

Tracking the transmission and evolution of MERS-CoV



In 2012, Middle East respiratory syndrome coronavirus (MERS-CoV) first emerged in a patient who died of severe pneumonia in Saudi Arabia.¹ Although most cases confirmed so far in the Middle East have been sporadic with an unknown source of infection, human-to-human transmission has been reported in health-care and household settings.²⁻⁴ However, the source of the virus and mode of disease transmission remain unknown despite detection of a small fragment of sequence identical to the EMC/2012 MERS-CoV in a *Taphozous perforatus* bat captured in Saudi Arabia⁵ and reports of cross-reactive antibodies to MERS-CoV in dromedary camels in Oman and the Canary Islands.⁶

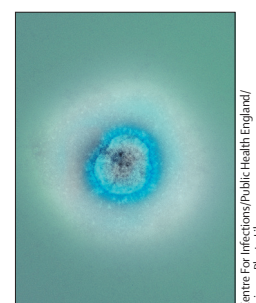
A hospital outbreak of MERS in the eastern province of Saudi Arabia was previously described,³ with full genome analysis of four isolates of the Al-Hasa outbreak combined with five previously identified MERS-CoV genomes. The investigators estimated that the time of most recent common ancestor (tMRCA) was August, 2011 (95% highest posterior density [HPD] November, 2009 to April, 2012), and showed that the four viruses formed a monophyletic clade. The study provided a better understanding of the transmission of MERS-CoV within family clusters^{2,7} and in health-care settings.⁴ Nevertheless, the four cases selected were closely linked epidemiologically within this outbreak involving four health-care facilities.³

In *The Lancet*, Matthew Cotten and colleagues⁸ further describe the geographical distribution and phylogenetic relation of MERS-CoV infections across time in Saudi Arabia. This study represents the largest number of MERS-CoV genomes described so far, with 13 complete and eight partial genomes (30–95% genome coverage) from 21 clinical MERS samples taken from the Al-Hasa outbreak and four other sites in Saudi Arabia (Riyadh, Buraidah, Bisha, and Hafr-Al-Batin). Each of the sequences was derived directly from clinical specimens of patients and thus avoided any mutations that would be introduced by tissue culture passage. The authors report three distinct MERS-CoV genotypes, whereas phylogeographic analyses suggest that the MERS-CoV zoonotic reservoir is geographically dispersed. Furthermore, genetic diversity in the Al-Hasa cluster suggests that the hospital outbreak might have been caused by more than one virus introduction. The

data obtained from clinical MERS samples from the Al-Hasa cluster and community outbreaks has recorded evolution of the MERS-CoV virus in this epidemic within Saudi Arabia, and the sequence variations also reveal remarkable multiple-tree clusters. The study has provided interesting data supporting circulation of MERS-CoV since the middle of 2011, with the estimated tMRCA as July, 2011 (95% HPD July, 2007 to June, 2012).⁸

Although the human exposures that result in infection remain unknown, this study has added the novel finding of three distinct MERS-CoV genotypes in Riyadh, with at least two distinct lineages probably circulating in Riyadh in October, 2012. Disease transmission patterns in the epidemic suggest both human-to-human transmission and sporadic zoonotic events. The current genome sequence set is not adequate to discriminate definitively between single or multiple zoonotic introductions, but the description of the pair of related genomes from Riyadh and Bisha and the description of cases in east and west Saudi Arabia in both major lineages of the tree suggest many zoonotic events. Overall, this is an interesting study that extends earlier findings.^{2,3} Although this report provides neither direct evidence of animal transmission nor the precise mechanism of transmission, the information is useful in tracing the source and transmission of MERS-CoV.⁸

There are some examples of the historical role and scientific value of molecular methods in tracing emerging severe acute respiratory infections. After the major outbreaks of SARS-CoV in 2003, researchers in many countries had applied molecular genome analysis to track the viral evolution and spread of the disease.⁹⁻¹¹ PCR has provided the scientific basis for direct examination of clinical samples for evidence of infection. Similar to MERS-CoV, sequence variations were reported in SARS-CoV obtained from different patients in this epidemic.⁹⁻¹¹ Cotten and colleagues⁸ have effectively shown that sequence variations in the MERS-CoV genome can be applied as a powerful molecular method in tracing the route of transmission, when used in conjunction with standard epidemiology. Furthermore, using the publicly released full genomic sequences of SARS-CoV in 2003, various molecular detection methods based on RT-PCR were developed. Most of the diagnostic assays were



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initially focused on RNA extracted from nasopharyngeal aspirates, urine, and stools, but assays based on the analysis of RNA extracted from plasma and serum were later developed.^{12,13} Such blood RNA assays (with one targeted at the nucleocapsid region and the other the polymerase region of the virus genome) allowed the more standardised quantitative expression of viral loads and became useful for early SARS diagnosis, with a detection rate of up to 80% during the first week of illness, when serology diagnosis of SARS was not sensitive at the early stage.^{12,13} These quantitative systems, if available, might be useful for the early diagnosis of MERS-CoV and can provide viral load information that might facilitate prognostic assessments of an infected individual.

With the increasing number of sporadic cases of MERS in the Middle East, more research is needed into the mode of transmission and exposures responsible for the sporadic introductions of MERS-CoV into human populations. Development of rapid and reliable diagnostic assays is also urgently needed so that health authorities can take appropriate public health measures to interrupt disease transmission and contain the virus.

David S Hui

Department of Medicine and Therapeutics, and Stanley Ho Centre for Emerging Infectious Diseases, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China
dschui@cuhk.edu.hk

I declare that I have no conflicts of interest.

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