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CHAPTER

8

The Middle East Respiratory Syndrome Coronavirus: An Emerging Virus of Global Threat

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ABBREVIATIONS

BtCoV	bat coronavirus
CoV	coronavirus
DPP4	dipeptidyl peptidase 4
HCoV	human coronavirus
MERS-CoV	Middle East respiratory syndrome coronavirus
PCR	polymerase chain reaction
PPE	personal protective equipment
SARS	severe acute respiratory syndrome

BACKGROUND AND OVERVIEW

Middle East respiratory syndrome coronavirus (CoV) (MERS-CoV) is a newly emerging zoonotic viral respiratory illness. Dromedary camels are thought to be the primary source of infection (de Wit et al., 2016). The first case of infection in humans was reported in June 2012 in Saudi Arabia from a 60-year-old man who later died of severe pneumonia and

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renal failure (Zaki et al., 2012; Khan, 2013). From 2012 to the end of 2017, the World Health Organization reported that a total of 2123 laboratories confirmed the cases of MERS-CoV infection and at least 740 deaths in 27 countries (case fatality rate 35%). Although sizable outbreaks have been noted in several countries, the latest being in South Korea (186 cases and 35 deaths) (Arabi et al., 2017), the vast number of cases (>80%) have been reported from Saudi Arabia (Fig. 8.1) (WHO, 2017).

This newly emerging, highly pathogenic respiratory virus is closely related to the virus that caused an outbreak of severe acute respiratory syndrome (SARS) in 2002–03. Both viruses are beta CoVs of zoonotic origin and cause similar clinical presentations. Although the natural reservoir of MERS-CoV infection and mode of transmission to humans is not known, one factor appears to be common to all primary cases; they are epidemiologically linked to the Middle East region. Most secondary cases, on the other hand, have occurred as a result of human-to-human transmission. Indeed, several well-documented outbreaks have occurred in healthcare settings, often in elderly men with comorbidities (Arabi et al., 2017; Chafekar and Fielding, 2018). Unlike SARS-CoV, MERS-CoV is an ongoing public health threat, particularly for the Middle East. The fact that there is no effective antiviral drug or approved vaccine available against MERS-CoV makes the threat even more worrisome (Zumla et al., 2016).

The Virus and Its Replication

MERS-CoV is an enveloped, single-strand, and positive-sense RNA virus, which belongs to the Coronaviridae family. Although CoVs are very common and can infect a variety of different animals, including cats, pigs, and bats, they rarely jump species barrier and infect humans. Human CoVs (HCoVs) were first isolated in mid-1960s, and until 2002, only two viruses, namely, HCoV-229E and HCoV-OC43, were known to infect humans (Forni et al., 2017). Currently, six CoVs have been shown to infect humans. Except for MERS-CoV and SARS-CoV, all others are associated with mild illnesses resembling common cold.

CoVs are grouped into four genera, α, β, γ, and δ. The β-CoVs are further subgrouped in four lineages or clades, A–D (Forni et al., 2017; Milne-Price et al., 2014). Although MERS-CoV and SARS-CoV belong to the same genus and both cause severe lower respiratory tract infection in humans, phylogenetic and sequencing data suggests that MERS-CoV is in fact more closely related to several bat CoVs (BtCoVs) than to SARS-CoV (Fig. 8.2) (Forni et al., 2017; Milne-Price et al., 2014). These findings suggest that MERS-CoV probably is originated from a BtCoV

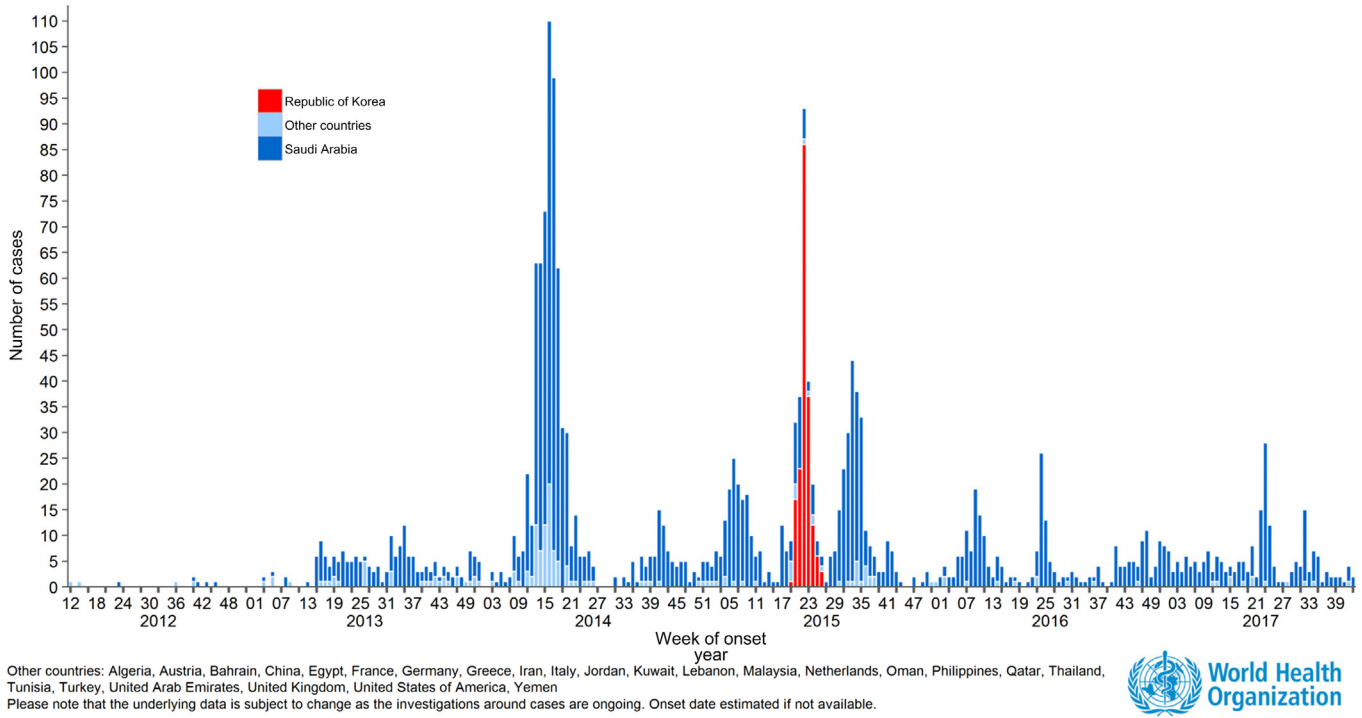

FIGURE 8.1 Confirmed global cases of MERS-CoV (2012–17). *MERS-CoV*, Middle East respiratory syndrome coronavirus. Source*: Adopted from WHO, 2017. Confirmed global cases of MERS-CoV. <http://www.who.int/emergencies/mers-cov/epi-17-november-2017.png?ua = 1> (retrieved 07.03.18.).*

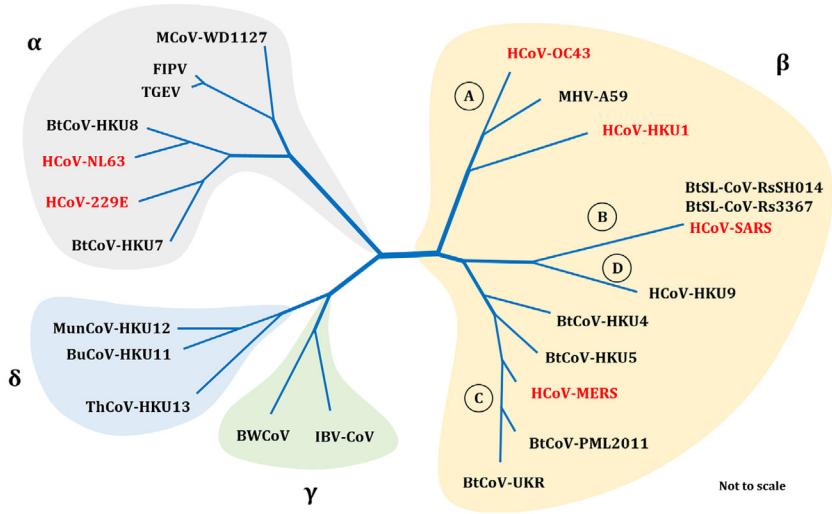

FIGURE 8.2 Phylogenetic tree (not to scale) of coronaviruses with representatives from each of the four genera, α, β, γ, and δ. Coronaviruses infect numerous species, including bat (Bt), beluga whale (BW), chicken (IBV), feline (FIPV), swine (TGEV), mink (M), murine (MHV), thrush (Th), bulbul (Bu), munia (Mun), and Humans (HCoV). Source*: Adapted from Milne-Price, S., Miazgowicz, K.L., Munster, V.J., 2014. The emergence of the Middle East respiratory syndrome coronavirus. Pathog. Dis. 71 (2), 119–134. doi:10.1111/2049-632X.12166.*

ancestor (Omrani et al., 2015; Chan et al., 2015a,b). The fact that CoVs are RNA viruses exhibiting high rates of mutation and recombination, and a propensity to cross species barrier, increases the risk of new variants emerging with higher virulence and transmission (Menachery et al., 2017; Sabir et al., 2015).

The replication cycle of MERS-CoV consists of a number of important steps: attachment and entry into host cell, uncoating and release of viral RNA, transcription and translation of viral specific genes, replication of viral genomic RNA, and assembly and release of progeny virions from the infected cell. As is typical of most RNA viruses, all of these steps take place in the cytoplasm of the host cell (de Wit et al., 2016). The initial attachment of MERS-CoV to its susceptible host cells is mediated by the viral envelop spike glycoprotein S binding to its cellular receptor, CD26 (also known as dipeptidyl peptidase 4, DPP4) (Lu et al., 2013; Raj et al., 2013). A number of different cell types express DPP4 and hence are susceptible to MERS-CoV infection including pneumocytes, alveolar macrophages, bronchial epithelia, vascular endothelium, as well as a subset of mononuclear cells (Meyerholz et al., 2016; Yu et al., 2017). Following attachment, the virus enters the susceptible cell by fusion of its envelope with the plasma membrane and/or via receptor-mediated

endocytosis (de Wit et al., 2016). Once in the cytoplasm of the target cell, the virus particle uncoats and the positive-sense viral RNA binds to ribosomes, and the viral RNA-dependent RNA polymerase is translated. This enzyme in turn transcribes full-length negative-sense RNA that forms the template for the production of positive-sense viral genome. The viral polymerase also generates various individual mRNAs that are translated into viral proteins. Viral structural proteins and viral genomic RNA are assembled into new virus particles in the rough endoplasmic reticulum-Golgi intermediate compartment and eventually released out of the cell by exocytosis. From the infected host, it appears that the virus is shed in nasal secretions (Adney et al., 2014). Interestingly, in bats, a recent study revealed that DPP4 receptor is rarely expressed in epithelial cells of respiratory tract, but highly expressed in epithelial cells of intestinal tract, indicating that fecal−oral is probably the main mode of transmission in bats (Widagdo et al., 2017). Of all the documented cases to date, there is no evidence for the transmission of the virus from bats or their droppings directly to humans. We also have limited data on the survival of the virus outside its host. When the virus was added to milk from dromedary camels, goats, or cow and stored at 4°C or 22°C, the virus could be recovered up to 72 and 48 hours, respectively (van Doremalen et al., 2013). Pasteurization of the milk, however, completely destroyed MERS-CoV infectivity (van Doremalen et al., 2013) (Table 8.1).

Epidemiology and Geographic Distribution

The current prevalent view is that MERS-CoV is a zoonotic virus that entered the human population in the Arabian Peninsula, via direct or indirect contact with infected dromedary camels. Studies indicate that the virus had been circulating in the camel population for decades, and only recently "jumped" the species barrier to infect humans. What are the factors that precipitated the virus to cross the species barrier are unknown. Most of the confirmed cases of MERS-CoV infection in humans have been via person-to-person transmission. The epidemiological elements in the transmission of MERS-CoV appear to be factors related to the virus, the host, and the environment. Cases have occurred as sporadic infections, family clusters, or outbreaks in healthcare settings (Kim et al., 2017; Oboho et al., 2015). Although the infection is limited and nonsustained, outbreaks in healthcare settings have been particularly extensive and worrisome. The nonspecific initial symptoms, late diagnosis, and inadequate infection control measures have all contributed to the outbreaks in healthcare settings (Oboho et al., 2015; Hunter et al., 2016; Kim et al., 2017). Although MERS-CoV cases have

TABLE 8.1 Major Features of Middle East Respiratory Syndrome Coronavirus.

Feature	Comment	References
General features of the virus	• Enveloped, ssRNA (+), nonsegmented virus, genome size 30 kb • Member of the Coronaviridae family, genus β-coronavirus, group C	Zaki et al. (2012)
Source of human infection	• Human–human: most common and often nosocomial • Dromedary camel–human: can occur but not common	Drosten et al. (2014); Memish et al. (2014a,b,c); Pebody (2013); Alhamlan et al. (2017); Kim et al. (2017)
Mode of transmission to humans	Droplets, aerosols, inhalation, and ingestion of camel milk	Kutter et al. (2018); van Doremalen et al. (2013)
Cell tropism and receptor	• Pneumocytes, alveolar macrophages, bronchial epithelial cells • Can infect cells from humans, monkeys, bats, and pigs • Infects via DPP4, also called CD26	Gierer et al. (2013); Lu et al. (2013); Raj et al. (2013); Yu et al. (2017); Zielecki et al. (2013)
Lab detection	• RT-PCR is commonly used for rapid diagnosis • Virus can be propagated in Vero and LLC-MK2 cells	Mackay and Arden (2015); Memish et al. (2014a,b,c)
Prevention and control	• Currently no approved vaccine available • Hand hygiene, wearing PPE, isolate those at risk	Kim et al. (2015); Mackay and Arden (2015)

DPP4, Dipeptidyl peptidase 4; *RT-PCR*, real-time polymerase chain reaction; *PPE*, personal protective equipment.

been detected in many countries around the world, almost all have been directly or indirectly linked to the Middle East region (Table 8.2). One of the most notable outbreaks outside the Middle East occurred in South Korea in May 2015 (Kim et al., 2017; Lee and Wong, 2015). A single infected man returning from the Middle East caused a hospital outbreak in which 185 individuals were infected (Kim et al., 2017). The epidemiological pattern observed in the Korean outbreak was similar to that observed in the Middle East; more males than females were affected, most of the 38 patients who died had underlying conditions

TABLE 8.2 The Leading Countries Affected by Middle East Respiratory Syndrome Coronavirus Infection.

Country	Number of cases	% of total cases (2040)
Saudi Arabia	1672	82.0
Korea	185	9.0
United Arab Emirates	83	4.1
Qatar	19	0.9
Jordan	28	1.4
Others	53	2.6

Based on data from WHO, n.d. MERS-CoV global summary and assessment of risk. <http://www.who.int/emergencies/mers-cov/risk-assessment-july-2017.pdf> (retrieved 21.07.17.) (WHO, n.d.). Laboratory confirmed cases as of July 2017.

such as respiratory disorders, cancer, hypertension, cardiovascular problems, or diabetes (Kim et al., 2017). It is noteworthy that the death rate was lower in the cases from South Korea compared to those reported from Saudi Arabia (23% vs 47%) (Virlogeux et al., 2016). The reason for this is not clear.

Although more than 80% of MERS-CoV cases have occurred in Saudi Arabia, the virus clearly has the potential of spreading to other countries. Thus there is an obvious need to detect, respond, and contain any outbreak of MERS-CoV cases if we want to prevent the global spread of the virus. Unfortunately, this is easier said than done. There are a number of risk factors prevalent in some of the countries of the Middle East which support the emergence and reemergence of infectious diseases (Buliva et al., 2017). These risk factors include political instability, famine and war, less developed healthcare infrastructure, weak public health and surveillance systems, increased population growth and mobility, climate change, and urbanization (Buliva et al., 2017). In order to prevent the emergence and spread of infectious diseases such as MERS-CoV, it is essential to address the underlying causes and risk factors. Needless to say, these are major challenges for any country, let alone the Eastern Mediterranean Region. To successfully address these challenges, it will require not only funding, establishment of robust and effective surveillance systems, and national and international corporations but also above all, peace and security in the region.

Source of Infection and Transmission

Infection with MERS-CoV, in its initial description, resembled "SARS-like" illness (Chan et al., 2015a,b). Further analysis of the

epidemiological, virological, and clinical aspects of MERS-CoV and SARS-CoV revealed important differences between the two viruses. Identifying unique aspects of MERS-CoV helped to explain how the epidemic evolved and the steps that could be taken to prevent its spread (Chan et al., 2015a,b). Serological studies have indicated that most dromedary camels in Africa and the Middle East, but not other animals such as sheep, goats, and cows, were seropositive for MERS-CoV (Reusken et al., 2013). Moreover, seroprevalence in dromedary camels appears to vary, with high rates reported in animals from Egypt, Ethiopia, Nigeria, and Sudan and lower rates in animals from Tunisia (Ali et al., 2017). Intriguingly, dromedaries from Australia, Canada, the United States, Germany, Netherlands, and Japan have been reported to be seronegative for MERS-CoV (Omrani et al., 2015). Importantly, population-based seroepidemiologic studies indicated that the seroprevalence of the virus was several folds higher in people who have been exposed to camels compared to those in the general population (Müller et al., 2015). Worldwide, it is estimated that there are around 30 million camels of which 95% are dromedaries. Dromedary camels are very popular in the Middle East where they are used not only for their meat and milk but also for cultural and recreational purposes. Whether camels are the primary reservoir for MERS-CoV infection in humans or merely an intermediate host for the transmission of the virus from a yet unidentified host remains to be proven (Fig. 8.3) (Mackay and Arden, 2015; Mohd et al., 2016).

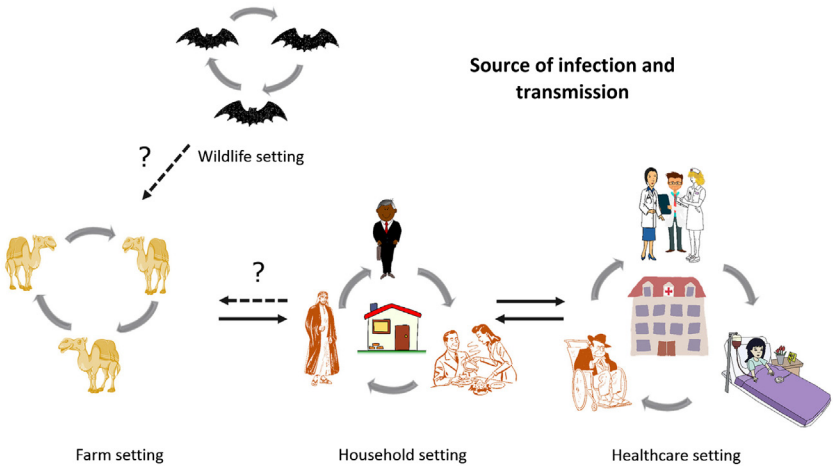

FIGURE 8.3 Source of infection and route of transmission of MERS-CoV. Dotted lines indicate possible, but not laboratory confirmed, direction of transmission. Solid lines indicate laboratory-documented direction of transmission. Most cases have occurred in healthcare settings, in patients with underlying medical problems. *MERS-CoV*, Middle East respiratory syndrome coronavirus.

Accumulating serologic and molecular evidence indicates that the virus in dromedaries is genetically similar to MERS-CoV in humans, supporting the notion that dromedary camels could be the potential source of infection to human (Haagmans et al., 2013; Memish et al., 2014a,b,c; Sabir et al., 2015). Indeed, MERS-CoV antibodies have been isolated in dromedary camels across the Arabian peninsula, North Africa, and Eastern Africa dating from as far back as the 1990s (Milne-Price et al., 2014; Omrani et al., 2015). This finding suggests that MERS-CoV may have been circulating in dromedaries for over 20 years before it was first recognized as a cause of human infection (Aly et al., 2017). In a recent study, a fatal case of MERS-CoV infection was reported in an individual who had direct contact with a dromedary camel (Azhar et al., 2014). Sequence analysis of the virus isolated from the case and the camel was identical, clearly indicating that MERS-CoV can indeed be transmitted from camels to human (Azhar et al., 2014). It appears that active infection with release of the virus in nasal secretions, particularly during the incubation period, is important for the transmission of the virus to humans (Alraddadi et al., 2016). Where and how the camels acquired the infection remains unknown. It has been hypothesized that bats could be the potential source (Fig. 8.3) (Anthony et al., 2017; Mohd et al., 2016; Omrani et al., 2015). Indeed, MERS-CoV-like viruses have been identified in certain species of bats (Anthony et al., 2017; Woo et al., 2006). The bats are present in most parts of the world and often infected with various zoonotic viruses. Thus it is plausible that at some point in the past, camels acquired the infection from bats, leading to a sustained infection in the camel population (Fig. 8.3). MERS-CoV RNA has been identified in the milk, nasal secretion, and feces of dromedary camels (Omrani et al., 2015). Since camels and humans are often in close contact, particularly in the Arab Gulf States, humans would be at increased risk of contracting the virus from actively infected animals (Mackay and Arden, 2015; Reusken et al., 2015). Indeed, MERS-CoV seropositivity in shepherds and those working in slaughterhouses in Saudi Arabia has been reported to be an order of magnitude higher than in the general population (Arabi et al., 2017). Although possible, no evidence currently exists to support the transmission of MERS-CoV from bats to humans directly. What is certain is that transmission of the virus can occur from camels to humans, but the process is still not fully understood (Al Hammadi et al., 2015; Memish et al., 2014a,b,c). One possibility is that some species of CoVs from camels and humans could recombine leading to the emergence of a new virus that can infect both, camels and human (Sabir et al., 2015).

Most MERS-CoV infections in humans occur through human-to-human contact (Arabi et al., 2017; Zumla et al., 2016). Available data on epidemiologic observations suggest that human-to-human transmission

occurs primarily through close contact with an infected individual. The mode of transmission is presumed to be via respiratory droplets or aerosols, with higher risk in situations where aerosols are generated, and inadequate personal protection or proper room ventilation is not present (Kutter et al., 2018). In the South Korean outbreak a total of 185 individuals were infected; 136 of whom were directly infected by just 3 cases, the so-called super spreaders. Late diagnosis, lack of infection control measures, poor communication and healthcare management procedures, and failure to quarantine the "super spreaders" were identified as major factors contributing to this large nosocomial outbreak (Kim et al., 2017).

Clinical Features and Diagnosis

CoV is a common cause of mild respiratory tract infection manifesting as common cold. It is estimated that approximately one-third of all upper respiratory tract infections in adults are due to CoVs. SARS-CoV and MERS-CoV are the exceptions. Both of these viruses have a high propensity to infect the lower respiratory track and lead to severe disease and death (de Wit et al., 2016). The finding that both of these viruses, but in particular, MERS-CoV, are able to evade the body's immune responses and infect a broad range of cells, explaining the widespread infection and development of severe disease (Mackay and Arden, 2015). It is noteworthy that, even in the absence of viral shedding in the upper respiratory tract, most symptomatic patients have abnormal chest radiographs (Fig. 8.4) (Assiri et al., 2013; de Wit et al., 2016).

The incubation period for MERS-CoV infection is about 5–6 days with most patients showing symptoms within 14 days of exposure (de Wit et al., 2016; Virlogeux et al., 2016). The initial clinical symptoms of MERS-CoV infection can range from asymptomatic to low-grade fever, cough, sore throat, myalgia, and less frequently diarrhea and vomiting. Progression to more severe disease is characterized by the symptoms of shortness of breath, severe pneumonia, respiratory distress syndrome, multiorgan failure, and death (Arabi et al., 2017; de Wit et al., 2016; Guery et al., 2013). The severity of the infection appears to vary depending on the age of the patient and any underlying conditions. Adults over the age of 50 years and with comorbidities such as diabetes, hypertension, chronic renal or lung disease, cancer, and heart disease are at increased risk of developing severe disease and death (Badawi and Ryoo, 2016). Although the vast majority of confirmed cases have been in male adults, children are also susceptible to infection, albeit at lower rate and with milder disease (Al-Tawfiq et al., 2016). Based on limited data, MERS-CoV infection in pregnancy can also lead to maternal and

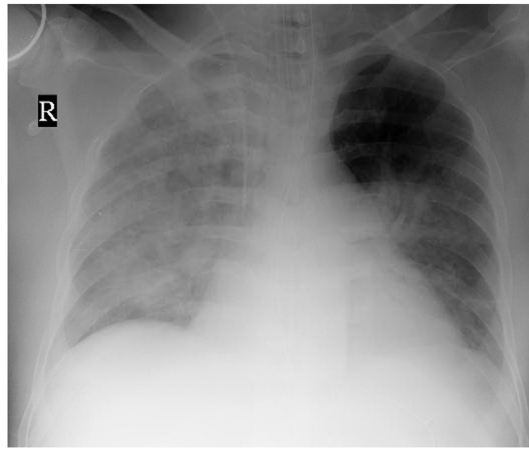

FIGURE 8.4 A typical case of MERS-CoV infection. A 65-year-old man presented with severe respiratory distress. The chest X-ray taken during the admission in ICU shows bilateral ground glass opacities, more in the right compared to the left side. *MERS-CoV*, Middle East respiratory syndrome coronavirus. Source*: Courtesy of Dr. Karuna M Das, Departmental of Radiology, College of Medicine and Health Sciences, UAE University.*

perinatal disease and death (Al-Tawfiq et al., 2016; Assiri et al., 2016). Not surprisingly, the severity of infection and the risk of transmission of MERS-CoV are significantly increased in environments such as hospitals (Cho et al., 2016; Hastings et al., 2016).

The clinical symptoms of MERS-CoV infection, especially in early stages of the infection, are typically nonspecific and can resemble a number of acute respiratory tract infections. However, acute febrile respiratory illness in a patient with a recent travel history to the Middle East or direct/indirect contract with a confirmed case of MERS-CoV should be enough suspicion to request laboratory testing for MERS-CoV. Studies indicate that viral replication and shedding is higher in lower compared to upper respiratory tract (de Wit et al., 2016; Memish et al., 2014a,b,c). Hence, for laboratory diagnosis, lower respiratory tract specimens such as tracheal aspirate, bronchoalveolar lavage, or pleural fluid are preferred over upper respiratory tract specimens such as nasopharyngeal swab (Mackay and Arden, 2015; Memish, et al., 2014a,b,c). It is essential that appropriate personal protective equipment (PPE) and infection control measures are implemented when dealing with suspected cases.

The assay of choice for the laboratory diagnosis of MERS-CoV is reverse transcriptase real-time polymerase chain reaction (RT-PCR) on respiratory samples. This assay was established soon after the identification of MERS-CoV back in 2012 (Zaki et al., 2012). RT-PCR is not only very sensitive but also importantly a fairly rapid technique, which is

essential for early diagnosis and quarantine implementation. The virus can also be cultured. A number of different cell lines are susceptible for in vitro infection, including Vero and LLC-MK2 cells (Zaki et al., 2012). However, cell culture approach is very slow and not easily adaptable to every diagnostic laboratory, hence the preference of RT-PCR. For determining past infection or for surveillance studies, the detection of antibodies to MERS-CoV using serological assay, such as enzyme linked immunosorbent assay (ELISA), can be performed (Mackay and Arden, 2015).

Treatment and Prevention

Currently, no specific antiviral therapy or vaccine is available for the treatment and prevention of MERS-CoV infection. Supportive care and prevention of complications are the main management options that are available. However, efforts are underway for the development of therapeutic and vaccine candidates. In a marmoset model of MERS-CoV infection, several compounds, including ribavirin, lopinavir/ritonavir, interferon-β1b, and interferon-α2B, alone or in combinations, have shown varying degree of success (Chan et al., 2015a,b; Falzarano et al., 2013). Similarly, passive immunotherapy with neutralizing antibodies against MERS-CoV has also shown some therapeutic value in inhibiting viral replication (Luke et al., 2016). In terms of vaccines, several potential candidates have been developed and are in different stages of clinical testing (Du et al., 2016). The possibility of developing an effective vaccine based on MERS-CoV spike protein is promising (Haagmans et al., 2015). In the absence of licensed antiviral or vaccine, current strategies of combating MERS-CoV infection are aimed at reducing the risk of animal-to-human and human-to-human transmissions. Strategies recommended include avoidance of drinking unpasteurized camel milk, limiting direct contact with a sick animal, avoidance of close contact, and sharing of utensils with an infected individual, using PPE when in direct contact with an infected person and proper hand hygiene. In addition, early recognition and laboratory confirmation of infected cases, segregation/isolation of infected cases, and contact tracing and strict implementation of infection control measures in healthcare settings are all essential for controlling and preventing of MERS-CoV infection and spread.

References

Adney, D.R., van Doremalen, N., Brown, V.R., Bushmaker, T., Scott, D., de Wit, E., et al., 2014. Replication and shedding of MERS-CoV in upper respiratory tract of inoculated dromedary camels. Emerg. Infect. Dis. 20 (12), 1999–2005. Available from: http://doi.org/10.3201/eid2012.141280.

Alhamlan, F.S., Majumder, M.S., Brownstein, J.S., Hawkins, J., Al-Abdely, H.M., Alzahrani, A., et al., 2017. Case characteristics among Middle East respiratory syndrome coronavirus outbreak and non-outbreak cases in Saudi Arabia from 2012 to 2015. BMJ Open 7 (1), e011865. Available from: http://doi.org/10.1136/bmjopen-2016-011865.

Al Hammadi, Z.M., Chu, D.K.W., Eltahir, Y.M., Al Hosani, F., Al Mulla, M., Tarnini, W., et al., 2015. Asymptomatic MERS-CoV infection in humans possibly linked to infected dromedaries imported from Oman to United Arab Emirates, May 2015. Emerg. Infect. Dis. 21 (12), 2197–2200. Available from: http://doi.org/10.3201/eid2112.151132.

Ali, M., El-Shesheny, R., Kandeil, A., Shehata, M., Elsokary, B., Gomaa, M., et al., 2017. Cross-sectional surveillance of Middle East respiratory syndrome coronavirus (MERS-CoV) in dromedary camels and other mammals in Egypt, August 2015 to January 2016. Euro Surveill. 22 (11). Available from: http://doi.org/10.2807/1560-7917.ES.2017.22.11.30487.

Alraddadi, B.M., Watson, J.T., Almarashi, A., Abedi, G.R., Turkistani, A., Sadran, M., et al., 2016. Risk factors for primary Middle East respiratory syndrome coronavirus illness in humans, Saudi Arabia, 2014. Emerg. Infect. Dis. 22 (1), 49–55. Available from: http://doi.org/10.3201/eid2201.151340.

Al-Tawfiq, J.A., Kattan, R.F., Memish, Z.A., 2016. Middle East respiratory syndrome coronavirus disease is rare in children: an update from Saudi Arabia. World J. Clin. Pediatr. 5 (4), 391–396. Available from: http://doi.org/10.5409/wjcp.v5.i4.391.

Aly, M., Elrobh, M., Alzayer, M., Aljuhani, S., Balkhy, H., 2017. Occurrence of the Middle East respiratory syndrome coronavirus (MERS-CoV) across the gulf corporation council countries: four years update. PLoS One 12 (10). Available from: http://doi.org/10.1371/journal.pone.0183850.

Anthony, S.J., Gilardi, K., Menachery, V.D., Goldstein, T., Ssebide, B., Mbabazi, R., et al., 2017. Further evidence for bats as the evolutionary source of Middle East respiratory syndrome coronavirus. mBio 8 (2). Available from: http://doi.org/10.1128/mBio.00373-17.

Arabi, Y.M., Balkhy, H.H., Hayden, F.G., Bouchama, A., Luke, T., Baillie, J.K., et al., 2017. Middle East respiratory syndrome. N. Engl. J. Med. 376 (6), 584–594. Available from: http://doi.org/10.1056/NEJMsr1408795.

Assiri, A., Al-Tawfiq, J.A., Al-Rabeeah, A.A., Al-Rabiah, F.A., Al-Hajjar, S., Al-Barrak, A., et al., 2013. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect. Dis. 13 (9), 752–761. Available from: http://doi.org/10.1016/S1473-3099(13)70204-4.

Assiri, A., Abedi, G.R., Al Masri, M., Bin Saeed, A., Gerber, S.I., Watson, J.T., 2016. Middle East respiratory syndrome coronavirus infection during pregnancy: a report of 5 cases from Saudi Arabia. Clin. Infect. Dis. 63 (7), 951–953. Available from: http://doi.org/10.1093/cid/ciw412.

Azhar, E.I., El-Kafrawy, S.A., Farraj, S.A., Hassan, A.M., Al-Saeed, M.S., Hashem, A.M., et al., 2014. Evidence for camel-to-human transmission of MERS coronavirus. N. Engl. J. Med. 370 (26), 2499–2505. Available from: http://doi.org/10.1056/NEJMoa1401505.

Badawi, A., Ryoo, S.G., 2016. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. Int. J. Infect. Dis.: IJID 49, 129–133. Available from: http://doi.org/10.1016/j.ijid.2016.06.015.

Buliva, E., Elhakim, M., Minh, T., Nguyen, N., Elkholy, A., Mala, P., et al., 2017. Emerging and reemerging diseases in the World Health Organization (WHO) Eastern Mediterranean Region—progress, challenges, and WHO initiatives. Front. Public Health 5. Available from: http://doi.org/10.3389/fpubh.2017.00276.

Chafekar, A., Fielding, B.C., 2018. MERS-CoV: understanding the latest human coronavirus threat. Viruses 10 (2), 93. Available from: http://doi.org/10.3390/v10020093.

Chan, J.F., Lau, S.K.P., To, K.K.W., Cheng, V.C.C., Woo, P.C.Y., Yuen, K.-Y., 2015a. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. Clin. Microbiol. Rev. 28 (2), 465–522. Available from: http://doi.org/10.1128/CMR.00102-14.

Chan, J.F.-W., Yao, Y., Yeung, M.-L., Deng, W., Bao, L., Jia, L., et al., 2015b. Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. J. Infect. Dis. 212 (12), 1904–1913. Available from: http://doi.org/10.1093/infdis/jiv392.

Cho, S.Y., Kang, J.-M., Ha, Y.E., Park, G.E., Lee, J.Y., Ko, J.-H., et al., 2016. MERS-CoV outbreak following a single patient exposure in an emergency room in South Korea: an epidemiological outbreak study. Lancet (London, England) 388 (10048), 994–1001. Available from: http://doi.org/10.1016/S0140-6736(16)30623-7.

de Wit, E., van Doremalen, N., Falzarano, D., Munster, V.J., 2016. SARS and MERS: recent insights into emerging coronaviruses. Nat. Rev. Microbiol. 14 (8), 523–534. Available from: http://doi.org/10.1038/nrmicro.2016.81.

Drosten, C., Meyer, B., Müller, M.A., Corman, V.M., Al-Masri, M., Hossain, R., et al., 2014. Transmission of MERS-coronavirus in household contacts. N. Engl. J. Med. 371 (9), 828–835. Available from: http://doi.org/10.1056/NEJMoa1405858.

Du, L., Tai, W., Zhou, Y., Jiang, S., 2016. Vaccines for the prevention against the threat of MERS-CoV. Expert Rev. Vaccines 15 (9), 1123–1134. Available from: http://doi.org/10.1586/14760584.2016.1167603.

Falzarano, D., de Wit, E., Rasmussen, A.L., Feldmann, F., Okumura, A., Scott, D.P., et al., 2013. Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. Nat. Med. 19 (10), 1313–1317. Available from: http://doi.org/10.1038/nm.3362.

Forni, D., Cagliani, R., Clerici, M., Sironi, M., 2017. Molecular evolution of human coronavirus genomes. Trends Microbiol. 25 (1), 35–48. Available from: http://doi.org/10.1016/j.tim.2016.09.001.

Gierer, S., Bertram, S., Kaup, F., Wrensch, F., Heurich, A., Krämer-Kühl, A., et al., 2013. The spike-protein of the emerging betacoronavirus EMC uses a novel coronavirus receptor for entry, can be activated by TMPRSS2 and is targeted by neutralizing antibodies. J. Virol. Available from: http://doi.org/10.1128/JVI.00128-13.

Guery, B., Poissy, J., el Mansouf, L., Séjourné, C., Ettahar, N., Lemaire, X., et al., 2013. Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: a report of nosocomial transmission. Lancet 381 (9885), 2265–2272. Available from: http://doi.org/10.1016/S0140-6736(13)60982-4.

Haagmans, B.L., Al Dhahiry, S.H.S., Reusken, C.B.E.M., Raj, V.S., Galiano, M., Myers, R., et al., 2013. Middle East respiratory syndrome coronavirus in dromedary camels: an outbreak investigation. Lancet Infect. Dis. Available from: http://doi.org/10.1016/S1473-3099(13)70690-X.

Haagmans, B.L., van den Brand, J.M.A., Raj, V.S., Volz, A., Wohlsein, P., Smits, S.L., et al., 2015. An orthopoxvirus-based vaccine reduces virus excretion after MERS-CoV infection in dromedary camels. Science (New York, NY) . Available from: http://doi.org/10.1126/science.aad1283.

Hastings, D.L., Tokars, J.I., Abdel Aziz, I.Z.A.M., Alkhaldi, K.Z., Bensadek, A.T., Alraddadi, B.M., et al., 2016. Outbreak of Middle East respiratory syndrome at Tertiary Care Hospital, Jeddah, Saudi Arabia, 2014. Emerg. Infect. Dis. 22 (5), 794–801. Available from: http://doi.org/10.3201/eid2205.151797.

Hunter, J.C., Nguyen, D., Aden, B., Al Bandar, Z., Al Dhaheri, W., Abu Elkheir, K., et al., 2016. Transmission of Middle East Respiratory syndrome coronavirus infections in healthcare settings, Abu Dhabi. Emerg. Infect. Dis. 22 (4), 647–656. Available from: http://doi.org/10.3201/eid2204.151615.

Khan, G., 2013. A novel coronavirus capable of lethal human infections: an emerging picture. Virol. J. 10, 66. Available from: http://doi.org/10.1186/1743-422X-10-66.

Kim, J.Y., Song, J.Y., Yoon, Y.K., Choi, S.-H., Song, Y.G., Kim, S.-R., et al., 2015. Middle East respiratory syndrome infection control and prevention guideline for healthcare facilities. Infect. Chemother. 47 (4), 278–302. Available from: http://doi.org/10.3947/ic.2015.47.4.278.

Kim, K.H., Tandi, T.E., Choi, J.W., Moon, J.M., Kim, M.S., 2017. Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in South Korea, 2015: epidemiology, characteristics and public health implications. J. Hosp. Infect. 95 (2), 207–213. Available from: http://doi.org/10.1016/j.jhin.2016.10.008.

Kutter, J.S., Spronken, M.I., Fraaij, P.L., Fouchier, R.A., Herfst, S., 2018. Transmission routes of respiratory viruses among humans. Curr. Opin. Virol. 28, 142–151. Available from: http://doi.org/10.1016/j.coviro.2018.01.001.

Lee, S.S., Wong, N.S., 2015. Probable transmission chains of Middle East respiratory syndrome coronavirus and the multiple generations of secondary infection in South Korea. Int. J. Infect. Dis. 38, 65–67. Available from: http://doi.org/10.1016/j.ijid.2015.07.014.

Lu, G., Hu, Y., Wang, Q., Qi, J., Gao, F., Li, Y., et al., 2013. Molecular basis of binding between novel human coronavirus MERS-CoV and its receptor CD26. Nature 500 (7461), 227–231. Available from: http://doi.org/10.1038/nature12328.

Luke, T., Wu, H., Zhao, J., Channappanavar, R., Coleman, C.M., Jiao, J.-A., et al., 2016. Human polyclonal immunoglobulin G from transchromosomic bovines inhibits MERS-CoV in vivo. Sci. Transl. Med. 8 (326), 326ra21. Available from: http://doi.org/10.1126/scitranslmed.aaf1061.

Mackay, I.M., Arden, K.E., 2015. MERS coronavirus: diagnostics, epidemiology and transmission. Virol. J. 12, 222. Available from: http://doi.org/10.1186/s12985-015-0439-5.

Memish, Z.A., Al-Tawfiq, J.A., Makhdoom, H.Q., Al-Rabeeah, A.A., Assiri, A., Alhakeem, R.F., et al., 2014a. Screening for Middle East respiratory syndrome coronavirus infection in hospital patients and their healthcare worker and family contacts: a prospective descriptive study. Clin. Microbiol. Infect. 20 (5), 469–474. Available from: http://doi.org/10.1111/1469-0691.12562.

Memish, Z.A., Al-Tawfiq, J.A., Makhdoom, H.Q., Assiri, A., Alhakeem, R.F., Albarrak, A., et al., 2014b. Respiratory tract samples, viral load, and genome fraction yield in patients with Middle East respiratory syndrome. J. Infect. Dis. 210 (10), 1590–1594. Available from: http://doi.org/10.1093/infdis/jiu292.

Memish, Z.A., Cotten, M., Meyer, B., Watson, S.J., Alsahafi, A.J., Al Rabeeah, A.A., et al., 2014c. Human infection with MERS coronavirus after exposure to infected camels, Saudi Arabia, 2013. Emerg. Infect. Dis. 20 (6). Available from: http://doi.org/10.3201/eid2006.140402.

Menachery, V.D., Graham, R.L., Baric, R.S., 2017. Jumping species—a mechanism for coronavirus persistence and survival. Curr. Opin. Virol. 23, 1–7. Available from: http://doi.org/10.1016/j.coviro.2017.01.002.

Meyerholz, D.K., Lambertz, A.M., McCray, P.B., 2016. Dipeptidyl peptidase 4 distribution in the human respiratory tract. Am. J. Pathol. 186 (1), 78–86. Available from: http://doi.org/10.1016/j.ajpath.2015.09.014.

Milne-Price, S., Miazgowicz, K.L., Munster, V.J., 2014. The emergence of the Middle East respiratory syndrome coronavirus (MERS-CoV). Pathog. Dis. 71 (2), 119–134. Available from: http://doi.org/10.1111/2049-632X.12166.

Mohd, H.A., Al-Tawfiq, J.A., Memish, Z.A., 2016. Middle East respiratory syndrome coronavirus (MERS-CoV) origin and animal reservoir. Virol. J. 13. Available from: http://doi.org/10.1186/s12985-016-0544-0.

Müller, M.A., Meyer, B., Corman, V.M., Al-Masri, M., Turkestani, A., Ritz, D., et al., 2015. Presence of Middle East respiratory syndrome coronavirus antibodies in Saudi Arabia:

a nationwide, cross-sectional, serological study. Lancet Infect. Dis. 15 (5), 559–564. Available from: http://doi.org/10.1016/S1473-3099(15)70090-3.

Oboho, I.K., Tomczyk, S.M., Al-Asmari, A.M., Banjar, A.A., Al-Mugti, H., Aloraini, M.S., et al., 2015. 2014 MERS-CoV outbreak in Jeddah—a link to health care facilities. N. Engl. J. Med. 372 (9), 846–854. Available from: http://doi.org/10.1056/NEJMoa1408636.

Omrani, A.S., Al-Tawfiq, J.A., Memish, Z.A., 2015. Middle East respiratory syndrome coronavirus (MERS-CoV): animal to human interaction. Pathog. Global Health 109 (8), 354–362. Available from: http://doi.org/10.1080/20477724.2015.1122852.

Pebody, R.G., 2013. Evidence of person-to-person transmission within a family cluster of novel coronavirus infections, United Kingdom, February 2013. Euro Surveill.: Bulletin Européen Sur Les Maladies Transmissibles = European Communicable Disease Bulletin 18 (11).

Raj, V.S., Mou, H., Smits, S.L., Dekkers, D.H.W., Müller, M.A., Dijkman, R., et al., 2013. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 495 (7440), 251–254. Available from: http://doi.org/10.1038/nature12005.

Reusken, C.B.E.M., Haagmans, B.L., Müller, M.A., Gutierrez, C., Godeke, G.-J., Meyer, B., et al., 2013. Middle East respiratory syndrome coronavirus neutralising serum antibodies in dromedary camels: a comparative serological study. Lancet Infect. Dis. 13 (10), 859–866. Available from: http://doi.org/10.1016/S1473-3099(13)70164-6.

Reusken, C.B.E.M., Farag, E.A.B.A., Haagmans, B.L., Mohran, K.A., Godeke, G.-J., Raj, S., et al., 2015. Occupational exposure to dromedaries and risk for MERS-CoV infection, Qatar, 2013–2014. Emerg. Infect. Dis. 21 (8), 1422–1425. Available from: http://doi.org/10.3201/eid2108.150481.

Sabir, J.S.M., Lam, T.T.-Y., Ahmed, M.M.M., Li, L., Shen, Y., Abo-Aba, S.E.M., et al., 2015. Co-circulation of three camel coronavirus species and recombination of MERS-CoVs in Saudi Arabia. Science (New York, NY) . Available from: http://doi.org/10.1126/science.aac8608.

van Doremalen, N., Bushmaker, T., Munster, V.J., 2013. Stability of Middle East respiratory syndrome coronavirus (MERS-CoV) under different environmental conditions. Euro Surveill.: Bulletin Europeen Sur Les Maladies Transmissibles = European Communicable Disease Bulletin 18 (38).

Virlogeux, V., Fang, V.J., Park, M., Wu, J.T., Cowling, B.J., 2016. Comparison of incubation period distribution of human infections with MERS-CoV in South Korea and Saudi Arabia. Sci. Rep. 6. Available from: http://doi.org/10.1038/srep35839.

WHO, 2017. Confirmed global cases of MERS-CoV. <http://www.who.int/emergencies/mers-cov/epi-17-november-2017.png?ua = 1> (retrieved 07.03.18.).

WHO, n.d. MERS-CoV global summary and assessment of risk. <http://www.who.int/emergencies/mers-cov/risk-assessment-july-2017.pdf> (retrieved 21.07.17.).

Widagdo, W., Begeman, L., Schipper, D., van Run, P.R., Cunningham, A.A., Kley, N., et al., 2017. Tissue distribution of the MERS-coronavirus receptor in bats. Sci. Rep. 7 (1), 1193. Available from: http://doi.org/10.1038/s41598-017-01290-6.

Woo, P.C.Y., Lau, S.K.P., Li, K.S.M., Poon, R.W.S., Wong, B.H.L., Tsoi, H., et al., 2006. Molecular diversity of coronaviruses in bats. Virology 351 (1), 180–187. Available from: http://doi.org/10.1016/j.virol.2006.02.041.

Yu, P., Xu, Y., Deng, W., Bao, L., Huang, L., Xu, Y., et al., 2017. Comparative pathology of rhesus macaque and common marmoset animal models with Middle East respiratory syndrome coronavirus. PLoS One 12 (2), e0172093. Available from: http://doi.org/10.1371/journal.pone.0172093.

Zaki, A.M., van Boheemen, S., Bestebroer, T.M., Osterhaus, A.D.M.E., Fouchier, R.A.M., 2012. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N. Engl. J. Med. 367, 1814–1820. Available from: http://doi.org/10.1056/NEJMoa1211721.

Zielecki, F., Weber, M., Eickmann, M., Spiegelberg, L., Zaki, A.M., Matrosovich, M., et al., 2013. Human cell tropism and innate immune system interactions of human respiratory coronavirus EMC compared to SARS-coronavirus. J. Virol. 87 (9), 5300–5304. Available from: http://doi.org/10.1128/JVI.03496-12.

Zumla, A., Chan, J.F.W., Azhar, E.I., Hui, D.S.C., Yuen, K.-Y., 2016. Coronaviruses—drug discovery and therapeutic options. Nat. Rev. Drug Discov. 15 (5), 327–347. Available from: http://doi.org/10.1038/nrd.2015.37.