World Health Organization

Efficacy trials of Rift Valley Fever vaccines and therapeutics

Guidance on clinical trial design

Meeting report

R&DBlueprint

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Introduction

Rift Valley fever (RVF) is a viral zoonosis that primarily affects animals but also has the capacity to infect humans. Infection can cause severe disease in both animals and humans. The disease also results in significant economic losses due to death and abortion among RVF-infected livestock. In 2016, RVF was listed as a priority pathogen for which urgent research and development (R&D) is needed, given the absence of efficacious drugs and/or vaccines against RVF and its potential to trigger public health emergencies. The need for safe and effective vaccines and treatments in humans was further underscored in the RVF roadmap for product R&D.

On 1 November 2019, WHO convened members of the R&D Blueprint working group on clinical trial design with RVF experts as well as national representatives from affected countries to discuss the science of vaccine and treatment evaluation for RVF and agree on principles on how to determine whether or not RVF therapeutic and vaccine strategies are safe and effective in humans. Deliberations were informed by key clinical and epidemiological considerations, also recognizing the critical knowledge gaps that well-designed clinical and epidemiological studies could help address to better inform the development of RVF therapeutics and vaccines.

Clinical and epidemiological considerations in the design of clinical trials for RVF therapeutics and vaccines

This section does not intend to summarize all the current knowledge on RVF clinical manifestations and epidemiology but intends to provide an understanding of the current clinical and epidemiological aspects of RVF that are critical to understand to help inform the design of clinical trials for RVF therapeutics and vaccines evaluation as well as what are the critical knowledge gaps that the scientific community must fill ahead of conducting clinical trials.

Epidemiological and ecological considerations

Rift Valley fever virus (RVFV) (genus: *Phlebovirus*, order: *Bunyavirales*) that was first isolated during an outbreak of sheep disease in Kenya in 1930. The virus has propensity to cause large outbreaks in livestock and humans. These outbreaks can be associated with devastating effects on domestic ruminates and with significant health, economic and nutritional impacts on humans. Over the last several decades, the virus has expanded its range. Outbreaks has circulated across Africa and the Middle East causing sporadic but severe outbreaks in Southern and East Africa, Egypt, Madagascar, West Africa and Saudi Arabia. Resurgence of severe outbreaks were reported in East Africa, South Africa and Madagascar.

RVFV is mainly transmitted to humans by contact with the blood or tissues of infected animals (e.g. during slaughtering, butchering, veterinary procedures). RVFV can also be transmitted to humans via the bite of an infected mosquito, although the extent to which mosquito contribute to disease transmission in humans and disease severity is unknown. Less commonly, RVFV can be transmitted to humans via infected knife and needle-stick injuries and by consuming raw milk from infected animals. Human-to-human transmission has not been documented. When a critical density of infected mosquitoes and susceptible animals is met (typically following extensive, heavy, and prolonged rainfall), large outbreaks can occur in the livestock and can be followed by sporadic cases in humans, and could re-occur in the same region after the waning of herd immunity. The occurrence and size of RVF outbreaks in humans are generally correlated with the occurrence and size of RVF outbreaks in livestock. In the absence of

outbreaks, virus circulation is maintained via a sylvatic cycle between mosquitoes, wildlife (wild ruminants) and livestock (e.g. sheep, cattle, goats). Camels may also play an important role in spreading the virus across Saharan regions. Despite extensive geographic dispersion, and wide range of susceptible arthropod vectors and vertebrate hosts, RVFV displays low genetic diversity. The ability of the RVFV to rapidly spread and adapt to different ecological conditions coupled with its relatively wide host and vector range implies there is a potential risk of introduction into non-endemic RVF geographic regions.

Clinical considerations

The majority of infections in humans are self-limiting and can be associated with moderate, non-fatal, flu-like febrile illness. It is important to distinguish the large proportion of infected individuals who recover without seeking medical attention during outbreaks, from the smaller patient population that can progress to more severe disease requiring hospitalization. Among these severely affected patients, morbidity and mortality increases significantly, and can rapidly overburden health care systems to provide adequate care in affected regions.

RVF incubation varies between 3 and 6 days. The clinical presentation is non-specific with more than 80% of clinical individuals with diagnosed disease report fever, headache, myalgia, malaise and less frequently arthralgia, nausea and vomiting. Severe cases are associated with 1 or more of the 3 following distinct syndromes:

- Ocular disease (2-20% of hospitalized patients with onset up to 15 days post symptom onset) may include visual disturbance, retinopathy, and exudative lesions. Permanent vision loss occurs in up to 50% of cases with ocular disease.
- Hepatitis (7-18% of hospitalized patients with onset up to 13 days post symptom onset) is associated with jaundice that often progresses to severe liver necrosis and a diffuse hemorrhagic syndrome.
- Meningoencephalitis (17-22% of hospitalized patients with onset between 7 and 60 days post symptom onset) is seen although the presence of virus in cerebrospinal fluid has never been evaluated. CSF studies in people have demonstrated pleocytosis, and in experimental animal models of infection direct detection of viral antigen in neurons and glial cells support direct infection of the brain by the virus. This finding has relevance for potential therapies, as these therapeutics will likely need to cross the blood-brain barrier to be efficacious.

Severe disease correlates directly with high virus load in blood and may depend on the mode of exposure and initial inoculating dose. Case fatality ratios between 3 and 50% have been reported among patients with severe disease from multiple countries. Despite almost 90 years of experience with RVF outbreaks and human disease, the exact frequency of severe cases and deaths across all RVF cases is unclear, but is estimated to be less than 2-3% overall.

A retrospective study from an outbreak in South Sudan demonstrated an association between a history of acute RVFV infection during pregnancy and an increased risk of fetal loss. This study suggested that infection of people with RVFV may be more closely associated with miscarriage and fetal demise than previously appreciated. Although there was no direct documentation of RVFV infection of miscarried fetuses, the correlation with acute antibody seropositivity suggested that vertical transmission could cause a significant disease burden in humans as seen in livestock. A better understanding of that burden is essential to aid the risk-benefit profile of experimental therapeutics and the optimal characteristics of a human RVF vaccine. Improved diagnostics, surveillance and healthcare infrastructure are needed to recognize and understand the wide spectrum of the disease and in order to inform the development of novel RVF therapeutics and vaccines.

Viraemia is very short persisting for a few days only after onset of clinical symptoms. This complicates the use of molecular genetic testing (RT-PCR) to confirm RVF cases in clinical trials. No rapid antigen-based test assays (rapid diagnostic tests) have been commercialized to date.

The need for additional research studies ahead of clinical trials

It was recognized that the conduct of epidemiological, ecological and clinical studies must be performed ahead of conducting clinical trials for RVF vaccines and treatments in order to better inform the design of such trials and to build research infrastructure in settings where clinical trials are likely to occur. Furthermore, large-scale research studies are seen as opportunities to a common standard of prevention and care across multiple sites and countries.

Ahead of clinical trials, participants emphasized the importance to conduct:

- Longitudinal research aimed at uncovering exact mechanisms of RVFV maintenance and persistence as essential to understand the complex interactions between the viral, vectorial, host, ecologic, anthropogenic and climatic factors which accumulate to drive large-scale emergence and transmission of the virus to susceptible hosts.
- Large-scale multi-country prospective cohort studies in hyper-endemic areas to determine RVF sero-incidence in at-risk populations, using a combination of both serology and virology tests, and to better understand the clinical spectrum of the disease and the occurrence of clinical manifestations associated with severe cases, including miscarriages.

Towards a One Health surveillance and vaccination approach

RVF surveillance is currently insufficient to launch appropriate timely outbreak responses and to allow for the evaluation of vaccines and therapeutics, although recent development in diagnostic tools help to enhance the sensitivity and specificity of surveillance strategies. A primary risk factor for RVF human disease is contact with infected livestock and aborted fetal materials, and human infections and cases generally occur after the start of an epidemic in animals. However due to limitations in livestock disease surveillance systems, in almost all known outbreaks the cases in humans were first detected before and recognised outbreak in animals. Thus, smaller outbreaks in people and animals often pass completely unnoticed. Further complicating the rapid detection of RVF outbreaks, some RVF outbreaks are only detected after ruling out other more common diseases displaying similar clinical symptoms. The public health response to a major RVF outbreak consists of control measures designed to prevent the spread of the disease in humans, and can include animal vaccination, active case finding and management, as well as community engagement strategies to raise awareness on the risk factors of RVF infection. Participants recognized that controlling outbreaks with animal vaccination only may be insufficient in preventing disease in humans as well.

Participants agreed that the evaluation of vaccines and therapeutics in humans will be difficult given outbreaks currently may occur in a given area every ten years and last for a relatively short time (three to seven months). However, evaluations of these countermeasures will be most feasible in RVF outbreak settings and will require accumulating evidence across multiple outbreaks and the recognition that surveillance must be significantly strengthened and fit-for-purpose in order to prospectively capture sufficient number of trial events required to provide conclusive evidence. Retrospective analysis of recent outbreaks suggest that a sufficient number of cases per affected site can occur to motivate the conduct of clinical trials. Therefore, efforts must be put in place to position regulatory and ethical approvals and technological and human resources in potential study sites to be prepared to detect outbreaks as early as possible to enable a prospective assessment of RVF cases in clinical trials.

Currently, there is no validated point-of-care diagnostic tool. Samples are being tested in a limited number of BSL-3 reference laboratories, often outside of affected countries. RT-PCR commercial kits can be used to confirm suspected RVF disease. However, there is a relatively narrow window in which virus is detectable in the blood (approximately 3-5 days post onset of disease) which argues against sole dependence on RT-PCR for case ascertainment. Therefore, a combination of both RT-PCR and IgM ELISA (IgM has a 6 weeks window in blood) testing is preferred. However, there is no validated commercial serology assay for human specimens and the quality of in-house tests is often unknown. The development of diagnostics designed to detect virus in other bodily fluids (e.g. urine) needs to be explored. Laboratory capacity and surveillance systems must be strengthened and diagnostic tests must be evaluated and validated prior to beginning vaccine clinical trials. Access to well-characterized samples and reference standards will be essential for test evaluation.

Mathematical models, informed by satellite data on land occupation and climatic conditions, have been used by national authorities of affected countries as early warning systems to anticipate where and when RVF outbreaks are likely to occur. However, those models do not consider livestock immunity and therefore tend to overestimate the occurrence of RVF outbreaks. Better integration of immunity data at the livestock population level is needed to help enhance the utility of that approach.

Participants recommended that an integrated One Health surveillance approach should be designed in order to enhance our ability to detect and respond to outbreaks by the time the epizootic is affecting livestock and as early as possible. An early outbreak detection system will be critical to enhance our ability to identify and enroll target populations in clinical trials. Participants suggested that an abortion-based surveillance in sentinel herds combined with an optimized use of mathematical model would significantly enhance RVF early outbreak detection.

Livestock vaccination / One Health approach

Because human epidemics of RVFV are often preceded by outbreaks in farm animals, an appropriate animal vaccination strategy may also be used to prevent human outbreaks. Therefore, participants recognized that livestock vaccination should be a key component of the global vaccination strategy in preventing human disease.

Three RVF veterinary vaccines are being routinely used in livestock to prevent RVF infection and abortions. All three vaccines are manufactured and licensed in South Africa and are being used in multiple African countries.

- The live-attenuated Smithburn vaccine is the oldest RVF veterinary vaccine and has been widely used in domestic livestock (e.g. cattle, sheep, goats), preferentially during each spring season ahead of the RVF season. The Smithburn vaccine should not be used in pregnant animals, as it can cause abortion or foetal malformation, particularly in sheep. The Smithburn vaccine should also not be used in lambs before 6 months of age, but should be used in lambs over 6 months from previously vaccinated mothers. The Smithburn vaccine was shown to elicit the strongest IgM response in sheep compared to the two other vaccines.

- The formalin-inactivated vaccine is used in a similar way to the Smithburn vaccine, but is safe to administer to pregnant animals and animals of all ages. However, a booster vaccination is needed 3-4 weeks after the first immunization to build immunity, bringing additional costs and schedule compliance issues.

- The naturally attenuated Clone 13 vaccine appears to be safer for use in domestic ruminates compared to the live-attenuated Smithburn vaccine but is less thermostable than the 2 other vaccines and requires an ultra-cold chain system.

The use of those vaccines was supported by animal challenge studies that demonstrated protection against symptoms and abortions in livestock. However, additional immunogenicity studies highlighted significant differences in seroconversion across livestock species and substantial uncertainties remain on whether the three RVF vaccines at the current dosing regimen are effective in preventing RVF transmission in animals and subsequently in humans, also recognizing that mosquitoes and wild animals may play a major role in propagating the virus.

Given the concerns on safety, effectiveness and potential reassortment of current veterinary vaccine approaches, the need for additional veterinary RVF vaccines for both preventive and reactive use was underscored as was the need to evaluate whether or not their use in livestock will provide clinical and public health benefits in humans. Lastly, the development of DIVA-compliant vaccines (DIVA: differentiating naturally infected from vaccinated animals) will provide strong incentives to animal vaccination.

In summary, a One Health surveillance and vaccination approach is needed to enhance our ability to detect and respond to RVF outbreaks and to enable an efficient and meaningful evaluation of vaccines and treatments. A One Health approach was also recognized to be pertinent in RVF vaccine development, as participants noted that one of the veterinary vaccine candidates (DDvax) may be repurposed for human vaccine development. However, dose and vaccination schedule will have to be established separately for animals and humans. Different vaccine formulations will also be required for animals and humans (e.g., single dose vials, multiple dose vials, adjuvants, thermostabilizers). Of note, GMP requirements will require different manufacturing procedures and quality control for an animal versus a human vaccine. Possible safety observations in animals (subjective, objective – e.g. occurrence of spontaneous abortion) could potentially complicate using a vaccine based on the same manufacturing platform in a One Health approach.

Vaccine evaluation to prevent RVF in humans

Single infection with RVFV is considered to induce lifelong immunity, indicating that the development of effective vaccines may be feasible. Furthermore, the existence of only one serotype of RVFV and high degree of conservation of genes encoding for surface glycoproteins indicate that a single vaccine variant should protect against all currently circulating RVFV genetic variants.

There are currently no licensed RVF vaccines for use in humans and no established correlates of protection. Neutralizing antibody responses have been associated with protection in several animal models and may be explored as parameters for determining immunity in humans. Access to well-characterized samples and reference standards can help better understand immunological markers of protection across various vaccine platforms. In the absence of correlates of risk, the demonstration of vaccine efficacy to inform licensure and policy-makers decisions is critical.

A draft Target Product Profile (TPP) for RVF vaccines was developed to provide aspirational guidance to vaccine developers and specifies targets for optimal vaccines and minimally acceptable vaccines from a public health perspective. According to the TPP, RVF vaccines for outbreak use, the setting for vaccine evaluation, are considered to protect high-risk people in conjunction with other outbreak control measures. In this setting, rapid onset of immunity must be demonstrated after a single vaccination.

Clinical trials for RVF vaccines: key methodological elements

Because a One Health vaccination strategy in outbreak response is needed, a One Health evaluation approach designed to generate evidence to support a broader use in that context would be ideal.

- In the event that both veterinary and a human RVF candidate vaccines would be ready for efficacy trials, a cluster-randomized factorial design which aims to evaluate the clinical effect of a human vaccine, an animal vaccine and its combination on human disease was proposed – compared with a non-interventional control arm (behavioural measures only including hygiene after animal contacts). Co-vaccination of humans and livestock in the combination arm would require a strong coordination of the veterinary and public health teams. This design would be the most efficient in that setting given the strong potential for complementarity of action between the vaccines in preventing RVF in humans. Two-stage randomization would take place, with clusters being randomized for the four possible arms, but with individual randomization occurring for those clusters to receive human vaccine, with vaccine and placebo randomized on the individual level. If the combination arm is infeasible to implement, a three-arm cluster-randomized trial would then be preferred.

- Alternatively, a multi-country individually-randomized placebo-controlled trial within outbreak areas where RVF transmission is occurring could be also appropriate in a first stage. In that case, the combination vaccination strategy could be evaluated post-licensure.

- Laboratory-confirmed RVF cases should be the primary endpoint. Laboratory-confirmation should be made using a combination of RT-PCR testing and IgM testing – as RT-PCR alone may be insufficient due to short viraemia (see above) to confirm RVF cases in a field vaccine efficacy trial setting.

- A case definition including mild to severe cases could be used for case ascertainment to increase the power of the trial, noting that vaccine effect may be lower in mild cases and that clinical benefit must be further assessed post-licensure in severe cases.
Secondary endpoints should include infection, severity of disease, and immunological correlates of risk and surrogates of protection. Assessing infection as a secondary endpoint requires DIVA testing.

- Target population for the human vaccine should include at-risk populations (e.g. farmers, butchers, veterinarians) within defined clusters, including adolescents and women of child-bearing age to better understand the safety profile in that population. Therefore, a vaccine with an appropriate risk-benefit profile for use in that population should be selected for evaluation.

- Ideally, all participants should have blood drawn before vaccination to determine the impact of baseline seropositivity on vaccine safety and efficacy. An adequate sampling scheme at several time points after vaccination could help contribute to design an immune correlate of risk or surrogate of protection. However, it is not expected that seroprevalence in humans would be high and would raise a scientific issue.

- Vaccine safety evaluation (and evaluation of vaccine efficacy) should include pregnant women in the context of i) spontaneous abortion as a possible clinical RVF complication in pregnant women and ii) spontaneous abortions observed as a vaccine consequence in animal vaccination.

Preliminary insights on the design of RVF therapeutic trials

Participants agreed that experimental RVF therapeutics should be designed to treat and prevent severe cases (e.g., patients that progress with ocular complications, haemorrhagic complications, renal failures, meningoencephalitis, miscarriages) as well as preventing deaths, but noted that the feasibility of conducting therapeutic interventions will be highly dependent on the ability to rapidly identify cases and initiate treatment.

Several experimental or repurposed drugs have shown effectiveness against RVFV in animal and in cell culture models, although none of the novel molecules has reached clinical trials. The high conservation of the RNA-dependent RNA polymerase sequence suggests that antiviral drugs targeting this essential enzyme should effectively inhibit replication of all known genetic lineages of the virus. Similarly, antibodies or cocktails of antibodies targeting the highly conserved virus surface antigens could also be useful across outbreaks caused by different RVF virus lineages. The need to prevent and treat meningoencephalitis highlights the importance of developing small molecules, other than immunoglobulin products and large antivirals, that are able to cross the blood-brain barrier, recognizing that encephalitis cases may not necessarily be driven solely by RVFV replications but also immunopathology processes resulting from infection.
The possibility of RVFV induced miscarriages highlights the importance of molecules with a favourable toxicity profile to be considered for pregnant women.

Ribavirin was evaluated in a clinical trial during a RVF outbreak in Saudi Arabia in 2000. The drug was given intravenously at various stages of clinical presentation, and mainly in people presenting with moderate disease. The trial was quickly stopped due an increased incidence of neurological disease in the treatment arm. Retrospective analysis of the trial should be performed to better understand the decisions of trial termination.

The design of therapeutics trials was not explicitly discussed at the meeting. However, participants agreed that randomized placebo-controlled trial should be performed to evaluate a promising molecule. Based on the experience from RVF case management and from other acute emerging pathogens, patient viral load measured by RT-PCR and time from patient symptom onset to treatment initiation are key covariates to consider in the design of therapeutic trials. Therefore, the design of a therapeutic trial should be integrated in a surveillance strategy where every effort should be made to identify and treat RVF symptomatic patients at the earliest opportunity as the clinical relevance of the treatment effect will be highly depend on the timing of the intervention, and because the detectable viral window in blood can be quite short. Based on the ribavirin experience in Saudi Arabia and given that the majority of RVF cases are mild to moderate, it will be essential to tailor the clinical case definition informing trial eligibility criteria with the risk-benefit profile of the drug under evaluation.

NEXT STEPS

1. To set up a working group to write a study protocol for a prospective large-scale multi-regions sero-incidence cohort study, that includes an active One Health surveillance component, in order to better identify populations with substantial risk of developing disease and to better understand who is more likely to progress to severe disease, in an effort to identify target populations for future clinical trials

2. To set up a working group to write a study protocol for a clinical trial to evaluate a RVF vaccine, based on the guidance provided in this document.

3. In parallel and in support of the above-mentioned studies:
   - To develop and standardize a fit-for-purpose clinical case definition for epidemiological studies and clinical trials.
   - To validate and standardize a fit-for-purpose molecular and serological assays for epidemiological studies and clinical trials.
   - To develop predictive models to better inform site selection of epidemiological studies and clinical trials.

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