



Short communication



Meeting report: CEPI workshop on Rift Valley fever epidemiology and modeling to inform human vaccine development, Nairobi, 4–5 June 2024

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ABSTRACT

Rift Valley fever (RVF) is a zoonotic viral disease that causes epidemics and epizootics among humans and livestock, resulting in substantial health and socioeconomic consequences. Currently, there are no RVF vaccines licensed for humans, but several candidates show promise in early-stage development. Existing gaps in RVF epidemiological data and challenges associated with predicting RVF outbreak risk complicate the planning of efficacy studies, making the pathway to licensure for promising candidates unclear. In June 2024, the Coalition for Epidemic Preparedness Innovations (CEPI) convened a two-day workshop in Nairobi, Kenya, to discuss RVF epidemiology, modeling priorities, and specific gaps relevant to human RVF vaccine development. The workshop included representatives from multiple RVF-endemic countries, key global collaborators, and international health organizations.

Workshop participants identified five key priorities: (1) **Looking beyond outbreaks:** There is a need to better characterize the complex One Health epidemiology of RVF and understand interepidemic persistence of the virus; (2) **Better data for better models:** Epidemiological modeling is crucial for research, prediction, and planning, but it requires accurate and representative data; (3) **New, improved and accessible diagnostics and serological assays:** These are needed to inform epidemiology and case definitions, without which RVF research will continue to suffer due to paucity of data and challenges in determining infection and exposure; (4) **Defining use cases, regulatory pathways, and implementation strategies for human vaccines:** Clarity on these topics will facilitate licensure and effective use of RVF vaccines; and (5) **People-centered approaches:** Community engagement and involvement of social and behavioral scientists are key to the success of human vaccine research and development and implementation, particularly as the virus impacts livestock and livelihoods.

Workshop participants welcomed a renewed focus for RVF epidemiology and modeling, and expressed enthusiasm for continued multidisciplinary collaborations to support enabling sciences for human RVF vaccine research and development.

1. Introduction

Rift Valley fever (RVF) is a zoonotic, vector-borne viral disease that has caused outbreaks across the African continent, the Indian Ocean islands, and parts of the Arabian Peninsula [1–4]. Rift Valley fever virus (RVFV) infection leads to loss of pregnancy in livestock species [5], can cause deaths in young livestock [5], has the potential to cause severe illness and death in humans [1], and can have profound effects on peoples' livelihoods and national economies [6]. RVF is considered a priority disease by multiple international organizations such as the World Health Organization [7,8], World Organization for Animal Health [5], Food and Agriculture Organization of the United Nations [9], Africa Centres for Disease Control and Prevention [10], and many countries across the African continent [11–14].

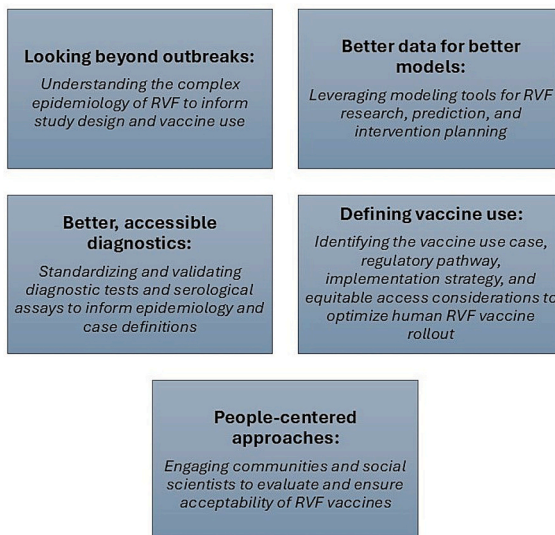
The Coalition for Epidemic Preparedness Innovations (CEPI) was established in 2017 to accelerate the development of vaccines and other biologic countermeasures against epidemic and pandemic threats, including RVF, ensuring that they can be accessible to all people in need [15]. Although a few RVF vaccine products are available for use in animals in some endemic regions, no RVF vaccine is currently licensed for use in humans [16,17]. As of 2024, CEPI has invested in the development of four human RVF vaccine candidates, with funding committed to advance vaccines into Phase I and Phase II clinical trials in RVF-endemic countries in East Africa [18]. However, for later stage development and licensure, an incomplete understanding of RVF epidemiology and the unpredictable nature of RVF outbreaks pose major challenges to planning pivotal vaccine efficacy studies and identifying appropriate pathways for the licensure of human RVF vaccines. For example, understanding when and where RVF human cases might occur, with

estimates of incidence and disease severity, would inform the selection of clinical trial designs and calculation of enrollment sample sizes.

In June 2024, CEPI convened a meeting of public health and animal health researchers, epidemiologists, modelers, regulators, funders, and decision-makers to discuss advances and gaps in epidemiology and modeling pertinent to the development of human vaccines for RVF. Objectives of the meeting were: (1) to enable the RVF research community to share recent findings regarding RVF biology and regional perspectives on RVF epidemiology, with a view to discussing how understanding RVF epidemiology insights can inform decisions on the feasibility and design of human RVF vaccine efficacy studies; (2) explore the role of epidemiological modeling in both outbreak prediction and the planning of potential efficacy studies; and (3) facilitate collaboration and knowledge sharing among global experts within the RVF research and decision-making community. Here we present the key points from the workshop presentations and discussions, emphasizing five key priorities (Box 1) identified for advancing RVF epidemiology and modeling efforts to support the development of human RVF vaccines.

2. Looking beyond outbreaks: Understanding the complex epidemiology of RVF to inform study design and vaccine use

The emergence and transmission of RVF are multifactorial, involving human, animal, vector and climatic components. Consequently, workshop presentations addressed various One Health aspects of RVF epidemiology, emphasizing the gaps in our current understanding of the virus and disease. Participants discussed the necessity of better characterizing the burden of disease, clinical outcomes, risk factors, and transmission dynamics to inform the planning and design of clinical



Box 1. Key priorities identified from the workshop on Rift Valley fever (RVF) epidemiology and modeling to inform human vaccine development.

trials.

2.1. RVFV infection in humans

Several workshop presentations and group discussions raised the importance of understanding the true incidence and clinical spectrum of RVF disease in humans, ranging from asymptomatic to mild and severe disease manifestations. This understanding is crucial for informing clinical case definitions, calculating study sample sizes, and determining appropriate clinical endpoints for vaccine efficacy studies. Additionally, as highlighted in a previous systematic review of RVF knowledge gaps [2], presenters discussed known risk factors for RVFV transmission to humans, including animal exposures such as slaughter, butchering, sheltering, handling aborted fetus or carcasses, and milking livestock. Importantly, however, differences in exposure risk (e.g., via vectors compared with direct exposure pathways) and related clinical severity, as well as the impact of comorbidities on infection and severity, are not well understood and would inform the identification of risk groups who should be prioritized for vaccination. Similarly, the prevalence of maternal/fetal complications from RVFV infection among pregnant women [19], as well as disease presentation and severity among immunocompromised individuals, also need to be addressed to define vaccination priority groups. Gaps in understanding RVF illness presentation and outcomes in individuals coinfecting with other common pathogens, like malaria, which might be prevalent in RVF-endemic countries were also discussed. These factors, coupled with the short-lived viremia, make it difficult to agree on a clear clinical case definition that can be used in clinical trials. Participants agreed that the aforementioned gaps would have direct links to informing human RVF vaccine clinical trials, in selecting the appropriate populations, outcomes, and study designs for vaccine efficacy studies.

2.2. RVFV infection in animals

Workshop presentations also examined current understanding of risk factors and outcomes of RVF in animals. Presenters highlighted the challenges in identifying livestock cases in the absence of systematic animal RVF surveillance, particularly during interepidemic periods. Although multiple seroprevalence studies in ruminant livestock have indicated transmission in non-outbreak periods, challenges remain in standardizing and interpreting serologic data, resulting in gaps in understanding seroprevalence fluctuations that indicate missed outbreaks

as well as baseline herd immunity. Furthermore, variations in livestock production systems, population structures, and settings (e.g., peri-urban versus pastoral), as well as individual factors such as animal movement, stress, nutrition, and coinfection can influence immunity and infection risk in livestock, resulting in differences in risk for RVFV exposure and onward transmission. Workshop participants also discussed the need to better understand use and effectiveness of RVF vaccines in livestock [20], both independently and in conjunction with human vaccination, to inform the use case and deployment of human RVF vaccines and to optimize RVF prevention strategies.

In addition to livestock, presentations highlighted unanswered questions regarding the role of wildlife as potential viral ecological maintenance hosts for RVFV; though evidence of infection has been documented in several wildlife species, the specific role these animals play in the transmission of RVFV remains largely unknown [21]. Presenters discussed the possibility that wildlife species could potentially serve as non-traditional animal models for understanding naturally occurring, non-severe RVF disease as they can be naturally infected with the virus, generally developing subclinical infection, and are often closely related to livestock species. However, challenges persist due to the lack of validated laboratory diagnostic tests and reagents for use in wildlife, as well as the absence of and adequate reference data to characterize immune responses across wildlife species.

2.3. Vector biology

Understanding how RVFV is maintained and transmitted by/among mosquitoes can inform outbreak prediction and the optimum timing of control measures, including vaccination. Workshop presentations on RVF vector biology discussed that although dozens of mosquito species from at least six genera are capable of transmitting RVFV in a laboratory setting [22], it is unclear to what extent these species and others contribute to transmission in the field. It is also important to understand vectorial capacity, a relative measure of transmission efficiency that collates ecological characteristics including vector/host density, life-span, survival, biting rate on susceptible hosts, and viral incubation period along with vector competence [23]. While some primary vector species overlap in different geographic regions, there are regional differences in mosquito vector species that serve as primary and secondary vectors of RVFV and contribute to geographic differences in viral ecology [24–29]. Gaps and opportunities for RVF vector ecology research included: enhancing vector surveillance and control strategies, including during interepidemic periods, further exploring vector invasion/expansion potential to understand and predict changes in RVFV distribution and epidemiology, further characterizing vector competence and vectorial capacity, understanding vertical transmission in mosquitoes, and further studying immunity and infection in mosquitoes. These areas of study would provide critical insights into the characterization of viral maintenance and transmission dynamics in different regions of endemicity. Discussions highlighted the complex relationship of climate and rainfall with vector emergence and transmission, with sustained rainfall, rather than a short periods of heavy rainfall, recognized as an important driver of outbreak potential. Other climate variables and patterns were also noted to contribute to outbreak risk, but this was dependent on specific ecosystems.

2.4. Regional perspectives on RVF epidemiology

Several presenters from East Africa, West Africa, Southern Africa, Europe, and the Middle East provided regional perspectives on RVF. In East Africa, RVF clusters have increased in frequency since 2008, largely corresponding to increases in temperature and rainfall in highland regions; additionally, some regions of East Africa, such as southwestern Uganda, appear to have high levels of sustained endemic RVFV transmission [30]. In West Africa, outbreaks and sporadic cases have been reported in multiple countries, particularly in Mauritania and Senegal.

Seroprevalence studies among both humans and animals have suggested transmission in several other countries as well [31]. In Southern Africa, several countries have experienced outbreaks and sporadic cases; notably, the interval between major outbreaks in South Africa has been as long as 34 years, raising questions about the interepidemic maintenance of the virus in this setting [32]. Finally, for Europe and the Middle East, prior outbreaks have been reported from the Arabian Peninsula and modeling studies suggest that the region has high potential for reintroduction and new outbreaks [33,34]. Additionally, RVFV circulation has been suggested in other countries such as Turkey based on seroprevalence studies [35]; however, workshop attendees discussed the challenge in interpreting serologic findings in the absence of outbreaks, and the need for externally validated serological assays. Participants discussed the risk of transboundary spread of RVF from endemic regions to currently naïve countries and the potential for expansion of the geographic range of this disease [36,37]. Presenters and discussants agreed that identifying areas with continuous (rather than sporadic) could inform site selection for future vaccine efficacy trials, and that multi-region or multi-country studies should consider variation in RVF epidemiology by location.

2.5. Interepidemic maintenance

As previously described, several discussions highlighted a significant gap in understanding how RVFV is maintained in interepidemic periods [38,39]. Seroprevalence studies in both humans and animals suggest that some level of transmission occurs between large outbreaks, but the degree to which this occurs is uncertain, limited by the capacity to detect acute cases outside of outbreaks. The role of mosquitoes in maintaining the virus during these interepidemic periods remains unclear; however, some prior studies have proposed that virus survival in mosquito eggs may not be a primary source of maintenance [38]. A better understanding of interepidemic transmission could enhance outbreak prediction and improve the estimation of complete RVF incidence and prevalence during both outbreak and non-outbreak periods, thereby facilitating clinical trial planning and design.

2.6. Genomic epidemiology

Presenters also discussed the potential of genomic epidemiology to address questions about the evolutionary and transmission dynamics of RVFV across different lineages, as well as the vaccine relevance of different circulating strains. While RVFV has previously been shown to be highly conserved and have low genetic diversity [40], variability in methods has previously led to inconsistency in naming lineages and thereby hindered analysis of lineage-specific epidemiology [2,33]. Workshop presentations highlighted the recent development of a lineage classification tool to standardize RVFV classification [41], and described how genomics has the potential to shed light on the changing ecology and geographic distribution of RVFV [33]. Genomic data can have direct relevance for RVF vaccine development by monitoring changes in the virus, including identification of mutations that might affect epidemiology and transmission, and by informing the design of diagnostic assays and vaccine candidates [40]. Participants discussed the potential utility of improved databases to more easily share and access global RVFV sequencing data.

3. Better data for better models: Leveraging modeling tools for RVF research, prediction, and intervention planning

Several presentations emphasized how epidemiological modeling can be a valuable tool to predict outbreak occurrence, evaluate intervention strategies, and simulate optimal clinical trial approaches. Participants discussed that models rely on accurate and representative input data, and thus can inform research and data collection priorities to fill existing data gaps.

3.1. Transmission dynamics and outbreak prediction

Several presenters discussed the utility of modeling methods to study transmission dynamics and to predict risk distribution and outbreak occurrence for RVF [42–47]. Models using global scale climate data (e.g., rainfall patterns and temperature) and other inputs (livestock and human density, vegetation and land use, movement patterns) can predict RVF hotspots and forecast the occurrence of RVF outbreaks, particularly as changes in environmental factors (e.g., precipitation and temperature) drive RVFV emergence and spread in the context of a changing climate [30]. However, the accuracy of these predictive models can vary [48]. Furthermore, the utility of results depends on the resolution of the model and in turn on data availability; the sparsity of RVF outbreak data, lack of routine, non-outbreak surveillance data, and limitations of other input data (e.g., unknown baseline human and livestock immunity) can pose challenges to these efforts. Therefore, strengthening of RVF surveillance and reporting in both humans and animals in at-risk settings can enhance outbreak prediction. Sensitive and accurate outbreak prediction models could facilitate the planning of clinical trials during outbreaks and help define early triggers for vaccine deployment in outbreak response settings, though the ability to extrapolate from one environment to another requires critical appraisal.

3.2. Clinical trial simulations

Presenters also highlighted how simulation models can be utilized to plan and improve vaccine efficacy studies, potentially informing study design, ethical considerations, and the interpretation of clinical trials [49]. They discussed the potential of simulations to determine the study type (e.g., individual vs. ring-cluster randomized controlled trial), clinical endpoints, and other features (e.g., sample size), using characteristics of the disease and population [50], and shared prior examples from diseases like Crimean Congo Hemorrhagic Fever, where simulation models using human and animal data were used to assess the feasibility of conducting phase III vaccine efficacy trials [51]. Workshop participants expressed enthusiasm for the utility of these approaches to inform efficacy studies for RVF vaccines, particularly given the complex transmission dynamics and ecology of the virus.

4. Better, accessible diagnostics: Standardizing and validating diagnostic tests and serological assays to inform epidemiology and case definitions

Multiple workshop presentations highlighted that improved RVF diagnostic tests would benefit surveillance, help address gaps in epidemiologic data, and facilitate future clinical trials for human RVF vaccines. As reported in a prior publication on RVF diagnostics [52], several commercial and non-commercial diagnostic testing methods are available for RVF, but external quality assessments and validation data for the performance of different tests are limited. While molecular assays (e.g., RT-PCR) can be used for case confirmation, the short period of viremia emphasizes the importance of validated serological tests for reliable detection of cases [52]. The availability of validated diagnostic tests, including point-of-care tests, is important for early detection of outbreaks, case confirmation, and the differentiation of vaccine-derived immunity from previous RVFV exposure, all of which would be essential for a successful vaccine efficacy study. The emerging availability of a commercial pen-side assay to detect RVFV antigen was suggested as a potential tool to screen livestock outside of large outbreaks and characterize interepidemic circulation. Furthermore, though seroprevalence studies have been increasingly used to understand RVFV distribution and epidemiology [53], workshop discussions highlighted the need for standardization of serological assays, methodology, and study designs to accurately and reliably interpret seroprevalence results. Local production of validated diagnostic assays in endemic regions could facilitate greater testing access.

5. Defining vaccine use: Identifying the vaccine use case, regulatory pathway, implementation strategy, and equitable access considerations to optimize human RVF vaccine rollout

Workshop presenters and participants also raised several broader questions about the use case for human RVF vaccines, regulatory pathways, access, and implementation, including demand for and deployment of human vaccines in the presence or absence of animal RVF vaccination.

5.1. Use case for human RVF vaccines

Multiple workshop discussions highlighted uncertainties in the use case for human RVF vaccines; specifically, participants considered whether the vaccine should be used in a post-outbreak campaign (“reactive”) approach versus a routine immunization approach (e.g. for high-risk groups). Discussions emphasized that both strategies might have unique advantages and challenges in terms of cost, feasibility, and uptake. While a reactive approach might conserve vaccine doses compared with a routine approach, the logistical and operational challenges for implementing rapid vaccination campaigns could be substantial. Workshop participants noted that simulation modeling to better understand if/how vaccination might influence outbreak size could inform use case decisions, as could addressing epidemiologic gaps about the duration of immunity and early warning predictors for outbreaks. Finally, participants raised questions about whether the use case would need to be standardized across countries, or whether local epidemiology of RVF (e.g., continuous transmission versus sporadic outbreaks) could be leveraged to adapt a context-specific use case and identify high-priority target groups (e.g., persons with frequent occupational exposure to livestock).

5.2. Potential pathways for regulatory approval

Presenters discussed the regulatory considerations for RVF vaccine development in both the Kenyan and African regional contexts. For pathogens like RVF with unpredictable outbreaks and for which there can be difficulties obtaining sufficient cases for traditional efficacy trials, alternate licensure pathways might exist, as recently used for US approval of a chikungunya vaccine [54]. The potential basis for licensure or emergency use authorization/listing for RVF vaccines would traditionally be efficacy data from a randomized controlled trial but could alternately be data generated by applying a correlate/surrogate of protection; in the latter case, post-approval real-world evidence data would likely be required. Depending on the vaccine deployment strategy, vaccine stockpile availability, and data generation feasibility, efficacy data could also be generated during an outbreak using an adapted, pre-reviewed outbreak response protocol. Presenters discussed how country-specific regulatory timelines could potentially be facilitated and expedited through review and coordination from regional platforms, such as the Africa Vaccine Regulatory Forum (AVAREF) [55] or efforts such as the Marketing Authorization for Global Health Products (MAGHP) [56].

5.3. Implementation and access

Alongside discussions about the use case for human RVF vaccines, participants also raised questions about how to optimize vaccine implementation, particularly in the context of available animal RVF vaccines. Presenters raised the possibility of concurrent human/animal vaccination via integrated delivery systems, which might facilitate logistics and uptake of vaccination; however, evaluating human RVF vaccine efficacy independently of the effects of animal vaccines, particularly during outbreaks, could pose a challenge for clinical trials utilizing outbreak response protocols. Workshop discussions also highlighted the importance of addressing the science-policy interface,

including how field epidemiology and modeling findings can guide resource prioritization, to ensure equitable access to future vaccines.

6. People-centered approaches: Engaging communities and social scientists to evaluate and ensure acceptability of RVF vaccines

Finally, workshop participants discussed that community acceptance will be critical for the success of RVF vaccine clinical trials, and thus early engagement of social scientists and local communities, to assess local perceptions, would benefit preparations for future studies. Researchers working in endemic areas agreed that a human-only vaccine implementation could prove difficult in regions where livestock carry high social and economic value [57], as community members might be inclined to prioritize animal vaccination to protect livestock as a resource, particularly given that the virus more commonly causes severe disease in animals compared with humans. Thoughtful, integrated, One Health approaches to community engagement will be required [58]. Discussions emphasized the potential utility of including qualitative data in epidemiologic studies to better characterize risk factors for RVFV transmission, for example to identify risk by specific types of exposures to animals (milking, butchering, handling carcasses, etc.) or food practices (e.g., consumption of raw milk [59] or mixing leftover/unsold milk with fresh milk for resale). Additionally, presenters highlighted the importance of end-to-end engagement and trust to ensure vaccine confidence and uptake. Participants discussed how understanding vaccine acceptability via community and stakeholder engagement might inform use case for human RVF vaccines; valuating community perceptions about when/how the vaccine is offered could identify successful strategies for deployment. For example, as RVF might be perceived by communities primarily as a disease of animal importance, contributing to animal losses and economic impacts, offering human vaccination in the absence of animal vaccination could be perceived as unnecessary and be challenged by the community. Participants also discussed that lessons learned from other One Health disease interventions (e.g., rabies vaccination [60]) could inform engagement strategies at the community level, as well as with decision-makers.

7. Conclusions

This workshop highlighted that RVF is a true One Health disease, requiring multidisciplinary approaches for surveillance, prevention, detection, and control. Despite considerable advances in understanding the virus, it continues to pose a risk for outbreaks, particularly in the face of the changing global climate. Linking together data on mosquito vector biology, climate, livestock and wildlife health, and human health will be important for predicting and responding to outbreaks, as well as designing and implementing interventions, including new RVF vaccines. Addressing epidemiological gaps through data collection, analysis, and modeling will benefit clinical trial planning for human RVF vaccines; strategic approaches to diagnostics, vaccine use case, regulatory pathways, and implementation are also needed. Findings from epidemiology/modeling studies could not only inform clinical trial planning, but also guide resource prioritization to ensure that interventions can be optimally and equitably deployed once available. Continued efforts to stimulate knowledge exchange and collaboration, as facilitated in this workshop, would benefit global efforts for RVF prevention and control.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: R. Gharpure, C. Vegvari, J. Auerbach, J.G. Breugelmans, J. Cramer, J. Heighway, P. Oloo, and H. Sneddon and P. Hart are employees of the Coalition for Epidemic Preparedness Innovations (CEPI), which currently funds four human RVF candidates. P.J. Wichgers Schreur, C. Punt and D. Luyimbazi are part of a consortium, funded by CEPI, that develops an RVF candidate vaccine, named hRVFV-4 s, for human use. B.H Bird is part of a consortium, funded by CEPI, that develops an RVF candidate vaccine, named DDVax®, for human use. No authors stand to materially or otherwise benefit from this work. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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