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Four-segmented Rift Valley fever virus induces sterile immunity in sheep after a single vaccination

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ABSTRACT

Rift Valley fever virus (RVFV), a mosquito-borne virus in the *Bunyaviridae* family, causes recurrent outbreaks with severe disease in ruminants and occasionally humans. The virus comprises a segmented genome consisting of a small (S), medium (M) and large (L) RNA segment of negative polarity. The M-segment encodes a glycoprotein precursor (GPC) protein that is co-translationally cleaved into Gn and Gc, which are required for virus entry and fusion. Recently we developed a four-segmented RVFV (RVFV-4s) by splitting the M-genome segment, and used this virus to study RVFV genome packaging. Here we evaluated the potential of a RVFV-4s variant lacking the NSs gene (4s-ΔNSs) to induce protective immunity in sheep. Groups of seven lambs were either mock-vaccinated or vaccinated with 10^5 or 10^6 tissue culture infective dose ($TCID_{50}$) of 4s-ΔNSs via the intramuscular (IM) or subcutaneous (SC) route. Three weeks post-vaccination all lambs were challenged with wild-type RVFV. Mock-vaccinated lambs developed high fever and high viremia within 2 days post-challenge and three animals eventually succumbed to the infection. In contrast, none of the 4s-ΔNSs vaccinated animals developed clinical signs during the course of the experiment. Vaccination with 10^5 $TCID_{50}$ via the IM route provided sterile immunity, whereas a 10^6 dose was required to induce sterile immunity via SC vaccination. Protection was strongly correlated with the presence of RVFV neutralizing antibodies. This study shows that 4s-ΔNSs is able to induce sterile immunity in the natural target species after a single vaccination, preferably administrated via the IM route.

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1. Introduction

Rift Valley fever virus (RVFV) is responsible for devastating disease in ruminants and occasionally humans. The virus causes recurrent outbreaks on the African continent, the Arabian Peninsula and several islands off the coast of Southern Africa. During outbreaks, abortion storms as well as high mortality among newborn ruminants are observed frequently. The majority of infected humans display flu-like symptoms whereas a small percentage of individuals develop severe disease, which may result in death. Transmission among ruminants is predominantly mediated by *Aedine* and *Culicine* mosquito vectors. Since these vectors are not confined to RVFV endemic areas there is a significant risk that RVFV will expand its territory in the near future [1–3]. Although humans can also be infected via mosquito bite, the majority of infections are attributed to exposure to infected tissues or body fluids [4].

RVFV is a member of the *Bunyaviridae* family, genus *Phlebovirus*, and comprises a segmented genome consisting of a small (S), medium (M) and large (L) RNA segment of negative polarity [5,6]. The L segment encodes the RNA-dependent RNA polymerase, responsible for transcription and replication of the viral genome. The M-segment encodes a glycoprotein precursor (GPC) protein that is co-translationally cleaved into two major structural glycoproteins; Gn and Gc, which are required for virus–cell attachment and membrane fusion. Additionally, the M-segment encodes a non-structural protein (NSm), with anti-apoptotic function [7,8] and a 78-kDa protein of unknown function that was shown to be incorporated into virions produced by mosquito cells [9]. The S segment encodes a nucleocapsid protein (N) in genomic-sense

Abbreviations: RVFV, Rift Valley fever virus; GPC, glycoprotein precursor; SC, subcutaneously; IM, intramuscular; IV, intravenously; RVFV-4s, four-segmented RVFV; 4s-ΔNSs, four-segmented RVFV lacking the NSs gene; S, small; M, medium; L, large; $TCID_{50}$, tissue culture infective dose 50%; FFU, focus forming unit; N, nucleocapsid protein; NSs, non-structural protein S-segment; NSm, non-structural protein M-segment.

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orientation and a nonstructural protein (NSs) in antigenomic-sense orientation. The N protein protects the viral genomic RNA from degradation and NSs, the major virulence factor of the virus, is involved in antagonizing host innate immune responses [10–14].

In African countries where the virus is endemic, RVFV outbreaks are controlled by vaccination with either inactivated vaccines or with the live-attenuated Smithburn and Clone 13 vaccines [4,15,16]. The formalin-inactivated vaccines offer optimal safety, but require multiple administrations to induce protective immunity, whereas the Smithburn and Clone 13 vaccines are effective with one administration [17,18]. The Smithburn vaccine was created by multiple intracerebral passaging of the virus in mice [19] and the Clone 13 vaccine is a natural RVFV isolate that contains a large (70%) internal deletion in the NSs gene [20]. Importantly, the Smithburn vaccine is not safe in pregnant and young target animals [21,22]. So far no safety concerns have arisen from a limited number of reported studies with Clone 13 in target animals [18,23]. A Clone 13-based vaccine was commercialized in South Africa by Onderstepoort Biological Products in 2010. Since that time, several million doses were applied in the field. However, as far as the authors are aware of, the experiences with application of this vaccine in the field await to be reported.

Currently, alternative live-attenuated viruses are being developed aiming to generate live vaccines with an even higher safety profile. The establishment of RVFV reverse genetics in 2006 has boosted this development [24]. In 2011, we developed intrinsically safe RVFV replicon particles which are highly effective in inducing a protective immune response [25,26]. However, large scale application of this nonspreading RVFV (NSR) in livestock requires optimization of the production process. More recently, as part of a study on RVFV genome packaging, we developed a novel live-attenuated RVFV. This virus, referred to as four-segmented RVFV (RVFV-4s), was found to be highly immunogenic in mice [27]. RVFV-4s was constructed by splitting the wild-type M-genome segment into two M-type genome segments encoding either the Gn or Gc protein.

Here, we evaluated the potential of a RVFV-4s variant lacking the NSs gene (4s-ΔNSs) to induce protective immunity in sheep,

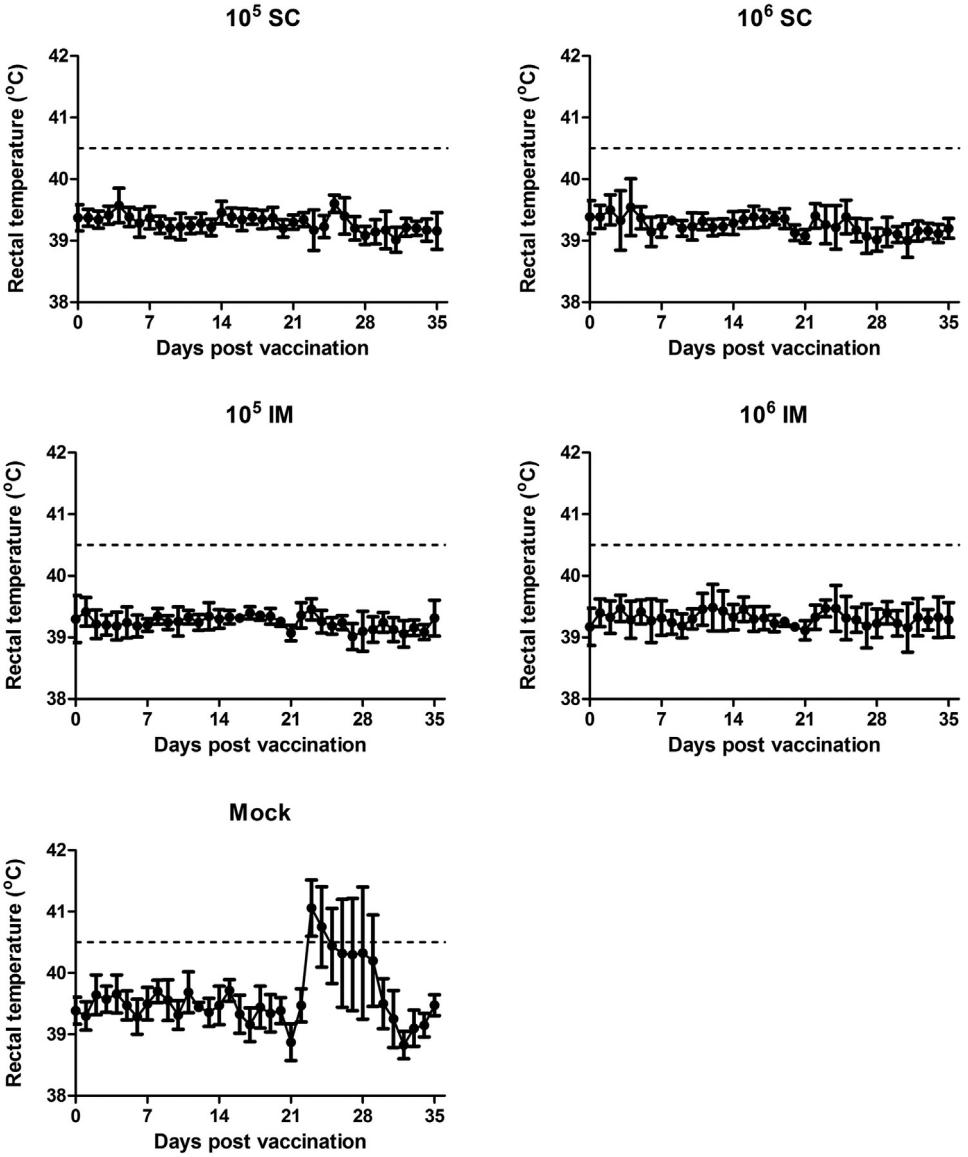

Fig. 1. Rectal temperatures of vaccinated and mock-vaccinated lambs. Rectal body temperatures (°C) were determined daily during the experimental period. Fever was defined as a body temperature above 40.5 °C (dashed line). Data are depicted as averages ($n = 7$) with standard deviation. Rectal body temperatures of mock-vaccinated lambs determined 23, 24 and 27 days post-vaccination are depicted as averages of 6, 5 and 4 measurements, respectively, since a lamb from this group died on each of these days.

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