



## Review Article

## Epidemiology, Clinical Manifestations, Treatment Approaches and Future Perspectives of Rift Valley Fever

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## ABSTRACT

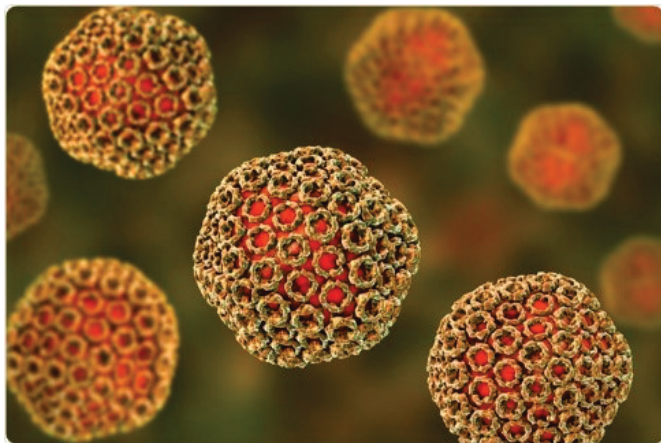
Rift Valley fever (RVF) is a mosquito borne viral disease that had been firstly revealed in Kenya in 1930. It has now become an endemic in all over multiple African states as well as in Arabian Peninsula. In the early days, RVF was assumed to be geologically restricted to only sub-Saharan Africa, thus, RVF generally had not been considered in the diagnosis of disease epidemics outside of the Africa. The loss of livestock had furthermore threatened the livelihood of people who were dependent on the animals for their food and income. Weakness, chills, headache, fever are considered to be the most common symptoms that arise in the patients suffering from RVF. Nevertheless, the choices for control of the RVF outbreaks have been restricted by the lack of approved human vaccines or other medications. Ribavirin, Favipiravir and various other antiviral drugs had shown to be effective against the rift valley fever. However, only supportive care had been used for the treatment of the RVF. For that purpose, Rift Valley Fever had now been prioritized by the World Health Organization (WHO) for urgent research and development of countermeasures for the control and prevention of future outbreak. In this review, we had highlighted the outbreak of Rift Valley Fever in various countries, its epidemiology, clinical manifestations, various medications that had been used for the treatment of this infectious disease and also the future prospectives regarding the RVF based on up-to-date data extracted from reputed journals and official websites.

## INTRODUCTION

An evolving arboviral disease Rift Valley fever (RVF), had affected humans as well as the livestock in the Middle East, western Indian Ocean and Africa. In Kenya, This disease was very firstly defined in 1930 after abrupt mortality in the lambs that arose on a farm in the region of Rift Valley [1]. Substantial rise in the adjacent regions arose in initial 2000s when this outbreak was reported in Yemen and Saudi Arabia. To this day, many of the Egypt region and Sub-

Saharan Africa is now considered to be endemic for Rift Valley fever virus (RVFV) or had been affected by infrequent outbreaks [2-7]. RVFV is adherent to the Bunyvirales order, Phenuiviridae family, of negative-sense RNA viruses. It consists of 3 genome segments: small (S) segment that had encoded nucleoprotein N as well as non-structural proteins, large (L) segment that encodes viral RNA-dependent RNA polymerase (RdRp) and medium (M)

segment that encodes surface glycoproteins Gc and Gn accompanied by nonstructural protein NSm. Humans could be exposed by the bite of mosquito or may be by the contact with the tissues and infected fluids. Numerous studies had suggested the transmission of vector-borne to be likely for humans [8]. Exposures of Zoonotic may be determined by much of homestead and occupational behaviors that have been performed with consistency. Occupational exposures had been exposed to provoke a larger occurrence than the individuals that have close contact with or caring for the animals at homestead, as well as is expected to be related to contact with some larger volume of animals and their fluids [9]. Another possibility is the Aerosolization, though it is very not likely route of transmission, as well as had been very much associated with a larger probability of the unembellished disease in the laboratory experiments [10]. About 1-2% of the cases had experienced symptoms of hemorrhagic fever, whereas approx. up to 50% of the hemorrhagic cases are very deadly [11]. Many In-vitro studies had previously proposed that, the hemorrhage that results by the Rift Valley Fever Virus infection caused by the rift valley fever virus (Figure 1) might be related to the expression levels of transcription factor I1H (TF1IH) [12]. It had been recommended that hemorrhagic cases of Rift valley fever virus infection might enhance risk of the nosocomial transmission for the healthcare workers as well as many other individuals providing care [13], so far human-to-human passage transmission via the nosocomial routes of contact had up till now to be documented. This review describes the epidemiology of the disease, clinical manifestations that were observed of Rift valley fever, a brief treatment and prevention approaches for the rift valley fever and also the future prospectives of this infectious disease built on the most current literature report since the outbreak.



**Figure 1:** Rift Valley Fever Virus (RVFV)

### Epidemiology

Very recently, RVFV had appeared to be recurring much

more often, by approximately many areas of the Eastern Africa going through the eruptions of Rift valley fever after each four years [2, 14]. Systemic investigations of seroprevalence studies and case reports had founded, Rift Valley Fever Virus been familiar in all the 5 African regions encircling 80% of all the countries belonging to African region [2]. The appearance of Rift Valley Fever in Arabian Peninsula in initial 2000s was expected to be occurred because of import of the disease-ridden mosquitos or may be livestock during the trade crosswise the Red Sea [15]. Livestock investigations had shown a very extensive range of Rift Valley Fever Virus seroprevalence, with less than one percent to approximately 50% in the cattle, camels and goats as well as equal to 90% of sheep, contingent on season, vicinity, age of animal, bioclimatic region and animal breed [16-20]. This virus had continued to blowout to many other portions of Africa that had not been formerly detected as well as introduction of the disease hooked on the other countries leftovers a very potential threat [2, 21, 22]. Many human cases succeeding epizootic eruptions could array from thousands to hundreds, along with many of the case fatalities amid to be found between 1% and 30% in the symptomatic individuals reporting to authorities of healthcare system [23, 24]. Incidence of Rift Valley Fever Virus infection might be misdiagnosed and underrated or lest adjacent to a known livestock eruption because of non-specific symptoms of disease as well as similarity to cocirculating pathogens [25, 26]. RVFV overlays with the other endemic viral diseases and with some identical disease manifestations, including West Nile virus (WNV) and Lassa fever possibly complicating treatment and diagnoses of the cases.

### Clinical manifestations

Majorly, the cases of RVF are very self-restrictive as well as could be recognized by slight frequently sub-clinical febrile sickness and also by means of incubation time of characteristically up to 4 to 6 days [27]. Symptoms mainly comprises of severe chills, malaise, dizziness, weakness, and headache [28]. Typically, many patients had suffered from a two phasic febrile phase, that had been recognized along with an unembellished headache. Some individuals alternatively, who had developed the very unembellished forms of Rift valley fever had been at very increased risk of the fatality. Liver infection is mostly characterized by the increase in lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase as well as decreased hemoglobin and count of platelet are significant [29]. Demise could happen mostly in about 3-17 days afterwards the initiation of these signs as well as deadly cases of Rift Valley Fever had showed diffuse gastrointestinal as well as hepatic necrosis. Many individuals had presented a reduced level of consciousness

that are suffering from RVF-induced encephalitis. In many cases, patients with RVF could grow a maculo or retinopathy (0.5 to 2%), that could affect in either one or both the eyes as well as could occur in either very initial or months afterward infection. Many studies had described that some patients could have loss of vision or also may have a blurry vision. Though, in many scenarios a fractional development in visualization over time had been recognized [30], yet, numerous individuals would experience complete or might be partial blindness [31].

### Various medications for Rift Valley Fever Virus

Mostly, antiviral treatments either be targeting the processes intrinsic to viruses, for example, binding of host cell and also the viral genome replication, or can moderate the host cellular progressions that are very significant for virus lifecycle.

**Table 1:** Summary of antiviral medications for treatment of Rift Valley Fever

Therapeutics	Mechanism	In-Vitro Results	Reference
Ribavirin ± poly(ICLC)	Nucleoside analog ± immunostimulant	78 µg/ml (Vero)	[32]
Suramin	Interaction of vRNA/N	22.3 µM (HEK 293T)	[33]
Favipiravir (T-705, AviganR) ± ribavirin	Nucleotide analog ± nucleoside analog	31 µM (Vero 76)	[34]
Sorafenib	RNA synthesis	6.4 µM (Vero)	[35]
Rapamycin	Inhibition of mTOR	11 µM (H2.35)	[36]
Bortezomib	Inhibition of Ubiquitin proteasome	0.01 µM (HSAEC)	[37]
GGY4137 (H2S-donor)	Reactive species scavenger	5 mM (Vero)	[38]

Existing approaches for the treatment of patients suffering with RVF as shown in Table 1 mainly focus on providing symptomatic care. RVFV ZH501, a pathogenic strain that had been isolated from a deadly human case during the first outbreak of Egyptian Rift Valley Virus in 1977 to 1978. This strain had been recognized as a select agent, as well as could be utilized at BSL4 or BSL3E containment. MP-12 strain had been established via the consecutive plaque channels of strain of Egyptian ZH548, that is 12 times more in the presence of a chemical mutagen, 5-fluorouracil. RVFV ZH548 had also been isolated from a febrile patient when it was Egyptian outbreak in 1977 to 1978 [39].

### Ribavirin

Ribavirin, a nucleoside analogue, had been considered as one of the few drugs that have been permitted for the therapy of particular viral hemorrhagic fevers [40]. Subsequently, the progress in 1980s, this had been considered to be very foremost anti-viral that had been investigated in the models suffering from infection with phlebovirus. In early investigations, it had presented a very high efficiency in vitro utilizing the preserved cell lines that had been separated by the African green monkey, many investigations had been rapidly extended towards a model of infection in mice with the tightly linked phlebovirus and the Punta Toro virus. At this time, therapy of ribavirin had very much decreased copying of the virus as well as the harshness of symptoms along with the 100% persistence at daily administration of 18.8 mg/kg subcutaneously, by primary therapy of 4 hours just before the subcutaneous infection. Inappropriately, side effect ribavirin profile, most commonly hemolytic anemia and inflammation, had been restricted its usage in the clinical settings. Encapsulation of the lipid had been very much effectively utilized in decreasing side effects via the administration of lesser but

more of the targeted doses, that results in the enhanced persistence of the mice that are infected [41].

### Favipiravir

Favipiravir, formerly developed by the Toyama Chemical (Japan), had been considered as a non-nucleoside inhibitor in influenza polymerase as well as had also received the support for using in contrast to the viruses of influenza in Japan as well as Phase-III clinical investigations had been finished in United states of America [42]. Prominently, favipiravir had been verified to be as effective as a broad spectrum anti-viral that is against a very broad spectrum of the RNA-viruses that includes yet had not been restricted to paramyxo-, arena-, filo-, as well as bunyaviruses. In preliminary, in-vitro studies had shown that the favipiravir is very extremely active against the bunyaviruses from diverse genera, that includes Rift Valley Fever Virus along with an EC50 of about 32 µM. Afterwards, the efficiency of favipiravir had been investigated in a model of hamster for Rift Valley Fever Virus ZH501. The treatment started 1-hour post-infection (HPI) along with a 200 mg/kg/day twice daily (BID) orally (PO) for 10 days protected 80% of SC infected animals along with 30 pfu RVFV ZH501. Ribavirin (75 mg/kg/day, BID, PO) had been a part of as a positive control as well as only bring about in the 20% of survival. In another investigation, by the use of an aerosol exposed model of Wistar-Furth rat, Caroline as well as his various colleagues had demonstrated that the animals that have received favipiravir inside the 1 HPI at 100 mg/kg/day BID per oral for 14 days had been completely covered from the deadly Rift Valley Fever Virus infection together with 50 pfu. Once the treatment had been started 48 HPI, the persistence rate was mainly considered to be 92% [43].

### Vaccines

At present, no vaccine is there for the prevention of Rift valley fever infection that had been permitted for use in the

animal in Europe or North America. Subsequently, initial isolation of the Rift valley fever virus, multiple vaccines against the RVF virus had been established, that includes the vaccines that had been produced via inactivation of formalin [44]; by attenuation via the in vivo serialized passage and can be via the in vitro chemical mutagenesis [39]; through the use of naturally founded attenuated mutant virus, recombinant virus vectors, viral subunits or by viral cDNA; as well as by using the recombinant live attenuated Rift valley fever virus that contains whole removals of the already recognized virulence genes. In the last 50 years, each of these methods had been leading to the extra refinements in safety and efficacy of the vaccines as well as had enhanced the understanding of RVF virus vaccinology. Vaccines that are Formalin-inactivated have been considered as safe, yet they also have problems for use in field because of characteristic requirement for three early inoculations over a period of one to two months that have been then followed by the annual booster inoculations [45]. Though, for use in human, a formalin-inactivated product had been formed in the middle of the 1970s further down a new innovative license of drug from the Food Drug Authority. The usage of this vaccine had been very firstly been beset at laboratory as well as on the other service personnel by large occupational hazard of contact to the virus. Though, now, no further produced as well is also in the restricted supply, TSI-GSD-200 had been verified as an effective, immunogenic, and safe in reducing the laboratory acquired infections between 598 human vaccines. The strain of live-attenuated Smith-burn Rift Valley Fever virus had been efficacious as well as immunogenic in the adult cattle and sheep, yet this had too caused teratologic effects in the fetuses or abortion in approximately 25% of the pregnant animals [46]. Therefore, this vaccine is very much probably inappropriate for the use in the areas that are separate of endemic zone of Rift Valley Fever virus activity.

#### Future perspectives

During the past years, further research had focused on the emergent pathogens with the goal of enhancing our preparation for any of the future outbreaks. RVFV had a complex ecological cycle that involves a very large range of livestock, vectors as well as wildlife species. Unfortunately, present surveillance is sub-optimal in several at-risk countries with numerous eruptions that remains unreported [47]. Preferably, proper surveillance measures would enable farmers to report unexplained disease in their livestock, which can be investigated and allow suitable measures to be implemented to reduce spread [48]. The development of specific therapeutics and vaccines is also of major importance. Disadvantages of current livestock vaccines and the absence of a licensed human vaccine

have limited our ability to effectively respond to outbreaks. More research is essential for a better understanding of viral maintenance during IEPs; the part of vertical transmission in mosquitoes and flow in wildlife in numerous ecological surroundings. Information of how diverse ways of human exposure, for example via mosquito bite or via contact with the infected animal products, affect the immune response as well as disease results are still missing. Moreover, the role cellular immunity plays in livestock as well as in humans is still uncertain. Lastly, a better understanding of the causes of the various manifestations of RVF disease might be helpful to rationalize why an infection is asymptomatic or connected with the clinical, sometimes fatal, illness. As a single serotype of RVFV causes disease in multiple species, opportunities exist to look more broadly at immunological differences between species as well as how they are affecting the disease results. Currently, the absence of a licensed human vaccine has limited our ability to effectively respond to outbreaks. More research is essential for a better understanding of viral maintenance during the emergency outbreak. A better understanding of the causes of the various manifestations of Rift Valley Fever disease might be helpful to rationalize why an infection is asymptomatic or connected with the clinical, sometimes fatal, illness. This review recommends various treatment and prevention approaches of the RVF and in future what measures should be adopted for this outbreak as well as also describes the clinical symptoms that appears in the individuals that suffer from the Rift valley fever, built on the most current literature report since the outbreak.

## CONCLUSIONS

Rift Valley Fever was first recognized as an outbreak in 1930. Symptoms of this infection arises usually from 4 to 5 days. Anti-viral such as ribavirin are thought to be an effective medication for the treatment of the rift valley fever. Although there had been a decent development in characterizing the virological, clinical and pathological features of RVFV infection, RVFV still causes outbreaks in African countries or in the Arabian Peninsula. The advances of safe, effective, highly immunogenic and economic vaccines for humans and animals would prevent RVF in endemic countries and further investigations are to be done to get the best possible treatment of the Rift valley fever.

## Authors Contribution

Conceptualization: MAW

Methodology: MS, AA

Formal analysis: AQ, SS, HZ, AA

Writing-review and editing: MAW, AA, AR, MS, AA, TP, DI

All authors have read and agreed to the published version of

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## Conflicts of Interest

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