Relevance of Rift Valley fever to public health in the European Union

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Abstract

Rift Valley fever (RVF), a vector-borne zoonotic disease caused by a phlebovirus (family Bunyaviridae), is considered to be one of the most important viral zoonoses in Africa. It is also a potential bioterrorism agent. Transmitted by mosquitoes or by direct contact with viraemic products, RVF affects both livestock and humans, causing abortion storms in pregnant ruminants and sudden death in newborns. The disease provokes flu syndrome in most human cases, but also severe encephalitic or haemorrhagic forms and death. There is neither a treatment nor a vaccine for humans. The disease, historically confined to the African continent, recently spread to the Arabian Peninsula and Indian Ocean. Animal movements, legal or illegal, strongly contribute to viral spread, threatening the Mediterranean basin and Europe, where competent vectors are present. Given the unpredictability of virus introduction and uncertainties about RVF epidemiology, there is an urgent need to fill the scientific gaps by developing large regional research programmes, to build predictive models, and to implement early warning systems and surveillance designs adapted to northern African and European countries.

Keywords: Europe, public health, Rift Valley fever, risk, surveillance, trade

Rift Valley fever (RVF) is a vector-borne zoonotic disease caused by a phlebovirus (family Bunyaviridae). RVF virus (RVFV) is an enveloped RNA virus characterized by a genome composed of three segments, designated L, M, and S, of negative or ambisense polarity [1]. Like many bunyaviruses, RVFV produces a non-structural protein encoded by the S segment, the NSs protein, which acts as a virulence factor [2]. It is transmitted from ruminants to ruminants by mosquito bites, mainly from the genera Aedes and Culex, but also from the genera Anopheles and Mansonia, as recently suggested in Madagascar and Kenya [3,4]. Direct transmission between ruminants through contact with viraemic fluids, i.e. blood or fetal liquid, is also strongly suspected. Humans are mostly contaminated after contact with aborted fetal material, i.e. placental membranes from infected ruminants, which contain large numbers of virus particles and blood. Furthermore, RVFV was observed or experimentally demonstrated to persist for long periods in different biotic or abiotic settings: a laboratory assistant was infected in a laboratory 4 months after the virus was handled in this laboratory; the virus may be isolated from carcase tissues such as spleen or liver between 36 and 72 h after death; and infected sheep plasma retained RVFV infectivity after 8 years of storage and shipment under a variety of refrigeration conditions [5–8]. Consequently, veterinarians and laboratory, agricultural and slaughterhouse workers may be at risk. If it exists, the viral load in raw milk is assumed to be low. The presence of virus in nasal and lachrymal secretions and the urine and faeces of infected animals has not been demonstrated [1,9]. To date, no human-to-human transmission of RVF has been documented.

The health and economic consequences of RVF outbreaks are severe. Besides losses resulting from animal trade control, RVFV infection causes abortion storms in pregnant ruminants and acute deaths in newborns. However, the severity of clinical signs depends on the species: sheep are more susceptible than goats, which are themselves more susceptible than cattle and camels. In adults, one may observe non-specific signs such as vomiting, diarrhoea, respiratory disease, fever, lethargy, and anorexia [10]. Although, in the majority of human cases, RVFV causes a mild illness with fever, headache, myalgia, and liver abnormalities, a minority of human cases of infection may lead to either retinitis with permanent vision loss, encephalitis, or...
haemorrhagic forms that may lead to death [11]. During the 2000 Saudi Arabia outbreak, the major clinical characteristics reported among 165 consecutive patients included a high frequency (75%) of hepatocellular failure, acute renal failure for 42% of patients, and haemorrhagic manifestations for approximately 19% of patients. A total of 56 patients died (33.9%) [12]. There is no aetiological treatment, for either animals or humans. Several vaccines are under development, but, to date, there are no licensed and commercially available vaccines to protect humans [13]. Regarding ruminants, the ‘Smithburn’ vaccine, a live attenuated vaccine, has been used for years in Africa. It cheaply and efficiently protects sheep and cattle with a single inoculation, but it may cause abortion or teratogenic effects in fetuses, and may present a risk of reversion to virulence: its use is thus reduced to endemic areas. A new, promising live attenuated vaccine candidate—clone 13—was obtained from a strain isolated from a mild human case in the Central African Republic [14,15]. This vaccine was recently registered and marketed in South Africa [16]. Owing to its severity, RVFV is considered to be a major zoonotic threat to the USA, and is number 3 on the list of the 17 most dangerous animal threats, behind highly pathogenic avian influenza and food and mouth disease [17].

Early detection and implementation of appropriate measures, which are essential to minimize the consequences of outbreaks, require a deep understanding of transmission, spread and persistence mechanisms. However, the epidemiology of RVF is complex. The disease is enzootic in many African countries and Madagascar, with outbreaks occurring every 5–15 years. However, the factors triggering outbreaks and the way in which the virus persists during inter-epizootic periods remain mostly unknown. RVF has been reported in four epidemiological systems:

1. ‘Dambo’ areas, in East Africa. Dambos are shallow depressions that can be 1 km in length and several hundreds of metres in width, and are often located in valleys near rivers. In these areas, a correlation between heavy rainfall events and RVF outbreak occurrence has been clearly demonstrated. Viral transmission from one *Aedes mcintoshi* mosquito generation to another by ‘vertical transmission’, and the survival of infected eggs in dry mud for several years, could explain the maintenance of the virus in the field during inter-epizootic periods [18,19].

2. Semi-arid areas of western Africa—Senegal and Mauritania—characterized by temporary areas of water. In these areas, a recent modelling study showed that outbreaks could not be directly related to heavy rainfall events, but mostly to abundant regular rainfall occurring throughout the rainy season, which is favourable for successive high density of the main vectors, i.e. *Aedes vexans* and *Culex poicilipes* [20]. The persistence of the virus may result from either the above-mentioned vertical transmission in *A. vexans* mosquitoes or from the regular introduction of the virus by nomadic herds [21].

3. Irrigated areas such as the Nile Delta or Senegal river basin, where permanent water may favour *Culex* population persistence, and thus RVFV transmission throughout the year [22–24].

4. Temperate and mountainous areas, as recently demonstrated in Madagascar, where transmission and spread result from local vector-borne transmission associated with specific cattle trade habits [25,26].

A role of wild ruminants, which is strongly suspected in southern Africa, needs further investigation [27].

RVFV was historically confined to the African continent until 2000, when it was reported for the first time in the Arabian Peninsula [28]; the geographical distribution of the virus has recently increased. Global changes, including climatic changes, may be involved. However, the natural history of RVF shows that animal movements, legal or illegal, have strongly contributed to the spread of the virus [29–31]. Infected mosquitoes, travelling in aircraft or cargo, could also be incriminated [32]. Unprecedented increases in the international trade and worldwide movements of humans, animals and animal products are thus likely to alter the epidemiological patterns of RVF. In fact, there is a large livestock trade between the sub-Saharan countries where the virus is circulating and northern African countries. The 2010 and 2012 Mauritanian outbreaks [33,34], associated with the recent detection of serologically positive camels in Morocco coming from the southern part of the Saharan desert in a north-western direction [35], demonstrated RVFV in northern Africa. Because of the illegal importation of ruminants and the short geographical distance between southern European coasts and northern Africa, the exposure of the Mediterranean basin and Europe to RVFV has increased. According to the European Food Safety Authority, the virus could be introduced by either legally or illegally imported infected animals, infected vectors, legally or illegally imported contaminated animal products, fomites, or vaccines; the first of these is the most plausible [36]. Even if this probability is considered to be very low, because trading in livestock from northern Africa and the Middle East to Europe is forbidden, this introduction into an area of a dense and naive ruminant population may be devastating [37]. Conversely, and because the virus can circulate with few or even no clinical signs, it could remain undetected and settle in endemic foci in areas where eco-climatic conditions are favourable. In fact, 50 mosquito species may transmit the virus, and some of them are
present in Europe [36,37]. Among them, Culex pipiens, whose European distribution is wide, is competent to transmit RVFV [38]. The distribution of Aedes albopictus, which is another potential vector of RVFV, has dramatically enlarged since its first introduction [39,40]. Established homogeneous populations have been identified in Albania, Croatia, France, Greece, Monaco, Montenegro, Italy, San Marino, Slovenia, and Spain [41]. The changing European climate could facilitate this spread to new areas [42], enlarging the distribution of areas suitable for RVFV transmission.

RVF should be suspected when a sudden abortion storm or sudden deaths of ruminants are associated or not with febrile syndrome in humans. Depending on the epidemiological status of the area, and the delay post-infection, diagnosis may be performed either by detection of live virus, viral antigen or viral nucleic acids within 1–10 days after the onset of the disease, or by detection of acute-phase (IgM) or chronic (IgG) antibodies, starting from 4 days post-infection [1]. Among recently validated tests, a sandwich ELISA for antigen detection (sAg-ELISA) was recently reported [43], having, respectively, 67.7% and 70% sensitivity for humans and sheep, and 97.9% and 100% specificity, and real-time reverse transcriptase isothermal amplification assays (RT-LAMP) have been developed and tested, allowing the detection of a wide spectrum of isolates and in clinical specimens in 30 min [44]. Inhibition ELISA tests for detecting IgG in all species, capture ELISA for IgM for bovines, caprines and ovines and sandwich ELISA for IgG for the same species are commercially available. Finally, the virus neutralization test, which is considered to be the reference standard, is highly accurate, with no or few cross-reactions with other phleboviruses [45,46]. However, this methodology requires live virus, and thus can be used only in biosafety level 3 laboratories [1].

Several control options are available, such as vaccines in animals, larvicides in vector breeding sites and/or insecticide spraying, animal trade control, and the provision of information to exposed human populations. However, the disease is usually well established in animal populations by the time when the first human cases are observed [13]: in endemic areas, animal vaccination is probably the best way to protect human health.

Regarding surveillance and virus-free areas, the use of a dense sentinel herd network for surveillance would be cost-prohibitive unless strictly focused on ecologically defined risky areas. Syndromic surveillance relies on the early detection of abnormal clusters of illness indicators rather than clinical signs, and thus reduces the time-lag between the onset of the outbreak and the diagnosis [47,48]. This methodology may be a useful alternative in the case of RVF, which may provoke non-specific signs, in either animals or humans: RVF human cases were detected in 2009 in Mayotte thanks to the surveillance for dengue-like syndromes [49].

In the Horn of Africa, RVF outbreaks can successfully be predicted with lead times of 2–4 months, thanks to remotely sensed data-driven models [50]. This early warning system is based on accurate knowledge of the disease epidemiology. As far as Europe is concerned, there is an urgent need to fill scientific gaps, i.e. to experimentally evaluate European potential vector competence and European ruminant breed susceptibility, and to assess the existence of ruminant to ruminant direct transmission. For implementation of a risk-based surveillance network, European areas that are potentially suitable for virus transmission need to be identified [51]: given the current lack of knowledge, the multi-criteria decision analysis method could be a valuable tool allowing the integration of expert knowledge, the available literature and data with trade—legal or illegal—information [52]. Furthermore, the epidemiological situation in northern African countries, and the risk of introduction via either animal movements or infected vector ‘travel’, should be assessed, as well as the performance of both existing northern African and European surveillance systems. In fact, a ‘one-health’ regional approach and a joint effort by human and animal health authorities is needed to control RVF in endemic countries and protect virus-free areas from introduction of the virus.

Transparency Declaration

The author declares having no conflict of interest related to the present article.

References


