-Rift Valley fever virus IgM antibodies with neutralising capacity. Moreover, the pregnant women who were positive for Rift Valley fever virus had characteristic clinical symptoms, as reported from several previous outbreaks. The women positive for Rift Valley fever virus that had miscarriage had more severe clinical symptoms than positive women with normal. Pregnancy but laboratory parameters did not different. Many other factors could affect the severity of a Rift Valley fever virus infection, but those were not studied here [17].

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 reverse transcriptase polymerase chain reaction, antigen-detection enzyme-linked immune sorbent assay, or isolation of live virus.
- ✓ After the cessation of viremia immunoglobulin can be detected transiently.
- ✓ Recovered patients will have persistent IgG antibodies for years after infection, and thus can be useful for determining sero-positivity and historical infection rates.
- ✓ Although some rapid diagnostic tests are in development none are available yet commercially. Currently, the availability of clinical testing is only though international reference laboratories such as the Centers for Disease Control and Prevention in Atlanta, Georgia, the Kenya Medical Research Institute, and the Onderstepoort Veterinary Institute in South Africa, among others [18].

- **Clinical 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.

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 categorized 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 in apparent.
- 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)
- ✓ In appetence
- ✓ Weakness and depression
- ✓ bloody or fetid diarrhoea
- ✓ more icterus than in lambs

• Adults (moderately susceptible)
- ✓ Often in apparent 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 o rapid, abdominal respiration prior to death

Within 24–36 hours

1. 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 o 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 epigastria discomfort, photophobia
- Recovery occurs within 4–7 days
- Complications: retinopathy, blindness, Meningo-encephalitis, hemorrhagic syndrome with jaundice, petechiae and death.

Lesions
- ✓ Focal or generalized hepatic necrosis (white necrotic foci of about 1 mm in diameter)
- ✓ Congestion, enlargement, and discoloration of liver with sub capsular hemorrhages
- ✓ Brown-yellowish color of liver in aborted fetuses
- ✓ Widespread cutaneous hemorrhages, 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
- Heart water
- Ovine enzootic abortion
- Toxic plants
- Bacterial septicaemias
- Rinderpest and Peste des petits ruminants
- Anthrax [19]

Differential diagnosis of RVF is challenging due to the broad overlap of symptoms with other haemorrhagic fevers. Specimens from any suspected cases need to be handled under enhanced BSL-3 conditions and transferred under biological hazard regulations to a respective reference laboratory, requiring trained biomedical professionals. Despite the wide range of commercial and laboratory- developed methods, currently there is not a validated point of care diagnostic tool. The commercially available RT- PCR kits can be used for case confirmation, but the short period of viremia requires a combination of the molecular assay with a serological test to ensure reliable detection of cases. The lack of published independent studies evaluating any of the commercial molecular and ELISA assays for humans complicate the use of these tests for large- scale surveillance. Similarly, the quality of in- house methods requires further cross- validation between laboratories to evaluate their applicability for wider use. The necessity for BSL-3 facilities and trained biomedical staff for handling of suspected RVFV samples is particularly challenging in remote areas, close to farms or animal slaughtering facilities where outbreaks are mostly likely to occur. The high overlap of disease symptomology with other febrile illnesses, as well as the need for use of reference laboratories for testing likely lead to underreporting of cases and ongoing virus trans-mission which eventually increases the epidemic risk associated with RVFV. Epidemiological studies in cohorts or areas with evidence of prior

outbreaks are recommended to enable estimation if the true disease burden and validation of existing molecular and serological tests, including RDTs when available [20].

Early detection of suspected cases is pivotal to ensure timely control measures are implemented to reduce the disease burden. The sudden onset of large numbers of abortions ('abortion storms') and mortalities among young animals in affected livestock, together with the appearance of the disease in humans, is considered characteristic of an RVF epidemic. In humans, the clinical recognition of acute haemorrhagic fever cases generally triggers an outbreak investigation in endemic regions. However, clinical diagnosis alone cannot be considered reliable as some animals, for example camels, may have in apparent infections. Moreover, infection of susceptible, adult non-pregnant ruminants is often subclinical and hence outbreaks outside of the lambing or calving seasons can be easily missed. The clinical signs of RVF in animals tend to be nonspecific and differential diagnoses includes brucellosis, Bluetongue, Wesselsbron disease, enterotoxemia, Bovine ephemeral fever, vibriosis, trichomonosis, Nairobi sheep disease, heart water, ovine enzootic abortion, toxic plant ingestion, bacterial septicaemias peste des petits ruminants, anthrax and Schmallenberg disease.

Laboratory tests

Reference laboratories are often responsible for the coordination of field sampling and testing but with heterogeneous laboratory coverage in some endemic regions, delays in diagnosing the disease commonly occur. Laboratory diagnosis would ideally rely upon a combination of serological and molecular approaches. The usefulness of the chosen assay is dictated by the disease kinetics i.e. the window in which particular virological markers (e.g. virus, viral RNA, IgG, IgM, hepatic lesions) are likely to be detected. There is likely to be some variability in disease kinetics between humans and animal species due to variation in susceptibility between species, and even within species. RVFV can be detected by classic virological methods which include virus isolation, histopathology, antigen detection, antibody detection and nucleic acid based assays. For reporting RVFV in animals, the Office International des Epizooties (OIE); World Organization for Animal Health, require laboratory confirmation by at least two positive results from a combination of different diagnostic approaches preferably for the same specimen i.e. either positive for virus/viral RNA and antibodies or positive for IgM and IgG with demonstration of rising titres between paired serum samples collected 2–4 weeks apart [21].

Prevention

- Communicate risks about the disease or epidemic, not only to share information on prevention and mitigation measures, but also to encourage informed decision-making, positive behavior change and maintenance of trust in the Red Cross Red Crescent response. This includes the identification of rumors and misinformation around disease—frequent during health emergencies—to manage them appropriately. Volunteers should use the most context-appropriate communication techniques (ranging from social media to face-to-face interactions).
- Community education and engagement activities to encourage the adoption of protective behaviors are as follows
    - ✓ Thoroughly cook/heat all animal products (blood, meat and milk) before consuming.
    - ✓ Safe handling of sick animals (e.g. practicing hand hygiene, wearing gloves and other appropriate individual protective equipment).
- Animal vaccination is the most effective way to prevent RVF outbreaks in areas where the disease is endemic. However, vaccination should not be done once the outbreak is ongoing because of a risk of intensifying the outbreak (e.g. during mass vaccination campaigns in case of re-use of needles or by transmission to non-infected animals from infected animals that may not be displaying signs of illness).
- Livestock quarantine, restricting the movement of livestock and slaughter bans are most effective during the pre-outbreak and outbreak phases.
- Avoid contact with blood, body fluids, or tissues of infected animals. People working with animals in RVF-endemic areas should wear appropriate protective equipment (such as gloves, boots, long sleeves, and a face shield) to avoid any exposure to blood or tissues of animals that may potentially be infected.
- Use only safe animal products. All animal products (including meat, milk, and blood) should be thoroughly cooked before eating or drinking.
- Protect yourself against mosquitoes and other bloodsucking insects. Use insect repellents and bed nets, and wear long sleeved shirts and long pants to cover exposed skin [22].

Treatment

➢ **Anti virals for RVF**

Generally, antiviral treatments either target processes intrinsic to the virus, such as host cell binding or replication of the viral genome, or modulate host cellular processes important for the lifecycle of the virus. The former viral targeting paradigm has proven very effective in both HIV and HCV, which are both now largely controllable and manageable diseases. These compounds exploit unique aspects of the viral lifecycle, such as viral DNA integration or replication of RNA

genomes in combination to improve patient outcome and limit the development of viable escape mutations. Host targeted antivirals function by modulating cellular processes, such as translation and lipid metabolism that are essential for viral replication. While these processes would also be necessary for viral replication, they could be modulated to slow viral replication and allow the host immune response to control viral infection without overt toxicity.

Current strategies for treatment of patients with RVF focus primarily on providing supportive care. While numerous groups have been focused on studying the molecular mechanisms involved in the lifecycle of RVFV, no US FDA-approved effective therapeutics are available at this time. This review will summarize the strategies and identified compounds that have been evaluated for their efficacy as antiviral therapeutics for RVFV infection. Compounds with antiviral efficacy in cell culture, as well as animal models, is summarized in. Studies discussed in this review have primarily used two RVFV strains, pathogenic ZH501 and vaccine strain MP-12. RVFV ZH501 is a pathogenic strain that was isolated from a fatal human case during the first Egyptian RVF outbreak in 1977–1978. This strain is considered a select agent, and must be used at BSL3E or BSL4 containment. The MP-12 strain has been developed by serial plaque passages of the Egyptian ZH548 strain 12-times in the presence of a chemical mutagen, 5-fluorouracil. RVFV ZH548 was isolated from a febrile patient during the Egyptian outbreak in 1977–1978. RVFV MP-12 is not considered a select agent and can be handled at BSL2, simplifying screening for antiviral compounds in proof-of-principle studies.

- **Ribavirin**

Ribavirin, a nucleoside analog, is one of the few drugs approved for treatment of selected viral hemorrhagic fevers. Since its development in the 1980s, it was the first antiviral being tested in models of phlebo virus infection. In initial studies it showed high efficacy in vitro using immortalized cell lines isolated from African green monkey, Rhesus macaque and human cervical carcinoma against a diverse panel of RNA and DNA viruses withEC50 values ranging from 1 to 1000 μg/ml, including an EC50 of 80 μg/ml against RVFV ZH501.Thesestudies were quickly extended to a mouse model of infection using the closely related Phlebovirus, Punta Toro virus. Here, ribavirin treatment significantly impaired virus replication and severity of symptoms with 100% survival at 18.8 mg/kg subcutaneous (SC) daily administration, with initial treatment 4 hours before SC infection. examined the efficacy of intraperitoneal (IP) ribavirin in an aerosol challenge model of pathogenic wild type RVFV ZH501 in BALB/c mice after infection with 1000 plaque forming units (pfu).In this study, mice exposed by the aerosol route were not protected from RVFV infection, which has important implications for treatment of humans infected to aerosolized RVFV, such as in either a slaughterhouse environment or intentional release context. IP administration of the Immunostimulant poly (ICLC) in combination with ribavirin showed enhanced efficacy against SC delivered RVFV ZH501 infection (250 pfu) compared with ribavirin alone in infected Swiss–Webster mice. Unfortunately, the side effect profile of ribavirin, most prominently inflammation and hemolytic anemia, has limited its use in clinical settings. Lipid encapsulation has been successfully used in reducing the side effects through administration of lower but more targeted doses, resulting in increased survival of infected mice.

- **Favipiravir**

Favipiravir (also known as T-705 or Avigan R), originally developed by Toyama Chemical (Japan), is a nonnucleoside inhibitor in the influenza polymerase and has received approval for use against influenza viruses in Japan, and Phase-III clinical studies have been completed in the USA. Importantly, favipiravir has been demonstrated to be efficacious as a broad-spectrum antiviral against a wide panel of RNA viruses, including but not limited tofilo-, arena-, paramyxo- and bunya viruses. Indeed, during the 2014–2016 West African Ebola outbreak favipiravir was used under emergency protocols and in registered clinical trials. In initial in vitro studies, Gowen *et al*., demonstrated that favipiravir is highly active against bunya viruses from different genera, including RVFV with anEC50 of 32 μM. Subsequently, efficacy of favipiravir was evaluated in a hamster model for RVFV ZH501. Treatment initiated 1 hour post infection (HPI) with 200 mg/kg/day twice daily (BID) orally (PO) for 10 days protected 80% of SC infected animals with 30 pfu RVFV ZH501. Ribavirin (75 mg/kg/day, BID, PO) was included as a positive control and only resulted in 20% survival. Performing a delayed treatment study, it appeared that the therapeutic window for favipiravir in hamsters did not extend much beyond 6 HPI, where the overall survival was 60%. In contrast, delaying treatment with ribavirin until 24 HPI was highly effective at protecting all animals from acute hepatic infection; however, nearly all ribavirin-treated animals ultimately succumbed tolate-onset encephalitis. Interestingly, favipiravir appeared to be more effective in protecting animals from both acute and late-onset encephalitis, but the treatment window was limited to approximately 6 HPI. Last, a synergistic effect in protecting against acute and late-onset encephalitis could be demonstrated (up to 40% survival) when infected hamsters were treated 24 HPI with both antivirals in combination in comparison to monotherapies with either drug at the concentrations tested. In a separate study, using an aerosol exposure Wistar–Furth rat model Caroline and colleagues could demonstrate that animals receiving favipiravir within 1 HPI at 100 mg/kg/day BIDPO for 14 days were fully protected from lethal RVFV infection with 50 pfu. When treatment was initiated 48HPI, survival was still at 92%. While surviving animals did not show any signs of clinical disease rats that received favipiravir and died during the course of the study had indications for neurological

disease with pathological changes in the brain in the form of meningitis and lymphocytic vasculitis [23].

➢ **Vaccines**

In endemic and non-endemic areas, vaccinating livestock against RVFV represents the most sustainable strategy to mitigate the impact of RVF on livestock agriculture. The earliest vaccines such as:

1. Inactivated vaccines.
2. live-attenuated Smithburn vaccine.
    i. They were developed from virulent RVFV isolates using conventional technologies.
    ii. Although these vaccines have contributed significantly to the control of RVF in endemic countries in Africa, their production and use has been associated with a certain level of risk and they lack important attributes, such as the ability to DIVA, for use in non-endemic countries.
    iii. In recent years, several research groups or laboratories have reported substantial progress in the development of novel vaccines.
    iv. While many of the vaccines were initially tested in mice in proof-of-concept studies, several have progressed to evaluation in the natural target host, sheep or cattle, or have
    v. Met the criterion of DIVA. In this review, we have broadly classified RVF vaccines into;
        1. Conventional vaccines [referring to vaccines produced using non-recombinant DNA technology methods.
        2. Novel vaccines [referring to vaccines produced using recombinant-nucleic acid technology adapted from the classification by USDA.

Novel vaccines are further categorized into:

1. Type I vaccines (composed of antigens produced by recombinant nucleic acid technology.
2. Type II vaccines (consisting of genetically attenuated viruses created by deletion of genes encoding virulence factors or proteins dispensable for virus replication) and
3. Type III vaccines (consisting of live viruses into which DNA encoding protective antigens are introduced (virus-vectored vaccines)

- **Conventional RVF Vaccines**

Formalin-Inactivated

The initial application of RVF vaccines started with inactivated vaccines. The RVFV Entebbe strain, isolated from a mosquito in Uganda, was the first virus strain used as a vaccine after being formalin-inactivated. A formalin-inactivated vaccine based on the Entebbe virus, named NDBR103, was manufactured using a mouse master seed that had undergone 176 intraperitoneal or intravenous passages in mice followed by amplification in African Green Monkey cells. In 1977 and thereafter, the NDBR103 vaccine was used to vaccinate 500 human volunteers, including a group of 963 UN soldiers on a three-dose regimen. Most vaccinees who received all three doses seroconverted. This vaccine was further developed into the inactivated vaccine TSI GSD 200 by the United States Army Medical Research Institute of Infectious Diseases (USAMRIID). Data from a 12-month vaccination trial using this vaccine preparation indicated the induction of long-term immunity in vaccinated humans after a primary three dose vaccination followed by a single six-month boost. A formalin inactivated vaccine, with virus grown in BHK-21 cells, is commercially available from the Onderstepoort Veterinary Institute in South Africa for veterinary use. Also, another formalin-inactivated vaccine (lot NBR103) developed for use in humans, which was prepared from the 180th mouse passage of Entebbe strain of RVFV grown in monkey kidney cell culture, is available and has been used to control outbreaks of RVFV in South Africa. Another formalin in-activated vaccine was prepared by the Veterinary Serum and Vaccine Research Institute (VSVRI)in Egypt from a local Egyptian RVFV isolated in 1977 (ZH501) and was used in Egypt to vaccinate livestock. The virus for this vaccine was also propagated in BHK-21 cells, inactivated with 0.5% formalin, and adjuvanted with aluminum hydroxide. Although inactivated vaccines induce neutralizing antibody titers, the requirement for a booster vaccination to induce a protective immune response makes their use in resource-limited settings, most notably in transhumance and pastoral communities in Africa, problematic. This represents a major reason for the search for a better alternative, e.g., live attenuated vaccines.

➢ **Live-Attenuated RVFV Vaccines**

Smithburn Vaccine

The modified live Smithburn vaccine is one of the oldest and most widely used vaccines for controlling RVF in Africa. The vaccine virus is a neurotrophic RVFV strain, isolated from a mosquito Eretmapodites spp. in Uganda in 194. The vaccine was first produced as an avianized (by repeated culture in a chick embryo) live-attenuated animal vaccine in South Africa in 1951 via serial passages in a mouse brain (passage 102) and embryonated chicken egg. Subsequently in 1958, the virus strain that has only been passaged in a mouse brain 103 times was used as the only stock for further vaccine development. Since 1971, the vaccine stock has been propagated in BHK-21 cells for the formulation of a freeze-dried vaccine for the immunization of susceptible livestock in South Africa, many other countries in Africa, and in Saudi Arabia. The same vaccine stock at passage 106 has been used in Kenya since 1960and the seed virus was used to produce a live-attenuated vaccine in Egypt in 1994. In the period between 1951 and 1986, until the time when sales records were made public, millions of Smithburn vaccine doses were sold in South Africa, Kenya, Zimbabwe, Namibia, Egypt, and Israel. In recent years, a substantial amount of vaccine doses, mainly originating from South Africa, have been used in eastern

Africa and Saudi Arabia. The appeal of a Smithburn vaccine in African countries and Saudi Arabia for controlling RVF is attributed to its relatively low cost and its ability to induce long-lasting immunity after a single administration. The latter attribute makes the vaccine practical for administration in livestock maintained under the traditional extensive management system including livestock owned by nomadic and pastoralist communities [24].

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