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.

42

An Overview of Middle East Respiratory Syndrome in the Middle East

ARSHAD HAROON TOOSY AND SEAN O'SULLIVAN

Introduction

Middle East respiratory syndrome (MERS) is an emerging infectious zoonotic disease caused by a novel coronavirus (CoV). MERS was first reported in 2012 in Jeddah, Kingdom of Saudi Arabia (KSA), and in Jordan, respectively.[1] The disease was considered a potential pandemic threat to public health in the Persian Gulf region.[2] (See also Chapter 19.)

Most known CoVs infect and circulate in animals, mainly bats, but a number of CoVs are known to cause human disease (see also Chapter 40).[3–5] The rapid emergence of MERS-CoV coupled with its limited geographic distribution has led to the suspicion that this is a zoonotic disease with an animal reservoir,[4] and the evidence supports the hypothesis that dromedary camels (DCs) are the reservoir host. In DCs MERS-CoV causes a mild, transient upper respiratory tract (URT) infection.[4–6]

A mild or asymptomatic disease has also been reported in humans, but this is not always the case. MERS-CoV infection in humans often results in a severe, life-threatening disease of the lower respiratory tract (LRT), with high mortality.[1,2,5] Immunocompromised, elderly people and those with comorbidities, usually with a history of close contact with infected DCs, are particularly susceptible.[7,8] In such cases the disease progresses rapidly, resulting in multiorgan failure and acute respiratory distress syndrome. Between 2012 and April 7, 2017, a total of 1936 confirmed human cases were reported to the World Health Organization (WHO), resulting in 690 fatalities (crude case fatality rate of 36%; see Fig. 42.1).[1,9] Potential clinical cases of MERS in DCs must be reported to the World Organisation for Animal Health (OIE) as an emerging infectious disease.[10]

Virology

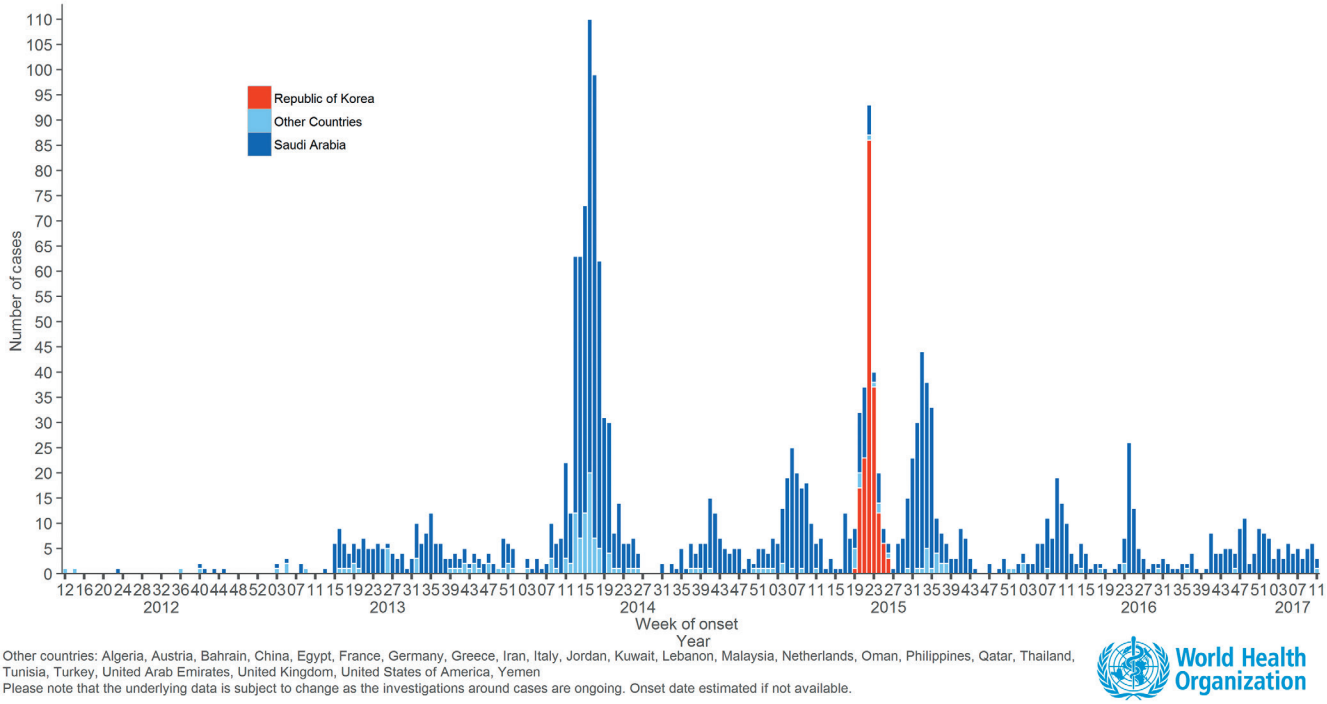
MERS-CoV is a member of the subfamily Coronavirinae, genus *Betacoronavirus*, subgroup lineage 2c.[11] MERS-CoV is a positive-sense enveloped single-stranded RNA virus and is the first lineage of 2c *Betacoronavirus* known to infect humans.[2,8] It is more closely related to bat CoVs HKU4 and HKU5 (lineage 2c) than to the severe acute respiratory syndrome CoV (SARS-CoV, (lineage 2b).[2,3] Recent genome sequencing analysis reported the genomic evolution rate (1.12×10^3 substitutions per site), suggesting that MERS-CoV diverged from its viral ancestor in March 2012.[12]

Analysis of human MERS-CoV sequences has identified several circulating genotypes. These distinct genotypes are phylogenetically classified into clades A, B, and, most recently, C, which correlate with outbreaks of MERS among humans.[4,5,8,12] The emergence of divergent MERS-CoV clades in humans since 2012 is consistent with several independent sporadic introductions into the human population from an animal reservoir, of which the camel was unquestionably the source.[6,8,12,13]

Pathogenesis

Host cell entry of MERS-CoV is mediated by the binding of MERS spike (S) proteins to a specific cellular receptor known as dipeptidyl peptidase 4 (DPP4).[11] DPP4 is expressed on the epithelial and endothelial cells of most human organ tissues in ex vivo studies using human tissue culture lines; this may account for the multisystem clinical spectrum of the MERS-CoV infection.[2,14]

A strain cultured from a fatal human case was experimentally inoculated into three DCs using intratracheal, intranasal, and conjunctival routes.[15] A mild transient disease resulted in submucosal inflammation and necrosis in the URT and LRT, but the alveoli remained unaffected.[15] Experimental inoculation of rhesus macaques *(Macaca mulatta)* and common marmosets *(Callithrix jacchus)* resulted in mild to severe LRT disease causing multifocal interstitial pneumonia in the macaques and extensive fatal pneumonia in the marmosets.[2,14,16]



• **Figure 42.1** Epicurve: global confirmed cases of Middle East respiratory syndrome–coronavirus (MERS-CoV), reported to the World Health Organization as of April 7, 2017 (*n* = 1936). (Reprinted from WHO Emergencies: MERS-CoV. <http://www.who.int/emergencies/mers-cov/en/>.)

Epidemiology

MERS-CoV belongs to a lineage commonly associated with bats, the closest relatives of which lineage were recently identified in Vesper bats (i.e., various species of the family Vespertilionidae) from Europe, Asia, and South Africa. Initial research efforts have focused on establishing an epidemiologic link between bats and humans.[3,4,6,17] There is no conclusive evidence to support the theory that bats are the source of human infection, although there is consensus that bats are the ancestral hosts of the disease.[4,5,17] A related MERS-like CoV virus, isolated from an African pipistrelle bat *(Pipistrellus hesperidus)* in Uganda, has shown high divergence of the S protein nucleotide sequence compared with an index MERS-CoV S protein sequence (46% amino acid identity divergence).[17] This suggests that the two viruses differ significantly in receptor binding properties, implying that the MERS-like CoV virus is not a zoonotic threat and supporting the theory of a common ancestry.[17]

To date the only direct link between bats and human disease was a single instance when an RNA sequence from a fatal human MERS index case showed a 100% nucleotide match of a polymerase chain reaction (PCR)–amplified sequence of a fecal pellet from an Egyptian tomb bat *(Taphozous perforates)* collected in the same area of Bisha, KSA.[18] The human fatality was an owner of four DCs, which also tested positive for the same strain of MERS-CoV.[18] At present, bat-to-human infection by MERS-CoV is considered to be purely speculative.[4]

Surveillance of DCs in KSA has shown that MERS-CoV clade B has been enzootic in the camel population in Arabia since at least 1992.[13] Several MERS-CoV serologic surveys confirm that the disease is not present in domesticated livestock (namely, horses, sheep, goats, and cattle) and is enzootic in the DC population across the Arabian Peninsula as well as in North and East Africa.[6,7,13,15,19–23] Historically, the camel was the mainstay of land-based trade transportation and was used extensively as a food source across the entire region prior to industrialization during the latter part of the 20th century.[5,10] The free movement of humans and animals across the region supports the widespread prevalence and genetic diversity of MERS-CoV in the DC populations of Arabia and East Africa today.[5,10]

The temporal dynamics of MERS infection in DCs in Al-Ahsa, KSA, was examined by collecting nasal swabs and lung tissue during postmortem examination from two independent groups of animals over the course of a year and testing these for MERS-CoV RNA by real-time reverse-transcriptase polymerase chain reaction (RT-rtPCR).[24] Positive samples were typically associated with young immunologically naive animals (<4 years of age) rather than adults (>4 years of age). Seasonal peaks were detected during the winter months and coincided with the calving season, less extreme environmental conditions, cooler ambient temperatures, and higher relative humidity, for the transmission of infection amongst susceptible individuals.[24] This seasonal peak has also been described in epidemic nosocomial outbreaks in humans that occur more frequently during the winter months.[25,26]

Extensive virologic evidence has been accumulated since 2012 supporting the epidemiologic link between DCs and humans in the transmission of MERS-CoV, although

strategic serosurveys of humans using samples collected after 2012 have been infrequent.[4,5,10] There is a paucity of baseline data to describe the proportion of the potentially infected human population for much of the Arabian Peninsula and all of East Africa, including the Horn of Africa.[10]

Transmission

The exact mechanism of transmission from camels to human remains uncertain.[10] Sustained close contact is most probably necessary for transmission by aerosolized droplets, as MERS-CoV viral RNA has been detected in air samples from a barn housing infected DCs in Qatar, and the virus may remain viable in aerosol for up to 45 minutes.[10,27–29] The potential public health risk resulting from aerosol-generating activities ranges from contamination of a room occupied by a symptomatic patient to slaughter practices.[8,24,30]

Aerosolized transmission of MERS-CoV has been attributed to hospital outbreaks in KSA and South Korea.[26,27,29] MERS-CoV spreads inefficiently from human to human, but transmission is effective in a hospital environment, where susceptible individuals are concentrated and the risks are amplified by poor infection prevention and control (IPC) protocols.[8]

In some reported cases of MERS, direct contact with camels was not apparent.[27,29] Camel-to-human transmission through other routes is, however, possible owing to the consumption of unpasteurized camel milk or raw camel meat and in traditional medicine, when camel urine is consumed as a natural remedy for a variety of ailments.[3,10] A recent survey has found that infected camels may shed MERS-CoV virus in milk and urine, and the virus has been shown to remain infectious for 3 days in milk stored at 4°C.[3,10] The transmission risks associated with the handling of camel products, raw milk, urine, and meat during animal slaughter are yet to be fully elucidated. Further studies are needed to demonstrate the potential of camel-to-human transmission.[8]

Diagnosis

Serologic methods with high sensitivity and specificity to detect MERS-CoV antibodies have been developed for use in seroepidemiologic studies. Methods include indirect immunofluorescence assays, enzyme-linked immunosorbent assays (ELISAs), protein microarray technology, and microneutralization (MN) assays.[13,20–22] Pseudoparticle virus neutralization tests (ppNTs) and conventional MN assays have also been used to detect neutralizing antibodies to MERS-CoV.[18]

Validated molecular assays have been developed.[10,13,19] RT-rtPCR is the preferred diagnostic method for the detection of MERS-CoV and has been endorsed by the WHO.[1] Confirmation of MERS in suspected cases requires the screening of samples targeting a number of genes specific to MERS-CoV, namely Up E, ORF 1a, ORF 1b, and N genes.[1,10,13,19]

Genetic deep sequencing methods (i.e., high-throughput sequencing) have been readily available to researchers since the disease was first reported.[12] Sequenced data have been used in these cases to successfully construct the phylogenetic tree between related viruses and hosts.[2,6,7,12]

Direct MERS-CoV antigen detection is possible but has been rarely performed.[10] Immunochromatography assays and monoclonal antibody-based capture ELISAs targeting the MERS-CoV nucleocapsid protein have been described.[20]

Since the virus was first reported in 2012, a range of comprehensive laboratory tests has been developed.[10,30] To better understand the disease, it has been important to collate sampling methodology data, laboratory results, and analyses in combination with clinical and epidemiologic data.[10] Until laboratory assays are fully validated, a combination of molecular and serologic laboratory tests is required to improve confidence in laboratory diagnosis during outbreaks.[30] In cases of mild or asymptomatic infection, full validation of serologic assays is required to rule out false-negative results.[31] Validation is also required to successfully apply newly developed diagnostic serology algorithms to inform public health decisions.[10,30,31]

Treatment

Therapeutic options for MERS-CoV are limited. Supportive treatment is indicated for hospitalized patients, but vigilance for complications is essential.[8] Empirical use of antimicrobial agents or steroids has not succeeded in reversing the progression of severe disease.[8,27,29] No specific drug or vaccine is currently available to treat MERS. Indeed, it has been stated that the complexity and time required for the development and registration process of drugs for human use impedes the ability to counter the rapid threat against an emerging infectious agent.[8] For example, there is no vaccine available against SARS-CoV because of the brevity of the threat to the public health.[2,8] It is likely that a MERS-CoV vaccine for human use may not be developed due to a lack of commercial interest, or if the threat posed by MERS-CoV declines in the meantime.[8]

Nevertheless, given the prevalence of MERS-CoV infection in the Middle East's DC population and due to the potential for spillover to the human population in direct contact with DCs, the development of a vaccine for use in DCs may be feasible.[4,5,32] A recent successful trial of a MERS orthopoxvirus vaccine has conferred mucosal immunity in the URTs of DCs.[32] Eradication of MERS-CoV from herds may be possible, if vaccines are administered to young, immunologically naive camels prior to exposure.[4,5,32]

Control and Prevention

Identification of the zoonotic source of MERS guides control strategies at the human-animal interface.[3,30] By preventing spillover of MERS-CoV from animals to humans, the risk of nosocomial and familial outbreaks in the Middle East could be eliminated.[3]

At present the implementation of intensive IPC measures in human health care is vital, including improving education and awareness among healthcare workers.[1,8] Most human cases have been linked to lapses in IPC, as one-fifth of viral infections have been reported among healthcare workers.[1,8] Stringent precautions while handling suspected MERS-CoV patients include the use of personal protective equipment (PPE) (i.e., disposable gloves, gowns, respiratory protection, and eye protection).[2,8,33] Immunocompromised individuals and those with preexisting medical conditions should avoid close contact with DCs.[2,8]

Public health authorities should adopt a standardized public health response protocol to include standardized case reporting methodology as defined by the WHO.[1,30] Standardization of case definitions aids accurate calculation of a case fatality ratio by including mild or asymptomatic cases.[30] The Health Authority of Abu Dhabi in the United Arab Emirates recently implemented a standardized reporting option for MERS, successfully incorporating it into existing epidemiologic surveillance systems with the aim of enhancing surveillance, educating healthcare workers, and ensuring laboratory capacity.[25]

In countries where MERS-CoV is enzootic in DCs, MERS control at the animal-human interface is unlikely to succeed unless appropriate preventive strategies are implemented.[5] These should include the following:

- Strict regulation of camel movement with imposition of a requirement for MERS clearance prior to the importation and transport of camels, including animals presented for slaughter.
- Camels with detectable MERS-CoV RNA should be quarantined and tested at regular intervals.
- Use of appropriate PPEs while handling DCs.
- Increased awareness among camel owners and the general public of the risks of consuming unpasteurized camel milk and urine. This may prove challenging given the depth of customs and beliefs in some areas.
- Accelerated development of safe and effective MERS vaccines for animal and human use.[5,33]

Conclusions

MERS-CoV has been observed for only 4 years, and vigilance is vital for the containment of the disease due to the high case fatality rate in humans and possible genetic instability of the virus.[8] Continued laboratory testing, genetic sequencing, analysis, timely data sharing, and clear communication are essential if such vigilance is to be effective.[8] Nonetheless, despite the potential for a pandemic outbreak at multiple mass gatherings during the Islamic calendar (Hajj, Eid, and Umrah) there were no reported outbreaks of MERS during or immediately after these events.[10] As such MERS-CoV is not a virus of pandemic concern.[10]

Since 2012 our understanding of MERS has increased greatly although gaps in knowledge still exist. The understanding of the disease's ecology—especially the interplay between camels, humans, and the environment—is still in its infancy. Aside from bats, the role that other wildlife may play in the ecology of MERS-CoV in East Africa and Arabia is yet to be elucidated.

Acknowledgments

The authors wish to thank the following: H. E. Ghanim Mubarak Al Hajeri and the senior management of Al Ain Zoo for their encouragement and support, Dr. Ahsan Ul Haq of Dubai Camel Hospital for his technical insight, and Dr. Andrew Higgins, Fellow of the Zoological Society of London and Honorary editor in chief of *The Veterinary Journal*, who reviewed the manuscript.

References

1. WHO MERS-CoV Global Summary and risk assessment, 5 December 2016 WHO/MERS/RA/16.1. http://www.who.int/emergencies/mers-cov/mers-summary-2016.pdf?ua=1. (Accessed 1 March 2017).
2. Banik GR, Khandaker G, Rashid H: Middle East respiratory syndrome coronavirus "MERS-CoV": current knowledge gaps, *Paediatr Respir Rev* 16(3):197–202, 2015.
3. Han H-J, Yu H, Yu X-J: Evidence for zoonotic origins of Middle East respiratory syndrome coronavirus, *J Gen Virol* 97(2):274–280, 2016.
4. Mohd H, Al-Tawfiq J, Memish Z: Middle East respiratory syndrome coronavirus (MERS-CoV) origin and animal reservoir, *Virol J* 13(1):87, 2016.
5. Omrani A, Al-Tawfiq J, Memish Z: Middle East respiratory syndrome coronavirus (MERS-CoV): animal to human interaction, *Pathog Glob Health* 109(8):354–362, 2015.
6. Haagmans B, Al Dhahiry S, Reusken C, et al: Middle East respiratory syndrome coronavirus in dromedary camels: an outbreak investigation, *Lancet Infect Dis* 14(2):140–145, 2014.
7. Azhar E, El-Kafrawy S, Farraj S, et al: Evidence for camel-to-human transmission of MERS coronavirus, *NEJM* 370(26):2499–2505, 2014.
8. Mackay IM, Arden KE: Middle East respiratory syndrome: an emerging coronavirus infection tracked by the crowd, *Virus Res* 202:60–88, 2015.
9. WHO Emergencies: MERS-CoV. Available at: http://www.who.int/emergencies/mers-cov/en/. (Accessed 8 April 2017).
10. Mackay IM, Arden KE: MERS coronavirus: diagnostics, epidemiology and transmission, *Virol J* 12(1):222, 2015.
11. Raj VS, Mou H, Smits SL, et al: Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC, *Nature* 495:251–254, 2013.
12. Cotten M, Lam TT, Watson SJ, et al: Full-genome deep sequencing and phylogenetic analysis of novel human betacoronavirus, *Emerg Infect Dis* 19:736–42B, 2013.
13. Alagaili A, Briese T, Mishra N, et al: Middle East respiratory syndrome coronavirus infection in dromedary camels in Saudi Arabia, *MBio* 5(2):e00884–14, 2014.
14. van den Brand J, Smits S, Haagmans B: Pathogenesis of Middle East respiratory syndrome coronavirus, *J Pathol* 235:175–184, 2015, doi:10.1002/path.4458.
15. Adney DR, van Doremalen N, Brown VR, et al: Replication and shedding of MERS-CoV in upper respiratory tract of inoculated dromedary camels, *Emerg Infect Dis* 20:1999–2005, 2014.

16. Yao Y, Bao L, Deng W, et al: An animal model of MERS produced by infection of rhesus macaques with MERS coronavirus, *J Infect Dis* 209(2):236–242, 2014.
17. Anthony SJ, Gilardi K, Menachery VD, et al: Further evidence for bats as the evolutionary source of Middle East respiratory syndrome coronavirus, *MBio* 8:e00373–17, 2017. https://doi.org/10.1128/mBio.00373-17. (Accessed 18 April 2017).
18. Memish Z, Mishra N, Olival K, et al: Middle East respiratory syndrome coronavirus in bats, Saudi Arabia, *Emerg Infect Dis* 19(11):2013.
19. Chu D, Poon L, Gomaa N, et al: MERS coronaviruses in dromedary camels, *Emerg Infect Dis* 20(6):1049–1053, 2014.
20. Hemida M, Perera R, Wang P, et al: Middle East respiratory syndrome (MERS) coronavirus seroprevalence in domestic livestock in Saudi Arabia, 2010 to 2013, *Euro Surveill* 18(50), 2013. pii=20659. Retrieved from http://dx.doi.org/10.2807/1560-7917.ES2013.18.50.20659. (Accessed 1 March 2017).
21. Meyer B, Müller M, Corman V, et al: Antibodies against MERS coronavirus in dromedaries, United Arab Emirates, 2003 and 2013, *Emerg Infect Dis* 20(4):552–559, 2014.
22. Reusken C, Ababneh M, Raj V, et al: Middle East respiratory syndrome coronavirus (MERS-CoV) serology in major livestock species in an affected region in Jordan, June to September 2013, *Euro Surveill* 18(50), 2013. pii=20662. Retrieved from http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20662. (Accessed 1 March 2017).
23. Raj V, Farag E, Reusken C, et al: Isolation of MERS Coronavirus from a Dromedary Camel, Qatar, *Emerg Infect Dis* 20(8), 2014.
24. Khalafalla A, Lu X, Al- Mubarak A, et al: MERS-CoV in upper respiratory tract and lungs of dromedary camels, Saudi Arabia, 2013–2014, *Emerg Infect Dis* 21(7):1153, 2015.
25. Al Hosani FI, Pringle K, Al Mulla M, et al: Response to emergence of Middle East respiratory syndrome coronavirus, Abu Dhabi, United Arab Emirates, 2013–2014, *Emerg Infect Dis* 22(7):1162, 2016.
26. Hunter J, Nguyen B, Aden D, et al: Transmission of Middle East respiratory syndrome coronavirus infections in healthcare settings, Abu Dhabi, *Emerg Infect Dis* 22(4):647, 2016.
27. Assiri A, McGeer A, Perl TM, et al: Hospital outbreak of Middle East respiratory syndrome coronavirus, *NEJM* 369:407–416, 2013.
28. Azhar EI, Hashem AM, El-Kafrawy SA, et al: Detection of the Middle East respiratory syndrome coronavirus genome in an air sample originating from a camel barn owned by an infected patient, *MBio* 5:e1450–e1514, 2014.
29. Oboho I, Tomczyk S, Al-Asmari A, et al: 2014 MERS-CoV outbreak in Jeddah—a link to health care facilities, *NEJM* 372(9):846–854, 2015.
30. de Sousa R, Reusken C, Koopmans M: MERS coronavirus: data gaps for laboratory preparedness, *J Clin Virol* 59(1):4–11, 2014.
31. Al Hammadi ZM, Chu DK, Eltahir YM, et al: Asymptomatic MERS-CoV infection in humans possibly linked to infected camels imported from Oman to United Arab Emirates, *Emerg Infect Dis* 21:12, 2015.
32. Haagmans B, van den Brand J, Raj V, et al: An orthopoxvirus-based vaccine reduces virus excretion after MERS-CoV infection in dromedary camels, *Science* 351(6888):77–81, 2016.
33. Centers for Disease Control and Prevention: Interim prevention and control recommendations for hospitalized patients with Middle East respiratory syndrome coronavirus (MERS-CoV). Available at: https://www.cdc.gov/coronavirus/mers/infection-prevention-control.html. (Accessed 18 April 2017).