Public Veterinary Medicine: Public Health

Evaluation of pathways for release of Rift Valley fever virus into domestic ruminant livestock, ruminant wildlife, and human populations in the continental United States

Thomas R. Kasari, DVM, MS, DACVIM, DACVPM; Deborah A. Carr, DVM, MPH; Tracey V. Lynn, DVM, MS, DACVPM; J. Todd Weaver, DVM, DACVPM

Objective—To evaluate the feasibility for Rift Valley fever virus (RVFV) to enter the continental United States by various routes as well as to identify states in which domestic and wild ruminant and human populations would be most vulnerable to exposure to RVFV.

Study Design—Pathways analysis.

Sample Population—Animals, commodities, and humans transported from RVFV-endemic countries to the continental United States between 2000 and 2005.

Procedures—Initially, agent, host, and environmental factors important in the epidemiologic aspects of RVFV were used to develop a list of potential pathways for release of RVFV into the continental United States. Next, the feasibility of each pathway was evaluated by use of data contained in governmental and public domain sources. Finally, entry points into the continental United States for each feasible pathway were used to identify the domestic and wild ruminant and human populations at risk for exposure to RVFV.

Results—Feasible pathways for entry of RVFV into the continental United States were importation of RVFV-infected animals, entry of RVFV-infected people, mechanical transport of RVFV-infected insect vectors, and smuggling of live virus.

Conclusions and Clinical Relevance—Domestic ruminant livestock, ruminant wildlife, and people in 14 states (Alabama, California, Florida, Georgia, Maine, Maryland, Massachusetts, Minnesota, New Jersey, New York, Pennsylvania, South Carolina, Texas, and Virginia) appeared to be most vulnerable to exposure to RVFV. Pathways analysis can provide the requisite information needed to construct an effective targeted surveillance plan for RVFV to enable rapid detection and response by animal health and public health officials. (J Am Vet Med Assoc 2008;232:514–529)

Rift Valley fever is an important foreign animal disease that, should it enter the United States, will have major adverse effects on domestic cattle, sheep, and goat production; in addition, there will be appreciable costs associated with disease control and eradication efforts.1 This virus is also one of a handful of viruses that cause viral hemorrhagic fever in humans, a severe multiple-system syndrome associated with fever, circulatory shock, and bleeding diathesis.2 The recent outbreak of RVF in Kenya and neighboring Somalia, the United Republic of Tanzania, and Sudan also underscores the ability of the virus to kill human and other animal hosts.3-5 High morbidity and associated fatalities in humans and livestock combined with interest by terrorists for malicious use of this virus also make RVFV a potential threat as a biological weapon.6-9

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVF</td>
<td>Rift Valley fever</td>
</tr>
<tr>
<td>RVFV</td>
<td>Rift Valley fever virus</td>
</tr>
<tr>
<td>PFU</td>
<td>Plaque-forming unit</td>
</tr>
<tr>
<td>MICLD50</td>
<td>Mouse intracerebral median lethal dose</td>
</tr>
</tbody>
</table>

From the National Surveillance Unit (Kasari) and Center for Emerging Issues (Lynn, Weaver), USDA,APHIS, Veterinary Services. Centers for Epidemiology and Animal Health, 2150 Centre Ave, Building B, Fort Collins, CO 80526; and the Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Rd, Bethesda, MD 20814 (Carr). Dr. Carr’s present address is 13th Aeromedical-Dental Squadron, 1223 Freedom Dr, Hickam Air Force Base, HI 96853.

The authors thank Dr. Angela James for technical assistance in summarizing mosquito ecology; Dr. Emily Piercefield for technical assistance in summarizing host susceptibility information, and Elizabeth McKenna and Diana Mitchell for technical assistance in extraction of data from databases. Address correspondence to Dr. Kasari.
In light of the importance of RVF as a zoonotic disease that animal and public health officials are determined to keep from entering the United States, the primary objective of the study reported here was to use pathways analysis methods to identify and evaluate various routes by which RVFV could enter the continental United States on the basis of the unique agent, host, and environmental interactions associated with the virus. Locations of domestic ruminant livestock, ruminant wildlife, and human populations at risk for subsequent exposure to RVFV were also identified.

Materials and Methods

Review of agent factors important in RVF—First reported in the Rift Valley of Kenya in 1930,11 RVF is caused by an RNA virus in the family Bunyaviridae and genus Phlebovirus.12 Rift Valley fever virus is also classified as an arbovirus (ie, arthropod-borne virus).13 The virus replicates quickly and achieves an extremely high concentration in the cytoplasm of host cells, particularly those of the liver and other reticuloendothelial organs. Infected animals typically have widespread severe cytopathologic changes in these tissues during the 30- to 72-hour incubation period of this disease. The virus survives well at ambient temperature and also when frozen or lyophilized.14,15,16 but it is quite sensitive to acidic conditions and readily inactivated by lipid solvents (eg, ether), detergents, and common disinfectants.14 Being an arbovirus, RVFV requires a blood-sucking arthropod to complete its life cycle.13 The preferred arthropod for RVFV is mosquitoes.15 In Africa where RVF is endemic, RVFV is found naturally in 23 species of mosquitoes from 5 genera (Aedes, Anopheles, Culex, Eretmapoites, and Mansonia spp).15 Aedes spp mosquitoes are considered the primary vectors of RVFV.17 Virus has also been isolated from Culicoides spp and Simulium spp flies, but their role in transmission of the virus is as yet unknown.15,16 These flies may simply be involved with mechanically transmitting RVFV, similar to several other genera of biting flies (Stomoxys spp, Glossina spp, and Tabanidae spp) and ticks (Rhipicephalus appendiculatus and Amblyomma variegatum) in natural conditions.17,18

Review of host factors important in RVF—The susceptibility to experimental infection, natural infection, or both with RVFV has been reported for many vertebrate species.1,2,5,9–11 (Appendices 1–5). However, relatively few of these species are important in the transmission of the virus. It must be remembered that for there to be transmission of RVFV between a vertebrate host and an insect vector, an infectious agent must be amplified in the vertebrate host’s circulation to reach a threshold level (ie, minimum logarithm of virus).27 Domestic ruminants, certain wildlife species, and humans are good at amplifying RVFV and warrant further comment about this important concept.

Domestic ruminants

In Africa, a continent where there are natural outbreaks of RVF, domestic ruminant livestock function as the initial amplifying host of RVFV.19 When there is severe disease, it is generally associated with an extremely high viremia (up to $10^{6.6}$ PFUs/mL28 or $10^{10.0}$ MICLD<sub>50</sub>/mL29) for approximately 7 days,22 which facilitates transmission of the virus to insect vectors.22 As a point of reference, the estimated threshold of RVFV required to infect mosquitoes ranges from $10^{3.1}$ to $10^{7.2}$ PFUs/mL30 or $10^{6.7}$ to $10^{8.7}$ MICLD<sub>50</sub>/mL.29 Infected insects, in turn, transmit RVFV to other uninfected but susceptible ruminant livestock, thus sustaining an RVF outbreak in field conditions. Animal-to-animal transmission of RVFV has been determined for experimental conditions but is not considered to be important in ruminant livestock in field conditions61 because RVFV is not typically excreted into the atmosphere as an aerosol by ill animals.17 A long-term carrier state has not been identified in domestic ruminant livestock.30

Wildlife

The role that ruminant wildlife species play in the life cycle of RVF is unclear because clinical disease, widespread abortions, or death have not been definitively determined in these animals. For example, in shared grasslands during epizootics of RVF, domestic ruminants have had clinical signs of disease, but ruminant wildlife have not.19 Furthermore, few ruminant wildlife species have been screened for exposure to naturally developing RVF (Appendix 1). However, in experimental conditions, ruminant wildlife develop antibodies to the virus and may even abort following inapparent infection.17

Wild nonhuman primates develop antibodies against RVFV,62 and experimentally infected rhesus monkeys (Macaca mulatta) are severely viremic ($10^{7.0}$ to $10^{8.9}$ PFUs/mL), which is well within the range required to infect mosquitoes with RVFV.68 Some of the rhesus monkeys had clinical signs compatible with hemorrhagic fever and died, whereas others survived despite transient severe viremia of several days duration. Similarly, several more species of African monkeys, which were injected with RVFV, also had a transient severe viremia of several days’ duration without evidence of clinical illness (Appendix 2). Transient but severe viremia in animals with experimental infection raises the question as to whether RVFV may be amplified in natural conditions to the extent that nonhuman primates may be a potential source of virus for mosquitoes that feed on them.

Wild rodents have limited resistance to RVFV infection. Consequently, there is a concern that these rodent species in nature may amplify the virus sufficiently to infect mosquitoes that may feed on them.40

Humans

Humans can yield threshold amounts of RVFV during the course of clinical disease. For example, during an outbreak of RVF in Egypt, viremia of $10^{5.1}$ to $10^{6.6}$ MICLD<sub>50</sub>/mL was measured in ill people, compared with viremia of $10^{9.3}$ to $10^{10.3}$ MICLD<sub>50</sub>/mL of serum in ill sheep.39 Although a number of laboratory workers have become infected with RVFV while handling the virus, indicating that aerosol transmission is a possibility,19 there has been no direct human-to-human transmission of RVFV in field conditions.30

Review of environmental factors important in RVF—When considering environmental factors that can influence the incidence and severity of disease, such physical factors as geographic location and climatic conditions immediately come to mind. However, less obvious are social, economic, or political factors as well as those of the agent as a biohazard. Each can be a part of the environmental landscape that influences whether there is disease in human and other animal populations. Important environmental factors can influence outbreaks of RVF.

**Geographic distribution of RVFV**

Historically, RVF is encountered in an enzootic or epizootic form along the eastern and southern coast of Africa and also in Madagascar.\(^{21}\) The virus has spread as far north as Egypt and has crossed over to the Arabian Peninsula countries of Saudi Arabia and Yemen.\(^{65}\) According to the World Organization for Animal Health,\(^{46}\) several countries reported overt clinical signs of RVF or laboratory evidence (e.g., serum antibodies or isolation of virus) of RVFV in susceptible domestic ruminant species between 1996 and 2004. These countries were the Central African Republic, Chad, Cote d’Ivoire, Gambia, Guinea, Iraq, Kenya, Madagascar, Malawi, Mauritania, Mozambique, Saudi Arabia, Senegal, Somalia, South Africa, the United Republic of Tanzania, Yemen, and Zimbabwe. In addition, Namibia, Sudan, and Zambia have had outbreaks of RVF in domestic ruminants before 1996.\(^{66}\) In general, countries with evidence of past outbreaks of RVF should probably be considered permanently infected with RVFV.\(^{67}\) Since 2005, Guinea, Kenya, Madagascar, Malawi, the United Republic of Tanzania, Somalia, Sudan, and Yemen have had a recurrence of clinical disease or infection (without clinical disease) involving domestic ruminant livestock and humans.\(^{4,5,66}\)

**Climate and weather**

In sub-Saharan East Africa, where RVF is endemic, RVFV is proposed to have a rain-dependent biphasic maintenance cycle. In the first phase, mosquito breeding habitats known as dambos (low-lying temporary wetlands) remain flooded for a sufficient number of days to allow eggs to hatch, which acquire RVFV infection transovarially from Aedes spp mosquitoes.\(^{17,40,44}\) Newly hatched and infected female mosquitoes then introduce the virus into domestic vertebrate populations, primarily ruminant livestock. These mosquitoes also replenish their habitat with more RVFV-infected eggs. For the second or epizootic phase of the maintenance cycle, extremely heavy rainfall creates standing water that stimulates the hatching of RVFV-infected eggs from Aedes spp mosquitoes, but it also provides excellent habitat for eggs to hatch from secondary vectors such as Culex thelerti mosquitoes.\(^{17,39,44}\) The epizootic-epidemic phase of the life cycle of RVFV is sustained by these secondary mosquito vectors.

An interepizootic period of 5 to 15 years in grassland areas and 25 to 35 years in drier areas typically occurs between the 2 phases of the maintenance cycle of RVF.\(^{55}\) During such periods, RVFV-infected eggs enter a dormant (latent) state of infection.\(^{31}\) Thus, transovarial transmission of RVFV to mosquito eggs is the most likely primary mechanism for maintenance of the virus during interepizootic periods when dry environmental conditions are unsuitable for active transmission of RVFV that involves primary and secondary mosquito vectors and a vertebrate host.\(^{51}\) Low-level transmission of the virus to ruminant livestock is probably also involved in maintenance of the virus during these interepizootic periods.\(^{61}\) Several rodent species\(^{40,42,45}\) (Appendix 3) and nonhuman primates\(^{67}\) may also contribute to maintaining the virus during interepizootic periods.

**Vector longevity**

In general, the life expectancy of adult mosquitoes in hot tropical areas is 1 to 2 weeks.\(^{68}\) In some cases, the life span of mosquitoes in such areas may be only 3 to 5 days. In more temperate regions, adult mosquitoes usually live 4 to 5 weeks.

**Movement of insect vectors**

Wind dispersal of virus-infected insects has been implicated in the spread of bluetongue,\(^{69,70}\) epizootic hemorrhagic disease,\(^{69}\) vesicular stomatitis,\(^{71}\) Akabane,\(^{70}\) Japanese encephalitis,\(^{72}\) western and eastern equine encephalomyelitis,\(^{73,74}\) and RVF to new geographic areas. Distance traveled by these insects ranged from 110 to 1,350 km (68 to 839 miles) during a transit period of < 24 hours.

Nonindigenous mosquito species have been found alive inside aircraft that landed at airports in the continental United States following international flights,\(^{76}\) probably because temperatures inside wheel bays, cargo hulls, and passenger compartments of aircraft are within the survival range of mosquitoes.\(^{77,78}\) Many species of adult mosquitoes overwinter as adults and are capable of surviving long periods (weeks to months) at relatively low temperatures, especially in a humid environment. In many instances, the temperature and humidity inside containers in ship cargo holds are likely to provide suitable conditions for the survival of adult mosquitoes during transcontinental ocean travel.\(^{4}\)

**Biohazard**

Although RVFV has not been involved in any of the > 100 confirmed incidents of illicit use of biological agents during the past century,\(^{7}\) terrorist groups may consider RVFV as an attractive target for illicit use against humans and other animals.\(^{8,9}\) Research facilities that house inventories of RVFV are a logical target for terrorist groups that want to obtain the virus. Because RVF is a zoonotic disease that is endemic and sometimes epidemic virtually everywhere in sub-Saharan Africa, research laboratories located in many of those countries as well as in non–RVFV-endemic countries in Europe, the former Soviet Union, and North America may have stocks of the virus available for research purposes.\(^{9}\)

**Pathways analysis**—Pathways analysis is a systematic assessment of the paths along which a disease agent
from another part of the world could enter the United States and establish an outbreak of disease in susceptible humans or other animal species. This technique is also applicable for delineating the paths along which an existing disease agent in the United States could spread to 1 or more new states or regions and establish an outbreak of disease. Pathways analysis, in turn, is integral to a risk assessment that has the purpose of estimating, in qualitative or quantitative terms, the likelihood of an outbreak of disease resulting from the identified pathway or pathways and the consequences of such an outbreak. Ultimately, a pathways analysis and the risk assessments that come from it help to guide development of surveillance plans for the disease agent in question.

Pathways analysis entails a 4-step process. The first step involves establishing an understanding of agent (pathogen), host, and environmental factors that are important in epidemiologic aspects of the disease in question; this understanding is based on the scientific literature, expert opinion, personal experience, or other sources of information. The second step involves developing a list of potential pathways for release of the disease agent into a susceptible livestock or human population on the basis of the aforementioned understanding of agent, host, and environmental interactions. The third step involves obtaining data from governmental and public domain sources as well as other information (eg, expert opinion) to evaluate the feasibility of each pathway. Finally, in the fourth step, entry points into the continental United States (for a foreign disease agent) or other states or regions (for a domestic disease agent) of each feasible pathway are used to identify the populations of domestic animals and humans (for a zoonotic disease) at risk for possible exposure to the disease agent in question.

Five pathways were evaluated for their feasibility with regard to release of RVFV into susceptible livestock or human populations in the United States. These pathways were importation of RVFV-infected animals, entry of RVFV-infected people, mechanical transport of RVFV-infected insect vectors, intercontinental windborne transport of RVFV or RVFV-infected insect vectors, and smuggling of live RVFV.

Results

Importation of RVFV-infected animals—No federal regulations exist for the legal importation of domestic or wild ruminant livestock into the United States from RVFV-endemic countries. Fortuitously, RVFV-endemic countries are also endemic for rinderpest or foot-and-mouth disease (or both); thus, federal regulations effectively prevent importation of domestic ruminant livestock into the United States when they originate from a country endemic for either of these diseases. Consistent with these regulations, no domestic ruminant livestock have been imported into the United States from any country in Africa or the Arabian Peninsula during the time frame (2000 through 2005) evaluated for the pathway analysis in the study reported here. However, ruminant wildlife species are allowed entry into the United States from countries where rinderpest or foot-and-mouth disease exist but only under strict import requirements and provided that the imported animal or animals will reside in a zoologic park. Such animals must be shipped under permit and go directly from the foreign port of embarkation to Newburg, NY, the only USDA Animal Import Center designated for ruminant wildlife species. During the past 5 years, ruminant wildlife species indigenous to Africa, including wildebeests and other antelope species, have been imported directly into the United States or into the United States via Mexico or Canada for use at private ranches and zoologic parks. Because federal regulations require a 30-day quarantine for animals shipped directly to the United States or a minimum 60-day residence in Canada or Mexico prior to shipment to the United States, it is unlikely that these animals would be viremic at the time of shipment to the continental United States.

According to US Department of Health and Human Services, CDC regulations, nonhuman primates may not be imported into the United States as pets under any circumstances; however, they are allowed to enter for bona fide scientific, educational, or exhibition purposes. Although there are no specific requirements to test these animals for RVFV prior to shipment, CDC regulations provide a degree of surveillance oversight for this disease.

Between 2000 and 2003, the Democratic Republic of the Congo, Mauritius, South Africa, and the United Republic of Tanzania (all RVFV-endemic countries) exported 20,301 nonhuman primates into the United States. Mauritius, which has never had RVF, exported the most animals (19,828 animals). Nonhuman primates also have been illegally imported into the United States. However, no illegal shipments of nonhuman primates or ruminant wildlife species from RVFV-endemic countries were seized during the time period evaluated in this pathways analysis.

Although rodents of African origin may be imported for scientific, exhibition, or educational purposes with a valid permit issued by the CDC, no evidence was found that rodent species susceptible to RVFV were exported to the United States during the time period evaluated for this pathways analysis. Furthermore, no other animal species that could amplify RVFV were exported to the United States during the time period included in this pathways analysis.

Summary of pathway feasibility

Currently, legal importation of domestic ruminant livestock species from RVFV-endemic countries is not a feasible pathway for the entry of RVFV into the United States. However, legal importation of wildlife species, including nonhuman primates, is a feasible pathway, but this is contingent on these animals circumventing quarantine procedures designed to detect RVF and other infectious diseases at both the country of origin and on entry into the United States. Although smuggling of wild or domestic ruminants from RVFV-endemic countries does not appear to be a feasible pathway, smuggling of wild nonhuman primates may be. The reasons for a lack of smuggling of wild or domestic ruminants may be attributable to the size of the animals (ie, not easy to conceal) as well as a lack of demand for them on the black market.
Entry of RVF-infected people—All 152 international airports and 170 sea or river ports of call in the United States are potential entry pathways for humans infected with RVFV. Between 2001 and 2004, 846,872 airline passengers from 15 African countries and Saudi Arabia entered the United States. Flights originating in South Africa, Egypt, Saudi Arabia, Ethiopia, and Ghana accounted for 80.96% of arriving passengers. Sixteen international airports received these passengers, with most of the passengers (606,005 [71.56%]) terminating their flights in New York at Kennedy International Airport. Other important airports were located in the District of Columbia, Georgia, Maryland, New Jersey, and Texas. Together, these airports were the destination for 97.77% of all passengers. The number of airline flights originating from non–RVFV-endemic countries (eg, those in Europe and Asia) that may have landed in 1 or more RVFV-endemic countries to pick up passengers, refuel, or fulfill other tasks could not be determined.

On entering the United States, 10,368 passengers from RVFV-endemic countries completed a questionnaire as a requirement of inspection of their luggage and personal items. More than half of them (5,429 [52.13%]) indicated that they were traveling to the United States to visit family members or friends. Although the questionnaire did not specifically ask where the family members or friends of these passengers lived, the 10 states with the largest populations of African immigrants are California, Florida, Georgia, Maryland, Massachusetts, Minnesota, New Jersey, New York, Texas, and Virginia. These states are probably at greater risk for introduction of RVFV within their borders, compared with the risk for other states, in the event that one of these passengers who traveled specifically to visit family members or friends is viremic at the time of landing. In addition, Africa and the Middle East, including the Arabian Peninsula, continue to be popular destinations for US citizens; 203,867 and 554,031 US citizens traveled via airlines to Africa and the Middle East, respectively, during 2005. During the time frame evaluated in this pathways analysis, no returning US citizens or airline passengers originating from African countries, Saudi Arabia, or Yemen were quarantined on arrival in the United States because of clinical signs of disease compatible with RVF. Furthermore, no cruise ships departed an RVFV-endemic country bound for the United States, nor did any ships depart from the United States bound for Africa or the Arabian Peninsula during the time period evaluated in this pathways analysis.

SUMMARY OF PATHWAY FEASIBILITY
In contrast to cruise ships, air transportation is a feasible pathway for entry of people into the United States who may be viremic with RVFV that was contracted while in an RVFV-endemic country. Airline passengers from the United States who are returning from visiting RVFV-endemic countries may also potentially contribute to release of the virus in the continental United States. However, it is unlikely that military service members returning from RVFV-endemic countries would contribute to release of the virus. The military services have comprehensive surveillance programs designed to mitigate health threats encountered during military deployments.

Mechanical transport of RVFV-infected insect vectors—We hypothesized that the most likely scenario of mechanical transport of an RVFV-infected vector would involve adult RVFV-infected mosquitoes being trapped inside containers filled with commodities bound for the United States or being confined within the hull of ships or aircraft that were transporting commodities or people. As many as 133 US ports and 116 airports have received shipments of domestic and international cargo in recent years. During 2000 through 2005, 46 RVFV-endemic countries exported 99 commodities into the continental United States through 36 ports of entry in 26 states and the District of Columbia. Philadelphia, New York City, and Charleston, SC, were the ports of entry used most frequently.

Inspecting cargo for insects is not a specific requirement of customs officials. In addition, no public health measures, such as disinsection, are required to be performed on a routine basis with respect to commercial aircraft entering the United States. During fiscal year 2000, inspectors at 8 US airports made 271,511 air cargo inspections and identified 9,370 reportable pests (3.58% detection rate). These data did not specify the genus and species of pests that were collected. However, military aircraft are disinfected as directed by command-level or higher authorities when it is determined that the point of embarkation has active vector-borne disease. On entering the United States, the CDC can require disinsection of a commercial aircraft when it is suspected of harboring insects of public health importance. Unfortunately, the Environmental Protection Agency has not approved any pesticides for use in the passenger cabin area of airplanes. Air curtains to defend against entry or exit of mosquitoes from aircraft cabins have been developed and tested for efficacy but currently are not in use by commercial airlines. The use of netting to cover doors that open to the cargo compartment of passenger aircraft is currently being evaluated.

During fiscal year 2000, inspectors at 8 US airports made 4,508,173 inspections of passenger baggage and identified 8,444 reportable pests (0.19% interception rate). Analysis of this information indicated that luggage and personal items of airline passengers can also harbor insect pests. Referring specifically to airline passengers from RVFV-endemic countries who entered the United States during the time period of the pathways analysis reported here, 13,875 passengers had their luggage and personal items inspected. Insects were found twice, but the genus and species were not reported.

SUMMARY OF PATHWAY FEASIBILITY
This pathway is feasible for introducing RVFV into the United States. Pests appear to enter the United States more frequently in air cargo than via air passenger baggage. Admittedly, the transit time for a cargo ship between RVFV-endemic countries and the United States could exceed the life span of mosquito species that are vectors for RVF and probably leave few survivors. By comparison, aircraft originating from an RVFV-endemic country can reach the United States within hours, and any RVFV-infected mosquitoes would be expected...
to survive the journey while being transported inside the cabin or cargo bay or the containers carried with-in. It is important to mention that for this pathway to be complete, the newly introduced infected mosquito vector does not need to become an established invasive species. A single RVFV-infected mosquito may be all that is needed to introduce the disease, assuming it transmits the virus to a susceptible ruminant or human host while consuming a blood meal and the host then amplifies the virus for domestic mosquito vectors.

**Intercontinental wind-borne transport of RVFV or RVFV-infected insect vectors**—The shortest distance across the Atlantic Ocean between Africa and the United States is approximately 4,830 km (3,001 miles).103 Unless there is a major meteorologic event, global wind speed typically is approximately 6.64 m/s (14.9 miles/h) near (10 m [33 ft]) the ocean surface but faster (8.6 m/s [19.3 miles/h]) when at a higher (80 m [262 ft]) altitude.6 Consequently, it is reasonable to assume that it would require approximately 6 to 8 days for wind leaving Africa to reach the continental United States. Because the maximum duration for mosquito flight is <30 hours,104 RVFV-infected mosquitoes are unlikely to survive being transported from Africa to the continental United States on wind currents, even those of a hurricane.

Viable bacteria and fungi isolated from samples of air collected in the Northern Caribbean have been traced to African dust storms.105 However, the feasibility of RVFV and RVFV-infected mosquito eggs being transported by wind currents for this long journey across the Atlantic Ocean, and remaining viable, is considerably less likely. As previously mentioned, RVFV is not typically excreted into the atmosphere as an aerosol by ill animals. However, even if RVFV were to be excreted in high concentrations as an aerosol during an outbreak of RVF, it is doubtful that these infectious airborne particles would reach the continental United States in viable form or at concentrations sufficient to cause infection in susceptible ruminants or humans because the RVFV has a short half-life when transmitted as an aerosol. Whereas dust particles are <500 µm in diameter,106 mosquito eggs are several millimeters in diameter.107 Thus, they are >1,000 times as large as dust particles. Because of their size, it is doubtful that mosquito eggs would be sufficiently affected by wind events to transport them long distances attached to or mixed among dust particles.

**SUMMARY OF PATHWAY FEASIBILITY**

Intercontinental wind-borne transport does not seem feasible for facilitating the introduction of RVFV, RVFV-infected adult mosquitoes, or RVFV-infected mosquito eggs into the continental United States.

**Smuggling of live RVF**—As mentioned previously, there are 152 international airports and 170 sea or river ports of call in the United States, all of which are potential entry pathways for humans who wish to illicitly transport RVFV.108,109 Furthermore, with the large number of airline passengers who enter the continental United States, it would be virtually impossible to screen each one. The virus could also be brought into the United States through entry points other than official ports of entry.

**SUMMARY OF PATHWAY FEASIBILITY**

Many experts agree that smuggling of live RVFV should be acknowledged as a feasible pathway.108 We are uncertain about the degree of importance that should be placed on this pathway because of an inability to predict illicit activities and a lack of an international system that tracks the number of laboratories that maintain stocks of the virus, the quantities of virus available, and movement of these viral stocks. However, conventional wisdom dictates that efforts should not focus as much on preventing an act of agroterrorism with a biological agent such as RVFV because it is impossible to prevent all disease introductions.109 Instead, efforts should focus on rapid detection and identification of disease incidents and in establishing mechanisms for a quick response to an outbreak of RVFV in the United States.

**Ruminant livestock, ruminant wildlife, and human populations in the United States at risk for exposure to RVF**—Regardless of which of the feasible pathways RVFV may follow to enter the continental United States, arguably the most important factor for sustaining an outbreak of RVF among domestic and wild ruminants and humans is having mosquito vectors present that can transmit the virus. In North America, mosquito species that are susceptible to RVFV infection in laboratory conditions include Aedes (Ochlerotatus) albopictus, Aedes (Ochlerotatus) canadensis, Aedes (Ochlerotatus) cantator, Aedes (Ochlerotatus) excrucians, Aedes (Ochlerotatus) sollicitans, Aedes (Ochlerotatus) taeniopygus, Aedes (Ochlerotatus) triseriatus, Culex salinarius, Culex tarsalis, Culex titttans, and Anopheles bradleyi-crucians.40,108 Aedes (Ochlerotatus) vexans, Culex pipiens pipsiens, and Culex pipiens quinquefasciatus should also be considered as potential vectors of RVFV in the continental United States.4 The geographic distributions of these mosquito species encompass the continental United States102 and often overlap; in addition, they coincide with the distributions for domestic ruminant livestock, ruminant wildlife, and humans, all of which can serve to amplify RVFV. Nearly all of the aforementioned mosquito species will feed on mammals, including humans.111,112 Thus, if RVFV is released into the United States, the large number of mosquito species that will readily feed on domestic and wild animals and humans suggests that RVF will likely be evident clinically as a zoonotic disease.

**Ruminant livestock**

On the basis of activities associated with the feasible pathways, domestic ruminant livestock species (sheep, goats, beef, and dairy cattle) in 14 states (Alabama, California, Florida, Georgia, Maine, Maryland, Massachusetts, Minnesota, New Jersey, New York, Pennsylvania, South Carolina, Texas, and Virginia) appear to be most vulnerable for exposure to RVFV. This deduction is based, in part, on the fact that Georgia, Maryland, New Jersey, New York, Pennsylvania, South Carolina, and Texas have the most activity in terms of airline passenger arrivals or commodities received from RVFV-endemic countries. In addition, California, Florida, Georgia, Maryland, Massachusetts, Minnesota, New Jersey, New York, Texas, and Virginia have large populations of African-born immigrants, some of whom are visited by...
friends and family members that could be viremic with RVFV from RVFV-endemic countries at the time of their visit to the continental United States. Because ports of entry in Alabama and Maine receive > 10% of some of the commodities exported from RVFV-endemic countries to the continental United States, these 2 states may also be vulnerable for exposure to RVFV.

Although Texas has the largest number of farms and inventory of ruminant livestock,113 the population of animals in New York may be at greatest risk for exposure to RVFV. Ports of entry in New York log the most activity in terms of receiving commodities and people from RVFV-endemic countries. New York is also an entry point for any ruminant wildlife species requiring quarantine after entering the continental United States by permit from an RVFV-endemic country. Furthermore, New York is home to a large population of African-born immigrants who may have friends and family members visit them from RVFV-endemic countries.

Camelids (llamas, alpacas, vicuñas, and guanacos) are found throughout all states in the continental United States and may be equally susceptible to RVFV infection. The top 5 states in number of camelids (57,984 [40.1%] of the entire camelid population in the continental United States) are California, Colorado, Oregon, Texas, and Washington.111

**Ruminant wildlife**

Free-roaming ruminant wildlife species, including moose (Alces alces), elk (Cervus elaphus), mule deer (Odocoileus hemionus), white-tailed deer (Odocoileus virginianus), big horn sheep (Ovis canadensis), mountain goats (Oreamnos americanus), pronghorn antelope (Antilocapra americana), and caribou (Rangifer tarandus) can be found in various habitats across the United States.114 In most cases, the actual number of free-roaming animals of each species is not precisely known.8 However, white-tailed deer have the widest geographic distribution of all free-roaming ruminant wildlife species that inhabit the continental United States. Thus, because of their ubiquitous distribution and growing conflicts with people within urban or suburban environments,115 they could be the first wildlife species to become infected with RVFV and develop clinical signs of RVF. In addition, > 600,000 captive deer, elk, and bison (Bison bison) are raised in the continental United States.113 Many other species of ruminant wildlife indigenous to Africa are confined to properties in the continental United States for hunting, exhibition, or breeding purposes. An accurate inventory of the various species is not available, although many of these animals are located in Texas.8

**Humans**

On the basis of activities associated with the feasible pathways, the 154,374,756 people in 14 states (Alabama, California, Florida, Georgia, Maine, Maryland, Massachusetts, Minnesota, New Jersey, New York, Pennsylvania, South Carolina, Texas, and Virginia)116 appear to be most vulnerable for exposure to RVFV. Among these, California has the highest population, followed by New York. There are 141 cities with a population of ≥ 100,000 people located in these states.

**Discussion**

The ultimate purpose of a pathways analysis is to provide information to decision-makers about the feasible route or routes that a disease agent (eg, RVFV) can use to enter a geographic region so that a surveillance plan can be developed for rapid detection of the organism. Four of the 5 pathways (importation of RVFV-infected animals, entry of RVFV-infected people, mechanical transport of RVFV-infected insect vectors, and smuggling of live RVFV) investigated for release of RVFV into the continental United States in the study reported here appeared to be feasible. Without considering the latter pathway, 14 states (Alabama, California, Florida, Georgia, Maine, Maryland, Massachusetts, Minnesota, New Jersey, New York, Pennsylvania, South Carolina, Texas, and Virginia) appeared to be most vulnerable for exposure of ruminant livestock, ruminant wildlife, and human populations to RVFV. This group of at-risk states could be altered in its entirety if the virus is released illicitly as part of an act of agroterrorism.

The appearance and rapid spread throughout the continental United States of West Nile virus, another zoonotic viral disease transmitted by mosquitoes, serves as a reminder to public health officials that improvement in the infrastructure for surveillance of vector-borne diseases is needed. In 1999, congressional funding allowed implementation of a surveillance program for West Nile virus in the 48 contiguous states and District of Columbia through collaboration between animal health and public health agencies.137 Emphasis was placed on surveillance of this virus in mosquitoes and dead birds and as a cause of neurologic disease in equine species and humans. Results of the pathways analysis for RVFV reported here again revealed the need to improve collaborations between animal health and public health agencies that are responsible for detection of zoonotic disease agents and subsequent response to their introduction. To that end, efforts are underway in various federal agencies to improve coordination and communication, including the formation of an RVF working group149 and enhancing technology transfer between agencies to improve diagnostic capability for this disease. The CDC and the USDA, APHIS, Veterinary Services have developed an enhanced surveillance mechanism that uses data captured for both humans and other animals. Additional information about this collaboration is available from the USDA, APHIS, Veterinary Services National Animal Health Surveillance System Web site.119 The success of this collaboration should help ensure the ongoing development of a more comprehensive approach to surveillance and control of vector-borne diseases such as RVF.

Analysis of the feasibility of the various pathways reported here was limited by several factors. First, data on human and animal movements were incomplete and lacked specific information necessary for optimum evaluation of these pathways. For example, during 2000 through 2003, 4 African countries exported nonhuman primates into the continental United States. The databases that provided this information did not list the final US destinations for these animals or their intended use. This information would have improved
It appears that there may well be a fundamental gap in basic maritime security that relates to the effective monitoring of the possible introduction of pathogens by insect vectors.¹ The US FDA conducts some inspections of shipping containers in accordance with food protection laws that extend back to 1907 and that tie specifically to visual inspection methods.² Currently, only approximately 20,000 of these inspections are conducted annually on the millions of containers that enter the United States via all ports of entry. The basis for these laws and the proscribed methods of inspection extend well before the advent of shipping via intermodal containers and therefore are not adequate in frequency or methods used to meet the potential risks associated with the modern maritime transportation system.³ Although many agencies other than the FDA could play a role in container inspection (namely, Customs and Border Protection, state agricultural departments, the CDC, and state public health agencies), none of the latter agencies routinely inspect intermodal containers carrying food products. The inspection of ships and containers of nonfood-containing commodities is performed on a substantially less frequent basis.⁴ Rift Valley fever is a zoonotic disease that causes substantial morbidity and fatalities in humans and other animals. The introduction and spread of West Nile virus into the continental United States revealed that improved collaboration and coordination for research and surveillance of zoonotic vector-borne diseases were needed. The pathways analysis reported here was conducted to assist in development of a surveillance plan for RVFV that enables rapid detection and response by animal health and public health officials. As part of the pathways analysis and surveillance planning efforts, several key gaps in knowledge were identified. Our ability to capitalize on the lessons learned from West Nile virus and the information obtained through this analysis can assist in the development of collaborative, interagency surveillance and response plans as well as a shared research agenda.

b. Peters CJ, Departments of Microbiology & Immunology and Pathology, Center for Biodefense & Emerging Infectious Diseases, University of Texas Medical Branch, Galveston, Tex: Personal communication, 2006.
c. Marfin A, Quarantine and Border Health Service, Division of Global Migration and Quarantine, CDC, Seattle, Wash: Personal communication, 2006.
d. Remis MS, Quarantine and Border Health Services Branch, Division of Global Migration and Quarantine, CDC, Atlanta, Ga: Personal communication, 2007.
h. Miller R, USDA, APHIS, Veterinary Services, Centers for Epidemiology and Animal Health, Center for Emerging Issues, Spatial Epidemiology Team, Fort Collins, Colo: Personal communication, 2006.

References

17. Davies FG, Martin V. Recognizing Rift Valley fever. FAO Animal

75. Sellers RF, Pedgley DE, Tucker MR. Rift Valley fever, Egypt

78. Lindgren T, Norback D. Cabin air quality: indoor pollutants and

vesicular stomatitis in North America, 1982–5. Epidemiol Infect
1990;104:313–328.

70. Sellers RF, Pedgley DE. Possible windborne spread to western
Turkey of bluetongue virus in 1977 and of Akabane virus in

71. Sellers RF, Maarouf AR. Trajectory analysis of winds and

72. Ritchie SA, Rochester W. Wind-blown mosquitoes and intro-
duction of Japanese encephalitis into Australia. Emerg Infect Dis

73. Sellers RF, Maarouf AR. Impact of climate on western equine
encephalitis in Manitoba, Minnesota and North Dakota, 1980–83.

74. Sellers RF. Eastern equine encephalitis in Quebec and Connecti-

75. Sellers RF, Pedgley DE. Tucker MR. Rift Valley fever, Egypt

76. Hughes JH. Mosquito interceptions and related problems in
aerial traffic arriving in the United States. Mosquito News

77. Perry G. Wheel well and cargo compartment temperatures of
large aircraft in flight: implications for stowaways. Aviat Space

78. Lindgren T, Norback D. Cabin air quality: indoor pollutants and
climate during intercontinental flights with and without tobac-

79. World Organization for Animal Health (OIE) Web site. Multian-
urnal animal disease status for a region and a disease. Available at:

80. US National Archives and Records Administration Web site.
Costs of federal regulations. Title 9—animals and animal prod-
ucts. Chapter I—Animal and Plant Health Inspection Service,
Department of Agriculture. Part 94: rinderpest, foot-and-mouth
disease, fowl pest (fowl plague). Sec. 94.1. Regions where rinder-
pest or foot-and-mouth disease exists; importations prohibited.

81. Import Tracking System database. Fort Collins, Colo: USDA-
Animal and Plant Health Inspection Service, Department of
Agriculture. Part 93: importation of certain animals, birds, and
poultry, and certain subpart D ruminants. Sec. 93.404. Import permits for ruminants and for ruminant
tests specimens for diagnostic purposes; and reservation fees for
space at quarantine facilities maintained by APHIS. Available at:
a257.g.akamail.net/7/257/2422/11Feb20053100/edocket.ac-

82. US National Archives and Records Administration Web site.
Cost of federal regulations. Title 9—animals and animal prod-
ucts. Chapter I—Animal and Plant Health Inspection Service,
Department of Agriculture. Part 93: importation of certain
animals, birds, and poultry, and certain subpart D ruminants.
Sec. 93.405. Import permits for ruminants and for ruminant
test specimens for diagnostic purposes; and reservation fees for
space at quarantine facilities maintained by APHIS. Available at:
a257.g.akamail.net/7/257/2422/11Feb20053100/edocket.ac-

83. US National Archives and Records Administration Web site.
Code of federal regulations. Title 9—animals and animal products.
Chapter I—Animal and Plant Health Inspection Service, Depart-
ment of Agriculture. Part 93: importation of certain animals,
birds, and poultry, and certain subpart D ruminants. Sec. 93.405.
Certificate for ruminants. Available at: a257.g.akamail.net/7/257/2422/11Feb20061500/edocket.access.gov/cfr_2006/Janq-

84. US Department of Health and Human Services Centers for
Disease Control and Prevention (CDC) Web site. Importation of
nonhuman primates. Available at: www.cdc.gov/ncidod/dq/non-

85. US National Archives and Records Administration Web site.
Code of federal regulations. Title 42—public health. Chapter I—Public Health Service, Department of Health and Human Ser-
71.53: nonhuman primates. Available at: a257.g.akamail.net/7/257/2422/09nov20051500/edocket.access.gov/cfr_2-


brary.laws.gov/IA_Pubs/CITES_Biennialreport00-01.pdf. Ac-
cessed Feb 10, 2006.

88. US Department of Health and Human Services Centers for
Disease Control and Prevention (CDC) Web site. Embargoed
African rodents and monkeypox virus. Available at: www.cdc.

89. Federal Aviation Administration Web site. International flight
information manual: entry, transit, and departure flights. Avail-
12, 2007.

90. Federal Aviation Administration Web site. Guide for private fly-

91. Vacationstogo.com Web site. United States (continental) ports. Available at:

92. The Intermodal Transportation Database [database online].
Washington, DC: US Department of Transportation, US Bureau of

93. Agricultural Quarantine Inspection database. Fort Collins,

94. Migration Policy Institute Web site. African-born residents of
the United States. Available at: www.migrationinformation.org/

95. US Department of Commerce Office of Travel and Tourism In-
dustries Web site. US Citizen Air Traffic to Overseas Regions,
Canada & Mexico 2005. Available at: timet.niaa.doc.gov/view/m-

96. US Department of Transportation Maritime Adminis-
Available at: www.marad.dot.gov/Marad_Statistics/2003%20Cruise%20Data%202003%20-

97. Armed Forces Pest Management Board Web site. DoD instruction 6490.03—implementation and application of joint medi-
cal surveillance for deployments. Available at: www.alpmb.org/

98. Federal Aviation Administration Web site. Airport to report all-
cargo data to FAA. Available at: www.faa.gov/airports_airtraffic/
airports/planning_capacity/passenger_allcargo_stats/reporting/

99. Lloyd’s Maritime Intelligence Unit, Vessel Movement Data Files
[database online]. Washington, DC: US Department of Trans-
portation, 2006. Available at: www.marad.dot.gov/MARAD_sta-

100. USDA Animal and Plant Health Inspection Service Plant Protec-
Available at: www.aphis.usda.gov/ppp/manuals/port/pdf_files/

101. USDA Animal and Plant Health Inspection Service, Depart-
ment of Agriculture. Part 71: Foreign quarantine, subpart F importa-
tions of nonhuman primates. Available at: www.cdc.gov/ncidod/dq/np-


### Appendix 1

Characteristics of disease associated with natural and experimental RVFV infection in domestic and wild ruminants.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Hazard category*</th>
<th>Type of infection</th>
<th>Clinical findings</th>
<th>Duration of disease</th>
<th>Case fatality rate (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domestic sheep</td>
<td>High</td>
<td>Natural, experimental</td>
<td>Fever, lethargy, signs of abdominal pain, and hepatic infection (icterus); encephalitis in animals that survive initial hepatic infection</td>
<td>1–2 days</td>
<td>90–100</td>
<td>10^10 MIPLD&lt;sub&gt;50&lt;/sub&gt;/mL logarithm of virus; may shed virus in feces; nearly total hepatocellular destruction; recovery from encephalitis is quick, with no sequelae, and immunity is long-lasting</td>
</tr>
<tr>
<td>Domestic goat</td>
<td>High</td>
<td>Natural</td>
<td>Fever, lethargy, signs of abdominal pain, with death 12 to 36 hours after onset</td>
<td>1–7 days</td>
<td>70–100</td>
<td>10^6 MIPLD&lt;sub&gt;50&lt;/sub&gt;/mL logarithm of virus; may harbor virus in spleen (viral persistence); may also shed virus in feces; nearly total hepatocellular destruction in animals that die; recovery from encephalitis is quick, with no sequelae, and immunity is long-lasting</td>
</tr>
<tr>
<td>Domestic cattle</td>
<td>High</td>
<td>Natural</td>
<td>Collapse, hepatitis, and encephalomyelitis; often die within 24 hours after onset</td>
<td>1–7 days</td>
<td>20–100</td>
<td>10^10 MIPLD&lt;sub&gt;50&lt;/sub&gt;/mL logarithm of virus; may also shed virus in manure</td>
</tr>
<tr>
<td>Buffalo</td>
<td>High</td>
<td>Natural</td>
<td>May be inapparent; possible abortions</td>
<td>Transient viremia</td>
<td>&lt; 10</td>
<td>Virus titer of 10^4 TCID&lt;sub&gt;50&lt;/sub&gt;/mL; may also shed virus in milk and feces</td>
</tr>
<tr>
<td>Camel</td>
<td>High</td>
<td>Natural</td>
<td>Inapparent infection except for high risk of abortions and illness in newborns</td>
<td>Brief viremia</td>
<td>Some fatalities in newborns</td>
<td>Logarithm of virus in blood may be high</td>
</tr>
<tr>
<td>Waterbuck</td>
<td>Low</td>
<td>Natural</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Positive for antibodies</td>
</tr>
</tbody>
</table>

*High hazard indicates that clinicians typically detect clinical signs of disease in some or all ill animals, there is amplified production of virus in vivo (and virus is pathogenic when inoculated into mice), and the animal serves as a possible source of virus for transmission by arthropod vectors to susceptible humans or other animals. Low hazard indicates inapparent infection, a low viral titer, and transient viremia; production of virus in vivo is probably insufficient to infect an arthropod vector.

MIPLD<sub>50</sub> = Mouse intraperitoneal median lethal dose.

Continued on next page.
## Appendix 2

Characteristics of disease associated with natural and experimental RVFV infection in humans and nonhuman primates.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Hazard category*</th>
<th>Type of infection</th>
<th>Clinical findings</th>
<th>Duration of disease</th>
<th>Case fatality rate (%)</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human (Homo sapiens)</td>
<td>High</td>
<td>Natural</td>
<td>Fever, headache, myalgia, and fatigue; infrequent (1% to 5%) hepatic; retinitis; rare (&lt;1%) meningoencephalitis; and DIC</td>
<td>4–10 days</td>
<td>Typically &lt; 1–20, but 50–100 when there is DIC</td>
<td></td>
<td>10&lt;sup&gt;5&lt;/sup&gt; MICLD&lt;sub&gt;50&lt;/sub&gt;/mL logarithm of virus in blood; greatest risk is contact with sheep; possible increased risk from consuming raw milk; lower risk for children</td>
</tr>
<tr>
<td>Nonhuman primate</td>
<td>High</td>
<td>Experimental</td>
<td>Mild fever, anorexia, and vomiting; approximately 20% hemorrhagic form with DIC and death</td>
<td>3–7 days</td>
<td>20</td>
<td>Up to 10&lt;sup&gt;7&lt;/sup&gt; PFUs/mL logarithm of virus in blood is possible; blood is infective for mice for up to 13 days after inoculation</td>
<td>27, 34–38</td>
</tr>
<tr>
<td>Rhesus macaque (Macaca mulatta)</td>
<td>High</td>
<td>Experimental</td>
<td>Febrile, but no other clinical signs observed</td>
<td>Viremic for up to 6 days</td>
<td>No death; developed antibodies against RVFV</td>
<td>Viremic blood lethal to mice</td>
<td>39</td>
</tr>
<tr>
<td>Green guenon (Cercopithecus calithrix)</td>
<td>High</td>
<td>Experimental</td>
<td>Viremic for up to 6 days</td>
<td>No death; developed antibodies against RVFV</td>
<td>Viremic blood lethal to mice</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Sooty mangabeys (Cercocebus fuliginosus)</td>
<td>High</td>
<td>Experimental</td>
<td>Febrile, but no other clinical signs observed</td>
<td>Viremic for up to 6 days</td>
<td>No death; developed antibodies against RVFV</td>
<td>Viremic blood lethal to mice</td>
<td>39</td>
</tr>
<tr>
<td>Patas guenon (Erythrocebus patas)</td>
<td>High</td>
<td>Experimental</td>
<td>Febrile, but no other clinical signs observed</td>
<td>Viremic for up to 6 days</td>
<td>No death; developed antibodies against RVFV</td>
<td>Viremic blood lethal to mice</td>
<td>39</td>
</tr>
<tr>
<td>African green monkey (Cercopithecus aethiops abaeus)</td>
<td>Moderate</td>
<td>Natural</td>
<td>Inapparent infection or transient fever with malaise for 1–2 days</td>
<td>Unknown</td>
<td>Unknown</td>
<td>None</td>
<td>36, 37</td>
</tr>
<tr>
<td>Baboon (Papio spp)</td>
<td>Moderate</td>
<td>Natural</td>
<td>Inapparent infection or transient fever with malaise for 1–2 days</td>
<td>Unknown</td>
<td>Unknown</td>
<td>None</td>
<td>21</td>
</tr>
</tbody>
</table>

*Moderate hazard indicates that clinicians may detect clinical signs of disease, but production of virus in vivo is probably insufficient to infect an arthropod vector.

DIC = Disseminated intravascular coagulopathy.

See Appendix 1 for remainder of key.
Appendix 3
Characteristics of disease associated with natural and experimental RVFV infection in rodents.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Hazard category*</th>
<th>Type of infection</th>
<th>Clinical findings</th>
<th>Duration of disease</th>
<th>Case fatality rate (%)</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse†</td>
<td>High</td>
<td>Natural, experimental</td>
<td>ND</td>
<td>Transient viremia</td>
<td>70–100</td>
<td>Logarithm of virus in blood of Guinea multiple-mammate mouse may be high; this mouse species may be reservoir host during interepizootic phase of RVFV maintenance cycle; logarithm of virus in Swiss Webster white mouse up to $10^{9.0}$ MIPLD₅₀/mL; blood from wood mouse, dormouse, and Swiss Webster white mouse is pathogenic when inoculated into other mice</td>
<td>19, 34, 40, 41</td>
</tr>
<tr>
<td>Rat‡</td>
<td>High</td>
<td>Natural, experimental</td>
<td>ND</td>
<td>Highly variable</td>
<td></td>
<td>Logarithm of virus in blood may be high; African grass rat, field rat, and Namaqua rock rat may be reservoir hosts during interepizootic phase of RVFV maintenance cycle</td>
<td>40, 42–45</td>
</tr>
<tr>
<td>Syrian (golden) hamster (Mesocricetus auratus)</td>
<td>High</td>
<td>Experimental</td>
<td>Transient viremia; acute hepatitis and death</td>
<td>&lt; 12 hours</td>
<td>70–100</td>
<td>Logarithm of virus in liver and blood may be as high as $10^{10.2}$ MIPLD₅₀/g and $10^{10.2}$ MIPLD₅₀/mL, respectively</td>
<td>34, 41, 45</td>
</tr>
<tr>
<td>Field vole (Microtus agrestis)</td>
<td>High</td>
<td>Experimental</td>
<td>Death preceded by lethargy then unconsciousness</td>
<td>30–60 hours</td>
<td>Almost always fatal</td>
<td>Blood is pathogenic when inoculated into mice</td>
<td>34</td>
</tr>
<tr>
<td>Gray squirrel (Sciurus carolinensis)</td>
<td>High</td>
<td>Experimental</td>
<td>ND</td>
<td>Death within 36 hours</td>
<td>Only 2 squirrels (1 died)</td>
<td>Blood is infective for mice</td>
<td>34</td>
</tr>
<tr>
<td>Gerbil (Gerbillus spp)</td>
<td>Moderate</td>
<td>Experimental</td>
<td>Necrotizing encephalitis</td>
<td>Unknown</td>
<td>100 at 3 weeks of age; 20 at 10 weeks of age</td>
<td>None</td>
<td>47</td>
</tr>
</tbody>
</table>

†Includes the Guinea multiple-mammate mouse (Mastomys erythroleucus), Swiss Webster white mouse (Mus spp), dormouse (Muscardinus avellanarius), and wood mouse (Apodemus sylvaticus). ‡Includes African grass rat (Arvicanthis niloticus), Namaqua rock rat (Aethomys namaquensis), laboratory rat (Rattus norvegicus), and field rat (Arvicanthis abyssinicus). ND = Not determined. See Appendices 1 and 2 for remainder of key.
## Appendix 4
Characteristics of disease associated with natural and experimental RVFV infection in other susceptible animals.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Hazard category*</th>
<th>Type of infection</th>
<th>Clinical findings</th>
<th>Duration of disease</th>
<th>Case fatality rate (%)</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domestic ferret (Mustela putorius furo)</td>
<td>High</td>
<td>Experimental</td>
<td>Incubation period 24–72 hours; fever, lethargy, anorexia, and tachypnea</td>
<td>At least 4–5 days</td>
<td>Usually fatal</td>
<td>Edematous pulmonary consolidation, focal hepatic necrosis, and hemorrhagic enteritis; blood is pathogenic to mice</td>
<td>48</td>
</tr>
<tr>
<td>Domestic dog (Canis familiaris; newborn, juvenile, and adult)</td>
<td>Moderate</td>
<td>Natural</td>
<td>Clinical disease in 1- to 7-day-old puppies; inapparent infection in juveniles and adults; some females may abort</td>
<td>Unknown</td>
<td>60–100 in newborns</td>
<td>$10^{2.2}–10^{3.8}$ MICLD$_{50}$/mL</td>
<td>22, 49–51</td>
</tr>
<tr>
<td>Domestic cat (Felis catus; newborn, juvenile, and adult)</td>
<td>Moderate</td>
<td>Natural</td>
<td>Clinical diseases in 1- to 21-day-old kittens; inapparent infection in juveniles and adults; some may abort</td>
<td>Unknown</td>
<td>70–100 in newborns</td>
<td>$10^{2.8}–10^{4.2}$ MICLD$_{50}$/mL</td>
<td>22, 49, 50, 52</td>
</tr>
<tr>
<td>Domestic horse (Equus caballus)</td>
<td>Low</td>
<td>Natural</td>
<td>Inapparent infection</td>
<td>Transient</td>
<td>Unknown</td>
<td>$10^{2.5}$ MIPLD$_{50}$/mL</td>
<td>21, 22, 27, 53</td>
</tr>
<tr>
<td>Domestic donkey (Equus asinus)</td>
<td>Low</td>
<td>Natural</td>
<td>Inapparent infection; some may abort</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>21, 31</td>
</tr>
<tr>
<td>African wild dog (Lycaon pictus)</td>
<td>Low</td>
<td>Natural</td>
<td>Newborns more susceptible than adults</td>
<td>Unknown</td>
<td>Unknown</td>
<td>7 of 65 with positive results on screening test</td>
<td>49</td>
</tr>
<tr>
<td>Lion (Panthera leo)</td>
<td>Low</td>
<td>Natural</td>
<td>Newborns more susceptible than adults</td>
<td>Unknown</td>
<td>Unknown</td>
<td>15 of 113 with positive results on screening test</td>
<td>49</td>
</tr>
<tr>
<td>Cheetah (Acinonyx jubatus)</td>
<td>Low</td>
<td>Natural</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>2 of 64 with positive results on screening test</td>
<td>49</td>
</tr>
<tr>
<td>Spotted hyena (Crocuta crocuta)</td>
<td>Low</td>
<td>Natural</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>0 of 65 with positive results on screening test</td>
<td>49</td>
</tr>
<tr>
<td>Jackal (Canis spp)</td>
<td>Low</td>
<td>Natural</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>3 of 22 with positive results on screening test</td>
<td>49</td>
</tr>
<tr>
<td>Domestic pig (Sus scrofa domestica)</td>
<td>Low</td>
<td>Natural</td>
<td>Resistant or inapparent infection</td>
<td>Brief viremia</td>
<td>Unknown</td>
<td>Unknown</td>
<td>21, 22, 27</td>
</tr>
<tr>
<td>Black rhinoceros (Diceros bicornis)</td>
<td>Low</td>
<td>Natural</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>19</td>
</tr>
<tr>
<td>White rhinoceros (Ceratotherium simum)</td>
<td>Low</td>
<td>Natural</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>19</td>
</tr>
<tr>
<td>Bat†</td>
<td>Low</td>
<td>Natural, experimental</td>
<td>No clinical signs observed in bats inoculated experimentally</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Uncommon to isolate virus from wild bats in nature; experimentally have low amounts of virus antigen in urine, liver, and brown fat</td>
<td>54, 55</td>
</tr>
<tr>
<td>Hippopotamus (Hippopotamus amphibius)</td>
<td>Low</td>
<td>Natural</td>
<td>Inapparent infection</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>19</td>
</tr>
</tbody>
</table>

*Includes Eptesicus capensis, Miniopterus schreibersii, Myotis tricolor, Myotis leisuri, Rhinolophus clivosus, Tadarida aegyptiaca, and Laephotis wintoni.*

See Appendices 1 and 2 for remainder of key.
Appendix 5

Various animals that have evidence of resistance to experimental and natural infection with RVFV.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Type of infection</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hedgehog (Genus and species not defined)</td>
<td>Experimental</td>
<td>None</td>
<td>34</td>
</tr>
<tr>
<td>Mongoose (Herpestes ichneumon)</td>
<td>Experimental</td>
<td>None</td>
<td>34</td>
</tr>
<tr>
<td>Guinea pig (Cavia porcellus)</td>
<td>Experimental</td>
<td>None</td>
<td>34</td>
</tr>
<tr>
<td>Domestic rabbit (Oryctolagus cuniculus)</td>
<td>Experimental</td>
<td>Typically resistant to infection but may rarely allow virus to survive for a short period in the blood</td>
<td>34, 48</td>
</tr>
<tr>
<td>Birds</td>
<td>Natural, experimental</td>
<td>Resistant in nature, but their cells may be infected in culture</td>
<td>15, 21, 22, 34, 56</td>
</tr>
<tr>
<td>Reptiles</td>
<td>Natural, experimental</td>
<td>Resistant in nature, but their cells may be infected in culture</td>
<td>15, 22, 34, 56</td>
</tr>
<tr>
<td>Amphibians</td>
<td>Natural, experimental</td>
<td>Resistant in nature, but their cells may be infected in culture</td>
<td>15, 22, 34, 56</td>
</tr>
</tbody>
</table>