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Review

One Health approach to Rift Valley fever vaccine development

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ABSTRACT

Since its discovery in the 1930s, Rift Valley fever virus (RVFV) spread across the African continent and invaded the Arabian Peninsula and several islands off the coast of Southeast Africa. The virus causes recurrent outbreaks in these regions, and its continued spread is of global concern. Next-generation veterinary vaccines of improved efficacy and safety are being developed that can soon be used for the widespread vaccination of livestock. However, due to regulatory and economic challenges, vaccine manufacturers have been reluctant to develop a human vaccine. Recent innovations in veterinary vaccinology, animal models and licensing strategies can now be used to overcome these hurdles. This paper reviews the historical impact of RVFV on human health and proposes strategies to develop and license a next-generation vaccine for both animals and humans.

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1. Introduction

Rift Valley fever virus (RVFV) is a zoonotic arbovirus endemic to the African continent, the Arabian Peninsula and several islands of the Indian Ocean located to the southeast of Africa. In these areas, the virus causes recurrent outbreaks among animals and humans. Domesticated ruminants, particularly sheep, are the most susceptible to disease. Infection of gestating ewes results almost exclusively in abortion and mortality ratios in newborn lambs can approach 100%. Cattle, goats and ruminant wildlife species are somewhat less susceptible, but losses among these herds can also

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be considerable. Although most human infections are benign, the virus is feared for its ability to cause hemorrhagic fever and encephalitis. RVFV has been isolated from over 30 mosquito species of which several have a global distribution. Collectively, these features explain why RVFV is considered one of the most serious arbovirus threats to human and animal health.

Next-generation veterinary vaccines will soon be available to control future epizootics. However, due to regulatory and economic challenges, vaccine manufacturers have been reluctant to develop a human vaccine. This paper reviews the historical impact of RVFV on human health and argues to use a common approach to develop vaccines for animals and humans by making use of recent innovations in veterinary vaccinology, animal models and licensing strategies.

2. The history of Rift Valley fever in humans

The first recorded epizootic of Rift Valley fever (RVF) occurred in 1930 on a farm located near the shores of Lake Naivasha in the Rift Valley of Kenya (Daubney et al., 1931a). The outbreak was characterized by hyperacute mortality among newborn lambs and abortions (Daubney, 1931; Daubney et al., 1931a,b; Findlay, 1932; Findlay and Daubney, 1931). A potential role for mosquitoes in the transmission cycle of the causative agent was recognized by scientists investigating the outbreak, who demonstrated that animals could be protected by mosquito netting or by moving the animals to the highlands, which were free from mosquitoes (Daubney et al., 1931b). All four Europeans engaged in the investigation of the outbreak developed symptoms reminiscent of dengue fever and further inquiries made clear that native shepherds experienced similar symptoms. This first confirmed outbreak of RVF is believed to have caused 200 human cases without fatalities (Daubney et al., 1931a,b).

Apart from infections acquired in the field, the first laboratory-acquired infections were reported by Findlay (1932) and Kitchen (1934), all without serious complications. In 1934, Schwentker and Rivers reported a laboratory-acquired infection in the United States (Schwentker and Rivers, 1934). After the acute phase, the patient developed thrombophlebitis during convalescence, and died from a pulmonary embolus 45 days after the onset of illness. This was the first indication that RVFV infection in man can result in life-threatening complications.

After the apparent absence of the disease for twenty years, a serious epizootic among sheep occurred in 1951 in South Africa. After performing a necropsy on a deceased bull, three veterinarians and two assistants became acutely ill. RVFV was isolated from the blood of one of the assistants, confirming the diagnosis (Mundel and Gear, 1951). In the same year, Joubert et al. (1951) and Gear et al. (1951) reported over 50 and 13 human cases, respectively, of a similar illness affecting veterinary surgeons, farmers and native labourers. A subsequent serosurvey suggested approximately 20,000 human cases had occurred without fatalities (Schulz, 1951). During this outbreak, retinal changes and loss of vision were for the first time described in detail (Freed, 1951; Schrire, 1951).

In 1975, South Africa again experienced a serious epizootic in which thousands of lambs and hundreds of sheep and cattle died. During this epidemic, the first human fatalities directly attributable to RVFV infection were reported (McIntosh et al., 1980; van Velden et al., 1977). The clinical manifestations of RVFV infections in 17 patients admitted to hospitals in Bloemfontein were reported by Van Velden et al. (van Velden et al., 1977). The onset of disease was generally sudden and involved chills, painful eyes, headache, backache, limb pains and tender muscles. Neurological complications were noted in 12 patients, which included meningeal irritation, confusion, coma, hypersalivation with teeth grinding, visual hallucinations, lock-in syndrome and rapid involuntary jerky movements. Two patients developed encephalitis which was fatal in both cases. Three fatal cases of hemorrhagic fever were reported, with symptoms including epistaxis, hematemesis, melena and hematuria (van Velden et al., 1977). McIntosh et al. reported 110 laboratory-confirmed cases and 7 fatal cases (McIntosh et al., 1980).

In 1977, a human RVFV epidemic occurred in Egypt, which is believed to represent the largest epidemic to date (Hoogstraal et al., 1979; Meegan, 1979; Meegan et al., 1979). The outbreak followed the completion of the Aswan dam, which was built to regulate the irrigation of the Nile delta and significantly increased the number of mosquito breeding sites. The Egyptian government reported 18,000 cases with 598 deaths, although others suggested that the number of clinical cases could have exceeded 200,000 (Meegan, 1979). A feature that may have contributed to the large number of human cases that occurred during the Egyptian outbreak was the involvement of mosquitoes from the *Culex* (*Cx.*) *pipiens* complex, which were not associated with RVFV epidemics before that time (Hoogstraal et al., 1979).

As in other RVFV outbreaks, the slaughtering of diseased animals is also believed to have played a major role in transmission of the virus to humans. In Egypt, sick animals are customarily slaughtered for consumption and this custom is intensified during epizootics. The efficient transmission of RVFV via this route was exemplified by Hoogstraal et al., who reported illness in all 8 persons who attended the slaughtering of a diseased sheep, of which 6 did not have physical contact with the animal (Hoogstraal et al., 1979). It is furthermore worthwhile to note that the large number of severe human cases that occurred during the Egyptian outbreak may be explained by a high incidence of schistosomiasis, a disease caused by parasites that target the liver (Meegan, 1979).

In 1986, the completion of the Diama dam resulted in the permanent presence of fresh stagnant water in the Senegal river basin and a dramatic increase in mosquito numbers. The year after, Mauritania experienced a serious outbreak of RVF resulting in an estimated 224 fatal human cases (Jouan et al., 1988). The virus re-emerged in this area and caused human fatalities in 1998, 2010 and 2012 (Nabeth et al., 2001; El Mamy et al., 2011; WHO, 2012).

The largest RVFV outbreak of Sub-Saharan Africa occurred in 1997–1998 in Kenya. In the Garissa district only, 171 fatalities were reported among an estimated 27,500 infected humans (Woods et al., 2002). The total number of human cases in Kenya and south Somalia was estimated at 89,000 with more than 400 being fatal (CDC, 1998). The outbreak spread to the south into Tanzania (Woods et al., 2002), resulting in an estimated 40,000 human cases (Anyamba et al., 2010). Mohamed et al., reported 511 suspected cases and a fatality ratio among 144 confirmed severe cases of 28.2% (Mohamed et al., 2010). The massive expansion of RVFV in these areas is believed to have resulted in the spread of the virus to the Arabian Peninsula.

In the fall of 2000, an outbreak occurred in the southern coastal provinces Asir and Jizan of the Kingdom of Saudi Arabia (CDC, 2000a,c) and another occurred in the El Zuhrah district of the Hodeidah governorate in Yemen (CDC, 2000b; WHO, 2000). An estimated 2000 people developed complications varying from ocular impediments to hemorrhagic fever and encephalitis. At least 245 people did not survive the infection, suggesting a case fatality ratio (CFR) among severe cases of 12% (Al-Hazmi et al., 2003; Madani et al., 2003). It was reported that most patients resided in or visited the floodplains of seasonal riverbeds, which contributed to the conclusion that the majority of human cases in this outbreak resulted from mosquito bites (Madani et al., 2003). Entomological studies demonstrated that two mosquito species were abundant in the outbreak areas, *Cx. tritaeniorhynchus* and

Aedes vexans arabiensis from which the virus was isolated (Jupp et al., 2002; Miller et al., 2002).

After exceptionally heavy rains at the end of 2006, RVFV caused outbreaks in Kenya, which were followed by outbreaks in Somalia and Tanzania in 2007. A total of 1062 human cases were reported with 315 fatalities (CFR 30%). Apart from continued RVFV activity in these areas, the virus spread to Sudan (Aradaib et al., 2013; Hassan et al., 2011) and in the following years to South Africa (Archer et al., 2011; WHO, 2010). During the same period, the virus re-emerged on Madagascar (Andriamandimby et al., 2010). In the outbreaks that occurred between 2007 and 2010, reported CFRs among severe cases varied from 4% to 44%.

3. Clinical manifestation of RVFV infection in humans

Apart from human infections in the field, several cases were reported among scientists involved in laboratory investigations (Findlay, 1932; Kitchen, 1934; Smithburn et al., 1949). The case reports of these events are still among the most detailed descriptions of the disease in humans. The incubation period is generally 3–6, most commonly 4 days, after which a sometimes biphasic febrile period follows that may last for several days. Patients may suffer from general malaise including a feeling of nausea, profuse sweating, sensation of fullness over the liver, vertigo, constipation, severe headache and pain in the back, shoulders and legs and may experience photophobia. Patients may suffer from visual defects resulting from retinal damage, which is not always associated with severe cases. Visual complications are in most cases transient but may be permanent in some patients. Patients may develop a maculopapular rash. The urine may be deep yellow in colour and the bowels constipated throughout the illness. Infection results in leukocytosis of predominantly polymorphonuclear cells and is followed by leukopenia. It is worthwhile to note that there is generally no enlargement of the spleen or superficial lymph nodes. Similar as in ruminants, focal necrosis of the liver is the most distinctive pathological finding in man.

The high case fatality ratios that were reported after certain outbreaks suggest that mild cases were not recorded in surveillance studies. Since generally only severe cases and associated mortality ratios are reported in literature, it is difficult to determine the percentage of infected people that develop these complications. However, available data suggests that about 1% of infected individuals develop complications that require hospitalization.

4. Transmission of RVFV to humans

During past RVF epidemics, most patients that suffered from severe complications were veterinary surgeons and people handling deceased animals or carcasses. In these cases, the virus is believed to have entered the body via abrasions of the skin, the conjunctival sac, or through mucous membranes of the respiratory tract. The number of human infections resulting from this route of exposure can be reduced by the use of gloves, gowns and face masks. Apart from the aforementioned risk factors, infection via the enteric tract can possibly occur by the consumption of raw meat or milk, although this remains to be experimentally confirmed (Al-Hazmi et al., 2003; LaBeaud et al., 2011; Mohamed et al., 2010). These potential risk factors can best be controlled by continuous public health education in high-risk areas, which should be intensified when a RVFV epidemic is predicted.

Disease in humans who had no recent contact with animals or animal products is attributed to mosquito bites. Interestingly, this mode of transmission is believed to have played a minor role during the epidemics in South Africa in 1951 (Joubert et al., 1951), Kenya in 1997–1998 (Woods et al., 2002) and Mauritania in 1987 (Jouan et al., 1989), but may have played a significant role during the outbreaks in Egypt in 1977 and the Arabian Peninsula in the year 2000. Meegan et al., proposed that the explosive epidemic in Egypt, which is believed to have resulted in over 200,000 clinical cases, could not have been maintained without extensive mosquito involvement (Meegan et al., 1980) and Madani et al. reported that 92 of 406 (23%) investigated Saudi patients were exposed to mosquito bites but not to animals or animal products (Madani et al., 2003). These observations suggest that care should be taken in making generalized statements about the relative importance of mosquitoes in the transmission of RVFV to humans.

5. Classical and next-generation vaccines

5.1. Classical vaccines

The first RVF vaccine was developed by Smithburn in the 1940s by intracerebral passage of the virus in mice. The resulting neurotropic Smithburn virus is still used as a veterinary vaccine and is produced by the Onderstepoort Biological Products Company (OBP, Onderstepoort, South Africa). The vaccine is inexpensive to produce and can provide long-lasting immunity by a single vaccination and has therefore been valuable for the control of RVFV in endemic areas. Due to residual virulence, however, vaccination of pregnant animals can result in abortions and fetal malformations. Consequently, the Smithburn vaccine was never considered for human application.

The first vaccine aimed for human application was developed by Randall and co-workers in 1962 (Binn et al., 1963; Randall et al., 1964, 1962). This vaccine was based on the Entebbe strain, which was originally isolated from mosquitoes in Uganda in 1944 (Smithburn et al., 1948). The pantropic Entebbe strain was propagated in primary monkey kidney cells and was inactivated by formalin. The vaccine induced neutralizing antibodies in humans, although multiple inoculations were required to achieve detectable neutralizing antibody titers in all vaccinated individuals (Randall et al., 1962). The potency of the vaccine remained unchanged upon storage for as long as 8 months at 4–6 °C and no untoward effects were reported after vaccination of more than 1000 individuals (Randall et al., 1962). The vaccine was subsequently produced by the National Drug Biological Research Company (NDBR), resulting in the NDBR-103 vaccine, and was used from 1967 to protect laboratory workers. The prescribed vaccination regimen included a three-dose primary immunization, followed by a booster immunization after 6–12 months (Kark et al., 1982, 1985).

To meet improved standards of vaccine manufacturing, the seed virus of the NDBR-103 vaccine was plaque purified and propagated on a well characterized diploid rhesus monkey cell and used to prepare a new vaccine. This vaccine was manufactured by The Salk Institute, Government Service Division (TSI-GSD), commissioned by the United States army, and became known as the TSI-GSD 200 vaccine. The most recent communication on the immunogenicity and safety of the TSI-GSD 200 vaccine reports the results collected over a period of 19 years (Rusnak et al., 2011). The combined results obtained from studies with the TSI-GSD 200 vaccine demonstrate that the vaccine was well tolerated and that the three-dose primary vaccination series induced 50% plaque-reduction neutralization ($PRNT_{50}$) titers $\geqslant$1:40 in 99% of vaccinated individuals, a titer believed to correlate with protection (Rusnak et al., 2011). Due to declining titers between 6 and 12 months after the primary vaccinations, administration of a booster dose 6 months after the primary vaccination was recommended (Rusnak et al., 2011). Although the TSI-GSD 200 vaccine has been valuable for

the protection of laboratory personnel, the requirement of a three-dose primary vaccination and booster vaccination makes clear that a more effective human vaccine is needed.

5.2. The MP-12 vaccine

In 1985, Caplen et al. demonstrated that serial mutagenesis of RVFV is a feasible approach to develop live, attenuated vaccines (Caplen et al., 1985). The virulent ZH548 strain was attenuated by passage of the virus in the presence of the mutagen 5-fluorouracil and the mutagenized virus, harvested after the 12th passage, was named MVP 12 (later named MP-12) (Morrill et al., 1987). By making use of reassortant viruses, each of the three genome segments was demonstrated to contain attenuating or temperature-sensitive mutations (Saluzzo and Smith, 1990). To gain further insight into the molecular basis of attenuation, Vialat et al., determined that the L, M and S segments accumulated 9, 12 and 4 mutations, respectively (Vialat et al., 1997). However, until today, it remains unclear how these mutations confer the attenuated phenotype of MP-12.

Inoculation of ewes during the second trimester of gestation resulted in low-level viremia but did not result in clinical signs and the ewes delivered healthy lambs (Morrill et al., 1987). Postpartum challenge of the MP-12-vaccinated ewes demonstrated that the vaccination protected from clinical disease. A second study confirmed the safety of the vaccine in gestating ewes (Morrill et al., 1991). In the same study, young lambs developed no untoward effects after vaccination, apart from pyrexia and transient low-level viremia. All lambs were protected from the virulent virus 14 days after vaccination. Similar to the results in sheep, MP-12 vaccination of gestating cattle resulted in low-level viremia, but also in this species, no untoward effects were noted and all vaccinated animals were protected from abortion (Morrill et al., 1997a). Since the MP-12 virus can cause post-vaccination viremia, the vaccine virus could transmit to the fetus and cause teratogenic effects or abortion. A study on the effects of *in utero* inoculation of MP-12 led the authors to suggest that fetal death and abortion following vaccination of gestating cows would be rare even when the fetus would be exposed to the MP-12 virus (Morrill et al., 1997b). Although the aforementioned studies suggested that the MP-12 vaccine can be safely applied during gestation, the vaccine was shown to cause teratogenic effects and abortions when administered to sheep during the first trimester of gestation (Hunter et al., 2002). A recent study investigating the efficacy and safety of a recombinant MP-12 virus and mutant derivatives seems to confirm the ability of MP-12 to cause fetal mortality (Morrill et al., 2013).

In 2003, Morrill and Peters reported a study on the pathogenicity and neurovirulence of the MP-12 virus in rhesus macaques (Morrill and Peters, 2003). In this study, intravenous administration of MP-12 resulted in low-level viremia and minimal and transient elevations in serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) values, whereas γ-glutamyltransferase (GGT) values remained within normal limits. However, no clinical signs were reported to occur. To investigate the potential neurovirulence of the MP-12 virus, monkeys were inoculated via intramuscular, intrathalamic and intraspinal routes. In a first trial, 1 of 5 monkeys became hyperesthetic and developed muscular tremors. In a second neurovirulence test, 2 out of 23 monkeys developed right or left leg paralysis. The combined results of the neurovirulence studies led the authors to conclude that the MP-12 virus is not innocuous but that residual pathological lesions were mild and in the order of severity of those observed in similar experiments with the 17D yellow fever vaccine (Morrill and Peters, 2003).

More recently, vaccine efficacy studies were performed with rhesus macaques. Vaccination via the intramuscular route did not result in untoward effects. Although no clinical signs were noted in the challenged control monkeys, vaccination prevented viremia (Morrill and Peters, 2011b). Interestingly, a subsequent study demonstrated that vaccination via different mucosal routes can also prevent viremia (Morrill and Peters, 2011a).

The potency and safety of the MP-12 vaccine was also studied in human trials, which so far has included 63 volunteers (Peters and Linthicum, 1994; Peters et al., 2008). The results of these studies await publication, although it was already reported that no serious adverse reactions and no signs of reversion to virulence were observed (Kortekaas et al., 2011b). The safety record of MP-12 was deemed sufficient to exclude the MP-12 virus from the Select Agent rule and the virus may therefore be handled in biosafety level-2 facilities in the United States.

5.3. The Clone 13 vaccine

The Clone 13 virus is a plaque-purified clone of the 74HB59 strain, originally isolated from a human case from the Central African Republic (Muller et al., 1995). The virus was found to contain a large (70%) deletion in the NSs gene and to be highly attenuated in mice (Vialat et al., 2000). The Clone 13 virus was however not completely avirulent in these studies, since 2 out of 16 inoculated mice died from delayed-onset neurological disorder and paralysis. However, studies on the safety and efficacy of Clone 13 in sheep (Dungu et al., 2010) and cattle (von Teichman et al., 2011) did not reveal any untoward effects and demonstrated high vaccine efficacy. In contrast to MP-12, the Clone 13 virus does not cause detectable viremia in vaccinated animals, minimizing the chance that the vaccine virus will transmit to the foetus or to mosquitoes feeding on a vaccinated animal. The study by Dungu et al., demonstrated that vaccination of 42 sheep did not result in elevated body temperatures or other signs of illness. Vaccination with Clone 13 during early and late pregnancy did not cause abortions and all ewes receiving a single vaccination with a dose of 10^5 plaque forming units (PFUs) were protected from the highly virulent RVFV strain 35/74.

The study by Von Teichman et al., demonstrated that a single vaccination of weaner calves with 10^5 PFUs of Clone 13 did not induce detectable post-vaccination viremia and protected the animals from challenge virus viremia and clinical signs (von Teichman et al., 2011).

The Clone 13 vaccine virus was commercialized by the OBP Company in South Africa in 2010 and several million doses have been used in the field since that time. An evaluation of the use of the Clone 13 vaccine virus in the field and, preferably, about its performance in controlled field studies, would greatly facilitate acceptance of this vaccine for potential use in currently unaffected areas, such as Europe and the US. Given its high safety and efficacy profile, the Clone 13 vaccine virus should be considered for exclusion from the Select Agent rule and be classified as a BSL-2 organism.

5.4. Live-attenuated vaccines of theoretical added safety

Despite the safety profile of the MP-12 and Clone 13 vaccine viruses, efforts are being made to further attenuate these viruses without compromising vaccine efficacy. In one of these approaches, a reassortant virus was created that comprises the M and L segments of the MP-12 virus and the S segment of Clone 13. Although briefly noted in the literature (Bouloy and Flick, 2009), the safety and efficacy of the resulting R566 vaccine awaits to be reported.

In a second approach, recombinant RVFV with deletions in NSs and/or the NSm-coding region(s) were created. The deletion of NSs is well known to result in an attenuated phenotype and its molecular basis is well established. After the demonstration that viruses lacking the pre-Gn (NSm) region are also viable (Gerrard et al., 2007), the effect of this mutation on virulence was addressed (Bird et al., 2007). Although it was found that a virus lacking the pre-Gn region retains high virulence *in vivo*, the pathogenicity of the virus was reduced when compared to the parent virus (Bird et al., 2007). These findings prompted the development of a recombinant virus, based on the human isolate ZH501, with a combined deletion of the NSs and pre-Gn (NSm)-coding regions. After demonstrating safety and efficacy of the ZH501-ΔNSs/ΔNSm vaccine (here referred to as Δ/Δ virus) in the rat model (Bird et al., 2008), studies were continued with sheep (Bird et al., 2011). In these studies no untoward effects upon vaccination with the Δ/Δ virus were noted, even when administered during the period when the risk of vaccine-induced teratogenicity is highest. The vaccine also provided solid protection from the wildtype recombinant virus, since no abortions were reported to occur in these studies. Due to the demonstrated safety of the Δ/Δ virus, it was removed from the US Select Agent list and downgraded to BSL-2 by the US Centers for Disease Control and Prevention and the National Institutes of Health. The Δ/Δ virus therefore seems a promising live, attenuated vaccine candidate for application in livestock and, potentially also humans.

A similar approach was recently described by Morrill et al. (2013). In this work, the attenuating mutations of the MP-12 virus were combined with a deletion in the NSs or NSm-coding region. A preliminary study on the immunogenicity of both candidates revealed that the recombinant MP-12_ΔNSs virus induced a poor neutralizing antibody response compared to the MP-12_ ΔNSm virus and further studies were therefore continued with the latter. No untoward effects were noted in gestating ewes after vaccination, and it is interesting to note that the MP-12_ ΔNSm was at least as potent as the parental MP-12 virus in the induction of neutralizing antibodies (Morrill et al., 2013). Results from a recent study suggest that this vaccine is comparably effective in sheep as the Δ/Δ virus (Weingartl et al., 2014), although it would be valuable to compare these two live, attenuated vaccines in a single animal trial.

Most recently, a recombinant virus was created that expresses the RVFV glycoprotein precursor gene from the NSs locus of the S genome segment (Brennan et al., 2011). This virus lacks the NSs gene and is further attenuated by the genome reorganisation. Studies addressing the safety and immunogenicity of the resulting two-segmented virus are awaited.

5.5. Vector vaccines

In the past decade, RVFV vaccines based on viral vectors were developed of which several could be evaluated for human application. Experimental vaccines based on the poxvirus modified vaccinia Ankara (MVA) were previously communicated (Lopez-Gil et al., 2013) and another, vaccinia virus-based vaccine candidate was recently shown to be safe and immunogenic in baboons (Papin et al., 2011). Experimental vaccines based on alphavirus replicons (Gorchakov et al., 2007; Heise et al., 2009) and the nonreplicating complex adenoviruses CAdVax (Holman et al., 2009) and ChAdOx1 (Warimwe et al., 2013) have been developed as well. Although these candidate vaccines have shown promise in rodent models, efficacy trials in target species are not yet reported in literature.

Our laboratory developed a vector vaccine based on the paramyxovirus Newcastle disease virus (NDV) (Kortekaas et al., 2010). A single vaccination induced neutralizing antibodies and protected lambs from viremia and clinical signs (Kortekaas et al., 2012). This vaccine, here referred to as NDV-GnGc, was developed for use in livestock, but several characteristics of the vaccine render it a particularly strong candidate for human application as well. The potential use of NDV as a vaccine vector for application in humans is well accepted (Bukreyev and Collins, 2008) and the fact that humans are not natural hosts of NDV minimizes the risk of vaccination failure due to pre-existing immunity against the vector.

5.6. Subunit and DNA vaccines

The development of Gn and Gc-based subunit vaccines was pioneered by the groups of Collett (Kakach et al., 1989, 1988) and Schmaljohn (Schmaljohn et al., 1989), who were the first to express the individual genes from vaccinia virus and baculovirus genomes, respectively, and studied the immunogenicity of the proteins. In more recent years, our laboratory developed a subunit vaccine based on the Gn ectodomain (Gn-e), which is the major target for neutralizing antibodies (de Boer et al., 2010). The Gn-e protein, formulated with Stimune® adjuvant, induced neutralizing antibodies after a single vaccination in both mice (de Boer et al., 2010) and lambs (Kortekaas et al., 2012) and protected lambs from viremia, pyrexia and clinical signs (Kortekaas et al., 2012). An experimental vaccine based on virus-like particles (VLPs) was also developed and was much more immunogenic in the mouse model, inducing high levels of neutralizing antibodies even in the absence of adjuvant (de Boer et al., 2010). This vaccine was not further evaluated in the sheep model since we anticipated that production of a veterinary vaccine using the established system would not be cost-effective. Both the Gn-e vaccine and the VLP-based vaccine could however prove to be attractive candidates for use in humans. VLP-based vaccines whose efficacies were demonstrated in rodent models were also developed in other laboratories (Koukuntla et al., 2012; Mandell et al., 2010a,b).

The major advantage of DNA vaccines is the ease of production. Whereas poor immunogenicity has been the major complication for product development in the past decades, improved technologies are expected to soon overcome this barrier (Li et al., 2012). Experimental DNA vaccines for the control of RVFV have been developed and have yielded promising results in rodent models (Bhardwaj et al., 2010; Boshra et al., 2011; Lagerqvist et al., 2009; Lorenzo et al., 2010; Spik et al., 2006; Wallace et al., 2006). First experiments with experimental DNA vaccines in sheep however suggest that improvement of immunogenicity is required to render this a feasible approach (Lorenzo et al., 2008).

5.7. Replicon particles

With the aim of developing a vaccine that optimally combines the safety of inactivated vaccines with the efficacy of live vaccines, our laboratory recently developed methods to produce RVFV replicon particles (Kortekaas et al., 2011a). A different method to produce similar particles has subsequently been reported by Dodd et al. (2012). RVFV replicon particles contain the L and S segments of RVFV, but lack the M genome segment, rendering the particles unable to spread autonomously. RVFV replicon particles induced high levels of neutralizing antibodies and cytokine and chemokine responses in mice (Dodd et al., 2012; Kortekaas et al., 2011a). The work of Dodd et al., furthermore demonstrated that mice can be protected from a lethal dose of RVFV already 24 h after vaccination. A single vaccination with the nonspreading RVFV (NSR) particles developed in our laboratory induced high levels of neutralizing antibodies in lambs and protected the animals from viremia and clinical signs (Kortekaas et al., 2012). Although all lambs were protected from viremia as determined by virus isolation, very small amounts of viral RNA were detected by our highly sensitive

quantitative real-time PCR (qPCR), demonstrating that protection was not sterile.

To further improve the NSR vaccine, we created novel NSR particles, which express the Gn gene from the S genome segment. A single vaccination with the resulting NSR-Gn vaccine provided sterilizing immunity in lambs (Oreshkova et al., 2013). The inherent safety of the NSR-Gn vaccine and its demonstrated remarkable efficacy in the natural target species suggests that this vaccine also holds great promise for human application.

6. Nonhuman primate models

Although demonstrated safety and efficacy in natural target species can facilitate the acceptance of a vaccine for human use, these properties are preferably demonstrated in species more closely resembling humans. Therefore, nonhuman primate models are required to complement pre-clinical data obtained in ruminants.

In 1988, Peters et al., reported that intravenous inoculation of rhesus macaques (*Macaca mulatta*) with RVFV can result in a disease resembling human hemorrhagic fever (Peters et al., 1988). The macaque model is however not optimal for preclinical evaluation of human vaccines, since only a percentage of animals develops severe disease. In 2012, a nonhuman primate model was developed that makes use of the common marmoset (*Callithrix jacchus*) (Smith et al., 2012). It was demonstrated that marmosets are more prone to develop severe disease than macaques, rendering this a preferred model to evaluate human vaccines. The histopathological changes in marmosets that were exposed via subcutaneous or intravenous routes were characterized by hepatocellular degeneration and necrosis, whereas marmosets exposed via the intranasal route developed histopathological changes in the brain. The marmoset model therefore seems suitable to study the ability of vaccines to protect from the two most serious complications of RVFV infection in humans, hemorrhagic fever and encephalitis. Recently, not only common marmosets but also African green monkeys developed meningoencephalitis after aerosol exposure to RVFV (Hartman et al., 2014). This recent progress in the development of nonhuman primate models could greatly facilitate licensing of a vaccine for human use.

7. Desired features of a human RVF vaccine

Vaccines for veterinary and human use share many desired features, although their prioritization differs. The preferred features of an ideal veterinary vaccine were previously listed by Bird and Nichol (Bird and Nichol, 2012). Here, those desired for a human RVF vaccine are listed (Table 1). It is important to note that none of these features is an absolute requirement and that an ideal vaccine will optimally combine those related to safety, efficacy and production characteristics. Features related to safety are the most important for a human vaccine, followed by efficacy, vaccine stability, and production costs. Whereas environmental safety and inability to replicate in mosquito vectors are important characteristics of veterinary vaccines (Bird and Nichol, 2012), these are considered of minor relevance for a human vaccine. Further, the ability to differentiate infected from vaccinated animals (DIVA) would be beneficial for veterinary vaccines, but this feature is also considered less relevant for human vaccines.

Table 1
Prioritized features of an ideal human Rift Valley fever vaccine.

- √ No vaccine-induced adverse reactions
- √ No viremia in vaccinates (live viruses)
- √ Knowledge-based attenuation (live viruses)
- √ Created by reverse-genetics (live viruses)
- √ Induces durable neutralizing antibody titers
- √ Efficacy: single dose, rapid, long lasting protection
- √ Inexpensive production, easy upscaling
- √ Long shelf-life and stability at room temperature
- √ Needle-free delivery

Considering that safety is the most important feature of human vaccines, a future outbreak of RVFV among humans will likely result in a demand for a subunit vaccine or a vaccine based on inactivated virus. However, the past experience with the inactivated TSI-GSD 200 vaccine suggests that more potent vaccines are required to effectively protect the human population. Vaccines based on subunits or inactivated virus can still be evaluated, but more effective adjuvants and vaccine delivery systems should be developed to improve their efficacy. At present, it is clear that vaccines based on live, attenuated viruses or replicon particles are most efficacious. These vaccines do not require adjuvants, which facilitates their translation from animal to human application and can provide optimal safety when they are rationally designed and created by reverse genetics.

8. Licensing strategies

The strategy to use a common approach for veterinary and human vaccine development is aimed to reduce development and licensing costs of a human vaccine. Development costs can be reduced when manufacturers of veterinary vaccines take into account guidelines for human vaccine manufacturing, whereas licensing costs can be reduced when data from veterinary registration trials are used as pre-clinical data for the licensing of a corresponding human vaccine.

As a first step towards the licensing of a vaccine for human use, safety must be demonstrated in phase I/II clinical trials. However, since efficacy trials cannot be performed in humans, a traditional phase III trial cannot be conducted. In 2002, the US Food and Drug Administration (FDA) established the Animal Rule to grant marketing approval of drugs and biologicals when human efficacy studies are either not ethical or feasible. Approval may follow when adequate and well-controlled animal studies demonstrate that the drug or biological is reasonably likely to produce clinical benefit in humans (FDA, 2013). Next-generation veterinary RVFV vaccines that come to market in the near future will have demonstrated efficacy in natural target species and their efficacy could be further addressed in the recently established nonhuman primate models, to allow licensing for human use under the FDA's Animal Rule.

A further innovative licensing strategy could make use of FDA regulation 314.510. Under this rule, the FDA may allow the licensing of a vaccine after a correlate of protection is demonstrated that is reasonably likely to provide clinical benefit, obtained in well controlled clinical studies. The presence of RVFV-specific neutralizing antibodies is considered a strong correlate of protection and was previously used to predict efficacy of the human TSI-GSD 200 vaccine. This correlate of protection could facilitate licensing of a novel human RVFV vaccine by minimizing unnecessary suffering of animals and reducing licensing costs.

Finally, when vaccines are available that are produced according to guidelines of human vaccine manufacturing and have been shown to be safe and potent in nonhuman primates, national human health services should consider the off-label use of such vaccines in human volunteers from occupational risk groups during outbreak situations.

9. Conclusions

Veterinary RVFV vaccines are undoubtedly the most efficient line of defence against human disease (Bird and Nichol, 2012). Even in situations where animals are not severely affected,

vaccination of livestock and other amplifiers of the virus should always be prioritized to prevent human disease. Nevertheless, history has taught us that RVFV outbreaks are generally recognized only after human cases are diagnosed (Hassan et al., 2011; Mundel and Gear, 1951). Even in the most positive scenario, where early warning systems are in place and veterinary vaccines can quickly be deployed, a human vaccine is still needed to protect veterinarians involved in vaccination programs as well as slaughterhouse workers and farmers. In the less likely events of intentional release or efficient spread by anthropophilic mosquito species, vaccination of the general public may be required.

When the above-listed veterinary vaccines are close to marketing, cost-effective industrial production systems will be in place and data from registration trials can be used as pre-clinical data of a corresponding human vaccine. After rendering the vaccine suitable for human use and vaccine safety has been demonstrated in phase I/II clinical trials, vaccine efficacy can be demonstrated in recently established nonhuman primate models to enable licensing under the Animal Rule or FDA regulation 314.510. By following this strategy, a human RVFV vaccine could come to market within the coming decade with relatively low development and licensing costs.

10. Disclaimer

The opinions, interpretations, conclusions and recommendations contained herein are those of the author and are not necessarily endorsed by the CVI-Lelystad.

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References

Al-Hazmi, M., Ayoola, E.A., Abdurahman, M., Banzal, S., Ashraf, J., El-Bushra, A., Hazmi, A., Abdullah, M., Abbo, H., Elamin, A., Al-Sammani el, T., Gadour, M., Menon, C., Hamza, M., Rahim, I., Hafez, M., Jambavalikar, M., Arishi, H., Aqeel, A., 2003. Epidemic Rift Valley fever in Saudi Arabia: a clinical study of severe illness in humans. Clin. Infect. Dis. 36, 245–252.

Andriamandimby, S.F., Randrianarivo-Solofoniaina, A.E., Jeanmaire, E.M., Ravololomanana, L., Razafimanantsoa, L.T., Rakotojoelinandrasana, T., Razainirina, J., Hoffmann, J., Ravalohery, J.P., Rafisandratantsoa, J.T., Rollin, P.E., Reynes, J.M., 2010. Rift Valley fever during rainy seasons, Madagascar, 2008 and 2009. Emerg. Infect. Dis. 16, 963–970.

Anyamba, A., Linthicum, K.J., Small, J., Britch, S.C., Pak, E., de La Rocque, S., Formenty, P., Hightower, A.W., Breiman, R.F., Chretien, J.P., Tucker, C.J., Schnabel, D., Sang, R., Haagsma, K., Latham, M., Lewandowski, H.B., Magdi, S.O., Mohamed, M.A., Nguku, P.M., Reynes, J.M., Swanepoel, R., 2010. Prediction, assessment of the Rift Valley fever activity in East and Southern Africa 2006–2008 and possible vector control strategies. Am. J. Trop. Med. Hyg. 83, 43–51.

Aradaib, I.E., Erickson, B.R., Elageb, R.M., Khristova, M.L., Carroll, S.A., Elkhidir, I.M., Karsany, M.E., Karrar, A.E., Elbashir, M.I., Nichol, S.T., 2013. Rift Valley fever, Sudan, 2007 and 2010. Emerg. Infect. Dis. 19, 246–253.

Archer, B.N., Weyer, J., Paweska, J., Nkosi, D., Leman, P., Tint, K.S., Blumberg, L., 2011. Outbreak of Rift Valley fever affecting veterinarians and farmers in South Africa, 2008. S. Afr. Med. J. 101, 263–266.

Bhardwaj, N., Heise, M.T., Ross, T.M., 2010. Vaccination with DNA plasmids expressing Gn coupled to C3d or alphavirus replicons expressing gn protects mice against Rift Valley fever virus. PLoS Neglected Trop. Dis. 4, e725.

Binn, L.N., Randall, R., Harrison, V.R., Gibbs Jr., C.J., Aulisio, C.G., 1963. Immunization against Rift Valley fever. The development of vaccines from nonprimate cell cultures and chick embryos. Am. J. Hyg. 77, 160–168.

Bird, B.H., Albarino, C.G., Hartman, A.L., Erickson, B.R., Ksiazek, T.G., Nichol, S.T., 2008. Rift valley fever virus lacking the NSs and NSm genes is highly attenuated, confers protective immunity from virulent virus challenge, and allows for differential identification of infected and vaccinated animals. J. Virol. 82, 2681–2691.

Bird, B.H., Albarino, C.G., Nichol, S.T., 2007. Rift Valley fever virus lacking NSm proteins retains high virulence in vivo and may provide a model of human delayed onset neurologic disease. Virology 362, 10–15.

Bird, B.H., Maartens, L.H., Campbell, S., Erasmus, B.J., Erickson, B.R., Dodd, K.A., Spiropoulou, C.F., Cannon, D., Drew, C.P., Knust, B., McElroy, A.K., Khristova, M.L., Albarino, C.G., Nichol, S.T., 2011. Rift Valley fever virus vaccine lacking the NSs and NSm genes is safe, nonteratogenic, and confers protection from viremia, pyrexia, and abortion following challenge in adult and pregnant sheep. J. Virol. 85, 12901–12909.

Bird, B.H., Nichol, S.T., 2012. Breaking the chain: Rift Valley fever virus control via livestock vaccination. Curr. Opin. Virol. 2, 315–323.

Boshra, H., Lorenzo, G., Rodriguez, F., Brun, A., 2011. A DNA vaccine encoding ubiquitinated Rift Valley fever virus nucleoprotein provides consistent immunity and protects IFNAR(−/−) mice upon lethal virus challenge. Vaccine 29, 4469–4475.

Bouloy, M., Flick, R., 2009. Reverse genetics technology for Rift Valley fever virus: current and future applications for the development of therapeutics and vaccines. Antiviral Res. 84, 101–118.

Brennan, B., Welch, S.R., McLees, A., Elliott, R.M., 2011. Creation of a recombinant Rift Valley fever virus with a two-segmented genome. J. Virol. 85, 10310–10318.

Bukreyev, A., Collins, P.L., 2008. Newcastle disease virus as a vaccine vector for humans. Curr. Opin. Mol. Ther. 10, 46–55.

Caplen, H., Peters, C.J., Bishop, D.H., 1985. Mutagen-directed attenuation of Rift Valley fever virus as a method for vaccine development. J. Gen. Virol. 66 (Pt. 10), 2271–2277.

CDC, 1998. Rift Valley Fever – East Africa, 1997–1998. MMWR. Morbidity and mortality weekly report 47, pp. 261–4.

CDC, 2000a. Outbreak of Rift Valley fever – Saudi Arabia, August-October, 2000. MMWR. Morbidity and mortality weekly report 49, pp. 905–908.

CDC, 2000b. Outbreak of Rift Valley fever – Yemen, August-October 2000. MMWR. Morbidity and mortality weekly report 49, pp. 1065, 1066.

CDC, 2000c. Update: outbreak of Rift Valley Fever – Saudi Arabia, August–November 2000. MMWR. Morbidity and mortality weekly report 49, pp. 982–985.

Daubney, R., 1931. Rift Valley fever. Lancet 218, 1367–1368.

Daubney, R., Hudson, J.R., Garnham, P.C., 1931a. Enzootic hepatitis or rift valley fever. An undescribed virus disease of sheep cattle and man from East Africa. J. Pathol. Bacteriol. 34, 545–579.

Daubney, R., Hudson, J.R., Garnham, P.C., 1931b. Enzootic hepatitis or Rift Valley fever: an undescribed disease of sheep, cattle and man from East Africa. J. Pathol. Bacteriol. 34, 545–579.

de Boer, S.M., Kortekaas, J., Antonis, A.F., Kant, J., van Oploo, J.L., Rottier, P.J., Moormann, R.J., Bosch, B.J., 2010. Rift Valley fever virus subunit vaccines confer complete protection against a lethal virus challenge. Vaccine 28, 2330–2339.

Dodd, K.A., Bird, B.H., Metcalfe, M.G., Nichol, S.T., Albarino, C.G., 2012. Single-dose immunization with virus replicon particles confers rapid robust protection against Rift Valley fever virus challenge. J. Virol. 86, 4204–4212.

Dungu, B., Louw, I., Lubisi, A., Hunter, P., von Teichman, B.F., Bouloy, M., 2010. Evaluation of the efficacy and safety of the Rift Valley Fever Clone 13 vaccine in sheep. Vaccine 28, 4581–4587.

El Mamy, A.B., Baba, M.O., Barry, Y., Isselmou, K., Dia, M.L., El Kory, M.O., Diop, M., Lo, M.M., Thiongane, Y., Bengoumi, M., Puech, L., Plee, L., Claes, F., de La Rocque, S., Doumbia, B., 2011. Unexpected Rift Valley fever outbreak, northern Mauritania. Emerg. Infect. Dis. 17, 1894–1896.

FDA, 2013. Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible Code of Federal Regulations.

Findlay, G.M., 1932. Rift Valley fever or enzootic hepatitis. Trans. R. Soc. Trop. Med. Hyg. 25, 229–265.

Findlay, G.M., Daubney, R., 1931. The virus of Rift Valley fever or enzootic hepatitis. Lancet 221, 1350–1351.

Freed, I., 1951. Rift valley fever in man, complicated by retinal changes and loss of vision. S. Afr. Med. J. 25, 930–932.

Gear, J., De Meillon, B., Measroch, V., Davis, D.H., Harwin, H., 1951. Rift valley fever in South Africa. 2. The occurrence of human cases in the Orange Free State, the North-Western Cape Province, the Western and Southern Transvaal. B. Field and Laboratory Investigation. S. Afr. Med. J. 25, 908–912.

Gerrard, S.R., Bird, B.H., Albarino, C.G., Nichol, S.T., 2007. The NSm proteins of Rift Valley fever virus are dispensable for maturation, replication and infection. Virology 359, 459–465.

Gorchakov, R., Volkova, E., Yun, N., Petrakova, O., Linde, N.S., Paessler, S., Frolova, E., Frolov, I., 2007. Comparative analysis of the alphavirus-based vectors expressing Rift Valley fever virus glycoproteins. Virology 366, 212–225.

Hartman, A.L., Powell, D.S., Bethel, L.M., Caroline, A.L., Schmid, R.J., Oury, T., Reed, D.S., 2014. Aerosolized Rift Valley Fever virus causes fatal encephalitis in African green monkeys and common marmosets. J. Virol. 88, 2235–2245.

Hassan, O.A., Ahlm, C., Sang, R., Evander, M., 2011. The 2007 Rift Valley fever outbreak in Sudan. PLoS Neglected Trop. Dis. 5, e1229.

Heise, M.T., Whitmore, A., Thompson, J., Parsons, M., Grobbelaar, A.A., Kemp, A., Paweska, J.T., Madric, K., White, L.J., Swanepoel, R., Burt, F.J., 2009. An alphavirus replicon-derived candidate vaccine against Rift Valley fever virus. Epidemiol. Infect. 137, 1309–1318.

Holman, D.H., Penn-Nicholson, A., Wang, D., Woraratanadharm, J., Harr, M.K., Luo, M., Maher, E.M., Holbrook, M.R., Dong, J.Y., 2009. A complex adenovirus-vectored vaccine against Rift Valley fever virus protects mice against lethal

infection in the presence of preexisting vector immunity. Clin. Vaccine Immunol. 16, 1624–1632.
Hoogstraal, H., Meegan, J.M., Khalil, G.M., Adham, F.K., 1979. The Rift Valley fever epizootic in Egypt 1977–78. 2. Ecological and entomological studies. Trans. R. Soc. Trop. Med. Hyg. 73, 624–629.
Hunter, P., Erasmus, B.J., Vorster, J.H., 2002. Teratogenicity of a mutagenised Rift Valley fever virus (MVP 12) in sheep. Onderstepoort J. Vet. Res. 69, 95–98.
Jouan, A., Coulibaly, I., Adam, F., Philippe, B., Riou, O., Leguenno, B., Christie, R., Ould Merzoug, N., Ksiazek, T., Digoutte, J.P., 1989. Analytical study of a Rift Valley fever epidemic. Res. Virol. 140, 175–186.
Jouan, A., Le Guenno, B., Digoutte, J.P., Philippe, B., Riou, O., Adam, F., 1988. An RVF epidemic in southern Mauritania. Annales de l'Institut Pasteur. Virology 139, 307–308.
Joubert, J.D., Ferguson, A.L., Gear, J., 1951. Rift Valley fever in South Africa: 2. The occurrence of human cases in the Orange Free State, the north-western Cape province, the western and southern Transvaal. A epidemiological and clinical findings. S. Afr. Med. J. 25, 890–891.
Jupp, P.G., Kemp, A., Grobbelaar, A., Lema, P., Burt, F.J., Alahmed, A.M., Al Mujalli, D., Al Khamees, M., Swanepoel, R., 2002. The 2000 epidemic of Rift Valley fever in Saudi Arabia: mosquito vector studies. Med. Vet. Entomol. 16, 245–252.
Kakach, L.T., Suzich, J.A., Collett, M.S., 1989. Rift Valley fever virus M segment: phlebovirus expression strategy and protein glycosylation. Virology 170, 505–510.
Kakach, L.T., Wasmoen, T.L., Collett, M.S., 1988. Rift Valley fever virus M segment: use of recombinant vaccinia viruses to study *Phlebovirus* gene expression. J. Virol. 62, 826–833.
Kark, J.D., Aynor, Y., Peters, C.J., 1982. A Rift Valley fever vaccine trial. I. Side effects and serologic response over a six-month follow-up. Am. J. Epidemiol. 116, 808–820.
Kark, J.D., Aynor, Y., Peters, C.J., 1985. A Rift Valley fever vaccine trial: 2. Serological response to booster doses with a comparison of intradermal versus subcutaneous injection. Vaccine 3, 117–122.
Kitchen, S.F., 1934. Laboratory infections with the virus of Rift Valley fever. Am. J. Trop. Med. 14, 547–564.
Kortekaas, J., Antonis, A.F., Kant, J., Vloet, R.P., Vogel, A., Oreshkova, N., de Boer, S.M., Bosch, B.J., Moormann, R.J., 2012. Efficacy of three candidate Rift Valley fever vaccines in sheep. Vaccine 30, 3423–3429.
Kortekaas, J., de Boer, S.M., Kant, J., Vloet, R.P., Antonis, A.F., Moormann, R.J., 2010. Rift Valley fever virus immunity provided by a paramyxovirus vaccine vector. Vaccine 28, 4394–4401.
Kortekaas, J., Oreshkova, N., Cobos-Jimenez, V., Vloet, R.P., Potgieter, C.A., Moormann, R.J., 2011a. Creation of a nonspreading Rift Valley fever virus. J. Virol. 85, 12622–12630.
Kortekaas, J., Zingeser, J., de Leeuw, P., de La Rocque, S., Unger, H., Moormann, R.J., 2011b. Rift Valley fever vaccine development, progress and constraints. Emerg. Infect. Dis. 17, e1.
Koukuntla, R., Mandell, R.B., Flick, R., 2012. Virus-like particle-based countermeasures against Rift Valley fever virus. Zoonoses Public Health 59 (Suppl. 2), 142–150.
LaBeaud, A.D., Muiruri, S., Sutherland, L.J., Dahir, S., Gildengorin, G., Morrill, J., Muchiri, E.M., Peters, C.J., King, C.H., 2011. Postepidemic analysis of Rift Valley fever virus transmission in northeastern kenya: a village cohort study. PLoS Neglected Trop. Dis. 5, e1265.
Lagerqvist, N., Naslund, J., Lundkvist, A., Bouloy, M., Ahlm, C., Bucht, G., 2009. Characterisation of immune responses and protective efficacy in mice after immunisation with Rift Valley Fever virus cDNA constructs. Virol. J. 6, 6.
Li, L., Saade, F., Petrovsky, N., 2012. The future of human DNA vaccines. J. Biotechnol. 162, 171–182.
Lopez-Gil, E., Lorenzo, G., Hevia, E., Borrego, B., Eiden, M., Groschup, M., Gilbert, S.C., Brun, A., 2013. A single immunization with MVA expressing GnGc glycoproteins promotes epitope-specific CD8+-T cell activation and protects immune-competent mice against a lethal RVFV infection. PLoS Neglected Trop. Dis. 7, e2309.
Lorenzo, G., Martin-Folgar, R., Hevia, E., Boshra, H., Brun, A., 2010. Protection against lethal Rift Valley fever virus (RVFV) infection in transgenic IFNAR(−/−) mice induced by different DNA vaccination regimens. Vaccine 28, 2937–2944.
Lorenzo, G., Martin-Folgar, R., Rodriguez, F., Brun, A., 2008. Priming with DNA plasmids encoding the nucleocapsid protein and glycoprotein precursors from Rift Valley fever virus accelerates the immune responses induced by an attenuated vaccine in sheep. Vaccine 26, 5255–5262.
Madani, T.A., Al-Mazrou, Y.Y., Al-Jeffri, M.H., Mishkhas, A.A., Al-Rabeah, A.M., Turkistani, A.M., Al-Sayed, M.O., Abodahish, A.A., Khan, A.S., Ksiazek, T.G., Shobokshi, O., 2003. Rift Valley fever epidemic in Saudi Arabia: epidemiological, clinical, and laboratory characteristics. Clin. Infect. Dis. 37, 1084–1092.
Mandell, R.B., Koukuntla, R., Mogler, L.J., Carzoli, A.K., Freiberg, A.N., Holbrook, M.R., Martin, B.K., Staplin, W.R., Vahanian, N.N., Link, C.J., Flick, R., 2010a. A replication-incompetent Rift Valley fever vaccine: chimeric virus-like particles protect mice and rats against lethal challenge. Virology 397, 187–198.
Mandell, R.B., Koukuntla, R., Mogler, L.J., Carzoli, A.K., Holbrook, M.R., Martin, B.K., Vahanian, N., Link, C.J., Flick, R., 2010b. Novel suspension cell-based vaccine production systems for Rift Valley fever virus-like particles. J. Virol. Methods 169, 259–268.
McIntosh, B.M., Russell, D., dos Santos, I., Gear, J.H., 1980. Rift Valley fever in humans in South Africa. S. Afr. Med. J. 58, 803–806.
Meegan, J.M., 1979. The Rift Valley fever epizootic in Egypt 1977–78. 1. Description of the epizootic and virological studies. Trans. R. Soc. Trop. Med. Hyg. 73, 618–623.
Meegan, J.M., Hoogstraal, H., Moussa, M.I., 1979. An epizootic of Rift Valley fever in Egypt in 1977. Vet. Rec. 105, 124–125.
Meegan, J.M., Khalil, G.M., Hoogstraal, H., Adham, F.K., 1980. Experimental transmission and field isolation studies implicating Culex pipiens as a vector of Rift Valley fever virus in Egypt. Am. J. Trop. Med. Hyg. 29, 1405–1410.
Miller, B.R., Godsey, M.S., Crabtree, M.B., Savage, H.M., Al-Mazrao, Y., Al-Jeffri, M.H., Abdoon, A.M., Al-Seghayer, S.M., Al-Shahrani, A.M., Ksiazek, T.G., 2002. Isolation and genetic characterization of Rift Valley fever virus from Aedes vexans arabiensis, Kingdom of Saudi Arabia. Emerg. Infect. Dis. 8, 1492–1494.
Mohamed, M., Mosha, F., Mghamba, J., Zaki, S.R., Shieh, W.J., Paweska, J., Omulo, S., Gikundi, S., Mmbuji, P., Bloland, P., Zeidner, N., Kalinga, R., Breiman, R.F., Njenga, M.K., 2010. Epidemiologic and clinical aspects of a Rift Valley fever outbreak in humans in Tanzania, 2007. Am. J. Trop. Med. Hyg. 83, 22–27.
Morrill, J.C., Carpenter, L., Taylor, D., Ramsburg, H.H., Quance, J., Peters, C.J., 1991. Further evaluation of a mutagen-attenuated Rift Valley fever vaccine in sheep. Vaccine 9, 35–41.
Morrill, J.C., Jennings, G.B., Caplen, H., Turell, M.J., Johnson, A.J., Peters, C.J., 1987. Pathogenicity and immunogenicity of a mutagen-attenuated Rift Valley fever virus immunogen in pregnant ewes. Am. J. Vet. Res. 48, 1042–1047.
Morrill, J.C., Laughlin, R.C., Lokugamage, N., Pugh, R., Sbrana, E., Weise, W.J., Adams, L.G., Makino, S., Peters, C.J., 2013. Safety and immunogenicity of recombinant Rift Valley fever MP-12 vaccine candidates in sheep. Vaccine 31, 559–565.
Morrill, J.C., Mebus, C.A., Peters, C.J., 1997a. Safety and efficacy of a mutagen-attenuated Rift Valley fever virus vaccine in cattle. Am. J. Vet. Res. 58, 1104–1109.
Morrill, J.C., Mebus, C.A., Peters, C.J., 1997b. Safety of a mutagen-attenuated Rift Valley fever virus vaccine in fetal and neonatal bovids. Am. J. Vet. Res. 58, 1110–1114.
Morrill, J.C., Peters, C.J., 2003. Pathogenicity and neurovirulence of a mutagen-attenuated Rift Valley fever vaccine in rhesus monkeys. Vaccine 21, 2994–3002.
Morrill, J.C., Peters, C.J., 2011a. Mucosal immunization of rhesus macaques with Rift Valley Fever MP-12 vaccine. J. Infect. Dis. 204, 617–625.
Morrill, J.C., Peters, C.J., 2011b. Protection of MP-12-vaccinated rhesus macaques against parenteral and aerosol challenge with virulent rift valley fever virus. J. Infect. Dis. 204, 229–236.
Muller, R., Saluzzo, J.F., Lopez, N., Dreier, T., Turell, M., Smith, J., Bouloy, M., 1995. Characterization of clone 13, a naturally attenuated avirulent isolate of Rift Valley fever virus, which is altered in the small segment. Am. J. Trop. Med. Hyg. 53, 405–411.
Mundel, B., Gear, J., 1951. Rift valley fever; I. The occurrence of human cases in Johannesburg. S. Afr. Med. J. 25, 797–800.
Nabeth, P., Kane, Y., Abdalahi, M.O., Diallo, M., Ndiaye, K., Ba, K., Schneegans, F., Sall, A.A., Mathiot, C., 2001. Rift Valley fever outbreak, Mauritania, 1998: seroepidemiologic, virologic, entomologic, and zoologic investigations. Emerg. Infect. Dis. 7, 1052–1054.
Oreshkova, N., Keulen, L., Kant, J., Moormann, R.J.M., Kortekaas, J., 2013. A single vaccination with an improved nonspreading Rift Valley fever virus vaccine provides sterile immunity in lambs. PLoS One 8, e77461.
Papin, J.F., Verardi, P.H., Jones, L.A., Monge-Navarro, F., Brault, A.C., Holbrook, M.R., Worthy, M.N., Freiberg, A.N., Yilma, T.D., 2011. Recombinant Rift Valley fever vaccines induce protective levels of antibody in baboons and resistance to lethal challenge in mice. Proc. Natl. Acad. Sci. U.S.A. 108, 14926–14931.
Peters, C.J., Jones, D., Trotter, R., Donaldson, J., White, J., Stephen, E., Slone Jr., T.W., 1988. Experimental Rift Valley fever in rhesus macaques. Arch. Virol. 99, 31–44.
Peters, C.J., Linthicum, K.J., 1994. Rift Valley Fever, Handbook of Zoonoses. CRC Press, Boca Raton, FL, pp. 25–138.
Peters, C.J., Pittman, P.R., Morrill, J.C., 2008. Genetic and Clinical Evaluation of MP-12: A Live Attenuated Vaccine for Rift Valley Fever Virus (RVFV). Vaccine 2nd Global Congress, Boston, MA.
Randall, R., Binn, L.N., Harrison, V.R., 1964. Immunization against Rift Valley fever virus. Studies on the immunogenicity of lyophilized formalin-inactivated vaccine. J. Immunol. 93, 293–299.
Randall, R., Gibbs Jr., C.J., Aulisio, C.G., Binn, L.N., Harrison, V.R., 1962. The development of a formalin-killed Rift Valley fever virus vaccine for use in man. J. Immunol. 89, 660–671.
Rusnak, J.M., Gibbs, P., Boudreau, E., Clizbe, D.P., Pittman, P., 2011. Immunogenicity and safety of an inactivated Rift Valley fever vaccine in a 19-year study. Vaccine 29, 3222–3229.
Saluzzo, J.F., Smith, J.F., 1990. Use of reassortant viruses to map attenuating and temperature-sensitive mutations of the Rift Valley fever virus MP-12 vaccine. Vaccine 8, 369–375.
Schmaljohn, C.S., Parker, M.D., Ennis, W.H., Dalrymple, J.M., Collett, M.S., Suzich, J.A., Schmaljohn, A.L., 1989. Baculovirus expression of the M genome segment of Rift Valley fever virus and examination of antigenic and immunogenic properties of the expressed proteins. Virology 170, 184–192.
Schrire, L., 1951. Macular changes in rift valley fever. S. Afr. Med. J. 25, 926–930.
Schulz, K.H., 1951. Rift Valley fever in South Africa, Special Report No. 5/51 Union Department of Health, Plague Research Laboratory, pp. 1–26.
Schwentker, F.F., Rivers, T.M., 1934. Rift Valley fever in man: report of a fatal laboratory infection complicated by thrombophlebitis. J. Exp. Med. 59, 305–313.
Smith, D.R., Bird, B.H., Lewis, B., Johnston, S.C., McCarthy, S., Keeney, A., Botto, M., Donnelly, G., Shamblin, J., Albarino, C.G., Nichol, S.T., Hensley, L.E., 2012.

Development of a novel nonhuman primate model for Rift Valley fever. J. Virol. 86, 2109–2120.
Smithburn, K.C., Haddow, A.J., Gillett, J.D., 1948. Rift Valley fever; isolation of the virus from wild mosquitoes. Br. J. Exp. Pathol. 29, 107–121.
Smithburn, K.C., Mahaffy, A.F., et al., 1949. Rift Valley fever; accidental infections among laboratory workers. J. Immunol. 62, 213–227.
Spik, K., Shurtleff, A., McElroy, A.K., Guttieri, M.C., Hooper, J.W., SchmalJohn, C., 2006. Immunogenicity of combination DNA vaccines for Rift Valley fever virus, tick-borne encephalitis virus, Hantaan virus, and Crimean Congo hemorrhagic fever virus. Vaccine 24, 4657–4666.
van Velden, D.J., Meyer, J.D., Olivier, J., Gear, J.H., McIntosh, B., 1977. Rift Valley fever affecting humans in South Africa: a clinicopathological study. S. Afr. Med. J. 51, 867–871.
Vialat, P., Billecocq, A., Kohl, A., Bouloy, M., 2000. The S segment of rift valley fever phlebovirus (Bunyaviridae) carries determinants for attenuation and virulence in mice. J. Virol. 74, 1538–1543.
Vialat, P., Muller, R., Vu, T.H., Prehaud, C., Bouloy, M., 1997. Mapping of the mutations present in the genome of the Rift Valley fever virus attenuated MP12 strain and their putative role in attenuation. Virus Res. 52, 43–50.
von Teichman, B., Engelbrecht, A., Zulu, G., Dungu, B., Pardini, A., Bouloy, M., 2011. Safety and efficacy of Rift Valley fever Smithburn and Clone 13 vaccines in calves. Vaccine 29, 5771–5777.
Wallace, D.B., Ellis, C.E., Espach, A., Smith, S.J., Greyling, R.R., Viljoen, G.J., 2006. Protective immune responses induced by different recombinant vaccine regimes to Rift Valley fever. Vaccine 24, 7181–7189.
Warimwe, G.M., Lorenzo, G., Lopez-Gil, E., Reyes-Sandoval, A., Cottingham, M.G., Spencer, A.J., Collins, K.A., Dicks, M.D., Milicic, A., Lall, A., Furze, J., Turner, A.V., Hill, A.V., Brun, A., Gilbert, S.C., 2013. Immunogenicity and efficacy of a chimpanzee adenovirus-vectored Rift Valley fever vaccine in mice. Virol. J. 10, 349.
Weingartl, H.M., Nfon, C.K., Zhang, S., Marszal, P., Wilson, W.C., Morrill, J.C., Bettinger, G.E., Peters, C.J., 2014. Efficacy of a recombinant Rift Valley fever virus MP-12 with NSm deletion as a vaccine candidate in sheep. Vaccine.
WHO, 2000. Outbreak of Rift Valley fever, Yemen, August–October 2000. Releve epidemiologique hebdomadaire/Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record/Health Section of the Secretariat of the League of Nations 75, pp. 392–395.
WHO, 2010. Rift Valley fever, South Africa – update. Releve epidemiologique hebdomadaire/Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record/Health Section of the Secretariat of the League of Nations 85, pp. 185, 186.
WHO, 2012. Outbreak news. Rift Valley fever, Mauritania. Releve epidemiologique hebdomadaire/Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record/Health Section of the Secretariat of the League of Nations 87, p. 438.
Woods, C.W., Karpati, A.M., Grein, T., McCarthy, N., Gaturuku, P., Muchiri, E., Dunster, L., Henderson, A., Khan, A.S., Swanepoel, R., Bonmarin, I., Martin, L., Mann, P., Smoak, B.L., Ryan, M., Ksiazek, T.G., Arthur, R.R., Ndikuyeze, A., Agata, N.N., Peters, C.J., 2002. An outbreak of Rift Valley fever in Northeastern Kenya, 1997–98. Emerg. Infect. Dis. 8, 138–144.