Invited chapter for *Seminars in Respiratory and Critical Care Medicine (SRCCM):"Respiratory Viral Infections"*

Title:

Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

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Abstract:

The past two decades have witnessed the emergence of three zoonotic coronaviruses which have jumped species to cause lethal disease in humans: severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2. MERS-CoV emerged in Saudi Arabia in 2012 and the origins of MERS-CoV are not fully understood. Genomic analysis indicates it originated in bats and transmitted to camels. Human-to-human transmission occurs in varying frequency, being highest in healthcare environment and to a lesser degree in the community and among family members. Several nosocomial outbreaks of human-to-human transmission have occurred, the largest in Riyadh and Jeddah in 2014 and South Korea in 2015. MERS-CoV remains a high-threat pathogen identified by WHO as a priority pathogen because it causes severe disease that has a high mortality rate, epidemic potential, and no medical countermeasures. MERS-CoV has been identified in dromedaries in several countries in the Middle East, Africa, and South Asia. MERS-CoV-2 causes a wide range of clinical presentations, although the respiratory system is predominantly affected. There are no specific anti-viral treatments although recent trials indicate that combination antivirals may be useful in severely ill patients. Diagnosing MERS-CoV early and implementation infection control measures are critical to preventing hospital-associated outbreaks. Preventing MERS relies on avoiding unpasteurized or uncooked animal products, practicing safe hygiene habits in health care settings and around dromedaries, community education and awareness training for health workers, as well as implementing effective control measures Effective vaccines for MERS-COV are urgently needed but still under development.

Key words: Coronavirus, Epidemic infections, Middle East respiratory syndrome (MERS) Coronavirus, (MERS-CoV)

Introduction:

During the past two decades three zoonotic coronaviruses have jumped species to cause epidemic lethal diseases in humans: The severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), The Middle East respiratory syndrome coronavirus (MERS-CoV), and the SARS-CoV-2. MERS-CoV first emerged in Saudi Arabia in 2012 is transmitted to humans from infected dromedary camels through direct or indirect contact. The Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) was described in 2002 in Guangdong Province, China [1,2]. The disease caused 8096 cases and 774 (9.6%) deaths over a four-month period from late 2002 to early 2003 [3]. SARS cases were described in Vietnam, Hong Kong, Canada, United Sates, Ireland, Vietnam, and Singapore [1,4–11] and all cases were linked to a patient who stayed in hotel M in Hong Kong [12]. Ten years later, a novel coronavirus was isolated from a patient in Saudi Arabia [13,14] and this is the MERS-CoV [15].

This chapter reviews the epidemiology, geographical distribution, origin and reservoirs of the MERS-CoV, transmission, risk factors, nosocomial and community outbreaks, clinical and laboratory features, diagnosis, management, and prevention of MERS-CoV.

MERS-CoV:

The MERS-CoV is a large, enveloped, positive strand RNA virus. The coronavirus is classified into four genera (alpha, beta, delta, and gamma) and human coronaviruses belong to the alpha or the beta genera [16]. There are four coronaviruses (HCoV 229E, NL63, OC43, and HKU1) that are well known since the 1960's to cause human common cold and gastrointestinal symptoms. These

viruses circulate in livestock, avian, bat, mouse and other wild animals. SARS belongs to the beta genera [17] and the MERS-CoV is classified in lineage C betacoronavirus [18].

The animal host for SARS was identified as bats with Himalayan palm civets (*Paguma larvata*), and raccoon dogs (*Nyctereutes procyonoides*) intermediate hosts [19–21], and for MERS-CoV it was linked to dromedary camels [22–32]. In the case of the 2019 nCoV, an evolutionary sequence analysis suggested snakes as the most likely reservoir [33]. In addition, there was a recombination of a bat coronavirus with an origin-unknown coronavirus in the spike (S) glycoprotein. This finding could explain reduced disease severity [33]. The receptors for the SARS-CoV is angiotensin 1-converting enzyme 2 (ACE2) [34,35], whereas, the receptor for the MERS-CoV is dipeptidyl peptidase-4 (DPP4) [36–38].

Epidemiology

MERS-CoV was first identified in 20212 in a clinical sample from a 60-year old man who was hospitalized at a Jeddah hospital with community-acquired pneumonia with subsequent renal and respiratory failure [13]. Subsequently several outbreaks of healthcare-associated infection occured among multiple healthcare facilities in Al-Hasa, in the eastern province of Saudi Arabia [39]. The largest outbreaks were reported in Riyadh and Jeddah in 2014 and the largest outside KSA in South Korea in 2015 caused by a traveller returining from Saudi Arabia. MERS-CoV remains a high-threat pathogen identified by WHO as a priority pathogen because it causes severe disease that has a high mortality rate, epidemic potential, and no medical countermeasures. In the MENA Region, 12 countries (Bahrain, Egypt, Islamic Republic of Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Tunisia, United Arab Emirates and Yemen) have so far reported laboratory-confirmed cases of MERS. Amongst these countries, imported cases that were associated with

travel were reported from Egypt, Lebanon, Tunisia and Yemen. As of March 2021, there were 2574 laboratory-confirmed cases with 885 (34.4%) deaths from 27 countries [40] **figure 1**.

Dromedary camels and human infection

Dromedary camels appear to be the major reservoir host and source of MERS-CoV infection in humans. However, the exact role of dromedaries in the transmission of the virus and the exact routes of transmission remain to be determined.The origin of MERS-CoV is thought to be bats as a fragment of 190-nucleotide of RNA-dependent RNA polymerase (*RdRp*) region of MERS-CoV genome was detected in a fecal pellet from an Egyptian tomb bat (*Taphozous perforates*) and this was identical to the sequence of the virus from the index case [41]. The intermediate host is thought to be the one-humped dromedaries (*Camelus dromedarius*). Line of evidence of the role of camels in the transmission of MERS-CoV relies on the fact that studies showed high prevalence of anti-MERS-CoV antibodies in dromedary camels in the Arabian Peninsula, North Africa and Eastern Africa [25,42–47]. A second line of evidence comes from the fact that RT-PCR detected MERS-CoV in oronasal and fecal samples of dromedary camels [48–54] especially among juvenile camels [48–50,54]. Replicating MERS-CoV was isolated in cell cultures from dromedary camels [22,49,52,55,56]. Similar and near-identical MERS-CoV strains were isolated from epidemiologically linked dromedary camels and their contacts [22,24,57,58].

Transmission, risk factors, Nosocomial and Community outbreaks,

A primary MERS-CoV infection case is defined by the WHO as a laboratory-confirmed MERS-CoV infection that had no direct epidemiological link to a human MERS-CoV infection and was acquired outside of a health-care facility presumably from direct or indirect contact with the

reservoir host—dromedary camels [59]. A secondary MERS-CoV case is defined by WHO as a laboratory-confirmed MERS-CoV infection with a direct epidemiological link to an individual with confirmed or probable MERS-CoV infection [59]. Primary MERS cases occur through direct or indirect contact with dromedary camels. Camel exposure has been reported in 1.7-54.9% of primary cases [26,60].

Although, multiple family clusters of MERS-CoV were described [61–63] the hallmark of MERS-CoV infection is healthcare associated infections [39,64–83]. In a hospital outbreak, 17 of 18 MERS cases were linked phylogenetically and epidemiologically [84]. An analysis of healthcare associated infections of MERS showed that 25% of cases were healthcare workers [85]. Nosocomial infections were associated with a high reproduction number of 1.0-5.7 at the start of the outbreaks and then decreased to < 1 within 2 to 6 weeks [85]. Secondary cases are usually the result of human-to-human transmission among close contacts within families [61–63], in the community, or more commonly in the healthcare settings [39,64–83]. Outbreaks of MERS-CoV infection in healthcare settings are the hallmark of MERS and such outbreaks had occurred in several hospitals in different countries such as the initial Al-Hasa outbreak (in 2013) [39], Madinah (in 2013) [65], Jeddah (in 2014) [64,79,86], Taif (in 2015) [71] and Riyadh (in 2014, 2015, 2016, 2017 and 2018) [40,83,87,88], Seoul, South Korea (2015) [89–91], and Amman, Jordan (in 2015) [92]. There are multiple factors contributing to the transmission of MERS-CoV in the healthcare settings such as: hospital design and adequacy of ventilation [64,71,77–79,86,90–98], healthcare workers related issues such as infection control practices [40,64,65,67–69,72,77–79,86,87,90–98], patients' flow and overcrowding in certain hospital departments like emergency room [64,78,79,86,90–98], aerosol generating procedures [39,40,78,90–97],

patients' characteristics [78,90–97] and social norms of multiple visitors [78,90–97], table 1. The cited MERS-CoV reproduction number is 0.8-1.3 [72,73].

Clinical features

***Incubation period*:** The median incubation period is 5.2 days (95% CI, 1.9 to 14.7) with a serial interval of 7.6 days (95% CI, 2.5 to 23.1) [39].

Clinical manifestations: As with other respiratory infectious diseases, a wide spectrum of clinical manifestation occurs in people with MERS-CoV infection: from the asymptomatic, mild, moderate, severe to fulminant disease [99]. Individuals with mild primary MERS-CoV infections are often missed by current surveillance systems since they usually do not present to health-care facilities [99]. Whilst a range of clinical symptoms have been reported, common presenting symptoms include ever cough, shortness of breath, [80,82,98,107] and up to one third of the MERS patients may have vomiting and diarrhea [39,82,98,107–109]. A summary of most common symptoms is shown in figure 2 [39,78].

Mortality and risk factors: The MERS-CoV case fatality rate is upto 35% and the fatalities are associated with increased comorbidities [100] and among critical ill patients [95,101–103]. Cases of primary infection may progress to severe disease and these cases tend to occur in those >65 years, those with comorbidities such as diabetes, cancer, chronic lung disease, chronic heart disease, chronic kidney disease and immunosuppressive states [26,99,104]. The most common comorbidities associated with MERS-CoV infection are shown in **figure 3** [39,100,105–108]. The 30-day mortality was associated with increased age (> 65 years), non-healthcare workers, pre-

existing comorbidities, severe disease, hospital-acquired infections and corticosteroid use [82,102–104].

The rate of asymptomatic MERS-CoV cases was 12.5% among 144 PCR laboratory-confirmed cases in April 2012-October 2013 and this rate increased to 25.1% among 255 confirmed cases in 2014 [109]. The proportion of asymptomatic cases reported among pediatric confirmed MERS-CoV cases were higher (41.9%-81.8%) [109]. The extent of the occurrence of asymptomatic individuals and the role they play in the transmission of MERS-CoV are not well characterized [109,110].

Although those patients have community pneumonia, it was not possible to predict if they have MERS or another etiology based on symptoms and signs upon presentation [102,105]. The use of visual triaging scores a sensitivity of 74.1% and an exceptionally low specificity of 18.6% for MERS-CoV infection [111].

The median time to hospitalization, ICU admission, mechanical ventilation and death were 5, 7, and 11 days, respectively [39,60]. In one outbreak, the time from onset to hospitalization was 7 days, 11 days for the development of respiratory distress and 16 days till ICU admission [112]. Severe MERS-CoV infection occurs mainly in primary rather than secondary cases, those who are immunocompromised or with multiple underlying comorbidities. Patients with severe disease may develop respiratory failure, acute kidney disease, acute liver injury, cardiac arrhythmias and coagulopathy [39,83,106,113]. The estimated median time from symptoms onset to the time of admission to the hospital was 5 days, to the ICU admission was 7 days, the need for mechanical ventilation was 11 days [39,60].

There is a low occurrence of childhood infection in SARS and MERS-CoV [114–117]. Pediatric patients tend to be less affected by MERS-CoV than adults. One study of contacts found a positivity rate of 1.6% among 616 children compared to 2.2% among 4440 in adults (P = 0.23) [118]. Admitted pediatric MERS-CoV cases constituted 2.4% of all admitted MERS-CoV in a referral hospital in Saudi Arabia [119]. In addition, the clinical disease seems to be milder in those <2 years of age compared to adult patients [115,116,120]. MERS-CoV was associated with a high case fatality rate of 28-64% [102,104,121]. However, the case-fatality rate is lower in healthcare workers of 7% [122].

The case fatality rate of patients with MERS-CoV infection ranges from 9% to 63.6% [101] [95,100,103]. The differences in the fatality rates are related to underlying medical conditions and host factors [101]. The cited case fatality rates are also inversely proportional to the contribution of patients with no or with mild symptoms [32,60,78,83,100,123]. The case fatality rate is much higher in those admitted to the ICU and those who require mechanical ventilation [95,101–103]. Predictors of death in MERS-CoV patients are being > 65 years of age, being a non-healthcare worker, the presence of underlying medical conditions, healthcare acquired infections and the use of corticosteroids or continuous renal replacement therapy (CRRT) or extra-corporeal membrane oxygenation (ECMO) [83,124–128]. On the other hand, ECMO use was associated with a lower mortality in one study [129].

Laboratory diagnosis and Laboratory Findings:

The diagnosis of MERS-CoV relies mainly on real-time PCR of respiratory tract samples. For SARS, the virus was detected in 80% of nasopharyngeal aspirate with real-time quantitative RT-PCR in the first 3 days, in 97% of stool in day 14, 42% of urine in day 15, and in serum at 80% day 1, 75%

day 7, 45% day 14 [130–134]. For MERS-CoV, the virus was found in the human urine and stool 12-26 days after symptom onset [135–139]. Diagnosis was based on positive nasopharyngeal or throat swabs of five of sex family members [140] and was on lower respiratory samples in the initial 41 cases [112]. The presence of various laboratory findings were reported such as leukopenia (14%), lymphopenia (34%), lymphocytosis (11%), and thrombocytopenia (36%) [100]. Impaired hepatic function tests were reported as well with increased lactate dehydrogenase (49%), alanine aminotransferase (11%) and aspartate amino transferase (15%) [100] and another study showed elevated hepatic panels in 50% of patients [141] and elevation of renal function tests [105,106,141,142].

Specific Treatment

No approved therapeutics are available for treatment of MERS-CoV infection. Studies showed superiority of interferon (IFN)-β compared to other IFN types [143] and that PEG-IFN-α had excellent cytopathic effect inhibition [144]. In addition, the combination of INF-α2b and ribavirin showed augmentation of action and reduction of IFN-α2b and ribavirin does [145]. Clinical data of IFN-α2b and ribavirin are based on retrospective studies and there two agents did not improve the survival of MERS patients [146–151]. However, one study showed that the case-fatality rate was 90% and 44% in RT-PCR positive vs. 44% in those with negative MERS-CoV test [107]. The survival rate was 78.3% for interferon beta, 75% for interferon alpha, and 68.4% for ribavirin [152]. In a randomized controlled trial of lopinavir-ritonavir and interferon-β1b vs. palcebo, the MIRACLE study showed that treatment within 7 days after symptom onset was associated with a lower 90-day mortality in the treatment arm (relative risk, 0.19; 95% CI, 0.05 to 0.75) [153]. The use of a human polyclonal IgG antibody (SAB-301) wa sshown to be safe and well tolerated in phase I clinical trail [154].

Vaccine development:

Immunologic evaluation of patients with MERS-CoV infection showed that the cytokine profile was of the Th2 type in symptomatic patients [155]. Patients with MERS had strong MERS-CoV-specific CD8 T-cell responses in those with severe and moderate disease and later there were developments of antibody and CD4 T-cell responses appearing later in the disease course [156]. Most of the studies showed the detection of T-cell and antibody responses 2–3 weeks after diagnosis and could be detected earlier in some patients [156,157]. However, MERS-CoV-specific antibodies were lower and transient in those with mild or subclinical disease and responses were detected for at least 2 years [157–160]. The development of MERS-CoV vaccine is under investigation in few clinical trials (table 2). The proposed vaccines rely on DNA platforms (GLS-5300 (INO-4700)) [161,162], or viral vectors such as modified vaccinia virus -based vaccine [163,164], and adenovirus-vectored vaccine [165–168]. Only few of these vaccine candidates had completed phase 1 clinical trials [161–163,165]. In one trial, after 2nd dose, 9 of 12 (75%) in the low-dose group and 11 (100%) in the high-dose group had seroconversion using a MERS-CoV S1 ELISA and had no serious side effects [163]. Another study showed seroconversion by S1-ELISA in 59 (86%) of 69 participants and 61 (94%) of 65 participants after two and three doses, respectively with no serious side effects [161]. The third trial showed that Neutralizing anti-MERS-CoV antibodies developed in 4 (44%) of 9 participants in the high-dose group

Conclusions:

MERS-CoV is a WHO priority pathogen for R&D since it has epidemic potential and it continues to circulate in the Middle East, 10 years since it first discovery as a new human zoonoses. Since

MERS-CoV is largely endemic among dromedary camels from across the Middle East and Africa, the risk of human will remain

LEGENDS TO FIGURES AND TABLES

FIGURE 1: Figure 1: Epicurve of MERS-CoV Infections around the Globe

FIGURE 2: A summary of most common symptoms among MERS-CoV patients

FIGURE 3: Common Comorbidities among patients with MERS-CoV Infection

Table 1: Contributing factors to the hospital outbreaks

Table 2: MERS vaccine developmental pipeline

Figure 1: Epicurve of MERS-CoV Infections around the Globe (from:

https://www.who.int/emergencies/mers-cov/MERS-epicurve-July-2019.png?ua=1)

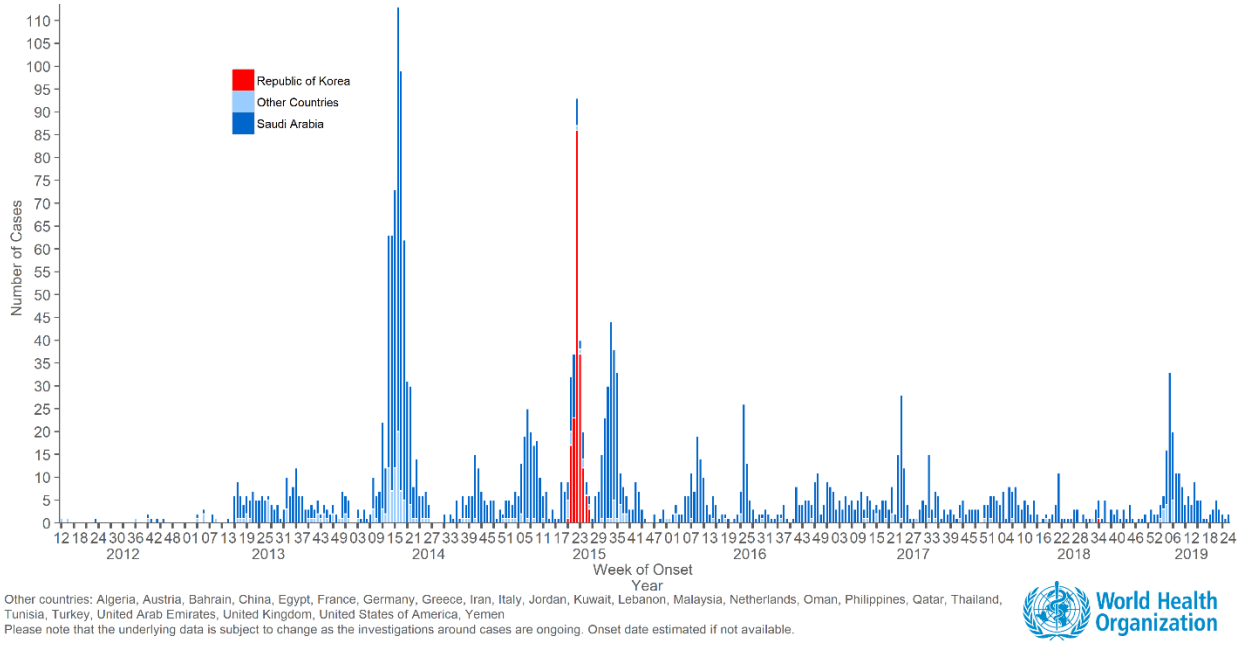

Figure 2: A summary of most common symptoms among MERS-CoV patients (Data from [39,79])

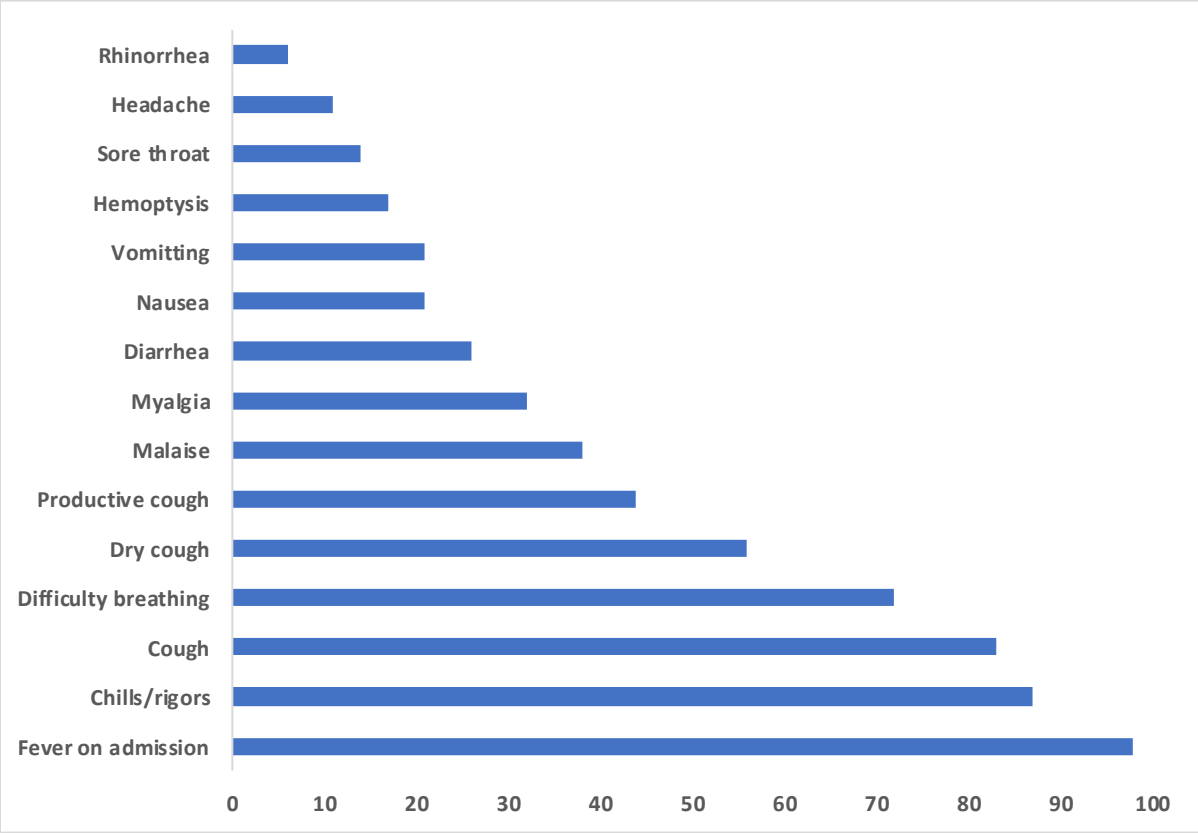

Figure 3: Most Common Comorbidities among patients with MERS-CoV Infection (Data from [39,100,105–108]

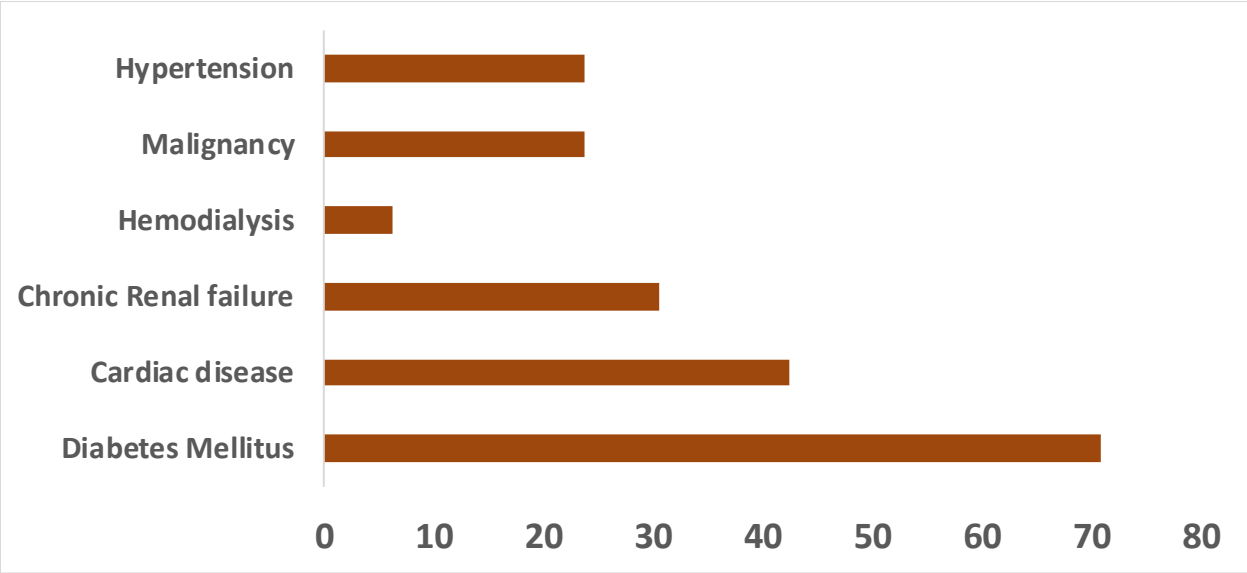

Table 1: Contributing factors to the hospital outbreaks

Factors	Reference
Hospital Design: No physical barriers between patients, inadequate separation of suspected MERS patients, lack of negative pressure rooms; Overcrowding	[64,71,94–98,77–79,86,90–93]
Healthcare Workers: Sub-optimal adherence to infection control measures, Contacts prior to MERS diagnosis and under-recognition; non-compliance with respiratory protection; unfamiliarity with MERS infection; under-recognition	[40,64,86,87,90–97,65,98,67–69,72,77–79]
Patients flow: Inadequate isolation of patients, multi-bedded rooms, widespread patients' movements	[64,78,96–98,79,86,90–95]
Aerosol generating procedures: Use of CPAP and nebulized medications and the performance of resuscitations	[39,40,97,78,90–96]
Patients' characteristics: Super-spreaders	[78,90–97]
Social Norms: "medical shopping", company of several friends and family members	[78,90–97]

Table 2: MERS vaccine developmental pipeline

Platform	Vaccine	Group	Clinical Phase	Clinical Trl Number	Trial Outcome report	Ref
DNA	GLS-5300 (INO-4700)	GeneOne Life Science/Inovio Pharmaceuticals/ International Vaccine Institute	Phase I, completed	NCT02670187	seroconversion by S1-ELISA in 59 (86%) of 69 participants and 61 (94%) of 65 participants after two and three doses	Modjarrad et al. (2019) [161]
DNA	GLS-5300 (INO-4700)	GeneOne Life Science/Inovio Pharmaceuticals/ International Vaccine Institute	Phase I/IIa, completed	NCT03721718	Not reported	[162]
Viral vector: Modified Vaccinia Virus Ankara (MVA) vector	MVA-MERS-S	CTC North GmbH & Co. KG	Phase I, completed	NCT03615911	After 2nd dose, 9 of 12 (75%) in the low-dose group and 11 (100%) in the high-dose group had seroconversion using a MERS-CoV S1 ELISA	Koch et al. (2020) [163]
Viral vector: Modified Vaccinia Virus	MVA-MERS-S_DF1	CTC North GmbH & Co. KG	Phase Ib, not yet recruiting	NCT04119440	Not reported	[164]

Viral vector: simian adenovirus -vectored vaccine	ChAdOx1 MERS	University of Oxford King Abdullah International Medical Research Center/University of Oxford	Phase I, recruiting	NCT03399578 NCT04170829	Neutralizing anti-MERS-CoV antibodies developed in 4 (44%) of 9 participants in the high-dose group	Folegatti et al. (2020) [165] [166]
Viral vector heterologous adenoviral -based	BVRS-GamVac-Combi	Gamaleya Research Institute of Epidemiology and Microbiology/Acellena Contract Drug Research and Development	Phase I/II, recruiting	NCT04128059	Not reported	[167]
Viral vector adenoviral -based vaccine	BVRS-GamVac	Gamaleya Research Institute of Epidemiology and Microbiology	Phase I/II, recruiting	NCT04130594	Not reported	[168]

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