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Review

Capripoxvirus-vectored vaccines against livestock diseases in Africa

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ABSTRACT

Five different viral diseases of livestock, lumpy skin disease (LSD), sheep pox (SPP), goat pox (GTP), Rift Valley fever (RVF) and peste des petits ruminants (PPR), circulate in the same regions of Africa, imposing a major burden on economic activity and public health. While commercial vaccines against these viruses are available, the cost of implementing regular vaccination regimens against multiple diseases is prohibitive for most African farmers. A single, affordable multivalent vaccine that simultaneously protects against all 5 diseases would therefore be of significant benefit to the livestock sector in Africa. It could also serve as a platform for the development of new vaccines of significance to other developing countries around the world. In this paper, we present an overview of the economic importance of livestock in Africa, the pathogens responsible for RVF, PPR, SPP, GTP and LSD and the vaccination strategies currently used to combat them. We then review experience with the development of attenuated capripoxviruses as vaccines against LSD, SPP and GTP and of recombinant capripoxvirus-vectored vaccines against RVF and PPR. We conclude the article by presenting the rationale for a single, multivalent capripoxvirus-vectored vaccine that would protect against all 5 diseases of livestock, and describe the approach being taken by a consortium of Canadian and South African researchers to develop such a vaccine.

Contents

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1. Introduction

Five viral diseases of livestock, lumpy skin disease (LSD), sheep pox (SPP), goat pox (GTP), Rift Valley fever (RVF) and peste des petits ruminants (PPR), cause tremendous losses of animals in Africa, imposing a major burden on economic activity and public health. All of these viral pathogens are co-localized in Africa (Fig. 1), potentially threatening livestock herds with multiple viral infections. An outbreak involving any single pathogen carries a significant risk, but the potential of animals being infected with multiple pathogens further exacerbates the risk of fatalities, since the compounded disease associated with each agent significantly reduces an animal's ability to survive (Malik et al., 2011). Although commercial vaccines are available to control these diseases, the cost of providing multiple large-scale vaccination regimens is prohibitive for most African farmers. The development of a single affordable vaccine against all of these diseases would therefore be of significant benefit to the livestock sector in Africa, and could serve as a platform for developing multivalent vaccines for use in other developing countries.

In this article, we present an overview of the pathogens responsible for RVF, PPR, SPP, GTP and LSD in African livestock and describe current vaccination strategies against the diseases. We then review experience with the development of attenuated capripoxviruses as vaccines against LSD, SPP and GTP and of recombinant capripoxvirus-vectored vaccines against RVF and PPR. We conclude the article by presenting the rationale for a single, multivalent capripoxvirus-vectored vaccine to protect against all 5

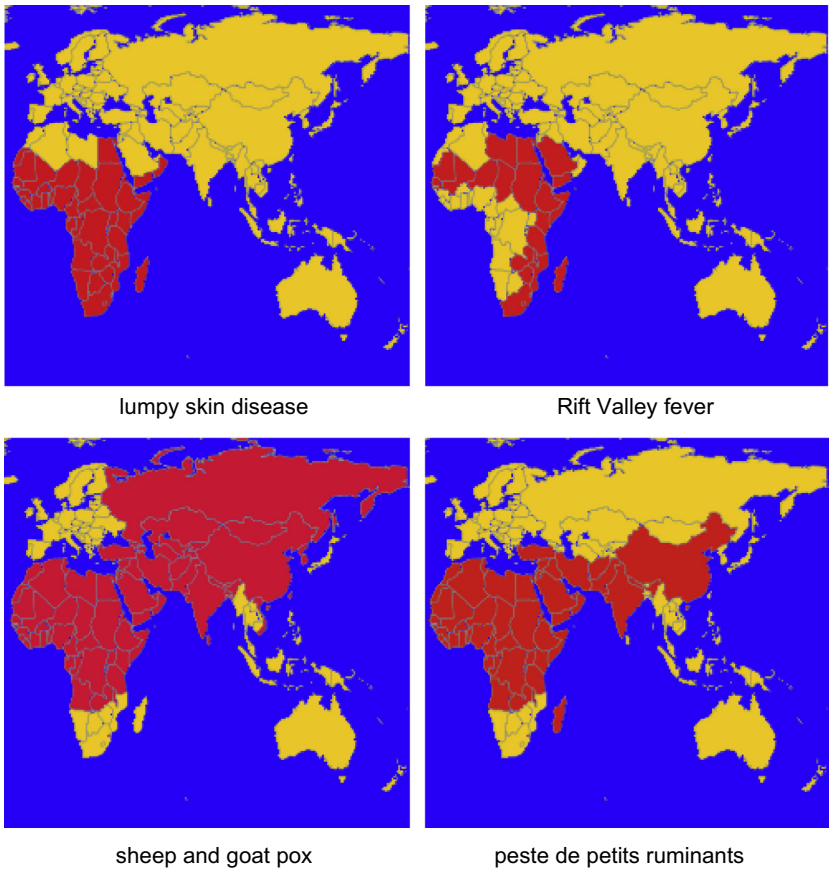

Fig. 1. Geographic distribution of small ruminant diseases (lumpy skin disease, Rift Valley fever, peste des petits ruminants, sheep pox and goat pox) over the past 25 years. Affected areas are indicated in red. The data were obtained from the OIE World Animal Health information database from 05/16/1987–05/16/2012.

diseases, and describe the approach we are taking to develop such a vaccine.

2. The economic importance of livestock in Africa

Agriculture is an important pillar in the economic development of African countries, accounting for more than 30% of gross domestic product (World Bank, 2011). The African Union estimates that, of the approximately one billion people on the continent, some 300 million are dependent on livestock for their livelihood (African Union International Bureau for Animal Resources, 2012). According to the Food and Agriculture Organization of the United Nations (FAO), the total number of sheep, goats and cattle in Africa approximates one billion animals (FAO, 2010), distributed in countries throughout the continent. While providing a means out of poverty for many, the livestock sector is constantly faced with the threat of endemic animal diseases. Africa is home to some of the most devastating livestock diseases known to man; it has been estimated that up to 25% of all livestock deaths can be attributed to infectious disease (McPeak et al., 2010) and overall economic losses are approximately 2 billion US dollars per year (African Union International Bureau for Animal Resources, 2012).

South Africa is considered to be the economic powerhouse of Africa. It is rich in minerals and industry, but agriculture and, specifically the livestock industry, are still critical for the overall health and wealth of the country. There are an estimated 24 million sheep, 6 million goats and 13 million cattle within the country that are at risk from viral and other diseases. Where possible, vaccination is practiced and sales for LSD and RVF vaccines alone for 2011 were over 3 million and 5 million doses, respectively (Onderstepoort Biological Products, South Africa, personal communication).

3. Strategies for combatting viral diseases of ruminants

In 2008, a framework was established between the WHO, FAO and OIE for a joint early warning system and global surveillance network for zoonotic and veterinary disease outbreaks. This program, called "One Health" (Joint document by the FAO, OIE, WHO, UNICEF, World Bank and UN System of Influenza Coordination, 14 October 2008), has since become a major international collaborative effort focusing on more than 20 zoonotic diseases, including RVF. One of its aims is the integration of international networks for detection, diagnostics and rapid response against transboundary diseases.

The One Health initiative should be broadened to include non-zoonotic, but economically important diseases of livestock such as LSD, SPP, GTP and PPR, which directly impact human health by causing severe production losses leading to food insecurity and economic hardship. The successful implementation of a broader One Health plan would have far-reaching implications for food security, as well as increasing public awareness of animal diseases that pose the greatest risk for the livestock industry in the developing world.

4. Major viral diseases of ruminants in Africa

In the following sections, we briefly summarize the clinical features and epidemiology of capripoxvirus diseases (SPP, GTP and LSD), RVF and PPR in Africa. Bluetongue is also an important livestock disease in the region, but because the causative agent has many serotypic variants, it is not currently possible to immunize animals against it with a single vaccine. We therefore do not discuss its features here. Some examples of recombinant capripoxvirus-vectored vaccines against single bluetongue serotypes are described in a later section.

4.1. Capripoxvirus diseases

4.1.1. Virus classification, epidemiology and disease

The members of the genus *Capripoxvirinae* are of particular concern to small ruminant and cattle farmers, and include sheep pox virus (SPPV), goat pox virus (GTPV) and lumpy skin disease virus (LSDV). All three contain double-stranded DNA genomes approximately 150 kb in size. They share a high degree of sequence homology, with 96% identity between SPPV and GTPV, and 97% identity between LSDV and both GTPV and SPPV genomes, suggesting that GTPV and SPPV are derived from a common LSDV ancestor (Tulman et al., 2002). The genomes of all three species encode for at least 147 genes; LSDV possesses an additional 9 genes which may play a role in its ability to infect cattle (Tulman et al., 2001).

While LSDV is mainly limited to the African continent (Fig. 1), it is spreading, with recent outbreaks in the Middle East, including Israel, Yemen and Oman. By constrast, SPPV and GTPV have a far wider geographic distribution, covering most of Africa, except for southern Africa and Madagascar, and Asia (Babiuk et al., 2008; Bhanuprakash et al., 2011). The ability of the these pathogens to spread rapidly is of major concern to countries bordering on capripoxvirus-endemic regions, especially as wildlife appear to be involved in the maintenance of the viruses; however, their precise role is poorly understood.

SPPV and GTPV generally display a host preference for either sheep or goats, but some isolates can cause disease in both species (Babiuk et al., 2009). Following an incubation period of 4–8 days, there is an increase in body temperature, heart rate and respiration, followed by the formation of macules in the skin (Bhanuprakash et al., 2006; Babiuk et al., 2008). These ultimately develop into pox lesions, which can affect over 50% of the skin surface. These lesions contain high viral loads (Bowden et al., 2008) and together with mouth lesions serve as the main source of virus for transmission to uninfected animals. The mortality rates of SPP and GTP range from 5–10% in local goat and sheep breeds in endemic areas, but imported exotic breeds may display rates as high as 100% (OIE, 2010).

LSDV shares a close phylogenetic relationship with SPPV and GTPV, but it only causes disease in cattle (OIE, 2010). It is also the only capripoxvirus for which mechanical transmission by *Aedes aegypti* mosquitoes has been demonstrated (Chihota et al., 2001). Signs of illness range from fever and depression to the formation of skin lesions. Reported mortality rates range from 2–12%, depending on the breed of cattle; lactating cows are at greatest risk (OIE, 2010).

4.1.2. Current vaccine strategies against SPP, GTP and LSD

Because the capripoxviruses have a high degree of sequence conservation and cross-immunity, an attenuated strain of any capripoxvirus should theoretically protect against all SPPV, GTPV and LSDV strains. The use of an attenuated capripoxvirus as a heterologous vaccine was first described over 20 years ago, when Kitching et al. developed a vaccine strategy utilising a strain of capripoxvirus which could confer protection against both SPP and GTP or either African or Asian origin (Table 3) (Kitching and Taylor, 1985; Kitching et al., 1987). Passive protection was demonstrated in sheep, using sera from goats and sheep previously infected with GTP or SPP virus (Kitching, 1986).

Over the years, a number of capripoxvirus vaccines have been developed by attenuating virulent field isolates through serial passage in cell culture (Table 3) (Davies and Mbugwa, 1985; Babiuk et al., 2008; Kitching, 2003). The most notable attenuated strains are the Romanian and RM-65 strains (SPP), the Mysore and Gorgan

strains (GTP), the South African Onderstepoort Neethling strain (LSD), and the Kenyan O240 strain (referred to as KS-1) (LSD, SPP and GTP) (OIE, 2010). The latter is of particular interest, since field studies have shown that O240 can confer a high degree of protection in both goats and sheep.

The attenuated O240 strain was derived from a sheep isolate and passaged in lamb testis and baby hamster kidney (BHK) cells; it induced mild local reactions when used to vaccinate sheep and goats (Kitching et al., 1987). However, initial infection studies in cattle showed that the O240 strain induced more severe reactions than existing SPP and GTP vaccines (Kitching et al., 1989). Further genomic studies found that O240 had a closer nucleic acid identity to LSDV than to SPPV or GTPV, suggesting that this sheep-derived capripoxvirus virus is in fact a strain of LSDV (Tulman et al., 2002). Almost 100 million doses of SPP, GTP and LSD live attenuated vaccines are now used annually (Medhi El Harak, Biopharma Lab, Morocco, personal communication). As LSD continues to spread rapidly, this figure is set to increase significantly.

4.2. Peste des petits ruminants

4.2.1. Virus classification, epidemiology and disease

Peste des petits ruminants virus (PPRV) is a paramyxovirus, and a member of the *Morbillivirus* genus, with a single, negative-stranded RNA genome. As with other members of the genus, the 15,948 base-pair PPRV genome is large in comparison to known RNA viruses, making it the largest known morbillivirus (Bailey et al., 2005). The virion contains 6 different proteins, including a nucleoprotein (N), viral RNA-dependent polymerase (L), an RNA-polymerase phosphoprotein co-factor (P), a matrix protein (M), a fusion protein (F) and hemagglutinin protein (H). As the F and H proteins are located within the viral envelope, they have been targeted for use in subunit/recombinant vaccines and have been shown to confer protection in small ruminants (Diallo, 2003).

As the name suggests, peste des petits ruminants primarily affects small ruminants such as goats and sheep, with symptoms ranging from ocular and nasal discharges to fever and necrotic lesions; 70–80% of cases lead to death within 10–12 days post-infection (Diallo et al., 2007). Virus transmission appears to be primarily through direct contact with infected animals with their fresh secretions or feces (Baron et al., 2011). PPR was originally described in the 1940's in Côte d'Ivoire, western Africa, and was originally thought to be a variant of rinderpest, differing only in its ability to infect smaller ruminants (Gargadennec and Lalanne, 1942). However, it was later found to join measles, rinderpest and canine distemper viruses as a fourth member of the genus *Morbillivirus* (Gibbs et al., 1979).

PPR was long considered to be limited to western Africa; however, in the 1980's, El Hag Ali et al. reported an outbreak in Sudan (El Hag Ali and Taylor, 1984), extending its known geographic distribution throughout sub-Saharan Africa, except for southern Africa (Fig. 1). Since then, PPR has also been reported across the Middle East, India, as well as the Tibetan region of China, where it was first reported in 2007 (Wang et al., 2009). Although only one serotype is known to exist, there are 4 distinct phlyogenetic lineages; isolates from 3 of these lineages only occur in Africa, while lineage 4 is found in both Africa and Asia (Shaila et al., 1996).

In the early 2000s, the FAO singled out PPR as one of the principal diseases when considering policies pertaining to poverty alleviation (African Union International Bureau for Animal Resources, 2012). As described in the following section, approved vaccines are available to help prevent outbreaks and are in widespread use. For example, in 2008 the Kenyan government committed more than one-third of its livestock vaccination budget to combating a national outbreak of PPR.

Table 1
Currently approved veterinary vaccines against Rift Valley fever and peste des petits ruminants.

Disease	Vaccine	References
Rift Valley fever	Smithburn Clone 13 Inactivated virulent RVFV	Smithburn (1949) Dungu et al. (2010) Kark et al. (1982)
Peste des petits ruminants	Nigerian 75/1 (most widely used), Sungri 96, Arasur 87, Coimbatore 97	Diallo et al. (1989, 2002), Saravanan et al. (2010), Khandelwal et al. (2011) and OIE (2010)

4.2.2. Current vaccine strategies against PPR

Due its relatively high degree of homology to rinderpest virus (especially the F- and H-proteins), vaccine strategies against PPR originally involved the use of a live, attenuated rinderpest vaccine. Although this vaccine did not elicit neutralizing antibodies against PPRV, animal studies showed that it conferred complete protection from PPR for at least one year, and that vaccinated animals rapidly generated neutralizing antibodies against the virus after challenge (Taylor, 1979). Since then, an attenuated strain of PPRV was developed by Diallo et al. based on the Nigerian 75/1 strain (Diallo et al., 1989), using serial passage of the virus in Vero cells (Table 1). Widespread field trials on more than 98,000 sheep and goats from 1989–1996 showed this strain's ability to provide protection for at least 3 years (OIE, 2010), and that challenged animals do not transmit virulent virus through physical contact (Diallo, 2004). Other attenuated PPRV strains have since been developed (Table 1), based on Asian isolates (lineage 4), 3 of them are referred to as Sungri 96, Arasur 87 and Coimbatore 97 (Saravanan et al., 2010).

These vaccines have been successful in preventing outbreaks of PPR, but a major drawback is that they are heat-labile, and thus require continuous cold-chain maintenance. Considering that PPRV is endemic in many poor countries with hot climates, maintaining a continuous cold-chain is problematic. To address this problem, it was found that attenuated PPRV, lyophilized in a Tris-trehalose formulation, can retain high titers for up to 6 days at 37 °C (Silva et al., 2011). Other examples of heat-stable vaccine candidates involve recombinantly expressing PPRV proteins, which can induce protective immune responses. Recent studies showed that recombinant peanut plants expressing the H-protein, when administered orally, can induce both neutralizing antibodies and cell-mediated immunity (Khandelwal et al., 2011). Because plant-based vaccines are more thermotolerant and do not require a continuous cold-chain from production to immunization, it was proposed that this could serve as a viable alternative to current attenuated vaccines.

A recombinant canine adenovirus expressing the H-protein of PPRV was also found to confer protection in goats (Qin et al., 2012). Neutralizing antibodies were observed following a single injection, and a second injection generated high antibody titers for up to 7 months. In another approach, the H- and F-proteins were expressed using Modified Vaccinia Ankara (MVA) virus as vector (Chandran et al., 2010). Both recombinant proteins were found to confer immunity in goats when expressed either together or separately. Another, more heat-stable capripoxvirus vector for recombinant expression of PPRV proteins is described later in this paper (Berhe et al., 2003; Diallo et al., 2002; Ngichabe et al., 2002).

4.3. Rift Valley fever

4.3.1. Virus classification, epidemiology and disease

Rift Valley fever virus (RVFV) is a tri-segmented, negative-stranded RNA virus in the *Bunyaviridae* family (Ikegami, 2012) RVFV is primarily pathogenic in small ruminants such as sheep and goats (Boshra et al., 2011a), however, a recent outbreak in

Table 2
Experimental vaccine candidates against Rift Valley fever and peste des petits ruminants.

Disease	Experimental vaccine	References
Rift Valley fever	Attenuated RVFV (MP-12)	Morrill et al. (1997a,b), Pittman et al. (1999)
	Recombinant viruses:	
	Adenovirus	Holman et al. (2009)
	Vaccinia	Kakach et al. (1988)
	Newcastle disease virus	Kortekaas et al. (2010a,b)
	Alphavirus	Gorchakov et al. (2007)
	Capripoxvirus	Wallace et al. (2006), Soi et al. (2010) and Ayari-Fakhfakh et al. (2012)
	Glycoprotein subunit	Wallace et al. (2006), de Boer et al. (2010)
	DNA vaccines	Wallace et al. (2006), Spik et al. (2006), Lagerquist et al. (2009), Boshra et al. (2011a,b) and Lorenzo et al. (2010)
Peste des petits ruminants	Recombinant capripoxvirus	Diallo et al. (2002), Diallo, 2003, Berhe et al. (2003) and Chen et al. (2010)
	Adenovirus	Qin et al. (2012)
	Vaccinia virus	Chandran et al. (2010)

Table 3
Currently approved live, attenuated capripoxvirus veterinary vaccines.

Disease	Capripoxvirus employed	Ruminant species targeted	References
Sheep pox and goat pox	Romanian (SPPV)	Goats	Kitching et al. (1987, 1989)
	RM-65 (SPPV)	Sheep	OIE (2010)
	Mysore (GTPV)		Davies and Mbugwa (1985)
	Gorgan (GTPV)		
	O240/KS-1 (LSDV)		
Lumpy skin disease	Onderstepoort (South Africa)	Cattle	Hunter and Wallace (2001)
	O240/KS-1		

Mauritania has suggested that larger ruminants, such as camels, may also serve as major viral amplifying hosts (El Mamy et al., 2011). In sheep, acute RVF can cause death within 24–48 h following detection, with non-fatal symptoms ranging from bloody diarrhea and fever, to widespread abortions in pregnant ewes (Shimshony and Barzilai, 1983). Human symptoms include photophobia, headaches, encephalitis and retinitis (Boshra et al., 2011a; Indran and Ikegami, 2012). As a zoonotic pathogen with human fatality rates ranging from 1% to 5%, RVFV has also been recognized as a potential bioterrorist agent (Ikegami et al., 2006). While current human fatality rates are relatively low, recent outbreaks in Kenya and Sudan have resulted in fatality rates approaching 20%, thereby presenting an increased threat to public health (Centers for Disease Control and Prevention (CDC), 2007) (Adam et al., 2010).

Although RVF has long been endemic in eastern and sub-Saharan Africa, major outbreaks have occurred in the Middle East and Egypt, as well as in countries in north-western Africa (Fig. 1). The latter is of particular concern, since it poses a potential route of natural transmission to Europe. Furthermore, RVFV has been shown to be transmitted by members of the *Aedes*, *Anopheles* and *Culex* genera of mosquitoes, of which several potential vector species are found in North America and Europe (Iranpour et al., 2011; Hartley et al., 2011). Furthermore, RVFV can withstand arid conditions, as evidenced by its ability to survive in dormant mosquito eggs for prolonged periods, permitting its infectious cycle to continue following favourable rainfall (Chevalier et al., 2010). While RVFV therefore remains a major threat to the African livestock industry, its potential to impact veterinary and human health outside the continent have renewed interest in the development of safe, heat-stable vaccines, able to provide long-term protection.

4.3.2. Current vaccine strategies against RVF

There are currently no commercially available RVF vaccines for humans, but vaccines approved for veterinary use in endemic countries such as South Africa include the live attenuated RVFV Smithburn strain (Bengis et al., 2010) and an inactivated virulent strain (Kark et al., 1982; Meadors et al., 1986) (Table 1). The Smithburn vaccine was developed in the 1940s (Smithburn, 1949) and has been shown to be effective if administered during inter-epidemic periods. However, multiple studies have shown that this attenuated strain can induce abortions in pregnant ewes, as well as illness in European cattle (Botros et al., 2006). Due to its potential for pathogenicity, use of the Smithburn vaccine has been limited to areas deemed at high risk for disease outbreaks.

A more recent live, attenuated strain has been developed, which has been shown to be effective, without the adverse effects associated with the Smithburn strain. Originally isolated from a mild case of RVF in the Central African Republic, strain 74HB59 (subsequently referred to as Clone 13) was found to confer protection in mice. Further studies demonstrated its ability to protect both sheep and calves from infection and clinical disease (Dungu et al., 2010). Clone 13 is now a registered RVF vaccine for use in South Africa and is being evaluated for final approval as a veterinary vaccine in other high-risk African countries, such as Kenya.

Several other vaccine candidates have also been described for RVF, including DNA vaccines, attenuated virus, inactivated virus, recombinant vectored vaccines and recombinant non-vectored vaccines (see literature citations in Table 2). In the case of recombinant vectored vaccines, several viral vectors have been shown to express the glycoproteins of RVFV and confer some degree of protective immunity in animals. These vectors include adenovirus, vaccinia virus, Newcastle disease virus, Venezuelan equine encephalitis virus and capripoxviruses (LSDV) (Table 2).

5. Capripoxviruses as recombinant vaccines and vectors

5.1. Introduction

Vaccinia virus (VV) was demonstrated to be a suitable vaccine expression vector in the early 1980s (Mackett et al., 1982), leading to the generation of several VV and other poxvirus recombinant

Table 4
Experimental recombinant capripoxvirus vaccines against livestock diseases in Africa.

Disease	Capripoxvirus employed	Protein expressed	Ruminant Species	References
Rinderpest	KS-1/O240	Fusion (F) protein Haemagglutinin (H) protein	Cattle	Romero et al. (1993) Romero et al. (1994a,b)
Peste des petits ruminants	KS-1/O240 (F- and H-protein)	Both Fusion (F) protein	Goats Sheep	Romero et al. (1995)
	AV41 (F- and H-protein)	Haemagglutinin (H) protein		Chen et al. (2010)
Bluetongue	KS-1/O240	VP7 NS1 NS3 VP2	Goats Sheep	Wade-Evans et al. (1996) Perrin et al. (2007)
Rift Valley fever	KS-1/O240 Onderstepoort vaccine strain	Glycoproteins Gn and Gc	Sheep	Soi et al. (2010) Wallace et al. (2006)

vaccines. The most successful of these to date is the recombinant VV-rabies glycoprotein vaccine construct used in Central Europe and the USA to control the spread of rabies in wildlife (Blancou et al., 1986; Horman et al., 2012).

Following on the success of using orthopoxviruses and avipoxviruses as recombinant vaccine vectors, recombinant capripoxviruses (KS-1) were generated expressing the rinderpest virus F (Romero et al., 1994b) and H genes in separate constructs (Romero et al., 1994a). These candidate vaccines protected cattle against virulent rinderpest virus challenge, and were heat-stable; as expected, they also conferred protection against LSD (Romero et al., 1993). A number of recombinant vaccines utilising either the KS-1 or South African Onderstepoort vaccine strains of LSDV as vectors have since been developed against a variety of pathogens affecting small and large ruminants and evaluated in animals (Table 4).

The cloning and recombination strategies utilised for developing capripoxvirus-vectored recombinant constructs was based on earlier work on VV. In the following examples, recombinant virus selection relied on incorporation of the *Escherichia coli* guanine phophoribosyl transferase (gpt) gene as a positive selection marker. Technologies for generating poxvirus-vectored recombinant vaccines have made significant advances in recent years; one of the most notable is the development of multivalent poxvirus-vectored recombinant vaccines. For example, a VV-vectored vaccine was recently developed for the expression of the H5N1 influenza virus haemagglutinin, N1 neuraminidase, NP nucleoprotein, and matrix proteins M1 and M2, together with IL-15, cloned end-to-end as a concatamer (Poon et al., 2009). This recombinant viral construct conferred complete protection in mice, providing evidence that multiple viral components could be co-expressed using a poxvirus backbone. Work of a similar nature was recently published using LSDV as vector and expressing an HIV polyprotein (Shen et al., 2011).

5.2. Capripoxvirus-vectored veterinary vaccines

5.2.1. Rinderpest

The idea of using a poxvirus vaccine to express rinderpest viral antigens was explored as early as the 1980's, when VV expressing the rinderpest H-protein was shown to be effective in rabbits (Tsukiyama et al., 1989). Vaccinated rabbits generated neutralizing antibodies, and did not exhibit any clinical signs associated with rinderpest when challenged with the virus. The same study also demonstrated that the recombinant VV-vectored vaccine was heat stable in a lyophilized state, confirming that it shouldn't require a continuous cold-storage chain, unlike many traditional vaccines.

With the advance of molecular biology techniques in the 1990s, it was shown that the incorporation of the rinderpest fusion (F-protein) gene into the capripoxvirus, KS-1, resulted in a protective multivalent vaccine that protected cattle against both LSD and rinderpest (Table 4) (Romero et al., 1993). Based on these results, it was proposed that, due to strong homology between the F-gene of rinderpest and those of other morbilliviruses, this vaccine-vector backbone could be used for other endemic morbillivirus diseases affecting goats and sheep, such as PPR. Further studies showed that the immunogenic hemagglutinin protein (H-protein) of rinderpest expressed in KS-1 could also confer protective immunity (Romero et al., 1994a). Subsequent studies found that this H-protein-expressing capripox construct provided a significant degree of long-term protection, with vaccinated cattle showing full clinical protection from LSD for up to 2 years (Ngichabe et al., 2002). However, in the case of rinderpest, 50% of cattle were protected following challenge after the same time period, and after 3 years, 30% of vaccinated animals still had immunity. The same animals had 100% immunity to LSD after 2 years, and 40% after 3 years. These findings demonstrate that LSDV-vectored vaccines can confer long-term immunity when administered to livestock.

5.2.2. Peste des petits ruminants

As in the case of rinderpest, KS-1 constructs expressing either the F- or H-protein genes of PPRV were successful as dual recombinant vaccines against both PPR and capripoxvirus (Table 4). The first such study incorporated the H-protein gene of PPRV into the TK gene of KS-1, in a manner similar to that used for rinderpest by Romero et al. (1994a,b) and (Diallo et al., 2002). The resulting recombinant virus was then administered in goats by subcutaneous inoculation. Challenge 3 weeks later with an otherwise lethal dose of PPRV demonstrated full protection, with no significant changes in white blood cell counts or body temperature. A similar construct expressing the F protein also conferred full protection, using a single dose as low as 0.1 plaque forming units (Berhe et al., 2003).

A more recent study evaluated the efficacy of both the H- and F-proteins of PPR when expressed in the attenuated goat poxvirus strain, AV41; antibody titers were evaluated in both goats and sheep (Chen et al., 2010). In both cases, seroconversion was observed following a single vaccination, although an improved immune response was observed in animals vaccinated with the H-protein construct. Virus neutralizing antibodies (VNA) were induced following a second vaccination, and significant titers were still detectable after 6 months. When challenged with virulent capripoxvirus, goats vaccinated with H-expressing capripoxvirus demonstrated no secondary lesions, while the negative control group developed generalized papules. When two doses were administered to goats previous immunized with a live attenuated capripoxvirus vaccine, the H-expressing GTPV vector still conferred immunity against PPRV, demonstrating the potential of capripoxviruses as vectors in the target species (Chen et al., 2010). However, while capripoxviruses expressing the recombinant H-protein elic-

ited neutralizing antibodies, those expressing the F-protein did not, suggesting that the H- and F-proteins elicit protection through different immune mechanisms (Romero et al., 1995).

5.2.2.1. Bluetongue. KS-1 has also been used as a recombinant vaccine vector for the expression of multiple bluetongue virus (BTV) proteins (Table 4). Using a strategy similar to that described for PPR and rinderpest, Wade-Evans et al., inserted VP7, the major core structural protein from BTV serotype 1, into the TK gene of KS-1 (Wade-Evans et al., 1996). Vaccinated sheep were assayed for antibody production, as well as protection against heterotypic viral challenge with BTV3 SA. Six of the 8 vaccinated animals survived, whereas all negative control animals died, indicating that a capripoxvirus-based recombinant vaccine against one BTV strain (out of 26) can confer at least some degree of cross-protection to other BTV strains. A separate study by Perrin et al. evaluated the degree to which KS-1 expressing BTV2 VP7, as well as BTV2 NS1, NS3 and VP2 proteins, could protect both goats and sheep from BTV challenge (Perrin et al., 2007). Seroconversion was observed for NS3, VP2 and VP7 (NS1 antibodies couldn't be detected for technical reasons), and cell-mediated immunity was observed from 14 days post-vaccination. Partial protection of sheep was obtained three weeks after vaccination with homologous challenge, confirming the ability of a capripoxvirus to be used as a recombinant vaccine vector against BTV.

5.2.2.2. Rift Valley fever. Although commercial RVF vaccines are available, there is a need for safer and more heat-stable vaccines. A number of recombinant capripoxvirus vaccines have been developed; most utilize the RVFV glycoproteins (Gn and Gc) as protective immunogens (Table 4). A study by Wallace et al. compared the efficacy of three different recombinant vaccine candidates, including bacterially expressed RVFV nucleocapsid and truncated Gn proteins, a DNA vaccine expressing both glycoproteins, and a LSDV construct utilising the Onderstepoort vaccine strain as vector expressing both RVFV glycoproteins (rLSDV-RVFV) (Wallace et al., 2006). The Smithburn strain was used as a positive control. The bacterial lysate containing truncated Gn, as well as the rLSDV-RVFV vaccine construct and the Smithburn strain, provided complete protection in mice, with no clinical signs following virulent viral challenge.

When rLSDV-RVFV was further evaluated in sheep, it was found that vaccinated sheep seroconverted for both RVFV- and LSDV-specific antibodies, and were protected from virulent virus challenge. In related studies, Soi et al. developed a similar construct using the KS-1 strain of LSDV as the vector, and found that vaccinated sheep produced neutralizing antibodies to RVFV and to LSDV (Soi et al., 2010). Following challenge with virulent RVFV and SPPV, they observed reduced fever and viremia, associated with both pathogens. Recently, a related KS-1-vectored RVFV vaccine construct was used, along with the attenuated RVFV Clone 13 vaccine, to validate the use of the inbred mouse strain, MBT/Pas, as a potential small-animal RVFV vaccine model (Ayari-Fakhfakh et al., 2012). Both vaccines induced neutralizing antibodies, stimulated lymphocyte proliferation, and provided protection from virulent RVFV challenge. Protection by Clone 13 was complete, whereas the rKS-1-RVF construct provided 75% protection.

6. Rationale for development of a multivalent capripoxvirus-vectored vaccine

6.1. Advantages of LSDV as a vaccine vector

As described in the previous section, capripoxviruses have been shown to be effective vaccine vectors for use against several ruminant pathogens, with dual or even multivalent vaccine potential. Their ability to express recombinant antigens and induce both cellular and humoral immune responses of long duration, plus their relative thermostability, make them appealing for use as vectors for recombinant veterinary vaccines in the developing world. Yet for livestock farmers in Africa, the prospect of using several such recombinant capripoxvirus vaccines to combat the numerous diseases affecting their herds would not be practical, as cost would remain a significant obstacle. However, the development of a single recombinant capripoxvirus construct expressing several protective immunogens from multiple pathogens could largely overcome this problem. An additional benefit of a multivalent recombinant vaccine is that it would enable differentiation between infected and non-infected, vaccinated animals (DIVA).

6.2. Current efforts and concerns in the development of a multivalent vaccine

Since LSDV has already been shown to be capable of expressing multiple foreign proteins (Poon et al., 2009), the possibility of using the virus as a vector for a single multivalent vaccine against multiple pathogens is theoretically possible, providing several important factors are considered:

6.2.1. The ability to express multiple antigens in high quantities

Previous work has shown that single immunogenic genes inserted within the TK gene of LSDV can be expressed to levels which induce immune responses, but there is little data demonstrating that multiple genes from different viruses would be expressed at the same level. It is therefore imperative that any additional genes targeted for expression also demonstrate sufficient levels of protein production. Although the TK gene has been the traditional site for foreign gene insertion in poxvirus vectors, a number of other sites are available for insertion in LSDV, such as the viral small subunit ribonucleotide reductase gene and at least one intergenic region (e.g. between LSDV ORFs 091 and 092) (Aspden et al., 2002; Cohen et al., 1997).

6.2.2. Increasing the immunogenicity of capripoxviral vectors

One possible way to increase the effectiveness of capripoxviral vectors would be to remove certain putative immunomodulatory genes. A number of immune evasive/suppressive genes have been identified for several poxviruses, including an interferon resistance gene (IFR), IL-10 homologue, dUTPase, GM-CSF inhibitory protein (GM-CSFR) and vesicular EGF homologue (vegf-e) (Rziha et al., 2000). The inactivation of one or a combination of these genes could serve to increase the efficacy of capripoxviral vectors in inducing improved host immune responses to expressed immunogens.

6.2.3. The choice of capripoxviral vector

This review has mainly focused on the use of two vaccine strains of LSDV, the KS-1 and Onderstepoort strains, as recombinant vaccine vector candidates. Both have successfully induced protective immunity in ruminants when expressing protective immunogens from various pathogens (Romero et al., 1993, 1994a,b; Aspden et al., 2002; Diallo et al., 2002; Wallace et al., 2006; Soi et al., 2010). A GTPV strain was recently shown to induce long-lasting and high-levels of neutralizing antibodies to PPRV in goats and sheep (Chen et al., 2010). However, as neither goat nor sheep pox currently occur in southern Africa, and LSDV KS-1 is effective in controlling sheep and goat pox (as well as LSD) in certain African countries, it will be more practical to choose a strain of LSDV as a multivalent vaccine vector for use in Africa – but which one?

The Onderstepoort vaccine strain has been used as an LSD vaccine in South Africa and other countries for over 40 years, and unlike KS-1, it has not induced severe side effects in some cattle breeds (Yeruham et al., 1994). However, there have been concerns in recent years regarding its long-term protective efficacy, promoting annual booster recommendations (Hunter and Wallace, 2001). Recently the efficacy of KS-1 was reported not to confer the expected protection in Ethiopia, with 22% illness and 2% death of vaccinated cattle from LSD (Ayalet et al., 2013). Whether or not the Onderstepoort LSDV strain can prove to be a better vector vaccine candidate than KS-1 is currently being evaluated. Work is also in progress to evaluate the effect on vaccine efficacy of removing putative immunomodulatory genes from both vaccine and field strains of LSDV, using knockout technology.

6.2.4. Optimizing vaccination/challenge conditions in small ruminants

Previous capripoxvirus-vectored vaccine candidates against PPR have been evaluated in livestock using virulent PPRV challenge strains. In contrast, LSDV-vectored recombinant vaccines against RVFV have been evaluated primarily in sheep using mild challenge strains of the virus, thereby leaving unresolved the conditions required for achieving full protection against virulent field strains in small ruminants.

Variables such as vaccine titres, route of delivery (intradermal vs. intramuscular or subcutaneous), as well as the possible use of adjuvants, should also be taken into consideration.

6.2.5. Selection of target antigens

As described in previous sections, capripoxviral vectors have been used to express RVFV glycoproteins, as well as PPRV H- and F-proteins. In the case of the RVFV glycoproteins, the generation of neutralizing antibodies and subsequent protection after challenge (see RVFV section) suggests that the induction of humoral responses associated with these proteins is conserved when they are expressed by a capripoxvirus. The same can be said of PPRV H-proteins (see PPRV section). In the case of the F-protein, the lack of a neutralizing antibody response suggests that its immunogenic properties are cell-mediated. When expressed as multiple components in a capripoxviral vector, one might therefore expect that their immunogenic properties will be retained, but until a single construct expressing both RVFV and PPRV proteins is evaluated in animals, one cannot be certain.

7. Development of a multivalent capripoxvirus-vectored vaccine

This article has discussed the general features, economic impact and current vaccine strategies against LSD, SPP and GTP), RVF and PPR, and described the development of capripoxviruses as vectors for recombinant vaccines to control these diseases. We believe it should be possible to generate a single stable, cost-effective multivalent capripoxvirus-vectored recombinant vaccine for the protection of ruminants against these diseases. The Canadian International Food Security Research Fund (CIFSRF), established by the Canadian government and administered by the International Development Research Centre (IDRC) in collaboration with the Canadian International Development Agency (CIDA), has enabled the establishment of a consortium of researchers with the necessary expertise from the ARC-Onderstepoort Veterinary Institute (ARC-OVI) (South Africa), the Vaccine & Infectious Disease Organization (VIDO) (University of Saskatchewan), the National Centre for Foreign Animal Disease (NCFAD) and the University of Alberta (Canada) to pursue this goal. The aim of this initiative is to develop a multivalent vaccine, comprising an LSDV vector, incorporating the protective antigens of RVFV and PPRV. Other antigens from pathogens such as bluetongue virus could be added to this vaccine in the future.

The first step in developing the LSDV-vectored vaccine is the identification and selection of an optimal LSDV vaccine vector. This will be done by evaluating different LSDV vaccines (Onderstepoort and KS-1) and LSDV gene knock-out constructs (with targeted removal of ORF 005, the IL-10-like gene, or ORF 008, the IFN-γ receptor-like gene, as both gene products having putative host immunomodulatory functions). These constructs will be tested in cattle for safety and efficacy against virulent LSDV challenge at the ARC-OVI. The most promising candidates will be selected for their ability to protect sheep and goats against SPPV and GTP, in testing to be performed in the high-containment facilities at the NCFAD. Following these trials, one vector will be chosen for insertion of the protective antigen genes from RVFV and PPRV. The RVFV glycoprotein genes will first be inserted into the LSDV TK gene under control of the VV p7.5K early-late promoter (Wallace et al., 2007). The PPRV F gene will then be inserted into an intergenic region of the resulting construct, under control of a synthetic early-late poxvirus promoter (Fig. 2). The construct will then be evaluated for RVFV and PPRV antigen expression *in vitro* (ARC-OVI).

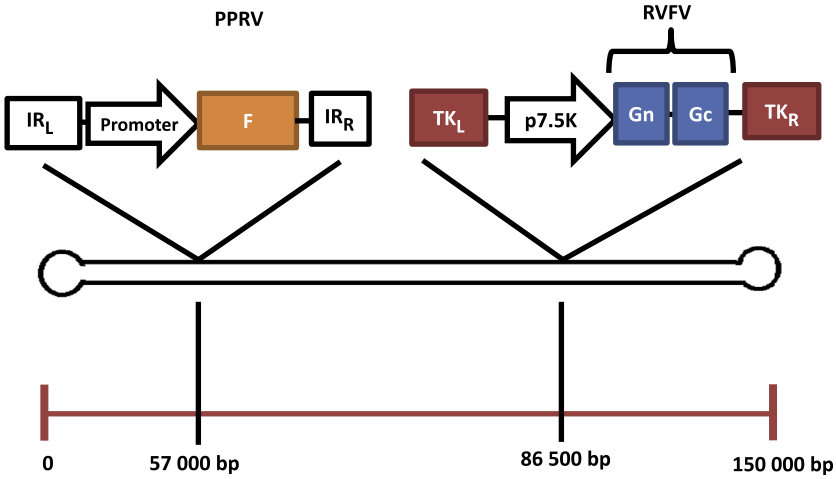

Fig. 2. Proposed insertion sites for both PPRV and RVFV genes in a single capripoxviral vector. The glycoproteins of RVFV have been previously shown to be successfully expressed within a disrupted capripoxvirus thymidine kinase (TK) gene (see section on RVFV), downstream from the VV early-late promoter p7.5K promoter. Other potential candidate insertion sites for the PPRV fusion (F) gene have also been described (see section on rationale) and include at least one intergenic region (IR).

Evaluation of the vaccine construct for efficacy against SPPV, GTPV and PPRV will then be completed at the NCFAD, and against LSDV and RVFV at the ARC-OVI. During the development of the vaccine, veterinary vaccine regulatory authorities and vaccine manufacturers will be consulted for licensing and manufacturing issues, should the experimental results look promising.

If effective, these measures could lay the groundwork for an Africa-wide strategy against small ruminant diseases. The concept of eradicating widespread ruminant diseases is not new. Rinderpest virus, a morbillivirus that affected large ruminants, posed a major threat to livestock for more than 1000 years. Early work, started at the Onderstepoort Veterinary Institute in South Africa by its founder, Sir Arnold Theiler, eventually led to the development of an immunogenic, heat-stable attenuated vaccine, and a concerted worldwide campaign finally led to the eradication of the disease (Roeder, 2011). Currently there are discussions on PPR as the next target for eradication, and the elimination of SPP and GTP is also technically feasible. In contrast, eradicating LSD and RVF will be more problematic, due to insect vectors and wildlife involvement. Since it is difficult to organize and gain political support for eradication campaigns, a new multivalent vaccine may make it possible to convince stakeholders and governments that the economic benefits of eradication are worth the effort, and that if campaign is initiated, it will be more effective to target several diseases simultaneously than to concentrate on one disease at a time. While it is unlikely that even the most optimistic outcome will lead to the complete eradication of these pathogens from Africa, the development of a multivalent vaccine offers a strategy to significantly reduce livestock losses and improve food security for many Africans.

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