A Research and Development Roadmap for Crimean-Congo Haemorrhagic Fever

2024 Update

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Contents

Acronyms and Abbreviations

AIGV	Aigai virus
BSL	Biological safety level
CCHF	Crimean-Congo haemorrhagic fever
CCHFV	Crimean-Congo haemorrhagic fever virus
CEPI	Coalition for Epidemic Preparedness Innovations
CFR	Case-fatality rate
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immunospot
EMA	European Medicines Agency
EQA	External quality assurance
FAO	Food and Agriculture Organization of the United Nations
FDA	U.S. Food and Drug Administration
GLOPID-R	Global Research Collaboration for Infectious Disease Preparedness
GPC	CCHFV glycoprotein precursor
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAZV	Hazara virus
ICTV	International Committee on the Taxonomy of Viruses
ICU	Intensive care unit
IFN	Interferon
IFNAGR-/-	Type I and type II interferon receptor knockout
IFNAR-/-	Type I interferon receptor A knockout
IL-6	Interleukin 6
IP-10	Interferon-induced protein-10 (aka CXCL10)
LDLR	Low density lipoprotein receptor
mAb	Monoclonal antibody
MCM	Medical countermeasure
MCP-1	Monocyte chemoattractant protein-1
nAb	Neutralising antibody

NGS	Next generation sequencing
NHP	Non-human primate
NP	CCHFV nucleoprotein
PEP	Post-exposure prophylaxis
PHEIC	Public health emergency of international concern
POC	Point-of-care
PRNT	Plaque reduction neutralisation test
R&D	Research and development
RCT	Randomised controlled trial
RDT	Rapid diagnostic test
RPA	Recombinase polymerase amplification
RT-LAMP	Reverse-transcription loop-mediated isothermal amplification
RT-PCR	Reverse-transcription polymerase chain reaction
STAT1-/-	Signal transducer and activator of transcription 1 knockout
TNF-α	Tumour necrosis factor-alpha
TPP	Target product profile
VEGF	Vascular endothelial growth factor
VHF	Viral haemorrhagic fever
WHO	World Health Organization
WOAH	World Organisation for Animal Health

Definition of Roadmap Terms

Challenges: inherent barriers or challenges (technical, financial, regulatory, governance, commercial etc.) that may influence the likelihood of success at various stages of CCHF MCM development. Identifying such challenges helps inform the nature and scope of activities required to achieve the desired R&D outcomes.

Critical Gaps: key unresolved questions or limitations in knowledge that are critical to the development of new countermeasures or interventions and that can be addressed through targeted R&D activities.

Strategic Goals: the high-level research priorities that must be addressed to meet the stated overarching Vision in the specified timeframe.

Milestones: the key actions necessary to achieve the roadmap's strategic goals; the milestones include target dates for completion and reflect SMART (specific, measurable, achievable, realistic/relevant and time-limited) criteria, where feasible.

Additional Research Priorities: further topics and issues that are relevant to the achievement of the strategic goals and milestones but are not of high enough priority to be considered milestones or not sufficiently specific or time-bound to be identified with SMART criteria. These span the breadth of activities from basic research, through product development and evaluation to supporting activities including development of key capacities and policies and routes to commercialisation.

Photo: thsulemani

Overview

Roadmap Purpose

This 'Research and Development Roadmap for Crimean-Congo Haemorrhagic Fever (CCHF): 2024 Update' is the culmination of broad consultation with leading experts from CCHF-affected countries, international product R&D experts and other stakeholders. The document identifies 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, aiming for *new medical countermeasures (MCMs) and other interventions to improve management of Crimean-Congo haemorrhagic fever (CCHF) by 2028 and limit transmission and control disease by 2030*. It specifies activities from basic research, through advanced product development and evaluation, licensure and manufacture, to sustainable supply and deployment. It is intended to serve as a framework to be used and adopted by CCHF-affected countries, research funders, R&D scientists and product developers, manufacturers, regulatory agencies, national authorities and policy makers.

Note This roadmap is a revised and updated version of an original work titled "*Crimean-Congo Haemorrhagic Fever (CCHF) Research and Development (R&D) Roadmap: November 2019 - Advanced Draft*" Geneva: World Health Organization (WHO) (WHO 2019a). This updated work was supported by the Wellcome Trust [grant number 226729/Z/22/Z]. The current adaptation was not created by WHO and WHO is not responsible for the content or accuracy of this adaptation. The original edition shall be the binding and authentic edition.

The recommendations in this 2024 roadmap update were presented at the 3rd International Conference on Crimean-Congo Haemorrhagic Fever (Welch et al 2024) and have been published as a commentary (Semper et al 2024).

Introduction

Crimean-Congo haemorrhagic fever (CCHF) is a medically significant tick-borne viral illness of humans for which there are no licensed specific treatments or vaccines. It has a reported case fatality rate (CFR) of up to 40% in some settings (WHO 2022a) and a wide and expanding geographical distribution. Globally, an estimated 3 billion people are at risk of CCHF (WHO 2018b) which is endemic in over 30 countries spanning four WHO Regions across southeastern Europe, the Middle East, western Asia, Africa, and the Indian subcontinent (figure 1). In Türkiye alone, it has caused 16,499 cases (Welch et al 2024) in the 22 years since its appearance in 2001 (Bakir et al 2005). The distribution of CCHF closely mirrors that of its principal reservoir and vector, hard-bodied ticks of the genus *Hyalomma* (Hoogstraal 1979), which are necessary to support the circulation of CCHF virus in natural tick/vertebrate foci (Gargili et al 2017). As the vector's range extends in response to changes in climate, environment and anthropogenic factors, CCHF is expected to become endemic in new geographies (Messina & Wint 2023), and disease incidence may rise. Indeed, in the last decade the first autochthonous cases of CCHF have been reported in Spain (Lorenzo Juanes 2023) and Portugal (ECDC 2024), and the virus has been found in *H. marginatum* ticks in southern France (Bernard et al 2024) and Corsica (Kiwan et al 2024).

The causative agent of CCHF is CCHF virus (CCHFV; species *Orthonairovirus haemorrhagiae*), an orthonairovirus in the *Bunyavirales* order (Kuhn et al 2024). CCHFV was named in 1973 by the International Committee on the Taxonomy of Viruses (ICTV) as the causative agent of two hitherto separate illnesses, Crimean fever [identified in 1944 (Hoogstraal 1979)] and Congo fever [identified in 1956 (Simpson et al 1967, Woodall et al 1967)]. CCHFV is an enveloped virus that contains a negative sense single stranded RNA genome with large (L), medium (M), and small (S) segments (Zivcec et al 2016). The L segment encodes the L protein which includes the RNA-dependent RNA polymerase (RdRp). The S segment encodes the nucleoprotein (NP) and the non-structural NSs protein. The M segment encodes the glycoprotein precursor (GPC), from which the PreGc/Gc and PreGn/Gn structural glycoproteins are sequentially cleaved, along with the non-structural protein NSm, and the secreted non-structural proteins GP160, GP85 and GP38. Gc-Gn heterodimers trimerise to form the virion spikes and mediate host cell entry via one or more cellular receptors, including the Low Density Lipoprotein Receptor (LDLR) (Monteil et al 2024, Xu et al 2024), while secreted GP38 mediates vascular leak (Pahmeier et al 2024) . Both are putative targets for new anti-CCHF therapeutics.

CCHFV is genetically diverse, in part because of a propensity to undergo RNA segment reassortment (Hewson et al 2004a, Lukashev et al 2016) and genetic recombination (Deyde et al 2006, Lukashev 2005). Until recently, it was classified into six main genotypes (genogroups) or clades (I-VI) based on the S segment

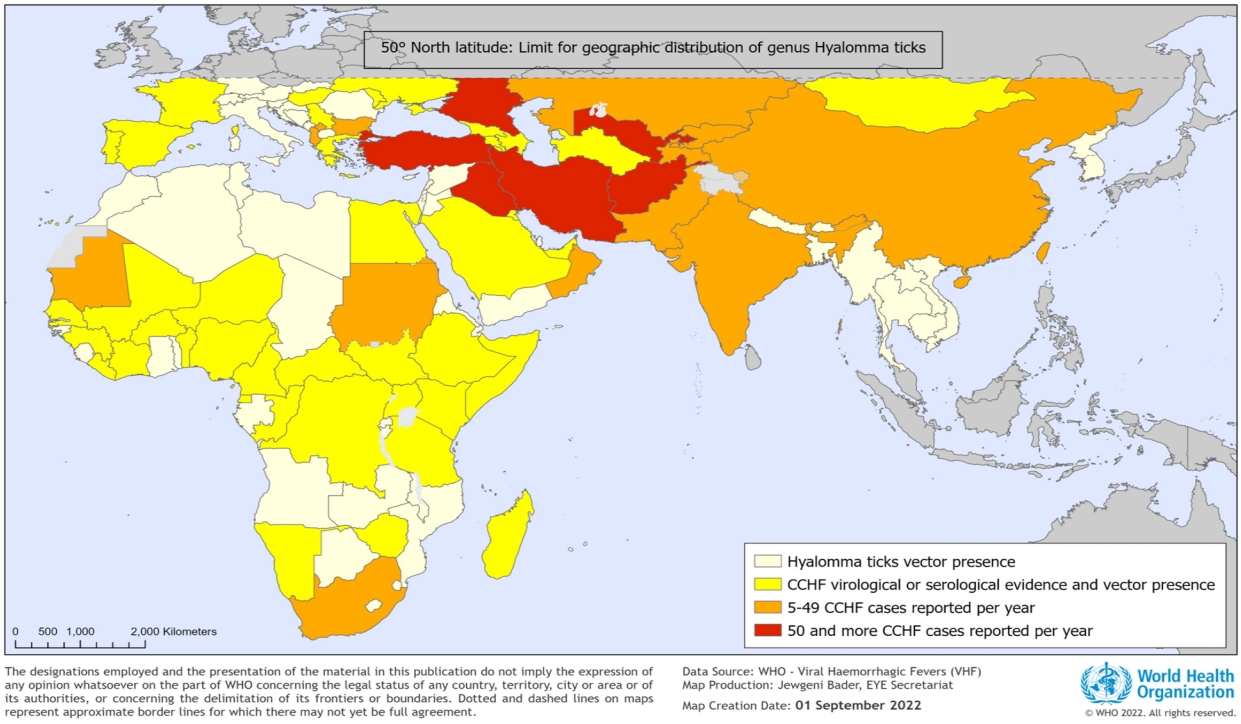

Figure 1: Geographic distribution in 2022 of *Hyalomma* spp. ticks (pale yellow), virological evidence of CCHFV in *Hyalomma* ticks (yellow) and human CCHF cases [5-49 cases annually (orange); 50 or more cases annually (red)]. Countries shaded grey have no evidence for the presence of *Hyalomma* ticks. Image provided by WHO.

Genotype/Clade	Alternative Name
I	Africa 1
II	Africa 2
III	Africa 3
IV	Asia 1, Asia 2
V	Europe 1
VI	Europe 2[1]

Table 1: Alternative designations of CCHFV genotypes (genogroups) based on phylogenetic analysis of the molecular sequence of the viral S segment. Classification into genotypes I-VI is based on (Carroll et al 2010, Deyde et al 2006). An alternative classification, based on the geographical origin of the virus is also in use (Chamberlain et al 2005, Hewson et al 2004b). This classification recognises seven groups, with both the Asia 1 and Asia 2 groupings corresponding to genotype IV.

[1]Note that genotype VI (Europe 2) has now been re-classified as a distinct virus, Aigai virus [species *Orthonairovirus parahaemorrhagiae* (Papa et al 2022)].

sequence (see table 1), which cluster geographically (Deyde et al 2006). Genotypes I–III are endemic in Africa, genotype IV circulates in Asia and genotype V occurs in Europe, although more than one genotype can circulate in some areas [e.g. Spain (Lorenzo Juanes et al 2023)]. Former genotype VI (Europe-2 or AP-92-like) is distantly related to known CCHFV isolates, with significant differences in the GP38 and mucin-like domain of the GPC. It has recently been reclassified as a distinct orthonairovirus species [Aigai virus (AIGV), *Orthonairovirus parahaemorrhagiae*] (Papa et al 2022). AIGV is generally considered to have low virulence in humans, but it has been associated with disease (Midilli et al 2009) including fatal CCHF (Salehi-Vaziri et al 2016). Its full pathogenic potential is still under investigation (Pickin et al 2022). The genetic variability of CCHFV has implications for the evaluation and selection of appropriate diagnostic tests (Gruber et al 2019), development of therapeutics and vaccines, bio-surveillance, pathogenicity and transmissibility.

In nature, CCHFV circulates unobserved in enzootic tick-vertebrate-tick cycles (Spengler et al 2016) (figure 2). Ticks are regarded as both the vector and main reservoir for CCHFV (Gargili et al 2017). In its *Hyalomma* tick reservoir, CCHFV can persist throughout a life stage, even during long periods of winter dormancy, and is transmitted from one life stage to the next (transstadial transmission or transstadial survival). CCHFV is also transmitted maternally to the next generation [transovarial or vertical transmission, (Gonzalez et al 1992)] and horizontally through co-feeding (Gordon et al 1993), whereby an (infected) feeding tick transmits CCHFV to its close (uninfected) neighbour when taking a blood meal on the same (uninfected) host. For two-host *Hyalomma* spp., typical vertebrate hosts for larvae and nymphs include hares, hedgehogs and ground feeding birds (e.g. corvids, partridges) (Spengler et al 2016) whereas adult ticks feed and mate on larger wild or domesticated ungulates including deer, cattle, sheep, goats, wild boar and camels. In animals, experimental infection with CCHFV does not cause overt signs of disease (Spengler et al 2016) but susceptible wildlife and domesticated animals do experience transient viraemia (Spengler et al 2016). Wild and domesticated ungulates can support high densities of *Hyalomma* ticks and through cofeeding, or CCHFV transmission during periods of transient viraemia, can infect a considerable number of ticks, thus serving as amplification hosts for the virus. Birds do not support CCHFV amplification (except for ostriches) but importantly do spread infected ticks to new geographies along their migration routes (Spengler & Bente 2017). Similarly, both ticks and virus are transported across borders through livestock movements. Given their roles in maintaining the enzootic cycle of CCHFV, both ticks and their vertebrate amplification hosts are potential targets for measures to prevent spillover of CCHFV to humans.

CCHFV is most commonly transmitted to humans either by infected ticks (through bites or crushing of engorged ticks), or through direct

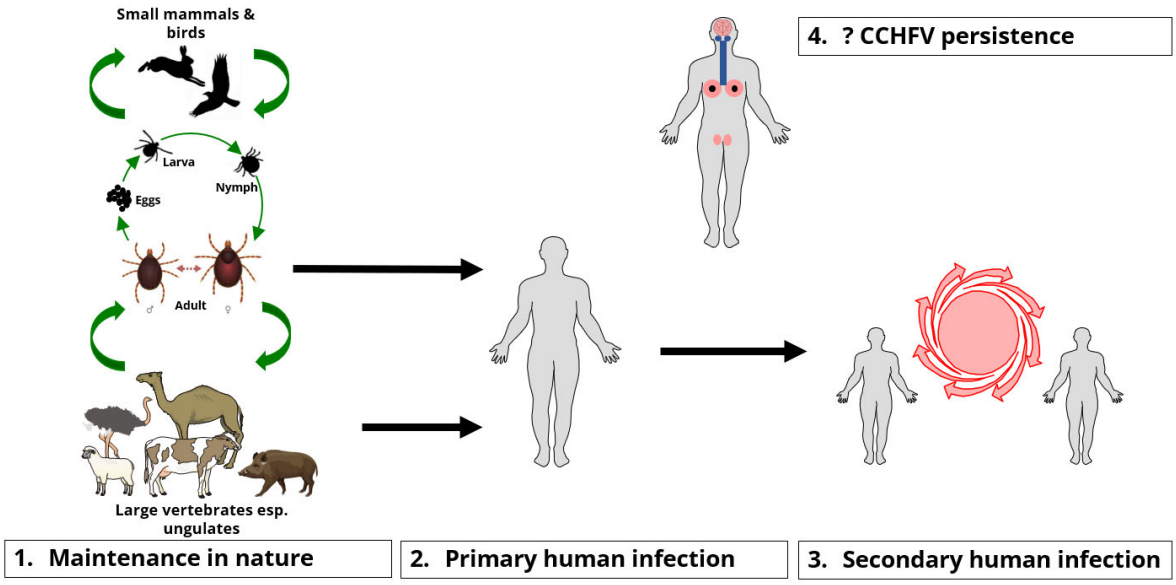

Figure 2: CCHF maintenance and transmission. CCHF virus is maintained in enzootic cycles involving ticks and small and large vertebrates, especially ungulates. Ticks are both the vector and reservoir for CCHFV. Animal infection causes transient viraemia; most animals do not show symptoms (panel 1). 80 to 90% of human CCHF cases are the result of primary CCHFV transmission through tick bites, or direct contact with blood or tissues of infected ticks or viraemic vertebrates, including wild animals and livestock (panel 2). Secondary human-to-human transmission occurs through direct contact with the blood, secretions, organs or other body fluids of infected persons. The highest transmission risk is when providing direct patient care (hospital or home nursing) or handling dead bodies (funerals) (panel 3). CCHFV may persist in immunoprivileged sites, such as the brain, reproductive organs and breast tissue (panel 4). Image adapated from and permission given by Dr Pierre Formenty (WHO) and Dr Tom Fletcher (LSTM).

contact with blood or tissues from infected livestock or wild animals. Human-to-human transmission in households is rare (Koksal et al 2014) but CCHFV can be transmitted nosocomially, mostly affecting healthcare workers (Gaina et al 2023, Naderi et al 2011, Pshenichnaya & Nenadskaya 2015, Tsergouli et al 2020). There is a need for prompt case identification and implementation of infection prevention and control to mitigate against nosocomial transmission (Fletcher et al 2017).

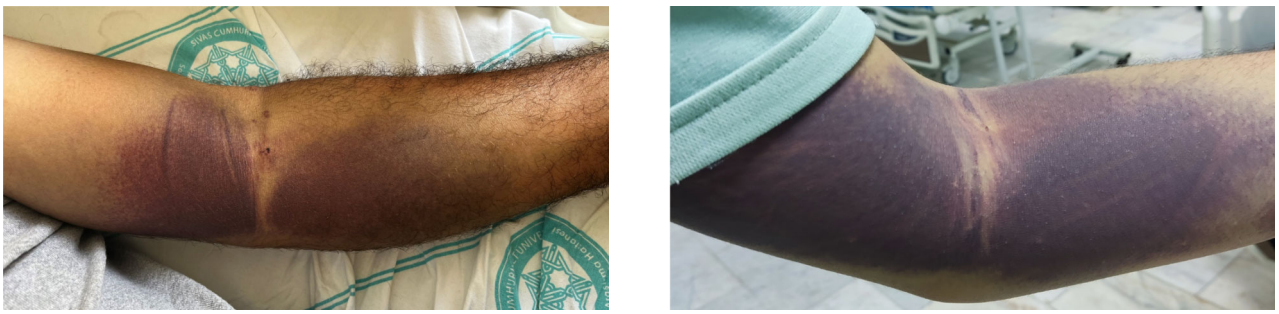

Figure 3: Clinical presentation of severe Crimean-Congo haemorrhagic fever with prominent large ecchymoses (left-hand image courtesy of Dr Nazif Elaldi, Sivas Cumhuriyet University Hospital, Türkiye; right-hand image courtesy of Dr Khdair Hazbar Razzaq Al-Asadi, Al-Hussein Teaching Hospital, Iraq).

Only humans experience clinically manifested CCHF disease. Many individuals infected with CCHFV remain asymptomatic, estimated to be 20% and up to 90% in two separate studies (Goldfarb et al 1980, Bodur et al 2012). Others may experience only mild/moderate non-specific symptoms including fever, myalgia, joint pain, headache, photophobia, nausea and vomiting. Where the disease progresses to haemorrhagic manifestations, symptoms include petechiae, ecchymoses on mucous membranes and skin (figure 3), bleeding from injection sites and epistaxis. Cases exhibiting haemorrhagic events are defined as severe CCHF. Altered haematology (e.g. thrombocytopenia, leukopenia/leukocytosis), blood chemistry (e.g. elevated aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase and creatine phosphokinase levels) and coagulation tests (e.g. prolonged prothrombin time and activated partial thromboplastin time) can be seen in the course of disease. Severe CCHF cases may rapidly progress to disseminated intravascular coagulation, major haemorrhages, haemodynamic instability, hepatic injury and neurological involvement. Death is usually due to kidney, liver or pulmonary failure, haemorrhages and shock. Published CFRs vary widely from 5 to 83% (Bente et al 2013), but rates up to 40% are more typically reported (WHO 2022a), although a recent systematic review and meta-analysis of global CCHF cases from 1964 - 2016 derived a mean CFR of 11.7% for acute CCHF (Belobo et al 2021). Prompt diagnosis enables timely patient management, with high viral load [>10^8 copies/mL (Duh et al 2007, Hasanoglu et al 2016)] or a depressed antibody response (Burt et al 1994, Saksida et al 2010) being indicators of poor prognosis. In survivors, the convalescent period starts 10 to 20 days after the first symptoms, with patients experiencing fatigue, tachycardia, hair loss, neuritis, hearing loss, loss of memory, and bradycardia (Ergönül 2006). Some symptoms may persist, suggestive of a postviral fatigue syndrome and can be explained partly by dysregulated metabolic pathways in the body (Ambikan et al 2023).

Basic research and product development and evaluation have been hampered by the need to work with CCHFV only at the highest levels of biocontainment [biosafety level (BSL)-3 and BSL-4] (Weidmann et al 2016). As a result, options for the diagnosis, treatment and prevention of CCHF are limited, with no diagnostic tests suitable for decentralised use and no licensed specific treatments or vaccines. General supportive treatment including intravenous fluids and electrolytes, blood products and other supportive care is the main approach for clinical management of mild/moderate and severe CCHF cases (Spengler & Bente 2015). No licensed drugs are specifically indicated for the treatment of CCHF and although ribavirin is used in some endemic countries, its efficacy for the treatment of CCHF is unproven (Johnson et al 2018). Additionally, there is currently no widely available CCHF vaccine that has been licensed to international standards for human use, although some affected countries produce vaccines for use in at-risk populations such as healthcare workers.

Humans are accidental hosts for *Hyalomma* ticks and consequently for CCHFV. Typically, CCHF disease occurs as isolated human cases or small sporadic localised outbreaks of viral haemorrhagic fever (VHF) (Spengler et al 2019), particularly in rural areas (Bente et al 2013), where human activity coincides with ticks and/or their natural hosts. Changes in environmental, socio-economic or anthropogenic factors that increase encounters between humans and infected ticks or viraemic animals may result in more sustained viral spillover and larger CCHF outbreaks, as seen after World War II in Crimea (Hoogstraal 1979) and in more recent years in Iraq (Alhilfi et al 2023, Atwan et al 2024), Afghanistan (Neyazi et al 2024) and Pakistan (Hussain et al 2024). CCHF is a particular public health challenge in low- and middle-income countries with fragile healthcare systems, where pastoralism brings humans into close contact with animals and ticks, and where animal movements are necessary for trade and livelihoods.

Given CCHF's high CFR, its potential to cause outbreaks of severe VHF and its wide and expanding geographical distribution, together with the lack of treatment options or vaccines, CCHF was one of the 'priority diseases' identified by WHO in 2017 and 2018 (WHO 2018a) as part of the WHO R&D Blueprint for Action to Prevent Epidemics initiative (WHO 2016). Pathogen-specific roadmaps were an integral component of the R&D Blueprint. Accordingly, in 2018, led by a taskforce of experts from CCHF-affected countries and product R&D specialists, work commenced to develop a WHO R&D Roadmap for CCHF (see Appendix), intended to focus and catalyse international R&D effort to ensure the coordinated development of medical countermeasures (diagnostics, therapeutics and vaccines) for CCHF, thus reducing the time for new medical technologies and products to reach affected countries. After public consultation, this was published as an advanced draft on the WHO website (WHO 2019a).

In November 2022, WHO announced plans to revise its epidemic preparedness strategy away from specific pathogens towards entire pathogen families (WHO 2022c), leading to its new pathogens prioritisation framework (WHO 2024), which focuses on viral families (and some bacteria), and on 'priority' and 'prototype' pathogens within a family. Considering the unique features of different pathogens such as CCHFV within the broader classification systems, pathogen-specific roadmaps are still important to inform future directions and investments in preparedness for emerging and outbreak-prone infectious diseases. Additionally, as the specified priority and prototype pathogen for the *Nairoviridae* family (WHO 2024), approaches used for CCHFV may translate to other family members.

In February 2023, the Wellcome Trust convened an expanded working group of 20 experts to review the 2019 advanced draft of the CCHF R&D Roadmap and generate an updated set of research priorities and timelines to guide investment and research in CCHF product R&D. This 2024 update reflects scientific

developments over the past five years and consensus opinion of the expert group.

Opportunities and Critical Barriers

Unlike some strictly episodic emerging diseases, in affected countries CCHF generally occurs in recognised geographic foci and according to a predictable seasonal pattern. This provides both a predictable demand for any new MCM or other intervention and an opportunity to plan and implement adequately sized clinical studies to determine the efficacy of new MCMs against CCHF. Nonetheless, no single country generally sees more than 1000-1500 confirmed CCHF cases a year (of which less than half will be moderate to severe), so the success of future R&D efforts will need to build on the experience WHO and the global scientific community has gained over recent years in conducting multi-country clinical trials.

A second opportunity for the control of CCHF is to target the virus' animal hosts and tick reservoir to mitigate CCHFV spillover to humans. Accordingly, this CCHF R&D Roadmap includes a 'vaccines for animal use' section (theme 5) with emphasis on developing vaccines to control tick vector infestations (de la Fuente & Ghosh 2024, Kasaija et al 2023). When used as part of integrated tick management strategies these might prevent transmission of CCHFV to humans and bring concomitant benefits for animal health. This One Health approach, which is arguably unique amongst the original WHO R&D Blueprint pathogens with epidemic potential, would take advantage of the less stringent regulatory requirements for animal vaccines, allowing selection of the most cost-effective vaccine platforms and a potentially more rapid route to market. Also, animals are likely to require fewer booster doses than humans since durable immunity is not required for commercial livestock herds that have a finite lifetime before slaughter. However, there will be a trade off since government veterinary services are less well funded than their human healthcare counterparts and new international funding initiatives and cooperatives may be needed to develop, manufacture and deliver sustainable and accessible One Health solutions such as vaccines (de la Fuente & Ghosh 2024, Samarasekera 2021). Such vaccines will need to be developed and evaluated in parallel with continuing basic research to further understand the complex interconnected determinants of spillover (Sorvillo et al 2020).

To exploit these opportunities to the full and deliver much needed effective countermeasure products for the control of CCHF, will crticially depend on:

- adequate funding for CCHF countermeasure product R&D and enabling research (including assay development, One Health surveillance and genomic sequencing),

- novel legal, regulatory, financing, manufacturing and procurement mechanisms to ensure sustainable access to MCMs for affected countries at affordable

prices,

- strong multisectoral collaboration between international agencies responsible for human health (WHO) and animal health [World Organisation for Animal Health (WOAH) and Food and Agriculture Organization of the United Nations (FAO)] for the benefit of human health, as well as that of animals and the environment,

- engagement with and collaboration between CCHF-affected and high resource countries, a robust and sustainable mechanism for regular review of progress against milestones and close coordination to minimise duplication of effort and maximise precious resources.

Roadmap Scope and Structure

The original WHO R&D Roadmaps were intended to focus on research and development leading to new and much-needed MCMs for emerging epidemic prone diseases. Three categories of MCM products were specified: diagnostics, therapeutics and vaccines.

This updated roadmap comprises five themes. The three MCM categories are considered in themes two to five. Recognising the possibility to vaccinate animals to control tick infestations and limit CCHFV transmission, in this document vaccines have been divided into two parallel themes, 'vaccines for human use' (theme four) and 'vaccines for animal use' (theme five). All four product-focused themes share the need for underpinning basic research (that does not directly lead to product development), integrated multisectoral One Health activities and, most critically, sustainable financing mechanisms. These cross-cutting issues and enabling activities are dealt with in theme one; without these, CCHF product development will fail to progress from the bench, through evaluation to use by affected communities.

For each theme, the main challenges and R&D gaps are identified followed by the key needs. These needs have then been prioritised to arrive at a set of strategic goals and milestones. An overarching Vision and ten Strategic Goals are specified in this Roadmap. These set the strategic targets and timelines for filling critical R&D gaps (e.g. One Health CCHF surveillance), and developing and evaluating countermeasures and interventions (diagnostics, therapeutics and vaccines for human or animal use) that will make a critical difference to how CCHF is managed in affected countries. The timelines are deliberately ambitious and are intended to build and maintain commitment and momentum over the lifetime of the roadmap. For each of the five themes, milestones specify the key steps towards meeting the corresponding higher level Strategic Goals. The more detailed actions necessary to achieve the milestones are specified as 'Additional Research Priorities'.

These span the breadth of 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 commericalisation.

For this roadmap to be effective it will need to be adopted, implemented and managed by affected countries and the international R&D community. Progress against the specified milestones and goals will need to be monitored and reviewed, at least annually. It is suggested that in Q4 2025, there should be a strategic review of progress made and further timelines for 2026-2030 should be set with the aim of delivering effective countermeasures for the control or prevention of CCHF by 2030.

Vision

To detect, control and prevent human CCHF disease using integrated One Health surveillance systems and readily available and affordable medical countermeasures, prioritising rapid diagnostics and specific therapeutics by 2028, followed by safe and effective vaccines to limit CCHF transmission or control disease in at-risk populations by 2030.

Photo: fikretozk

1. Cross Cutting Issues and Enabling Activites

Challenges and Critical Gaps

- Financial considerations pose a major challenge for the development of and access to diagnostics, therapeutics and vaccines for CCHF. R&D for products to detect, treat and control CCHF lags behind that for many of the other original R&D Blueprint priority pathogens and CCHF has so far not been prioritised by funding partnerships such as the Coalition for Epidemic Preparedness Innovations (CEPI) and the Global Research Collaboration for Infectious Disease Preparedness (GLOPID-R). CCHF has also been neglected by private-sector product developers in part due to a perceived limited commercial market to incentivise investment.

- The COVID-19 pandemic highlighted global inequities in access to new MCMs and technologies and over-reliance on a limited number of developers and manufacturers in affluent countries (Farlow et al 2023). CCHF disproportionately affects hard-to-access communities in low- to middle-income countries. For any new MCM with proven efficacy to benefit affected communities, the products will need to be affordable, accessible and sustainable. This will require innovative delivery models for industry or international philanthropic public-private partnerships that ensure equitable access (Torreele et al 2023). For example, where CCHF-affected countries are involved in the investigation of a new MCM and provide data that helps bring the product to market, this should be recognised through guaranteed access to the product at an affordable price, that is protected for the lifetime of the product.

- Traditional frameworks for regulatory approval of new human therapeutics or

vaccines involve pre-clinial evalutation followed by multiple phases of clinical trials that require many thousands of patients to determine efficacy. The lengthy, complex and expensive regulatory process is a disincentive to product developers, especially when the size of the final market is small. Furthermore, for CCHF, which causes sustained but low levels of disease, rarely exceeding 1000 cases a year in any one country, traditional approval routes may not be feasible. Emergency use pathways (e.g. WHO 2022b) can only be used if CCHF causes a public health emergency, meaning alternative regulatory approaches may need to be considered, that use surrogate human endpoints to indicate clinicial benefit (e.g. accelerated or adaptive approval pathways) or determine effficacy primarily based on studies in animal models of CCHF [e.g. the Animal Rule, US Food and Drug Administration (Allio 2018)].

- As a tick-borne zoonotic infection amplified in vertebrate hosts, there is a need for integrated multisectoral CCHFV surveillance at the regional, national and international level, reporting not only human CCHF cases (according to a standardised case definition), but also monitoring CCHFV in ticks and animal hosts (Mhamadi et al 2022) to provide evidence for action, better characterise CCHFV dynamics at the human-tick-animal interface and identify opportunities to target animals to prevent CCHFV transmission to humans. Surveillance should include pathogen genomic sequencing to identify and characterise circulating and emerging CCHFV strains, detect new variants and keep pace with viral evolution and spread. This will require a strengthening of national capabilities, agreements and mechanisms for data sharing in real time and cooperation and coordination between the human and animal health sectors for the good of public-health disease prevention and control (see milestone 9.1).

- CCHF CFRs ranging from below 5% up to 40% are widely reported. CCHF-affected countries with the highest incidence of CCHF cases (e.g. Türkiye and Russia) report some of the lowest CFRs. This may reflect geographical differences in case ascertainment, the use of different case definitions and differences in the clinical management of CCHF cases and underscores the need for more harmonised CCHF case definitions. It is also possible that CCHFV genomic variations or host genetic factors contribute to the observed differences in virulence (Fajs et al 2014), disease severity and CFRs, as seen in NHP models of CCHF disease (Arnold et al 2021).

- The role of the host adaptive immune response in the control of acute CCHFV infection and in protection against re-infection with homotypic or heterotypic CCHFV viruses is largely unknown, as is its possible contribution to the severe pathology seen in some CCHF cases. This knowledge gap has hampered the rational design of candidate CCHF vaccines and immunotherapeutics and relevant correlates

of protection for CCHF vaccine studies remain to be determined (Rodriguez et al 2022). Clearance of viraemia in human CCHF follows the appearance of anti-NP IgM responses, suggesting a role for adaptive humoral immunity (Rodriguez et al 2022), despite NP being an internal viral protein. However, in human disease, antibody titres and the potency of neutralising antibodies (nAb) do not show a strong correlation with disease outcome (Rodriguez et al 2022), and neutralising antibodies from CCHF survivors that target the surface exposed Gc protein rarely give therapeutic protection in murine models (Fels et al 2021). Non-neutralising antibodies targeting GP38 (Shin et al 2024) and Gc-specific CD8 T cells (Goedhals et al 2017, Rao et al 2023) are likely to also contribute to control of CCHFV infection. Further detailed dissection of the immune response during CCHF disease resolution is needed but is limited by the need for sophisticated assays and high-containment facilities which are not widely available in CCHF-affected countries.

- Pre-clinical evaluation of candidate therapeutics and vaccines has been hampered by the lack of animal models that replicate the immunopathogenesis seen in human CCHF. Recently, progress has been made with both non-human primate (NHP) and small animal models [reviewed in (Garrison et al 2019)]. CCHFV does not readily cause disease in immunologically intact adult rodents, so development of small animal models of CCHF has relied on mice that are permanently (e.g. STAT1-/-, IFNAR-/-, IFNAGR-/- knockouts) or transiently (Garrison et al 2017) immunosuppressed. Through disruption of elements of the interferon (IFN) receptor signalling pathways (type 1 IFN, type 2 IFN or both) these models display lethal or severe CCHF disease (Garrison et al 2019) but the permanently immunosuppressed models are not ideal for CCHF vaccine studies. More recently, an immunocompetent murine model has been developed that uses a mouse-adapted CCHFV variant to cause severe, but rarely fatal, inflammatory disease in adult mice (Hawman et al 2021). Mice develop high viral loads in multiple tissues, severe liver pathology, and an immune response consistent with several aspects of CCHF patient responses. The first immunocompetent NHP models used cynomolgus macaques which were reported to recapitulate several aspects of human severe sometimes fatal CCHF (high viral loads, coagulation disorders, elevated inflammatory cytokines and liver pathology) (Haddock et al 2018). In subsequent studies, disease severity and outcome has been variable using the same CCHFV strain or another human clinical isolate (Hawman et al 2024, Smith et al 2019). The cynomolgus macaque model is now regarded to be mild-to-moderate and rarely lethal. An alternative NHP model has recently been reported that uses the rhesus macaque and a CCHFV strain serially passaged in cynomolgus macaques; it exhibits mostly mild but occasionally moderate disease (Hawman et al 2024).

Key Needs

- Funding sources for product R&D and public health-driven incentives that encourage innovation and secure commitments to develop and manufacture CCHF MCMs at a price that is (and remains) affordable and prioritises equitable access for endemic and affected countries.

- Non-traditional regulatory mechanisms that enable large, adaptative phase 3 platform trials of investigational drugs and candidate vaccines for humans in high-risk populations across multiple sites and countries, based on efficacy in pre-clinical animal models and early human (phase 1 and 2) immunogenicity data, to provide robust results on their safety and efficacy as rapidly as possible.

- Integrated One Health surveillance systems covering CCHF case incidence, CCHFV prevalence and genomic sequencing in vector, animal and human populations and CCHF seroprevalence in animals and humans, to determine geographical risk, the burden of disease, detect circulating, re-emerging and new CCHFV variants, identify high incidence sites for MCM trials, and to assess the impact of vector control measures (see 'vaccines for animal use') and MCMs over time in order to refine implementation strategies.

- Agreed standardised CCHF case definitions for epidemiological and clinical use and harmonised CCHF clinical management guidelines, including stratification of disease severity, for routine clinical use and for use by sites taking part in randomised controlled trials (RCTs) of new CCHF therapeutics or vaccines.

- Well-characterised assays of CCHFV-specific cellular and humoral immunity especially those suitable for use outside high containment, supported by standard reagents and common operating procedures, to allow evidence-based comparisons of clinical studies in different countries.

- Immune correlates of protection against CCHF that are relevant to human disease and can be used as measures of protective efficacy in animal vaccination studies and human clinical trials.

- A detailed understanding of the pathogenesis induced by different CCHFV genotypes in humans and different pre-clinical animal models. CCHF vaccines and therapeutics will need to be effective against all genotypes and the most severe CCHF disease presentations, while identification of less pathogenic CCHFV variants may theoretically allow their use at lower containment.

- Continued development of improved and reproducible pre-clinical models of CCHF disease, focusing on immunocompetent small animals, coupled with application of correlates or surrogates of protective immunity in both large and small animals.

Strategic Goals and Aligned Milestones

Strategic Goal 1: By Q4 2024, leverage funding opportunities for CCHF product R&D and evaluation and by Q4 2025 develop a financial investment model (value proposition) for sustainable and equitable access to MCMs for CCHF-affected countries.

Milestone 1.1: By Q4 2024, work with existing private, public and non-profit research funders to leverage funding for development and evaluation of CCHF MCMs.

Milestone 1.2: By Q1 2025, commission an analysis of the health, economic and societal burden of CCHF and the business case and options for investment to deliver sustainable and equitable access to MCMs in CCHF-affected countries.

Strategic Goal 2: By Q4 2026, implement integrated, multisectoral One Health action in a minimum of two CCHF affected countries with different circulating CCHFV genotypes, encompassing comprehensive surveillance (including genomic sequencing) of CCHFV in humans, animals (wildlife and livestock) and vectors.

Milestone 2.1: By Q4 2024, agree and implement standardised CCHF case definitions for epidemiological use, and by Q1 2026, adopt these into routine practice in a minimum of four high-incidence countries.

Milestone 2.2: By Q4 2024, identify CCHF-affected countries with the infrastructure for genomic sequencing and assess the training and resource requirements to implement routine genomic surveillance of CCHFV (and broader orthonairovirus species e.g. AIGV) in ticks, wildlife, livestock and humans.

Milestone 2.3: By Q4 2025, in at least two CCHF affected countries, establish a national plan for integrated multisectoral CCHF surveillance, championed by human health, veterinary health and wildlife agencies.

Milestone 2.4: By Q4 2026, have an integrated One Health surveillance system in operation in at least two countries for CCHFV detection and genomic surveillance in humans, animals and ticks, with regular reporting.

Strategic Goal 3: Through coordinated international studies, by Q4 2026, characterise the pathogenesis and mechanisms of immune protection of CCHF and support the development of better pre-clinical animal models and improved diagnostics, therapeutics and vaccines.

Milestone 3.1: By Q4 2024, agree and implement standardised CCHF case definitions for clinical use, and harmonised CCHF clinical management guidelines, including stratification of disease severity, for routine clinical use and for use by clinical trial sites.

Milestone 3.2: By Q4 2024, create an inventory of CCHFV isolates and challenge viruses, identifying any gaps in genotype coverage, and by Q4 2025 establish a process for equitable access to isolates for evaluation as pre-clinical challenge strains, including benefit sharing agreements with endemic countries and associated processes for international transfer of materials.

Milestone 3.3: Enhance the in-country capability to characterise the protective immune response to human CCHF through introduction of harmonised immunological assays, standardised protocols and international collaboration, with suitable assays operating in at least one potential clinical trial site in a CCHF-affected country by Q2 2025.

Milestone 3.4: By Q2 2025, agree which CCHFV genotypes are needed to evaluate MCMs (therapeutics & vaccines) to demonstrate broad protection against the most severe CCHF disease presentations.

Milestone 3.5: By Q4 2025, identify and characterise relevant animal models of CCHF disease or CCHFV infection that are acceptable to regulatory authorities for use in the pre-clinical evaluation and regulatory approval pathway of novel CCHF vaccines and therapeutics.

Additional Research Priorities

Research

Characterise and catalogue existing archived CCHFV isolates, including their suitability for use as challenge strains for pre-clinical evaluation of CCHF MCMs.

Identify the adaptive immune response and mechanisms of protection against CCHF disease in humans, natural animal amplification hosts and relevant small animal and NHP models and identify the correlates of protection for use in

vaccine studies and for vaccine licensure.

Develop and validate assays that quantify CCHFV viral load when used with a standard calibrant for monitoring disease and antiviral drug/vaccine efficacy studies.

Develop, standardise and validate assays to assess the CCHFV immune response. Specifically, IgM and IgG ELISAs, functional antibody assays and assays of cell mediated immunity (e.g. flow cytometry, ELISPOTS etc.) that can be deployed to selected study sites in affected countries, subject to biocontainment capabilities. **Develop** selected assays to the regulatory standards required for MCM market authorisation e.g. ISO15189, ISO17025.

Continue to develop non-infectious CCHFV pseudoviruses and related molecular tools suitable for use at lower containment (e.g. BSL-2) for evaluating CCHFV molecular diagnostic tests and for use in measuring neutralising antibody potency. **Develop** selected assays to the regulatory standards required for MCM market authorisation e.g. ISO15189, ISO17025.

Identify the pathogenic processes and mechanisms of immune protection in animal models and amplification hosts of CCHFV and **develop and characterise** more relevant pre-clinical models of CCHF disease, including, challenge with CCHFV strains and clinical isolates representing different genotypes and harmonisation of CCHFV challenge protocols.

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 national biobanks of well characterised clinical samples. A greater understanding of pathogenesis and immune response may identify potential therapeutic targets at different stages of disease.

Design therapeutic trials so that in parallel they help **increase understanding** of the basic immunology and pathophysiology of human CCHF.

Through collaboration between affected countries and international centres of expertise, **sequence** complete CCHFV genomes circulating in humans, animals and ticks (including non-coding sequences) and **enhance capacity** for sharing sequence and metadata. This will determine the geographic variability and distribution of CCHFV and may identify genomic configurations that may lead to less or more virulent CCHFV strains.

Continue to review the utility of next generation sequencing, especially portable solutions for epidemiological use in the field (e.g. contact tracing, source of infection) as well as metagenomics in the field for One Health broad *Nairoviridae* surveillance.

Product Development

Ensure MCMs under development cover a range of CCHFV antigenic targets to enable thier use in the assessment of live attenuated vaccines and/or as confirmatory diagnostic

tests.

Key Capacities

Develop SOPs and training for roll-out of IgM and IgG serology assays (with international reference standards for calibration and harmonisation) and virus neutralisation assays using non-infectious CCHFV based reporter pseudoviruses to clinical trial sites, subject to local biocontainment conditions.

Develop SOPs and training for roll-out of One Health field genomic NGS assays and bioinformatic solutions (with international reference standards for calibration), subject to local data sharing regulations, to be performed in endemic and affected countries.

Deliver 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.

Agree and **adopt** standardised animal model or surrogate system(s) for the assessment of CCHFV virulence, needed for assessment of cross-protective efficacy of new CCHF MCMs.

Policy and Commercialisation

Through WHO Target Product Profile (TPP) process, **ensure** manufacturers can provide affordable and sustainable supplies of MCMs for routine and outbreak use.

Working with key decision makers in CCHF-affected countries, **develop and agree** WHO recommended standardised case definition(s) for CCHF, needed for case ascertainment, characterising clinical samples in repositories and multi-country clinical trials of CCHF MCMs.

Building on current national best practice, **develop, agree and publish** WHO guidelines for the clinical management of CCHF patients to improve CCHF case management and for adoption by sites participating in multi-centre clinical trials.

Periodically **review** and **update** WHO guidelines for clinical management of CCHF using evidence gathered from clinical trials and analysed according to GRADE methodology.

Agree on terms for equitable access to CCHF clinical samples, tick and clinical virus isolates held in national repositories in CCHF-affected countries for use in experimental animal challenge models, ensuring retention of sovereignty and benefits sharing in accordance with the Nagoya protocol where applicable.

For products intended for human use or animal use, **ensure** early engagement with relevant national authorities and regulators in affected countries to facilitate product evaluation and licensure and agree measures for manufacture, distribution and access provisions.

Share experiences between affected and un-affected countries to increase preparedness in countries at risk from CCHF.

Photo: melissamn

2. Diagnostics

Challenges and Critical Gaps

- Prompt laboratory confirmation of CCHFV infection in acutely ill patients is required for adequate and timely treatment, infection control and outbreak detection. In most affected countries, CCHF is diagnosed by referring samples to centralised reference laboratories for testing (Mazzola & Kelly-Cirino 2019). Testing is rarely available in peripheral healthcare settings where the cases typically occur, leading to delays in diagnosis and appropriate management.

- Molecular diagnostic tests [e.g. reverse-transcription polymerase chain reaction (RT-PCR)] provide the highest detection sensitivity and specificity and are the methods of choice for early diagnosis of active CCHFV infection (Mazzola & Kelly-Cirino 2019). Real time RT-PCR tests have superior performance and shorter turnaround time for results, with the added benefit that the cycle threshold (Ct) value can be used as a proxy for viral load. However, although, some commercial RT-PCR tests are available, their performance across all circulating CCHFV genotypes is not known (Vanhomwegen et al 2012) and they may fail to detect a newly emerged genomic variant.

- Serological detection of CCHFV-specific IgM and/or IgG antibodies is less affected by viral genetic variation and can be used in later phases of illness. Serological detection may be unreliable early in infection (< 3 days after disease onset) and in cases of severe disease, where the antibody response is typically weak or absent (Saksida et al 2010). Where molecular tests are negative, it is good practice to carry out secondary IgM testing (Bartolini et al 2019).

- In-house and commercial serological and molecular tests exist for detection and diagnosis of CCHF [reviewed in (Bartolini et al 2019, Mazzola & Kelly-Cirino 2019)]. The cost and supply chain make some commercial

tests less accessible to low-income countries, highlighting the need for more accessible and cost-effective diagnostics (Papa 2019) . Some assays in widespread use for animal serosurveillance (Sas et al 2018) do not have regulatory approval as *in vitro* diagnostic devices for human use.

- Current diagnostic options for CCHF require a well-developed laboratory infrastructure and highly trained staff (Mazzola & Kelly-Cirino 2019). There is an urgent need to devolve testing out to more peripheral settings through development of affordable near-patient molecular tests based, for example, on isothermal amplification [e.g. RT-LAMP (Febrer-Sendra et al 2023) or RPA (Bonney et al 2017)] and point-of-care (POC) rapid antigen detection tests (e.g. lateral flow tests) with operational characteristics suited to use in low-resource and/or low-capacity settings. Preliminary TPPs for CCHF diagnostics suited to these use cases have been developed (WHO 2019b).

- Blood (plasma or serum) is the main specimen type used for CCHFV molecular diagnostics. More information is needed on the utility of alternative sample types (dried blood spots, urine, oral fluid, semen etc.) for the diagnosis and monitoring of CCHF. This will support development of minimally invasive diagnostics more suited for use in low-income countries with inadequate laboratory infrastructure and logistical or societal barriers to sample collection.

Key Needs

- Sustainable access to commercial nucleic acid and serology tests for CCHFV at an affordable price for use in diagnostic and reference laboratories in affected countries.

- Sustainable access to commercial near-patient molecular tests and/or POC tests for CCHFV antigen detection at an affordable price for use in affected countries.

- A network of distributed repositories of well-characterised clinical samples from CCHF patients and accompanying metadata, held and maintained in their countries of origin, to be used to assess and validate diagnostic test performance (including sensitivity, specificity and limit of detection) across different CCHFV genotypes. Visibility of samples available across the network of participating sites will be via a centralised sample inventory management system, and the repository will include harmonised arrangements for patient consent and confidentiality, anonymous sample collection, access, governance and benefit-sharing. Wherever possible, samples would be used in the originating nation following pre-agreed protocols.

- A finalised TPP for CCHF diagnostics that gives use scenarios and specifies desired characteristics, features and performance criteria for CCHF diagnostics in particular settings.

- Published data on the performance of existing and developmental commercial CCHFV molecular or antigen detection assays against all circulating CCHFV genotypes, including limits of detection and assay dynamic range, ideally reporting on evaluations carried out by CCHF-affected countries.
- Quality assurance of diagnostic testing within and between CCHF-affected countries through distribution of national proficiency panels and regular regional external quality assurance (EQA) schemes spanning the most prevalent circulating CCHFV genotypes.

Strategic Goals and Aligned Milestones

Strategic Goal 4: Affordable and sustainable nucleic acid and serology tests that conform to published Target Product Profiles (TPPs) accessible for use in CCHF-affected countries by Q4 2024, followed by the development, evaluation and introduction of near-patient molecular and/or point-of-care antigen detection tests by Q4 2026.

Milestone 4.1: By Q3 2024, publish TPPs for molecular and serological CCHF diagnostic tests suitable for use (i) in reference laboratories, (ii) for decentralised near-patient testing and (iii) POC rapid antigen detection tests (with minimal requirements for biosafety precautions and staff training).

Milestone 4.2: Develop the ethical, biosafety, governance, legal and funding infrastructure for a network of distributed sample repositories in CCHF-affected countries, holding well-characterised CCHF clinical samples and metadata, with at least one national repository to be operational in a CCHF-affected country by Q4 2024, with sample access protocols and prospective sample collection in place.

Milestone 4.3: By Q4 2025, in collaboration with national laboratories in countries with relevant sample repositories, use well-characterised clinical samples covering all circulating CCHFV genotypes, to evaluate analytical and clinical performance of commercial real-time RT-PCR tests (qualitative and quantitative) and IgM and IgG serological tests, supplemented by national and regional EQA schemes, applying sample access and benefit sharing procedures as agreed.

Milestone 4.4: By Q4 2024, develop one or more commercial molecular tests suitable for near-patient diagnosis of CCHF, with clinical evaluation by Q4 2025 in relevant healthcare settings in more than one CCHF-affected country following a standardised protocol.

Milestone 4.5: By Q2 2025, develop one or more commercial antigen detection tests suitable for POC use, with clinical evaluation by Q4 2026 in relevant healthcare settings in more than one CCHF-affected country following a standardised protocol.

Additional Research Priorities

Research

Investigate the utility of alternative sample types (dried blood spots, urine, oral fluid, semen etc.) for the diagnosis and monitoring of CCHF particularly in low-income countries with inadequate laboratory infrastructure and logistical or societal barriers to sample collection; this will support development of minimally invasive diagnostics.

Develop and characterise anti-CCHFV antibodies that target conserved epitopes with broad specificity across CCHFV genotypes for use in antigen detection tests; this could include mAbs developed for therapeutic purposes.

Develop safer sample collection / inactivation systems for use with future near patient and POC tests, including tests for animal use in high-risk settings e.g. abattoirs.

Product Development

Finalise and publish TPPs for CCHF diagnostic tests covering different use scenarios.

Ensure molecular diagnostic MCMs under development cover all circulating CCHFV genotypes to enable their use in the assessment of live attenuated vaccines and/or as confirmatory diagnostic tests.

Develop international antigen, antibody and nucleic acid reference standards for CCHFV to allow comparison between different tests and different clinical trials of vaccine or therapeutic efficacy.

Develop and determine the analytical characteristics (sensitivity, specificity, limits of detection, dynamic range) of new near-patient and POC diagnostic tests (nucleic acid or antigen detection).

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.

Adapt near patient and POC antigen detection tests with operational characteristics suited to use in low-resource and/or low-capacity settings for testing livestock prior to slaughtering as a control measure to reduce the risk of human infection through handling highly viraemic,

infectious animals/animal products.

Develop one or more commercial multi-species ELISA kits to detect anti-CCHFV antibodies for serosurveillance in animals and capable of differentiating naturally infected from vaccinated animals (DIVA) to monitor the effectiveness of experimental animal vaccines targeting CCHFV.

Develop 'fever panels' – diagnostic tests that ideally use a common platform to distinguish CCHF from related illnesses with similar presentation (e.g. Ebola virus disease or Lassa fever in West Africa) or more common diseases (e.g. leptospirosis, rickettsioses, hantaviral infections).

Key Capacities

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

In CCHF-affected countries, **establish and maintain** archives of well-characterised CCHF clinical samples (and virus isolates), including convalescent patient samples and samples from seropositive animals, covering all CCHFV genotypes to evaluate diagnostic tests.

Share best-practice and **expand** existing in-country proficiency testing schemes to other affected countries and **develop** regular EQA schemes between CCHF-affected countries that take advantage of virtual sample repositories to maximise coverage of circulating genotypes.

Policy and Commercialisation

Quantify the demand for CCHF diagnostics in routine use (in endemic countries, the military, international labs diagnosing imported infections) and in emergencies and **define** the value proposition for prospective diagnostic product developers.

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.

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 CCHFV 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 framework or initiative, where necessary, that offers economic incentive to diagnostic test developers to minimise the cost

-per-test so assays are affordable in resource limited settings. One option that can be considered to reduce cost to target countries is local manufacture that ensures validated manufacture and performance assurance.

Develop a concept of use for POC RDTs in endemic and outbreak scenarios, including an assessment of the training and biosafety needs and the risk of nosocomial transmission.

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 commerical diagnostic tests in their country.

Ensure adequate preparation for field testing diagnostics in affected countries, including ethical approval and infrastructure requirements.

Photo: AlexRaths

3. Therapeutics

Challenges and Critical Gaps

- No licensed drugs are specifically indicated for the treatment of CCHF and therapeutic options are limited (Spengler & Bente 2015). The broad spectrum antiviral ribavirin, a synthetic nucleoside analogue, is used in some affected countries for treatment of CCHF patients although its efficacy has been questioned (Johnson et al 2018, Soares-Weiser et al 2010) and large RCTs have been called for. There is potential benefit from using ribavirin for post-exposure prophylaxis (PEP) of CCHF, particularly if administered early (up to 48 hrs) after exposure, when it can reduce both the chance of infection and fatal outcome (Ergönül et al 2018, Leblebicioglu et al 2016).

- In the absence of a specific therapy, general supportive care remains the main approach to managing CCHF (Leblebicioglu et al 2012, Spengler & Bente 2015). This includes measures to replace fluid loss and correct electrolyte imbalance, and use of blood products including platelet suspensions, packed red cells and fresh frozen plasma when needed. For severe cases, management in ICUs where respiratory support and other supportive care can be given and if necessary, haemodialysis, can save lives.

- Some existing licensed antivirals, notably the nucleoside analogue favipiravir (T-705 ; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) approved for human use to treat influenza and COVID-19, have shown efficacy for control of CCHFV infection in animal models of CCHF disease (Hawman et al 2020, Hawman et al 2018, Tipih et al 2023). Phase 2 and 3 clinical trials are needed to determine the effectiveness of favipiravir and other repurposed and novel nucleoside analogues for management of CCHF.

- Some clinical benefit has been reported for conventional immunotherapeutic strategies, including intravenous administration of

convalescent plasma (Suleiman et al 1980, van Eeden et al 1985) or purified CCHFV hyperimmunoglobulin (Keshtkar-Jahromi et al 2011, Kubar et al 2011, Vassilenko et al 1990). Again, there are no published clinical trials of the clinical efficacy of these approaches.

- The precise role of antibodies against different CCHFV antigens in virus clearance or protection against infection is poorly understood. Nonetheless, candidate antibody-based therapeutics with protective activity in pre-clinical models are emerging. An engineered bispecific antibody [DVD-121-801, derived from non-competing Gc-specific nAbs from human CCHF survivors Fels et al 2021)], non-neutralising mAbs targeting GP38, particularly c13G8 (Durie et al 2022) [a human chimeric version of the murine mAb 13G8 (Golden et al 2019)], two human non-neutralising GP38-specific antibodies ADI-46138 and ADI-58048 (Shin et al 2024), and NP-specific mAbs [e.g. mAb-9D5, (Garrison et al 2024)], all show promise for CCHF treatment or post-exposure prophylaxis, administered alone or as antibody cocktails.

- In murine models, non-neutralising GP38-specific antibodies are thought to act by inhibiting vascular leak (Pahmeier et al 2024). This points to a role for GP38 as a viral toxin that causes endothelial hyperpermeability and a possible target for future anti-CCHF therapeutics to reduce disease severity.

- Recent identification of LDLR as a widely expressed entry receptor for CCHFV (Monteil et al 2024, Xu et al 2024) that interacts with CCHFV Gc-Gn could lead to the development and evaluation of novel targeted antivirals, for example soluble LDLR decoys, to reduce CCHFV infections (Monteil et al 2024).

Key Needs

- Effective treatments (repurposed or novel) for CCHF, validated by pre-clinical studies and well-designed multi-centre clinical trials and available to affected countries at an affordable price.

- Study sites in CCHF-affected countries with the capability to conduct RCTs of candidate CCHF therapeutics. This includes clinical, laboratory and data management infrastructure, trained personnel, the ability to stratify cases according to disease stage, severity and viral load, and robust local R&D governance procedures.

- Operational and governance protocols produced in consultation with national regulatory authorities for adaptative platform trials, that give the flexibility to alter the therapies (existing, repurposed and novel) under investigation as promising candidates emerge from pre-clinical and phase 1 testing.

- Continuing basic research to develop a pipeline of small molecule inhibitors specifically targeting CCHFV, its secreted glycoproteins or cellular receptor(s), with

evaluation in pre-clinical studies.

- An improved understanding of the protective immune response in CCHF and continuing R&D to evaluate monoclonal antibodies that give heterologous protection (e.g. non-neutralising antibodies targeting GP38 or anti-nucleoprotein mAbs) and assess their efficacy as immunotherapeutics in NHP models and in humans.

- Equitable access protocols guaranteeing sustainable and affordable supply as a condition of new CCHF therapies being put forward into clinical trial in endemic countries.

Strategic Goals and Aligned Milestones

Strategic Goal 5: Address the immediate need for effective treatments for CCHF by evaluating existing antivirals with potential activity against CCHFV, commencing Phase 2 RCTs by Q4 2024.

Milestone 5.1: By Q3 2024, agree the framework for selecting suitable existing antivirals and finalise protocols for platform trials (phase 2 and 3 dose regimen and RCTs), consulting with relevant national regulatory authorities and in-country clinical leads.

Milestone 5.2: By end Q4 2024, start patient enrolment to phase 2 trials of an existing therapeutic to evaluate efficacy against CCHF disease and establish pharmacokinetic data and optimum dosing.

Strategic Goal 6: 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 in CCHF patients by Q4 2026.

Milestone 6.1: Progress promising therapeutic monoclonal antibodies through relevant pre-clinical models of CCHFV infection and into first in-human studies by Q3 2025.

Milestone 6.2: By Q4 2026, start patient enrolment to a phase 2 trial in at least one CCHF-affected country to evaluate the efficacy of new drugs or biologicals (e.g. antibody therapy) in CCHF patients.

Strategic Goal 7: By Q4 2028, take one or more successful therapeutics (existing, repurposed or novel) forward to phase 3 RCTs in more than one affected country to establish full efficacy against the spectrum of CCHF disease and the most pathogenic CCHFV genotypes.

Milestone 7.1: By Q4 2027, agree the framework for selection of lead candidates (existing, repurposed or novel) and finalise protocols for adaptive platform trials (phase 3 RCTs) in multiple CCHF-affected countries, consulting with relevant national regulatory authorities and in-country clinical leads.

Milestone 7.2: By Q4 2028, for selected lead candidates, start patient enrolment to phase 3 trials in at least two CCHF-affected countries with different circulating CCHFV genotypes.

Additional Research Priorities

Research

Collect available data about licensed antivirals with broad antiviral activity that might be suitable for the treatment of CCHF and use to prioritise candidates for further clinical evaluation.

Conduct clinical studies in multiple sites spanning more than one affected country and ethnic background to determine the therapeutic efficacy of repurposed antivirals e.g. favipiravir.

Determine the efficacy of oral and/or intravenous ribavirin and the optimum dosing regimen through RCTs on well-characterised CCHF cases stratified according to disease stage and severity.

Revisit *in vitro* and *in vivo* studies into the efficacy of arbidol (an anti-influenza drug targeting the viral haemagglutinin) against CCHFV, using biologically-relevant dosing schedules.

Apply high-throughput screening assays (e.g. Welch et al 2017) to **identify and screen** *in vitro* existing antiviral drugs and discover new small molecule inhibitors of CCHFV that can be progressed to pre-clinical evaluation.

Develop a high-throughput pipeline for evaluation of novel inhibitors using (i) surrogate viruses at low containment (e.g. Hazara virus, HAZV), (ii) further evaluation in small animal models with HAZV (at low containment), and (iii) evaluation with CCHFV at high containment.

Develop and conduct studies of therapeutic efficacy and safety of CCHFV antibody therapy in pre-clinical models of CCHF and in humans.

Determine the optimum package of supportive care for the management of CCHF patients alone and in combination with antivirals and other therapeutic measures.

Investigate potential for post-exposure prophylaxis (PEP) with any effective therapeutics e.g. antivirals or therapeutic antibodies, including application of compassionate-use pathways since clinical trials of PEP are not feasible.

Review the literature on the efficacy of therapeutics that improve the patients' immune response (e.g. cytokines/cytokine receptor inhibitors to reduce inflammation or improved endothelial stabilisation) in management of other VHFs and COVID-19 and **evaluate** efficacy of candidate immunomodulators for management of CCHF.

Product Development

Continue to develop and characterise monoclonal and polyclonal (e.g. ovine or fully-human polyclonal) antibodies and test their therapeutic efficacy across all CCHFV genotypes (and genotypes I, II, III and IV in particular) in relevant pre-clinical CCHF animal models and in humans.

Key Capacities

Strengthen laboratory capabilities (including haematology and biochemistry) in healthcare institutions in affected countries which are routinely managing CCHF cases.

Establish ability for early CCHF diagnosis at prospective clinical study sites e.g. using clinical diagnosis according to agreed case definition (see Milestone 3.1) and reference real-time RT-PCR for confirmation; also ability 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.

Policy and Commercialisation

Develop and publish WHO TPPs for CCHF therapeutics, both classical small-molecule drugs and/or biologicals.

Develop criteria for product testing and prioritisation using the TPPs.

Using the TPP process, **engage** with manufacturers of marketed antivirals that may have activity against CCHFV to facilitate screening and preclinical testing.

Constitute an expert working group 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.

Develop and agree on protocol(s) for clinical trials (e.g. multi-centre platform RCTs) of existing antivirals (e.g. favipiravir) or new candidates and agree surrogate markers/biomarkers for disease stratification and as study end points.

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.

Photo: wacomka

4. Vaccines for Human Use

Challenges and Critical Gaps

- There is currently no safe or effective vaccine widely available for human use, although a vaccine has been licensed for human use in Bulgaria. This was developed in Russia in the 1970s and uses an inactivated crude preparation of CCHFV amplified in the brains of suckling mice which does not conform to modern regulatory standards and cannot be produced at scale (Ahata & Akçapınar 2023, Mousavi-Jazi et al 2012, Papa et al 2011).

- A cell-culture derived formalin-inactivated vaccine (CKKA or KIRIM-KONGO-VAX) that is immunogenic and protective in murine models (Canakoglu et al 2015, Pavel et al 2020), has completed phase 1 safety and immunogenicity trials in Türkiye [NCT03020771 The Scientific and Technological Research Council of Turkey (2017)]. However, the manufacturing process for this vaccine requires high containment facilities and is not easily scalable.

- A number of candidate CCHF vaccines have been developed that use a wide variety of platform technologies and CCHFV antigens [reviewed in (Ahata & Akçapınar 2023, Dowall et al 2017, Tipih & Burt 2020)], but they have shown variable protective efficacy in available animal CCHF challenge models. Three are progressing through phase 1 human studies: a modified vaccinia virus Ankara (MVA)-vectored vaccine which encodes CCHFV GPC [MVA-CCHF; Dowall et al 2016; ISTCTN14935155; University Hospital Southampton NHS Foundation Trust (2021)]; a chimpanzee adenovirus (ChAdV)-vectored vaccine which encodes CCHFV GPC [ChAdOx2 CCHF; Saunders et al 2023; ISRCTN12351734; Oxford Vaccine Group (2023)] and a DNA vaccine encoding NP [N-pVAX; Hawman et al 2023; EUCT2023-508556-18-00; Karolinska Institute (2024)]. mRNA vaccines are in pre-clinical development (Appelberg et al 2022).

- The relative importance of CCHFV-specific antibodies (both neutralising and non-neutralising) and cell-mediated immunity in disease resolution and in vaccine-induced protection remains to be determined. This knowledge gap has hampered the rational design of candidate CCHF vaccines and correlates of protection for CCHF vaccine studies remain to be determined (see 'cross-cutting issues and enabling activities; Strategic Goal 3).

- The failure to advance most CCHF vaccine candidates beyond pre-clinical testing in part reflects the expense of conducting human studies and obtaining product licensure. CCHF vaccine development has yet to be prioritised by funding partnerships such as CEPI and has also been neglected by private-sector product developers (see 'cross-cutting issues and enabling activities').

- Commercial vaccine manufacturers are likely deterred from investing in developing, evaluating and licensing CCHF vaccines due to the limited size and value of the final market, particularly if the use scenario for CCHF vaccines is to target at-risk occupations and communities rather than national populations.

Key Needs

- Effective CCHF vaccines for human use that 1) are safe and scalable to manufacture 2) are readily accessible with adequate supply chains and 3) can protect against an appropriate range of geographically circulating CCHFV genotypes.

- Prioritisation of CCHF vaccine candidates that meet published TPPs based on efficacy in pre-clinical testing and the use of vaccine platforms suited to rapid adaptation.

- Immunocompetent small animal models and relevant and measurable correlates or surrogates of protection that are acceptable to national regulators, to accelerate the progress of CCHF vaccine candidates through pre-clinical testing and into human trials (see 'cross-cutting issues and enabling activities' and Strategic Goal 3).

- Quantification of the global market value and public health need for CCHF vaccines, including vaccination strategies for different at-risk populations and epidemiological scenarios and the utility of regional vaccine stockpiles for timely response to outbreaks.

- A novel and agile regulatory pathway to licensure for limited market value vaccines such as those needed to prevent and respond to the ever-present threat of CCHF.

- Accessible and sustainable supplies of CCHF vaccines in affected countries, with options for technology transfer, in-country manufacture and preferential rates for those affected countries that contribute to vaccine R&D through provision of isolates, hosting clinical trials etc.

Strategic Goals and Aligned Milestones

Strategic Goal 8: Prioritise and progress the best human CCHF vaccine candidates from development to licensure, leveraging novel funding and regulatory mechanisms when necessary, with effective, affordable prophylactic CCHF vaccines for human use deployed in at least two CCHF-affected countries with different circulating CCHFV genotypes by Q4 2030.

Milestone 8.1: Work with high-risk communities to establish acceptable characteristics for human CCHF vaccines, with use-case scenarios and TPPs defined and published by Q2 2025.

Milestone 8.2: Working with the appropriate national regulators, take at least one CCHF vaccine candidate that meets the TPP for CCHF vaccines and with proven efficacy against prevalent CCHFV genotypes (and notably genotypes I to IV) in relevant animal models, into human phase 1 safety and early immunogenicity trials by Q4 2025 followed by phase 2 trials in endemic settings by Q4 2026.

Milestone 8.3: Prioritise and progress promising early-stage developmental human CCHF vaccines that meet the TPP through relevant animal models by Q4 2026.

Milestone 8.4: Take the lead vaccine candidates into phase 3 trials in high-incidence regions in more than one CCHF-affected country by Q1 2028, using harmonised case descriptions, case stratification and shared laboratory protocols.

Additional Research Priorities

Research

Identify the adaptive immune response and mechanisms of protection against CCHF disease in humans, natural animal amplification hosts, relevant small animal models and NHPs and identify the correlates of protection for use in vaccine studies and for vaccine licensure (see ‘cross cutting issues & enabling activities’)

Assess efficacy of existing CCHF vaccine candidates against all CCHFV genotypes (and notably genotypes I to IV) using pre-clinical challenge models.

Develop prototype vaccines for CCHF exploiting genetically modified orthonairoviruses (e.g. HAZV expressing CCHFV glycoproteins) with lower pathogenicity for which pre-clinical models can be operated at lower biological containment.

Develop, standardise and validate virus neutralisation assays e.g. PRNTs for all circulating CCHFV genotypes, preferably using non-infectious CCHFV-based reporter pseudoviruses and vector systems with efficient glycoprotein processing, pseudovirus assembly and surface expression. **Calibrate** assays against the international CCHFV immunoglobulin standard, if available.

Product Development

Collect available data about candidate CCHF vaccines and **prioritise** candidates for further clinical evaluation based on TPPs, efficacy in pre-clinical models, cross-genotype protection and adaptability of the platform technology.

Continue to develop new candidate human CCHF vaccines against multiple CCHFV antigens and test them in pre-clinical animal models.

Synthesise and evaluate using *in vitro* and *in vivo* models, existing vaccine candidates that have so far only been designed *in silico* (e.g. Mears et al 2022, Sana et al 2022).

Key Capacities

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 (see 'cross-cutting issues and enabling activities').

With national authorities, **identify** study locations and populations in CCHF-affected countries with high incidence of human CCHF disease with a view to phase 2 and 3 clinical vaccine trials.

Policy and Commercialisation

Engage with funding agencies and private or philanthropic organisations to leverage funding for CCHF vaccine studies (see 'cross-cutting issues and enabling activities').

Develop and publish TPPs for CCHF vaccines for human use, covering vaccines for preventive and reactive use. Consider combination/multivalent vaccines and clauses for accessibility of final product e.g. at cost access for CCHF-affected countries that host clinical trials.

Build the strategic case in public health and economic terms for human CCHF vaccines, taking into account different use cases (at-risk groups in endemic foci/epidemic use/travel/military) and considering the need for maintaining national or regional stockpiles for rapid mobilisation in the event of a major outbreak.

Develop and agree on protocol(s) for clinical trials of promising candidate CCHF vaccines in endemic 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 regulatory agencies to discuss the most appropriate pathways to licensure for CCHF vaccines. To future-proof vaccines against the emergence of new CCHFV variants, this might include allowances for making subtle modifications to a licensed vaccine based on immuno-bridging data rather than requiring a full licensure dossier.

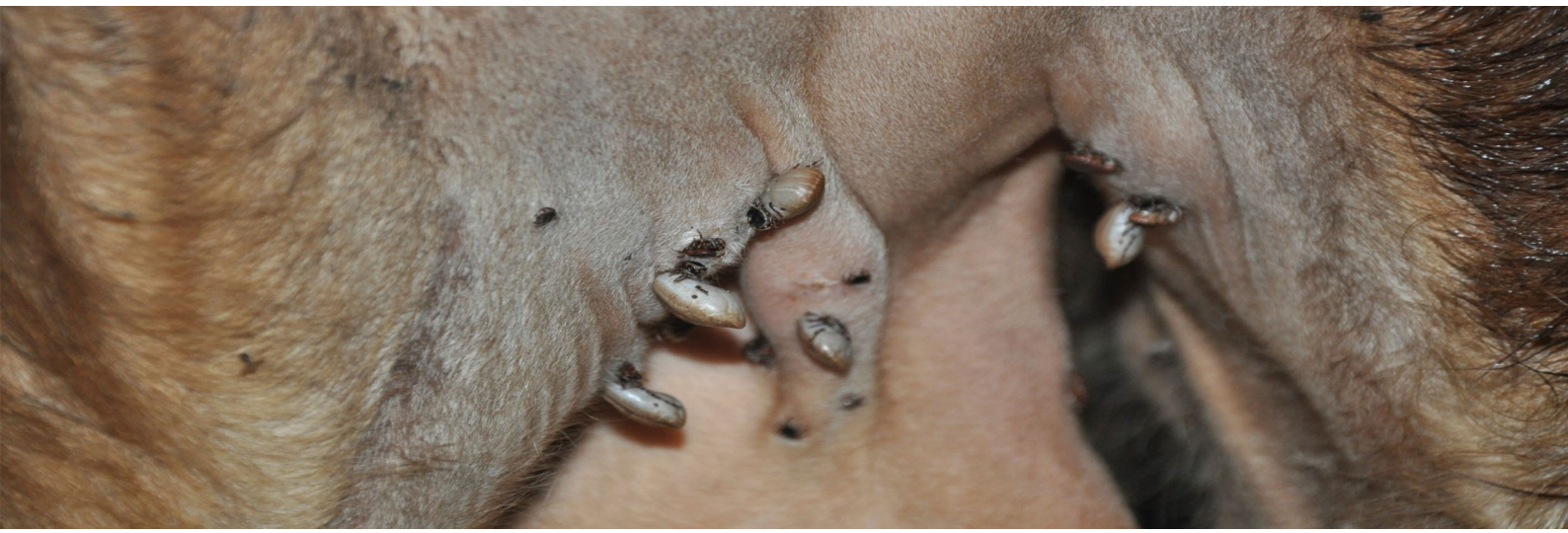

Photo: Dr Zati Vatansever

5. Vaccines for Animal Use

Challenges and Critical Gaps

- Transmission of CCHFV to humans typically occurs at the human-animal interface, through bites from infected ticks or exposure to viraemic livestock during slaughter or husbandry (Hawman & Feldmann 2023). As yet, targeting this interface has not been exploited as a strategy to reduce the incidence of CCHF in endemic settings.

- Ticks and tick-borne diseases reduce the fitness of livestock causing substantial economic loss (Estrada-Peña & Salman 2013, Hurtado & Giraldo-Ríos 2018). To control tick populations feeding on livestock, chemical acaricides are in widespread use worldwide but are harmful to the environment and food supply (de la Fuente 2018, Pathak et al 2022) and acaricide overuse and misuse has led to resistance in some tick species, including *Hyalomma* ticks (Abbas et al 2014, Kamran et al 2021). Acaricide use is therefore not an environmentally sustainable option for reducing CCHFV transmission from livestock to humans.

- To reduce acaricide use, alternative sustainable tick control solutions are needed that can be used as components in integrated tick management strategies. One such approach is to vaccinate livestock with anti-tick vaccines (de la Fuente et al 2016, Rodríguez-Mallon 2023). These vaccines induce antibodies in the vertebrate host against tick antigens. When the antibodies enter the feeding tick they interfere with its attachment, feeding, metabolism and/or reproductive fitness (Kasaija et al 2023). Ticks may detach prematurely or suffer a decline in fitness leading to reduced numbers in subsequent generations. Indirectly, these vaccines can also reduce the prevalence of some tick-borne pathogens in livestock (de la Fuente et al 1999).

- Commercial anti-tick vaccines, based on the antigen BM86, are available for the control of

the cattle tick *Rhipicephalus microplus* (de la Fuente et al 2007, Rodríguez-Mallon 2023) but their efficacy varies and is poor for other tick genera, including *Hyalomma* spp. ticks. Vaccine candidates that target *Hyalomma* spp. are under development (Manjunathachar et al 2019, Nandi et al 2023, Parthasarathi et al 2023, Rafiq et al 2022, Song et al 2022).

- The use of commercial anti-tick vaccines for cattle has been most successful and sustained in countries in which vaccine provision and use has been mandated. In the absence of a centralised supply and national framework for implementation and monitoring, use of anti-tick vaccines has been intermittent and interrupted by commercial changes and discontinuous funding (de la Fuente et al 2007).

- Theoretically, anti-CCHF vaccines for livestock use might reduce viraemia in infected animals and induce anti-CCHFV host antibodies which, on entering the gut of the feeding tick, could neutralise the virus thus preventing dissemination to the salivary glands and eggs. However, because animals do not develop overt disease when infected by CCHFV, there is no economic incentive to develop anti-CCHFV veterinary vaccines. Combining an anti-CCHFV animal vaccine with an anti-tick vaccine that benefits animal health may be more acceptable and modelling suggests that these dual approaches may be the most effective means to reduce CCHFV spillover (de la Fuente et al 2020, Sorvillo et al 2020). Addition of moieties targeting other pathogens of consequence to animal health e.g. *Babesia* or *Theileria* spp, may bring additional gains.

- The relative importance of innate immunity and adaptive immunity in controlling viral load and preventing disease in the animal CCHFV amplification host remains to be determined. This knowledge gap has hampered the rational design of candidate animal CCHF vaccines.

- For evidence-based design of One Health vaccines, a better understanding is needed of the interconnected determinants of CCHFV maintenance in nature and of spillover to humans, including the likely impact of anti-tick and/or CCHFV livestock vaccines across all stages of CCHFV's enzootic cycle. Sorvillo *et al* (Sorvillo et al 2020) have listed the many knowledge gaps in this area in terms of both tick and host factors. To fill these gaps will need laboratory studies of virus transmission between ticks and their hosts (Gargili et al 2013) and field studies of natural tick/host populations.

Key Needs

- Proof-of-concept for the efficacy of anti-*Hyalomma* livestock vaccines, both under controlled laboratory conditions and in the field, measuring parameters including tick burden, density of infected ticks, animal fitness and ultimately reduction in CCHF

prevalence in human populations.

- Proof-of-concept for the efficacy and acceptability of using dual target livestock vaccines against CCHFV and tick antigens for the benefit of human and animal health.

- Proof-of-concept for the added benefit of multi-valent vaccines that target tick antigens, CCHFV and one or more pathogens of veterinary importance e.g. *Babesia* or *Theileria* spp.

- Integrated One Health surveillance systems monitoring CCHFV prevalence in vector, animal (wildlife and livestock) and human populations to assess the impact of vector control measures on the virus' enzootic cycle over time, in order to refine implementation strategies (see 'cross-cutting issues and enabling activities').

- Analysis of the impact of livestock vaccines (anti-tick and/or anti-CCHFV) on CCHFV maintenance in wildlife and wildlife-associated ticks.

- Cost/benefit analysis of (1) anti-tick vaccines, (2) anti-CCHFV animal vaccines and (3) combined anti-tick and anti-CCHFV vaccines for animal (livestock) and human health, considering the possible gains from reducing the burden of all *Hyalomma*-borne infections in livestock and balanced against the reductions in acaricide use.

- Economic and social/behavioural science studies to determine the acceptability of animal vaccination *versus* acaracide use to national governments, veterinary services and farmers.

- Analysis of options for ensuring affordable and sustainable supplies of veterinary vaccines (anti-*Hyalomma* +/- anti-CCHFV) to CCHF-affected communities, including technology transfer, in-country manufacture and preferential rates for those affected countries that contribute to vaccine R&D e.g. through hosting veterinary trials, and the possibility of combining them with routine veterinary vaccinations against diseases of economic importance.

- Continued basic research into improved anti-*Hyalomma* vaccine candidates with cross-protective efficacy against several *Hyalomma* spp. and in different hosts and investigation of innovative approaches (e.g. targeting tick microbiota) to reduce tick fitness and vector capacity.

- Continued basic research into the determinants of CCHFV maintenance in nature and of spillover to humans, building datasets for critical parameters that can be used in mathematical models to assess risk and predict the possible outcomes of experimental interventions such as vaccines for tick vector control.

Strategic Goals and Aligned Milestones

Strategic Goal 9: By Q4 2024, evaluate novel immunisation strategies, including animal vaccines for control of tick-vectors and/or CCHFV, for their ability to reduce tick vector infestations and limit transmission and spread of CCHF virus, and their acceptability and affordability.

Milestone 9.1: By Q4 2024, set up a One Health consortium ideally co-convened by WHO, WOAH and FAO, with responsibility for the strategic assessment of animal anti-tick and/or anti-CCHFV vaccines and for oversight of their scientific development, evaluation and pathway to market authorisation.

Milestone 9.2: By Q4 2024, complete a proof-of-concept study of an experimental anti-*Hyalomma* spp. vaccine or veterinary CCHFV vaccine in controlled field studies in livestock in a high endemicity setting.

Strategic Goal 10: If the proof-of-concept study is successful, determine the broader applicability of the approach and by Q2 2026, start multi-country in-use evaluation to measure the effect on tick infestation on livestock, livestock fitness and CCHF incidence in humans.

Milestone 10.1: By Q4 2025, establish scalable vaccine platform(s) suited to rapid adaptation to different *Hyalomma* spp. and antigens, CCHFV genotypes and potentially other tick-borne pathogens of veterinary importance.

Milestone 10.2: By Q2 2026, initiate coordinated in-use studies covering different livestock species in more than one high-endemicity setting to determine the applicability of the approach of using animal anti-tick and/or anti-CCHFV vaccines.

Additional Research Priorities

Research

Model the costs and benefits of animal anti-tick and CCHFV vaccines. **Consider** the possible gains from reducing the burden of all *Hyalomma*-borne infections in livestock and the reductions in acaricide use.

Evaluate the efficacy of existing anti-tick vaccines against *Hyalomma* spp. under controlled conditions and in the field.

Sequence whole genomes from *Hyalomma* spp. ticks from different geographies to determine the extent of antigenic variation and identify novel targets for anti-tick vaccine development.

Apply modern vaccinomics approaches to **identify** and fully **characterise** candidate tick-protective antigens for the development of next-generation anti-*Hyalomma* spp. vaccines, focusing on chimeric antigens predicted to be effective in different hosts and/or against several *Hyalomma* species.

Generate data about combining anti-tick/CCHFV vaccines with existing veterinary vaccines against diseases of economic importance.

Develop diagnostic assays to differentiate CCHFV-infected from vaccinated animals (DIVA reagents) for use with animal CCHFV vaccines (see 'diagnostics').

Identify the innate and adaptive immune response mechanisms that control viral load in the susceptible animal CCHFV amplification hosts for use in the rational design of animal CCHF vaccines.

Develop and characterise one or more *in vivo* models of CCHFV transmission between tick and host, and use to **investigate** e.g. vector competence, the importance of co-feeding transmission and early evaluation of anti-tick vaccines.

Conduct studies to increase the understanding of the enzootic cycle of CCHFV in different endemic settings and address some of the knowledge gaps identified by Sorvillo *et al* (Sorvillo et al 2020).

Evaluate in the field the impact of anti-tick and/or CCHFV livestock vaccines on levels of tick infestation, density of infected ticks and CCHFV seroprevalence in wildlife.

Apply innovative approaches (e.g., targeting tick microbiota) to reduce tick fitness and vector capacity.

Product Development

Continue to develop and test new candidate anti-tick vaccines against multiple tick vector antigens with broad coverage of the major *Hyalomma* species.

Continue to develop and test new candidate animal CCHF vaccines against multiple CCHFV

antigens with broad coverage of the major circulating CCHFV genotypes.

Constitute an international expert working group to select the most appropriate anti-*Hyalomma* vaccine candidates and platforms, being mindful of the need for flexibility to readily add or replace antigenic targets to maximise performance for particular regions and *Hyalomma* spp.

Key Capacities

Build knowledge of CCHFV seroprevalence in livestock and wild animals in endemic countries and regions through implementation of animal (livestock and wildlife) surveillance programmes. Data will inform economic analyses of benefits of anti-tick vaccines and support predictive statistical models of CCHFV prevalence (see 'cross-cutting issues and enabling activities').

Encourage the development and in-country coordination of region-specific epidemiologic surveillance mechanisms and reporting with sufficient dissemination (e.g. on government websites or other internet-based platforms) to reliably assist in current and future veterinary vaccine trial design and planning (see 'cross-cutting issues and enabling activities').

Policy and Commercialisation

Co-convene a tripartite (WHO, WOAH and FAO) One Health consortium responsible for the strategic assessment and cost-benefit analysis of animal anti-tick and/or anti-CCHFV vaccines as a means to control human CCHF disease, to improve livestock management and to reduce environmental spillover of acaricides.

Build the strategic case in public health, animal health and economic terms for anti-*Hyalomma* tick vaccines.

Early engagement with Ministries of Agriculture and Veterinary Services to consider the utility and acceptability of anti-tick and/or anti-CCHFV vaccines for livestock administration. Consider multi-valent anti-tick vaccines targeting CCHF *and* an economically important livestock disease.

Work with regulatory agencies responsible for marketing authorisations for veterinary vaccines to **agree on** the pathway to market for anti-*Hyalomma* vaccines alone or in combination with CCHFV immunogens.

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Appendix

Developing the CCHF R&D Roadmap

2018-19

The advanced draft CCHF R&D Roadmap (WHO 2019a) was developed according to WHO methodology and guidelines. A taskforce of ten experts from CCHF-affected countries and international research and product development groups was responsible for drafting the roadmap and for iterative revisions following the closed and public consultations summarised in table S1. The taskforce was guided by a comprehensive baseline situation analysis (BSA), which identified gaps in current knowledge and needs for further research and product development for CCHF countermeasures.

Meeting	Location	Date
CCHF R&D Roadmap Taskforce Meeting	Geneva, Switzerland	5-6 Feb 2018
CCHF R&D Roadmap Technical Consultation	Annecy, France	5-6 Mar 2018
CCHF R&D Roadmap Taskforce Teleconference	N/A	4 May 2018
CCHF R&D Roadmap Public Consultation	WHO Website	20 Jul-20 Aug 2018
WHO SAB Review	N/A	31 Aug 2018

Table S1: Timetable of workshops and consultations that led to the development of the advanced draft CCHF R&D Roadmap

2023-24

For the 2024 update to the CCHF R&D roadmap, the original taskforce of experts was expanded to 20 and invited to a face-to-face meeting in London, UK (13-14 February 2023). The experts reassessed the R&D priorities for CCHF in the context of advances made over the intervening four years and reviewed and edited iterative revisions of this 2024 update.