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# Knowledge gaps in therapeutic and non-therapeutic research on the Middle East respiratory syndrome

3 years after the first identified case of the Middle East respiratory syndrome coronavirus (MERS-CoV) infection, no specific treatment with proven effectiveness exists. More than 1600 people infected with the virus from 26 countries have been reported to WHO, including more than 600 related deaths.[1] As a result of a large hospital outbreak at King Abdulaziz Medical City, Riyadh, Saudi Arabia,[2] between August and September, 2015, the Saudi Arabian Ministry of National Guard Health Affairs organised a 2 day research initiative workshop on Sept 9–10, 2015, to make recommendations for therapeutic (panel 1) and non-therapeutic (panel 2) research on MERS-CoV. Recognising the crucial role of scientific and political partnerships, the Ministry of National Guard Health Affairs invited key representatives of regional and international health agencies and experts in basic and translational science, diagnostics, therapeutics, epidemiology, infection prevention and control, clinical research, and public health. Several pharmaceutical companies presented the status of MERS-CoV treatment candidates in development. Primary objectives were to exchange knowledge and prioritise potential treatments for assessment in clinical trials in Saudi Arabia.

Promising treatments discussed at the meeting included immunotherapy with MERS-CoV-specific antibodies (convalescent plasma, monoclonal, or polyclonal antibodies) in addition to several new and repurposed small molecule drugs. All of these candidates will need to be assessed in phased clinical trials after demonstration of

***Panel 1:* Key recommendations for MERS-CoV treatment from the research initiative workshop**

- Although much fundamental preclinical study has been done, further assessment of the most promising drugs with appropriate animal models is the optimum next step before clinical trials are started
- These preclinical studies should begin immediately, with clinical studies beginning soon after
- In view of the episodic nature of Middle East respiratory syndrome coronavirus (MERS-CoV) infections in human beings and generally low numbers of cases at hospitals or health-care systems, international collaboration among scientists, clinicians, hospitals, extra-hospital health sectors, regulators, and funders is key for efficient and effective implementation of these clinical trials
- An efficient stepwise approach to the generation of scientifically valid clinical research has to drive and inform eventual incorporation of new treatments into clinical practice
- Relevant parties should continually assess progress, including a multisectoral follow-up meeting to incorporate the most advanced data to better inform the care of patients with MERS-CoV
- Standardised case report forms should be developed to accommodate observational studies and clinical trials, with tiered data collection requirements that reflect the varying capacity for research across different environments and the standard definitions of variables that allow data to be combined across multiple studies or trials.[3,4] These forms will help to create integrated databases that include epidemiological, microbiological, immunological, and clinical data; specimen repositories; and storage banks to inform subsequent MERS-CoV scientific inquiry
- With an understanding of the risks associated with development of a new treatment, researchers should use a portfolio approach to assess multiple complementary approaches and should prioritise the approaches that are most advanced in the scientific and development process for first assessment.
- A therapeutics research infrastructure should consider an adaptive clinical trial design that allows either efficient sequential or parallel assessment of treatments, in comparison with a concurrent control group— ideally taking the form of an allocation-concealed, randomised, blinded (to the intervention) clinical trial
- Outcomes and endpoints for clinical trials should be realistic. Although demonstration of a reduction in mortality is the ideal goal of any treatment-based clinical trial, the ability to validly show a mortality reduction can be hampered by the likelihood that an absolute mortality reduction greater than 5–10% is, historically, unlikely for many interventions and especially so when used after an infection has caused severe illness and organ dysfunction, and by the likely infeasibility for studies to enrol the thousands of patients necessary to show a less than 10% absolute reduction in mortality. Therefore, although measuring mortality is essential, trials should consider other important endpoints, including biological markers of effect (eg, viral load in biological samples), especially for early phase clinical assessments

***Panel 2:* Studies to address non-therapeutic research gaps for MERS-CoV from the research initiative workshop**

**Studies in man**

- Undertake population-based seroprevalence studies to improve understanding of the full extent and severity profile of Middle East respiratory syndrome coronavirus (MERS-CoV) infection, as opposed to only detecting the sickest patients[5,6]
- Study the serological response over time in patients infected with MERS-CoV to inform optimum sequencing of immunological and non-immunological-based treatments
- Identify specific and modifiable risk factors for MERS-CoV infection in primary patients infected from non-human sources, and in hospital infected cases (requiring control populations)[1,5]
- Undertake collaborative case series and cohort studies to identify predictors and prognostic markers of worsening illness, which might help to identify at-risk patients for specific interventions
- Assess MERS-CoV associated pathophysiology through safely performed, substitute decision maker-consented biological specimen and post-mortem tissue sampling
- Improve understanding of the mechanisms and durations of viral shedding to inform physicians of the infectious potential of asymptomatic and clinically recovering patients
- Assess the modes of virus transmission in health-care settings, including viral endurance in the environment and the potential role of airborne and droplet transmission to human beings, to inform infection prevention and control measures[1,5]
- Establish the operating characteristics of different specimens (eg, nasopharyngeal swab, induced sputum, tracheal aspirates, bronchoalveolar lavage, urine, and blood) and diagnostic tests to achieve rapid, highly sensitive, and specific test algorithms to assist rapid and efficient case identification and treatment
- Establish viral kinetics over time in patients infected with MERS-CoV
- Assess the effect of adherence to infection prevention and control procedures in hospitals on nosocomial transmission risk

**Studies in animals and assessment of camel-to-human transmission**

- Undertake prevention studies, including animal and human vaccine development
- Adopt one-health approach, including research to improve understanding of transmission at the animal–human interface of MERS-CoV and the role of vaccines for both animals and human beings[5]
- Assess the potential for MERS-CoV to cause reinfection in dromedary camels and human beings after primary disease or vaccination, or both, and the characteristics leading to prolonged active infections
- Undertake anthropological studies to inform knowledge on animal–human interactions and camel-to-human transmission
- Characterise the reservoir of infection in animals, including viral shedding in dromedaries and camel-to-camel transmission[7]

safety and anti-MERS-CoV efficacy in appropriate animal models. At present, none of these treatment candidates have sufficient clinical data to support their use in clinical care. Because this knowledge base is evolving dynamically, new evidence should be continually reassessed.

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We declare no competing interests.

1 WHO. Middle East respiratory syndrome coronavirus (MERS-CoV). http://www.who.int/csr/disease/coronavirus_infections/en/ (accessed Nov 23, 2015).
2 Kingdom of Saudi Arabia, Ministry of National Guard Health Affairs. Preventive measures upgrade to address coronavirus in KAMC-R. http://ngha.med.sa/English/MediaCenter/News/Pages/XVAugVI.aspx (accessed Nov 23, 2015).
3 Dunning JW, Merson L, Rohde GG, et al. Open source clinical science for emerging infections. *Lancet Infect Dis* 2014; **14:** 8–9.
4 Van Kerkhove MD, Broberg E, Engelhardt OG, Wood J, Nicoll A, CONSISE steering committee. The consortium for the standardization of influenza seroepidemiology (CONSISE): a global partnership to standardize influenza seroepidemiology and develop influenza investigation protocols to inform public health policy. *Influenza Other Respir Viruses* 2013; **7:** 231–34.
5 Ben Embarek PK, Van Kerkhove MD. Middle East respiratory syndrome coronavirus (MERS-CoV): current situation 3 years after the virus was first identified. *Wkly Epidemiol Rec* 2015; **90:** 245–50.
6 WHO. Middle East respiratory syndrome coronavirus (MERS-CoV): summary of current situation, literature update and risk assessment. July 7, 2015. http://www.who.int/csr/disease/coronavirus_infections/risk-assessment-7july2015/en/ (accessed Nov 26, 2015).
7 Food and Agriculture Organization of the United Nations. Regional workshop on MERS-CoV and One Health. Doha Declaration. April 27–29, 2015. http://www.fao.org/ag/againfo/programmes/en/empres/documents/docs/Doha_Declaration_2015.pdf (accessed on Nov 26, 2015).