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Review Article

Rift Valley Fever; An Emerging Viral Zoonosis

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ABSTRACT

Rift Valley fever virus (RVFV) is an arthropod-borne virus that causes periodic epizootics and epidemics in sub-Saharan countries of Africa and Egypt. This Class A bio-defense agent primarily infects livestock resulting in abortions and high mortality in young animals. RVFV is implicated as the cause of hemorrhagic fever, encephalitis, retinitis and fatal hepatitis in humans. Though currently confined to Africa and the Arabian Peninsula, RVFV has the potential to be introduced into other countries by mosquito transmission or contact with infected tissues and aerosolized material. Inactivated and the experimental live attenuated RVFV vaccines generated for conferring protection in animals and humans suffer from safety, potency and cost issues. Therefore, there is an urgent need for developing safe and effective marker vaccines that rapidly elicit protective immunity against RVFV infection. Recently, there have been some steps taken towards development of novel vaccine strategies to address this issue. This paper will review RVFV biology, exiting and upcoming prophylactic approaches taken towards controlling RVFV infection in endemic or previously unaffected countries.

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INTRODUCTION

Rift Valley fever (RVF) is a viral zoonosis spread by insect vectors. The etiological agent Rift Valley fever virus (RVFV) belongs to the *Bunyavirus* family and was first isolated in the Rift Valley of Kenya in 1931 (Daubney, 1931). RVFV infections in livestock are manifested by abortion storms in pregnant animals and high mortality rates, especially in new born or young animals. In humans, infection with RVFV typically leads to a mild flu-like illness of short duration lasting for a week or so, but in in a small proportion (1-2%) of infected individuals complications like permanent blindness, liver infection and hemorrhagic fever may occur (Madani, Al-Mazrou et al., 2003;Ikegami & Makino, 2011). The ability of RVFV to cross national or international boundaries, the fact that this virus can replicate in a wide range of insect vectors has raised concerns that RVFV can spread to previously unaffected areas of the world. In addition it is considered a potential bioweapon agent (Lim, Simpson et al., 2005). Prior to 1977, RVFV was confined to Sub-Saharan countries, however in 1977, RVFV was the cause of a sudden and dramatic outbreak in Egypt (Meegan, 1981). There were no reports of RVFV isolation from West and Central Africa prior to 1974, but the disease established itself later on, leading to major outbreaks in Mauritania in 1987 and 1998 (Jouan, Coulibaly et al., 1989). Saudi Arabia and Yemen reported two simultaneous outbreak of RVFV infection in 2000 (Shoemaker, Boulianne et al., 2002). More recently (2006-2007) RVFV outbreaks in Kenya, Somalia and Tanzania resulted in human cases and deaths (MMWR, 2007). The ability of RVFV to cause explosive "virgin soil" outbreaks among animals and humans accompanied by high morbidity and mortality warrants the need for immunoprophylactic measures for this significant veterinary and public health threat. Several traditional and newer approaches to vaccinate livestock and humans against RVFV have been developed or tested in animal models in the last 30-40 years (Ikegami & Makino, 2009;Indran & Ikegami, 2012;Kortekaas, Zingeser et al., 2011). This review summarizes RVFV biology and various approaches that have been employed so far towards the development of a safe and efficacious vaccine to protect livestock and humans against the devastating effect of Rift Valley fever.

VIRUS MORPHOLOGY AND CLASSIFICATION

The family *Bunyaviridae* contains five genera namely *Bunyavirus*, *Phlebovirus*, *Nairovirus*, *Hantavirus* and *Tospovirus*. All genera infect vertebrates with the exception of *Tospovirus* which harbor plant viruses. RVFV is a typical member of the genus *Phlebovirus*. The virions of the *Bunyaviridae* family are spherical, measuring 90 to 100 nm in diameter, and have a bilayered lipid envelope with three circular nucleocapsids, each with helical symmetry. The virus genome contains three; single-stranded negative sense RNA segments. These segments are the large (L) segment (~6.4 kB) expressing virus RNA dependent RNA polymerase, medium (M) segment (~3.8kB) encoding at least four proteins in a single open reading frame (ORF), two of which are structural glycoproteins Gn and Gc and two are non-structural proteins, the 14kD NSm and a 78kD NSm+Gn fusion peptides (Gerrard, Bird et al., 2007;Gerrard & Nichol, 2007;Schmaljohn, 2001). The small (S) segment (~1.6kB) encodes the virus nucleoprotein (N) and the non-structural (NSs) in the genomic and anti-genomic orientation respectively (Schmaljohn, 2001). As seen with all negative sense RNA viruses, the RVFV genome is transcribed and replicated only when complexed with RNA polymerase and nucleocapsid protein, forming ribonucleoproteins (RNPs). The structural glycoproteins encoded by the M segment ORF are initially expressed as polyprotein precursors for the two mature structural glycoproteins that are processed together post-translationally. The carboxy terminal parts of NSm and Gn contain signal peptides that likely function in translocation of

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Gn and Gc into the endoplasmic reticulum (ER) and the Golgi retention signal on Gn helps localize Gn and Gc to the Golgi compartment. Mature virions are formed intracellularly by budding into the Golgi complex (Pettersson, 1996). Since bunyaviruses lack a matrix (M) protein to link the structural glycoproteins with the RNPs, a direct interaction between the envelope glycoproteins and RNPs could be a possibility.

BIOLOGY OF RIFT VALLEY FEVER VIRUS INFECTION

RVFV causes disease primarily in sheep, goat and cattle although in some outbreaks, disease is only observed in lambs. The incubation period could be of short duration (12 hours) in experimental infections, however, it can go anywhere from 24 to 36 hours or even longer in natural infections. Following infection, animal develops high fever, exhibits acute abdominal pain and may succumb to infection within 24 to 36 hours after the onset of clinical signs. In newborn lambs, the disease follows a rapid course, without any specific symptomatology, and is highly fatal where the mortality rate can be as high as 95%. Adult sheep and cattle infected with the virus exhibit fever, loss of appetite, profuse salivation, nasal discharge, abdominal pain and bloody or fetid diarrhea. In some cases, severe jaundice can develop with an overall low (10-30%) fatality rate in adult animals depending upon nutritional status. Abortion storms irrespective of the stage of pregnancy and neonatal mortality are hallmarks of RVFV epizootics.

In humans, RVFV infection is usually mild with a short incubation period of 4 to 6 days. Patients usually experience fever, myalgia, arthralgia, nausea, vomiting, and altered vision. However, in some rare circumstances, infection may progress to severe and sometimes fatal complications (Al-Hazmi, Ayoola et al., 2003;Borio, Inglesby et al., 2002;Madani, Al-Mazrou et al., 2003) such as retinitis leading to permanent blindness, brain infection, acute hepatitis and hemorrhagic fever which was observed in around 1% of infected individuals in the 1977 RVFV epidemic in Egypt (Meegan, 1979). Encephalitis is most likely associated with confusion and coma. A high incidence of eye infection was reported during the 2000 epidemic in the Arabian Peninsula (Madani, Al-Mazrou et al., 2003). It has been found that hemorrhagic syndrome is the main cause of death. Infected individuals have fever for two to four days and then exhibit jaundice, hemorrhages such as hematemesis, melena, hemorrhagic gingivitis, and petechial and purpuric cutaneous lesions. Hepatic necrosis has been one of the hallmark lesions found at autopsy. The meningoencephalitic syndrome is reported in some individuals, which occurs one or two weeks after the febrile period.

ANIMAL AND PUBLIC HEALTH SIGNIFICANCE

RVF in livestock was first reported as an enzootic hepatitis with extensive hepatic necrosis. RVF was originally categorized as a disease of livestock, before the Egyptian epidemic in 1977 involving human cases. It was implicated in causing high mortality rates in new-born animals and abortions in pregnant animals. In 1950 during the epizootic of RVF in South Africa 100,000 sheep died and approximately 500,000 aborted (Gerdes, 2004). In the successive outbreaks RVFV caused great economic losses in livestock resulting from death of domesticated animals and restrictions in trade and export of animals several months after the end of outbreaks.

Human infections typically occur as a result of infected mosquito bites, skin or aerosol exposure during necropsy, handling of infectious aborted fetal materials or during slaughtering of infected animals (Schmaljohn, 2001). In most human cases, the disease is manifested as a self-limiting febrile illness, which progresses to more serious complications in 1-2% of infected individuals with a hospitalized case fatality of 10-30% (Schmaljohn, 2001). The Egyptian outbreak in 1977 was the first outbreak involving humans with an estimated 200,000 cases resulting in 623 deaths from severe complications of disease (Meegan, 1979). Later in 1987, a large outbreak of RVFV infection in Mauritania and Senegal affected 89,000 individuals (Jouan, Coulibaly et al., 1989). In the Arabian Peninsula in 2000, an estimated 2000 cases and 245 deaths were reported (Shoemaker, Boulianne et al., 2002). Recently, in 2006-2007 outbreaks in Kenya, Somalia and Tanzania resulted in estimated 1062 reported human cases and 315 deaths resulting from that outbreak (MMWR, 2007). The magnitude of RVF outbreaks in human and animal populations and the widespread vector population highlights the importance of developing preventive measures to meet the challenge in the face of an outbreak in non-endemic areas of the world.

EPIDEMIOLOGY AND TRANSMISSION

Most important RVF epidemics and or epizootics followed after periods of unusually heavy rainfall or in conjunction with building of dams. Therefore, the distribution of large RVF disease outbreaks is linked to the presence of water. Water plays an important role in the life of most blood feeding arthropods which limit the choice of breeding sites. Outbreaks of RVF associated with heavy rainfall erupt in the south and east Africa, while in the comparatively drier north and West Africa outbreaks are associated with irrigated lands. *El Nino* activity resulted in outbreaks of RVF in the horn of Africa in 1997/98. Epizootics of RVF are characterized by long inter-epizootic periods and are cyclical in nature. These cycles can be anywhere from five to fifteen years in wetter areas which changes to fifteen to thirty years in comparatively drier areas. During inter-epizootic periods virus may be present in an endemic cycle between mosquitoes and livestock species and possibly gets amplified within the livestock and may then transmit to humans which act as dead end host. In areas experiencing heavy rainfall where the water table is sufficiently raised promote virus activity with low level transmission to livestock associated with Aedine mosquitoes that breed in *dambos* which are seasonally waterlogged, predominantly grass covered depressions (Gerdes, 2004).

Once the virus activity is seen in a region then that area becomes permanently infected with the virus. North and West African countries observe RVF outbreaks from mosquitoes that breed in large rivers and dams. Approximately 20 countries in Africa and Madagascar are infected and 23 mosquito species are involved in the epizootic/enzootic transmission cycles of RVF. *Culex sp.* is the major vector for virus transmission in Egypt, where no other mosquito spicies is capable of transovarian transmission (Mellor & Leake, 2000). New outbreaks in Egypt could possibly be the result of infected mosquitoes coming out of overwintering, re-introduction of the virus with infected livestock transport or air-borne transmission from neighboring infected countries. The 1977 outbreak in Egypt is thought to be associated with the air-borne transmission when unusual southerly winds probably played significant role in bringing mosquitoes up from the north of Sudan.

IMMUNE RESPONSE TO RVFV INFECTION

Most viral infections trigger both innate and adaptive immune responses in host. Although little is known about the cell mediated immune response, it is a common feature among bunyavirus infections that the humoral or antibody mediated immune response plays an important role in protection. The viral nucleoprotein (N) appears to be immunogenic, but antibodies are also raised against the envelope glycoproteins Gn and Gc, harbouring neutralizing epitopes (Collett, Purchio et al., 1985;Collett, 1987). It is well documented in previous

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scientific experiments that neutralizing antibodies have a protective effect against a virulent RVFV challenge and passive transfer of RVFV immune serum is protective against lethal RVFV disease in animal models (Francis & Magill, 1935;Schmaljohn, Parker et al., 1989;Bhardwaj, Pierce et al., 2012;Ross, Bhardwaj et al., 2012; Bhardwaj, Heise et al., 2010). The induction of neutralizing antibody response is a favored tool for the development of an effective RVFV vaccine. Studies on RVFV have revealed the role of non-structural protein NSs as a major virulence factor (Bridgen, Weber et al., 2001;Naslund, Lagerqvist et al., 2009). Researchers have now unearthed the mechanisms used by RVFV NSs protein to combat the host immune response (Bouloy, Janzen et al., 2001;Vialat, Billecocq et al., 2000).

In order to develop a safe and effective vaccine, it is of utmost importance to understand the correlates of protection. The correlates of immune protection for RVFV have not been elucidated, but there is strong evidence that neutralizing antibodies are a major contributor to protective anti-RVFV immune responses. Resolution of disease in animals that survive infection correlates with the generation of anti-RVFV antibody responses. In genomic analysis of the 33 RVFV strains isolated from Africa and Saudi Arabia during RVFV outbreaks from 1944 to 2000 revealed little virus diversity, with genomic identity differences of only approximately 5% and 2% at the nucleotide and amino acid levels, respectively (Bird, Khristova et al., 2007). This could allow development of one universal vaccine that can confer protection against all RVF virus lineages across the globe.

DIAGNOSIS

RVFV disease outbreaks usually follow heavy rains and consequently high density of mosquitoes. It appears as a sudden onset of abortions in sheep and cattle at all stages of pregnancy. Such an outbreak may also be accompanied by sudden death of newborn animals (lambs and calves) following an acute febrile illness. Liver lesions found by histopathological examinations are pathognomonic, however laboratory confirmation is required. During an outbreak, virological and serological examinations provide the confirmatory diagnosis. In the case of live animals specimens include heparinized blood and serum but in case of dead animals tissue samples from liver, spleen, kidney, lymph nodes and heart blood must be obtained for laboratory diagnosis.

Earlier, RVFV was isolated by inoculating infectious sera samples into lambs but, once mice were shown to be susceptible to RVFV (Findlay, 1931), rodents became an important animal model for virus isolation. With time mice were replaced by tissue cultures using Vero cells or mosquito cells being for virus isolation (Digoutte, Jouan et al., 1989). Virus replicates rapidly in mice, hamster and non-human primate cell lines like Vero, BHK or CER.

Serological tests for disease diagnosis include complement fixation, immunodiffusion, indirect immunofluorescence (IFA), hemagglutination inhibition (HAI) and virus neutralization (Swanepoel, Struthers et al., 1986). Enzyme linked immune-sorbent assay (ELISA) based on inactivated RVFV antigens obtained either from tissue culture or infected mouse brain have been developed and validated for sero-diagnosis of RVF in livestock and humans (Paweska, Barnard et al., 1995;Paweska, Burt et al., 2003;Paweska, Smith et al., 2003;Paweska, Burt et al., 2005;Paweska, Mortimer et al., 2005). More recently RVFV recombinant nucleocapsid (rNp) based indirect ELISA have been developed and subsequently validated in humans and African buffalo (Paweska, Jansen van Vuren et al., 2007;Paweska, van Vuren et al., 2008). Although IgG antibodies are produced early in infection, but IgM ELISAs are favored for rapid diagnosis (Niklasson, Peters et al., 1984).

RIFT VALLEY FEVER VACCINATION

No specific treatments are currently available to prevent RVF. RVFV is sensitive to several antiviral agents and interferon treatment *in vitro*. Experimental studies in RVFV infected rhesus macaques have shown that ribavirin and recombinant interferon alpha are effective as prophylactic drugs, but the chemotherapeutic efficacy for the disease has not been demonstrated (Gowen, Wong et al., 2008;Morrill, Jennings et al., 1989;Peters, Reynolds et al., 1986). Passive antibody therapy by administration of serum or immune plasma may be effective but impractical in an epizootic. The economic importance of disease in livestock industry and the highly pathogenic nature of the virus coupled with the absence of effective treatment against this zoonotic disease encourage vaccine development to prevent the virus infection.

COMMERCIALLY AVAILABLE OR EXPERIMENTAL VACCINES

Live attenuated and inactivated killed vaccines for RVF are in use in many African countries (WHO/FAO, 1983). The live attenuated Smithburn neurotropic strain was developed by brain passages of the virulent Entebbe strain in suckling mice and embryonated chicken eggs (Smithburn, 1949). Although this strain provides long lasting immunity but due to incomplete attenuation it is still neurotropic and cause a number of abnormalities in central nervous system (CNS) of fetuses. Vaccination of pregnant livestock (sheep and cattle) may also result in abortion and stillbirth (Botros, Omar et al., 2006;Yedloutschnig, Dardiri et al., 1981). Thus the use of live attenuated vaccine was limited to enzootic areas of Africa or to control and epizootic.

Inactivated killed vaccines are recommended for use outside of enzootic areas in Africa. Formalin-inactivated wild type RVFV vaccines have also been used in Egypt and South Africa (El-Karamany RM, 1981). The formalin-inactivated vaccines are although safe but are very expensive to produce requiring booster inoculations to maintain a durable level of immunity. One of the major problems to livestock vaccination is the long-time gap between successive epizootics and their irregular appearance. This, as a consequence makes it difficult for veterinarians to convince livestock owners to vaccinate their animals on a regular basis. Recent advances in the surface ocean temperature determinations and satellite imagery based predictions of the regions at higher than usual risk of RVF activity may allow the timely vaccination of animals before potential epizootics (Linthicum, Anyamba et al., 1999).

Formalin-inactivated RVF vaccines have been developed for immunization of laboratory and field workers at risk of exposure however, these vaccines are unlikely to be used at larger scale (Meadors, III, Gibbs et al., 1986;Randall, Binn et al., 1964). The only vaccine currently cleared for human use (TSI-GSD-200) is a killed product available only from the United Stated Army Medical Research and Materiel Command (USAMRMC). This vaccine is limited in supply and requires an initial three dose series for protective immunity followed by annual booster inoculations required to maintain that immunity (Pittman, Liu et al., 1999).

A live-attenuated RVF vaccine strain (MP-12) developed for use in livestock and humans is in experimental stages and being tested for its safety and efficacy (Caplen, Peters et al., 1985;Lihoradova & Ikegami, 2012;Morrill, Jennings et al., 1987;Morrill, Carpenter et al., 1991;Morrill & Peters, 2003;Gowen, Bailey et al., 2013). In a recent study, recombinant form of highly virulent ZH501 strain lacking NSm and NSs was

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found to induce protective immune responses in pregnant sheep (Bird, Albarino et al., 2008). Extensive laboratory based studies in the past have shown that MP-12 is safe and efficacious against virulent virus challenge not only in ewes and pregnant cows, but also in neonatal calves and lambs (Hubbard, Baskerville et al., 1991;Morrill, Jennings et al., 1987;Morrill, Carpenter et al., 1991). Under experimental conditions, the vaccine does not induce any fetal anomaly in pregnant sheep and cattle. The American Committee on Artrhopod-Borne Viruses (ACAV) Subcommittee on Arbovirus Laboratory Safety (SALS) has determined that the MP-12 vaccine strain may be handled at BSL-2, providing additional safety to humans involved in vaccine production (US Department of health and human services, 1993). Studies in rhesus macaques have shown that MP-12 vaccine is less neurovirulent than Smithburn strain. The results of a recent MP-12 vaccine study in rhesus macaques have shown that the virus is markedly attenuated for rhesus monkeys as adjudged by the clinical signs, mortality and histopathology in the virus challenged animals. However, there were some residual neurovirulence lesions associated with the vaccine virus MP-12 (Morrill & Peters, 2003).

A naturally attenuated strain called clone 13, isolated from a human RVFV infection was found to be highly immunogenic for mice and is currently being tested in South Africa. This viral strain has a large deletion in the gene coding for the non-structural protein NSs, which is the major virulent factor of RVFV (Vialat, Billecocq et al., 2000).

NOVEL VACCINE CANDIDATES

Experimental studies and field experience with the available live-attenuated RVF vaccines has revealed their ability to cause abortion, teratogenicity, CNS pathology in livestock or suitable animal models thus making there widespread use questionable, especially in the non-endemic areas, or during inter-epizootic periods. Among many other significant limitations of commercialization of live attenuated vaccines, one major drawback is that they do not allow for the differentiation of naturally infected from vaccinated animals (DIVA). This is of prime importance if the vaccination strategy is to be used to boost efforts to limit an accidental or malicious release of wild-type RVFV in non-endemic areas (Henderson, 2005). To address these issues novel vaccine candidates have been identified.

One of the earlier works on developing recombinant RVFV vaccines involved the use of vaccinia virus and bacteria. Immunization of animals with vaccinia virus recombinants or bacteria expressing RVFV Gc and/or Gn glycoprotein(s) was shown to elicit neutralizing antibody responses and was able to confer protection in animals from virulent virus challenge even with the use of vaccinia expressing Gn alone (Collett, 1987). Similar results were obtained in a related study using vaccinia virus recombinants (Dalrymple, 1989). However, there are concerns over the use of vaccinia virus in the recombinant vaccines due to its wide host-range specificity.

Research on baculovirus expressed proteins lead to the research involving use of *Autographa californica* nuclear polyhedrosis virus (AcNPV) to express portions of the RVFV M gene segment which were found to elicit high-titered neutralizing antibody responses and were protected from challenge. Passive transfer of sera from immunized mice to naïve mice protected the later mice from challenge 24 hour post transfer (Schmaljohn, Parker et al., 1989).In the recent years there have been advances in the development of poxviruses as vaccine vectors (Soi, Rurangirwa et al., 2010;Papin, Verardi et al., 2011). Using thymidine kinase gene insertion, a recombinant lumpy skin disease virus-vectored recombinant vaccine (rLSDV-RVFV) expressing RVFV glycoproteins was developed and was able to elicit neutralizing antibodies in laboratory animals and was able to protect mice from challenge (Wallace & Viljoen, 2005;Wallace, Ellis et al., 2006). Recently, Adenovirus and Newcastle disease virus have been tested to deliver RVFV antigens and were found to be successful in inducing protective anti-RVFV immune responses in experimental animal studies (Holman, Penn-Nicholson et al., 2009;Kortekaas, de Boer et al., 2010;Kortekaas, Dekker et al., 2010;Kortekaas, Antonis et al., 2012).

Reverse genetics based approach was utilized in developing RVFV vaccine candidates harbouring deletions of complete virus genes with known roles in virulence (NSs, NSm). Administration of these attenuated viruses induced robust anti-RVFV antibody titers and conferred protection in mice from subsequent challenge with virulent RVFV strain (Bird, Albarino et al., 2008).

DNA-based and subunit vaccines represent a novel means of expressing vaccine antigens *in vivo* for the generation of both antibody and cellular immune responses. In some recent studies by our group and others, DNA and subunit vaccines against RVFV were evaluated and was shown to induce anti-RVFV immune responses in mice (Bhardwaj, Heise et al., 2010;Bhardwaj, Pierce et al., 2012;Lagerqvist, Naslund et al., 2009;Lorenzo, Martin-Folgar et al., 2010 ;Spik, Shurtleff et al., 2006;Wallace, Ellis et al., 2006;de Boer, Kortekaas et al., 2010;Kortekaas, Antonis et al., 2012). Virus challenge with a lethal dose of virulent RVFV virus strain post-immunization was also shown to be protective in mice (Bhardwaj, Heise et al., 2010;Gorchakov, Volkova et al., 2007;Heise, Whitmore et al., 2009;Lagerqvist, Naslund et al., 2009;Lorenzo, Martin-Folgar et al., 2010;Spik, Shurtleff et al., 2006;Bhardwaj, Pierce et al., 2012).

In the last few years, alphavirus expression systems have been used for the delivery and expression of heterologous genes both *in vitro* and *in vivo*. Sindbis (SINV) and Venezuelan Equine Encephalitis virus (VEEV) expression systems are based on the use of self-replicating RNAs called replicons in which the structural genes, encoded by the subgenomic RNAs, are replaced by the genes of interest, such as vaccine antigen. Venezuelan equine encephalitis virus (VEE) and Sindbis virus (SINV), based replicon vectors were found to be effective in inducing protective immune response in a recent study by our group and others (Bhardwaj, Heise et al., 2010;Gorchakov, Volkova et al., 2007;Heise, Whitmore et al., 2009).

CONCLUSION

Rift Valley Fever virus represents a significant threat to human health and there is a pressing need for the development of improved vaccines against this pathogen. Although existing inactivated and experimental live attenuated vaccines show promise, they have limitations with respect to efficacy or safety. There is significant research undergoing towards generating protection against RVF, still we lack data describing correlates of protection. To overcome this, new candidate vaccine strategies have surfaced in the recent past. Novel recombinant subunit vaccine candidates are based on the surface glycoproteins of the virus expressed in prokaryotic or eukaryotic system and have shown some promise. DNA and vector based vaccines have the ability to stimulate both cellular and humoral arms of immune responses. The novel vaccine candidates will serve as a benchmark for the development of future vaccine approaches so that the best vaccine strategy can be taken forward for clinical trials. Not only will these studies directly assess the potential of the proposed RVFV vaccine strategies, but they also have the potential to significantly enhance our general understanding of anti-RVFV immunity, which can be applied to further development of these RVFV vaccine technologies.

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