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Editorial

Tempering the risk: Rift Valley fever and bioterrorism

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Rift Valley fever virus (RVFV) is an arthropod-borne pathogen that primarily affects ruminants in eastern and sub-Saharan Africa first described following an outbreak on a farm in Kenya in 1931. Periodic outbreaks of RVFV since that time have resulted in significant losses to the African livestock industry as well as large numbers of infections in some of the most impoverished human populations. In one 2006/2007 outbreak across Kenya, Somalia and Tanzania alone, there were an estimated 145 000 human cases, and the ban imposed on imports after the 1997/1998 outbreak in Somalia led to a collapse of the vital livestock industry. Previously ignored, it is only in the past decade that the international community has started to take an increased interest in the disease. This followed the recognition of its potential to spread beyond the confines of the African continent after a large outbreak in Saudi Arabia in 2000. There has also been acknowledgement of the widespread presence of arthropod vectors capable of transmitting RVFV in many non-endemic regions of the world. This has led to a range of increased efforts in better understanding the virus and developing tools to predict outbreaks, combat the disease and limit its spread (Anyamba *et al.* 2010; Pepin *et al.* 2010).

However, a more longstanding, parallel interest in the disease has also developed internationally; one centred around the biosecurity implications of the virus. The United States for instance, included RVFV as a candidate pathogen in its offensive biological weapons programme; a programme officially closed in 1969 (Borio *et al.* 2002). In more recent times, the classification of the virus as a potential bioterrorism agent has spurred investment and activity, particularly in the area of vaccine development and diagnostics (Borio *et al.* 2002; Sidwell & Smee 2003).

While biosecurity interest has contributed to this increased funding over the past few decades, most notably from military sources such as the US Army Medical Research Institute of Infectious Diseases (USAMRIID), it may have acted as an impediment to international collaboration, with research being restricted to fewer, more expensive laboratories. After the signing of the US Patriot Act of 2002 and the classification of RVFV as a 'select agent', visiting experts and scientific collaborators are, for instance, now required to provide fingerprints, signed affidavits and be registered with intelligence services before working with the pathogen. Such measures are likely to act as a disincentive amongst scientists wanting to study the virus and could ultimately serve to drive experts to dedicate their efforts to other pathogens with fewer working restrictions (Animal & Plant Health Inspection Service, Centre for Disease Control & Prevention 2005, 2011). These restrictions have also been applied in parts of Europe as well, with national legislation such as the Anti-terrorism, Crime and Security Act 2001 of the UK, which also includes RVFV as a potential bioterrorism agent. For comparison and contrast, we include the current lists of biological agents and toxins around which bioterrorism legislation has been passed in the US and UK in Table 1.

Focus on US policy internationally stems from its greater leadership role within the global community and the influence and impact its decisions have on people and institutions far beyond its borders. With large numbers of laboratories worldwide affected by US policy either directly through funding or indirectly as a result of political influence, restrictions have also resulted in the transfer between laboratories of RVFV samples for culture also becoming constrained and increasingly expensive. This undermines efforts to lower the industrial production costs of existing vaccines and of commercial kits for virus neutralisation and ELISA diagnostic tests (currently the prescribed tests for international livestock trade) (World Organization for Animal Health 2008). Expertise and experience thus tends to remain confined to a limited number of laboratories and companies by and large located in high income countries where investigation of the disease is neither a significant economic or health priority nor considered sufficiently profitable for drug companies. The resulting monopolies on expert technical knowledge and skills not only delays progress in developing new therapies

Table 1 Biological agents and toxins (US and UK Governments)

US (National Select Agent Registry 2012)	UK (HMSO 2001)
US Department of Health and Human Services (HHS) select agents and toxins	Chikungunya virus
Abrin	Congo-crimean haemorrhagic fever virus
Botulinum neurotoxins*	Dengue fever virus
Botulinum neurotoxin producing species of *Clostridium**	Dobrava/Belgrade virus
Conotoxins (Short, paralytic alpha conotoxins containing the following amino acid sequence $X_1CCX_2PACGX_3X_4X_5X_6CX_7$)	Eastern equine encephalitis virus
	Ebola virus
Coxiella burnetii	Everglades virus
Crimean-Congo haemorrhagic fever virus	Getah virus
Diacetoxyscirpenol	Guanarito virus
Eastern equine encephalitis virus†	Hantaan virus
Ebola virus*	Hendra virus (Equine morbillivirus)
*Francisella tularensis**	Herpes simiae (B virus)
Lassa fever virus	Influenza viruses (pandemic strains)
Lujo virus	Japanese encephalitis virus
Marburg virus*	Junin virus
Monkeypox virus†	Kyasanur Forest virus
Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments (Reconstructed 1918 Influenza virus)	Lassa fever virus
	Louping ill virus
	Lymphocytic choriomeningitis virus
	Machupo virus
Ricin	Marburg virus
Rickettsia prowazekii	Mayaro virus
SARS-associated coronavirus (SARS-CoV)	Middleburg virus
Saxitoxin	Mobala virus
South American Haemorrhagic Fever viruses:	Monkey pox virus
Chapare	Mucambo virus
Guanarito	Murray Valley encephalitis virus
Junin	Ndumu virus
Machupo	Nipah virus
Sabia	Omsk haemorrhagic fever virus
Staphylococcal enterotoxins A, B, C, D, E subtypes	Polio virus
T-2 toxin	Powassan virus
Tetrodotoxin	Rabies virus
Tick-borne encephalitis complex (flavi) viruses:	Rift Valley fever virus
Far Eastern subtype	Rocio virus
Siberian subtype	Sabia virus
Kyasanur Forest disease virus	Sagiyama virus
Omsk haemorrhagic fever virus	Sin Nombre virus
Variola major virus (Smallpox virus)*	St Louis encephalitis virus
Variola minor virus (Alastrim)*	Tick-borne encephalitis virus (Russian Spring–Summer encephalitis virus)
*Yersinia pestis**	

Table 1 (*continued*)

US (National Select Agent Registry 2012)	UK (HMSO 2001)
Overlap select agents and toxins	
Bacillus anthracis *	Variola virus
Bacillus anthracis Pasteur strain	Venezuelan equine encephalitis virus
Brucella abortus	Western equine encephalitis virus
Brucella melitensis	West Nile fever virus
Brucella suis	Yellow fever virus
*Burkholderia mallei**	
*Burkholderia pseudomallei**	
Hendra virus	
Nipah virus	
Rift Valley fever virus	
Venezuelan equine encephalitis virus†	
US Department of Agriculture (USDA) select agents and toxins	
African horse sickness virus	
African swine fever virus	
Avian influenza virus†	
Classical swine fever virus	
Foot-and-mouth disease virus*	
Goat pox virus	
Lumpy skin disease virus	
Mycoplasma capricolum†	
Mycoplasma mycoides†	
Newcastle disease virus†‡	
Peste des petits ruminants virus	
Rinderpest virus*	
Sheep pox virus	
Swine vesicular disease virus	
USDA Plant Protection and Quarantine (PPQ) select agents and toxins	
Peronosclerospora philippinensis (Peronosclerospora sacchari)	
Phoma glycinicola (formerly Pyrenochaeta glycines)	
Ralstonia solanacearum	
Rathayibacter toxicus	
Sclerophthora rayssiae	
Synchytrium endobioticum	
Xanthomonas oryzae	

*Denotes Tier 1 Agent.

†Select agents that meet any of the following criteria are excluded from the requirements of this part: Any low pathogenic strains of avian influenza virus, South American genotype of eastern equine encephalitis virus, West African clade of Monkeypox viruses, any strain of Newcastle disease virus which does not meet the criteria for virulent Newcastle disease virus, all subspecies Mycoplasma capricolum except subspecies capripneumoniae (contagious caprine pleuropneumonia), all subspecies Mycoplasma mycoides except subspecies mycoides small colony (Mmm SC) (contagious bovine pleuropneumonia), any subtypes of Venezuelan equine encephalitis virus except for subtypes IAB or IC and vesicular stomatitis virus (exotic): Indiana subtypes VSV-IN2, VSV-IN3, provided that the individual or entity can verify that the agent is within the exclusion category.

‡A virulent Newcastle disease virus (avian paramyxovirus serotype 1) has an intracerebral pathogenicity index in day-old chicks (Gallus gallus) of 0.7 or greater or has an amino acid sequence at the fusion (F) protein cleavage site that is consistent with virulent strains of Newcastle disease virus. A failure to detect a cleavage site that is consistent with virulent strains does not confirm the absence of a virulent virus.

Box 1: US CDC and NIAID categorisation of bioterrorism agents and biodefense priority pathogens.

Category A pathogens are those organisms/biological agents that pose the highest risk to national security and public health because they

- Can be easily disseminated or transmitted from person to person;
- Result in high mortality rates and have the potential for major public health impact;
- Might cause public panic and social disruption; and
- Require special action for public health preparedness.

Category B pathogens are the second highest priority organisms/biological agents. They:

- Are moderately easy to disseminate;
- Result in moderate morbidity rates and low mortality rates; and
- Require specific enhancements for diagnostic capacity and enhanced disease surveillance.

Category C pathogens are the third highest priority and include emerging pathogens that could be engineered for mass dissemination in the future because of:

- Availability;
- Ease of production and dissemination; and
- Potential for high morbidity and mortality rates and major health impact.

and vaccines but also increases their costs by limiting production capacity and competition. Increased sales costs of vaccines in particular have put at risk well-established mechanisms of international cooperation in global infectious disease surveillance. This risk was highlighted in 2006 and 2007 with Indonesia's refusal to share H5N1 samples with WHO (Sedyaningsih *et al.* 2008).

The potential risks of RVFV to animal health are indeed significant and so the deliberate release of the agent would have indirect health effects on human populations through the destruction of the livestock industry in particular. Although the possibility of industrial sabotage or 'agroterrorism' is thus real, the potential direct bioterrorism risk to human health of RVFV is far more limited. On the most important criteria of pathogenicity and transmissibility, RVFV is a poor candidate choice as an anti-human bioterrorism agent, with no recorded cases of human-to-human transmission and a relatively low mortality rate of 1–2% in humans. Complicated infections, characterised by haemorrhagic fever or encephalitis, are similarly limited to about 1% of infected cases (Pepin *et al.* 2010).

Box 2: An excerpt from the proceedings of the 'Responding to the Consequences of Chemical and Biological Terrorism.' joint seminar held between the US Department of Health and Human Services, US Public Health Service (PHS) and the Office of Emergency Preparedness (OEP) in July 1995.

> "If I wanted to disrupt the Mideast peace process between Israel and the PLO, I would infect one small, young lamb with Rift Valley fever virus. I would hold that lamb in a confined area for about 48 hours; at that point in time the lamb is very sick. I bleed 200 milliliters from his heart; I keep that blood from clotting by means of heparin. If the heparin is not available to me, I have picked up some small stones, and I have sterilized them in boiling water. I add those stones to the fluid, and I shake it up, and I prevent clotting. Then I harvest the lung and the liver and get 600 milliliters of blood and organs. I add 5,400 milliliters of a 5-percent skim milk solution, homogenize again in a Waring blender, filter, filter, filter. I filter it through several layers of gauze, and I get 5,900 milliliters containing 1 × 1010, 10,000,000,000 units of virus. Using my old pal Calder's mathematical model, if I disseminate that as a line source, perpendicular to the wind, 2 milliliters per meter, and I walk along for 2,950 meters, I will infect 50 percent of the population 0.4 of a kilometer downwind; 30 percent of the population at 1.5 kilometers downwind; and 10 percent of the population 3 kilometers downwind. I have hedged here. I have used very good meteorological conditions. The ridge height, or course I am walking along spraying, is zero feet. The transport wind is 5 miles per hour, which is very good for transport of a BW agent. Your diffusion parameter is n = 0.4, the beta factor is 0.8, and I have selected deliberately to bias the thing in my favor, a stability condition of a very strong inversion (US Department of Health & Human Services USPHS, Office of Emergency Preparedness 1995)."

While aerosolised droplet transmission of the virus is clearly possible, with notable recorded transmissions occurring in abattoir and laboratory workers from infected animal specimens and parts, this is not a unique feature amongst a plethora of infectious diseases. RVFV with its low mortality and relatively low human-to-

human transmissibility in comparison with other viral haemorrhagic fever (VHF) viruses such as Ebola, Marburg or Lassa, should have its risk profile assessed independently. As such, while the US Centre for Disease Control (CDC) has indeed categorised VHF viruses as category A bioterrorism agents (Box 1); it specifically refers to filoviruses (e.g. Ebola and Marburg) and arenaviruses (e.g. Lassa) in this regard, and RVFV does not appear at all in its list of potential bioterrorism agents (Centre for Disease Control & Prevention 2012). Expert commissions have, however, at times tended to band all VHFs together, resulting in legislation that has overplayed the specific risk of RVFV to human health (Borio *et al.* 2002). For instance, the US National Institute of Allergy and Infectious Diseases, using the same categorisation as the CDC, includes RVFV specifically as a category A agent thus incorrectly implying high pathogenicity and high human-to-human transmissibility (National Institute of Allergy & Infectious Diseases 2011).

While it is not inconceivable that a variety of state and non-state actors may attempt to develop RVFV as a biological weapon, its large scale effectiveness seems limited to causing economic damage through the deliberate infection of livestock (Borio *et al.* 2002). In the event that the virus was selected for development as a bioterrorism agent, the current wide ranging restrictions placed on legitimate scientists and vaccine/diagnostic kit manufacturers working with the virus are unlikely to act as a significant deterrent to entities determined to obtain live RVFV samples for culture and study. With the virus so widespread in so many parts of Africa, obtaining live samples from an array of vertebrate hosts and culturing it thereafter is a relatively simple process (Box 2) (US Department of Health & Human Services USPHS, Office of Emergency Preparedness 1995). Such restrictions thus potentially hinder the development of necessary biological solutions for wider disease control and also provide a false sense of security.

Bunyaviruses, like RVFV, are known to be easily cultivated *in vitro* and can therefore be prepared in large quantities (Sidwell & Smee 2003; Pepin *et al.* 2010). With new advances in recombinant techniques, there may thus be a heightened sense of wariness around the potential for a more pathogenic (to humans) variant of the virus being produced by bioterrorists. For RVFV in particular, this is tempered to an extent in comparison with other bunyaviruses as it is believed to have a relatively low tolerance to genetic mutation (Pepin *et al.* 2010). As such, while it is important to recognise that evolving technologies mean that RVFV still poses a theoretical bioterrorism risk, it is arguably more important to recognise that the virus causes very real morbidity and mortality naturally and that this consideration should take precedence in the worldwide approach to combating the disease.

Rift Valley fever virus disease hurts some of the most impoverished communities in the developing world through both its direct health and indirect economic effects and is an infection that has suffered decades of chronic under-investment in its control. In recent years, there has been a welcome increase in interest globally in combating this disease, and these efforts should be encouraged. However, to fully benefit from this increased interest, international policies related to biosecurity concerns around the virus should be revisited and tempered. This would not only enable better, more efficient focus on pathogens that do constitute a significant biosecurity risk, but also importantly, allow the global community to accelerate the progress being made towards improving RVFV control.

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