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MERS: Progress on the global response, remaining challenges and the way forward

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ABSTRACT

This article summarizes progress in research on Middle East Respiratory Syndrome (MERS) since a FAO-OIE-WHO Global Technical Meeting held at WHO Headquarters in Geneva on 25–27 September 2017. The meeting reviewed the latest scientific findings and identified and prioritized the global activities necessary to prevent, manage and control the disease. Critical needs for research and technical guidance identified during the meeting have been used to update the WHO R&D MERS-CoV Roadmap for diagnostics, therapeutics and vaccines and a broader public health research agenda. Since the 2017 meeting, progress has been made on several key actions in animal populations, at the animal/human interface and in human populations. This report also summarizes the latest scientific studies on MERS since 2017, including data from more than 50 research studies examining the presence of MERS-CoV infection in dromedary camels.

1. Background: Middle East Respiratory Syndrome

Since its identification in the Kingdom of Saudi Arabia (KSA) (Zaki et al., 2012) and Jordan (Hijawi et al., 2013) in 2012, Middle East Respiratory Syndrome (MERS) has become a global public health threat. Typical of an emerging zoonosis, Middle East respiratory syndrome coronavirus (MERS-CoV) has an animal reservoir, i.e. dromedary camels in which the virus causes little to no disease (Mohd et al., 2016). Many details about the extent of circulation and the mechanisms of transmission within dromedary camel herds, or factors related to zoonotic transmission and differences in circulating MERS-CoV strains, remain unknown. The virus has repeatedly spilled over from dromedary camels to humans, principally in countries on the Arabian Peninsula, causing significant morbidity and mortality (World Health Organization, 2017a; Azhar et al., 2014). Clusters of cases in the community and among family members are rare (World Health Organization, 2017a; Drosten et al., 2014). However, delays in diagnosis in hospitals has sometimes led to secondary cases among health care workers, patients sharing rooms or family members as a result of unprotected direct contact with a patient before isolation. This human-to-human transmission in health care facilities can sometimes be amplified, causing very large outbreaks, as has been seen in the Middle East and in the Republic of Korea, with significant public health and economic impacts (Hijawi et al., 2013; Assiri et al., 2013; Al-Abdallat et al., 2014; Drosten et al., 2015; Al Hosani et al., 2016; Ki, 2015; Park et al., 2015). As of August 2018, more than 2249 human cases from 27 countries have been reported to the World Health Organization (WHO) (World Health Organization, 2017a).

The FAO, OIE and WHO Tripartite have regularly brought together affected member states, public health and animal officials, and academics to discuss what is known and unknown about the zoonotic origin of MERS-CoV (World Health Organization, 2016; FAO, 2016, 2014; WHO Regional office for the Eastern Mediterranean, 2013a). The purposes of these meetings and workshops have been to advocate for more surveillance and research on MERS-CoV in animals and humans, to share information about how MERS-CoV is transmitted between animals, from animals to humans and between humans, to describe the diseases it causes, and to develop policies and guidelines for detection,

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reporting of animal and human infections, and prevention of human cases and clusters.

In the two years since the last international technical consultation on MERS-CoV in 2016 [13], there have been notable improvements in surveillance and reporting of human cases, multidisciplinary research, cross-sectoral collaboration at country level, public awareness about the disease, and laboratory and surveillance capacity in affected countries. In addition, a number of countries in the Arabian Peninsula and in Africa have engaged in research activities and surveillance of camel populations to shed light on the wider distribution of this virus or investigate transmission patterns and routes for viral shedding. As a follow-up to previous meetings (World Health Organization, 2016; FAO, 2016, 2014; WHO Regional office for the Eastern Mediterranean, 2014; WHO Regional office for the Eastern Mediterranean, 2013b, 2013c), FAO, OIE and WHO Tripartite held a Global Technical Meeting on MERS-CoV with representatives from Ministries of Health and Ministries of Agriculture, subject matter experts, researchers, funders and industrial partners from 25 to 27 September 2017 in Geneva, Switzerland (see Supplementary Information) (World Health Organization et al., 2017). The objectives were to review the latest scientific evidence on MERS-CoV, further enhance cross-sectoral collaboration and communication during preparedness and response activities, and identify research priorities given the advancements in our knowledge.

With 130 participants, this was the largest MERS-CoV Technical Meeting to date and the first meeting attended by representatives from both affected and at risk countries. That is, countries which have reported human infection, countries with evidence of MERS-CoV in dromedary camels but no reported human cases, and countries at risk for importation (countries without infected camels that have close ties to affected countries through expatriate workers, travel to affected countries for medical procedures and/or frequent international travel).

2. Findings from the global technical meeting

There is strong consensus among all stakeholders that dromedary camels are the main source of transmission to humans. In 2014, OIE identified MERS-CoV as an emerging disease with zoonotic potential in camels and thereby creating expectations of reporting positive camels by countries (OIE, 2014a) and recently published a MERS-CoV case definition (OIE, 2017) for the reporting of confirmed and suspected infection in camels.

Not all countries face the same risks. For example, countries that have the infected reservoir (dromedary camels) differ from those countries in which dromedary camels show no evidence of current or past infection (Fig. 1). There may also be differences in spillover potential in countries with documented zoonotic transmission, compared to those without, due to several factors including potential differences in husbandry practices, cultural, social, medicinal, occupational exposures, prevalence of underlying chronic medical conditions, or genetic factors in human populations, and MERS-CoV viral differences (Wong et al., 2015). As such, technical and risk mitigation guidance to protect human health and research priorities differ by region.

The findings from the Global Technical Meeting are summarized below:

i. Surveillance needs: Surveillance in animals and humans to limit zoonotic transmission

Routine human surveillance for MERS-CoV in KSA (Abdulaziz et al., 2017) and throughout the Middle East has improved since the identification of the virus in humans in 2012, but there is significant variation in the quality and extent of surveillance between countries. In other parts of the world, surveillance is limited. Since it is known that MERS-CoV is enzootic in areas of Africa and Asia where dromedary camels are found, heighted awareness and surveillance for zoonotic MERS is required. This is currently lacking and remains a knowledge gap.

One exception is the notable effort to identify potential MERS-CoV infection among pilgrims travelling back from the Middle East. Since 2012, event-based surveillance among pilgrims returning from Hajj, Umrah and other religious events in KSA has been conducted by KSA and countries sending pilgrims. While many return reporting respiratory symptoms, no MERS-CoV infections have been identified among returning pilgrims (Muraduzzaman et al., 2018; Barasheed et al., 2014; Atabani et al., 2016; Koul et al., 2017; Annan et al., 2015; Ma et al., 2017; Memish et al., 2014a, 2014b; Refaey et al., 2017; Al-Abdallat et al., 2017; Matthew et al., 2015; Alqahtani et al., 2016; Win et al., 2016; Yavarian et al., 2018; Kapoor et al., 2014).

Among animals, field surveys conducted to date have included several domestic and wildlife species including dromedary camels (*Camelus dromedarius*) and Bactrian camels (*Camelus bactrianus*), goats, bats, cattle, sheep, chickens, swine, ducks, buffalo and equids. Field studies in dromedary camels have been conducted in a number of countries (Table 1). To date, MERS-CoV RNA or MERS-CoV-specific antibodies have been identified in dromedary camels a number of countries (Table 1) except Australia (Hemida et al., 2014), Kazakhstan (Miguel et al., 2016), and the Netherlands (Reusken et al., 2013a). Other livestock such as alpacas (*Vicugna pacos*), llamas (*Llama pacos*), young goats, rabbits and pigs have been shown to be susceptible to experimental infection (Crameri et al., 2016; Adney et al., 2016; Vergara-Alert et al., 2017).

Despite improvements, routine surveillance in dromedary populations is limited. The lack of surveillance information about MERS-CoV circulation in dromedary camels restricts our understanding of the transmission dynamics and epidemiology in dromedary camel populations. Meeting participants agreed that surveillance should be integrated into existing surveillance systems, particularly in at-risk countries, similar to One Health approaches developed for avian influenza, and existing human respiratory disease surveillance systems set up for influenza-like illness (ILI) or severe acute respiratory infections (SARI).

Currently, a limitation in our ability to mitigate spillover from dromedary camels to humans is a lack of clarity on the mode(s) of transmission between dromedary camels and humans, the extent and epidemiology of MERS-CoV circulation in dromedary camels in large parts of Africa and South Asia, and on why zoonotic transmission is limited across Africa, large parts of the Middle East, and some parts of South Asia despite high seroprevalence in dromedary camels (Chu et al., 2018) (Table 1).

FAO has outlined the meeting participants conclusions on priorities for MERS-CoV surveillance and management of PCR positive dromedary camels, coordinated outbreak investigation of community acquired cases with dromedary exposure, testing of animals at quarantine and entry points, food safety and environmental contamination, risk communication and awareness raising for MERS-CoV among animal owners and intersectoral collaboration and coordination in an updated Doha Declaration first published in 2015 (FAO, 2015) (REF/hyperlink). In dromedary camels, longitudinal studies to evaluate the natural history, shedding profile and immunity were highlighted as key research priorities. Meeting participants agreed that further understanding of differences in viral strains and transmission dynamics, including the role of immunity in acquiring infection and shedding virus, the geographic range of spillover events, and environmental, behavioral or host-related risk factors for zoonotic transmission should be prioritized.

ii. Research needs: Hospital transmission and infection prevention and control

Countries face significant challenges in the early identification and diagnosis of MERS in humans due to the non-specificity of clinical symptoms (Arabi et al., 2017a; TheS-Coesearch, 2013; Arabi et al., 2017b; Al-Tawfiq et al., 2017; Al-Tawfiq and Hinedi, 2018; Hui et al.,).