Summary report on the

Meeting on prevention and control of Crimean–Congo haemorrhagic fever in the Eastern Mediterranean Region

WHO-EM/CSR/103/E

Muscat, Oman
7–9 December 2015

World Health Organization
Regional Office for the Eastern Mediterranean

WHO-EM/CSR/103/E

Summary report on the

Meeting on prevention and control of Crimean–Congo haemorrhagic fever in the Eastern Mediterranean Region

Muscat, Oman
7–9 December 2015

World Health Organization
Regional Office for the Eastern Mediterranean

Document WHO-EM/CSR/103/E

Contents

1. Introduction.....1

2. Summary of discussions 4

3. Recommended actions 14

4. Next steps.....15

1. Introduction

Crimean–Congo haemorrhagic fever (CCHF) is the most widespread tick-borne virus disease of humans caused by a virus in the genus *Nairovirus* of the family *Bunyaviridae*. The disease is endemic in many regions such as Africa, Asia, eastern and southern Europe and Central Asia. Ixodid ticks, especially those of the genus *Hyalomma*, are both a reservoir and a vector for the virus. CCHF virus has been isolated from 30 species of ixodid ticks. Numerous domestic and wild animals, such as cattle, goats, sheep, small mammals, rodents, birds in which the infection is mainly asymptomatic, serve as amplifying hosts for the virus.

Humans are infected by tick bites or through exposure to the blood or tissues of infected animals. The majority of cases are reported among animal herders, livestock workers, and slaughterhouse workers. Health workers and family members can contract CCHF through contact between unprotected skin or eye mucosa and body fluids of infected patients and Performance of aerosol-generating medical procedures in CCHF patients due to inadequate infection prevention and control can also lead to nosocomial distribution of an infection among medical personnel.

The onset of CCHF is sudden, with unspecific signs and symptoms such as high fever, headache and vomiting. As the illness progresses, within 2–5 days severe and uncontrolled bleeding, multi-organ failure and eventually death may occur.

CCHF is one of the rapidly emerging viral haemorrhagic fevers in occurring across many countries of the Eastern Mediterranean Region. Sporadic human cases and outbreaks of CCHF have been reported from Afghanistan, Islamic Republic of Iran, Iraq, Kuwait, Oman, Pakistan, Saudi Arabia, Sudan and the United Arab Emirates. The

situation remains particularly alarming in Pakistan where the trend of CCHF has been steadily increasing, from 62 cases in 2012 to 154 cases in 2014, with the fatality rate ranging from 20% to 30%. In 2014, Oman reported 18 cases of CCHF, including one death, nearly 15 years after the first case of CCHF was reported in the country.

The high risk of nosocomial outbreaks of CCHF was first recognized in 1976 in Pakistan when a laparotomy was performed on a patient with abdominal pain, haematemesis and melaena. Eleven secondary cases in hospital staff resulted in 3 deaths, including deaths of a surgeon and an operating-theatre attendant. Since then, similar nosocomial outbreaks were reported in Afghanistan, Islamic Republic of Iran, Iraq, Sudan and the United Arab Emirates with high mortality among hospital staff. Anecdotal evidence indicates that such transmission occurred in health care workers as a result of contact with infected blood or body secretions from patients while providing medical care in hospitals.

Review of published literature and unpublished data sources shows that many of these nosocomial infections in health care workers were the result of poor application of basic infection control measures, as well as paucity of knowledge and lack of proper understanding among health care workers of the mode of transmission and nosocomial risks of viral haemorrhagic fevers. These reported incidents underline the need for educating the health care workers on strict implementation of infection control measures within health care facilities while providing care to suspected and confirmed patients with viral haemorrhagic fevers.

Available evidence also indicates that the CCHF may spread further in the Region in the future. Climate factors may contribute further spread of the vector and to a consequent expansion of the geographic range of CCHF from its current transmission focus in Afghanistan, Islamic

Republic of Iran and Pakistan to other countries, with the highest risk to be expected in the neighbouring countries with already established endemicity. International travel, increasing human population densities, wider dispersal of competent vectors and increased trans-boundary movement of animals, goods and agricultural products may also further escalate the spread of CCHF in the Region.

In view of increasing burden of the disease in the Region and in the absence of a comprehensive preventive and control strategy for CCHF, the WHO Regional Office for the Eastern Mediterranean organized a meeting on prevention and control of CCHF on 7–9 December 2015 in Muscat, Oman. The objectives of the meeting were to improve understanding of the epidemiology and risk factors for transmission of CCHF in the Region, identify gaps in current knowledge for effective response and develop a set of strategic actions for prevention and control of CCHF.

The meeting was hosted by the Ministry of Health of Oman. The participants included representatives of the ministries of health and ministries of agriculture from the Islamic Republic of Iran, Oman, Russia and Turkey, staff from WHO and the Centers for Disease Control and Prevention (CDC, Atlanta) as well as infectious disease experts, laboratory scientists and vector/tick control experts attending the meeting in an individual capacity as WHO Temporary Advisers. The WHO Temporary Advisers attending the meeting completed the required WHO declaration of interests and no conflicts of interest with the subject matter of this meeting or with WHO were identified. Before and during the meeting, the participants had access to documents and published literature related to the issues discussed from WHO and other sources. The goal of the meeting was to develop a set of strategic actions for prevention and control of CCHF in the Region through a consultative process by identifying the main gaps in

preventive measures such surveillance, laboratory detection, vector/tick control, infection control, risk communication as well as by identifying current knowledge and information gaps for prevention and early detection and control of human infections.

The meeting covered six thematic areas: 1) surveillance for CCHF at the animal–human interface; 2) laboratory diagnosis of CCHF in human health sector; 3) clinical case management and infection control; 4) vector/tick control in animal health sector; 5) social mobilization and risk communication; and 6) intersectoral collaboration and coordination. A separate session was held on current knowledge gaps for effective control of CCHF. Each session was facilitated by an expert in the relevant field who presented the current best practices drawn on evidence accumulated so far as well as current challenges in enhancing public health efforts in each of the areas either due to existing information/knowledge gaps or owing to poor understanding or inappropriate practices.

2. Summary of discussions

Epidemiological situation, risk factors and key challenges

Sporadic human cases and outbreaks of CCHF have been reported from Afghanistan, Islamic Republic of Iran, Iraq, Kuwait, Oman, Pakistan, Saudi Arabia, Sudan and the United Arab Emirates. Moreover, serological studies among livestock have identified presence of the disease in Egypt. The disease is reportedly endemic in Afghanistan, Islamic Republic of Iran and Pakistan, particularly in the border area of the three countries where the movement of nomads with their animals is concentrated. Trade in animals and animal skins within Pakistan, and between Pakistan, Islamic Republic of Iran and Afghanistan is thought to play a major role in the spread of CCHF

among people who handle animals or their skins, slaughter infected animals and come into close contact with ticks or CCHF patients.

The situation remains alarming in Pakistan where the trend of CCHF has been steadily increasing in the past three years. The number of reported cases was 62, 100 and over154 in 2012, 2013 and 2014, respectively, with the fatality rate ranging from 20% to 30%. Since 2013, there has been a geographical expansion and increase in the length of the transmission period of CCHF in the country. Areas which were not in the traditional endemic belt for the disease (such as Punjab and Islamabad) have reported laboratory-confirmed cases. During 2014, cases were reported weekly from different provinces across the country, unlike the bi-seasonal pattern (March–May and August–October) observed the previous years.

In June 2011, the first human infection of CCHF was diagnosed in Oman for the first time ever after about 15 years. In October 2014, the Ministry of Health of Oman reported a total of 18 human cases of CCHF, including one death, in a number of Omani governorates (North Al Batinah, South Al Batinah, Dhahirah and Dakhiliyah). All the CCHF cases were infected through contact with slaughtered or livestock animals. In 2015, the country reported 16 human infections of CCHF. While most of the reported human infections of CCHF occur among people involved in the agriculture and livestock occupations, secondary transmission associated with health care occasionally occurs in hospitals and other health care settings. Such transmissions have occurred in Pakistan in 2014 and also in Iraq, Sudan and the United Arab Emirates in the past.

Despite the CCHF being the most widespread tick-borne viral infection and one of the most rapidly emerging viral haemorrhagic fevers in humans, occurring across many countries in the Region, the true burden

of the disease is poorly understood. Although viral haemorrhagic fevers are notifiable diseases in most countries in the Region, data on CCHF are not readily available from the routine surveillance systems. This may be due to poor recognition of CCHF by physicians because cases tend to occur singly and sporadically in rural areas, and many patients develop a mild, nonspecific illness, without a recognizable haemorrhagic fever syndrome. As well, limited laboratory diagnosis capacity and poor reporting practices may result in under reporting.

Better understanding of CCHF epidemiology is needed for a comprehensive prevention and control programme addressing human as well as animal and tick populations. However, a number of challenges exist. First, it is difficult to prevent or control CCHF infection in animals and ticks as the tick-animal-tick cycle usually goes unnoticed and the infection in domestic animals is usually not apparent. Also, the tick vectors are numerous and widespread, so tick control with insecticides is only a realistic option for well-managed livestock production facilities which is usually not the case in the Region.

Second, in the absence of a vaccine, the only way to reduce infection in humans is by raising awareness of the risk factors and educating people about the measures they can take to reduce exposure to the virus. However, as the populations at risk of CCHF are nomads, farmers and animal herders living in remote and disadvantaged areas, reaching them for information, education and communication and social mobilization activities would require considerable efforts and innovative approaches.

Third, controlling infection in health care settings requires strict adherence to standard infection control measures including basic hand hygiene, use of personal protective equipment, safe injection practices and safe burial practices. However, a number of health care-associated CCHF outbreaks in the past as well as several large outbreaks of

Middle Eastern respiratory syndrome (MERS) in hospitals occurring recently suggest that infection prevention and control measures are not being adequately adhered to even in some of the most advanced health care settings in the Region.

Fourth, risk estimation methods of areas and forecasting of epizootic diseases are not well developed yet. As result the medical networks are not prepared or vigilant for urgent reactions.

Other emerging issues, experiences from the countries and information gaps

The animal–human interface is an important feature of the disease. Hence there is need for greater collaboration between the health, agriculture and veterinary sectors during the pre-epidemic preparedness phase, during alerts and case confirmation, and during outbreak response. Several mechanisms such as multisectoral coordination committees or scientific committees exist in endemic countries. Examples from the countries show that such committees can bring together all the key sectors at the same table to assess new possible high-risk areas, conduct joint risk assessment, training and investigation, develop written guidance and implement joint public health measures.

However, to institutionalize the process, there is need for a framework document with clearly defined terms of reference for national coordination mechanism and activities among key sectors involved in prevention and control of CCHF and other zoonotic diseases, specifically the ministries of health and agriculture.

The surveillance case definition for human infection of CCHF is not yet standardized. Different endemic countries have different definitions. Lack of a unified case definition in countries was

identified as a major gap. This contributes to varied mortality rates across the countries; some countries pick up patients with severe disease and bleeding at a late stage and have very high mortality while others have much more sensitive system for earlier case findings and recognition and resultantly have a low mortality rate.

For example, the Islamic Republic of Iran for is considering changing its current case definition to sudden onset fever with history of tick bite or relevant history of exposure to animals. The current case definition is for advanced stage of the disease when the clinical symptoms of the disease manifest with haemorrhagic symptoms (i.e. sudden onset fever with haemorrhagic manifestation, and relevant history of exposure). Applying such case definitions will lead to mild cases being missed out in endemic areas where haemorrhagic manifestations are not so common, possibly due to host factors or strain of the circulating virus.

There is need for consensus in establishing a standard case definition for CCHF. Initially, this could be one that covers most of the viral haemorrhagic fevers given their similarity in epidemiology, presentation and symptomatology.

In countries with no reported human infection so far, discussions continued on the value of conducting sero-epidemiological surveys among high-risk populations including agriculture workers, abattoir workers and camel owners. However, we will need to develop a standard protocol for conducting these studies in the Region. It was also discussed that such serological surveys, using a standardized protocol, can include other viral haemorrhagic fevers to identify hotspots for CCHF and other such fevers in the Region. There is also need for molecular epidemiology studies to help us understand circulating genotypes of CCHF in the Region.

One of the limitations for conducting animal surveillance for CCHF is lack of commercially available primers for real-time polymerase chain reaction (RT-PCR) tests and serological diagnostic kits for testing infected animals. There is an urgent need for developing appropriate guidance documents for conducting surveillance for CCHF in animal health sector using standardized methods and data collection tools in the endemic countries. Such surveillance data can be used to generate mapping for high-risk areas. In the absence of routine animal surveillance, data can be collected on ticks and on infected animals using sero-surveys. Even though CCHF primarily is not a disease of animals, sero-surveys for vector (i.e. ticks) and in animal reservoirs have an important role in risk assessment and mapping. More work will be need in this area by the ministries of agriculture and the Food and Agriculture Organization of the United Nations (FAO) as the role of serological surveys to define animal reservoir of CCHF virus in both endemic and non-endemic countries is not well defined.

Laboratory diagnosis

Serology remains the cornerstone for laboratory diagnosis of CCHF. However, one of the limitations of using serological tests for laboratory confirmation is that the CCHF virus-specific IgM antibodies appear late in the course of the disease and are therefore not useful for early confirmation. The presence of CCHF virus in the blood of a suspected patient can be diagnosed early using RT-PCR. However use of PCR test result for surveillance purposes remains costly.

Currently, there are also some knowledge gaps on viral loads at various clinical stages of recovery. Such knowledge may help in better understanding of evolution of the CCHF infection in humans. Given the fact that early diagnosis of CCHF is of paramount importance to establish effective symptomatic treatment early, there would be need

to develop rapid diagnostic tests and nucleic acid tests to enhance diagnosis and early case detection in primary care settings

Drawing on the experience from the Ebola virus disease outbreak in Africa in 2014–2015, this could be achieved within one year with strong collaboration between the countries endemic for CCHF, WHO and the manufacturers. CCHF positive samples from the affected countries will be needed for this purpose to facilitate development of rapid diagnostic tests for CCHF, which can be used point of care.

Case management and infection control

Currently, there is no definitive treatment for CCHF. The treatment is mainly supportive. There is evidence, however, that establishing an early diagnosis and treating the cases early with supportive treatment offer better clinical patients' outcome. The use of ribavirin, though not yet officially recommended by WHO, has been tried by a number of countries with demonstrable clinical outcome.

Experiences from Islamic Republic of Iran, Russia and Turkey show that early detection and appropriate case management is associated with low case fatality rate and better clinical outcomes. The U.S. Federal Drug Administration has given exceptional approval for the use of ribavirin in patients with CCHF due to the availability of limited data. CDC also recommends the use of ribavirin in treatment of viral haemorrhagic fevers. In the absence of any randomized control trial data on the effectiveness of ribavirin, countries may decide on the use of ribavirin in active cases as well as for prophylactic purpose among health care workers with "unprotected" exposure to needle stick injuries while caring for a patient with CCHF.

There is also a need to draw and achieve a consensus on standard case management for CCHF in order to increase the chance of survival of CCHF patients. An algorithm for diagnosis and case detection for early identification of cases would be of great value. Based on the current knowledge, asymptomatic spread of the disease is not well understood. Therefore, guidance is needed on screening of contacts of the patient after discharge.

Meanwhile, there is need for randomized control trials for efficacy studies to validate the use of ribavirin. Studies to determine viral load at various clinical stages of recovery are also needed for better understanding of evolution of the CCHF infection in humans.

Infection among health care workers appears low despite the reported nosocomial outbreaks reported from CCHF in a number of countries in the Region. In health care settings, transmission due to splash and needle-stick injuries have occurred, however the risk is generally low. Reports from Russia and Turkey also demonstrate the possibility of CCHF transmission during aerosol-generating medical procedures. There are still many unknowns; studies are needed in this regard to determine modes of transmission in the health care setting, what works and what does not work in terms of infection prevention and control.

The available current knowledge and evidence on the mode of transmission of CCHF virus justify implementation of standard infection prevention and control measures in health care settings, isolation and cohorting of patients as well as contact precautions based the invasive procedures to be applied for case management of CCHF patients.

The animal farm workers and abattoir workers as well as individuals involved in backyard slaughtering in endemic areas remained at increased risk of infection owing to the risk of occupational exposure.

Use of protective equipment and safety procedures for abattoir workers need to be considered which will also require further in-depth work. Additionally, there is need for recommendations on quarantine procedures for cross-border movement of cattle, safety procedures and protective equipment for abattoir workers.

Risk communication and community engagement

Effective risk communication remains central to prevent primary infection especially among animal handlers, slaughterhouse workers and agriculture farmers. While some countries presented examples of best practices for effective social mobilization and public awareness programmes, there is a need to standardize risk communication messages that are evidence-informed and also help in avoiding stigma and unnecessary panic. It is important to highlight that periodic surveys are required to determine the effectiveness of the risk communication messages among the public that are able to influence risky behaviours.

In this regard, there is also need for relevant sectors, health and agriculture, to work together to identify the means, including persuasion, provision of safer alternatives, and legislation, to address high-risk practices associated with increased exposure to CCHF such as backyard slaughtering of animals without proper protection in an endemic area. The media can play a key role in disseminating CCHF awareness and behaviour change messages to the general public. During outbreak situations, communication with the public should be guided by transparency to avoid panic among the population. This should be done in collaboration with relevant health promotion sectors to ensure that the messages are not associated with fear or stigma.

Other knowledge gaps

In this session, a number of important knowledge gaps from the public health perspectives were identified.

- The drivers for increasing number of human infections from CCHF and its spread in the Region.
- The types of different genotypes of CCHF virus currently circulating in the Region.
- Sequelae of infection and duration of natural protection after acute infection.
- Asymptomatic spread of the disease among close contacts of patients at households.
- Information on viral loads at various clinical stages of recovery to determine period of infectiousness and natural immune response.
- Period of infection control measures to be applied for patients diagnosed with CCHF and discharge criteria.
- Mode of transmission for human-to-human transmission at households and in health care settings.
- The effectiveness, safety and prognostic value of the use of antiviral drugs such as ribavirin for patients diagnosed with CCHF as well as for post-exposure prophylactic use.
- The role of serological surveys to define animal reservoir of CCHF virus in both endemic and non-endemic countries.
- Effectiveness and period of quarantine measures for infected animals and screening of cross border movement of infected animals from endemic countries for reducing human exposure.
- Burden and magnitude of the disease in human populations in both endemic and non-endemic countries.
- Pathogenesis and drivers for emergence of CCHF in non-endemic countries.

- Appropriate surveillance methods for detection of the infectious niche in ticks/vectors and animals.
- The role of wild animals, whether they are infected, or whether they are reservoirs of infection.
- The role of mice, cats and dogs in CCHF transmission, especially those that have been in contact with infected farm animals.

3. Recommended actions

1. Given the importance of quantitative virus load determination for clinical management (and antiviral dosage, etc.) there is need to develop assays for CCHF RNA quantification that are rapid, precise, easy to implement in resource-limited settings, and sufficiently robust to operate under field conditions.
2. In the absence of any means to detect a suspected case of CCHF at the point of care, there is need to develop rapid diagnostic kits and nuclei acid tests to enhance diagnosis and early case detection in primary care settings.
3. As currently no effective treatment exists for management of CCHF cases and various published and unpublished literature/information shows evidence on the efficacy of ribavirin, there is an urgent need for a randomized control trial to validate or refute the efficacy of ribavirin as treatment against CCHF.
4. Given the discrepancy in the use of case definitions used by several countries for surveillance purposes, there is need to standardize case definitions for early detection of CCHF patients in both endemic and non-endemic countries to be used uniformly and consistently across all endemic and high risk countries in the region.
5. In view of the fact that the clinical manifestations of CCHF during its initial clinical phase resemble many other arboviral diseases, especially dengue fever in endemic countries and influenza and respiratory diseases during the winter season, there is a need to

develop an algorithm as an aid to help the clinicians to establish the presumptive/initial clinical diagnosis of the patients rapidly on the basis of presenting clinical, epidemiological, occupational and other demographic characteristics.

6. As there is limited knowledge and understanding on the burden of CCHF as well as its animal reservoir in the Region, it is recommended to conduct sero-epidemiological studies on CCHF both for human and animal health in the Region including in non-endemic countries.
7. In view of the inconsistencies noted between the risk communication messages produced and published by several countries, there is need to develop a set of risk communication messages for the high risk groups through a collaborative engagement between the animal and human health sectors that are evidence-informed, consistent and follow the currently available knowledge and best practices.
8. Given the lack of evidence, best surveillance practices for animal health to early detect the potential risk of spillover of CCHF virus in human health should be identified and discussed with FAO and the International Organization for Animal Health (OIE) in order to reach a consensus on surveillance strategies in ticks and other animal reservoirs of the virus.
9. As little is known about climate and others natural factors of CCHF spreading the Region, study and research protocols should be developed for CCHF risk estimation and spatial-temporal forecasting of CCHF activity.

4. Next steps

- A manuscript will be prepared from the meeting report and would be published as a short communication in a peer-reviewed journal.
- Working groups will be set up from among the meeting participants to address some of the key gaps identified and highlighted in the

meeting. These issues include standardizing surveillance case definition, developing a case management algorithm, developing guidance for animal and human surveillance, infection control practices in health care settings, risk communication messages.

- As little is known about the burden of CCHF and the genotypes of CCHFV circulating in the Region, study and research protocols will be developed for conducting sero-prevalence of CCHF and molecular epidemiology studies would be conducted for determining circulating genotypes of CCHF in the Region.
- Standard health education messages will be developed in collaboration with health promotion experts to ensure that they achieve desired objectives and also to ensure that they are suitable for the general public.
- WHO will facilitate development of rapid diagnostic tests (i.e. RDTs) building upon the experience and expertise established for the development of Ebola RDTs.
- The possibility of conducting randomized control trials on the safety and efficacy of ribavirin in collaboration of CCHF endemic countries will be addressed in coordination with WHO headquarters.
- Development of standard guidance on infection prevention and control for management of CCHF patients in hospitals drawing on literature review will be considered.
- A strategic framework for CCHF prevention and control in the Region will be developed and presented to the countries before the end of 2016.
- Development of framework will be considered for CCHF activity forecasting and ranking of risk estimation in the Region.

World Health Organization
Regional Office for the Eastern Mediterranean
P.O. Box 7608, Nasr City 11371
Cairo, Egypt
www.emro.who.int