Commentary for Lancet Infectious Diseases

Title:

Confronting the persisting threat of the Middle East Respiratory Syndrome to global health security

Authors:

***Stanley Perlman, Esam I Azhar, David S Hui, Alimuddin Zumla**

Institutional affiliations:

Department of Microbiology and Immunology, University of Iowa, Iowa City, IA, USA; Department of Pediatrics, University of Iowa, Iowa City, IA, USA. (**Stanley Perlman**: Email: stanley-perlman@uiowa.edu)

Special Infectious Agents Unit, King Fahd Medical Research Centre and Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia. (**Esam I Azhar**: Email: eazhar@kau.edu.sa)

Division of Respiratory Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, New Territories, Hong Kong, China; Stanley Ho Center for Emerging Infectious Diseases, The Chinese University of Hong Kong, Prince of Wales Hospital, New Territories, Hong Kong, China. (**David S Hui**. Email: dschui@cuhk.edu.hk)

Division of Infection and Immunity, Center for Clinical Microbiology, University College London, London, UK; and NIHR Biomedical Research Centre, UCL Hospitals NHS Foundation Trust, London, UK (**Alimuddin Zumla**. Email: a.zumla@ucl.ac.uk)

Word count: 883 words

References: 15

*Correspondence: Prof Stanley Perlman: Email: stanley-perlman@uiowa.edu

The Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) is a priority zoonotic pathogen of humans highlighted in the WHO Research and Development (R&D) Blueprint list requiring urgent action[1] because it has epidemic potential, a high fatality rate with no specific treatment or vaccine, and a wide geographical distribution of the host reservoir of dromedary camels in the Middle East, Africa and Asia.[2]

As of April 19th 2019, a total of 2,421 laboratory-confirmed MERS cases, with 870 deaths (CFR: 34.5%) were reported to WHO since September 2012 globally.[3] The majority of these cases (2,031 cases) occurred in the Kingdom of Saudi Arabia (KSA) and the largest outbreak outside the Middle East occurred in South Korea in May 2015 with 186 cases illustrating its epidemic potential.[4] There has been a recent upsurge in MERS cases in the KSA and Oman, with 189 from July 2017 to June 2018 vs. 126 cases in the first quarter of 2019.[3] Worryingly, whilst MERS-CoV continues to circulate in the Middle East, progress in advancing priority R&D on the epidemiology, rapid diagnostics, treatments, vaccines, including regional One-Human-Environmental-Animal Health (ONE-HEALTH) activities[5] have been slow. Importantly, despite numerous WHO MERS expert group and other stakeholder meetings which have defined urgent priority research needs, major knowledge gaps in the epidemiology, transmission, pathogenesis, and phylogenetic evolution of MERS-CoV remain.[6,7]

Major opportunities for conduct of appropriate longitudinal and cross-sectional studies to fill these gaps from the recurrent community and nosocomial outbreaks of MERS in KSA are being missed. In contrast, numerous studies performed after the 2015 MERS outbreak in South Korea, yielded important epidemiological, clinical, virological and management outcome data.[8] MERS-CoV sequence variants were detected during the Korean outbreak, with some mutations incorporated into circulating virus. Remarkably, the most extensively studied mutations, which occurred in the surface(S)glycoprotein[8] were not predicted. The S protein was critical for virus entry and during the Severe Acute Respiratory Syndrome (SARS) epidemic and it evolved to bind more tightly to its cellular receptor. In contrast changes detected in MERS-CoV-surface(S)glycoprotein[9] appeared to decrease binding and were expected to decrease virulence and transmissibility. Alternately, these changes could be beneficial to the MERS-CoV, resulting in evasion of the antibody response.

MERS-CoV transmission occurs in the community, household settings or within healthcare facilities.[2,3] Nosocomial outbreaks were a major feature but have decreased due to increased awareness and implementation of infection control measures.[10] Whilst zoonotic transmission from camels is thought to be the primary mode of transmission, a substantial proportion of patients describe no camel contact.[2,6,10,11] MERS-CoV infection of camels throughout Africa is common although there no convincing serological or virological evidence of human MERS-CoV infection in this continent.[12] The key questions are why did human MERS-CoV infection only arise in the Middle East in 2012 and not in Africa and how do patients without camel contact acquire the disease? Sequence analysis of MERS-CoV isolated from patients in the Middle East revealed mutations in the virus, most of which were transient, with reversion to wild type sequence,[13] inconsistent with continuing adaptation to humans. Many of the virus variants were observed circulating in camels at the same time[14], suggesting continuing camel-to-human transmission, which might have obscured adaptive changes in the human virus. Small differences in sequences were observed when East African and KSA MERS-CoV isolates were compared, with more substantial differences, including deletions detected in West African MERS-CoV.[15] While these differences may contribute to diminished transmission, another possibility is that there may be differences in human-camel contact in Africa and the Middle East. Camel workers and owners have the close contact with camels and thus have higher rates of MERS-CoV immunopositivity (3-67%) than in the general population (0.15%).[11-13] Camel workers have mild or subclinical disease, and they might transmit MERS-CoV either directly or indirectly to more susceptible individuals, such as those with co-morbidities, who would present as sporadic cases.

These studies point to several priority research directions and interventions to decrease the persistent threat of MERS-CoV transmission. *First*, continuous sequence analysis of MERS-CoV in endemic countries are required to establish viral evolution as was the case in the Korea outbreak. *Second*, greater understanding of camel-human interactions and patterns of camel grazing in Africa and the Middle East may provide insight into transmission differences. *Third*, an effective vaccine for humans is the best way to prevent spread of MERS but logistical issues due to small number of sporadic MERS cases in different geographical locations need to be overcome. Alternatively, vaccination of juvenile camels may block transmission. *Fourth*, development of antiviral and other therapies for MERS-CoV would improve patient outcomes and, by decreasing virus burden, would decrease transmission. *Finally*, continued efforts to educate CWs about infection control measures, such as handwashing and wearing protective gear when handling camels, especially juvenile ones with upper respiratory tract infections, will be critical in minimizing transmission.

The persistence of MERS-CoV transmission in the Middle East seven years after first discovery, and the numerous unanswered priority questions regarding MERS [6,7] raised recurrently at WHO

MERS expert group annual meetings, now requires a major stepup change from the current status quo. Serious financial and political commitments, especially from MERS-endemic countries, are required to establish and take forward an effective multidisciplinary ONE-HEALTH consortia forward to establish more effective multidisciplinary research collaborations, if we are to prevent MERS-CoV evolving into the next global pandemic.

Author declarations:

All authors have an academic interest in MERS-CoV. Prof Sir Ali Zumla is a member of the PANDORA-ID-NET Consortium funded by Grant RIA2016E-1609) from the European and Developing Countries Clinical Trials Partnership (EDCTP2) programme and he is in receipt of a National Institutes of Health Research (NIHR) senior investigator award.

References

1. WHO. List of Blueprint priority diseases. 2018. https://www.who.int/blueprint/priority-diseases/en/ -accessed April 24th 2019.

2. Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. Lancet. 2015 Sep 5;386(9997):995-100

3. FAO-WHO. FAO-WHO situation update: MERS-CoV 2019. http://www.fao.org/ag/againfo/programmes/en/empres/mers/situation_update.html - accessed April 19th, 2019.

4. Hui DS, Perlman S, Zumla A. Spread of MERS to South Korea and China. Lancet Respir Med. 2015 Jul;3(7):509-10.

5. Zumla A, Dar O, Kock R, Muturi M, et al. Taking forward a 'One Health' approach for turning the tide against the Middle East respiratory syndrome coronavirus and other zoonotic pathogens with epidemic potential. Int J Infect Dis. 2016 Jun;47:5-9.

6. FAO-OIE-WHO MERS Technical Working Group. MERS: Progress on the global response, remaining challenges and the way forward. Antiviral Res 2018; 159: 35-44.

7. Kelly-Cirino C, Mazzola LT, Chua A, Oxenford CJ, Van Kerkhove MD. An updated roadmap for MERS-CoV research and product development. BMJ Glob Health 2019; 4(Suppl 2): e001105.

8. Kim YS, Aigerim A, Park U, et al. Sequential Emergence and Wide Spread of Neutralization Escape Middle East Respiratory Syndrome Coronavirus Mutants, South Korea, 2015. Emerg Inf Dis 2019; 25(6).

9. Cotten M, Watson SJ, Zumla AI, et al. Spread, circulation, and evolution of the Middle East respiratory syndrome coronavirus. mBio 2014; 5(1). pii: e01062-13. doi: 10.1128/mBio.01062-10.

10. Hui DS, Azhar EI, Kim YJ, et al Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. Lancet Inf Dis 2018; 18(8): e217-e27.

11. Conzade R, Grant R, Malik MR, et al. Reported direct and indirect contact with dromedary camels among laboratory-confirmed MERS-CoV cases. *Viruses* 2018; **10**(8): 425.

12. Chu DKW, Hui KPY, Perera R, et al. MERS coronaviruses from camels in Africa exhibit region-dependent genetic diversity. Proc Natl Acad Sci2018; 115(12): 3144-9.

13. Cotten M, Watson SJ, Zumla AI, et al. Spread, circulation, and evolution of the Middle East respiratory syndrome coronavirus. *mBio* 2014; **5**(1). pii: e01062-13. doi: 10.1128/mBio.01062-13

14. Sabir JS, Lam TT, Ahmed MM, et al. Co-circulation of three camel coronavirus species and recombination of MERS-CoVs in Saudi Arabia. *Science (New York, NY* 2016; 351: 81-4.

15. Chu DKW, Hui KPY, Perera R, et al. MERS coronaviruses from camels in Africa exhibit region-dependent genetic diversity. *Proc Natl Acad Sci*2018; **115**(12): 3144-9