

Safety and Efficacy profile of Commercial Veterinary Vaccines against Rift Valley Fever Disease

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Abstract

Rift valley fever (RVF) is an infectious illness with serious clinical manifestations and health consequences in humans and a wide range of domestic ruminants. The virus transmitted either by mosquito bites or through exposure to blood, body fluids or infected animal tissues. As with other viral diseases the prevention and control of RVF relies heavily on immunization of susceptible herds with safe and cost-effective vaccine, that able to confer long-term protective immunity. Interestingly, several strains of RVF vaccines have been developed and available in commercial production. The two most prominent among these vaccines are Formalin-Inactivated vaccine, and live attenuated Smithburn vaccine. Although, both are immunogenic and widely used in control programs, they proved to be accompanied by significant concerns. The first one requires multiple doses for protection, and the other has been reported to cause abortion and fetal malformation in pregnant ewes, as well as a possible reversion to virulence. Recently, a newly described RVF vaccine registered and extensively used in South Africa and Namibia named Clone13. Safety and efficacy trials proved the vaccine as safe in pregnant ewes as highly immunogenic, along with its potential for differentiating infected from vaccinated animals(DIVA). In conclusion, with the exception of Clone13 vaccine, RVF vaccines presently available in markets are not fulfill the requirements of safety and potency. Various novel candidate vaccines against RVF are under development, presumably safer and more immunogenic than currently available in markets, have not seen the light yet. Consequently, incentive plans should be introduced to companies to bring those promising candidates to markets.

Key words : RVF, Live Vaccine, Clone 13

Introduction

Rift valley fever (RVF) is a life-threatening disease of domestic ruminants and humans, included in OIE list as a notifiable and transmissible disease of serious socio-economic impacts and public health concerns^[1]. The causative agent is mosquito-borne virus belongs to the family Bunyaviridae, genus phlebovirus^[2]. It was first reported among livestock in Kenya in 1931, since then it has been reported as occurring in most African countries^[3]. The first appearance of RVF virus in new geographical areas outside Africa was reported in Jazan region, south-west Saudi Arabia in 2000, with 886 confirmed cases involving 124 deaths^[4]. The socio-economic impact of the RVF epidemics has been higher specially to populations who were totally dependent on livestock income.

The negative impacts not only affecting livestock producers, but also extended to various stakeholders in the marketing chain including, livestock traders, slaughterhouses, casual laborers, butchers and non-agricultural sectors^{[5],[6]}.

As there is no specific treatment for RVF, vaccination of susceptible animals with safe and cost-effective vaccine during non-epidemic periods, remains the only effective method to build sufficient immunity able to limit the overall scope of epidemics and preventing viral human infections^[7]. Although, several adverse effects had been associated with vaccination^[8], the numerous advantages and the benefits derived have promoted the use of vaccines rather than chemotherapy. Apart from the fact that vaccination is the only available method to prevent viral infections in the absence

of broad spectrum antiviral, they are mostly environmentally friendly and contribute indirectly to preventing drug resistance and pharmaceutical residues in food^[9]. Furthermore, they have a significant impacts not only on reducing losses or improving health and production, but also on human health through increasing safe food supplies and preventing zoonotic diseases^[10].

A successful vaccination program depends on a proper selection for the vaccine, as well as, good handling practices (in accordance with manufacturer’s instruction). Vaccine type and timing should be done according to the epidemiological aspect of targeted area. Generally, live attenuated vaccines are more preferable to inactivated ones in endemic zones and considered the primary available option for controlling the disease in high risk areas during inter-epizootic period or at an outbreak warning. While, inactivated vaccines are recommended specifically in free areas. However, during an outbreak time of RVF disease, vector control, public education, quarantine , slaughter pan , probably are the most effective measures against the disease.

Obviously, commercial production of good quality vaccines tend to be a biggest challenge, as the cost of sustained vaccination campaigns against RVF, is beyond the capacity

of most countries suffering regular outbreaks. Additionally, outbreaks of RVF usually occurred at irregular intervals and most commonly following exceptionally heavy rains, these events have led to refuse annual vaccination during long inter-epizootic periods which in turn both decreases the demand for vaccines and preventing the manufacturers from maintaining strategic stocks due to limited shelf-life^[11].

Reliable information about vaccination in endemic zones are scarce. With the exception of Saudi Arabia, South Africa and Egypt, all affected countries have not practiced routine vaccination. In Egypt control of RVF, based on alternation between live and inactivated vaccines concurrent with periodical vector control. Live vaccine had been used at intermittent periods before, during or after outbreaks in unidentified manner might be a significant factor in disease persistence and maintaining endemicity of RVF in Egypt^[12].

In Saudi Arabia, a control program based on sustain vaccination campaigns, along with vector control has been implemented, since the disease was first recognized. Despite, some serological evidences of RVF occurrence, vaccination seems to play a significant role in control, as long as, no clinical disease in humans and animals has been reported yet^[13]. Table(1)

Country	Type of vaccine	Vaccine Schedule	Historical Outbreaks
Saudi Arabia	Live attenuated (Smithburn strain)	Annual Vaccination	2000
South Africa	Live attenuated (Clone13)	Annual Vaccination (high risk zones)	-1950-1974-1981- 1996-1999-2010
Egypt	Inactivated Vaccine	Biannual Vaccination	1977-1993-1996-2003
Kenya	Live attenuated(Smithburn strain)	At outbreak warning	1931-1936-1968-1978-1997-1951-2006

Table (1): Vaccination program in Africa and Arabian Peninsula

Presently, two main types of vaccines with different development techniques are available for immunization against RVF, including, live attenuated vaccines and in-activated vaccines^[14]. Attenuation of live vaccines was accomplished by in-vitro passage through a series of cell cultures so as to produce a version of a virus attenuated to such a level unable to cause disease in animals, together with inducing a rapid onset of long lasting immune response similar to that of natural infection. While, inactivation obtained by growing the virus in culture media before treated with heat

or chemicals such as Formalin to destroy the ability of viruses to replicate^[15]. Although, inactivated vaccines are biologically safe, more stable and have no residual viruses or risk of reversion as attenuated vaccines, they are known to be less protective, needed high antigenic mass and strong adjuvant to stimulate the immune system. Moreover, they continued to be associated with slow onset of immunity, local reactogenicity and residue, risk of incomplete inactivation, hazards to personnel , as well as, not very efficient without multiple injections^[16]. To date, there is no

licensed vaccines against RVF available to immunize humans, while various strains for livestock now licensed and commercially produced including Smithburn vaccine, Formalin-inactivated vaccine and Clone 13. These vaccines produced by three different laboratories: Onderstepoort biological products limited (OBP) in South Africa, Kenya veterinary vaccine producing institute

(KEVEVAPI), and Egypt's Veterinary Serum and Vaccine Research Institute (EVSRI). The objectives of this review is to: (1) summarize commercially available RVF vaccines for veterinary use in Africa and Arabian peninsula, (2) highlight the safety-efficacy profile and drawbacks of these vaccines according to previous safety-efficacy trials, (3) review different vaccination strategies adopted in countries experiencing RVF outbreaks. Table (2)

Commercial Vaccine Name	Vaccine Type	Form	Company	Adjuvant	Packing	Instructed dose	Use in pregnant animals
Rift Valley Fever (Inactivated)	Inactivated	Liquid	Onderstepoort Biological Products	Aluminum Hydroxide	Available in bottles of 100ml	Sheep and Goats 1ml s/c Cattle 2ml s/c	YES
Rift Valley Fever (Live)	Live attenuated	Freeze-dried	Onderstepoort Biological Products	NO	Available in bottles of 100 doses	Cattle, Sheep and Goats 1ml S/C	NO
RVF CLONE 13	Live attenuated	Freeze-dried	Onderstepoort Biological Products	NO	Available in bottles of 100 doses	Cattle, Sheep and Goats 1ml s/c	YES
Rift Valley Inactivated Vaccine	Inactivated (Zagazig H501 strain)	Liquid	Veterinary Serum and Vaccine Research Institute	Aluminum Hydroxide	Available in bottles of 100 doses	Sheep and Goats 1 ml s/c Cattle 2 ml s/c	YES
RIFTVAX TM	Live attenuated Smithburn Strain	Freeze-dried	Kenya veterinary vaccine producing institute	NO	Available in bottles of 100 doses	Sheep and Goats 1ml s/c Cattle 2 ml s/c	NO

Table (2): Commercially available vaccines against RVF [42].

Smithburn vaccine:

Smithburn vaccine strain is derived from the virulent Entestrain, isolated from mosquitoes in Uganda and developed by serial passages in mouse brains to be able to induce immunity in ewes and their offspring after subcutaneous inoculation [17]. Currently, produced in OBP and KEVEVAPI in freeze-dried form. The recommended dose is 1ml of the reconstituted vaccine administered via subcutaneous route for the immunization of sheep, goats and cattle. According to manufacturer's instructions, the vaccine can cause abortion or fetal malformation in a small percentage of animals, particularly sheep, as well as, a slight febrile reaction may occur on the second to fourth day following inoculation. Accordingly, the use should be restricted to non-pregnant animals above six months age before or at the mating season so as to ensure maternal antibodies and to avoid abortion as well [18]. Despite these adverse outcomes, it has been widely used for many years as the major control measure as a cost-effective vaccine in most endemic zones, since the first introduction of the virus [19]. Likewise, in Jazan region, Saudi Arabia it has been used as the gold standard vaccine for several years as a prevention and control measure, since 2000 outbreak. It has also been proved through serological surveys to be effective and highly beneficial in controlling infections, as no notable clinical signs in animals nor humans have been reported yet [20]. Published efficacy studies conducted in the same region

in sheep and goats reported that, the vaccine was highly immunogenic and able to induce long lasting antibodies, irrespective to variations among vaccine batches. The level of herd immunity induced by Smithburn strain vaccine significantly declined with elapse of years. The percentage of IgG positive animals declined from 95% to 66.7% after one year, and it would decline to zero after six years and eleven months [21]. On the contrary, some safety and potency concerns associated with Smithburn vaccine. The vaccine was neither able to produce proper protective antibodies in all animal species particularly cows, nor safe in immunocompromised animals and pregnant during gestation period leading to high abortion. Larger efficacy and safety study conducted to investigate antibody response to Smithburn vaccine in cattle reported that, twenty-eight cows out of 120 pregnant cows and buffaloes were aborted within three days after vaccination. Moreover, the isolation of the virus from aborted fetus has proved in utero transmission of the vaccine virus [22]. Furthermore, the vaccine virus not only causes abortion and death of fetus at parturition, but also caused harmful changes in internal organs and propagated inside hepatic cells in a manner similar to natural infection [23].

Formalin-Inactivated vaccine

The lyophilized vaccine containing 2% (HAS) was first prepared in African green Monkeys Kidney cell and proved to be

immunogenic, highly resistant to thermal deterioration, and could be used as reference vaccine^[24]. Commercially produced from OBP and EVSVRI, the virus strain adapted for growth in baby hamster Kidney (BHK-21) cell, with aluminium hydroxide gel adjuvant for immunization of cattle, sheep, and goats, irrespective to the age and stage of pregnancy^[25]. A safe version of inactivated vaccines with minor side effects named TSI-GSD 200, was developed in USA by using a new master seed of the Entebbe strain to protect personnel who either work in laboratories or would be exposed to RVF infection, after receiving three doses on days 0, 7 and 28, to provide good long immunity with neutralizing antibody titers (1:140)^[26]. The safety and efficacy profile of inactivated vaccines have been further investigated in several trials. The immunization of susceptible cattle, sheep and goats with inactivated vaccine would induce higher neutralizing antibodies persisted for 9 months in cattle with evidence of protection against virulent RVF virus in pregnant ewes^[27]. A comparative study conducted to assess the response in cattle to live and inactivated RVF vaccines revealed that, a booster dose of inactivated vaccines after 5 months of the first vaccination was safe and able to evoke a good response^[28]. Further studies conducted to evaluate inactivated OBP vaccine as it is extremely difficult to maintain low temperatures during vaccine transportation. The vaccine was stored in different temperatures (4°C, 25°C, and alternation between (4°C AND 25°C) for a week. It was found that the vaccine was stable, well tolerated with mild or limited adverse reactions, and induced long-lasting neutralizing antibodies may persist for 21 months post booster dose, at any age and any stage of pregnancy. These neutralizing antibodies, its efficacy not adversely affected by variation in temperature during transportation^{[29],[30]}.

Clone13 vaccine:

Although, Formalin-Inactivated vaccine and live-attenuated Smithburn vaccine are widely used in control, both of them may be accompanied by safety problems. The first one requires three doses for protection, and the second has a risk to cause abortion and fetal malformation in pregnant animals^[31]. Drawbacks of these vaccines stressed the need for alternative vaccines in terms of safety and efficiency. Consequently, a massive progress and several initiatives have been done for the evolution of modern vaccines. Recent studies have shown that, RVF virus vaccines containing deletions of the NSs and NSm genes are highly attenuated, confer protective immunity with no detectable viremia and could be useful in control of RVF virus in endemic regions, as well as, allow for DIVA^[32]. The commercial OBP vaccine named (RVF Clone13) was recently registered, marketed in a form of freeze-dried live attenuated virus (clone13 strain) and extensively used in South Africa^[33]. Clone13 is a naturally attenuated isolate of RVF virus with a large deletion in the S segment. It was cloned by plaque purification of non-fatal human case isolate (74HB59 strain), obtained during 1974 RVF outbreak in Central African Republic

and proved to be highly immunogenic leading to long-lasting immunity as well^[34]. Published efficacy and safety studies of clone13 vaccine have shown that the vaccine protects animals properly without inducing undesirable clinical signs, such as abortion in pregnant ewes, pyrexia or fetal malformation in their offspring^[35]. Recent efficacy and safety studies conducted on sheep and goats in Senegal stipulated that the vaccine was safe at stages of pregnancy and didn't induce adverse effects. Additionally, antibodies level persisted up to 1 year after vaccination^[36]. However, some safety studies raised concerns about the possibility of genetic reassortment between S segment in Clone13 vaccine and virulent strains in field^[37]. Furthermore, little is known about the persistence duration of antibodies to clone13 vaccine in sera. Although, the currently available commercial vaccines have made a great contribution to RVF control over the past 80 years, they are associated with safety and efficacy concerns, including, but not limited to: risk of abortion- pyrexia- fetal malformation- teratogenic effects- viraemia- risk of reassortment- short shelf life- revaccination and risk of incomplete inactivation in killed vaccines. The gap in the safety and immunity explains the need for new promising candidates currently under development, such as subunit vaccines, virus vector and replicons^{[38],[39]}. RVF vaccine quality control Pan African Veterinary Vaccine Centre (AU-PANVAC) is a recognized reference centre for vaccine quality control, involved in certifying veterinary vaccines either produced or imported to the continent in particular all batches of RVF vaccines, to be in compliance with standards of potency and requirements of quality assurance to ensure its purity, safety, efficacy and stability. The production of good quality vaccine is critical for vaccination strategies particularly in endemic zones. Interestingly, the quality control of RVF vaccines is assessed under Bio-safety level 3 (BSL 3) laboratory due to potential for occupational infections^[40]. Currently, two types of RVF vaccines were submitted to the centre including, live-attenuated Smithburn vaccine and inactivated vaccines prepared from virulent field strain. Tests performed to certify the quality control of live RVF vaccine batches involving: Freedom from bacterial, fungal and viral contamination. Safety on susceptible animals and laboratory animals. Identity test using Reverse Transcriptase-Polymerase Chain Reaction. Potency using intra-cerebrally inoculation of vaccine in infant mice or Vero Cells and assessment of immune response on vaccinated sheep. Stability test using assessment of potency after incubation of the RVF vaccine at 37°C for one week. Residual Moisture content using the gravimetric method. While tests for quality control of inactivated RVF vaccines including: Freedom from bacterial, fungal and viral contamination. Safety on susceptible animals and laboratory animals. Identity test using Reverse Transcriptase-Polymerase Chain Reaction. Potency using assessment of immune response on vaccinated sheep. Completion of inactivation using inoculation of vaccine into susceptible cell culture. Residual Inactivant content using colorimetric method^[41].

With the exception of Clone13, commercial vaccines that currently available in markets are lacking safety, potency and potential for DIVA. Live attenuated Smithburn reported to cause abortion and fetal malformation in pregnant ewes. Formalin-inactivated vaccine requires multiple doses for production. Even Clone13 has a risk of potential reversion to virulence, and more studies from different areas should be done to determine the duration persistence of IgG antibody in sera of vaccinated animals. There are ongoing efforts to develop several novel RVF candidate vaccines involving subunit vaccines, virus vector and replicons. Incentives for commercial companies to invest in vaccine development should be considered.

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