Summary report on the

International scientific meeting on Middle East respiratory syndrome coronavirus (MERS-CoV)

WHO-EM/CSR/100/E

Cairo, Egypt
5–6 May 2015

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Regional Office for the Eastern Mediterranean

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1. Introduction

The Middle East respiratory syndrome coronavirus (MERS-Cov), first detected in 2012 in a patient in Saudi Arabia, continues to evoke global concern and remains a serious threat to global health security. Following its identification, cases have continued to increase over the past three years and hundreds of human infections have been reported globally of which approximately 35% were fatal. The majority of cases (over 85%) reported to date globally have been from the countries of the Middle East. Since the detection of the virus in 2012, several important knowledge and information gaps continue to haunt the global scientific communities regarding the exact mode and route of transmission of the virus in humans and animals, as well as the human behaviour that results in infection. The absence of such crucial information has impeded the development of effective public health control measures and intervention strategies to minimize the risk of disease transmission.

Several scientific initiatives have recently been launched in both the animal and human health sectors in many countries and these international scientific efforts have generated important evidence on multiple aspects of the virus including its origin and reservoir. These initiatives have elicited important information and lessons surrounding the current global response to the outbreaks of MERS, especially in the areas of surveillance, infection control, screening and triaging of patients and prevention and control of nosocomial infections in health care settings.

Against this background, an international scientific meeting was organized in Cairo, Egypt, from 5 to 6 May 2015. The meeting was the fourth such meeting and aimed to share new information and research findings that have emerged since the last scientific meeting

on MERS-CoV held in December 2013 and also to discuss key knowledge gaps. The specific objectives of the meeting were:

- to discuss and review public health measures that have proven most effective in controlling the spread of the virus to date;
- to present, share and disseminate new scientific information and study findings associated with the virus in humans and animals; and
- to identify key knowledge gaps that need to be filled in order to improve public health understanding and outbreak response in both community and hospital settings.

The meeting participants included experts from both human and animal health sectors from Jordan, Oman, Saudi Arabia and the United Arab Emirates. Also in attendance were representatives of international health agencies: United States Centers for Disease Control and Prevention, Atlanta; United States Naval Medical Research Unit 3 (NAMRU-3); Institute of Virology, University of Bonn, Erasmus Medical Centre in the Netherlands; Institute Pasteur, Mount Sinai Hospital, Toronto, Canada; China Faculty of Medicine; Chinese University of Hong Kong, the Food and Agriculture Organization of the United Nations (FAO) and World Organisation for Animal Health (OIE).

Dr Ala Alwan, WHO Regional Director for the Eastern Mediterranean, inaugurated the meeting. He noted that although global understanding of the epidemiology of the virus had greatly improved since the detection of this virus in 2012, several important knowledge gaps still remained. The meeting would be an opportunity to review the lessons learnt to date as well as the critical information and knowledge gaps that were limiting global action to prevent and contain the threat of MERS-CoV.

The two-day meeting comprised several scientific sessions, each of which included individual presentations from the Member States, WHO and other international agencies. The individual presentations were followed by plenary discussions. During the plenary discussions, the information presented by the speakers was analysed and synthesized to identify the remaining knowledge gaps that are necessary to address both for the animal and human health sector in order to optimize the public health understanding and global response to MERS-CoV infections.

2. Summary of discussions

2.1 Review of public health measures that have proven to be most effective in controlling the spread of the virus

The current body of evidence does not show any change in the epidemiology of the virus or its transmission characteristics. Globally, a total of 23 countries reported laboratory-confirmed cases so far with no community acquired cases reported from outside the Region. Over 80% of cases reported to date occurred in countries of the Arabian peninsula. The transmission pattern seen so far in these countries represented repeated sporadic introduction of the virus mostly from dromedary camels to humans resulting in limited human-to-human transmission. Either direct or indirect contact with dromedaries continues to be the primary risk factor for human infections that are acquired in the community.

Secondary transmission continues to occur among close contacts of laboratory-confirmed symptomatic cases, but mostly in health care settings. Males with a median age of 49 years account for the majority of cases. About 35% of the reported cases are fatal, mostly those with underlying medical conditions.

Hospital clusters of MERS-CoV cases, smaller in size with an average of 10 to 20 nosocomial transmissions per hospital outbreak, continue to be reported. Health care workers have accounted for close to 21–22% of all reported infections from MERS-CoV to date. However, evidence has shown that secondary transmissions from MERS-CoV can be averted by applying the currently available knowledge on virus transmission and practices systematically. Some of the measures that have proven value in limiting hospital-acquired infections from MERS include the following.

- Preventing close contact through appropriate triaging and rapid isolation
- Limiting exposure through appropriate staff protection: containing the spread of the virus in the environment through improved hospital preparedness, application of essential infection prevention and control measures and improved staff preparedness

The current body of knowledge suggests that MERS-CoV infections in camels produce only minor and largely subclinical infection. Therefore, active and targeted laboratory-based surveillance needs to be established for camels with the objective of monitoring the occurrence of MERS-CoV infections in camels and its seasonality, as well as tracing forward or backwards human exposure with a view to limiting the transmission risk between camels and from camels to humans. The current body of knowledge also suggests that dromedary camels which are positive for MERS-CoV need to be quarantined for a minimum period of 8–10 days to prevent transmission to humans.

The evidence favouring zoonotic transmission of MERS-CoV has important public health implications for many communities, including the general public, farmers, camel handlers and trade officials who are involved with the camel industry. These findings cause concern as

camels are culturally and economically important in throughout the Arabian peninsula and thus many people feel protective towards them. The risk communication messages for the high risk group of camel handlers need to be validated using the recent evidence

A regional workshop on MERS-CoV and One Health, hosted by the government of Qatar and organized by FAO in Doha, from 27–29 April 2015, summarized the agreed on mechanisms for intraregional and global cooperation in investigations, research and knowledge sharing and the role of international and regional organizations at the human–animal interface. The meeting issued the Doha Declaration, in which it recommended that all camels testing positive for MERS-CoV by the real-time polymerase chain reaction technique need to be notified to OIE regardless of epidemiological link to human cases.

2.2 Sharing new scientific information and study findings associated with the virus in humans and animals

After more than three years since the virus was first detected, information on specific risk factors and exposures, how the virus is transmitted, and the extent of infection in human and animal populations and advances in therapeutics and diagnostic assays remains limited.

There is no evidence to date that the disease seen in humans caused by the MERS-CoV has any seasonal trend. Since the current evidence suggests that dromedary infection precedes human infection, and the calving season of camels usually peaks during the period of December to February, without any longitudinal time series surveillance data collected over time from camels, it might be difficult to substantiate any evidence if the virus circulation in camel follows any seasonal trend. In the absence of such information, multiple events involving camels that are known to have occurred during the springtime in the countries of

Arabian peninsula could explain why comparatively higher number of community-acquired human infections were reported during the springtime in the past. These events involving camels might have provided opportunities for increased human exposure, particularly at a time when the weaning/calving period of dromedary camels also peaks.

Several studies conducted concurrently have demonstrated that MERS-CoV is widespread in camel populations in the Region and current evidence suggests that human infection is associated with exposure to camels, particularly dromedary camels. Work by several groups has shown that dromedaries from countries in Africa (Egypt, Ethiopia, Kenya, Nigeria, Sudan and Tunisia) and in the Arabian peninsula (Jordan, Oman, Qatar, Saudi Arabia and United Arab Emirates) have shown high rates of MERS-CoV seropositivity in serum samples collected during the past two decades. These studies have been performed on archived serum samples collected more than 30 years ago and the tests performed include serology using microneutralization tests. These findings suggest long-term circulation of MERS-CoV or MERS-like CoV in dromedaries. However, in the absence of viral RNA, such serological findings do not explain whether the MERS-CoV was circulating in these countries in dromedary camels before the first human infection was detected in 2012.

There are also several ongoing studies in animal populations of the Arabian peninsula, central Asia and African countries to detect MERS-CoV antibody in animal populations. MERS-CoV antibodies have been found in camel populations of Jordan, Oman, Qatar, Saudi Arabia and United Arab Emirates. To date, there has been no evidence of circulation of MERS-CoV in any other animal species except camels. There is also no proof of circulation of MERS-CoV in central Asia.

Some of the ongoing research determined that the MERS-CoV isolates from Egypt and Nigeria (African strains, Clade-A) are genetically divergent from other MERS-CoV strains seen in the Arabian peninsula (Clade-B). Although the phylogenetic sequencing shows divergence between strains, these variations do not translate into a change in antigenic expression. The MERS-CoV sequences from camels in Saudi Arabia and Qatar were closely related to sequences found in humans and did not show major genetic variability that would support long-term evolution of MERS-CoV in camels. An urgent task would be to characterize the diversity of MERS-related CoV in other camels in Africa to elucidate whether the current epidemic MERS-CoV strains have evolved towards more efficient human transmissibility.

A study to identify risk factors for primary MERS-CoV illness in humans was conducted in Saudi Arabia. The study used a case–control design enrolling 30 primary case-patients and 116 matched controls. The study findings, which were published recently, show that during the two-week period preceding illness, case-patients were more likely than controls to have had direct dromedary exposure and to keep dromedaries in or around the home; or to have visited a farm where dromedaries were present.

Significantly higher sero-prevalence of MERS-CoV antibodies were found among people working with dromedary camels, especially those having close, regular and direct contact with camels. Camel-exposed humans (camel shepherds, slaughterhouse workers, etc) had higher sero-prevalence rates for MERS-CoV compared to the general population. One cross-sectional sero survey conducted in Saudi Arabia testing over 10 000 survey samples from 13 provinces found 0.15% of individuals to have MERS-CoV neutralizing antibody and who were healthy and asymptomatic. All were male with a median age of 42 years.

A case contact study conducted in Saudi Arabia showed minor human-to-human transmission as MERS CoV replicated mainly in the lower respiratory tract. The study findings led to the conclusion that sporadic and silent transmission of MERS-CoV in humans probably occurs from the source. Young camels, probably, act as amplifiers. The asymptomatic carriers, mainly young or middle-aged camel-exposed males, pass on the infection to elderly, co-morbid people who become symptomatic. Nosocomial infection occurs in hospital when there is hygiene deficit, invasive procedures and immune-compromised patients.

Nosocomial transmission has been a hallmark of MERS-CoV and caused an upsurge of cases during the spring of 2014 in Jeddah, Saudi Arabia and also in the United Arab Emirates. The following risk factors for nosocomial transmission from MERS-CoV were found to be common in every hospital outbreak.

- Absence of physical barriers between critical care unit and intensive care unit beds and short distance between patient beds.
- Inappropriate isolation procedures for suspected patients and poor compliance with adequate infection control measures by health care workers as well as inappropriate use of masks.
- Inappropriate washing or changing facilities for health care workers.
- Use of continuous positive airway pressure devices, nebulized medications, resuscitation in intensive care and invasive procedures conducted on patients with renal dialysis.
- Overcrowding in the emergency room and lack of triaging and inadequate infection control practices in the emergency rooms.
- Weak surveillance system in the hospitals to follow up actively and identify cases with nosocomial risk.

An action point from a previous technical meeting in Riyadh in March 2014 was addressed. In an effort to expand support of laboratory

responses to MERS-CoV, four laboratory specific recommendations were made. WHO addressed the need for continued participation in collecting serum for use in designing a serum panel to compare sera from convalescent patients. The serum panel will be designed to compare the performance of different serological assays. The Regional Office has agreed to help with the serum collection and to date, three countries from the Region have agreed in principle to contribute. It was also suggested that serum from populations samples collected from the countries without MERS-CoV circulation can also be added to the panel in order to establish a serum panel of different coronaviruses.

The Modified Virus Ankara (MVA) based vaccines are the best candidate MERS-CoV vaccines for humans and dromedary camels. Unpublished data from a proof of principle experiment on vaccine development in camels indicate that vaccination with candidate MVA-MERS CoV spike vaccine reduces the excretion of the virus from the nose of infected camels. The vaccines may be potentially used in a combined approach to reduce the transmission of MERS-CoV by inducing mucosal immunity in dromedary camels. In addition to a potential vaccine in camels, findings from Saudi Arabia showed a combined Ribavirin and pegylated interferon alpha 2b regime significantly improved patient survival 14 days after diagnosis of MERS-CoV.

2.3 Identify current knowledge gaps that can contribute to better public health understanding and response to MERS-CoV

A number of important knowledge gaps were identified in this session. These include the following.

- What is source and origin of MERS-CoV? Are there any intermediate hosts for the virus?

- Do any host-genetic factors play an important role in efficient transmission from camels to humans (versus those at highest risk)
- What is the viral load and period of infectivity for human-to-human transmission?
- What are the exposure risk factors for health care workers?
  - What specific exposures put the health care workers at highest risk of illness?
  - Are there any exposure risk differentials for health care workers in emergency room vis-à-vis the intensive care unit or renal dialysis unit?
- Are there any differences in human behaviour that puts certain group of people at higher risk illness or infection?
- Is there any seasonal trend of the disease?
- How do variations in viral load in camels affect the transmission to humans?
  - What role do asymptomatic animals play transmitting the virus to humans?
- Why does MER-CoV appear to have such a focalized geographical region?
  - What factors (behavioural/environmental/viral) are driving camel to human transmission?
  - How do these factors differ from those present in African countries?
- What is the role of mildly symptomatic cases in transmission?
  - Do unrecognized mild cases act as a reservoir of infection?

3. The way forward

In the event of current knowledge gaps, it was agreed that limiting exposure to primary human infections and improving hospital infection control measures in all health care settings are key to prevent escalation of outbreaks of MERS-CoV. This can be achieved through:

- application of evidence-based infection prevention and control practices in all health care environment consistently and systematically by implementing the entire eight core components of an infection prevention and control programme;
- conducting surveillance at the animal–human interface for early detection of primary, mild and possibly asymptomatic human infections;
- enhancing surveillance for severe acute respiratory infection (SARI) and testing a small number of cases routinely for MERS-CoV, which can lead to better understanding of transmission events occurring among primary cases as well as monitoring seasonality of the disease which to date has not been established;
- creating and disseminating clear, context-specific and evidence-based guidance for risk communication for high risk populations; and
- conducting active surveillance at the animal–human interface when a positive laboratory-confirmed case with epidemiological link to humans is detected.

Improving collaboration between the human and animal health sectors is critical for field investigations, surveillance and research, especially for quarantine of infected camels, and other disinfection measures in accordance with WHO recommendations and the Doha Declaration. At the same it is important to develop or update guidance for investigation at the animal–human interface, especially quarantine and mitigation measures to prevent infection of humans from camels.

4. Concluding session

The Regional Director noted that the findings emerging from the meeting would require translation into a set of concrete policy actions and recommendations to improve global public health response to the threats of MERS-CoV. WHO would continue to work with countries to

update some of the currently available public health recommendations on MERS-CoV in light of the new findings and information.

The meeting provided a useful summary of the ongoing research currently being conducted by countries as well as by other international health partners on MERS-CoV. It also served as a reminder that while advances have been made in closing key information and knowldge gaps, much still needs to be done. Much of the new scientific data presented in the meeting and lessons learned so far on global response to MERS-CoV were the result of multidisciplinary approaches and joint collaborative efforts between the human and animal health sectors. This is an approach that should persist as WHO continues to work with countries to bridge the existing knowledge gaps on MERS-CoV.

The Regional Office will consider convening a technical advisory group comprising scientists and public health experts from the countries affected by the outbreak of MERS-CoV as well as from international health partners. The main function of this group would be to advise WHO on how to address through collaborative work the key knowledge gaps that must be overcome in order to mount a better public health response to the threat of MERS-CoV.

The meeting concluded with a proposal that WHO convene another international scientific meeting on MERS-CoV in the future to review progress on actions taken.

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