Efficacy trials of Crimean-Congo haemorrhagic fever vaccines and therapeutics
Guidance on clinical trial design

Meeting report
Introduction

Crimean-Congo haemorrhagic fever (CCHF) constitutes a public health threat because of its epidemic potential, its high case fatality ratio (4-40%), its potential for nosocomial outbreaks and the lack of effective treatment and prophylaxis. CCHF is endemic in all of Africa, Southern Europe, the Middle East and in Asia. In 2016, CCHF was listed as a WHO priority pathogen for which urgent research and development (R&D) is needed. The need for safe and effective CCHF vaccines and treatments was underscored in the CCHF roadmap for product R&D aiming to prevent or mitigate CCHF disease by 2030.

On 31 October 2019, WHO convened members of the R&D Blueprint working group on clinical trial design with CCHF experts as well as national representatives from affected countries to discuss the science of vaccine and treatment evaluation for CCHF and to agree on principles and approaches to determine whether or not CCHF vaccines and therapeutics are safe and effective. 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 CCHF therapeutics and vaccines.

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

This section does not intend to summarize all the current knowledge on CCHF clinical manifestations and epidemiology but rather to highlight aspects of CCHF that are critical to help inform the design of clinical trials for CCHF 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 considerations

CCHF is a widespread disease caused by a tick-borne virus (CCHF virus [CCHFV], genus Orthonairovirus, family Nairoviridae) consisting of one serogroup and 7 genetic clades. CCHF is endemic in Africa, the Balkans, the Middle East and Asian countries south of the 50th parallel north, the current geographical limit of the principal Hyalomma tick vector – and can cause severe viral haemorrhagic fever outbreaks during the tick season, with case fatality rates ranging from 4–40% among hospitalized patients.

The CCHF virus is transmitted to humans mainly by tick bites (~70%) and through contact with infected animal blood or tissues during and immediately after slaughter and also can be transmitted by contacts with biological fluids of patient with CCHF (nosocomial transmission). The majority of cases have occurred in people involved in the livestock industry, such as agricultural workers, slaughterhouse workers and veterinarians. Nosocomial outbreaks were also documented in settings with poor Infection Prevent and Control measures. Human-to-human transmission has been documented in rare circumstances, although seroprevalence studies have shown limited seroconversion in contacts of CCHF cases. Seroprevalence surveys have also been used to identify areas with high risk of CCHF transmission to target the training of healthcare workers and social mobilization strategies ahead of the tick season. In highly endemic areas, such as Tokat and Sivas provinces in Turkey, the CCHF IgG seroprevalence has been as high as 12.8% in rural populations. However, there is a lack of systematic epidemiological data collection from endemic countries and the annual incidence is unknown in most of endemic countries. Sero-incidence studies in well-defined clusters and environmental spatio-temporal risk mapping will be critical to better inform the design of vaccine and treatment trials.
Clinical considerations

The clinical spectrum of illness and disease severity in patients with CCHF is broad and highly variable across regions. It is estimated that up to 88% of infections may be sub-clinical. The incubation period ranges from 1-13 days, depends on the mode of acquisition, (typically 1-3 days after tick bite), and has been shown to be shorter in fatal cases. There is currently no documentation of patient reinfection with CCHF.

Data from a large patient cohort in Turkey (n=1670) showed that the most common complaints at presentation were fever (90%), fatigue (90%), headache (70%), myalgia (70%) and nausea (65%). Haemorrhagic manifestations were reported in 23% of patients at admission (haematomas, ecchymosis, epistaxis, vaginal bleeding), an occurrence much higher than what is observed with other viral haemorrhagic fevers. It remains unclear whether the vascular permeability at the level of endothelium cells is directly linked with viral replication in cells or indirectly through the excess release of pro-inflammatory cytokines. Thromboelastometry monitoring techniques will help better understand bleeding mechanisms and help rationalize the use of blood products in case management. Leucopenia (88.9%), thrombocytopenia (93.2%) and elevated transaminases (85.9%), LDH (75.8%) and CK (65.9) were the most common laboratory abnormalities at presentation.

High viral load on admission, haemorrhagic manifestations, elevated APTT, elevated ALT and low platelet counts are considered to be important prognostic factors with disease severity and progression to death. Most patients are RT-PCR positive on admission becoming negative by the fifth day of illness. On admission, a study reported that 42% of patients are IgM positive, with all patients seroconverted by day 8 of illness, continuing to 30 days and that 50% of patients are IgG positive, with >95% seroconversion by day 8 of illness. The presence of antibodies in CCHF has been suggested to be an important prognostic factor in survival, although no correlation between IgM titers and death or severity has been established. The recent development of a non-human primate model susceptible to CCHF infection will help better understand CCHF pathogenesis and immunology and its implication for vaccine and therapeutic approaches.

Considerations on CCHF surveillance systems

CCHF surveillance is currently insufficient to allow for appropriate outbreak response and to guide the evaluation of vaccines and therapeutics, although recent development in diagnostic tools helped enhance the sensitivity and specificity of surveillance strategies. The presence of the virus in the serum of CCHF infected patients is relatively short. Therefore, several countries have chosen a combination of commercial quantitative RT-PCR and serological IgM assays for confirmatory diagnosis of CCHF suspected cases to increase the sensitivity of surveillance systems, while other countries are only using qualitative RT-PCR testing. Multiplex panels to distinguish CCHF from other viral haemorrhagic fever is being increasingly used in Africa to increase the specificity of surveillance systems. Many meeting participants agreed that with current transmission patterns the evaluation of vaccines and therapeutics in humans will be feasible in an CCHF outbreak setting by accumulating evidence across multiple outbreaks. Given the low case rates, current unpredictability of outbreaks in rural areas, and time needed to set up research infrastructure in response to each outbreak, it was recognizing that surveillance must be significantly strengthened and fit-for-purpose in order to prospectively capture the sufficient number of trial events required to provide conclusive evidence. In particular, improved surveillance for early detection and continuous monitoring of CCHF cases is critical for improved case management and in the perspective of evaluating antivirals and biological products targeting the virus. Testing is generally being performed in national reference laboratories, outside of affected areas, and there is currently no point-of-care testing options. Access to well-characterized samples across regions will better inform test validation.
It is also unclear whether the observed variability in disease severity across regions is due to strain-specific differences or to differences in surveillance, community engagement and case management strategies, the key components of the public health response to CCHF outbreaks. Multiple RT-PCR assays are being used to detect distinct regional circulating CCHF strains and there is often a lack of standardization of case definition between and within affected countries.

Continuous efforts to improve and standardize case management and prevention procedures across countries is critical to help reduce disease mortality and to better inform the design of vaccine and therapeutic approaches, especially in the perspective of a large-scale multi-country clinical trials. A One Health surveillance approach, integrating better surveillance in animals susceptible to CCHF infection, could also enhance our ability to detect and respond to outbreaks.

Participants recognized that the conduct of epidemiological and clinical studies must be performed ahead of conducting clinical trials for CCHF vaccines and treatments in order to inform the design of clinical trials, pave the way to clinical trials by building research infrastructure in settings where clinical trials are likely to occur, as well as to improve and standardize case management and prevention procedures across sites and countries. Participants agreed that, in areas where sero-prevalence studies are suggesting high-endemicity of CCHF, a prospective large-scale multi-regions sero-incidence cohort study, that includes an active One Health surveillance component, is needed 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. The proposed study requires the use of standardized diagnostic tools and case definition across study sites.

**Evaluation of therapeutics to treat CCHF patients**

There are currently no specific therapeutics designed to treat CCHF patients. Immunotherapies, host-response modifiers, and synthetic antivirals targeting CCHF RNA synthesis are being considered. The antiviral ribavirin has been widely used off-label in several health facilities, although its use is not systematic and is being administered according to different treatment guidelines across health facilities. A systematic review of the evidence on ribavirin effect in treating CCHF patient suggest that there are substantial uncertainties on whether or not ribavirin is safe and effective in treating CCHF patients. Therefore, participants underscored the need to generate reliable evidence to determine whether or not ribavirin is safe and effective in treating CCHF patients, especially given the cost at which the drug is purchased and given the uncertainties on the quality of the product being procured.

Participants agreed that experimental CCHF therapeutics should be designed to treat and prevent severe CCHF cases and reduce mortality, but noted that the relevance of conducting therapeutics efficacy trials highly depends on the ability to rapidly identify cases and start treatment initiation. The design of a therapeutic trial should be integrated in a surveillance strategy where every effort should be made to identify and treat CCHF symptomatic patients at the earliest opportunity using adaptive study designs across multiple outbreaks to improve patient survival and to improve the clinical relevance of the treatment, especially as the detectable viral window is short. Patient viral load on admission measured by RT-PCR and time from patient onset to treatment initiation should be recorded as important covariates in estimating treatment effect.
Efficacy trials for RVF therapeutics: key methodological elements

- A multicenter, individually-randomized, placebo-controlled trial comparing ribavirin plus optimized standard of care (oSOC) versus oSOC with placebo was proposed to evaluate whether ribavirin improves survival in patients with confirmed CCHF compared to placebo. Randomization should be stratified by treatment centers to balance treatment allocation between treatment centers and reduce confounding by inter-site heterogeneity in mortality. Clusters should be reactively added to the study in the event of a major outbreak, highlighting the importance of early outbreak detection.

Day 28 mortality should be the primary endpoint of therapeutic trials. Secondary endpoints should be designed to evaluate the safety of ribavirin and to evaluate whether ribavirin reduce viral load and some of the important clinical symptoms in CCHF patients compared to placebo. Study data should not be released unless the trial was stopped, for efficacy, futility, or reaching its targeted number of study endpoints.

Evaluation of CCHF vaccines

There are currently no licensed CCHF vaccines for humans recommended for international use. An inactivated CCHF vaccine, based on a European strain and cultivated in suckling mouse brain, has been used since 1974 to prevent CCHF in military and medical personnel, farmers, and other persons living or working in CCHF endemic regions of Bulgaria. The similar vaccine, based on circulated strains in the South of Russia was developed in Russia in the beginning of 70s of the past century. Clinical trials demonstrated a good efficiency, but investigations were not continued. The vaccine is indicated to confer protective immunity following subcutaneous administration at days 0 and 30 followed by booster doses at one year and then every five years. The Bulgarian Ministry of Health reported a 4-fold reduction in the number of reported CCHF cases over 21 years following initiation of vaccination. However, there are substantial uncertainties on whether the observed reduction in the number of cases is directly linked to the use of the vaccine or with other factors, notably factors affecting the tick population or contact with ticks or infected livestock and education.

The lack of appropriate and standardized animal models for CCHF has hampered vaccine development. The development of new promising animal models susceptible to CCHFV infection (e.g. IFNAR-/- mice, STAT-1 mice, cynomolgus macaques) allows for better vaccine screening and validation strategies to guide the preclinical evaluation. However, these models need to be improved and standardized (e.g. selection of viral strains, reagents, challenge methods) to better recapitulate clinical features in humans, to better guide the selection of candidate vaccines to be considered for evaluation in humans, as well as in the perspective of bridging animal with human immunogenicity data.

Several vaccine development approaches (e.g. inactivated, subunit, viral-vectored) have been considered for use in humans and have shown various levels of efficacy in mouse challenge models. However, none of the candidate vaccines have entered clinical evaluation. Most of the vaccine constructs are based on the CCHF spike glycoproteins, although the highly-conserved nucleoprotein may play an important role in protecting across several CCHF strains. Two first-in-human Phase 1 studies are planned for a MVA-based prime-boost candidate and DNA vaccine candidate in 2020 to primarily assess the safety of the products in healthy adults.
Animal data suggested that both humoral and cellular immunity are required for protection, although there is no established correlates of protection. 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 protection, the demonstration of vaccine clinical efficacy to inform licensure and policy-makers decisions is critical.

**Efficacy trials for RVF vaccines: key methodological elements**

A double-blind individually-randomized placebo-controlled clinical trial should be designed to determine whether or not a CCHF vaccine is safe and effective.

Laboratory-confirmed CCHF illness should be the primary endpoint. Laboratory-confirmation should be made using a combination of RT-PCR testing and IgM testing assuming a serological assay can be adequately validated for specificity. Although CCHF vaccines should be designed to protect against severe CCHF disease, a case definition including mild to severe cases could be considered for case ascertainment to increase the power of the trial for the purpose of clinical evaluation, noting that the vaccine effect may be lower in preventing CCHF mild disease. In that case, clinical benefit must be further verified 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 should include at-risk adults and adolescents (e.g. farmers, butchers, veterinarians) within defined clusters. The definition of a cluster should be informed by the results of the large-scale sero-incidence that must be conducted ahead of the clinical trial potentially supplemented by the use of appropriately validated risk models. Clusters should be reactively added to the study in the event of a major outbreak, highlighting the importance of early outbreak detection. If the vaccine were found to be safe and effective, the clinical benefit of the vaccine will need to be further demonstrated in special populations (e.g. pregnant women, younger children, HIV+).

All participants should have blood collected 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.

Study data should not be released until the trial is stopped, for safety, efficacy, futility, or reaching its targeted number of study endpoints.
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 CCHF vaccine, based on the guidance provided in this document.

3. To set up a working group to write a study protocol for a clinical trial to evaluate ribavirin in treating CCHF patients and other investigational therapeutics, based on the guidance provided in this document.

4. 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.