



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



ELSEVIER

EDITORIAL



<http://www.elsevier.com/locate/jiph>



The Middle East respiratory syndrome puzzle: A familiar virus, a familiar disease, but some assembly still required

Research and observations to date have provided some of the pieces for the Middle East respiratory syndrome (MERS) puzzle, but more are needed. MERS-coronavirus (CoV) appears to be an enzootic, seasonal cause of upper and lower respiratory tract infections in African and Arabian Peninsula camels [1]. Camel trading may have a role in distributing the virus [2,3]. Transmission of MERS-CoV from camels to humans occurs rarely and transmission between humans is sporadic and inefficient. MERS-CoV does not currently pose a pandemic threat despite detection in two dozen countries.

Disease course and the proportion of fatal cases

In the Kingdom of Saudi Arabia where 89% of human cases have been found, severe MERS is notable for its impact among older men with comorbid diseases including diabetes mellitus, cirrhosis and various lung, renal and cardiac conditions [4,5]. Among confirmed cases, fever, cough and upper respiratory tract signs and symptoms occur first, followed within a week by progressive lower respiratory tract distress and lymphopaenia [5]. Patients often present to a hospital with pneumonia (or worse) and secondary bacterial infections have been reported [5,6]. Disease can progress to acute respiratory distress syndrome and multiorgan system failure [5]. MERS has killed approximately 40% of reported cases but this is very likely to be an inflated value [7]. No specific antivirals or vaccines exist; a range of therapeutic options have been tried with no evidence to date of clear or consistent benefit.

Immediate detection of the virus

MERS-CoV is a relatively stable virus with an RNA genome of approximately 30,000 nucleotides. It uses dipeptidyl peptidase 4 as a receptor molecule and it grows more rapidly and destructively in culture than SARS-CoV [3]. Laboratory confirmation of infection is routinely by RT-PCR with lower respiratory tract samples conferring the best positivity rates [5]. Viral RNA has also been detected in human and camel upper respiratory secretions more than a month after initial detection and in human sera, urine and stool two weeks or more after symptom onset as well as in camel faeces and rarely in household contacts' throat swabs [8–11].

Retrospective detection of viral infection

The widespread seropositivity of camels has been well defined [3]. Studies of health worker or household contacts of confirmed cases, adult blood donors or children hospitalized with unspecified lower respiratory tract disease have not reported neutralizing antibody to MERS-CoV [12–14]. Similarly, human sera from animal workers have not contained neutralizing antibodies [13,15]. Here, antibody absence may reflect sampling from 2012 or earlier, before MERS-CoV had established itself. Alternatively, current serological assays may not be sufficiently sensitive to detect seroconversion in mild and subclinical disease, or such cases may not mount an immune response. However, a recent large study of sera, mostly collected

<http://dx.doi.org/10.1016/j.jiph.2015.07.001>

1876-0341/© 2015 Published by Elsevier Limited on behalf of King Saud Bin Abdulaziz University for Health Sciences.

after 2012, successfully identified seroconversions among 0.15% of human sera from six of the Kingdom's 13 provinces. Antibodies were present more frequently among those occupationally exposed to animals, but often without a remembered history of illness [16]. Given the low proportion, it is not surprising that a much smaller number of sera collected in 2014 did not show evidence of seroconversion among camel herders and others despite close camel contact [17]. MERS-CoV RNA is shed from mild or subclinical infections, explaining how MERS-CoV transmission could side-step the camel and also why fewer than half of human cases report camel contact [2,18]. The description of a health worker who shed viral RNA from the upper respiratory tract for more than 40 days without signs of disease further supports the concept of occult spread [9].

Partial and missing pieces characterize the MERS puzzle

Despite changes to healthcare leadership over the past three, the Kingdom has continued to publicly communicate deidentified case information. These data harbour gaps, errors and inconsistencies in need of correction, but have generally been more useful than those made public during other recent emerging viral outbreaks including influenza A(H7N9) virus in China or H5N1 in Egypt.

Well-planned case–control studies have yet to be conducted for MERS and, while unjustified as a routine procedure, PCR-based testing of contacts and less severe community acute respiratory illnesses could provide valuable interim data applicable to any emerging and poorly understood human pathogen. Such testing is currently not recommended in the Kingdom, but close monitoring and investigation of all contacts, including asymptomatic contacts, is a recommendation of the World Health Organization (WHO) [19] and has proven feasible elsewhere. For a newly emergent virus which currently appears to kill two-fifths of those whom it infects, such additional testing may deduce a smaller proportion of fatal cases and better determine the extent of active yet mild MERS-CoV infection in the wider community [7].

Not all MERS-CoV infections lead to severe disease and death but the true proportion that have, remains unknown. Human CoVs (229E, OC43, HKU1, NL63) may cause a similar impact in the Kingdom's older male and comorbid population as may other

respiratory viruses, yet the prevalence and impact of most non-influenza respiratory viruses remains unclear. More respiratory virus epidemiology will better quantify the damage viruses cause to the public health of the Kingdom, where a portion of the male community has, or is working towards comorbidities of kidney, heart and lung disease, combined with obesity.

Animal model data could be developed to understand whether infectious MERS-CoV resides in droplets propelled from ill patients. Also, the real-world risk of self-inoculation from contaminated hard surfaces remains unquantified. Solving these mysteries could inform transmission reduction. Non-human primates could prove most useful here, not only to examine the infectivity of droplets but also that of spiked milk and meat preparations to test the hypothesis that infection may occur after ingestion.

It is unknown whether mild or subclinical human MERS cases shed infectious virus (they do shed viral RNA), produce an antibody response or whether current serological tools have the sensitivity to detect such a response. A suitably powered, prospective cohort study recruiting from several provinces with previously high case loads might be useful to capture the moment of infection, the full spectrum of pathology, viral shedding, seroconversion and to determine the sensitivity of available assays. Use of regular and frequent sampling, collection of detailed clinical histories, completion of electronic diaries and use of RT-PCR and serological testing would create a valuable puzzle-solving resource.

More wild, imported and local farm animal testing in the Arabian Peninsula, and in Africa, will uncover whether animals apart from camels, such as mice, rats, birds, bats or baboons, play a role in harbouring or transmitting MERS-CoV, and other viruses, to humans or camels. Should other animals be involved, their environments may also provide further insight into transmission and complete the holistic 'One Health' approach to understanding current and future emerging viral threats.

In 2015, the annual MERS outbreak began earlier and appears to have been brought under control more quickly than in previous years however sporadic cases and clusters often follow the annual peak. The majority of reported MERS cases occurred in association with a healthcare setting and health worker infections spike as healthcare venues became hubs for viral transmission. It remains unclear if this is where most transmission occurs, or just where the most obvious clinical outcomes collect and are observed. Better selection

and implementation of tried and trusted infection prevention and control measures is needed to reduce human-to-human infections here [19]. Such measures would also reduce transmission of other respiratory viruses, which are capable of increased morbidity and mortality among the Kingdom's at-risk and hospitalized populations.

Incomplete and missing pieces of the MERS puzzle limit our understanding of how and from where MERS-CoV spreads. The knowledge gaps hinder strategic infection prevention and control and restrict the tailoring of public health messages seeking to prevent exposure to infection by breaking habits and generally reducing risk. Finding the missing pieces will also help define how best to clean hospital surfaces during and after a patient's stay, when trained health workers should don protective equipment and what that equipment should be. The aim is to reduce overall morbidity and mortality due to respiratory infections but particularly the seasonal occurrence of MERS-CoV outbreaks in hospitals. The lack of immediacy exhibited by the Kingdom, from where most cases have been reported, continues to draw criticism from many levels [20,21]. Three years on, assembly of the puzzle that is MERS still requires the commitment to collaborate, focus, organize and communicate effectively, leading to outcomes of application and action.

Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Not required.

References

- [1] Wernery U, Corman VM, Wong EY, et al. Acute Middle East respiratory syndrome coronavirus infection in livestock dromedaries, Dubai, 2014. *Emerg Infect Dis* 2015;21(6):1019–22.
- [2] Gossner C, Danielson N, Gervelmeyer A, et al. Human–dromedary camel interactions and the risk of acquiring zoonotic Middle East respiratory syndrome coronavirus infection. *Zoonoses Public Health* 2014.
- [3] Mackay IM, Arden KE. Middle East respiratory syndrome: an emerging coronavirus infection tracked by the crowd. *Virus Res* 2015.
- [4] Thabet F, Chehab M, Bafaqih H, AlMohaimed S. Middle East respiratory syndrome coronavirus in children. *Saudi Med J* 2015;36(4):484–6.
- [5] Al-Hameed F, Wahla AS, Siddiqui S, et al. Characteristics and outcomes of Middle East respiratory syndrome coronavirus patients admitted to an intensive care unit in Jeddah, Saudi Arabia. *J Intensive Care Med* 2015.
- [6] Arabi YM, Arifi AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Ann Intern Med* 2014;160(6):389–97.
- [7] Scientific Advisory Council MoH, Saudi Arabia. Infection prevention/control and management guidelines for patients with Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection; 2014 <http://www.moh.gov.sa/en/CCC/StaffRegulations/Corona/Documents/GuidelinesforCoronaPatients.pdf> [accessed 27.04.15].
- [8] Adney DR, van DN, Brown VR, et al. Replication and shedding of MERS-CoV in upper respiratory tract of inoculated dromedary camels. *Emerg Infect Dis* 2014;20(12):1999–2005.
- [9] Al-Gethamy M, Corman VM, Hussain R, Al-Tawfiq JA, Drosten C, Memish ZA. A case of long-term excretion and subclinical infection with Middle East respiratory syndrome coronavirus in a healthcare worker. *Clin Infect Dis* 2015;60(6):973–4.
- [10] Hemida MG, Chu DKW, Poon LLM, et al. MERS coronavirus in dromedary camel herd, Saudi Arabia. *Emerg Infect Dis* 2014;20(7).
- [11] Drosten C, Meyer B, Muller MA, et al. Transmission of MERS-coronavirus in household contacts. *N Engl J Med* 2014;371(9):828–35.
- [12] Gierer S, Hofmann-Winkler H, Albuali WH, et al. Lack of MERS coronavirus neutralizing antibodies in humans, eastern province, Saudi Arabia. *Emerg Infect Dis* 2013;19(12):2034–6.
- [13] Aburizaiza AS, Mattes FM, Azhar EI, et al. Investigation of anti-Middle East respiratory syndrome antibodies in blood donors and slaughterhouse workers in Jeddah and Makkah, Saudi Arabia, fall 2012. *J Infect Dis* 2014;209(2):243–6.
- [14] Hall AJ, Tokars JI, Badreddine SA, et al. Health care worker contact with MERS patient, Saudi Arabia. *Emerg Infect Dis* 2014;20(12):2148–51.
- [15] Memish ZA, Alsahly A, Masri MA, et al. Sparse evidence of MERS-CoV infection among animal workers living in Southern Saudi Arabia during 2012. *Influenza Other Respir Viruses* 2015;9(2):64–7.
- [16] Muller MA, Meyer B, Corman VM, et al. Presence of Middle East respiratory syndrome coronavirus antibodies in Saudi Arabia: a nationwide, cross-sectional, serological study. *Lancet Infect Dis* 2015.
- [17] Hemida MG, Al-Naeem A, Perera RAPM, Chin AWH, Poon LLM, Peiris M. Lack of Middle East respiratory syndrome coronavirus transmission from infected camels. *Emerg Infect Dis* 2015;21(4).
- [18] World Health Organization. Update 15: summary and literature update as of 9 May 2014; 2014 http://www.who.int/entity/csr/disease/coronavirus_infections/MERS_CoV_Update_09_May_2014.pdf?ua=1 [accessed 24.04.15].
- [19] World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV): Summary of Current Situation, Literature Update and Risk Assessment – as of 5 February 2015; 2015 <http://www.who.int/entity/csr/>

- disease/coronavirus_infections/mers-5-february-2015.pdf?ua=1 [accessed 15.05.015].
- [20] Reuters. Saudi Arabia: U.N. Experts Criticize Response to MERS Virus as Inadequate; 2015 <http://www.nytimes.com/2015/02/24/world/middleeast/saudi-arabia-un-experts-criticize-response-to-mers-virus-as-inadequate.html> [accessed 22.04.15].
- [21] Kelland KR. Special Report — Saudi Arabia takes heat for spread of MERS virus; 2014 <http://uk.reuters.com/article/2014/05/22/uk-saudi-mers-special-report-idUKKBN0E207Z20140522> [accessed 24.04.15].

Ian M. Mackay
*Public and Environmental Health Virology
Laboratory, Forensic and Scientific Services,
Department of Health, Archerfield, Queensland,
Australia*

Katherine E. Arden
*The University of Queensland, St Lucia,
Queensland, Australia*

Available online at www.sciencedirect.com

ScienceDirect