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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.,).

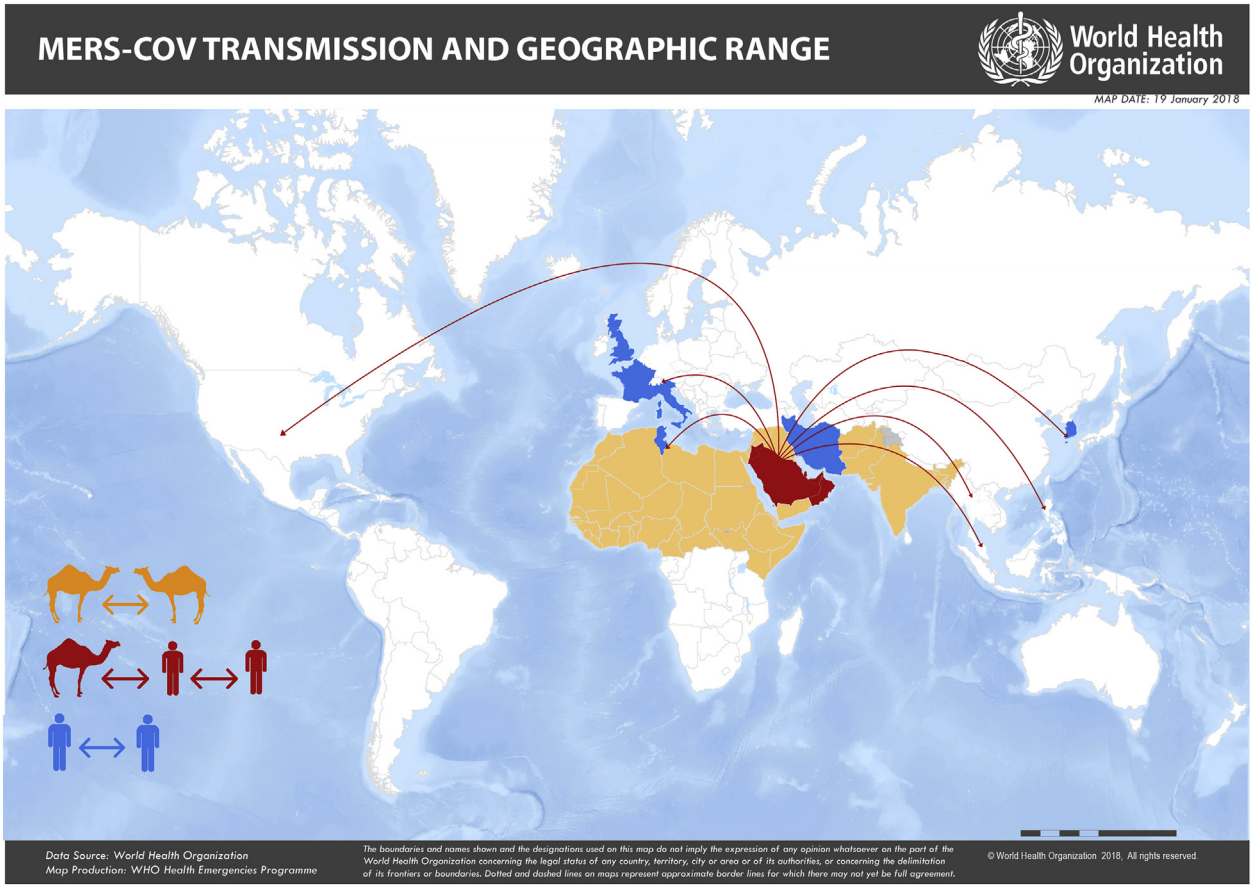

Fig. 1. MERS-CoV transmission and geographic range. Countries highlighted in red and orange indicate the geographic range of MERS-CoV in dromedary camels. Those in red have had documented spillover (camel-to-human) transmission with subsequent human-to-human transmission. Countries in blue are those with reported human-to-human transmission. (Source: WHO). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The spectrum of illness ranges from no symptoms (or asymptomatic infection) to severe disease including pneumonia, acute respiratory disease syndrome, organ failure and death, with a case fatality ratio 35.5% among reported cases (World Health Organization, 2012). The delay in identification and recognition of signs and symptoms compatible with MERS and delay in early isolation of patients has reduced the ability to prevent transmission between people in health care settings, notably in emergency departments, cardiac care centers and renal dialysis units (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; Ahmed et al., 2018; Amer et al., 2018).

Our understanding of human-to-human transmission in health care settings has improved through experimental and observational studies conducted in countries during such outbreaks. For example, studies of respiratory pathogens (Yu et al., 2007; Tran et al., 2012; Thompson et al., 2013) and MERS-CoV conducted in the Middle East (Assiri et al., 2013; Oboho et al., 2015; Hunter et al., 2016; Balkhy et al., 2016) and the Republic of Korea (Bin et al., 2016; Kim et al., 2016a, 2016b; Nam et al., 2017) illustrate that aerosol-generating procedures and non-invasive ventilation, combined with inappropriate infection prevention and control practices and lack of adherence to standard practices had an important role in facilitating human-to-human transmission in health care settings. The role of environmental contamination has been evaluated in a number of hospitals following the 2015 outbreak in the Republic of Korea and collaborative, experimental studies are being conducted to evaluate the viability and persistence of MERS-CoV on surfaces and in the air (Bin et al., 2016; Kim et al., 2016a; van Doremalen et al., 2013). The role of mild or asymptomatic cases in transmission chains, however, remains unclear (Omrani et al., 2013; Memish et al., 2014c; Al-Gethamy et al., 2015; Moon and Son, 2017; Al-Abdely et al., 2018), warranting targeted epidemiological and clinical studies to be conducted among contacts during outbreaks, especially in health care facilities.

Countries which have reported health care-associated outbreaks have implemented a variety of strategies to improve infection prevention and control and reduce human-to-human transmission in hospitals, including the introduction of a visual triage system prior to entrance to the emergency departments, the restructure of emergency department layouts for better triage of patients with respiratory symptoms, the standardization and training and re-training of infection prevention and control practices at facilities with high hospital staff turnover, and the auditing of health care facilities for adherence to infection prevention and control measures.

iii. Product research and development needs: Clinical management, diagnostics and medical interventions

The WHO R&D Blueprint, a global strategy and preparedness plan that allows the rapid activation of R&D of epidemic pathogens, aims to fast-track the development and use of effective point-of-care diagnostic tests, vaccines and medicines that can be used to save lives and avert large scale crises. Since 2015, MERS-CoV has been included in the annual WHO R&D Blueprint list of prioritized pathogens for accelerated research and development on diagnostics, vaccines and therapeutics (World Health Organization). In addition, MERS-CoV has a specific roadmap for product research and development, outlined by WHO in

Table 1
Field studies of evidence of MERS-CoV infection in dromedary camels. ppNT: pseudoparticle neutralization; MN: microneutralization; CI: confidence interval; VNT: virus neutralizing antibodies test.

Country	Number of camels	Evidence of MERS-CoV infection
Australia	25	No evidence for MERS-CoV infection in dromedary camels (Hemida et al., 2014)
Bangladesh	55	17 (31%) samples were seropositive (Ariful et al., 2018)
Burkina Faso	525	Seropositivity rates ranged from 73.2% (95% CI): 48.6–88.8) to 84.6% (95% CI: 77.2–89.9) and virus detection from 0% (95% CI: 0–0) to 12.2% (95%CI: 7–20.4) (Miguel et al., 2017)
Egypt	2825	Of 2825 nasal swabs, RNA detection rate was 15% by RT-PCR. Of 2541 sera samples, the overall seroprevalence was 71%. (Ali et al., 2017)
	1078	Of 1031 serological tests, 871 (84.5%) had MERS-CoV neutralizing antibodies. Of 1078 nasal samples, 41 (3.8%) were positive for MERS-CoV using MERS-CoV PCR (Ali et al., 2015)
	110	4 (3.6%) nasal swab specimens tested positive for presence of MERS-CoV RNA. Antibodies against MERS-CoV were detected in 48 (92.3%) of 52 serum samples (ref 48) (Chu et al., 2014)
	110	103 (93.6%) sera collected neutralized MERS-CoV using ppNT (Perera et al., 2013b)
	43	34 (79.1%) dromedary camels were positive for MERS-CoV antibodies using MN (Muller MA et al., 2014)
Ethiopia	632	Seropositivity rates ranged from 85.1% (95% CI: 71.8–92.7) to 99.4% (95% CI: 95.4–99.9) and the viral RNA detection rates from 0% (95% CI: 0–0) to 15.7% (95% CI: 8.2–28.0)[95]
	188	Seropositivity was 93% in adult dromedary camels and 97% for juvenile dromedary camels (Chantal et al., 2014)
Iran	186	8 (4.3%) samples positive using RT-PCR (OIE, 2014b)
Israel	411	254 (61.8%) were positive for MERS-CoV antibodies using VNT; All nasal samples were negative for the presence of MERS-CoV RNA (David et al., 2018)
	71	51 (71.8%) sera samples had MERS-CoV neutralizing antibodies (Harcourt et al., 2018)
Jordan	11	Neutralizing antibodies to MERS-CoV were found in all sera from dromedary camels (Reusken et al., 2013c)
	45	42 nasal swabs tested positive for the presence of MERS-CoV nucleic acid (van Doremalen et al., 2017)
Kazakhstan	455	No evidence for MERS-CoV infection in dromedary camels (Miguel et al., 2016)
Kenya	774	228 (29.5%) were positive using rELISA test (Corman et al., 2014)
	335	Seroprevalence of MERS-CoV antibodies in the sampled population was 46.9% (95% CI 41.4–52.5) (Deem et al., 2015)
Kingdom of Saudi Arabia (Azhar et al., 2014; Hemida et al., 2013, 2014, 2017; Alagaili et al., 2014; Briese et al., 2014; Maged et al., 2014, 2015; Kasem et al., 2017; Ziad et al., 2014)	203	150 (74%) sampled were found to have antibodies to MERS-CoV by ELISA (Alagaili et al., 2014)
	1309	158 (12.1%) nasal swabs were positive for MERS-CoV (Sabir et al., 2016)
	698	The overall prevalence of MERS infection in camels in animal markets and slaughterhouses by rtRT-PCR was 56.4%
	99	High levels of seropositivity in two herds demonstrated – in on herd, all samples had MERS-CoV antibodies (Hemida et al., 2017)
	310	280 (90.3%) samples were positive using ppNT (Hemida et al., 2013)
	171	144 (84.2%) sera samples had specific antibodies against MERS-CoV (Harrath and Abu Duhier, 2018)
	9	2 (22.2%) nasal samples were positive using RT-PCR (Ziad et al., 2014)
	9	1 (11.1%) nasal samples were negative for MERS-CoV RNA. All serum samples had high titers of MER-CoV antibodies (Azhar et al., 2014)
	131 archived sera	118 (90.1%) had detectable ppNT antibody titres to MERS-CoV (Hemida et al., 2014)
Kuwait	63	5 (7.9%) nasal samples were positive using RT-PCR (WAHIS Interface, 2014)
Mali	570	502 (88.1%) were positive for antibodies against MERS-CoV (Falzarano et al., 2017)
Morocco	343	Seropositivity rates ranged from 48.3% (95% CI: 18.3–79.5) to 100% (95% CI:100-100) and viral RNA detection rates from 0% (95% CI: 0–0) to 7.6% (95% CI: 1.9–26.1)[95]
Nigeria	358	Seropositivity was 94% in adult dromedary camels and 93% for juvenile dromedary camels (Chantal et al., 2014; Chu et al., 2015)
	132	14 (11%) nasal swabs were positive using RT-qPCR (Chantal et al., 2014; Chu et al., 2015)
	2529	MERS-CoV RNA was detected in 4/38 (10.5%) of camels aged < 2 years, in 31/1400 (2.2%) aged 2–4 years and in 20/1091 (1.8%) aged > 4 years (So et al., 2018)
Oman	76	5 (6.6%) proved positive in all applied RT-qPCR and RT-PCR assays. (Nowotny and Kolodziejek, 2014)
	50	50 (100%) had protein-specific antibodies against MERS-CoV (Reusken et al., 2013d)
Pakistan	565	315 (55.8%) samples exceeded the ELISA signal cutoff. Of these, 223 (39.5%) were confirmed using MN (Saqib et al., 2017)

(*continued on next page*)

Table 1 (*continued*)

Country	Number of camels	Evidence of MERS-CoV infection
Qatar	14	3 (21.4%) nasal samples were positive using RT-PCR (Haagmans et al., 2014)
	105	62 (59.0%) camels showed evidence for virus shedding in at least one type of swab at the time of slaughter (Farag et al., 2015) Antibodies to MERS-CoV S1 were found in 100 of 103 (97.1%) dromedary camels tested by micro-array technology (Farag et al., 2015)
	53	1 (1.9%) nasal swab had full viral genome isolated (Raj et al., 2014)
	33	7 (21.1%) showed evidence for active virus shedding and 5 (15.2%) had viral RNA in camel milk (Reusken et al., 2014)
	10	9 (90%) sera samples had MERS-CoV–specific antibodies. All nasal swab specimens were negative by PCR (Chantal et al., 2016)
Spain (Canary Islands)	105	15 (14%) had protein-specific antibodies against MERS-CoV (Reusken et al., 2013d)
Somalia	86	25 (87.5%) dromedary camels were positive for MERS-CoV antibodies using MN (Muller MA et al., 2014)
Sudan	60	49 (81.7%) dromedary camels were positive for MERS-CoV antibodies using MN (Muller MA et al., 2014)
Tunisia	204	Seropositivity was 30% for animals ≤2 years of age and 54% for adult dromedary camels (Chantal et al., 2014)
UAE	1113	42 (3.7%) nasal swabs yielded positive results (Muhairi et al., 2016)
	843	786 (93.2%) sera samples were positive for antibodies against MERS-CoV (Sung Sup et al., 2015)
	11	9 (81.8%) sera samples were positive for antibodies supported by similar results in a MERS-CoV recombinant partial spike protein antibody ELISA (Alexandersen et al., 2014)
	651	632 (97.1%) had antibodies against MERS-CoV (Meyer et al., 2014)
	376	108 (28.7%) nasopharyngeal samples positive for MERS-CoV (Li et al., 2017)
	254	234 (92.1%) sera samples were positive for MERS-CoV IgG (Sung Sup et al., 2015)
	6	6 (100%) nasopharyngeal swabs tested positive for MERS-CoV (Paden et al., 2018)

2015 (Modjarrad et al., 2016). Recent updates on product research and development, presented at the Global Technical Meeting, are below.

2.1. Diagnostics

The nonspecific, and sometimes unusual, clinical presentation of MERS in humans, makes early diagnosis difficult in health care facilities. While several highly specific and sensitive molecular and serologic assays exist for diagnosis in animals and humans (Drosten et al., 2014; Corman et al., 2012a, 2012b; Lu et al., 2014; Perera et al., 2013a; Reusken et al., 2013b; Müller et al., 2015; Song et al., 2015), there was a clear call from representatives from affected countries for the development of a rapid diagnostic test to improve identification and isolation of primary human cases in health care facilities. A full landscape analysis of MERS-CoV diagnostics will be published separately (Van Kerkhove, personal communication).

2.1.1. Therapeutics

At the Global Technical Meeting, several therapeutics (including convalescent plasma, lopinavir/ritonavir, ribavirin, interferon and novel therapies including polyclonal antibodies and broad-spectrum antivirals) in development were presented. However, small case numbers make the evaluation of their impact on morbidity and mortality from MERS-CoV infection difficult (Arabi et al., 2017a; Arabi et al., 2017b; Arabi et al.; Al-Dorzi et al., 2016; Sheahan et al., 2017; Ko et al., 2018; Arabi et al., 2017c). Several pre-clinical and phase I-III studies are under way or in the design phase (outlined by the WHO R&D Blueprint: http://who-blueprint-mapping-tool.surge.sh/). WHO is currently evaluating all available evidence on therapeutics to update guidance on clinical management of patients and in the process to develop standardized clinical trial protocols that could be used in affected countries to evaluate promising therapeutic candidates.

2.2. Vaccines for humans

WHO has identified target product profiles for MERS-CoV vaccines which include a dromedary camel vaccine for the reduction of zoonotic transmission, a human vaccine for long term protection of high risk individuals, such as those working with infected dromedary camels or health care workers, and a human vaccine for reactive use in outbreak settings (World Health Organization, 2017b).

Currently, no MERS-CoV-specific or licensed human vaccines are available (Modjarrad et al., 2016; World Health Organization, 2017c). Several human vaccine candidates for coronaviruses, including MERS-CoV, are at various stages of development and five general vaccine technology platforms have been developed and target the MERS-CoV spike protein (Modjarrad et al., 2016; Okba et al., 2017). WHO, the Ministry of Health in KSA and the International Vaccine Institute (IVI) have continued to further align efforts to develop coronavirus vaccines (Excler et al., 2016) and the Coalition for Epidemic Preparedness and Innovation (CEPI) has included MERS-CoV as one of three priority pathogens for financing of a human vaccine. Understanding correlates for protection and having a reliable animal model remain essential for evaluating coronavirus vaccine candidates, including MERS-CoV.

2.3. Vaccines for camels

There was a clear call from Global Technical Meeting participants to accelerate the development of a dromedary camel vaccine in order to evaluate the potential to reduce spillover transmission to humans. The acceptability, cost-effectiveness and feasibility of a dromedary camel vaccine will also need to be evaluated and compared to other intervention strategies, such as human vaccination of high risk groups (e.g., those with occupational exposure). Because MERS-CoV is endemic in dromedary camel populations in the Middle East and elsewhere, multiple intervention strategies, including personal protective measures and the strategic implementation of a camel vaccine, are likely needed to reduce transmission from dromedary camels to humans.

Table 2
List of prioritized research and progress on MERS-CoV research, as discussed at the September 2017 meeting. *Based on an enhanced understanding of the virus, the Doha Declaration (FAO, 2015) is undergoing revision with a focus on guiding surveillance techniques, management of dromedary camels shedding the virus, research, regional and inter-sectoral coordination, risk communication, food and environmental safety practices, and biosecurity measures. The update includes explicit guidance on import testing, quarantine procedures, and management of shedding animals. These recommendations and priority actions in the Doha Declaration will be delivered as a separate document after validation by stakeholders in affected and at risk countries.

Population focus	Prioritized research*	Progress since the September, 2017 Meeting
In dromedary camel populations*	• Conduct natural history studies and evaluate evidence of re-infection • Conduct value chain and production system analyses • Improve surveillance to evaluate seasonal/temporal variation, if any, in camel viral shedding • Identify critical points for interventions and interruption of within species and zoonotic transmission • Accelerate the development of vaccine candidates	• The report "MERS-CoV at the Animal-Human Interface – An Update of the 2015 Doha Declaration" published outlining priority actions in surveillance, testing of animals at quarantine and entry points, management of PCR positive dromedary camels, coordinated outbreak investigation of community acquired cases with dromedary exposure, food safety and environmental contamination, risk communication and awareness raising for MERS-CoV among animal owners and intersectoral collaboration and coordination • Repeat cross-sectional and cohort surveillance studies ongoing in dromedary camels in Jordan, Egypt, Ethiopia, Kenya. • FAO protocol on repeat cross-sectional and cohort surveillance studies dromedary camels *available upon request.* • Camel value chain analysis ongoing in Jordan, Egypt, Ethiopia, Kenya. • WHO-IVI Joint Workshop on MERS-CoV human and dromedary vaccines, 26–27 June 2018 Seoul, Korea
At the animal-human interface	• Map virus circulation and geographic range of MERS-CoV in humans and dromedary camels • Evaluate geographic extent of spillover to humans in Africa, the Middle East and South Asia • Conduct animal/human serological and virological studies in specific locations to evaluate risk factors for human infection and exact routes of zoonotic transmission, including food/oral routes, if any • Conduct social science and anthropological studies to describe and quantify exposures to dromedary camels and identify opportunities for risk-mitigating interventions	• Revision of camel/human field study methodology (WHO-Protocol and questionnaires available: Cross-sectional seroepidemiologic study of MERS-CoV infection in high-risk population sin contact with dromedary camels) published • Camel/human field studies are ongoing/or planned in Algeria, Egypt, Ethiopia, Kenya, Mauritania, Niger, Pakistan and Sudan. • Protocol developed: Anthropological study to describe and general population contact patterns with dromedary camels (WHO protocol available upon request: *Multi-site study to describe frequency and patterns of contact with dromedary camels, and assess other potential and known risk factors for MERS-CoV infection* • National and sub-national Rapid-response team training involving human and animal health sectors developed and implemented in several at risk countries in the Middle East and Africa • MERS-CoV Situational Updates provided by FAO and WHO monthly
In human populations	• Accelerate the research, development, implementation and evaluation of medical countermeasures to reduce morbidity and mortality associated with MERS • Identify the risk factors for healthcare workers in hospital settings and role of administrative and environmental control for transmission of infection • Understand the role of silent/asymptomatic cases in transmission of infections in humans and whether any specific behaviors may result in human infection form non-human sources; • Conduct targeted epidemiological studies in clinical settings to better understand immune response and duration of infectiousness • Integrate testing for MERS-CoV into existing respiratory disease surveillance systems to identify extent and spectrum of mild infection in the community	• WHO-IVI Joint Workshop on MERS-CoV human and dromedary vaccines, 26–27 June 2018 Seoul, Korea • Funding for development of clinical trial protocols for MERS treatment and vaccines received and protocols in development in consultation with WHO R&D Blueprint and affected member states. • Country workshops held to integrated MERS-CoV preparedness and response plans into larger national respiratory disease preparedness and response plans • MERS-CoV virus persistence studies ongoing under experimental conditions • Protocol developed (available upon request) to provide guidance on the collection of surface samples to evaluate MERS-CoV persistence in hospital settings where MERS patients are treated

At least two promising camel vaccine candidates are currently in development and being evaluated in field trials (Haagmans et al., 2016; Alharbi et al., 2017). Stakeholders agreed that the current funding mechanisms need to include risk-mitigating options that target the animal-human interface to prevent zoonotic transmission. These funding pathways would enable the development of camel vaccine candidates. Stakeholders also agreed that prior to camel vaccine implementation, consultation with camel owners and government agencies, feasibility studies including exploring opportunities for commercial manufacturing and incentives for camel vaccination and an assessment of potential trade implications, would all be critical.

In June 2018, WHO and the International Vaccine Institut (IVI) held a joint workshop update the status of human and animal MERS-CoV vaccine development, and identify and prioritize activities to accelerate vaccine research and development. The meeting was held in Seoul, Korea on 26–27 June and included 120 experts and professionals from industry, academia, international organizations and government agencies around the world, including the Coalition for Epidemic Preparedness Innovations (CEPI), the Korean Ministry of Food and Drug Safety (KMFDS) and the Korea Centers for Disease Control and Prevention (KCDC).

3. The way forward

The Global Technical Meeting served as an opportunity to review the available evidence and best practices for control of this epidemic threat six years after the virus was first detected in humans. This covered our understanding of the virus, our ability to detect and respond to cases in animal and human populations, how we communicate our findings and how our work impacts policy decisions to protect animals and prevent human infections.

During the Global Technical Meeting, the latest findings from scientific studies and knowledge gained from collaborative research and surveillance were shared across animal, environmental and human sectors. FAO, OIE and WHO strongly believe that to effectively address zoonoses, including MERS-CoV, a One Health approach to prevent, detect, contain, eliminate and respond to animal and public health risks from zoonotic high threat respiratory pathogens such as MERS-CoV and should involve all relevant sectors, the public and animal health and academic research community, industry and affected communities. We acknowledged the progress that has been made, and importantly, discussed the challenges that need to be addressed so that we can minimize the future public health and economic impacts of this epidemic prone virus. Our aim was to articulate a clear action plan to address these remaining unknowns and to foster better collaboration between sectors and with subject matter experts willing to support member states.

Given the marked expansion in research related to MERS-CoV conducted in the past two years, FAO, OIE and WHO agree that global surveillance and research activities must now be focused on achieving the following major public health goals: reducing zoonotic transmission, detecting and identifying suspected cases early, providing safe and effective treatment to reduce human morbidity and mortality, and significantly reducing human-to-human transmission in health care settings.

The critical needs for research and technical guidance identified during the Global Technical Meeting have been used to inform the WHO R&D MERS-CoV Roadmap (Modjarrad et al., 2016) and a broader Research Agenda for MERS-CoV and other high threat coronaviruses. This research agenda serves as a catalyst to focus, align and mobilize partners to address outstanding knowledge gaps in relation to MERS-CoV across five technical areas:

i) virus origin and characteristics,
ii) epidemiology and transmission,
iii) clinical management and infection prevention and control,
iv) product development and implementation (Modjarrad et al., 2016) and
v) impact of interventions and operational research. The meeting identified a large number of remaining priorities and the organizing committee has summarized the main research needs in Table 2.

Now is the time to devote more effort to long term planning for MERS-CoV. We believe more focused efforts in our activities and investments to address scientific and public health research questions, accelerate promising medical interventions and are more strategic on where activities are conducted globally will go further to address remaining public health unknowns. While there have been improvements in the ability to prevent human-to-human transmission once a MERS case is identified, these are not sufficient to prevent a large event with substantial public health and economic consequences.

Competing financial interests

The authors have no competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/mmcdoino.

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