

## Rift Valley Fever: Scientific Pathways Toward Public Health Prevention and Response

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As humankind strides into the second decade of the 21st century, we can take pride in advances that have enhanced the lives of many around the world. The planet is a very different place from what it was during the 19th century. The connectivity experienced through global travel and communications was unthinkable then, when technology was about to affect nearly every facet of life. And yet, scourges that infested the industrial world at that time, then nearly disappeared during the early 1900s, in the industrialized world, like cholera and typhoid fever,<sup>1–3</sup> continue to rage in Africa and Asia<sup>4–7</sup> in these modern times. Despite technologic advancements, these diseases are classic indicators of inadequate infrastructure, showing persisting societal failures.

While the “classic” diseases continue to rage, new highly fatal diseases have emerged or reappeared during the 21st century, such as severe acute respiratory syndrome (SARS),<sup>8,9</sup> Nipah virus encephalitis,<sup>10</sup> and avian influenza<sup>11</sup> with adverse global or regional public health and economic impact. These events have shown how ecologic changes brought on by factors associated with increasing human population size, like massive consumption of natural resources and encroachment on environments, have brought animals (and the pathogens that infect them) in close contact with immunologically naive humans. Once introduced into humans, those pathogens that are transmitted from human to human can spread with lightning speed by global and regional commercial markets and travel.

Advancing technologies are creating exciting possibilities for prevention and control of emerging infectious diseases. They include: far-reaching and constantly improving communications tools, including use of mobile text messaging resulting in improved surveillance approaches,<sup>12</sup> and state-of-the-art satellite imagery and mapping capacity to forecast and detect ecologic changes and climate anomalies relevant to disease prevalence.<sup>13,14</sup> In addition, monitoring of animal and insect vector mobility and geographic distributions and, development of highly sensitive diagnostic tools for use in human, animal, and vector surveillance are enhancing the ability to detect new pathogens or changes in reservoir patterns for known pathogens. These new capacities will dramatically affect the ability to detect early, and, ultimately to forecast in advance, the emergence of disease threats so that effective measures can be taken to avert or minimize the public health impact.

Rift Valley Fever (RVF) is an illustrative model for assessing the impact of climate and ecology on its periodic re-emergence and spread, as well as for the potential that modern technologies and public health advancements can contribute to disease forecasting, prevention, and control.<sup>12</sup> Rift Valley fever is caused by a phlebovirus that infects animals and mos-

quitoes and can be spread by animal secretions and mosquito bites.<sup>15</sup> Studies suggest that the virus is maintained in soil within floodwater *Aedes* mosquito eggs during inter-epidemic periods; rapid, and potentially massive amplification can occur during heavy rains and flooding, when mosquito eggs synchronously mature into larvae and adult mosquitoes.<sup>16</sup> The virus then infects a large number of immunologically naive animals, which then infect exposed humans (who may also be infected by mosquito bites), causing a severe often fatal, hemorrhagic illness in a small percentage of those infected.<sup>17</sup> The virus has also been moved long distances through livestock trade practices<sup>18,19</sup> (and potentially through movement of infected mosquitoes), creating disease potential in regions without previous exposure to the virus.

The public health response to the outbreak of RVF in east Africa during 2006–2007<sup>20</sup> suggested that diagnostic and epidemiologic advances have already impacted Africa in the 21st Century. The 2006–2007 outbreak was detected, reported, and confirmed within a 1 week period following the appearance of an initial cluster of cases of a febrile hemorrhagic illness.<sup>20</sup> When compared with the previous RVF outbreak in Kenya occurring less than 10 years before,<sup>21</sup> the remarkably swift outbreak detection, etiologic confirmation, and public health responses were made possible by advances in communication, major enhancements in diagnostic technologies (like real-time polymerase chain reaction [PCR]) and local diagnostic capacity (functioning within country). Government-led bans on animal slaughtering (supported by local imams and a critical step, given the rapid approach of Eid al-Adha, during which animals are killed, and portions given to the poor), restrictions on movement of livestock, and vector control programs were quickly implemented; while improvements in effectiveness of the interventions are undoubtedly possible, they likely had substantial effect in preventing illnesses and mortality. This is especially likely, given data from this outbreak, showing that direct exposure to infected animal secretions (most likely to occur through slaughtering) was associated with mortality from RVF infection.<sup>22</sup>

### THE WORKSHOP

After completion of the outbreak, 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, organized a workshop entitled “Rift Valley Fever: Scientific Pathways to Public Health Prevention and Response.” The May 2008 workshop, held in Nairobi, was attended by more than 100 scientists and researchers from Africa and around the world. It included presentations of findings from many of the investigations that were carried

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out during the outbreaks in Kenya and in Tanzania, focusing on human and veterinary descriptions of the magnitude and characteristics of the outbreaks, risk factors, molecular epidemiology, diagnostics, pathology, forecasting, and economic and behavioral assessments. This Supplement includes nine papers presented and discussed at the workshop and provides a compendium of knowledge gained during the 2006–2007 RVF outbreak investigations.

In addition, during the workshop, FAO and partners presented a draft decision tool for systematic approaches for preparedness, detection, and response to future RVF outbreaks. The discussions were dynamic around pivotal issues contained within the draft—the decision tool was finalized during a subsequent meeting. It is included in this Supplement to increase the use of this issue for public health officials, scientists, and organizations focused on preventing and minimizing the impact of future Rift Valley Fever outbreaks.

In addition to relevance to RVF prevention and control, the specific approaches discussed during the workshop provide windows into how hybrids of traditional and cutting-edge capacities and technologies could be fashioned into public health systems for forecasting of outbreaks and to trigger effective measures to prevent and respond early effectively to disease threats. The areas discussed include human diseases surveillance with Integrated Disease Surveillance and Response (IDSR), veterinary disease and mortality surveillance and serologic surveys, entomologic surveys, ecologic and climatologic imagery and disease forecasting, genetic sequencing, pathogen discovery, and gross pathology and immunohistochemistry. Many pathogens that have emerged over the last 35 years, including *Legionella*,<sup>23</sup> Hantavirus-sin nombre virus (the cause of hantavirus pulmonary syndrome),<sup>24</sup> and Nipah virus,<sup>10</sup> among many others, were subsequently shown to have caused illness for years before the outbreaks that led to their identification. In the case of Nipah virus, retrospective studies showed that pigs in Malaysia were infected, possibly as early as 1996, 2 years before the massive outbreak occurred in pigs and humans.<sup>25</sup> The SARS outbreak led to intensive study and identification of other human coronaviruses as causes of respiratory tract infection.<sup>26</sup> In the future, it may well be possible to identify pathogens and their disease potential before they wreak disease and societal disruptions associated with major outbreaks.

Compared with high incidence diseases that cause suffering and death daily in Africa, like pneumonia and diarrheal disease, AIDS, TB, and malaria, RVF does not compete in terms of direct public health impact. However, outbreaks result in substantial hardship, directly through illness and through direct economic impact (as a result of animal deaths and abortions, and because of a variety of commercial bans).<sup>27</sup> While likely a substantial underestimate, the outbreaks caused more than 700 cases in Tanzania and Kenya with at least 230 deaths<sup>20,28</sup> (although initial reports provided higher numbers).<sup>29</sup> The economic impact of the outbreak was more widely felt than had previously been appreciated. Beyond livestock producers in the affected areas, traders, slaughter-house workers, butchers, transporters, and a range of small-scale businesses, such as operators of food kiosks who served these workers, all incurred losses. It was reported that significant numbers of livestock traders and butchers were unable to resume their business activities after the bans on livestock movement and slaughter were lifted because of depletion of capital.<sup>27</sup>

Like SARS, avian influenza, Nipah encephalitis, bovine spongiform encephalopathy, and many other emerging infectious diseases, RVF outbreaks highlight the critical role of veterinary health surveillance and outbreak response capacity for human health security. For Kenya, the 2006–2007 RVF outbreak dramatically showed an acute need to support animal health and regulatory activities, making palpable the meaning and value of a “One Health” approach. During the workshop, there was agreement that One Health needs clearer definition and there was a call for showing and assessing the feasibility and effect of a combined veterinary-human health program in at least one district or province in a country in Africa.

#### GAPS IN KNOWLEDGE AND TOOLS: A RESEARCH AGENDA

A variety of gaps in knowledge and in available tools were identified during workshop discussions to be important for controlling RVF in endemic and naive countries in Africa and the Arabian Peninsula. These include the following:

**1. The role of domestic and wild vertebrate animals in the maintenance of the virus during inter-epidemic periods (IEPs) is not fully understood.** There is increasing evidence that active infection of livestock, albeit in small numbers, continues after epidemics, as evidenced by detection of immunoglobulin M (IgM) antibodies in 1–3% of animals and IgG antibodies in animals born and tested during the IEPs.<sup>30</sup> Neutralizing antibodies are detectable in non-domesticated animals (wildlife) in Kenya and Southern Africa.<sup>31</sup> However, it is not clear how relatively important these infections are in the maintenance of the virus when compared with the role of floodwater *Aedes* mosquitoes.

**2. There is a need to enhance existing RVF risk prediction models by including spatial and population parameters to achieve higher precision and confidence.** The RVF risk prediction models are currently focused on Eastern and Southern Africa and are based on cyclic climatic variations in the region in consideration of prior epidemics in the region. Future models should include spatial information from other regions that have recently experienced RVF epidemics, including West Africa, North Africa (primarily the Nile valley in Egypt), and the Arabian Peninsula. Higher specificity of forecast models will be needed for them to be confidently used to activate action-steps, which require commitment of public health resources, especially when considering how those resources are often limited. Specificity of the model may be increased by including animal surveillance to document the degree of herd immunity (high levels should limit potential of disease outbreaks even when climatic risks exist), and entomologic surveillance to identify potential for disease spread.

**3. A threshold of immunity required in livestock (proportion of animals with natural or vaccine-induced immunity) to prevent epizootics and human epidemics has not been defined.** Following an RVF epizootic, the majority of livestock within the affected area are immune. The proportion of immune animals within an area with a history of RVF where flooding has been forecasted, might influence the likelihood that a sufficient number of animals would become infected by floodwater *Aedes*, resulting in an outbreak. Understanding that threshold would inform the process of enhancing specificity of prediction models and would be helpful to target vaccine coverage during inter-epidemic periods or early during an outbreak.

**4. There are challenges with using livestock vaccination to control RVF just before and during epidemics.** Livestock vaccination during various stages of an RVF epidemic, including the pre-epidemic period is only successful if it is part of a broader RVF control program. Effective and sustained RVF control programs have not been implemented or sustained in most areas prone to RVF epidemics. Because the onset of protective immunity after vaccination is delayed, there is questionable benefit in vaccinating in areas where an epizootic of RVF has already begun. Indeed, there are challenges in attempting to implement livestock vaccination programs during epidemics, including inaccessibility of infected areas caused by flooding, and concern that mass vaccination campaigns in animals can serve to spread the virus (through the practice of multiple injections using the same needle and syringe). Effective use of vaccine would have to occur very early in an outbreak, and would currently require availability of adequate quantities of an efficacious one-dose live vaccine to rapidly induce immune responses. Optimal strategies, like perimeter vaccination around outbreak foci should be evaluated and refined during field simulation exercises.

**5. Better characterization of geographic susceptibility to RVF (RVF-prone areas) is needed.** Studies in eastern Africa countries of Kenya, Somalia, and Tanzania have shown that periodic RVF epidemics have affected specific regions of the affected countries.<sup>32</sup> A recent longitudinal analysis of RVF outbreaks in Kenya showed that certain administrative districts in six of the eight provinces are highly vulnerable to severe RVF epidemics affecting livestock and humans, occurring every 3 to 8 years (mean = 3.6 years).<sup>33</sup> However, little is known about factors that make regions prone to RVF outbreaks. Potential factors may include topography and soil types contributing to potential for flooding and to distribution and density of competent vectors.<sup>20,34</sup>

**6. The lack of readily available vaccines to protect humans at high risk of infection and paucity of commercially available diagnostic assays for use by regional reference laboratories interfere with disease control efforts.** Currently, there are no licensed, commercially available vaccines available to prevent RVF in humans. A number of candidate vaccines are under development and in various phases of testing. Despite the obvious need in certain settings, taking a vaccine to licensure will require unique approaches given limited perceived market value.

The absence of commercially available rapid diagnostic tests for RVF limits the capacity for early recognition of an outbreak. In areas where other systemic febrile illnesses, like malaria and dengue, are endemic, diagnosis and appropriate management are challenging.

**7. There is a need to better characterize the contribution of mosquitoes in transmitting asymptomatic RVF infection versus symptomatic and severe RVF disease to humans.** Although findings from the 2006–2007 investigation concluded that animal exposure was responsible for severe RVF disease,<sup>22</sup> the role of mosquito transmission was inconclusive, because of the difficulty in elucidating the number of mosquito bites during an outbreak. Understanding the role is important—while mosquitoes appear to be a critical reservoir for the virus and during flooding initiate an outbreak by transmitting to animals, it is unclear whether vector control is a critical component of disease control once an outbreak is ongoing.

**8. Assessments are needed of the effectiveness and feasibility for mosquito larval control in “RVF-prone areas” or in areas**

**where RVF models have forecasted a high risk of disease.** Use of larvacides over large geographic areas where RVF has occurred before would be a major undertaking of uncertain value. Studies to evaluate the use and feasibility of such efforts within such geographic areas were felt to be helpful.

**9. Combination vaccines are needed against important livestock diseases, such as RVF, lumpy skin disease, and sheep and goat pox.** Getting vaccines into livestock in low resource areas is challenging. Being able to immunize against multiple diseases simultaneously would increase the likelihood of optimal vaccine coverage.

**10. Bidirectional communication methods need to be developed and assessed to promote early detection of clusters of suspicious cases and to communicate behavioral change messages to people living in areas where a risk has been identified.** Methods are needed to improve behavioral change messaging to reduce risk in areas with forecasted or ongoing outbreaks, and evaluating the use of text messaging by mobile phones to improve early reporting of suspicious events in animals and humans. Text messaging is evolving to be able to accomplish these bidirectional tasks; however, demonstration pilots are needed to further develop, test, and refine the concept.

## OVERARCHING PERSPECTIVES

This outbreak, and others like it, led to a substantial and lengthy diversion of limited public health human and financial resources (intended for use for the high impact endemic diseases, described previously) for intensive responses to the crisis. Thus, focusing on improvements in forecasting, detection, prevention, and response to outbreaks is of high value. Forecasting techniques, surveillance and diagnostic enhancements, and developing sustainable rapid public health response capacity are cross-cutting and transferable for use in combating other diseases; thus, the RVF outbreak provided a vista for recognizing needs for public health capacity strengthening. Addressing those shortcomings should yield broad benefits.

Rift Valley fever is a disease associated with a complex set of factors that make disease outbreaks likely, involving animals, mosquitoes, climate, ecology, and commercial trade. Its prevention and control is not straightforward. The papers and decision-tools provided within this Supplement show excellent progress in knowledge-gained, provide the substrate for current strategies for preventing and responding to outbreaks, and serve as the bases for a research agenda.

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