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Rift Valley Fever Virus: A Real Bioterror Threat

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Abstract

Rift Valley fever virus is recognized as an important bioterror and agroterror threat to Western countries including the United States. Once introduced, the virus would be readily spread by native mosquito populations and potentially become endemic. While infection often results in severe morbidity and mortality in both humans and livestock, there are currently no FDA or USDA-licensed vaccines. The development of effective countermeasures and implementing surveillance and diagnostic capabilities are critical. Ultimately, the presence of RVFV would lead to severe long-term negative impacts for healthcare, agricultural and travel economic sectors.

Introduction

Rift Valley fever virus (RVFV) is a zoonotic arthropod-borne pathogen that often results in severe morbidity and mortality in both humans and livestock. The lack of prophylactic and therapeutic measures, the potential for human-to-human transmission, and the significant threat to livestock associated with RVFV make this pathogen a serious bioterror threat.

RVFV can be propagated easily and efficiently with simple cell culture systems *in vitro* [1]. The potential to use RVFV as a bioweapon is further enhanced by the ability to manipulate the virus through either rational genetic approaches or through various passaging schemes to produce altered agents that could escape detection and/or existing prevention and control methods [1]. As such, RVF virus is considered a potential threat as a biological weapon [2] that could have dramatic direct (morbidity and death) and indirect (international trade restrictions) impact in countries that are currently free of the virus. Because of its clear disease potential, aerosolized RVFV could be used as a bioterror or agroterror weapon to threaten humans and ruminants and devastate the economy [3]. Importantly, unlike other potential bioterror agents (i.e., Crimean-Congo hemorrhagic fever virus, Nipah virus and Ebolavirus), the vectors for RVFV transmission are present in the Western hemisphere.

Background

New highly fatal diseases have emerged or reappeared during the last 4 decades such as severe acute respiratory syndrome (SARS) [4-5], *Legionella* [6], hantavirus pulmonary syndrome (Sin Nombre virus) [7], Nipah virus encephalitis [8-9], avian influenza [10-11], West Nile encephalitis [12-13] and Rift Valley fever with adverse global or regional public health and economic impact [14]. Most emerging infectious diseases are the result of epizoonotic transmission from animals to man [15-16]. RVFV presents one of the most important non-endemic bioterror threats to the Western hemisphere. RVFV was first identified in 1931 as the causative agent of enzootic hepatitis of sheep in Kenya [17] and has since then spread across most of the African continent and more recently emerged on the Arabian peninsula [18-19]. RVF manifests itself in the vast majority of individuals (90% show clinical signs of disease) that become infected, unlike a WNV infection, which has no clinical manifestation in 80% of infected individuals. Historically, while infections in humans are typically mild and present as self-limiting febrile illnesses, RVFV infections progress to more severe disease including fulminant hepatitis, encephalitis, retinitis, blindness, or a hemorrhagic syndrome in approximately 2% of affected individuals [20-21]. However, statistics from recent outbreaks suggest that the case fatality rate from RVFV infections is significantly increasing (>30%) in naive populations [1, 14, 22-23]. For example, during the 2006-2007 Rift Valley fever outbreak in East Africa, RVF was diagnosed in over 1000 patients in multiple locations in Kenya, Somalia and Tanzania [24-27] and over 300 patients died [28]. As recently as 2010, there was a RVFV outbreak in South Africa with at least 237 human cases reported including twenty-six deaths [29-30] http://www.nicd.ac.za/outbreaks/rvf/docs/RVF_Interim_Report_2010_10_01.pdf .

There are similarities between the public's awareness of RVFV and its perception of the West Nile virus (WNV) threat before 1999. WNV was not considered a threat to the USA prior to its emergence in New York in 1999 [31]. However, within six years, WNV had become endemic across the USA [13]. Interestingly, while the WNV transmission route is limited to two mosquito genera [32] (*Aedes and Culex*) and has a limited effective host range, RVFV is readily transmitted through a broad range of mosquito genera including *Aedes, Anopheles, Culex*, *Eretmapoites* and *Mansonia*, and by other vectors including sand flies [33]. Importantly, RVFV has a much broader effective host-range compared to WNV, capable of causing severe disease in sheep, goat, cattle, water buffalo, and humans. Recent studies have illustrated the ability of RVFV to utilize the dominant mosquito species of a given geographical location [34-37], which indicates that there is no natural blockade to protect naive countries from the spread of the virus. This presents a real threat for RVFV incursions into other parts of the world, including Europe [34] and the United States [38]. However, differences in RVFV transmission rates can be affected by local mosquito populations [39].

Human RVFV infections are usually preceded by transmission from wild to domestic animal hosts, recognized by sudden and devastating impact on livestock [20, 40-41]. In sheep, mortality in lambs under 2 weeks of age approaches 100%, reaches 30% in older animals and abortions approach 100%. Cattle also show high abortion rates (up to 100%) with adult mortality averaging 10% [21, 42].

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Because of the potential for severe consequences during such outbreaks, RVFV is considered a major zoonotic threat to the US. Homeland Security Presidential Directive/HSPD-9 established a national policy to defend the agriculture and food system against terrorist attacks, major disasters, and other emergencies (http://merln.ndu.edu/archivepdf/hls/WH/20040203-2.pdf), including the establishment of a National Veterinary Stockpile (NVS). RVFV is #3 on the list of the 17 most dangerous animal threats, behind only highly pathogenic avian Influenza and Food and mouth disease (http://www.aphis.usda.gov/vs/ep/functions.html). RVFV is classified as an Overlap Select Agent by the Department of Health and Human Services (HHS), US Department of Agriculture (USDA) [43-44] and as a high-consequence pathogen with the potential for international spread by the World Organization for Animal Health (Office International des Épizooties) [45]. RVFV is also classified as a Category A High Priority Pathogen by the National Institute for Allergy and Infectious Diseases (NIAID) (http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/research/CatA.htm) and is on the Center for Disease Control (CDC) Bioterror Agent list (http://www.bt.cdc.gov/agent/agentlist-category.asp#a)[44]. As described previously [46], RVFV is clearly recognized as a biothreat by The US Commission on the Prevention of Weapons of Mass Destruction (WMD) Proliferation and Terrorism [47] and several risk assessment studies have illustrated the potential spread of RVFV once introduced into Europe or the USA [48-52] (http://ppmq.ars.usda.gov/research/publications/Publications.htm?seq_no_115=235466&pf=1) (http://nabc.ksu.edu/assets/uploads/rift_valley_report.pdf). RVFV working groups have produced scientific opinions, threat assessments and recommended action plans (surveillance, diagnostics, vector control), for the management of RVFV including the European Food Safety Authority (EFSA) [48], the Animal and Plant Health Inspection Service (APHIS) Centers for Epidemiology and Animal Health multi-agency and university working group on RVFV (reviewed in Kasari *et al* [49], the USDA's Agricultural Research Service's (ARS) Arthropod-Borne Animal Diseases Research Laboratory (ABADRL) in collaboration with ARS, Center for Medical, and Veterinary Entomology and the USDA, APHIS.

(http://ppmq.ars.usda.gov/research/publications/Publications.htm?seq_no_115=235466&pf=1), the Global Disease Detection Division at CDC-Kenya along with the Regional Emergency Office for Africa (REOA) Food and Agriculture Organization (FAO) and the Global Emerging Infections Surveillance Systems office of the U.S. Army Medical Research Unit in Nairobi, in collaboration with the Kenya Ministries of Health and of Livestock (reviewed in [14]) and ARBO-ZOONET [53], reviewed in Korketaas et al [23]. Taken together, these works strongly conclude that RVFV is a real threat and it is only a matter of when – not if – RVFV is intentionally or accidentally introduced into the Western hemisphere.

Surveillance and diagnosis

The capacity for surveillance, handling large numbers of samples and diagnostics is extremely limited in the US and other Western nations should RVFV be introduced/emerge, with a low probability of early detection and response with control measures. Physicians and veterinarians are unaccustomed to the clinical signs of RVFV which will likely delay a positive diagnosis. The ability to handle human and animal samples and specimens is problematic because RVFV must be handled under high containment, and a very limited number of such facilities are available.

In endemic areas, RVFV infection is most often diagnosed using a combination of clinical judgment (recognition of acute hemorrhagic fever cases) and available diagnostic testing [54]. Newer, multiplexed PCR and reverse-transcription (RT)-PCR enzyme hybridization assays are being developed that can simultaneously detect multiple pathogens, including many hemorrhagic fever viruses [55-56], and should be used in conjunction with ELISA-based [57] methodologies. A focus on practical field deployable diagnostics is critical since RVF outbreaks occur most commonly in remote locations. Importantly, the real-time RT-loop-mediated isothermal amplification (RT-LAMP) assay for RVFV presents a similar sensitivity and specificity as real-time PCR, but is a single-step reaction that is faster and less expensive, and can be assessed with the unaided eye [58-59].

Vaccines

Public health and animal health agencies agree that it is now a priority to develop RVFV countermeasures (whether for humans, animals, or both: the "One Health" initiative [60]) that will yield highly effective, long-term protective immunity [1, 54]. The ideal RVF vaccine would confer protection after a single dose, be nonpathogenic with no potential for reversion to wild-type virus, be safe for production in standard vaccine facilities, and present long-term stability at ambient temperatures. The development of safe and efficacious RVFV vaccines has proven to be quite difficult (summarized in Bouloy and Flick 2009 [1] and Bird et al. 2009 [21] and references therein). Unfortunately, there is currently no licensed vaccine available for human use in the USA or Europe.

In addition, because of the animal-trade embargoes imposed during RVF epizootics, the design of commercial livestock vaccines should allow for the differentiation of naturally infected and vaccinated animals (DIVA) [1, 61]. A vaccine to prevent the amplification cycle of RVFV in livestock would greatly reduce the risk of human infection by preventing livestock epizootics. The partially attenuated Smithburn modified live virus vaccine was developed for livestock applications, but it can lead to abortions or teratology in pregnant animals. In addition, the risk of reversion to full virulence precludes its use in countries where RVFV is not known to be endemic. A formalin-inactivated version of this vaccine is available, but increased production costs combined with the need of multiple inoculations to protect animals present critical disadvantages in outbreak situations [46]. A formalin-inactivated RVFV vaccine, TSI-GSD-200, has limited availability in the US for protection of military personnel and laboratory workers. As with most inactivated antiviral vaccines, several inoculations (including annual boosters) are needed to maintain immunity. In addition, this vaccine is in short supply and expensive.

While live attenuated and genetically engineered RVFV strains are highly immunogenic and do not require boosting, they do present safety concerns regarding reversion to virulence [1, 62]. MP12 is efficacious in livestock and was recently tested in human clinical trials with promising results [63]. However, one study showed that abortion (4%) and teratogenic effects (14%) occurred in pregnant sheep [64], and since MP12 attenuation is based on several single point mutations, concerns about reversion are valid. Clone 13, a natural RVFV isolate [65-66], a MP12/Clone 13 reassortant, R566 (M. Bouloy *et al.*, unpublished data) and a ΔNSs/ΔNSm ZH501 strain are being developed that have excellent preclinical safety profiles [67]. These vaccine candidates have NSs or both NSs/NSm gene partial or complete deletions which prevent the virus from hijacking the type 1 IFN pathway, make reversion almost impossible, and satisfy the DIVA concept. Other approaches include expression of RVFV glycoproteins by recombinant Lumpy skin disease

virus (LSDV) and adenovirus-based platforms and alphavirus replicon vectors [1, 21].

Recent RVFV vaccine developments focus on virus-like particle (VLP)-based platforms which avoid issues associated with live-attenuated vaccines. Expression of structural proteins of many non-enveloped and enveloped viruses leads to the formation of VLPs [68] and references therein). Structural similarity with the wild type virus combined with the lack of viral genetic material makes this vaccine platform ideal to generate safe vaccine candidates [68-69]. Efficient generation of RVF VLPs has been demonstrated by several groups using either mammalian cell or insect cell derived systems. Promising immunological data (e.g., high neutralizing antibody titers) and full protection in mice and rat challenge studies were achieved, demonstrating that VLP-based RVFV vaccine candidates are a promising RVFV vaccine approach [1, 70-73].

Alternatively, DNA-based (virus-free) vaccines such as gene-gun immunizations with cDNA encoding RVFV structural proteins have been shown to induce neutralizing antibody titers in mice, but some immunized animals still developed clinical signs of infection after sublethal challenge [74].

Th rapeutics

For treatment of symptomatic RVF, no highly effective RVFV-specific therapeutics currently exist [1]. However, beyond supportive care, there is hope that viable antiviral therapeutic options will emerge. With the exception of ribavirin as an approved drug, few compounds are licensed as approved antiviral drugs for the hemorrhagic fever viruses [75]. Furthermore, the effectiveness of ribavirin is limited due to side effect complications and lack of specificity [1, 76-78]. The aryl-methyldiene rhodanine derivative LJ001 prevents virus–cell fusion and has broad-spectrum activity against enveloped viruses such as RVFV, and might provide utility as a therapeutic [79]. Potential broad-spectrum therapeutic activity has also been suggested for bavituximab which targets phosphatidylserine on enveloped viruses and virus-infected cells [80]. Pyrazinecarboxamide compounds have also been shown to be useful for post exposure antiviral therapy as broad spectrum antiviral inhibitors [81-83].

Outbreak prediction and control

RVF presents an informative model for assessing the impact of climate and ecology on its periodic reemergence and spread, as well as for the potential that modern technologies and public health advancements can contribute to disease forecasting, prevention, and control [28]. While important risk assessment and surveillance strategies for RVFV in Western countries that rely on statistical tools including landscape epidemiology and phylogeography have been suggested [84], to date no plans have been officially implemented. As described in Breiman et al. 2010, RVF is a disease associated with a complex set of factors that make disease outbreaks likely including animals, mosquitoes, climate, ecology, and commercial trade [14]. Its prevention and control is not straightforward. Livestock trade practices has moved the virus long distances [19, 85] (potentially including the movement of infected mosquitoes), creating the potential for disease in regions without previous exposure to the virus [14]. Landscape attributes influence spatial variations in disease risk or incidence. As described by Lambin et al. 2010, integrated analyses at the landscape scale allows a better understanding of interactions between changes in ecosystems and climate, land use and human behavior, and the ecology of vectors and animal hosts of infectious agents [86]. As noted in LaBeaud et al. 2010 [54], because RVFV outbreaks generally follow anomalous heavy rainfall in endemic areas [87-89], meteorological forecasting of extreme weather events has been shown to be a useful tool to predict RVFV activity [90]. Future research will need to focus on providing early warnings so that prediction can have greater impact on mobilization of preventive interventions and outbreak management [54].

Conclusions

RVFV was reportedly weaponized by the US offensive biological weapons program, illustrating the real threat and utility of RVFV as a bioweapon (http://cns.miis.edu/cbw/possess.htm). Bioterrorism, trade, world travel and the presence of mosquito species capable of transmitting the virus make RVFV a major threat to Western countries [46]. Coupled with the fact that there is currently no FDA-or USDA-approved RVFV vaccine for human or veterinary use, there is a clear need for more RVFV vaccine research and development [1, 21, 62]. It has been proposed that a single infected person or animal which is able to enter Europe or the USA would be sufficient to initiate a major outbreak before RVFV would be detected. This would quickly lead to the spread of RVFV and cause a severe strain on health care systems as human infections become more common. Wide-spread public panic might also ensue because of the knowledge that a hemorrhagic fever is circulating in the population. A severe economic impact is inevitable and will be felt in almost all economic sectors, from agriculture to healthcare and travel, likely for years post-identification. Although important strides have been made regarding awareness and preparation for RVFV, this pathogen still presents one of the most important viral disease threats to the Western hemisphere.

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