World Health Organization

Crimean-Congo Haemorrhagic Fever (CCHF)

Research and Development (R&D) Roadmap

November 2019 – Advanced draft

R&DBlueprint

Powering research to prevent epidemics

Roadmap for Research and Product Development against Crimean-Congo Haemorrhagic Fever (CCHF)

Roadmap purpose

The WHO R&D Blueprint for Action to Prevent Epidemics establishes a platform for R&D preparedness that is intended to accelerate research and product development in advance of and during epidemics caused by the world's most significant infectious disease threats. A cornerstone of the WHO R&D Blueprint framework is the development of R&D Roadmaps for each of the priority pathogens within its scope. The R&D Roadmaps are intended to focus and catalyse international R&D effort to ensure the coordinated development of medical countermeasures (diagnostics, therapeutics and vaccines) thus reducing the time for new medical technologies and products to reach affected countries in a public health crisis.

This R&D Roadmap for Research and Product Development against Crimean-Congo Haemorrhagic Fever (CCHF) is the product of broad consultation with leading experts from CCHF-affected countries, international product R&D experts and other stakeholders. It sets the direction and timelines for future CCHF product research and development activities and prioritises the development of those countermeasures that are most needed by CCHF-affected countries.

Context and background

Crimean-Congo Haemorrhagic Fever (CCHF) is a tick-borne zoonotic disease with high case fatality rates in humans and the potential to cause outbreaks. Of the epidemic-prone diseases prioritised by the WHO R&D Blueprint, CCHF is the most widespread, found in around 30 countries across Europe, Asia, Africa, the Middle East, and the Indian subcontinent and is expected to continue to expand its range.

In most affected countries, CCHF is diagnosed by referring samples to reference laboratories for molecular testing; testing is rarely available in peripheral healthcare settings where the cases typically occur. Although ribavirin has been used for treatment there are questions about its efficacy, so general supportive care remains the main approach to managing CCHF. There is currently no safe or effective vaccine widely available for human use, nor is there an alternative to acaricides for control of the tick vector.

Unlike some strictly episodic emerging diseases, in affected countries CCHF occurs in recognised geographic foci and generally according to a seasonal pattern. This should facilitate the planning and implementation of studies to determine the efficacy of new medical countermeasures against CCHF. Nonetheless, no single country sees more than 1000 confirmed cases a year, so the success of this Roadmap and future R&D efforts will depend on collaboration between CCHF-affected and high resource countries, and on close coordination by WHO and others to minimise duplication of effort and to maximise precious resources.

Although this Roadmap focuses on the development of new or improved products and medical countermeasures, other public health preparedness actions are also critical for successful prevention of CCHF disease epidemics. Foremost amongst these is the need for regional, national and

international surveillance, reporting not only human CCHF cases (according to a standardised case definition) but also monitoring tick and animal reservoirs for evidence of CCHFV or seroconversion. This will require agreements and mechanisms for data sharing in real time and cooperation and coordination between the human, animal and environmental health sectors for the good of public-health disease control.

Roadmap structure

The first two sections of this CCHF R&D Roadmap, the Vision and Strategic Goals, set the strategic targets and timelines for developing countermeasures and interventions (diagnostics, therapeutics and vaccines) that will make a critical difference to how CCHF is managed in affected countries. These are deliberately ambitious and intended to build and maintain commitment and momentum over the lifetime of the Roadmap.

In the subsequent three sections, each countermeasure is considered in turn, starting with Landmark Goals (Milestones) that set the steps towards meeting the corresponding higher level Strategic Goal(s) and Vision. Priority research areas specify the activities that will be needed to ensure effective and coordinated development and deployment of countermeasures, from basic research, through product development and evaluation to supporting activities including development of key capacities and policies and routes to commercialisation.

Vision

To be able to reduce death and morbidity from CCHF through safe and affordable effective treatments informed by rapid, reliable, simple-to-use and easily accessible diagnostics by 2023,

and

To be able to prevent or mitigate CCHF disease through deployment of safe, affordable and effective vaccines or other preventive measures by 2030.

Strategic goals

The following goals define the strategic priorities for developing improved diagnostics (goal 1), therapeutics (goals 2 and 3) and vaccines and products for vector control (goals 4 and 5). An additional goal (goal 6) highlights the need for continued basic research that does not directly lead to product development, but is a critical enabler for both therapeutic and vaccine development.

1. Affordable, qualified nucleic acid and serology tests accessible for use in CCHF-affected countries by 2021 followed by the development and introduction of near-patient and/or point-of-care tests by 2023.

2. Address the need for effective treatment for CCHF by evaluating existing antivirals with potential activity against CCHF in well-designed multi-centre clinical trials, commencing Phase II trials by end 2021 and Phase III trials by 2023.

3. Develop and assess new drugs, biologicals and/or their combinations for their efficacy as CCHF therapies in relevant animal models through to early clinical trials by 2023.

4. Prioritise and progress the best human CCHF vaccine candidates from development to licensure, leveraging novel funding and regulatory mechanisms where necessary, with a lead candidate entering phase I trial by end 2021 and phase II trial by 2023.

5. By 2020 evaluate through proof-of-concept studies alternative immunisation strategies including animal CCHF vaccines and/or vaccines for tick-vector control for their ability to limit transmission and spread of CCHF virus and their deployability.

6. Through coordinated international studies, by 2025, characterise the pathogenesis and mechanisms of immune protection of CCHF disease in humans and support the development of better animal models and improved diagnostics, therapeutics and vaccines.

In 2025, there will be a strategic review of progress made against these goals. Further timelines for 2025-2030 will be set following that review with the aim of delivering effective countermeasures for the prevention of CCHF by 2030.

Diagnostics

Landmark goals / milestones

(refer to strategic goal 1)

- By January 2020, define Target Product Profiles (TPPs) for molecular and serological CCHF diagnostic tests suitable for use (i) in reference laboratories and (ii) decentralised near-patient use, followed by TPPs for rapid point-of-care tests (with minimal requirements for biosafety precautions and staff training) by 2022.
- By 2021, through international collaboration, qualify commercial real-time RT-PCR tests (qualitative and quantitative) and IgM and IgG serological tests using panels of well-characterised clinical samples that cover the main circulating CCHF virus strains.
- By 2022, develop and qualify one or more commercial tests suitable for near-patient diagnosis of CCHF, including evaluation in relevant healthcare settings in CCHF-affected regions to a standardised protocol.
- By 2023, develop and qualify commercial tests suitable for point-of-care use, including evaluation in relevant healthcare settings in CCHF-affected regions to a standardised protocol.

Priority Research Areas

Research

- **Characterise** existing archived CCHFV isolates and determine coverage of known circulating clades.
- Through collaboration between affected countries and international centres of expertise, **continue to sequence** complete CCHFV genomes circulating in man, animals and ticks

(including non-coding sequences) to determine full geographic variability as adjunct to evaluation of best diagnostic tests.

- **Continue to review** the utility of next generation sequencing (especially metagenomics) for CCHF diagnostic use (including contact tracing and epidemiological approaches), particularly using portable solutions e.g. MinIon in the field.
- **Investigate** utility of alternative sample types (urine, oral fluid, semen etc) for the diagnosis and monitoring of CCHF disease; this will also provide knowledge about CCHFV persistence in body fluids and may support development of non-invasive diagnostics.
- **Develop and characterise** anti-CCHFV antibodies for use in antigen detection tests; this could include mAbs developed for therapeutic purposes.
- **Develop** safer sample collection / inactivation systems for use with future point-of-care tests.
- **Continue** to develop non-infectious CCHFV pseudoviruses for evaluating CCHFV molecular diagnostic tests and for use in neutralisation assays (*cross-cutting – needed for CCHF vaccine evaluation*).

Product development

- **Develop and publish** TPPs for CCHFV diagnostic tests covering different use scenarios (see Landmark goal).
- **Continue to develop and determine** the analytical characteristics (sensitivity, specificity, limits of detection) of new near-patient and point-of-care diagnostic tests (nucleic acid or antigen detection).
- **Ensure** tests under development cover a range of CCHFV antigenic targets to enable their use in the assessment of live attenuated vaccines and/or as confirmatory diagnostic tests (*cross-cutting – needed for CCHF vaccine evaluation*).
- **Develop and validate** assays that quantify CCHFV viral load when used with a standard calibrant for monitoring disease and antiviral drug/vaccine efficacy studies (*cross-cutting – needed for CCHF therapeutics and vaccine evaluation).*
- **Develop** international antigen, antibody and nucleic acid reference standards for CCHFV to allow inter-test comparisons *(cross-cutting –needed for comparison between clinical trials of vaccine and therapeutic efficacy).*
- **Develop 'fever panels'** – diagnostic tests that use a common platform to distinguish CCHF from related illnesses with similar presentation (e.g. ebola or lassa in W Africa or more common disease e.g. leptospirosis, rickettsiae*) (cross-cutting for all WHO R&D Blueprint priority pathogens).*
- **Continue to develop and test** commercial serology assays for detecting IgM and IgG antibodies to CCHFV for use in supplementary diagnostic tests, for epidemiology and surveillance during outbreaks, and for evaluation of vaccine immunogenicity and durability.
- **Develop** one or more commercial multi-species ELISA kits to detect anti-CCHFV antibodies for monitoring CCHFV in animals.

Key capacities

- **Build local capability** (biosafety, laboratory, training & competence) in CCHF-affected countries for sample characterisation, archiving and use in diagnostic evaluation according to standardised procedures.

- In CCHF-affected countries, **establish and maintain** archives of well-characterised CCHFV isolates covering the full range of CCHFV clades to evaluate coverage of molecular diagnostic tests.
- In CCHF-affected countries, **establish and maintain** biobanks of well-characterised samples from CCHF cases with accompanying clinical information and samples from seropositive animals to use in the evaluation of diagnostic tests.
- **Develop** proficiency panels and regular EQA schemes which are accessible for CCHF-affected countries.

Policy & commercialisation

- **Establish** a fast-track WHO pre-qualification process (for non-emergency use) and the necessary resources to facilitate the laboratory evaluation and validation of CCHF diagnostics, to make qualified tests available.
- Starting with countries with existing CCHF clinical sample/virus archives, **ensure** early engagement with national authorities and decision makers in affected countries to secure support for the validation of commercial diagnostic tests in their country (by 2019).
- **Agree** terms of equal access to CCHF samples and virus isolates ensuring accordance with the Nagoya protocol where applicable.
- **Ensure** adequate preparation for field testing diagnostics in affected countries, including ethical approval and infrastructure requirements.
- **Agree** on gold standard diagnostic test(s) to use as the benchmark in studies that evaluate the analytical performance of new CCHF diagnostic tests.
- **Agree** with regulators the role of engineered non-infectious CCHF pseudoviruses and *in silico* tests to validate strain coverage of molecular diagnostics as a means to reduce the number of clinical samples needed for test validation.
- **Develop** diagnostic testing algorithms for different settings including surveillance, case-detection, triage in an outbreak etc.
- **Develop** a business case, defining the demand for CCHF diagnostics in routine use (in endemic countries, the military, international labs diagnosing imported infections) and in emergencies.
- **Develop** framework or initiative, where necessary, that offers economic incentive to diagnostic test developers so that assays can be made affordable to affected target countries. One option that can be considered to reduce cost to target countries is local manufacture that ensures validated manufacture and performance assurance.
- **Ensure** early engagement with national authorities in affected countries to facilitate licensure and distribution and access provisions.
- Through TPP process, **ensure** test manufacturers can provide adequate affordable stocks for routine and outbreak use.
- **Share** experiences between affected and un-affected countries to increase preparedness in countries at risk from CCHF.
- **Develop** a concept of use for point-of-care RDTs in endemic and outbreak scenarios, including an assessment of the training and biosafety needs and the risk of nosocomial transmission

Therapeutics

Landmark goals / Milestones

(refer to strategic goals 2 and 3)

- By mid-2020 , produce protocols in consultation with national regulatory authorities for dose regimen and subsequent randomised controlled trials to assess the efficacy and safety of existing therapeutic products, alone or in combination therapy against CCHF.
- By 2021, initiate first evaluation of the therapeutic potential of antibody therapy in a relevant preclinical model of CCHFV infection.
- By end 2021, start patient enrolment to phase II trials of an existing therapeutic to evaluate efficacy against CCHF disease and establish pharmacokinetic data and optimum dosing.
- By 2023, take successful therapeutics forward to a phase III randomised controlled trial in more than one affected country to establish full efficacy against CCHF disease.

Priority Research Areas

Research

- **Collect** available data about licenced antivirals with broad antiviral activity that might be suitable for the treatment of CCHF and use to prioritise candidates for further clinical evaluation.
- **Identify and screen** *in vitro* existing antiviral drugs to discover new small molecule inhibitors of CCHFV that can be progressed to preclinical evaluation.
- **Determine** the efficacy of oral and/or intravenous ribavirin and the optimum dosing regimen through clinical trials on well-characterised CCHF cases stratified according to disease stage and severity.
- **Conduct** clinical studies in multiple sites spanning more than one affected country and ethnic background to determine the therapeutic efficacy of existing antivirals e.g. favipiravir, arbidol.
- **Develop and conduct** clinical studies of therapeutic efficacy and safety of CCHF antibody therapy in pre-clinical models of CCHF.
- **Determine** the optimum package of supportive care for the management of CCHF patients alone and in combination with antivirals and other therapeutic measures.
- **Introduce** and **assess** the value of rapid coagulation tests in CCHF case management.
- **Investigate** potential for post-exposure prophylaxis (PEP) with any effective therapeutics e.g. antivirals or antibodies. Will require compassionate-use pathways since clinical trials of PEP are not feasible.
- Design therapeutic trails so that in parallel they help **increase understanding** of the basic immunology (especially cell-mediated) and pathophysiology of human CCHF *(cross-cutting & supports strategic goal 6).*

- **Develop** standardised ELISPOT or other assay(s) of T cell function that can be deployed to selected clinical trial sites subject to biocontainment capabilities *(cross-cutting and supports strategic goal 6).*
- **Develop and characterise** more relevant pre-clinical models of CCHF in immunocompetent animals, including harmonisation of protocols, CCHFV isolates etc. *(cross-cutting and supports strategic goal 6).*

Product development

- **Continue to develop and characterise** monoclonal and polyclonal (e.g. ovine) antibodies and test their therapeutic efficacy in relevant pre-clinical CCHF animal challenge models.

Key capacities

- **Assess** laboratory capacity in CCHF endemic areas under consideration as clinical trial sites and where necessary, **enhance** capacities.
- **Establish** ability for early CCHF diagnosis at study sites e.g. using clinical diagnosis according to agreed case definition and reference real-time RT-PCR for confirmation *(cross-cutting – needed for vaccine evaluation).*
- **Establish** ability at clinical trial sites to stratify cases by e.g. viral load (requires quantitative assay), severity of clinical disease (e.g. clinical chemistry; biomarker measurements using 'omics technologies) and duration of infection *(cross-cutting – needed for vaccine evaluation).*
- **Support** establishment of capability to investigate cell-mediated immunity in CCHF e.g. flow cytometry, ELISPOT assays etc at selected clinical trial study sites with appropriate biocontainment infrastructure *(cross-cutting – needed for vaccine evaluation & strategic goal 6).*

Policy & commercialisation

- **Develop and publish** TPPs for CCHFV therapeutics, both classical small-molecule drugs and /or biologicals.
- **Develop** criteria for product testing and prioritisation using the TPPs.
- **Constitute** a working group within the WHO CCHF R&D blueprint taskforce to select the most appropriate therapeutic candidates and doses for clinical evaluation. Annual numbers of CCHF cases are limited so the research effort has to be prioritised.
- Working with key decision makers in CCHF-affected countries, **develop and agree** WHO recommended case definition(s) for CCHF for routine use and for use in clinical trials *(cross-cutting – needed for vaccine evaluation).*
- **Develop and agree** protocol(s) for clinical trials (e.g. multi-centre randomised clinical trials) of existing antivirals (e.g. favipiravir) and agree surrogate markers/biomarkers for disease stratification and as end points other than mortality.
- **Engage** with research ethics committees and regulators in endemic countries to gain acceptance of clinical trial protocols so that local, national or multi-national protocols can be developed in advance to ensure readiness for therapeutic evaluation studies, especially in preparedness for outbreak use.
- Using the TPP process**, engage** with manufacturers of marketed antivirals that may have activity against CCHFV to facilitate screening and preclinical testing.

- **Develop and publish** WHO guidelines for the clinical management of CCHF patients using evidence gathered from clinical trials and analysed according to GRADE methodology.

Vaccines and Vector Control

Landmark goals / Milestones

Human CCHF vaccines

(Refer to strategic goals 4 and 6)

- Working with the appropriate national regulators, take at least one CCHF vaccine candidate that meets the TPP for CCHF vaccines and with proven efficacy in relevant animal models, into human phase 1 safety and early immunogenicity trials by end 2021 and phase II trials by 2023.
- Prioritise and progress 5 early-stage developmental human CCHF vaccines through relevant animal models by 2025.
- By 2025, identify and characterise relevant animal models of CCHF which recapitulate the pathogenesis and immune protective mechanisms of the human disease and are acceptable to regulatory authorities for use in the preclinical evaluation and regulatory approval pathway of novel CCHF vaccines and therapeutics.

Animal vaccines and vaccines for vector control

(Refer to strategic goal 5)

- By mid-2020, initiate discussions to set up a One Health consortium to be co-convened by WHO and OIE with responsibility for the strategic assessment of animal anti-tick vaccines as a means to cost-effectively control human CCHF disease, to improve livestock management and to reduce environmental spillover of acaricides and to facilitate their scientific development and evaluation
- By end 2020, complete a proof-of-concept study of experimental anti-tick vaccines and/or veterinary CCHF vaccine(s) in relevant animal models.

Priority Research Areas

Research

Human CCHF vaccines

- **Develop, standardise and validate** assays to assess the CCHF immune response. Specifically IgM and IgG ELISAs and assays of cell mediated immunity (e.g. flow cytometry, ELISPOTS etc) *(cross-cutting – needed for diagnostics activities).*
- **Develop, standardise and validate** virus neutralisation assays e.g. PRNTs, preferably using non-infectious CCHFV-based reporter pseudoviruses, using systems with improved efficacy over VSV and Lentivirus models. Calibrate assays against the International antibody standard if available.

- **Increase understanding** of the basic immunology and pathophysiology of human CCHF by detailed monitoring of patients and survivors in CCHF-affected countries and by establishing biobanks of well characterised samples *(cross-cutting and strategic goal 6).*
- **Identify** immune correlates of protection (cellular and humoral immunity) against CCHF that are relevant to human disease and can be used as measures of protective efficacy in animal vaccination studies *(cross-cutting and strategic goal 6).*
- **Develop and characterise** more relevant pre-clinical models of CCHF in immunocompetent animals, including harmonisation of protocols, CCHFV isolates etc. Animal models are needed to 'de-risk' vaccine candidates and give proof-of-concept for success *(cross-cutting and strategic goal 6).*
- **Identify** the adaptive immune responses and protective mechanisms in humans and NHPs against CCHF disease and identify the correlates of protection for use in vaccine studies *(cross-cutting and strategic goal 6).*

Animal vaccines and vaccines for vector control

- **Model** the costs and benefits of animal CCHF vaccines and anti-tick vaccines. Consider the possible gains from reducing the burden of all *Hyalomma*-borne infections in livestock and the reductions in acaricide use.
- **Develop** diagnostic assays to differentiate infected from vaccinated animals (DIVA reagents) for use with animal CCHFV vaccines.
- **Evaluate** the efficacy against *Hyalomma* spp. of existing anti-tick vaccines.
- **Implement** an antigen discovery programme to identify *Hyalomma* antigen targets that block tick feeding or pathogen transmission as useful targets for anti-tick vaccine development.
- **Develop and characterise** one or more animal models of CCHFV transmission by the *Hyalomma* tick, including models of co-feeding transmission, suitable for the evaluation of anti-tick vaccines.
- **Implement studies** to increase the understanding of the enzootic cycle of CCHF (identifying the main animal reservoirs and competent tick vectors).

Product development

- **Continue to develop** new candidate human CCHF vaccines against multiple virus antigens and test them in preclinical animal models.

Key capacities

- **Calculate** the burden and cost of CCHF disease in affected countries.
- **Encourage the development and in-country coordination** of region-specific epidemiologic surveillance mechanisms and reporting with sufficient dissemination (e.g., on MOH websites or other internet based platforms) to reliably assist in current and future vaccine trial design and planning.

Human CCHF vaccines

- With national authorities, **identify** study locations and populations in CCHF-affected countries with high incidence of human CCHF disease with view to phase II and III clinical vaccine trials.

- **Establish** ability for early CCHF diagnosis at study sites e.g. using clinical diagnosis according to agreed case definition and reference real-time RT-PCR for confirmation *(cross-cutting – needed for therapeutics evaluation).*
- **Establish** ability at clinical trial sites to stratify cases by e.g. viral load (requires quantitative assay), severity of clinical disease (e.g. clinical chemistry; biomarker measurements using 'omics technologies) and duration of infection *(cross-cutting – needed for therapeutics evaluation).*
- **Roll-out** IgM and IgG serology assays (with international reference standards for calibration if available) and virus neutralisation assays using non-infectious CCHFV based reporter pseudoviruses to clinical trial sites, subject to local biocontainment conditions *(cross-cutting – needed for therapeutics evaluation).*
- **Support** establishment of capability to investigate cell-mediated immunity in CCHF e.g. flow cytometry, ELISPOT assays etc at selected clinical trial study sites with appropriate biocontainment infrastructure *(cross-cutting – needed for therapeutics evaluation).*

Animal vaccines and vaccines for vector control

- **Build knowledge** of CCHFV seroprevalence in livestock and wild animals in endemic countries and regions through implementation of animal surveillance programmes. Data will inform economic analyses of benefits of anti-tick vaccines and support predictive statistical models of CCHFV prevalence.

Policy & commercialisation

- **Build the strategic case** in public health and economic terms for human CCHF vaccines and for anti-*Hyalomma* tick vaccine. For human CCHF vaccines, consider different use cases (at-risk groups in endemic foci / epidemic use / travel / military).

Human CCHF vaccines

- **Develop and publish** TPPs for CCHFV vaccines for human use, covering vaccines for preventive and reactive use. Include clauses for accessibility of final product.
- Working with key decision makers in CCHF-affected countries, **develop and agree** WHO recommended case definition(s) for CCHF for routine use and for use in clinical trials *(cross-cutting – needed for therapeutics evaluation).*
- **Develop and agree** protocol(s) for clinical trials of promising candidate CCHF vaccines in normal and outbreak settings, ensuring inclusion of special populations.
- **Engage** with research ethics committees and regulators in endemic countries to gain acceptance of clinical trial protocols so that local, national or multi-national protocols can be developed in advance to ensure readiness for vaccine studies, especially in preparedness for outbreak use.
- **Engage** with funding agencies to arrange funding for CCHF vaccine studies.
- **Consider** whether a special licencing mechanism is needed e.g. a mock-up dossier, to permit subtle modifications to accommodate geographical variations in CCHFV clades.

Animal vaccines and vaccines for vector control

- **Early engagement** with Ministries of Agriculture/Veterinary Services to consider utility / acceptability of anti-tick and/or anti-CCHF vaccines for animal administration. Consider polyvalent vaccines targeting CCHF but also an economically-important animal disease.