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Review

Rift Valley fever virus: A review of diagnosis and vaccination, and implications for emergence in Europe

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ABSTRACT

Rift Valley fever virus (RVFV) is a mosquito-borne virus, and is the causative agent of Rift Valley fever (RVF), a zoonotic disease characterised by an increased incidence of abortion or foetal malformation in ruminants. Infection in humans can also lead to clinical manifestations that in severe cases cause encephalitis or haemorrhagic fever. The virus is endemic throughout much of the African continent. However, the emergence of RVF in the Middle East, northern Egypt and the Comoros Archipelago has highlighted that the geographical range of RVFV may be increasing, and has led to the concern that an incursion into Europe may occur. At present, there is a limited range of veterinary vaccines available for use in endemic areas, and there is no licensed human vaccine. In this review, the methods available for diagnosis of RVFV infection, the current status of vaccine development and possible implications for RVFV emergence in Europe, are discussed.

1. Introduction

Rift Valley fever virus (RVFV) is a mosquito-borne virus of the genus *Phlebovirus*, family *Bunyaviridae* [1]. The RVFV genome is composed of three segments of single-stranded RNA, referred to as large (L), medium (M) and small (S) [2]. The bunyavirus ribonucleoproteins corresponding to each genomic segment appear circular when observed by electron microscopy [3], although a simplified schematic detailing the individual genome segments and gene order is shown in Fig. 1. The L segment encodes the viral RNA-dependent RNA polymerase (L protein) [4]. The S segment encodes the nucleoprotein (N) and the non-structural NSs protein, which is a major determinant of virulence [5,6]. The M segment encodes at least four proteins: the structural glycoproteins Gn and Gc, the non-structural protein Nsm, and a large 78-kDa glycoprotein (LGp) [7]. The structural glycoproteins mediate binding and entry via receptors on the target cell membrane. The function of the 78-kDa glycoprotein is unclear, although it is thought to be incorporated into virions matured in mosquito cells, where it may facilitate transition between different host species, and function during replication in the mosquito host [8]. However, due to its ability to form a complex with the Gc glycoprotein [9], the 78-kDa glycoprotein may constitute a target for the immune system, and could potentially contribute to novel vaccine development'. Additionally, the virus does not encode a matrix protein so the surface glycoproteins interact directly with the ribonucleoprotein [9].

RVFV is the causative agent of Rift Valley fever (RVF), a zoonotic disease affecting both ruminants and humans. In ruminants, RVF is characterised by neonatal mortality and an increased incidence of abortion or foetal malformation [2,10,11]. Sheep are the species of domestic animal most susceptible to RVFV infection, and new-born lambs in particular [10,11]. Mortality rate is significantly influenced by the age of the animal; newborn lambs are highly susceptible, with a mortality rate of greater than 90% in lambs less than a week old, associated with acute necrotic hepatitis [9,12,13]. However, the mortality rate in adult ruminants is generally lower, at 10–30% [14]. The abortion rate can range between 40 and 100% [13] (Fig. 2).

In comparison to the course of disease observed in animals, pregnant woman and neonatal infants are not preferentially affected [15]. Human infection with RVFV is generally asymptomatic, and the majority of those with clinical symptoms present with a short febrile illness and no long term sequelae [16]. In some cases, fever recurs with headaches for up to 10 days followed by two weeks of weakness before recovery [17]. However, a small

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0264-410X/

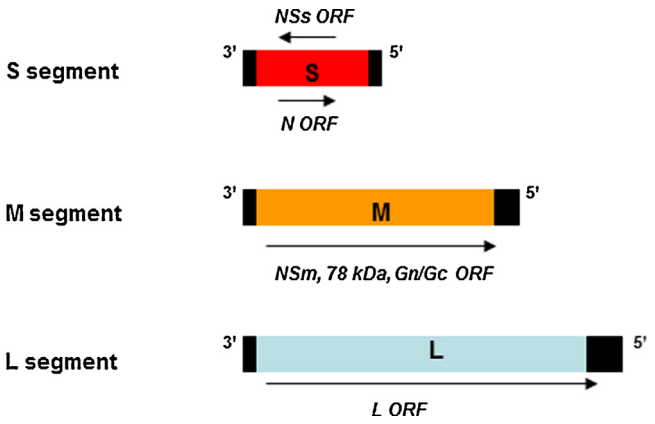

Fig. 1. Schematic representation of the segmented RNA genome of RVFV, detailing the small (S), medium (M) and large (L) segments in linear representation, adapted from [47]. The black shaded areas of this schematic diagram, denoted at the 3′ and 5′ end of each segment, represent terminal sequences that are complementary to each other, forming panhandle structures that give rise to a circular appearance when observed using electron microscopy [15].

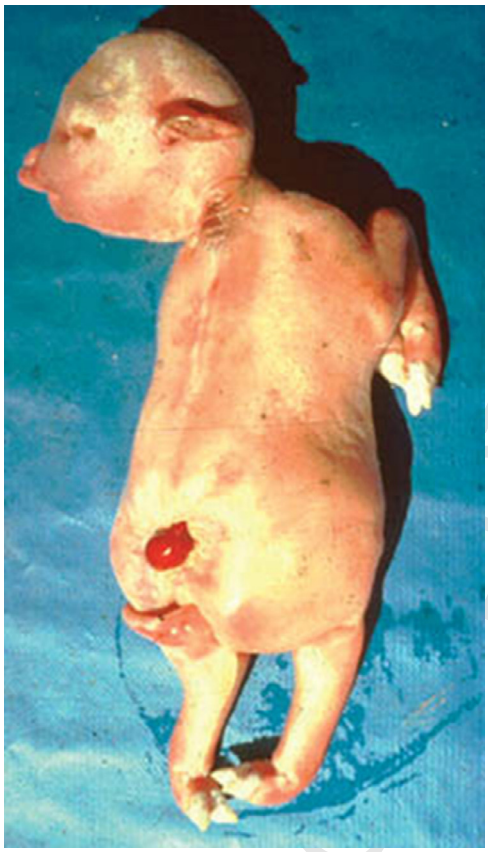

Fig. 2. Aborted sheep foetus. Picture courtesy of Professor Coetzer, University of Pretoria, South Africa, made available through the Food and Agriculture Organization (FAO) Corporate Document Repository (http://www.fao.org/docrep/006/y4611e/y4611e05.htm) [accessed on 12th June 2015].

minority develop severe RVF disease, exhibiting early symptoms of acute hepatitis with associated, jaundice, renal failure and haemorrhagic complications [18,19]. Haemorrhagic manifestations may include macular rash across the trunk of the body, ecchymosis on limbs and eyelids, bleeding from the gums and gastrointestinal mucosal membranes, low blood pressure, hematemesis, melaena and hepatosplenomegaly [20,21]. If the patient survives the hepatitis, neurological manifestations may include loss of vision and signs of encephalitis [16]. The risk of fatality increases for patients with jaundice, encephalitis or haemorrhagic disease, with a fatality rate of 1–3%, which can be as high as 50% in patients with haemorrhagic complications [16]. Long-term sequelae are observed in a small number of patients, where neurological disorders resulting from encephalitis may lead to blindness, hemiparesis, quadraparesis, incontinence, hallucinations, locked-in syndrome or coma [22–24]. The transmission cycles of RVFV are summarised in Fig. 3.

Animals become infected through a bite from an infected mosquito, and there are a number of mosquito vectors that have been shown to be naturally infected with RVFV, predominantly of the *Culex* and *Aedes* genera (reviewed in [25]). In addition, there can also be animal-to-animal infection through direct contact with infected tissues or fluids [15], and animals may also become infected through the re-use of needles during vaccination; particularly in regions with limited resources [26]. There may also be the potential for lactating animals to infect their young via milk [27–29]. Human infection can also arise from a mosquito bite [30]. However, humans can also become infected through exposure to infected animals or animal tissues, since infected animals, and sheep in particular, can display high titre viraemia [31]. Following infection with RVFV, both the innate and adaptive immune responses are important for virus clearance [14,32]. Along with an innate immune response, natural infection with RVFV in domestic ruminants leads to the development of a neutralising antibody response, elicited by the viral glycoproteins (Gn and Gc) and the nucleocapsid protein [33–35].

The disease was first reported in 1930, as a result of investigations into a high abortion rate amongst pregnant ewes accompanied by a high mortality rate of newborn lambs, on a farm in the Rift Valley region of Kenya, and the causative agent identified as a virus [10]. Many of the people who had come into contact with infected animals and tissues developed illness characterized by fever, headaches and malaise; one individual developed a second fever accompanied by headaches, and retained defective vision for a number of weeks afterwards. Subsequently, periodic outbreaks occurred in Kenya and other east African countries including Tanzania and Zambia [36,37], until RVFV was identified in South Africa in 1951 [38]. The disease is now considered to be endemic in sub-Saharan African countries, with periodic major outbreaks occurring throughout much of the African continent, associated with episodes of heavy rainfall and flooding [39] (Fig. 4). Over the past forty years, RVFV has been detected in African countries outside its traditional enzootic region, including Egypt in 1977 [40], and the West African countries Mauritania and Senegal in 1987 [41,42]. A further outbreak occurred in Mauritania in 2010 [43]. In 1990, an outbreak of RVF was confirmed outside of mainland Africa for the first time, on the Indian Ocean island of Madagascar [44]. In 2000, RVFV was also detected in Saudi Arabia and Yemen [14,45], and by 2007 its geographical range included the French island of Mayotte in the Comoros Archipelago [46]. Likely explanations for the detection of epizootics outside the usual RVFV enzootic regions are the commercial movement of infected animals and possibly windborne movement of infected mosquitoes [47]. The emergence of RVF in the Middle East and Mayotte has highlighted that RVFV may be increasing its geographical range, giving rise to the concern that it may potentially reach the Mediterranean basin, and a gateway into Europe. Outbreaks of RVFV cause a significant disease burden, with large numbers of livestock and humans affected. The outbreak in Saudi Arabia in 2000 resulted in the death of an estimated 40,000 animals from a range of species, with 8000–10,000 abortions in ruminants [48]. Therefore, an incursion of this zoonotic virus into Europe could potentially have a devastating impact on the livestock industry in multiple countries, along with a significant impact on animal and human health. The current status of diagnosis and vaccine development for RVFV infection are reviewed, and the factors

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