Rift Valley Fever: Insights into Abortive and Zoonotic Disease

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ABSTRACT

RVFV, also known as the Rift Valley fever virus (genus Phlebovirus family Phenuiviridae), is an arbovirus infection that causes Rift Valley fever (RVF). Whenever RVFV shows up, it spreads epidemics among the local population and causes epizootics in livestock. Animals and people in Africa and the Arabian Peninsula have been affected by RVF, a disease spread by mosquitoes and caused by the RVFV. In RVF epidemics, animals contract the virus through mosquito bites, leading to substantial viral amplification and spread to nearby regions through livestock movement and mosquito migration. Following animal slaughter or the handling of embryonic materials, direct contact with infected animals or mosquito bites are the subsequent ways in which the virus is transmitted to humans. Real-time polymerase chain reaction (RT-PCR) reverse transcription can be used to identify RVFV. The most common symptom of RVF in pregnant animals is an abrupt, violent abortion. Animals with the virus may have up to 100% abortion rates because it directly targets the developing embryo. In young animals, the mortality rate can reach 100%. When this disease progresses from apparent to acute, it causes fever, weakness, and bloody diarrhea in adults, but it causes fever, loss of appetite, and death in young animals. RVFV infections in humans usually show no symptoms at all and go away on their own. After an incubation period of 4-6 days, symptoms of RVF, including fever, chills, fragility, headache, and joint and muscular pain, become apparent. An almost simultaneous, marked increase in the number of abortions performed on pregnant ruminants is the telltale sign of an RVF epizootic. Known as "abortion storms," these widespread abortion occurrences allow one to distinguish RVF from several other common infectious causes of abortion in ruminants, including toxoplasmosis, salmonellosis, chlamydiosis and Q fever (Coxiella burnettii). The one health approach is essential in combating this rapidly spreading infection. RVF can be effectively managed and prevented by focusing on the interconnectedness of human, animal, and environmental health.

Keywords: RVFV, Zoonosis, Abortion, Vector borne, RT-PCR, One-health.

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1. INTRODUCTION

The Rift Valley fever virus (genus Phlebovirus family Phenuiviridae; RVFV) is an arbovirus infection that causes rift valley fever (RVF). RVFV appears regularly, causing epizootics in livestock and epidemics in people living nearby. Furthermore, RVFV transmission is vertical among human and vector mosquito populations (Ahmed et al. 2020). The RVFV causes RVF, a mosquito-borne disease that has impacted both humans and animals across Africa and the Arabian Peninsula. The World Health Organization (WHO) views RVF as a priority for research and intervention since previous RVF epidemics have caused devastating public health catastrophes in affected nations. RVFV is highly contagious and has been associated to abortion and infant death in cattle, goats, and sheep (De Glanville et al. 2022).

Vector-borne transmission of RVFV is widely acceptable (Rissmann et al. 2017). Animals become infected with the virus by mosquito bites during RVF epidemics, which results in significant viral amplification and dissemination to neighboring areas via livestock and mosquito migration. The virus is subsequently spread to people by mosquito bites or direct contact with infected animals, such as during animal slaughter or the handling of embryonic materials. The symptoms of RVF in ruminants include a high fever, hemorrhagic diarrhea, high mortality among young animals, and abortion storm among pregnant animals. (Halawi et al. 2019). Pregnant animals frequently abort, which makes post-infection herd recovery difficult, and many generations of animals are lost during the outbreaks. For families and communities that rely on the sale of animal foods, milk, and byproducts as a source of revenue, rapid herd size reductions can also result in severe resource and financial pressure (Grossi-Soyster et al. 2019).

Even after 10 days, RVFV can be detected by using RT-PCR (reverse transcription real-time polymerase chain reaction). The levels of the antibodies immunoglobulin M (IgM) as well as immunoglobulin G (IgG) grow on days 4 and 7, respectively, after the onset of symptoms, and are identifiable by serological assay for at least 42 days for IgM and several years for IgG, respectively (Paweska et al. 2003). The three segments that make up the RVFV genome are short (S), medium (M), and large (L). The non-structural proteins (NS) and nucleocapsid (N) proteins are made by translating the overlapping open reading frames (ORF) that make up the S segment. The M segment encodes two glycoproteins (Gn and Gc) as a non-structural protein (NSm). The L segment also contains the RNA-dependent RNA polymerase (RDRP) gene (Ikegami 2012).

Modern RVF research aims to learn more about the disease's abortive and zoonotic nature. This includes determining the molecular mechanisms underlying the virus's propensity to cause fetal mortality and birth abnormalities in pregnant animals its ability to be transmitted from animals to people. Other goals include the development of new diagnostic tools and therapeutic interventions, assessing the risk of RVF outbreaks, and implementing early detection and response strategies to prevent disease spread. The purpose of this chapter is to increase knowledge about RVF and its effects in order to better protect human and animal populations.

2. EPIDEMIOLOGY

The epidemiology of RVF is poorly understood, particularly in terms of viral maintenance during inter-epizootic intervals (IEPs). A single species of *Aedes*, mistaken as *Aedes lineatopennis* before 1985 and later identified as *Aedes* (Neomelaniconion) McIntosh, has demonstrated the ability to transmit the virus to its offspring (Wright et al. 2019). It is reasonable to believe that RVFV can survive in the eggs of these species during the dry season and then hatch whenever the rains arrive (Linthicum et al. 1985).

Flooding caused by severe rainfall results in massive increases in mosquito populations that can lead to RVF epizootics, affecting vast numbers of livestock. Because of the relationship between RVFV infection and weather conditions, rainfall and changes in vegetation have been used to forecast RVF epidemics (Anyamba et al. 2010). Massive increases in mosquito populations due to flooding caused by excessive rains can produce RVF epizootics, impacting large numbers of animals. Due of the correlation between RVFV infection and climate, meteorologists have used precipitation and plant growth patterns to predict RVF epidemics. (Lumley et al. 2017). According to research on those insects, more than 53 varieties of mosquitos caught in the wild during an epizootic proved positive for RVFV (Kenneth J Linthicum et al. 2016). Even though more than 65 species have been identified as potential vectors, most of them are *Aedes* and *Culex* species (Mansfield et al. 2015).

Following the 1930s discovery of RVFV, outbreaks began to occur frequently from the 1950s (McMillen and Hartman 2018). In 1950s and 1951s, there were significant epidemics in South Africa and Kenya(Murithi et al. 2011). A second outbreak in South Africa in 1974-1975 led to the first human fatalities there. About 110 human cases were reported, culminating in seven fatalities (McIntosh and Gear 1980). Egypt experienced the greatest RVF outbreak between 1977 and 1979, with an estimated 200,000 human cases leading to 598 verified deaths (Laughlin et al. 1979). Due to unusual high rains, a significant epidemic in East Africa in 1997-1998 led to an estimated 89,000 human cases and 478 fatalities (Hebdomadaire 1998).

Heavy rains in 2018 resulted in an unexpected increase in RVFVs in East African countries like Rwanda, Kenya, Uganda, and Tanzania. This RVF outbreak was the deadliest in Rwandan history, resulting in the loss of two veterinarians and a large number of ruminant lives. Nomadic by clinical signs, not genetic approaches, were used for the majority of diagnoses of RVF in Cattle because of the tiny ruminant's limited economic and cultural relevance in Rwanda (Dutuze et al. 2020). According to RVF geographical distribution, the disease was confined to Sub-Saharan Africa until the year 2000, and then spread to the Arabian Peninsula and the rest of North Africa in 2008 and 2009. Serological research in ruminants and human populations in the Sahrawi refugee camps (Tindouf Province) along the Western Sahara (Algeria) border, in Mauritania, and southern Morocco found RVF-specific IgG antibodies in camels and goats. Geographical distribution of RVFV is shown in Fig. 1.

3. CLINICAL MANIFESTATIONS

3.1. ANIMALS

In pregnant animals, RVF manifests mostly as a sudden and violent abortion. Abortion rates in infected animals may be as high as 100% since the virus attacks the developing embryo directly (Michel Pepin et al. 2010). Animals of different ages and species have different mortality and morbidity rates. The mortality rate was as high as hundred percent in young animals (Gerdes 2002). Fever, loss of appetite, and death occur in young animals with this disease, while fever, weakness and bloody diarrhoea occur in adults as the disease advances from apparent to acute (Busquets et al. 2010). Due to their immature immune systems, young animals are more susceptible to RVF infection and its related consequences. As a result, they become more vulnerable to viral infections, and the virus has a greater potential to harm their growing tissues. Young animals may also be more susceptible to contracting RVF because they are more likely to come into contact with mosquitoes or other vectors that carry the virus.

3.2. HUMANS

In humans, RVFV infections typically cause no symptoms and resolve on their own (Archer et al. 2013). Symptoms of RVF, such as fever, chills, fragility, headache, and joint and muscular pain, become noticeable

Table 1: Symptoms caused by RVFV in animals and humans.

Species	Symptoms of RVFV
Animals	Diarrhea, Decreased milk production, Loss of appetite, Abdominal pain, Weakness, Nasal discharge, Abortion or being born dead.
Humans	Headache, Muscle pain, Joint pain, Encephalitis, Vision disorders, Bleeding from nose gums and skin, Hepatitis.

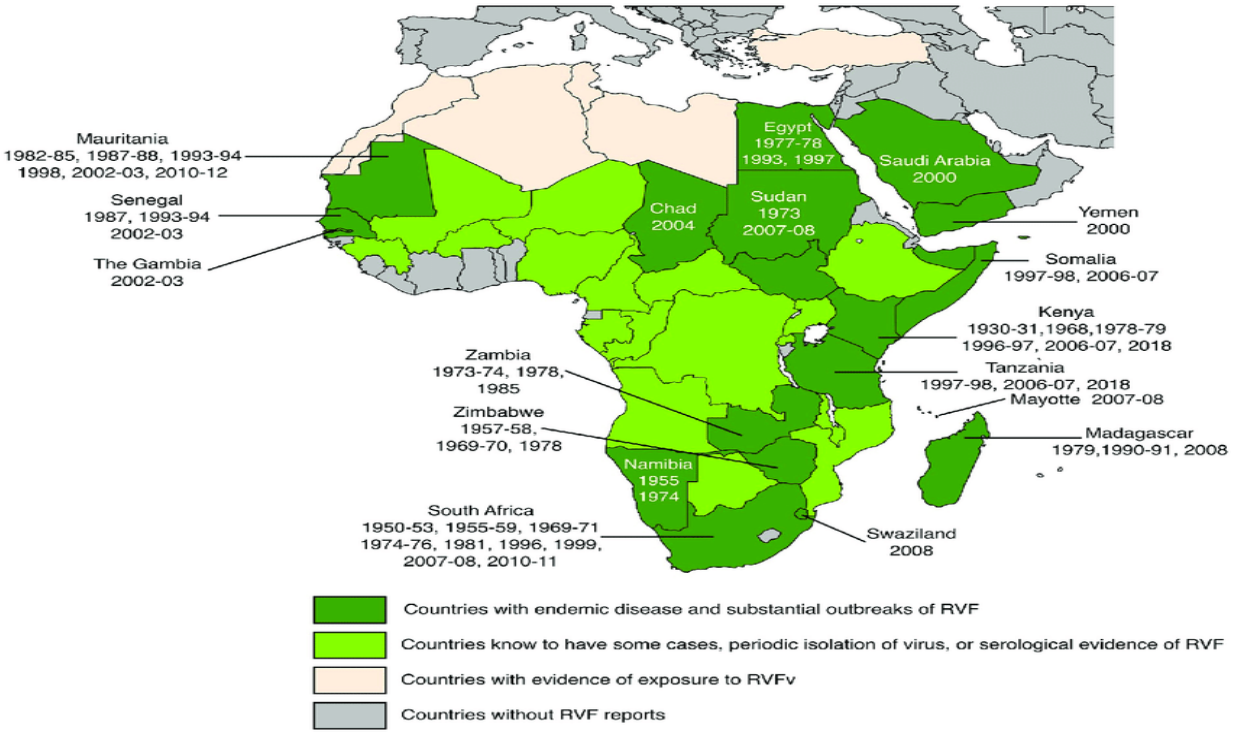

Fig. 1: Geographical distribution of Rift Valley fever (Gerdes 2004).

after an incubation period of 4-6 days. These symptoms will be followed by jaundice, red eyes, vomiting, diarrhea, and an inability to sleep (Seufi and Galal 2010). In addition to these symptoms, RVFV infection can cause blood loss, low haemoglobin levels, low platelet counts, rashes, and general malaise (Baudin et al. 2016). About 1-2% of instances have serious repercussions, and among those are 1. Headaches, irritability, haziness, confusion, coma, encephalitis, and visual hallucinations are all symptoms of a neurological disorder (Seufi and Galal 2010). 2. Ocular abnormalities like retinitis and vision loss (Yoser et al. 1993). 3. Symptoms of hemorrhagic fever with abnormalities in the liver include high body temperature, muscle pain, and bleeding from the mucous membranes(Kahlon et al. 2010). Acute RVFV infection and miscarriages are significantly associated with pregnant women with fever (Baudin et al. 2016). The summary of various symptoms caused by RVFV in animals and humans is shown in Table 1.

4. DIAGNOSIS OF RVF

RVF is diagnosed using a variety of approaches, including virus isolation (Anderson Jr et al. 1989), antigen detection (Meegan et al. 1989) and nucleic acid amplification techniques (Garcia et al. 2001) and by detection of specific antibodies (Swanepoel et al. 1986). In the acute phase of the illness, when a fever is present, RVFV is readily isolated from serum or whole blood samples as well as from the liver, spleen, and

brain of freshly decomposed carcasses/cadavers as well as aborted fetuses. Cell cultures, newborn mice, and hamsters are used to detect the virus (Stear 2005). However, the procedures required to isolate viruses are expensive and time-consuming. An RVF pandemic could present significant challenges for regulatory healthcare authorities due to diagnostic delays caused by the use of conventional virus isolation and identification techniques, especially in countries outside the virus's natural geographical borders. So, researchers are currently working on nucleic acid techniques for rapid RVFV detection and diagnosis.

RVFV detection and quantification PCR assays with high sensitivity, such as RT-PCR, have been reported (Sall et al. 2002) and real-time detection PCR (RTD-PCR) based on TaqMan probe technology (Bird et al. 2007). Real-time reverse-transcription loop-mediated isothermal amplification assays (RT-LAMP) targeting the big RNA segment were created and tested more recently for identifying a variety of RVFV isolates and clinical samples (Le Roux et al. 2009). The detection limit of RT-LAMP was reported to be 0.065 TCID50 per reaction volume (Le Roux et al. 2009) as well as 10 RNA copies per test (Peyrefitte et al. 2008), and there was complete agreement between the RT-LAMP, TaqMan-based RTD-PCR, and virus isolation data (Le Roux et al. 2009). Similar results were found when the assay was used to screen multiple clinical samples from humans as well as animals that had been exposed to the virus in the wild during earlier RVF outbreaks in Africa. Positive clinical specimens can be tested for particular viral genomic targets in less than 30 minutes using the RT-LAMP. Because it may be performed using simple and affordable equipment, the LAMP assay is well-suited for usage in low-resource environments and as a portable device during RVF epidemics in remote regions. In addition to its high levels of analytical and diagnostic dependability, as well as its rapid detection speed (Peyrefitte et al. 2008). During the RVF outbreak that occurred in Kenya in 2006, researchers utilised quantitative real-time RT-PCR, also known as qRT-PCR, to identify individuals with high viremia, which is connected to a bad prognosis (Njenga et al. 2009). In this study, RVFV-RNA levels obtained by qRT-PCR were compared to infectious virus titers to confirm the case. Compared to non-fatal cases, fatal RVF cases exhibited infectious virus concentrations of 105.2 infectious virus particles/mL of blood and viral RNA levels that were over 3-fold higher (mean = 8.6 106 viral RNA copies/mL of serum). The findings in Kenyan (Njenga et al. 2009) and Saudi Arabian(Bird et al. 2007). Patients that were collected during the RVF outbreak in 2000 show that qRT-PCR can quickly identify patients who have a high viral infection and a bad prognosis. This makes it possible for these patients to be prioritized for special or extensive clinical care.

However, it should be emphasized that the conclusive diagnosis or confirmation of RVF, as well as any other suspicious VHF case, should not be solely on a single PCR result. This is because RVF can cause symptoms that are similar to those of VHF. The tests for the identification of nucleic acids need to be carried out in conjunction with other processes, such as the detection of type-specific antibodies for RVFV. In this respect, it is crucial to remember that viremia in RVFV-infected persons is very short-lived, and the majority of infected patients and adult ruminants have subclinical or mild illnesses; nonetheless, IgM and IgG antibodies are easily detectable quickly after viral exposure (Paweska et al. 2005). In addition, the majority of the techniques involving nucleic acids require highly specialized equipment for laboratory use, pricey reagents, and properly educated laboratory people, all of which may only be accessible sometimes if outbreaks arise in far-flung places and prompt detection is necessary.

Several immunological methods allow for the rapid identification of viral antigens in blood and other types of tissue. Some of these methods are immunodiffusion on agar gel with homogenized tissues and immunostaining on liver, spleen, and brain impression smears or cryostat slices. With these tests, it is possible to find the RVFV antigen in affected cells. Histopathological analysis of liver tissue from affected animals reveals a distinct cytopathology (Stear 2005). Antigen detection ELISAs (enzyme-linked immunosorbent assays) for RVFV have also been described. However, the majority of these experiments utilized chemicals that were both costly to produce and posed a biohazard risk to laboratory workers (Zaki et al. 2006). Recently(Zaki et al. 2006) Multiple virus-specific antigens (Gs, Gn, N, NSs) were put to use in immunofluorescence tests with a collection of rat IgG monoclonal conjugates. It has a high sensitivity for

RVFV detection in patient samples, however its utilization requires working with amplified virus in tissue culture. Several RVFV infections in laboratories have been documented, indicating that the virus is extremely infectious for humans (Smithburn et al. 1949). Recently, a completely risk-free approach for antigen detection using a sandwich ELISA (sAg-ELISA) was reported as a potential solution. With its recombinant nucleocapsid protein (recNP)-based internal controls for monitoring regular test performance, this kit can be used for surveillance and diagnosis outside of places where the virus is endemic (P Jansen Van Vuren and Paweska 2009). After inactivation at 56 °C for 1 hour in the presence of 0.5% Tween-20 (v/v), the nucleo capsid protein (NP) of RVFV was identified using the assay. RVFV strains obtained in different parts of the world over the course of 53 years were successfully identified using the sAg-ELISA because of its lack of cross-reactivity with related African phlebo viruses or other members of the family *Bunyaviridae*. The limit of detection was determined to be between log10(102) and log (103) TCID50/reaction volume. The sAg-ELISA was 67.7% sensitive, 97.97% specific, and 100% specific when compared to the results of virus isolation in serum from experimentally infected sheep and RVF patients. The approach demonstrated perfect accuracy when testing organ tissues from both naturally infected buffalo fetuses and artificially infected mice. The presence of NP antigens in infected culture supernatants was analyzed as soon as 8 hours post-inoculation with 105.8 TCID50/mL RVFV. The assay's speed makes it ideal for first-pass viral detection during in vitro isolation. Because of its excellent specificity, security, and convenience of use, the sAg-ELISA is an invaluable diagnostic tool that may be utilized in African laboratories that are less well-equipped as well as for the regular differential diagnosis of VHF (Jansen Van Vuren and Paweska 2009).

RVF diagnosis frequently uses serum samples. In domestic ruminants, viremia titers between 105.6 and 109.0 mouse LD50/mL have been observed (Swanepoel et al. 1986), and humans have a mouse LD50/mL of 108.6 while an adult African buffalo has a TCID50/mL of 105.4(Davies et al. 1981). Although viremia in RVFV-infected individuals can reach high titers, this state of infection only lasts for a short period of time. As a result, its utility in viral detection methods for RVF epidemic detection is limited. The use of an ELISA panel that tests for both viral antigens and IgM antibodies is recommended for detecting recent RVFV infection. Alternatively, RVFV can persist in elevated titers in the ovine brain and liver lasting 21 days, and in the spleen for up to 30 days(Swartz et al. 1981). While the sAg-ELISA has a high degree of diagnostic precision for detecting RVFV in tissues that have been infected, these samples typically contain virus levels that are 10- to 100-fold above the detection limits of the assay (Morrill et al. 1987). Therefore, it is suitable for testing products made from human corpses and aborted foetuses. In the midst of an RVF epidemic, unexpectedly high rates of abortion and mortality among young animals are noticeable.

Infectious diseases can be diagnosed using serological testing, clinical observations, epidemiological history or when seroconversion is proven. Sero diagnostic techniques are also commonly utilized in epidemiological studies to demonstrate disease freedom. Traditional techniques for determining whether or not a patient has RVFV antibodies include haemagglutination inhibition, complement fixation, indirect immunofluorescence, and viral neutralization tests (VNT) (Stear 2005). The disadvantage of these techniques include health risks to laboratory personnel (McIntosh and Gear 1980) and restrictions on their use in regions of the world where RVF is not prevalent. Recent infection can be confirmed by testing for IgM antibody expression in an ELISA or by observing seroconversion, which is defined as a 4-fold or greater increase in antibody titer in paired serum samples (Paweska et al. 2007).

Although it is the gold standard, the VNT is laborious, costly, and takes 5-7 days to perform. It can be done using just tissue cultures and regular stocks of live viruses. As a result, it is infrequently employed and only in extremely specialized reference laboratories. However, from the perspective of using the VNT as a diagnostic discriminator in validation studies, it is crucial to remember that RVFV infection induces lifelong neutralizing immunity and that there is no evidence for the existence of serological subgroups or major antigenic variation between virus isolates of different chronologic or geographic origins (Coetzer and

Tustin 2004). With minimal cross-neutralization with other *phleboviruse* , the VNT is quite accurate (Tesh et al. 1982). However, work with a live virus requires the use of dedicated biocontainment labs.

Recent advances in ELISA technology have resulted in a number of formats that are proving to be invaluable in disease monitoring and control initiatives, import/export veterinary certification, as well as monitoring of immune response in vaccinations, and they are based on inactivated antigens extracted with sucrose and acetone and obtained from either tissue culture or mouse brain(Pepin et al. 2010). They are able to replace existing diagnostic methods, which pose hazards to one's health and need isolation in high security institutions outside of RVF-endemic areas, with techniques that are extremely reliable, safe, and accurate. Nonetheless, bio-containment facilities are required to lessen the likelihood of infecting laboratory personnel during the production of the antigen for these tests. In order to overcome these obstacles, the recNP of RVFV is the basis of a novel indirect ELISA for the detection of particular antibodies in human as well as animal serum. (Paweska et al. 2008). The nucleocapsid protein appears to have significant levels of conservation among members of the *Bunyaviridae* family. (Gauliard et al. 2006) and studies on antigenic cross-reactivity in animals (Swanepoel et al. 1986) and the indirect ELISA based on recNP (Paweska et al. 2007) failed to offer proof that additional African phleboviruses could make it difficult to reliably diagnose RVF. Since NP is the most abundant and immunogenic viral element in the RVFV virion, it seems to be the best candidate for creating immunological reagents for antigen detection testing. The simplicity of mass-producing a recombinant RVF NP that is both soluble and very pure (Petrus Jansen van Vuren et al. 2007) will enable fully automated, less expensive sera bulk screening. The development and validation of next-generation diagnostic immunological reagents and tests, such as those based on RVFV recombinant antigens and implemented in ELISA formats, is strongly encouraged. The test reagents have been made safe for routine use in RVF-free environments by cloning and expressing RVFV antigens, which eliminates the possibility of laboratory infections and residual viruses. Although it has not yet been shown through rigorous validation trials, it is expected that recombinant antigen-based ELISA will be at least as precise as ELISA based on the virus's full inactivated antigen for identifying the virus in livestock populations from different areas.

5. PATHOGENESIS

Human illnesses, often acquired through contact with contaminated animal tissues, pose a hazard to their jobs as veterinarians, farm workers, and abattoir staff (Archer et al. 2013), manifesting as mild febrile sickness or subclinical infection. However, the infection can occasionally progress to a serious illness manifesting as hemorrhagic fever syndrome, encephalitis, retinal degeneration, or other consequences. The effects of these disease kinds are typically severe, with high mortality or long-term vision and brain function damage. There is a viremia in the early stages of the disease, 1-4 days post infection, which decreases as levels of antibodies rise. A vasculitis associated with viremia can cause thrombosis and other vascular problems, frequently appearing days to weeks after the original infection. In highly vulnerable species like sheep and mice, liver infection plays a significant role in infection; this develops within the acute infection phase and may become the main pathological characteristic (Bingham and van Vuren 2020).

RVF hemorrhagic fever syndrome is characterized by haemorrhages and multi-organ failure. It is brought on by fulminant hepatic necrosis and vasculitis, two conditions that cause disseminated intravascular coagulopathy by preventing the renewal of clotting factors in the liver (hepatic necrosis) and depleting them in the vasculature (vasculitis), respectively. Clinical symptoms include diarrhea, jaundice, hematemesis, bleeding from the gums, conjunctivae, and other mucous membranes, as well as vomiting (Swanepoel 2004). Viral load, cytokine responses, and coagulation pathways significantly

influence disease severity (Jansen van Vuren et al. 2015). In a tiny percentage of instances, encephalitis may appear days or weeks after the first feverish episode, and its clinical manifestation may depend on the location of infection foci in the brain (Ikegami and Makino 2011). An area of localized necrosis with mononuclear cell perivascular cuffing is seen on histological examination (Van Velden and McIntosh 1977).

RVFV antibodies are typically present even when encephalitis occurs, suggesting that the illness is caused by immunologically mediated injury in response to lingering infection. Like many viral encephalitis, recovery might take a while and have different results. Local ocular vascular thrombosis is likely followed by retinal degeneration, which can develop during the first febrile illness or up to four weeks later (Swanepoel 2004). It may be connected to uveitis and retinal detachment. Different types of vision loss can be persistent and frequently permanent (Ikegami and Makino 2011).

Sheep, and especially young lambs, are particularly susceptible to RVFV infection. Abortions are typically the first sign of infection in a herd, and they can be quite common, with up to 100% of pregnant ewes losing their lambs (Swanepoel 2004). Infection of several fetal tissues, including the placenta's fetal-maternal interface, results in abortion (Oymans et al. 2020). Lambs that are infected and live to adulthood are typically feeble and only live a few days. Animals exposed to experimentally transmitted diseases develop viremia from days 1 through 7, peaking around day 2 (Wilson et al. 2016).

However, adult sheep may occasionally experience fatal sickness, primarily brought on by hepatic necrosis, vasculitis, and related conditions. However, this is less common because of adult sheep's relative tolerance. Clinical symptoms include bloody diarrhea, congested mucous membranes, lethargy and weakness (Swanepoel 2004). Hepatic necrosis, vasculitis, renal tubular necrosis, and lymphoid necrosis are among the main lesions (Odendaal et al. 2019). While usually not as severe, the sickness in other ruminants can be similar to that in sheep. The most frequent result of infection is abortion in pregnant cattle, goats, and camelids, while young animals seem extremely susceptible (Rippy et al. 1992). Rodents and non-human primates are used as laboratory models to study human infection and vaccination (Ross et al. 2012). Replication cycle of RVFV is shown in Fig. 2:

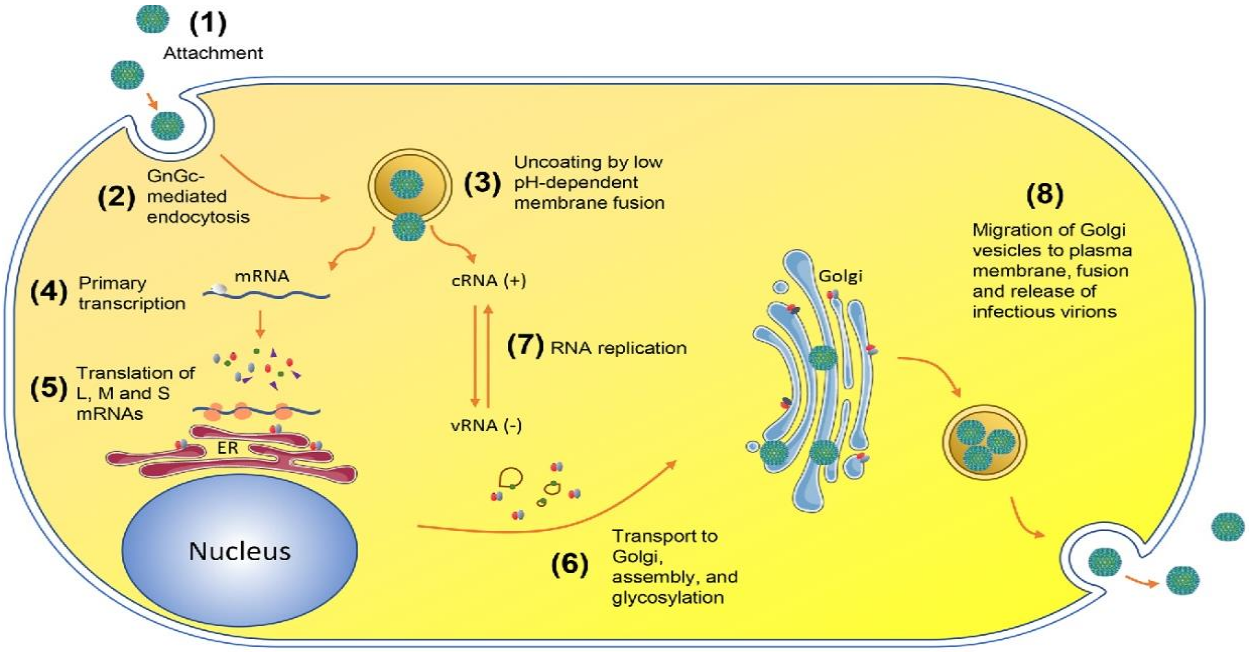

Fig. 2: Replication cycle of RVFV (Wright et al. 2019).

6. ZOONOTIC NATURE

RVFV infection can spread to people by mosquito bites or contact with contaminated blood, tissue, or bodily fluids. Additional ways to become infected include handling contaminated placentas, fetal and maternal blood from animals that have been put to death, and consuming raw milk or uncooked meat from sick animals (Helmy et al. 2017). Around 240 of the 400 recognized zoonotic illnesses are transmitted from animals to humans, accounting for around 60% of all pathogen-caused human infections. Millions of fatalities and an astounding billion incidences of human illness arise from this year, costing the economy hundreds of millions of dollars over only the last two decades. Most newly emerging infectious diseases during the past 70 years have been zoonotic. Additionally, endemic zoonosis has grown. Some zoonosis are becoming increasingly or solely dependent on humans as the transmission host as a result of new diseases, ecological changes, and social pressures (Seetah et al. 2020).

Human fatalities have been high during RVF epidemics due to a variety of causes, including contact with newly slaughtered diseased sheep meat and a lack of awareness about public health. Risk factors for human RVF infection include but are not limited to: age, sex, occupation (via contact with animal blood or bodily fluids), water, nutrition, social status, and poor sanitation (Nyakarahuka et al. 2018). Camel, wild animal, and vulnerable cattle host populations exist in Egypt without immunization (Gad et al. 1995),the ongoing of sick slaughter animals for human food and the ongoing importation of animals, particularly camels, from enzootic nations like Africa and Sudan. Humans can become infected with RVF by eating meat infected with RVFV (Fawzy and Helmy 2019).Transmission of RVFV from animals to humans is shown in Fig. 3:

7.REPRODUCTIVE IMPLICATIONS

There were indications of reproductive failure, including abortions, the ejection of healthy, macerated, and mummified fetuses, the delivery of frail and stillborn piglets, and neonatal fatalities. Several samples of live piglets tested positive for RVFV antibodies and antigen/RNA, whereas a small number of aborted fetuses did. Both viral and non-infectious factors, as well as their pathophysiology, may contribute to these reproductive failures (Pozzi and Alborali 2012). It was established that RVFV was the most likely cause since the pigs were taken from an enclosed breeding herd that adhered to stringent biosecurity and disease control laws and regulations. These circumstances, which are helpful against management causes, led to the conclusion that RVFV was the most likely culprit. This is because to the fact that widespread pathogenic diseases that have been associated to stillbirth, embryonal deaths, mummies and infertility were not likely to be the reason. During the epidemic of RVF in South Africa in the 1950s, pregnant sows and ewes both experienced abortions, which our data confirm, supporting Weiss' field observations from that time period (Weiss 1957).

Teratogenicity in pig farms, which can be brought on by hereditary factors, nutritional factors, toxins, or infectious agents, is a widespread problem around the world, with documented incidence rates ranging from 0.11% to 4.96% (Straw et al. 2009). In this study, 9% of the piglets had congenital abnormalities in both the neonates and the aborted fetuses (Coetzer 1980). The researchers made this discovery after observing that the mouse brain passaged and live-attenuated Smith burn vaccine strains when administered to pregnant sheep between the ages of 42 and 74 days into their pregnancies, caused spontaneous abortions and teratogenic outcomes such as arthrogryposis (Coetzer and Barnard 1977).

8. IMPACT ON PREGNANCY

The hallmark sign of an RVF epizootic is a significant increase in the number of abortions that take place in pregnant ruminants almost simultaneously. These widespread abortion occurrences, also known as "abortion storms," make it possible to differentiate RVF from a number of other common infectious

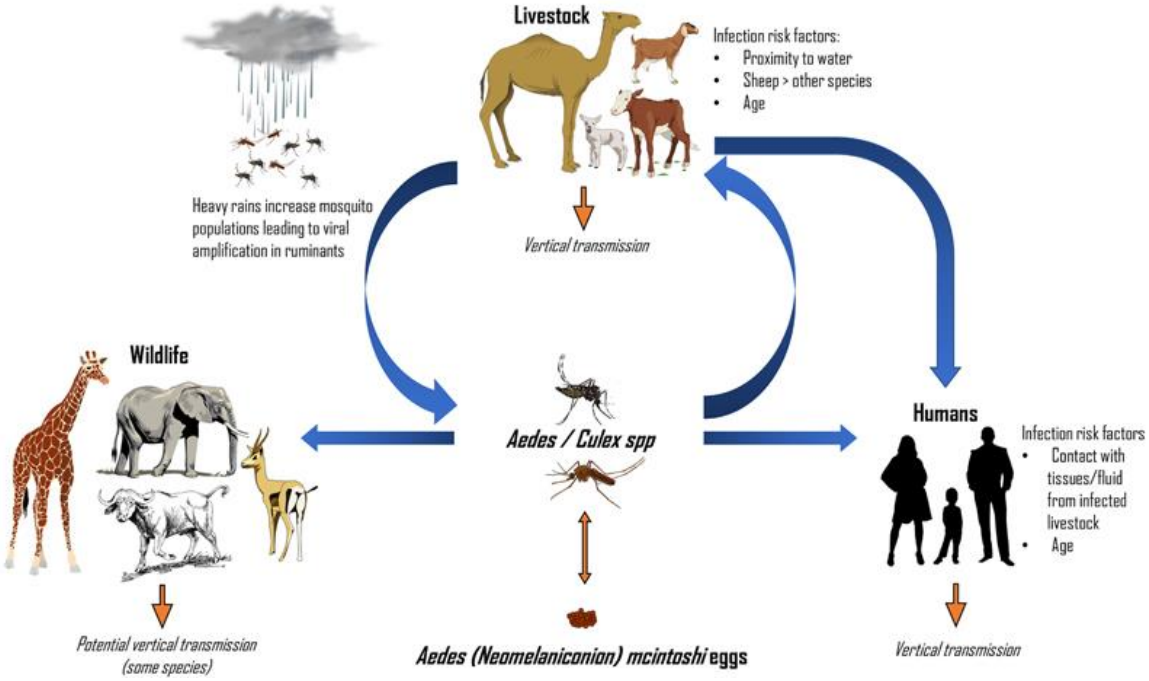

Fig. 3: Rift Valley fever virus cycle (Wright et al. 2019)**.**

causes of abortion in ruminants, such as Q fever (*Coxiella burnettii*), salmonellosis, chlamydiosis, listeriosis, or toxoplasmosis. This differentiation is made possible by the fact that widespread abortion occurrences have been given the name "abortion storms." An active surveillance technique using sentinel herds is unaffordable in non-endemic nations. On the other hand, reliable passive surveillance-based processes that depend on the detection and prompt reporting of significant abortion occurrences to national authorities (for example, more than twenty percent of pregnant animals in a herd suddenly aborting with accompanying signs and symptoms of jaundice within survivors) could provide an inexpensive means to detect the increase of this major veterinary and human health threat (Michel Pepin et al. 2010).

Large quantities of virus particles are present in aborted fetal tissues and placental membranes, and these particles have the potential to either directly contaminate the environment or infect nearby animals. It is possible for animals to contract RVFV either by the bite of a mosquito that is already infected with the virus or through direct contact with infected tissue from animals, bodily fluids, or fetuses. This is especially true in situations that are associated with abortions(Theiler and Medicine 1957). A study looking at the prevalence of abortion during the 1977 epidemic in Egypt found no rise above the average frequency of abortions, indicating that the relationship between RVFV infection and human abortion is less obvious than in ruminants(Abdel-Aziz et al. 1980). However, a study published in 2016 revealed for the first time a significantly elevated risk of miscarriage following laboratory-confirmed RVFV infection during pregnancy. However, compared to cattle, people have a decreased risk of abortion. Additional research is required to better understand the mechanisms driving pregnancy loss brought on by RVF (Wright et al. 2019).

9. CONTROL OF RVFV

The One Health strategy advocated by RVFV requires the participation of the following groups: The danger of further transmission of the disease among all affected species can be reduced by (1) Prompt diagnosis,

alert, treatment of the affected individuals and animals, and provision of alerts by medical and veterinary physicians, diagnosticians, epidemiologists, and public health specialists, (2) Wildlife experts who need to know how the disease spreads among animals and what role it plays in animal populations, (3) Entomologists to learn about the vector's biology, its role in RVFV epidemiology, and to provide direction on vector control, (4) The disease's impact on ecology and the natural world must be evaluated by ecologists, (6)It is the responsibility of governments and policymakers to implement the policies and provide the funding essential to One Health's focus on prevention and control. The economic and social implications of RVF sickness on populations should be assessed, according to economists and social scientists, (7) Vaccinologist to develop and supply antiviral vaccinations medical treatment (for both humans and animals) and vector control (through insecticides, acaricides, and larvicides) are provided by the eighth sector: the pharmaceutical industry. According to the One Health strategy, in order to decrease outbreaks in people, it is necessary to (1) provide a safe and effective RVFV vaccine to susceptible animals under government supervision, (2) set up a reliable surveillance system with a rapid reporting programme for the disease, and other measures, (3) conduct epidemiological research to identify risk factors, and (4) instruct veterinary and medical health professionals on the diagnosis and treatment of suspected cases (Fawzy and Helmy 2019).

10. PREVENTION OF RVFV

RVFV infections in livestock are now thought to be prevented only by vaccination. However, a lot can still be done to improve the current livestock vaccines. Additionally, the lack of any licensed human vaccinations makes it difficult to use techniques to prevent spillover into humans (Faburay et al. 2017). It would be desirable to replicate the durable protection from exposure to nature. In the USA, MP-12 and TSI-GSD-200 are the two vaccines now recognized as investigational new human drugs (Dungu et al. 2018). The US Army developed TSI-GSD-200, a formalin-inactivated vaccine, to protect those whose work may expose them to infection. It has a great safety profile, but it requires numerous boosters to be effective, and even then, over 10% of vaccines have low nAb titers or fail to seroconvert (Pittman et al. 1999).

The most frequently used commercial vaccination for livestock, named after its creator Smith burn, is a live-attenuated RVFV that develops long-lasting immunity after a single injection (Faburay et al. 2017). However, the Smith burn vaccination cannot be given to pregnant animals because residual virulence increases the chance of abortion (Botros et al. 2006). Genetic reassignment with wild-type RVFV is also possible, but this is unlikely to result in a pathogenicity rise beyond that of the wild-type virus. A novel RVFV vaccine would have the added benefit of distinguishing between infected and vaccinated animals (DIVA). The antibody profile obtained by utilizing live-attenuated RVFV as a vaccine, such as Smith burn, is identical to natural infection, making outbreak mapping challenging in the face of vaccination. The advantage of subunit vaccinations is that they do not contain all RVFV antigens. It is feasible to distinguish between animals that have been naturally exposed and those that have been vaccinated by assessing reactions to the N protein, which is not present in the vaccine (Wright et al. 2019).

Clone 13 was one of several viral clones identified from a human patient infected with the 74HB59 strain in the Central African Republic. It was discovered to be naturally attenuated due to a significant loss in the NSs gene, the key virulence factor, and subsequent infection in mice demonstrated that it did not cause disease (Muller et al. 1995). Clone 13 has been shown in cattle, sheep, and goats to be safe and immunogenic after a single injection (Njenga et al. 2015). On the other hand, overdose tests in pregnant ewes have revealed that clone 13 can pass the placental barrier and generate teratogenic

consequences (Makoschey et al. 2016). Several promising vaccine candidates are now being developed to overcome the shortcomings of current vaccinations, especially single dose efficacy and safety issues. In sheep, a subunit vaccination based on the GnGc glycoproteins demonstrated 100% effectiveness (Faburay et al. 2016). Another vaccine, RVFV-4s, which has the M segment separated into two portions that encode Gn and Gc independently, has provided sterile immunity in lambs after a single inoculation (Schreur et al. 2015). Furthermore, vaccinated pregnant sheep revealed no teratogenic effects or presence of the RVFV-4s virus in their fetuses' blood or organs (Schreur et al. 2017).ChAdOx1 RVF is another possibility, a replication-deficient chimpanzee adenovirus vectored vaccine encoding the Gn and Gc glycoproteins. In sheep, goats, and cattle, ChAdOx1 RVF showed 100% effectiveness against RVF viral challenge (Warimwe et al. 2016). The ChAdOx1 RVF is also intended for use in humans, where the ChAdOx1 vector expressing additional antigens has shown a great safety profile (Stylianou et al. 2015).

11. FUTURE DIRECTIONS

11.1. FUTURE DIRECTION ACCORDING TO THE ONE HEALTH APPROACH IS

11.1.1. COLLABORATIVE AND INTERDISCIPLINARY RESEARCH

Future research on RVF should be collaborative and interdisciplinary, bringing together experts from environmental science, public health, and both human and veterinary medicine. Through such initiatives, the causes of the disease's origin and spread will be found, and practical control strategies will be created.

11.1.2. PREVENTION AND CONTROL STRATEGIES

The creation of RVF prevention and control strategies must be prioritized. These covers creating novel diagnostic instruments, vaccinations, and antiviral medications. Effective surveillance and control measures must also be implemented if the disease is to be stopped from spreading.

11.1.3. ENHANCING REPRODUCTIVE HEALTH

Future RVF research should aim to enhance animal reproductive health, emphasizing the one-health approach. This entails figuring out the molecular processes that lead to fetal demise and birth abnormalities and creating fresh preventative measures.

11.1.4. RAISING AWARENESS

To implement effective control measures, there must be a greater understanding of RVF and its effects on the health of people, animals, and the environment. Raising public knowledge will make it easier to put early detection and quick response measures into place, lessening the effects of RVF outbreaks.
Overall, the fight against RVF as a zoonotic and abortive illness will require a one-health approach. It will be essential to conduct collaborative and multidisciplinary research and effective preventative and control strategies, improve reproductive health, and create awareness.

12. CONCLUSION

There were clear distinctions between the clinicopathological outcomes of RVFV infection in domestic pigs, sheep, and cattle, as well as parallels in these outcomes, according to this study and earlier ones

as well. Similarities included reproductive problems, the ability to transmit the virus vertically, the capability to detect anti-RVFV antibodies and viral RNA in the offspring born to infected sows, the absence of clinical indications in immature and non-pregnant animals, and the presence of macroscopic lesions typical of RVFV infection, particularly in the liver, spleen, and kidneys. Between this investigation and others carried out in pigs, lambs, and rats, there were a lot of inconsistencies with clinicopathological results and laboratory analysis of samples from experimentally infected animals. These contradictions were characterized by negative results for several, but one or two analytes. On histology, liver lesions in infected pigs were most commonly characterized by mild necrosis and non-lipid glycogen-filled vacuoles. These lesions differed from their counterparts in domesticated ruminants in that neonatal piglets were subclinically infected with the virus. In contrast to what may be observed in domestic ruminant animals, where significant pan-necrosis can be found, wild ruminants do not suffer from this condition.

In conclusion, Rift Valley fever (RVF) is a viral infection that has the potential to be zoonotic as well as abortive. Insights have been gained into the molecular mechanisms behind the virus's abortive character and the elements that lead to its genesis and dissemination in humans. Even though RVF research has made great strides, there is still much to be done in terms of creating efficient defence and enhancing animal reproductive health. The one health approach is essential in combating this developing infectious illness by highlighting the interdependence of human, animal, and environmental health and encouraging interdisciplinary and collaborative efforts in prevention, control, and treatment. It is hoped that by continuing to concentrate on these areas, RVF may be effectively managed and prevented, safeguarding both animal and human populations from this significant virus.

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