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Severe Middle East Respiratory Syndrome (MERS) Pneumonia

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Introduction

Middle East Respiratory Syndrome (MERS) is a viral respiratory infection, which ranges from asymptomatic infection to severe pneumonia, caused by a novel coronavirus named Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Coronaviruses are a family of viral pathogens that could cause animal and human disease. MERS-CoV is closely related to the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) but from a different lineage. The objective of this chapter is to describe the epidemiology, virology, clinical manifestations, management and prevention of MERS.

Epidemiology

Between September 2012, until the end of May 2019, the World Health organization (WHO) has been notified of 2374 laboratory-confirmed case of MERS-CoV infection from 27 countries with 823 associated deaths resulting in a case fatality rate of 35%. Saudi Arabia has been the major reporting country with a total number of 2008 cases and 749 deaths (a case fatality rate of 37.3%) (**Table 1**) (World Health Organization, 2019, Mar 31).

Table 1 Countries with reported cases of MERS-CoV.[a]

Country	*Number of reported cases*
Eastern Mediterranean Region and North Africa (EMRO)	
Saudi Arabia	2008
United Arab Emirates	86
Jordan	28
Oman	24
Qatar	19
Iran	6
Kuwait	4
Tunisia	3
Lebanon	2
Algeria	2
Egypt	1
Bahrain	1
Yemen	1
Europe	
United Kingdom	5
Germany	3
France	2
Netherland	2
Austria	2
Greece	1
Italy	1
Asia	
Republic of Korea	187
Thailand	3
Philippines	2
Malaysia	2
China	1
Turkey	1
North America	
USA	2
Total	2399

[a]WHO reported cases as of March 2019.
WHO- MERS situation update, March 2019-http://www.emro.who.int/pandemic-epidemic-diseases/mers-cov/mers-situation-update-march-2019.html.

The virus was first isolated in June 2012 from respiratory specimens of a Saudi patient from Jeddah, Saudi Arabia, who presented with severe pneumonia that progressed to Acute Respiratory Distress Syndrome (ARDS), renal failure, multi-organ failure and eventually lead to death (Zaki et al., 2012). In the same week, a patient with a recent history of travel to the United Kingdom (UK) for medical care for severe pneumonia and acute kidney injury, was reported to have the same coronavirus (Wise, 2012). A retrospective investigation of an outbreak of pneumonia among 13 patients that took place in Jordan in April 2012 revealed that the cases were caused by the same virus (Al-Abdallat et al., 2014). Subsequently, many cases and clusters of infection with the same virus were reported (see epidemiology below). The novel virus was first called HCoV-EMC, after the Erasmus Medical Center, where it was first identified (Zaki et al., 2012) but it was subsequently named MERS-CoV reflecting the fact that the majority of cases were from the Arabian Peninsula (de Groot et al., 2013).

MERS cases occur as sporadic cases or as clusters or hospital outbreaks. The first large hospital outbreak of MERS-CoV occurred in April 2013, in a single hospital in Al-Hasa, Eastern Province of Saudi Arabia, where a cluster of 23 confirmed cases and 11 probable cases were detected (Assiri et al., 2013b). A large surge in the number of reported cases occurred in March and April 2014, reaching to more than 500 cases. Most of those reported cases were part of hospital outbreaks in different cities in Saudi Arabia and Al Ain, United Arab Emirates. The largest hospital outbreaks occurred in Jeddah, Saudi Arabia with 255 laboratory-confirmed MERS cases (Oboho et al., 2015). Another hospital outbreak occurred in Riyadh, Saudi Arabia with 45 laboratory-confirmed cases (Fagbo et al., 2015). The first report of MERS-CoV from North America was in April 2014 for a physician who worked in Saudi Arabia and started to have symptoms after returning to the United States (Kapoor et al., 2014). Another imported case to the United States was confirmed in Florida in May 2014 (The Florida Department of Health, 2018, Dec 10). In May 2015, a large outbreak occurred in South Korea. The index case was a 68-year-old Korean patient who had recently come from a business trip to the Arabian Peninsula (that included Saudi Arabia, Bahrain, United Arab Emirates and Qatar). This index case resulted in infection among 26 patients who further spread the infection nationwide, leading to a total of 186 MERS cases across 16 hospitals with 36 deaths (19.3% case

fatality rate) (Ki, 2015). One month later, in July 2015, another large hospital outbreak took place in a large tertiary care center in Riyadh, Saudi Arabia with 130 cases and 51 deaths (39.25% case fatality rate) (Stone et al., 2016). A subsequent outbreak occurred in Jordan in August 2015, with 16 cases across three hospitals, and seven deaths (43.7% case fatality rate) (Payne et al., 2018). Smaller outbreaks continued to occur in 2016–18 although the number of patients and the magnitude of the outbreaks were less compared to earlier years, presumably due to better infection control practices and earlier identification of cases.

Transmission

Transmission of MERS-CoV in humans occurs through animal-to-human transmission or, human-to-human transmission in the community. Additionally, nosocomial transmission of MERS-CoV occurs frequently. All transmission described up-to-date, occurred in residents in or travelers to the Arabian Peninsula, or are traced to contact with patients with a history of recent travel to the Arabian Peninsula.

Animal-Human Transmission

Animals seem to play an important role in the transmission of the MERS-CoV. Earlier studies have suggested that bats might be the potential reservoir of MERS-CoV. This hypothesis that was based on the close proximity of MERS-CoV—phylogenetically- to Tylonycteris bat coronavirus HKU4 (Ty-BatCoV HKU4) and Pipistrellus bat coronavirus HKU5 (Pi-BatCoV HKU5) (Woo et al., 2012). A study from Saudi Arabia, a phylogenetically MERS-CoV identical short gene segment, was detected in a fecal sample of one of the 29 captured bats near the home of a laboratory-confirmed MERS-CoV patient (Memish et al., 2013a). However, live MERS-CoV has never been recovered from bats. Further studies are needed to further establish the role of bats in transmission to humans including larger surveillance studies with full viral genome sequencing. Epidemiologically, it seems unlikely that bats are the direct source of human cases, since none of the community-acquired laboratory-confirmed MERS cases had clear bat exposure.

Dromedary camels are thought to be a host for MERS-CoV. Direct contact with dromedary camels within 14 days prior to infection was identified as an independent risk factor for MERS (Gossner et al., 2016). Camel-human transmission was also suggested in a 44-year-old, previously healthy man from Jeddah, Saudi Arabia who was admitted to the intensive care Unit (ICU) with severe MERS pneumonia, and died 15 days after admission. The patient had owned a herd of 9 camels and used to visit them daily until 3 days prior to his admission. Four out of the nine camels were sick with nasal discharge, 1 week prior to the patient's onset of symptoms. The patient had significant contact with camels' excretions. Respiratory specimens from the patient and one of his camels showed identical MERS-CoV full genome sequencing. Moreover, serum antibodies for MERS-CoV were positive in both the patient and the camel, with the camel seropositivity preceded the patient's seropositivity suggesting that direction of transmission was from the camel to the patient. A large cross-sectional study from Saudi Arabia identified MERS-CoV infected patients who had a history of camel contact. The investigators obtained nasal swabs and serum samples from 584 dromedary camels and found that 12.6% of the studied camels were MERS-CoV polymerase chain reaction (PCR) positive, and 70.9% of them were MERS-CoV antibodies positive. Furthermore, 10 of the full genome sequences of the camel MERS-CoV were identical to their contacted patients (Kasem et al., 2018). This data suggests an important role for camels in the transmission of MERS-CoV. However, in a cohort of 1125 patients with laboratory-confirmed MERS, camel contact was reported only in 235 patients (20.9%), denied by 276 patients (24.5%), and not reported in the other 614 patients (54.6%) (Conzade et al., 2018).

Human-Human Transmission

Hospital-based outbreaks and community-based clusters described above suggest strongly that human-human transmission does occur. The transmission was more commonly observed in healthcare-based outbreaks, compared to community clusters. The number of close contacts who got infected by patients with confirmed MERS-CoV appears to be low, although, it was evident that some patients were spreading the infection to a disproportionally large number of individuals (super spreaders) (Hui, 2016). This phenomenon was clearly described in more than one outbreak. The first outbreak which identified the super spreader phenomena was the Korean outbreak, in which a single imported index case resulted in a total of 186 cases. It was thought that 83% of transmission in the Korean outbreak was linked epidemiologically to five super spreaders (Korea Centers for Disease and Prevention, 2015) The same phenomenon was also described in a large outbreak in Riyadh, Saudi Arabia, where 6 out of the 130 cases, contributed to 58.7% of the transmission (Alenazi et al., 2017). However, it remains unclear if an asymptomatic individual who carries MERS-CoV can transmit the virus to others.

Community Transmission

The first family cluster was reported from Riyadh, Saudi Arabia, where three laboratory-confirmed cases and one probable case were diagnosed, and two out of the four patients died (Memish et al., 2013b). In a study that investigated 26 index cases of MERS and their 280 household contacts, the secondary transmission rate was found to be 4% ([95% CI, 2 to 7] (Drosten et al., 2014).

Healthcare-Associated Transmission

As described above, transmission was more commonly seen in hospital-based outbreaks compared to family community transmission, particularly in emergency department (ED). This was clearly illustrated in the Korean outbreak, where a single imported case had led to a total of 186 cases, 185 of which were nosocomial transmission (Kim et al., 2017) The main identified reasons for hospitals-based transmission were over-crowdedness of ED, late recognition of suspected MERS cases and inadequate infection control measures and proper isolation of suspected cases (Stone et al., 2016). Environmental surfaces in hospitals is a potential source of transmission. In one study, a viable MERS-CoV was detected in 15 out of 68 surface swabs collected from patient's rooms, restrooms and common corridors (Kim et al., 2016).

Virology

MERS-CoV is the sixth coronavirus that affects humans. It lies within the lineage C of the genus Betacoronavirus (CoV) in the family Coronaviridae under the order Nidovirales. It has close phylogenetic proximity to two bat coronaviruses, Tylonycteris bat CoV HKU4 (Ty-BatCoV-HKU4) and Pipistrellus bat CoV HKU5 (Pi-BatCoV-HKU5). Like the other coronaviruses, it is an enveloped single-stranded RNA virus which replicates in the host-cell cytoplasm. The size of Its RNA genome is approximately 30 kb. It has structural proteins, called the E, M, and N proteins, and membrane protein called the Spike (S) protein, which plays an important role in the virus attachment and entry into the host cells.

Due to the large increase in the number of diagnosed cases in April 2014, there was a concern that MERS-CoV could have undergone mutation that led to increased virulence or transmissibility of the virus; however, this assumption was proven unlikely (Drosten et al., 2015).

Histopathology

The pathogenesis and histopathology of MERS-CoV is poorly understood and understudied. Post-mortem autopsies were rarely performed on MERS patients due to cultural reasons in the Arabian Peninsula. Most of the knowledge we have about the histopathology of MERS-CoV comes from in vitro, ex vivo, animal experiments and limited post-mortem reports. In a 33-year-old male, who died of MERS-CoV infection, post-mortem analysis of histopathology finding of pulmonary and extra-pulmonary tissue were examined under transmission electron microscopy which showed necrotizing pneumonia, pulmonary diffuse alveolar damage, acute kidney injury, portal and lobular hepatitis and myositis with muscle atrophic changes. The brain and heart were histologically unremarkable. Ultra-structurally, viral particles were localized in the pneumocytes, pulmonary macrophages, renal proximal tubular epithelial cells and macrophages infiltrating the skeletal muscles (Alsaad et al., 2018).

Case Definition

In the beginning of the outbreak, the WHO had proposed a case definition for MERS-CoV infection for epidemiological purposes, that was last updated on July 27, 2018. The United States (US) Center of Disease Control and Prevention (CDC) and the Saudi Ministry of Health (MOH), each had developed a case definition for suspected, confirmed and probable MERS-CoV infection (**Table 2**).

Clinical Manifestations

Incubation Period

In one of the earlier outbreaks in Saudi Arabia, the median incubation period for MERS-CoV infection was 5.2 days (95% CI 1.9–14.7 days) (Assiri et al., 2013b). Similarly, in the south Korean Outbreak, in 2015, the median incubation period was 6.3 days (95th percentile 12.1 days) (Korea Centers for Disease and Prevention, 2015). Therefore, MERS should be suspected in patients presenting with respiratory infection, and residence in or travel to the Arabian Peninsula within the last 14 days prior to onset of symptoms.

Demographic Features

Most of reported MERS patients have been in the adult age group. Only 31 pediatric cases were reported, most of which were detected on contact tracing screening (42% were asymptomatic), and among symptomatic cases, presence of comorbidities like congenital disease were commonly present (Al-Tawfiq et al., 2016). The mean age in one of study was 56.3 years (Balkhy et al., 2016). In another study, that described the epidemiological, clinical characteristics and demographics of 47 MERS-CoV infected patients, 82.9% of laboratory-confirmed cases were more than 40 years of age with a median age of 56 years. The male: female ratio was 3.3:1. Eighty nine percent of patients required ICU admission, and the median time to death was 14 days (ranging from 5 to

Table 2 Case definition of MERS-CoV.

	Saudi MOH[a]	
Suspected MERS-CoV Case		
Age Group	*Clinical*	*Epidemiological link*
Adult[b]	Severe pneumonia or ARDS (based on clinical or radiological evidence)	Not required
	Unexplained deterioration of a chronic condition of patients with congestive heart failure or chronic kidney disease on hemodialysis	Not required
Children and adults	Acute febrile illness ($T \geq 38.0^{\circ}C$) with/without respiratory symptoms OR gastrointestinal symptoms (diarrhea or vomiting), AND leukopenia (WBC $\leq 3.5 \times 10^9$ /L) or thrombocytopenia (platelets $< 150 \times 10^9$/L)	Within 14 days before symptom onset: 1. Exposure to a confirmed case of MERS-CoV infection *OR* 2. Visit to a healthcare facility where MERS-CoV patients(s) has recently(within 2 weeks) been identified/ treated *OR* 3. Contact with dromedary camels or consumption of camel products(e.g. raw meat, unpasteurized milk, urine)
Confirmed MERS-CoV Case		
A Confirmed case is defined as a suspected case with laboratory confirmation of MERS-CoV infection.		
WHO[c]		
Probable MERS-CoV Case		
A febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or Acute Respiratory Distress Syndrome) *AND* Direct epidemiologic link with a laboratory-confirmed MERS-CoV case *AND* Testing for MERS-CoV is unavailable, negative on a single inadequate specimen or inconclusive.		
A febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or Acute Respiratory Distress Syndrome) that cannot be explained fully by any other etiology *AND* The person resides or traveled in the Middle East, or in countries where MERS-CoV is known to be circulating in dromedary camels or where human infections have recently occurred *AND* Testing for MERS-CoV is inconclusive.		
An acute febrile respiratory illness of any severity AND Direct epidemiologic link (2) with a confirmed MERS-CoV case *AND* Testing for MERS-CoV is inconclusive		
Confirmed MERS-CoV Case		
A person with laboratory confirmation of MERS-CoV infection irrespective of clinical signs and symptoms		

[a]Saudi Ministry of Health Guidelines, updated on 21st May 2018.

[b]Adult are defined >14 years of age.

[c]World Health Organization interim case definition updated 27th July 2017.

Middle east respiratory syndrome coronavirus; Guidelines for healthcare professionals: https://www.moh.gov.sa/CCC/healthp/regulations/Documents/MERS-CoV%20Guidelines%20for%20Healthcare%20Professionals%20-%20May%202018%20-%20v5.1%20%281%29.pdf.

36 days) (Assiri et al., 2013a). One study from Saudi Arabia, have compared critically ill MERS-CoV patients with critically ill Non-MERS-CoV patients, and had found that MERS-CoV patients tend to be younger, more likely to require mechanical ventilation and had higher mortality (Arabi et al., 2017). There were eight reported MERS-CoV infection during pregnancy, from Jordan, United Arab Emirates and Saudi Arabia, three of them ended with maternal death (Assiri et al., 2016).

Pulmonary Manifestations

In the beginning of the epidemic, the typical presentation of reported MERS was severe pneumonia, with Acute Respiratory Distress Syndrome (ARDS) with or without acute kidney injury, but as the surveillance and testing had increased, milder or even asymptomatic cases have been described. In a cohort of 47 patients, with MERS-CoV infection, the clinical presentation were fever (93%), cough (83%), shortness of breath (72%), myalgia (32%), diarrhea (26%), sore throat (21%), vomiting (21%), abdominal pain (17%) and hemoptysis (17%) (Assiri et al., 2013a).

A study that compared 330 critically ill MERS-CoV infected patients with 220 critically ill patients with non-MERS severe acute respiratory infection (SARI) found that MERS patients were younger than non-MERS SARI patients (median [Q1, Q3] 58 [44, 69] vs 70 [52, 78] and were more likely to be males (68.2% vs 58.1%) and to be healthcare workers (9.7% vs 0.0%). Chronic comorbidities were prevalent (any comorbidity, 80.3% in MERS SARI, 91.4% in non-MERS SARI). After onset of symptoms, MERS-COV patients presented to ER with a median of 5 days and admitted to ICU after 7 days, which was 2 days longer compared to non-MERS-CoV SARI patients. Mechanical ventilation was required for 85.2% of patients with MERS-CoV patients. At the time of ICU admission, patients with MERS-CoV were more likely to be hypoxemic, compared with non-MERS SARI patients (ratio of arterial oxygen partial pressure to fractional inspired oxygen- PaO2/FiO2: 106.3 [66.2, 160] vs 176 [104, 252]) (Arabi et al., 2017).

Extra-Pulmonary Manifestations

Many cases of MERS present with gastrointestinal manifestations with or without respiratory symptoms. Among the critically ill patients, the most described extra-pulmonary manifestations were acute kidney injury and shock (Arabi et al., 2014). Very few patients were reported to have neurological symptoms, in addition to the pneumonia (Arabi et al., 2015).

Primary infections were more likely to be severe, as opposed to secondary cases. Secondary MERS infection tends to cause a milder or asymptomatic disease, however severe disease has been described. Secondary cases are more likely to be younger with no comorbidities. Asymptomatic infections have bee also described in patients with dromedary camel's contacts who were identified during surveillance (Al Hammadi et al., 2015). Mortality rates were reported to be higher in older age group, male gender and patients with comorbidities (Assiri et al., 2013a).

Severe MERS Pneumonia Among Healthcare Workers

Numerous cases of MERS occurred among healthcare-workers; leading in some of them to severe illness resulting in admission to ICU. In a study that examined 32 critically ill healthcare-workers with MERS, 43.75% were nurses and 25% were physicians. 34.4% were having comorbidities, mainly chronic kidney disease (15.6%). Fever at presentation, was found in 30/32 (93.8%), cough in 25/32 (78.1%), and gastrointestinal symptoms in11/32 (34.4%). Eight out of the 32 (25%) healthcare workers died (Shalhoub et al., 2018).

Laboratory Findings

Among all hospitalized patients with severe MERS pneumonia, the most commonly observed laboratory abnormalities were lymphopenia (34%), thrombocytopenia (36%) and raised lactate dehydrogenase (LDH) (49%). Other abnormalities like leukopenia (14%), lymphocytosis (11%), raised aspartate aminotransferase (AST) (15%), raised alanine aminotransferase (ALT) (11%), and raised lactate dehydrogenase (49%) were also observed (Assiri et al., 2013a). In a cohort of 330 critically ill MERS-CoV patients, leukopenia was observed in 20.2%, thrombocytopenia in 58.7%, raised ALT in 56.3%, and raised AST in 86.8% (Arabi et al., 2017).

Imaging Findings

Most of the reported symptomatic cases with severe MERS pneumonia had abnormal chest-X-ray. Abnormalities ranged from mild to extensive changes. Peripheral ground-glass opacities were the most frequently found abnormality on CXR, in 55 studied case (Das et al., 2015) Other findings include, unilateral or bilateral airspace opacities, increased broncho-vascular markings, patchy infiltrates, interstitial changes, nodular opacities, reticular opacities, reticulo-nodular shadowing, pleural effusions, and ARDS pattern. Among inpatients who had chest computed tomography scan (CT scan), the most frequent findings were peripheral and bibasilar opacities bilaterally.

Diagnosis

In patient presenting with severe pneumonia, MERS should be suspected based on the presence epidemiologic links (residence or travel from the Arabian Peninsula especially if there is history of contact with camels, contact with a person infected with MERS or working or being treated in a hospital where MERS patients are managed). Such links should lead to application of appropriate infection control measures (see below) and to initiate diagnostic work up for MERS.

Diagnosis of MERS is based on a positive real-time reverse transcriptase polymerase chain reaction (rRT-PCR), obtained from a respiratory specimen. Nasopharyngeal or oropharyngeal swab of the upper respiratory tract are often used in patients who are unable to produce lower respiratory samples. However, lower respiratory samples (sputum, endotracheal aspirate, or broncho-alveolar lavage) are preferred as they generally have better yield. In patients with suspected MERS, it is recommended to send more than one specimen since a negative test does not exclude the diagnosis.

In a cohort of critically ill patients with MERS pneumonia, the diagnosis of MERS was based on samples from the nasopharynx in 167 of 311 (54%) and from the lower respiratory tract (sputum, endotracheal aspirates, or broncho-alveolar lavage) in 144 of 311 (46%). The diagnosis was established from the first sample in 76% of patients, from the second sample in 16% of patients and from 3 to 5 repeat samples in 8% of the patients. Initial negative samples collected before positive ones were predominantly from the upper respiratory tract (81.5%) (Arabi et al., 2017).

Several serological assays have been used including enzyme-linked immune sorbent assay (ELISA) and immunofluorescence assay (IFA), which are typically used for screening, and neutralization techniques which are used for confirmation. A three different, indirect ELISA have been developed and validated based on MERS-CoV nucleocapsid protein (N), spike (S) ectodomain (amino acids 1–1297) and S1 subunit (amino acids 1–725) (Hashem et al., 2019). A single positive serological test, in the absence of

positive PCR is considered a probable case, in the setting of suspected MERS-CoV. However, a four-fold increase in MERS-CoV antibody titer by neutralization tests is considered a confirmed case.

Coinfections

Viral pathogens were identified in 5% of critically ill patients with MERS pneumonia which included other coronaviruses, respiratory syncytial virus, and influenza A virus. Bacterial co-infections are described in 18% of critically ill patients with MERS pneumonia, with Acinetobacter Species, Pseudomonas Species, *Klebsiella pneumoniae and Staphylococcus aureus* being the most frequent isolates (Arabi et al., 2017).

Management

There is no specific antiviral therapy for MERS-CoV infection up to date, although several modalities of treatment options have been tried or are under investigation. The mainstay of management of MERS-CoV infection is supportive care.

Empiric Antimicrobial Therapy

Patients with suspected severe MERS pneumonia-CoV infection might have other respiratory pathogens as a cause of their symptoms. Therefore, the WHO recommends starting appropriate empirical antimicrobial therapy as soon as possible, to cover community acquired or nosocomial associated pathogens, based on the presentation from the community or the hospital and based on local epidemiology and guidelines, until the microbiological diagnosis is confirmed.

Supportive Therapy

Supportive therapy is the mainstay of management of severe MERS pneumonia, which includes mechanical ventilation, vasopressor support, and renal replacement therapy if needed. Oxygen rescue therapy like extracorporeal membrane oxygenation (ECMO) has been used in patients with refractory hypoxemia. In one case-control study of patients with MERS, the rescue use of ECMO compared to a matched control with no-ECMO was associated with reduced in-hospital-mortality (65% compared 100%) (Alshahrani et al., 2018). Another retrospective study, found that critically ill healthcare workers who died because of MERS were more likely to have received ECMO than not, probably because the severity of pneumonia that led to use of rescue therapy, rather than use of ECMO itself (Shalhoub et al., 2018). Corticosteroids have been used frequently in MERS patients. A study that accounted for time-varying confounding demonstrated that corticosteroid use was not associated with difference on mortality although it was associated with prolongation of viral RNA shedding (Arabi et al., 2018b).

Specific Therapy

Data on other human coronaviruses, and in vitro activity of specific therapies were used to identify potential new therapy for MERS-CoV. Examples of those include: combination of ribavirin and interferon, lopinavir-Ritonavir, mycophenolate mofetil, convalescent -plasma, and, monoclonal and polyclonal antibodies (**Table 3**).

The efficacy of ribavirin/interferon combination was suggested to be promising in vitro and animal experiments and cell culture. In a study where two cell viral cultures lines grew MERS-CoV, high concentrations of ribavirin or interferon alpha 2 b were needed to inhibit viral replication, when each of the drugs was used alone, however, comparable inhibition was observed when combing them at a lower concentration (Falzarano et al., 2013a). Similar findings were observed in rhesus macaques model of MERS-CoV infection. Among animals who received combination of ribavirin and interferon alpha 2 b 8 hours after inoculation did not develop respiratory symptoms and had no or very minimal chest x-ray findings of infiltrate compared to the control group. Also, the treated group had a moderately lower viral genome copies and fewer severe lung histopathological changes (Falzarano et al., 2013b). Data on humans are based on retrospective studies. In retrospective cohort of 20 patients with severe MERS-CoV pneumonia, ribavirin and interferon combination therapy started at median day three after diagnosis, showed improved 14-day survival, compared to 24 patients who received only supportive therapy, however 28-day survival was not different between the 2 groups (Omrani et al., 2014). Other retrospective studies showed no difference in mortality between patients treated with ribavirin interferon combination, and patients who received supportive therapy (Al-Tawfiq et al., 2014; Shalhoub et al., 2015). The largest cohort study which adjusted for time-varying confounders showed that ribavirin with interferons (alpha 1a and 1b and beta 1a) was not associated with difference in mortality or viral shedding. None of the patients received interferon beta 1b (Arabi et al., 2019).

Lopinavir-ritonavir efficacy was studied in-vitro in animals with severe MERS-CoV infection, in which it showed favorable outcome (Chan et al., 2015). There is an ongoing randomized placebo controlled trial evaluating oral lopinavir-ritonavir in combination with subcutaneous interferon beta-1b in hospitalized patients with MERS (NCT02845843) (Arabi et al., 2018a).

The use of passive immune therapy with convalescent plasma was suggested as a potential therapeutic option. A study that examined the feasibility of convalescent plasma therapy for MERS was limited by the small pool of donors with sufficient titers of MERS-

Table 3 Summary of treatment options for MERS-CoV.

Treatment option	*Status*	*References*
Ribavirin/interferon combination	Ribavirin/interferon showed efficacy in and in vitro and in a rhesus macaques model. Data in humans are based on retrospective studies. The largest cohort that accounted for time-varying confounders did not demonstrate efficacy. There may be differences in efficacy among different interferons, as interferon beta-1b has the lowest inhibitory concentrations in vitro	Falzarano et al. (2013a) and Falzarano et al. (2013b)
Lopinavir-ritonavir	Lopinavir-ritonavir showed efficacy in in vitro and in a marmoset model. It is being tested in combination with interferon beta-1b in a randomized controlled trial (MERS-CoV Infection treated With A Combination of Lopinavir /Ritonavir and Interferon Beta-1b (MIRACLE), NCT02845843)	Chan et al. (2015)
Convalescent plasma	The feasibility of the option is limited due to the paucity of donors	Arabi et al. (2015)
Monoclonal antibodies	Several monoclonal antibodies exist with promising efficacy in in vitro and in animal studies	
Polyclonal antibodies	Polycolonal antibodies demonstrated promising efficacy in in vitro and in animal studies. Phase I trial has been completed. Plans for phase II trial are undergoing	Beigel et al. (2018)
Mycophenolate mofetil	Efficacy has been suggested in vitro but harm in a marmoset model	Chan et al. (2015)
Remdesivir	This new drug has promising efficacy in in-vitro and in animal studies. Phase I trial has been completed. Phase II trial is ongoing in Ebola survivors	Agostini et al. (2018)

CoV antibodies which may be related to the short-lasting immune response (Arabi et al., 2016). Several monoclonal antibody preparations have been developed. Humanized bovine transchromosomal polyclonal antibodies against MERS-CoV have been developed and undergone testing in a phase I trial (Beigel et al., 2018). A phase II trial in humans is being planned.

Mycophenolate mofetil efficacy against MERS-CoV was suggested in vitro studies. However, it was associated with harm in a marmoset model (Chan et al., 2015).

Remdesivir (GS-5734) which is the monophosphoramidate prodrug of the c-adenosine nucleoside analog GS-441524, has recently been reported to inhibit SARS-CoV, MERS-CoV and bat-CoV, in vitro. It has also been found to be therapeutic and prophylactic in SARS-CoV infected mouse modules (Agostini et al., 2018).

Prevention

Infection Control

Most of the reported hospital-based outbreaks were attributed to lack of adherence to proper infection control practice, delayed suspected cases identification, and to overcrowded emergency room and inappropriate triage. Addressing issues related to infection control practice and proper triaging of patients with suspected MERS-CoV, had resulted in a decline in the number and the magnitude of hospital outbreaks (Balkhy et al., 2016). The WHO and US CDC have published guidance for MERS prevention in healthcare institutes. As per the WHO recommendations, patients who have probable or confirmed MERS should be under contact and droplet precautions with eye protection. The patient should be under airborne precaution, when performing an aerosol generating procedure (AGP) like tracheal intubation or bronchoscopy. The US CDC, on the other hand, recommends contact and airborne precautions for all suspected or confirmed MERS-CoV patients. Viral shedding from respiratory secretions has been found to be at least 3 weeks from onset of symptoms. Therefore isolation precaution should not be discontinued until a negative PCR is obtained. Patients with suspected or confirmed MERS-CoV, who does not require admission, can be isolated at home.

Animal Contact

It is recommended to avoid contact with camels, both direct or indirect contact like consuming raw camel's milk or meat. This is particularly for high risk individuals, such as patients with heart failure, chronic lung disease and immunosuppression. People who have to be in contact with camels should observe infection control precautions, including washing hand before and after contact, and use of appropriate personal protective equipment's (PPE) when dealing of a suspected or confirmed infected camels. It is important to note that the infected camels may not be symptomatic or might only have mild symptoms. The Saudi Authorities had made

certain measures to reduce camel-human transmission, like banning camels in the Holy Areas, and moving the camels markets outside the cities.

Travel Restriction

The WHO did not place any travel restriction to any country that have reported MERS-CoV cases. Saudi Arabia, where most of the laboratory-confirmed cases have been reported, annually hosts millions of Muslims to perform Hajj and Omrah (pilgrimage), with no documented related cases of MERS to date. There were 2 Dutch patients who developed MERS after returning from 2014 hajj, but the two cases were thought to be acquired from a camel market and raw milk consumption rather than human-human transmission during Hajj.

MERS-CoV Vaccine

There is no licensed human vaccine for MERS-CoV till now, however, many experimental candidate vaccines are under development. Another approach is to vaccinate camels, as the source of infection for many human cases, and good progress has been made in this area (Alharbi, 2017).

Mortality and Predictors

As of end of December 2018, the global case fatality rate for MERS-CoV infection was reported as 35.3% (806/2279). It is thought this number overestimates the case fatality rate of the disease, because milder and asymptomatic cases are likely to be underrepresented in the reported cases. This was suggested in a study that estimated the number of undetected human symptomatic cases to be 62% (Cauchemez et al., 2014).

In a cohort of 47 MERS-CoV infected patients, case fatality rate was higher with increasing age (Assiri et al., 2013a). In another study that studied 939 MERS-CoV infected patients, independent risk factors for mortality were, age more 80 years, underlying cardiac comorbidity or cancer, and healthcare acquisition of the virus (Alsahafi and Cheng, 2016). In a South Korean cohort of 159 patients, risk factors for death were older age and underlying comorbidities (Majumder et al., 2015).

References

Agostini, M.L., Andres, E.L., Sims, A.C., Graham, R.L., Sheahan, T.P., Lu, X., Smith, E.C., Case, J.B., Feng, J.Y., Jordan, R., Ray, A.S., Cihlar, T., Siegel, D., Mackman, R.L., Clarke, M.O., Baric, R.S., Denison, M.R., 2018. Coronavirus susceptibility to the antiviral Remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. MBio 9.

Al Hammadi, Z.M., Chu, D.K., Eltahir, Y.M., Al Hosani, F., Al Mulla, M., Tarnini, W., Hall, A.J., Perera, R.A., Abdelkhalek, M.M., Peiris, J.S., Al Muhairi, S.S., Poon, L.L., 2015. Asymptomatic MERS-CoV infection in humans possibly linked to infected dromedaries imported from Oman to United Arab Emirates, May 2015. Emerging Infectious Diseases 21, 2197–2200.

Al-Abdallat, M.M., Payne, D.C., Alqasrawi, S., Rha, B., Tohme, R.A., Abedi, G.R., Al Nsour, M., Iblan, I., Jarour, N., Farag, N.H., Haddadin, A., Al-Sanouri, T., Tamin, A., Harcourt, J.L., Kuhar, D.T., Swerdlow, D.L., Erdman, D.D., Pallansch, M.A., Haynes, L.M., Gerber, S.I., 2014. Hospital-associated outbreak of Middle East respiratory syndrome coronavirus: A serologic, epidemiologic, and clinical description. Clinical Infectious Diseases 59, 1225–1233.

Alenazi, T.H., Al Arbash, H., El-Saed, A., Alshamrani, M.M., Baffoe-Bonnie, H., Arabi, Y.M., Al Johani, S.M., Hijazi, R., Alothman, A., Balkhy, H.H., 2017. Identified transmission dynamics of Middle East respiratory syndrome coronavirus infection during an outbreak: Implications of an overcrowded emergency department. Clinical Infectious Diseases 65, 675–679.

Alharbi, N.K., 2017. Vaccines against Middle East respiratory syndrome coronavirus for humans and camels. Reviews in Medical Virology 27.

Alsaad, K.O., Hajeer, A.H., Al Balwi, M., Al Moaiqel, M., Al Oudah, N., Al Ajlan, A., Aljohani, S., Alsolamy, S., Gmati, G.E., Balkhy, H., Al-Jahdali, H.H., Baharoon, S.A., Arabi, Y.M., 2018. Histopathology of Middle East respiratory syndrome coronovirus (MERS-CoV) infection—Clinicopathological and ultrastructural study. Histopathology 72, 516–524.

Alsahafi, A.J., Cheng, A.C., 2016. The epidemiology of Middle East respiratory syndrome coronavirus in the Kingdom of Saudi Arabia, 2012-2015. International Journal of Infectious Diseases 45, 1–4.

Alshahrani, M.S., Sindi, A., Alshamsi, F., Al-Omari, A., El Tahan, M., Alahmadi, B., Zein, A., Khatani, N., Al-Hameed, F., Alamri, S., Abdelzaher, M., Alghamdi, A., Alfousan, F., Tash, A., Tashkandi, W., Alraddadi, R., Lewis, K., Badawee, M., Arabi, Y.M., Fan, E., Alhazzani, W., 2018. Extracorporeal membrane oxygenation for severe Middle East respiratory syndrome coronavirus. Annals of Intensive Care 8, 3.

Al-Tawfiq, J.A., Momattin, H., Dib, J., Memish, Z.A., 2014. Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: An observational study. International Journal of Infectious Diseases 20, 42–46.

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 Journal of Clinical Pediatrics 5, 391–396.

Arabi, Y.M., Arifi, A.A., Balkhy, H.H., Najm, H., Aldawood, A.S., Ghabashi, A., Hawa, H., Alothman, A., Khaldi, A., Al Raiy, B., 2014. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. Annals of Internal Medicine 160, 389–397.

Arabi, Y.M., Harthi, A., Hussein, J., Bouchama, A., Johani, S., Hajeer, A.H., Saeed, B.T., Wahbi, A., Saedy, A., Aldabbagh, T., Okaili, R., Sadat, M., Balkhy, H., 2015. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). Infection 43, 495–501.

Arabi, Y.M., Hajeer, A.H., Luke, T., Raviprakash, K., Balkhy, H., Johani, S., Al-Dawood, A., Al-Qahtani, S., Al-Omari, A., Al-Hameed, F., Hayden, F.G., Fowler, R., Bouchama, A., Shindo, N., Al-Khairy, K., Carson, G., Taha, Y., Sadat, M., Alahmadi, M., 2016. Feasibility of using convalescent plasma immunotherapy for MERS-CoV infection, Saudi Arabia. Emerging Infectious Diseases 22, 1554–1561.

Arabi, Y.M., Al-Omari, A., Mandourah, Y., Al-Hameed, F., Sindi, A.A., Alraddadi, B., Shalhoub, S., Almotairi, A., Al Khatib, K., Abdulmomen, A., Qushmaq, I., Mady, A., Solaiman, O., Al-Aithan, A.M., Al-Raddadi, R., Ragab, A., Al Mekhlafi, G.A., Al Harthy, A., Kharaba, A., Ahmadi, M.A., Sadat, M., Mutairi, H.A., Qasim, E.A., Jose, J., Nasim, M., Al-Dawood, A., Merson, L., Fowler, R., Hayden, F.G., Balkhy, H.H., 2017. Critically ill patients with the Middle East respiratory syndrome: A multicenter retrospective cohort study. Critical Care Medicine 45, 1683–1695.

Arabi, Y.M., Shalhoub, S., Mandourah, Y., et al., 2019. Ribavirin and interferon therapy for critically Ill patients with middle east respiratory syndrome: A multicenter observational study. Clinical Infectious Diseases. https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciz544/5523209?redirectedFrom=fulltext.

Arabi, Y.M., Alothman, A., Balkhy, H.H., Al-Dawood, A., Aljohani, S., Al Harbi, S., Kojan, S., Al Jeraisy, M., Deeb, A.M., Assiri, A.M., Al-Hameed, F., Alsaedi, A., Mandourah, Y., Almekhlafi, G.A., Sherbeeni, N.M., Elzein, F.E., Memon, J., Taha, Y., Almotairi, A., Maghrabi, K.A., Qushmaq, I., Al Bshabshe, A., Kharaba, A., Shalhoub, S., Jose, J., Fowler, R.A., Hayden, F.G., Hussein, M.A., 2018a. Treatment of Middle East respiratory syndrome with a combination of lopinavir-ritonavir and interferon-beta1b (MIRACLE trial): Study protocol for a randomized controlled trial. Trials 19, 81.

Arabi, Y.M., Mandourah, Y., Al-Hameed, F., Sindi, A.A., Almekhlafi, G.A., Hussein, M.A., Jose, J., Pinto, R., Al-Omari, A., Kharaba, A., Almotairi, A., Al Khatib, K., Alraddadi, B., Shalhoub, S., Abdulmomen, A., Qushmaq, I., Mady, A., Solaiman, O., Al-Aithan, A.M., Al-Raddadi, R., Ragab, A., Balkhy, H.H., Al Harthy, A., Deeb, A.M., Al Mutairi, H., Al-Dawood, A., Merson, L., Hayden, F.G., Fowler, R.A., 2018b. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. American Journal of Respiratory and Critical Care Medicine 197, 757–767.

Assiri, A., Al-Tawfiq, J.A., Al-Rabeeah, A.A., Al-Rabiah, F.A., Al-Hajjar, S., Al-Barrak, A., Flemban, H., Al-Nassir, W.N., Balkhy, H.H., Al-Hakeem, R.F., Makhdoom, H.Q., Zumla, A.I., Memish, Z.A., 2013a. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: A descriptive study. The Lancet Infectious Diseases 13, 752–761.

Assiri, A., Mcgeer, A., Perl, T.M., Price, C.S., Al Rabeeah, A.A., Cummings, D.A., Alabdullatif, Z.N., Assad, M., Almulhim, A., Makhdoom, H., Madani, H., Alhakeem, R., Al-Tawfiq, J.A., Cotten, M., Watson, S.J., Kellam, P., Zumla, A.I., Memish, Z.A., 2013b. Hospital outbreak of Middle East respiratory syndrome coronavirus. The New England Journal of Medicine 369, 407–416.

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. Clinical Infectious Diseases 63, 951–953.

Balkhy, H.H., Alenazi, T.H., Alshamrani, M.M., Baffoe-Bonnie, H., Arabi, Y., Hijazi, R., Al-Abdely, H.M., El-Saed, A., Al Johani, S., Assiri, A.M., Bin Saeed, A., 2016. Description of a hospital outbreak of Middle East respiratory syndrome in a large tertiary Care Hospital in Saudi Arabia. Infection Control and Hospital Epidemiology 37, 1147–1155.

Beigel, J.H., Voell, J., Kumar, P., Raviprakash, K., Wu, H., Jiao, J.A., Sullivan, E., Luke, T., Davey Jr., R.T., 2018. Safety and tolerability of a novel, polyclonal human anti-MERS coronavirus antibody produced from transchromosomic cattle: A phase 1 randomised, double-blind, single-dose-escalation study. The Lancet Infectious Diseases 18, 410–418.

Cauchemez, S., Fraser, C., Van Kerkhove, M.D., Donnelly, C.A., Riley, S., Rambaut, A., Enouf, V., Van Der Werf, S., Ferguson, N.M., 2014. Middle East respiratory syndrome coronavirus: Quantification of the extent of the epidemic, surveillance biases, and transmissibility. The Lancet Infectious Diseases 14, 50–56.

Chan, J.F., Yao, Y., Yeung, M.L., Deng, W., Bao, L., Jia, L., Li, F., Xiao, C., Gao, H., Yu, P., Cai, J.P., Chu, H., Zhou, J., Chen, H., Qin, C., Yuen, K.Y., 2015. Treatment with Lopinavir/ritonavir or interferon-beta1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. The Journal of Infectious Diseases 212, 1904–1913.

Conzade, R., Grant, R., Malik, M., Elkholy, A., Elhakim, M., Samhouri, D., Ben Embarek, P., Van Kerkhove, M., 2018. Reported direct and indirect contact with dromedary camels among laboratory-confirmed MERS-CoV cases. Viruses 10, 425.

Das, K.M., Lee, E.Y., Al Jawder, S.E., Enani, M.A., Singh, R., Skakni, L., Al-Nakshabandi, N., Aldossari, K., Larsson, S.G., 2015. Acute Middle East respiratory syndrome coronavirus: Temporal lung changes observed on the chest radiographs of 55 patients. AJR. American Journal of Roentgenology 205, W267–W274.

de Groot, R.J., Baker, S.C., Baric, R.S., Brown, C.S., Drosten, C., Enjuanes, L., Fouchier, R.A., Galiano, M., Gorbalenya, A.E., Memish, Z.A., Perlman, S., Poon, L.L., Snijder, E.J., Stephens, G.M., Woo, P.C., Zaki, A.M., Zambon, M., Ziebuhr, J., 2013. Middle East respiratory syndrome coronavirus (MERS-CoV): Announcement of the Coronavirus Study Group. Journal of Virology 87, 7790–7792.

Drosten, C., Meyer, B., Müller, M.A., Corman, V.M., Al-Masri, M., Hossain, R., Madani, H., Sieberg, A., Bosch, B.J., Lattwein, E., Alhakeem, R.F., Assiri, A.M., Hajomar, W., Albarrak, A.M., Al-Tawfiq, J.A., Zumla, A.I., Memish, Z.A., 2014. Transmission of MERS-Coronavirus in Household Contacts. The New England Journal of Medicine 371, 828–835.

Drosten, C., Muth, D., Corman, V.M., Hussain, R., Al Masri, M., Hajomar, W., Landt, O., Assiri, A., Eckerle, I., Al Shangiti, A., Al-Tawfiq, J.A., Albarrak, A., Zumla, A., Rambaut, A., Memish, Z.A., 2015. An observational, laboratory-based study of outbreaks of middle East respiratory syndrome coronavirus in Jeddah and Riyadh, kingdom of Saudi Arabia, 2014. Clinical Infectious Diseases 60, 369–377.

Fagbo, S.F., Skakni, L., Chu, D.K., Garbati, M.A., Joseph, M., Peiris, M., Hakawi, A.M., 2015. Molecular epidemiology of hospital outbreak of Middle East respiratory syndrome, Riyadh, Saudi Arabia, 2014. Emerging Infectious Diseases 21, 1981–1988.

Falzarano, D., De Wit, E., Martellaro, C., Callison, J., Munster, V.J., Feldmann, H., 2013a. Inhibition of novel beta coronavirus replication by a combination of interferon-alpha2b and ribavirin. Scientific Reports 3, 1686.

Falzarano, D., De Wit, E., Rasmussen, A.L., Feldmann, F., Okumura, A., Scott, D.P., Brining, D., Bushmaker, T., Martellaro, C., Baseler, L., Benecke, A.G., Katze, M.G., Munster, V.J., Feldmann, H., 2013b. Treatment with interferon-alpha2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. Nature Medicine 19, 1313–1317.

Gossner, C., Danielson, N., Gervelmeyer, A., Berthe, F., Faye, B., Kaasik Aaslav, K., Adlhoch, C., Zeller, H., Penttinen, P., Coulombier, D., 2016. Human-dromedary camel interactions and the risk of acquiring zoonotic Middle East respiratory syndrome coronavirus infection. Zoonoses and Public Health 63, 1–9.

Hashem, A.M., Al-Amri, S.S., Al-Subhi, T.L., Siddiq, L.A., Hassan, A.M., Alawi, M.M., Alhabbab, R.Y., Hindawi, S.I., Mohammed, O.B., Amor, N.S., Alagaili, A.N., Mirza, A.A., Azhar, E.I., 2019. Development and validation of different indirect ELISAs for MERS-CoV serological testing. Journal of Immunological Methods 466, 41–46.

Hui, D.S., 2016. Super-spreading events of MERS-CoV infection. Lancet 388 (10048), 942–943. https://doi.org/10.1016/S0140-6736(16)30828-5.

Kapoor, M., Pringle, K., Kumar, A., Dearth, S., Liu, L., Lovchik, J., Perez, O., Pontones, P., Richards, S., Yeadon-Fagbohun, J., Breakwell, L., Chea, N., Cohen, N.J., Schneider, E., Erdman, D., Haynes, L., Pallansch, M., Tao, Y., Tong, S., Gerber, S., Swerdlow, D., Feikin, D.R., 2014. Clinical and laboratory findings of the first imported case of Middle East respiratory syndrome coronavirus to the United States. Clinical Infectious Diseases 59, 1511–1518.

Kasem, S., Qasim, I., Al-Hufofi, A., Hashim, O., Alkarar, A., Abu-Obeida, A., Gaafer, A., Elfadil, A., Zaki, A., Al-Romaihi, A., Babekr, N., El-Harby, N., Hussien, R., Al-Sahaf, A., Al-Doweriej, A., Bayoumi, F., Poon, L.L.M., Chu, D.K.W., Peiris, M., Perera, R., 2018. Cross-sectional study of MERS-CoV-specific RNA and antibodies in animals that have had contact with MERS patients in Saudi Arabia. Journal of Infection and Public Health 11, 331–338.

Ki, M., 2015. 2015 MERS outbreak in Korea: Hospital-to-hospital transmission. Epidemiology and Health 37, e2015033.

Kim, S.H., Chang, S.Y., Sung, M., Park, J.H., Bin Kim, H., Lee, H., Choi, J.P., Choi, W.S., Min, J.Y., 2016. Extensive viable Middle East respiratory syndrome (MERS) coronavirus contamination in air and surrounding environment in MERS isolation wards. Clinical Infectious Diseases 63, 363–369.

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. The Journal of Hospital Infection 95, 207–213.

Korea Centers for Disease Control and Prevention, 2015. Middle East respiratory syndrome coronavirus outbreak in the Republic of Korea, 2015. Osong Public Health and Research Perspectives 6, 269–278.

Majumder, M.S., Kluberg, S.A., Mekaru, S.R., Brownstein, J.S., 2015. Mortality risk factors for Middle East respiratory syndrome outbreak, South Korea, 2015. Emerging Infectious Diseases 21, 2088–2090.

Memish, Z.A., Mishra, N., Olival, K.J., Fagbo, S.F., Kapoor, V., Epstein, J.H., Alhakeem, R., Durosinloun, A., Al Asmari, M., Islam, A., Kapoor, A., Briese, T., Daszak, P., Al Rabeeah, A.A., Lipkin, W.I., 2013a. Middle East respiratory syndrome coronavirus in bats, Saudi Arabia. Emerging Infectious Diseases 19, 1819–1823.

Memish, Z.A., Zumla, A.I., Al-Hakeem, R.F., Al-Rabeeah, A.A., Stephens, G.M., 2013b. Family cluster of Middle East respiratory syndrome coronavirus infections. The New England Journal of Medicine 368, 2487–2494.

Oboho, I.K., Tomczyk, S.M., Al-Asmari, A.M., Banjar, A.A., Al-Mugti, H., Aloraini, M.S., Alkhaldi, K.Z., Almohammadi, E.L., Alraddadi, B.M., Gerber, S.I., Swerdlow, D.L., Watson, J.T., Madani, T.A., 2015. 2014 MERS-CoV outbreak in Jeddah—A link to health care facilities. The New England Journal of Medicine 372, 846–854.

Omrani, A.S., Saad, M.M., Baig, K., Bahloul, A., Abdul-Matin, M., Alaidaroos, A.Y., Almakhlafi, G.A., Albarrak, M.M., Memish, Z.A., Albarrak, A.M., 2014. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: A retrospective cohort study. The Lancet Infectious Diseases 14, 1090–1095.

Payne, D.C., Biggs, H.M., Al-Abdallat, M.M., Alqasrawi, S., Lu, X., Abedi, G.R., Haddadin, A., Iblan, I., Alsanouri, T., Al Nsour, M., Sheikh Ali, S., Rha, B., Trivedi, S.U., Rasheed, M.A.U., Tamin, A., Lamers, M.M., Haagmans, B.L., Erdman, D.D., Thornburg, N.J., Gerber, S.I., 2018. Multihospital outbreak of a Middle East respiratory syndrome coronavirus deletion variant, Jordan: A molecular, serologic, and epidemiologic investigation. Open Forum Infectious Diseases 5 ofy095.

Shalhoub, S., Farahat, F., Al-Jiffri, A., Simhairi, R., Shamma, O., Siddiqi, N., Mushtaq, A., 2015. Ifn-alpha2a or Ifn-beta1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: A retrospective study. The Journal of Antimicrobial Chemotherapy 70, 2129–2132.

Shalhoub, S., Al-Hameed, F., Mandourah, Y., Balkhy, H.H., Al-Omari, A., Al Mekhlafi, G.A., Kharaba, A., Alraddadi, B., Almotairi, A., Al Khatib, K., Abdulmomen, A., Qushmaq, I., Mady, A., Solaiman, O., Al-Aithan, A.M., Al-Raddadi, R., Ragab, A., Al Harthy, A., Al Qasim, E., Jose, J., Al-Ghamdi, G., Merson, L., Fowler, R., Hayden, F.G., Arabi, Y.M., 2018. Critically ill healthcare workers with the middle east respiratory syndrome (MERS): A multicenter study. PLoS One 13, e0206831.

Stone, J., Balkhy, H., Ozcan, C., 2016. Unique case of papillary fibroelastoma originating from the right interatrial septum. International Journal of Cardiology 223, 251–253.

The Florida Department Of Health. (2018), Dec 10. *Middle East Respiratory Syndrome (MERS)* [Online]. Available: http://www.floridahealth.gov/diseases-and-conditions/mers/index.html [Accessed 2019, April 27].

Wise, J., 2012. Patient with new strain of coronavirus is treated in intensive care at London hospital. BMJ 345, e6455.

Woo, P.C., Lau, S.K., Li, K.S., Tsang, A.K., Yuen, K.Y., 2012. Genetic relatedness of the novel human group C betacoronavirus to Tylonycteris bat coronavirus HKU4 and Pipistrellus bat coronavirus HKU5. Emerging Microbes & Infections 1, e35.

World Health Organization. (2019), Mar 31. *Middle East respiratory syndrome coronavirus (MERS-CoV)* [Online]. Available: https://www.who.int/emergencies/mers-cov/en/ [Accessed 2019, April 27].

Zaki, A.M., Van Boheemen, S., Bestebroer, T.M., Osterhaus, A.D., Fouchier, R.A., 2012. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. The New England Journal of Medicine 367, 1814–1820.