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NARRATIVE REVIEW

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Rift valley fever (RVF) viral zoonotic disease steadily circulates in the Mauritanian animals and humans: A narrative review

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Abstract

Background and Aim: Rift valley fever (RVF) virus (RVFV) is reportedly steadily circulating in Mauritania being repeated in 1987, 2010, 2012, 2015, and 2020. Mauritania seems a preferred niche for RVF virus due to its persistent outbreak there. Lately, nine Mauritanian wilayas confirmed 47 (23 fatalities with 49% CFR) human cases between August 30 and October 17, 2022. Most of the cases were largely among livestock breeders associated with animal husbandry activities. The review aimed at understanding the origin, cause, and measures to counter the virus.

Methods: The facts and figures from the various published articles sourced from databases including Pubmed, Web of Science, and the Scopus as also some primary data from health agencies like WHO, CDC, and so forth were evaluated and the efficacy of countermeasures reviewed.

Results: Among the reported confirmed cases, it was found that 3–70 year age-group males outnumbered the females. Deaths after fever occurred primarily due to acute hemorrhagic thrombocytopenia. Human infections often occurred through zoonotic transmission mainly through mosquitoes in the population contiguous to

cattle outbreak, a conducive site for local RVFV transmission. Many transmission cases were through direct or indirect contact with blood or organs of the infected animal.

Conclusion: RVFV infection was predominant in the Mauritanian regions bordering Mali, Senegal, and Algeria. High human and domesticated animal density as also the existing zoonotic vectors further contributed to RVF virus circulation. Mauritanian RVF infection data confirmed that RVFV was zoonotic that included small ruminants, cattle, and camel. This observation hints at the role of transborder animal mobility in RVFV transmission. In light of this, preventive approaches with effective surveillance and monitoring system following the One Health model is extremely beneficial for a free and fair healthy world for all.

KEYWORDS

diagnosis and complications, epidemiology, etiological agent, Mitigation strategy, public health response, Rift valley fever (RVF)

1 | INTRODUCTION

The first Rift valley fever (RVF) outbreak was reported from the Rift valley in 1915, hence the name. The RVF virus was then first isolated from a sheep in a Kenyan farm in 1931.[1] Since then, owing to the trade of infected livestock, and high rainfall with extensive flooding sporadic RVF outbreaks are being reported in sub-Saharan Africa (Figure 1).[2] Its spread to Saudi Arabia and Yemen in 2000, first reported RVF case outside the African continent, could be attributed to the trading of infected livestock. That it could reach to other places including the Asia and the Europe (https://www.who.int/news-room/fact-sheets/detail/rift-valley-fever) is concerning.

Setting in severe illness, the viral zoonosis RVF is typically endemic to sub-Saharan Africa affecting domesticated animals like goat, sheep, cattle, buffalo, and camels, although it potentially could infect humans too. RVF viral disease transmits from infected animals to humans through contact with their body fluids, blood, or tissues or through the bite an infected mosquito. RVF illness causes major economic losses due to deaths and abortions among livestock.[3] RVF virus is circulating steadily in Mauritania with reported epidemics in 1987, 2010, 2012, 2015, and 2020. Between August 30 and October 17, 2022, nine of the 15 Mauritanian wilayas (regions) reported a total of 47 confirmed human RVF cases with 23 fatalities (49% CFR) predominantly among livestock breeders.[4] Males outnumbered the females among the confirmed cases (M:F:4.4:1), the age group ranging between 3 and 70 years with 22 years median age. Almost all the deaths were in hospitals due to hemorrhagic syndrome with symptoms like acute thrombocytopenia and fever (petechiae, hematemesis, gingivorrhagia).[4] RVF contracting virus circulates in small ruminants, camels, and cattle in eight Mauritanian wilayas. Till recently, 12 wilayas in all including the nine that share borders with three nations, Mali, Senegal, and Algeria, have reported confirmed human or animal illnesses. Due to RVF prevalence in most wilayas, the animal density, and the large human and animal mobility to neighboring nations, the regional spread of the outbreak cannot be ruled out even in the face of the outbreak response being managed through One-Health strategy.[4]

2 | THE FIRST REPORTED CASE OF THE PRESENT OUTBREAK

The Mauritania Ministry of Health alerted the WHO of a RVF outbreak on August 30, 2022 after polymerase chain reaction (PCR) test done on a 25-year-old male animal breeder from the Tintane moughataa in the Hodh El Gharbi wilaya at the National Institute for Public Health Research lab confirmed a RVF case on August 29.[4] The patient first showed up at a clinic on August 25 with hemorrhagic (epistaxis) syndrome and acute thrombocytopenia. He was shifted to a nearby hospital the next day where he passed away on August 29.

3 | ANIMAL CASES

While nine wilayas have reported RVF cases in human as of October 17, 2022, 12 wilayas have reported eight confirmed and four suspected animal cases. Potential animal RVF cases was alerted from sentinel herd monitoring that notified animal deaths and abortions in Aioun moughataa, Hodh El Gharbi wilaya. RVF outbreak in animals was subsequently identified in Hodh El Gharbi and seven other (Adrar, Assaba, Guidimakha, Hodh Echargui, Tagant, Tiris Zemmour, and Trarza) wilayas. Out of the 1148 samples of animal origin (from cattle, camel, and small ruminants) were analyzed between August 18 and October 10, 2022, positive cases were 277 (24.1%). IgM ELISA in cattle and small ruminants, and RT-PCR tests in camels revealed 5.2% (5/96), 25.9% (159/614), and 25.8% (113/438) positive cases.[4,5]

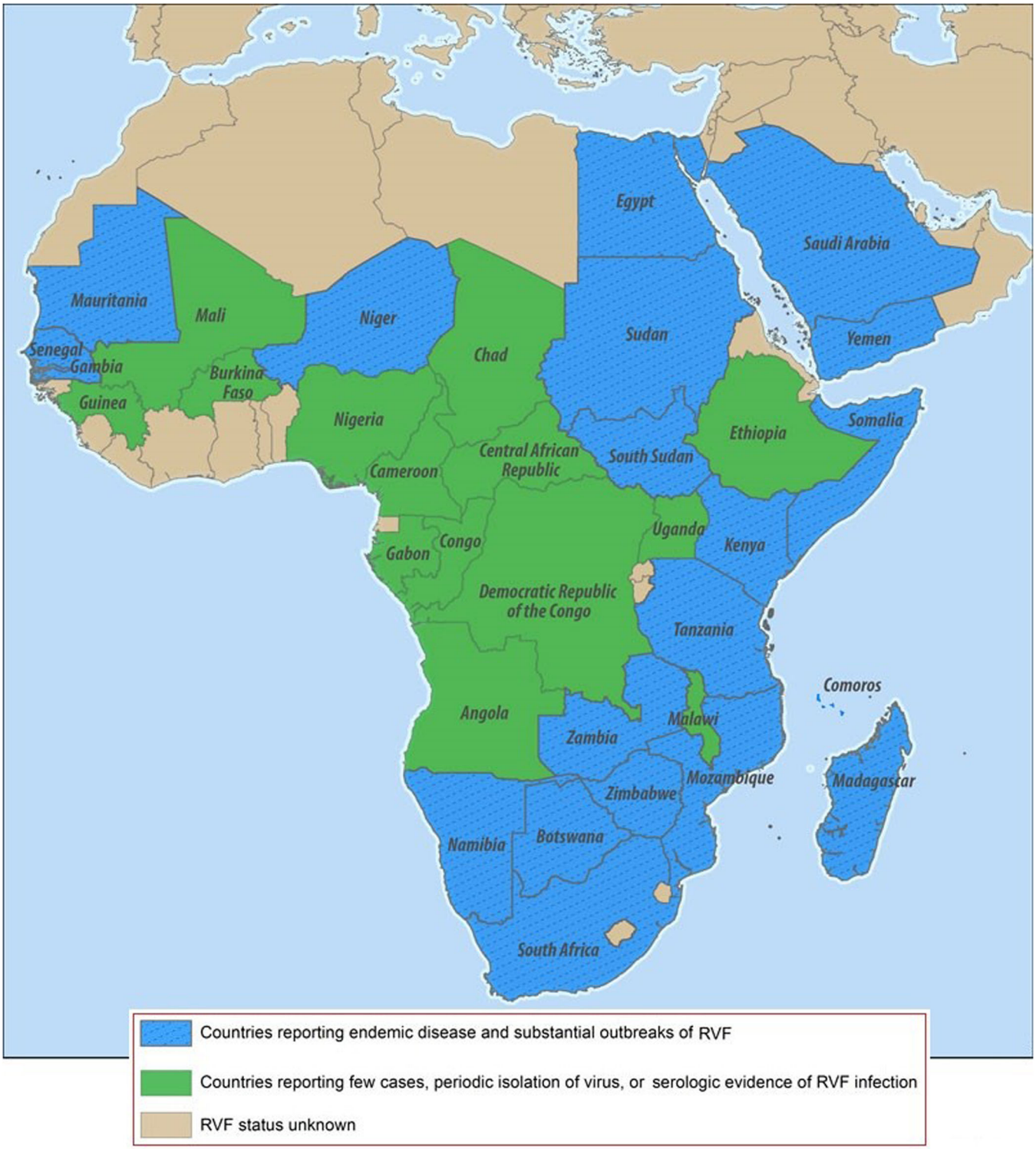

FIGURE 1 Distribution map of RVF reported cases in the sub-Saharan Africa (https://www.cdc.gov/vhf/rvf/outbreaks/distribution-map.html). The reported cases are high in almost whole of the Southern peninsula while the status in the northern part is ill-reported. RVF, Rift valley fever.

4 | EPIDEMIOLOGY

Typical RVF hosts in the sub-Saharan Africa are domesticated animals like goat, sheep, cattle, buffalo, and camel.[6] Although the disease mostly affects animals, RVF can also infect humans. While mosquito-bite brings in the disease in humans, the infection could also be by touching the blood or organs of the infected animal.[2] The high-risk occupational groups include farmers, herders, abattoir staff, and veterinarians. Consuming unpasteurized or raw milk from the diseased animals can also transmit the infection in humans. However,

evidence of human–human RVF transmission is not yet reported. Even while RVF frequently results in serious illness in animals, it can manifest as a moderate flu in humans to fatal hemorrhagic fever. Most RVF-infected humans either show no or only moderate symptoms (fever, weakness, back pain, and dizziness).[4] Serious symptoms like encephalitis (swelling of brain), bleeding, and eye damage are experienced by only a tiny proportion (8%–10%) of the RVF patients. Mauritania reported 25 fatalities (CFR 32%) and 78 recorded human infections of the RVF outbreak from September to November 2020. Out of the recorded cases, 94 camels, 89 small ruminants, and 3 cattle were among the 186 RVF-contracted animals.[4]

5 | THE ETIOLOGICAL AGENT

RVF virus belongs to family Bunyaviridae and genus *Phlebovirus*. It is an RNA virus with segmented (in three segments) ribonucleic acid. RVF is a viral disease primarily of veterinary importance. It infects domesticated and wild animals including lions, elephants, bats, and rodents, and humans too through direct contact with the diseased animals or mosquito bite (*Aedes* sp.).[2,4] Handling infected animals especially in the abattoir and eating contaminated meat could also transmit.[7] Human–human viral transmission is yet to be reported. RVF virus was detected in Eastern African region in 1931 that later spread throughout the African continent. Due to globalization and increased human and animal movements, RVF spreading to other parts of the world has all possibility. In view of its flexible and multiple modes of transmission, the WHO listed it as a potentially emerging microbe that could be a public health emergency to address.[7,8]

RVF virus (RVFV) continues to be a threat due to the fact that it remains in the environment through the transovarial transmission with mosquitoes both as reservoirs and vectors. Other mosquito species (like *Anopheles* and *Culex*) and other insects including sand-flies can also transmit.[2] Wild animals have also been noted as reservoirs, and the enzootic life cycle of the virus facilitates its survival.[9] The epizootic life cycle of the virus is active during excess rainfall seasons wherein mosquitoes proliferate extensively. It results in infecting the livestock including domesticated animals like cattle, sheep, goat, as also humans.[10]

6 | RVFV DIAGNOSIS AND COMPLICATIONS

RVFV infection in humans is usually self-limiting. However, it may develop into severe conditions including fatal hemorrhage.[11] Its infection may lead to obstetric complications and neonatal infections among pregnant women. Due to the nature of the virus to potentially cause life threatening infections, RVFV can only be handled in a biosafety level-3 laboratory. The unavailability of such infrastructure in the endemic regions could potentially contribute to diagnosis and transmission complications. As per the WHO, definitive RVF diagnosis in humans could be done through RT-PCR, Loop-mediated isothermal amplification (LAMP), next generation sequencing (NGS), and detection of antigens and antibodies (IgM and IgG) by ELISA of the clinical specimen.[12] Endemic circulation of RVFV was identified in KwaZulu-Natal province, South Africa, evident by the presence of IgG and IGM antibodies in the tested population presenting fever-like symptoms. The most common symptoms among the seropositive individuals included fever, headache, and arthralgia.[13] In a study in Botswana, antibodies were also verified in individuals with no clinical symptoms.[14] In an Ethiopian study, 13.2% seroprevalence was recorded in humans and 62% in camels.[15]

The pandemic potential of RVFV and the unavailability of approved vaccines and therapeutic agents is a matter of serious concern with regard to public health.[16] Coordinated effort between the public and animal health administrations in line with the One Health approach to control the spread sporadic diseases like RVF is suggested. It could be achieved by antibodies and RT-PCR based surveillance programmes to screen and diagnose RVF in humans and domesticated animals.[17–19] Antibodies against viral nucleo- and glycoproteins could facilitate the diagnosis.[20] A low-density lipo-protein receptor-related protein 1 (Lrp1) was identified as a potential receptor for viral glycoprotein attachment and the entry of the virus into the cells. Clustered repeatedly interspaced short palindromic repeats (CRISPR) studies also noted that other host proteins including heat shock protein (Grp94), and receptor-associated protein were critical in RVFV infection.[21] Nonstructural NS protein of RVFV was identified as a potential virulence factor that was neurotoxic and could damage brain cells.[22,23] RVFV infection can cause hepatitis, hemorrhage, and leukopenia in humans, and it could affect different tissues generally resulting in ocular and neurological pathology.[24] The pathophysiology of RVFV infection appears to be complex. Both innate and acquired immunity play a key role in the pathogenesis and disease outcome. RVFV infection commonly led to the necrosis/lesions of the liver, endothelial damage, ascites, pulmonary, and lymph node congestion and edema in humans and animals. Necrosis, hemorrhage, multiorgan failure, and circulatory shock may result in death.[25]

7 | PUBLIC HEALTH RESPONSE

The 2018–2019 RVFV human outbreaks in France noted that more than 70% of the infections were related to exposure to blood and body fluids of the infected animals.[26] More than 98% of the human patients infected with RVFV in Sudan revealed that their domesticated animals either died or had suffered from abortion before they had encountered the symptoms. This confirms the ease of animals-to-humans spread of RVFV.[27] Keeping in view previous outbreaks, the epidemic response in Mauritania is being managed using One Health model including creating One Health technical committee to coordinate the response at the national level. Camels might be crucial in local amplification of RVFV in Mauritania.[28] Weekly meetings

between the human health and animal health coordination committees are held in the affected wilayas. In-depth epidemiological and entomological investigations, daily meetings, community senitization, provision of medications and personal protective equipment, improving the diagnostic and management capabilities of health facilities in the affected areas, and mobilizing the partners for material and financial support are the priorities.[29]

8 | RISK ASSESSMENT

Mauritania encountered RVF in 1987, 2010, 2012, 2015, and 2020. Transmission can be during animal slaughter, through contact with tainted blood or tissues, and through the bite of the carrier mosquito.[2,4,29] The illness spreading to humans after the confirmed case of circulation of the virus in animals in various regions throughout the majority of wilayas is highly likely. High animal densities, insufficient sanitation services, and unstable environmental conditions all contribute to the growth of vectors and the transmission of the virus. Copious rainfall this year leading to flood in the majority of these wilayas, dumping of used tyres, used containers and debris have all contributed to increased vector breeding sites.[4]

Although the global risk of RVF is estimated low, but the risk of its spread at regional levels is moderate. Since Mauritania is an agro-pastoral nation, the transmission risk increases owing to the movement of animals in search of pasture and water. Regular pastoral cross-border movements raise the danger of disease being disseminated to neighboring nations.[30] As indicated earlier, nine of the 15 wilayas of Mauritania border Mali, Senegal, and Algeria, and 14 of them have reported confirmed human, confirmed animal, and suspected animal cases.[31] The wilayas of Assaba, Adrar, Hodh El Chargui, Hodh El Gharbi, Guidimakha, and Tiris Zemmour border Mali, and Brakna, Gorgal, Guidimakha, and Trarza border Senegal. The transhumance practise, defined by pastoralism and the movement of livestock under the care of herders, is common in Mauritania and transborder into Mali and Senegal. The risks are further high as RVF is not among the illnesses subject to vaccination control in animals, and some nations in the subregion rely on Mauritanian markets to supply their livestock.[4]

9 | MITIGATION STRATEGY

Human infections frequently occur adjacent to cattle outbreaks in a setting that favors local transmission of RVFV by mosquito vectors. Mosquito species like *Culex poicilipes*, *Culex quinquefasciatus*, *Culex antennatus*, *Culex univitattus*, *Mansonia africana*, *Aedes vexans*, and *Mansonia uniformis* reportedly are the RVFV transmission vectors.[29] However, the majority of the infected human cases were allegedly through direct or indirect contact with blood or organs of infected animal.[2,4,29] Due precaution needs to be followed while handling ill human or animal including their fluids and laboratory samples. Awareness campaigns on risk factors for RVF transmission and the preventative measures like vector management and protection from mosquito bites are crucial to reduce the human infections and fatalities cases.[4]

Prior rigorous animal immunization could stop RVF outbreaks. Vaccination campaign during an epizootic is not advised as it could potentially facilitate pathogenic reassortments. Since animal cases of RVF epizootics occur before human cases, active animal health surveillance system for early warning to the veterinary and human health authorities may be established. Although no human-to-human RVF transmission has been documented, there is a theoretical possibility that the healthcare personnel could contract the virus after contacting with the contaminated blood or tissue of a patient. Thus, specimen-handling healthcare professionals could follow preventive measures before handling a suspected or confirmed RVF case.[5] Based on the currently available information regarding this, the WHO advises against implementing any travel or trade restrictions to Mauritania or other affected regions.

10 | VACCINES

Most of the human RVF cases are relatively mild, of short duration and may be self-healing, although general supportive therapy for severe cases is suggested. Recently, an inactivated viral vaccine was developed, licensing and commercialization of which is awaited, and tried to protect domesticated animals and laboratory personnel at high risk of RVF exposure.

The first RVF vaccine was developed as a formalin-inactivated NDBR103 Entebbe strain isolated from mosquito to control RVF in Uganda.[32] Formalin or ethyleneamine inactivated RVF vaccine is prepared for veterinary use. The most widely used and the oldest live attenuated Smithburn vaccine using Ugandan *Eretmapodites* spp. began in 1944.[33] Having several disadvantages, live attenuated vaccines are prohibited in the pregnant and in RVF-free countries. As such, no vaccine is authorized in the European Union for human use. A novel formalin-inactivated vaccine TSI-GSD200 was developed by the US Army's Medical Research Institute of Infectious Diseases (USAMRIID).[3] Another live attenuated one MP-12, capable of producing sufficient antibody titer for protection against RVF, was developed by the USAMRIID for both human and veterinary use. It can potentially benefit pregnant animals protecting the newborn.[34] Other vaccine forms using state-of-the-art technology include that of subunit protein, DNA,[35,36] virus replicon particle,[37] virus-like particle,[38] virus vectored,[39] and genetically modified live vaccines.[40]

11 | DISCUSSION

Mauritania has steadily witnessed five RVF epidemics in spates from 1987 till 2020. Nine Mauritanian regions reported infections largely among the livestock breeders[4] allegedly handling goat, sheep, cattle, buffalo, and camel[6] recently, where the males of 3–70 years

age-group outnumbered the females among the confirmed cases. Twelve including the nine wilayas having common borders with Mali, Senegal, and Algeria are affected. Thus, regional spread of the outbreak cannot be ruled out even against the One-Health strategy.[4,41] Global spread of RVF has every possibility due to increased human and animal mobility. All deaths occurred with hemorrhages, acute thrombocytopenia, and fever symptoms.[4] Small ruminants, camels, and cattle are the major known RVF virus carriers. While humans are infected through mosquito bite, contacting blood, or organs of the infected animals could also cause,[2] especially in high-risk occupational groups like farmer, herder, abattoir staff, and veterinarian. *Anopheles* and *Culex* mosquitoes and insects like sand-fly could also transmit.[2] RVF virus continues as a threat due to its persistence in the environment. Although RVF infection in humans is usually self-limiting, it may develop severity including fatal hemorrhage,[11] leading to obstetric complications and neonatal infections. Definitive RVF diagnosis could be done through RT-PCR, LAMP, NGS, and antibody (IgM and IgG) detection through ELISA.[12] The pandemicity of RVFV and the unavailability of approved therapeutic and therapeutic measures are public health concerns.[16] State-of-the-art vaccine technology involving subunit protein, DNA,[35,36] virus replicon particle,[37] virus-like particle,[38] virus vectored,[39] and genetically modified live vaccines[40] could be tried. RVF illness causes major economic losses due to deaths and abortions among livestock.[3] High animal densities, insufficient sanitation services, and unstable environmental conditions contribute to the growth of vectors and viral transmission. Awareness campaigns on risk factors for RVF transmission and the preventative measures like vector management and protection from mosquito bites could reduce human infections and fatalities.[4]

12 | CONCLUSION

In light of the overwhelming healthcare situation the world has witnessed and is witnessing in the ongoing pandemic era, it is only prudent to be critical about a malady that is seemingly endemic and consider it as potentially pandemic until and unless it is epidemiologically verified and validated otherwise. To ensure a free and fair healthy world for one and all, preventive approaches with effective surveillance and monitoring system following the One Health model is extremely beneficial and recommended. As heavy rainfall, flood water runoff through rivers and canals helped in spreading the disease on previous instances, the epidemic response team needs to be managed through national level One Health model. Strengthening the surveillance, sanitation standards and policies is suggested. Environmental survivability of RVF-infected *Aedes* spp. eggs also needs assessment.

AUTHOR CONTRIBUTIONS

Ranjan K. Mohapatra: Conceptualization; writing—original draft. **Lakshmi V. S. Kutikuppala**: Writing—original draft. **Venkataramana Kandi**: Writing—original draft. **Snehasish Mishra**: Writing—review and editing. **Ali A. Rabaan**: Writing—review and editing. **Sharo Costa**: Writing—review and editing. **Zahraa Haleem Al-qaim**: Writing—review and editing. **Bijaya K. Padhi**: Writing—review and editing. **Ranjit Sah**: Conceptualization; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

TRANSPARENCY STATEMENT

The lead author Snehasish Mishra, Ranjit Sah affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

All data included within the manuscript.

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