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Review on Camel Middle East Respiratory Syndrome Corona Virus Infection, its Public Health Importance and Economic Impacts

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Abstract: Middle East Respiratory Syndrome is caused by the MERS corona-virus species with single stranded RNA belonging to the genus beta-corona-virus which is distinct from SARS corona virus and the common cold corona-virus. Therefore the objectives of this paper wereto review public health importance and economic impacts of Middle East Respiratory Syndrome and to recommend the disease for further research. The disease was first detected in 2012 in Saudi Arabia. The incubation period is a median of 5–7 days and the most common presenting symptoms as fever, cough, shortness of breath in and myalgia of people and there were also frequent GIT symptoms with diarrhea, vomiting, abdominal pain and 72% of people required mechanical ventilation as well as death also can be observed. Zoonotic infections may arise from domestic animals as well as wild life. Diagnosis of the infection based on clinical evidence or Laboratory Testing (radiological, Medical imaging) and history of traveling across the countries. Prevention of the disease is wearing (PPE) and avoiding contact with camels and to eat only fully cooked camel meat, pasteurized camel milk and to avoid drinking camel urine. At present, no vaccine or specific treatment is available, although serious attempts to develop preventive therapy are ongoing. However, serious cases, hospital inpatient care is required to reduce the risk of complications such as organ failure and secondary infections. Globally MERS-CoV outbreak resulted in an estimated economic loss of $16 billion and it is believed that the infection toll on the overall global economy and particularly the Saudi economy will also be enormous. Therefore, understanding public health important and it is economically significant disease is very essential in order to consider the transmission dynamics of the infection and to design cost effective management strategy to prevent human and animal's infection and losses in economy.

Key words: Dromedary Camel · Economy · MERS-Cov · Public Health · Respiratory Syndrome 2

INTRODUCTION

Middle East Respiratory Syndrome (MERS), also known as camel flu [1], is a viral respiratory infection caused by the MERS corona-virus (MERS-CoV), a species with single stranded RNA belonging to the genus beta-corona-virus which is distinct from SARS corona-virus and the common cold corona-virus [2]. Middle East respiratory syndrome corona-virus (MERS-CoV) was first detected in 2012 in respiratory specimens of a patient from Saudi Arabia with severe viral pneumonia leading to acute respiratory distress syndrome and death [3]. Zoonotic infections may arise from domestic animals as well as wild life. As Serological studies reported, from domestic livestock but dromedary camels were the only species from which antibodies specific to MERS-CoV have been detected [4-7]. Symptoms may range from mild to severe [8]. They include fever, cough, diarrhea and shortness of breath [9]. Disease is typically more severe in those with other health problems [8]. Mortality is about one third of diagnosed cases. Although Saudi Arabia is the most affected country, the infection is distributed in different

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parts of the world [9]. Some limited secondary transmission has been associated with some travel-associated patients.Between April 2012 and December 2019, 2499 laboratory-confirmed cases of MERS-CoV infection, including 858 deaths (34.3% mortality) were reported from 27 countries to WHO, the majority of which were reported by Saudi Arabia (2106 cases, 780 deaths). 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.

Therefore the objectives of this paper were;

- To review public health importance and economic impacts of Middle East Respiratory Syndrome and
- To indicate risk factors on transmission routes of Middle East Respiratory Syndrome and to recommend the disease for further research.

Historical Background of MERS-Cov Disease: SARS-CoV was first identified in humans in Guangdong, China, in November, 2002 and subsequently spread rapidly worldwide to 29 countries, resulting in 8098 human SARS cases with 774 deaths (9.6% mortality) [10]. The SARS epidemic ended abruptly in July, (2003) and no human cases of SARS have been detected over the past 15 years. MERS-CoV was first identified as causing human disease when it was isolated from a lung sample of an adult patient who was admitted at a hospital in Jeddah, Saudi Arabia, with severe pneumonia and died of multi-organ failure [11]. A retrospective study then linked MERS-CoV to a hospital outbreak in April, 2012, in Jordan [12]. MERS-CoV is considered a zoonotic pathogen, with MERS-CoV-infected dromedary camels being the animal source of infection to humans [13, 14].Unlike SARS-CoV, which was contained within a year of emerging, MERS-CoV continues to circulate and cause human disease with intermittent sporadic cases, community clusters and nosocomial outbreaks in the Middle East with considerable risk of spreading globally [15]. Several outbreaks of human-to-human MERS-CoV transmission have occurred, the largest outside the Middle East occurring in South Korea in 2015 [16]. This outbreak was associated with substantial morbidity and mortality, as well as having substantial economic, social and health security effects [17]. SARS-CoV-2 (initially named 2019-nCoV) was detected in December 2019 after sequencing of clinical samples.The transmission modes, pathogenesis, diagnosis, clinical features, management, infection control and development of new therapeutics, vaccines and also highlights unanswered questions and priorities for research, improved management and prevention.

Etiology: Middle East Respiratory Syndrome is caused by the MERS corona-virus (MERS-CoV), a species with single stranded RNA belonging to the genus beta-corona-virus which is distinct from SARS corona virus and the common cold corona-virus [18].

MERS-CoV, SARS-CoV and SARS-CoV-2, are members of the *Coronaviridae* family of the order Nidovirales. Other human corona viruses generally cause mild respiratory infections (eg, HCoV-229E, HCoV-NL63, HC oV-OC43 and HcoV-HKU1). MERS-CoV, like SARS-CoVand SARS-CoV-2, can cause highly lethal disease in humans. MERS-CoV is a large single-strand positive-sense RNA virus [19]. The 30–31 kb coronavirus genome encodes a large number of proteins, which might confer versa utility in adapting to new environments and enhance cross-species transmission. MERS-CoV has four structural proteins: spike (S) protein, envelope (E) protein, membrane (M) protein and nucleocapsid (N) protein. The S protein is a type I trans-membrane glycoprotein located as a trimer on the virus surface and consists of S1 and S2 subunits. It has crucial roles in binding, fusion and entry into host cells. The S1 subunit has a receptor binding domain that binds to the host cellular receptor dipeptidyl peptidase 4 (DPP4). MERS-CoV enters host cells via binding of its S protein to the host cell DPP4 [20]. The structures of the S protein of MERS-CoV and other corona viruses have been determined using cryo-electron microscopy. Structure, genome organization and replication of MERS-CoV encodes a large replicase-transcriptase poly-protein (rep1A and rep1B), which is processed into 16 non-structural proteins (nsp). These proteins are required for the formation of the replicase-transcription complex, for cleavage of the poly-protein and for immune evasion. Structural proteins (spike [S], envelope [E], membrane [M], nucleo-capsid [N] and accessory proteins (ORFs 3, 4a, 4b, 5, 8b) are encoded in the end third of the 3' end of the genome. MERS-CoV binds to its cellular receptor DPP4 via the S protein, which is processed by host proteases to expose a fusion peptide. The viral genome is then released into the cytoplasm, where it is translated on host ribosomes into rep1A and rep1B proteins [20]. The poly-protein is cleaved by two viral-encoded proteases, encoded by nsp3 and nsp5. Proteins

involved in genome and sub-genome replication and transcription include nsp12 (the RNA-dependent RNA polymerase (RdRP) and two associated proteins, nsp7 and nsp8 [21]. MERS-CoV transcription involves the synthesis of sub-genomic RNAs, which encode the structural and accessory proteins located at the 3' end of the genome. Sub-genomic and genomic RNAs are co-terminal, sharing the same 5' leader and 3' sequences. Sub-genomic RNAs code for structural and accessory proteins (ORF3, 4a, 4b, 5 and 8b). ORF8b is encoded within the N gene (marked with purple lines). These accessory proteins are believed to have immune evasive properties, but are not essential for replication and are variably deleted in human and camel virus isolates [22].

Genomic replication occurs on membrane structures such as double membrane vesicles (DMVs), convoluted membranes (CM) and vesicle packets (VP), which are merged DMV that have been formed from the rough endoplasmic reticulum (RER) by the combined action of nsp3, nsp4 and nsp6 (lower right)[23]. After synthesis on replicase-transcription complexes, RNA is encapsidated by the N protein and transported to the ERGIC (endoplasmic reticulum–Golgi compartment), where budding into membranes containing the S, E and M proteins occurs before release from the cell. 3CLPro = chymotrypsin-like protease [23].

Epidemiology: A primary MERS-CoV infection is defined by WHO as a laboratory-confirmed MERS-CoV infection that has 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 [24]. A secondary MERS-CoV infection 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 [24].The epidemiological patterns of MERS-CoV in humans have remained consistent since MERS-CoV was first identified in 2012 [25]. Primary cases often report direct or indirect contact with dromedary camels and present across a wide clinical spectrum from mild to severe fulminant disease. Individuals with severe primary MERS-CoV infections are often older than 65 years with co morbidities and symptoms can present late. Individuals with mild primary MERS-CoV infections are often missed by current surveillance systems since they usually do not present to health-care facilities. Secondary cases have resulted from human-to-human transmission among close contacts. To date, secondary transmission has occasionally occurred between close contacts of individuals with laboratory-confirmed MERS-CoV in household settings [26]. However, secondary transmission in health-care facilities has repeatedly occurred in several countries and has, on occasion, resulted in large outbreaks such as Jeddah, Saudi Arabia (2014), Seoul, South Korea (2015) and Riyadh, Saudi Arabia (2015, 2016 and 2018). In health-care settings, human-to-human transmission occurs between patients, between patients and healthcare workers and from patients to visitors.Approximately half of the MERS-CoV cases reported to WHO to date have resulted from human-to-human trans-mission in health-care facilities [26].

Several studies have reported disease severity and mortality risk factor data from patients in the Middle East and South Korea [28]Ahmed and colleagues[12] collected the daily information on MERS-CoV cases posted online by the Saudi Arabian Ministry of Health between Dec 2, 2014 and Nov 12, 2016 and reviewed 660 laboratory-confirmed cases of MERS. 114 They showed mortality at day 3 (13.8%), day 30 (28.3%) and overall (29.8%). Patients older than 60 years were more likely to die (45.2% mortality) from their infections than were younger patients (20%).

Geographical Distribution: Laboratory-confirmed MERS-CoV human infections [24] are reported to WHO as a requirement under the International Health Regulations (2005). The geographical distribution of countries reporting laboratory-confirmed human MERS cases and the numbers reported over time are shown in Figures 2 and 3. Between April, 2012 and end of December, 2019, 2499 laboratory-confirmed human cases of MERS-CoV infection, including 858 deaths (34.3% mortality) were reported from 27 countries in all continents (Figure 2) to WHO, the majority of which were reported by Saudi Arabia (2106 cases, 780 deaths).

Modes of MERS-CoV Transmission: The origin of all primary human MERS-CoV infections remains unknown. Dromedary camels are a host reservoir species for the MERS-CoV [29]. The emergence ofMERS-CoV from dromedary camels is facilitated by the presence of a highly similar viral receptor (DPP4) in humans. Hypothetically, MERS-CoV present in dromedary camels may have emerged from CoVs in bats that also use DPP4 as an entry receptor through nasal fluids, faeces and, potentially, in their milk and urine [30].

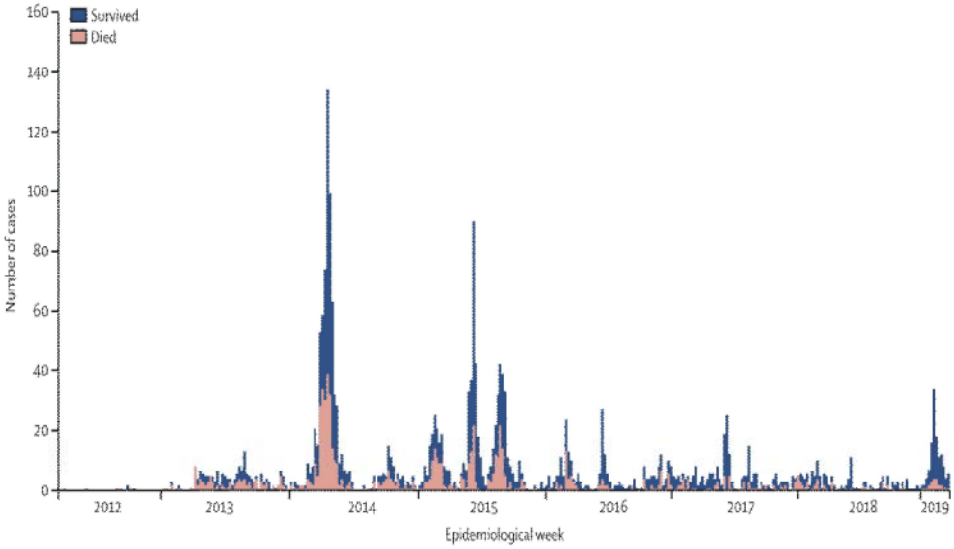

Fig. 1: Global MERS reported to WHO from 2012-2020
Sources: [27]

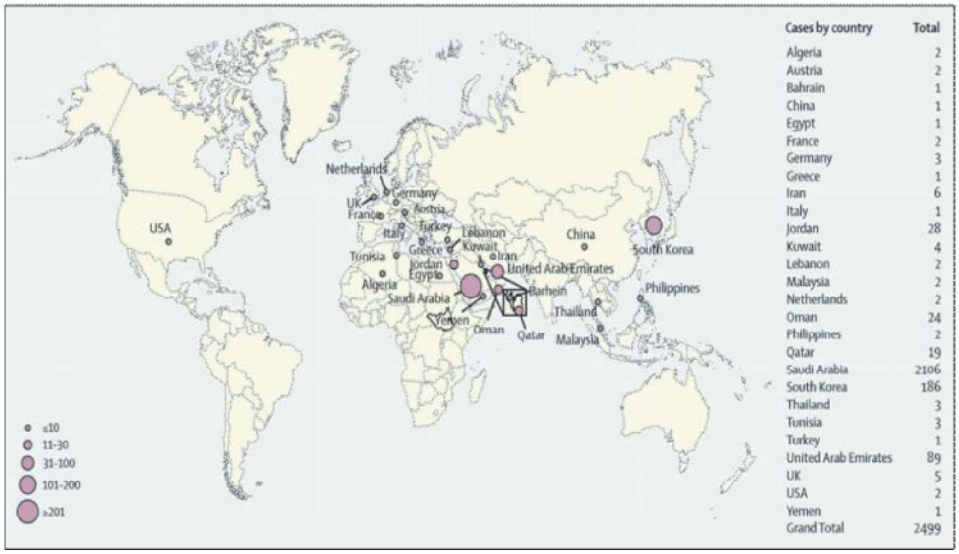

Fig. 2: Geographical distribution of reported human infections of MERS-CoV
Sources: [27]

Table 1: Saudi Arabia and South Korea Outbreak of MERS CoV

	Saudi Arabia Outbreak	South Korea Outbreak
	Middle East (Asia)	Far East (Asia)
City/province	Riyadh, Jeddah	Seoul, Daejeon, Gyeonggi province
Period	12 April – 9 June 2014	4 May – 15 June 2015
Overall case number	402	150
Health-care Personnel (%)	27%	17%
Main transmission routes	Health-care center associated	Health-care center associated
Previous MERS case before outbreak	Yes	No
Admission to health-care facility	34%	30%
Emergency department	8%	49%
Visit to patient at health-care facility	17%	29%
Annual outpatient department visit (per individual)	4.5	14.6%
Annual number of hospital admission (per 100 individuals	10.5	16.1

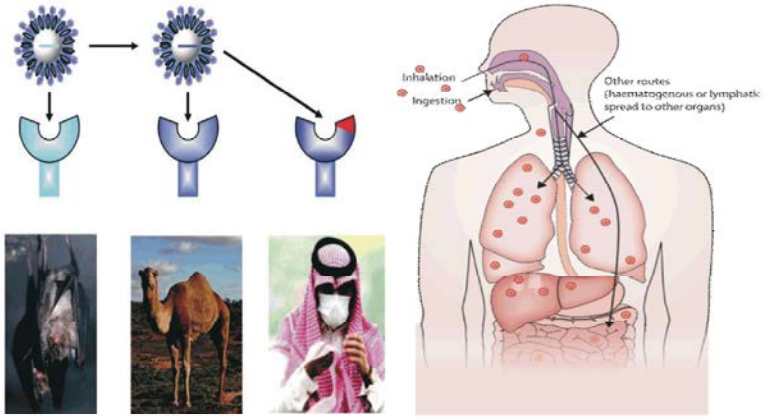

Fig. 3: Ways of transmission of MERS-CoV
Sources: [27].

Humans can acquire MERS-CoV through direct or indirect contact with infected dromedary camels or infected patients [24]. However not all cases infected in the community reported contact with dromedary camels. The transmission of MERS-CoV from dromedary camels to humans is now well documented in the Arabian Peninsula [31]. But the extent to which this transmission is occurring in countries outside the Arabian Peninsula requires definition. Experimental infections have shown that infected dromedaries shed MERS-CoV from their nasal secretions with minimal signs of illness, which is limited to rhinorrhea [32].Full-genome phylogenetic analysis indicates that evolution of diverse MERS-CoV lineages in camels have caused human infections, perpetuating a low barrier for interspecies transmission [32]. However, African MERS-CoV lineages in camels imported into Saudi Arabia have not established themselves in camels in Saudi Arabia indicating potential differences in transmission dynamics and selection pressure [14]. Analysis of population dynamics shows that Arabian viruses can maintain endemicity without introduction of additional lineages[14]. WHO is supporting molecular and serological studies at the dromedary–human interface in several countries in Africa and south Asia [33].The phylogenetic relationship of complete genomes of MERS-CoV strains obtained from camels and humans has been published [34].

Health-care-associated outbreaks of MERS-CoV affecting inpatients, health-care workers and visitors are characteristic of MERS and account for approximately 50% of reported cases [26, 35]. Large nosocomial outbreaks have occurred in Abu Dhabi in United Arab Emirates, Seoul in South Korea and several cities in Saudi Arabia. In June, 2017, an outbreak of 34 MERS-CoV cases (including 17 in health-care workers) occurred in a hospital in Riyadh, Saudi Arabia [36] where the primary case was a 47-year-old man admitted for emergency intubation. Before a diagnosis of MERS, this individual had contact with 220 health-care workers, patients and visitors. Another 2017 outbreak in Riyadh involved three hospitals, with 44 MERS cases in patients, health-care workers and family members. The outbreak arose from three severely ill people who were diagnosed with MERS late in the disease course and involved in a super spreading event [37].

In 2015, South Korea had the largest MERS-CoV outbreak outside the Middle East with 186 cases reported, resulting from a single imported case from an individual who had returned from travelling in the Middle East. The outbreak included 185 secondary cases who acquired infection in 16 health-care facilities and 80% of transmission events were attributed to five super spreading events [35].

Risk Factors: Known risk factors for MERS-CoV acquisition, transmission and outbreaks are noted. MERS patient data reported to WHO includes information on exposures and known risk factors during the 14 days before symptom onset, or during the 14 days before laboratory confirmation was reported (in the case of asymptomatic infection). Exposure data include travel history to endemic countries, direct or indirect contact with dromedary camels or their products, contact with humans with MERS-CoV infection and visits to health-care facilities containing patients infected with MERS-CoV are risk factors for acquiring MERS-CoV infection

[35]. MERS-CoV has been detected in camel products (e.g., raw milk, meat, blood, urine, or birth products); however, genomic studies to definitively show transmission from these products to humans have not yet been done. Human primary intestinal epithelial cells, small intestine explants and the intestinal tract are highly susceptible to MERS-CoV and can sustain viral replication[38].Transmission via contact with contaminated hospital environments is possible during outbreaks, although genomic studies providing an evidence base are lacking. Since environmental contamination is a potential source of infection, it is prudent to take precautionary infection control measures. Patients older than 60 years were more likely to die (45.2% mortality) from their infections than were younger patients (20%).Several factors are associated with severe disease and high mortality rates in patients with MERS. These factors include male sex, comorbid pre-existing illnesses (such as obesity, diabetes mellitus, cancer, chronic heart, lung and kidney disease and immune-compromised states), low serum albumin, thrombocytopenia, lymphopenia, concomitant infections and positive plasma MERS-CoV RNA. DPP4 receptors are upregulated in the lungs of smokers and patients with chronic obstructive pulmonary disease, which might explain why patients with co-morbid lung diseases are prone to severe illness [39].In the 2015 Korean outbreak, the case-fatality rate was 20.4% (39 of 186 patients died), the in-hospital mortality was 19.4% (36 of 186 patients), 7-day mortality (from symptom onset) was 3.8% (seven of 186) and 28-day mortality was 17.7% (33 of 186). Host factors associated with mortality in this outbreak were older age (>60 years), smoking history, pre-existing pneumonia, abnormal renal function and co-morbidity. Low albumin, altered mentality and high pneumonia severity index score at admission were risk factors for mortality[16, 17]

Economic Importance of MERS-CoV: Although some efforts in estimating the impact of MERS-CoV outbreak on selected sectors of the economy in some countries like South Korea have been madethe direct medical costs of managing this epidemic that struck more than 24 countries and affected Saudi Arabia the most have not been estimated. The estimated costs of managing MERS cases in this study can be utilized to project the aggregate direct medical cost of managing MERS cases in Saudi Arabia. As of June 2019, 2058 cases of MERS were reported in the Kingdom. The cost of managing these patients at hospitals would range from $2, 630, 967.78 (based on the lowest cost identified in the present analysis, i.e., $1278.41 × 2058) to $156, 383, 201.10 (based on the highest cost, i.e., $75, 987.95 × 2058) with a mean cost of $26, 644, 987.74 ($12, 947.03 × 2058) and a median cost of $3, 842, 903.4 ($1867.30 × 2, 058) [10].

These estimates include only the cost of inpatient MERS cases management and do not consider the costs associated with the implementation of infection control policies that were implemented right after the MERS-CoV outbreak, such as the cost of shutting down certain hospital wards.3 Moreover, it must be acknowledged that projected cost estimates in managing MERS cases in Saudi Arabia were based on expenses incurred for 24 MERS cases only and do not represent the diverse cases of MERS in the country. Despite these limitations, it should be emphasized that this is the first effort to highlight the direct medical cost of managing MERS cases in Saudi Arabia, a country where more than 80% of MERS cases were reported [10].

Prevalence of MERS-CoV: Studiesin Ethiopia, Burkina Faso and Morocco reported that the prevalence of MERS-CoV sero-positivity in Ethiopia, Burkina Faso and Morocco is ranges between 85.1- 99.4%, 73.2-89.9% and 48.3-100% respectively. Studied on sero-positivity of MERS-CoV in camel in different parts of Ethiopia such as Akaki, Ayssaita Dubti, Melke Warer and Yabelo. The highest prevalence is reported in Metehara that the prevalence of MERS-CoV in camel is 99.4%. The prevalence of MERS-CoVsero-positivity in Assaita Dubti, Melkawarer and Akaki is 85.8, 99.0 and 99.4% respectively. The lowest prevalence of MERS-CoVsero-positivity is recorded in Yabelo (85.1%) [40]. During the MERS-CoV outbreak, cases of MERS-CoV infection were reported in 27 countries, among which 12 were located in the Eastern Mediterranean region. Although this virus spread throughout the Middle East, most con?rmed cases (n¼1882) were in Saudi Arabia with 729 deaths, comprising a fatality rate of 38.7%.11 Cases outside the Middle East most often occurred among travelers who had visited the region [41].

Pathogenesis and Pathology: The mechanisms underlying the pathogenesis of MERS-CoV remain to be defined because autopsies are generally not done either for religious and cultural reasons or to prevent environmental contamination with subsequent infection of health-care workers. Therefore, there are few data on the histo-pathological changes in patients with MERS-CoV

infection, even in severe disease [42]. The only two autopsies available showed that viral infection was confined predominantly to the respiratory tract although viral particles were detected in the kidney in one of the reports [43]. Further, ex vivo human kidney cultures were shown to support productive MERS-CoV infection [44].However, it is not known whether infection of this organ contributes to worse outcomes compared with infections confined to the respiratory tract. Viral RNA, but not infectious MERS-CoV, was detected in the blood for at least 2 weeks after diagnosis. Whether this viral RNA represented an extra-pulmonary infection is not clear, since MERS-CoV neutralizing antibody was detected in the serum at the same time in some patients [45]. Pathological changes in the lungs include evidence of focal hemorrhagic necrotizing pneumonia with exudative diffuse alveolar damage, indistinguishable from findings detected in severe pneumonia caused by other viral agents. Several experimentally infected animal models for MERS have been developed [46]. Methods for gene silencing and editing are being further developed, therefore it is likely that additional viral and host factors important in MERS-CoV pathogenesis will be identified. MERS-CoV pathogenesis reflects a balance between corona virus-induced protective and pathogenic host immune responses and direct cytotoxic effects of the virus [47]. According to studies of patients infected with SARS-CoV and of mice and other animals infected experimentally with MERS-CoV, successful resolution of MERS and long-term protection from re-infection likely requires well-coordinated innate and adaptive B-cell and T-cell responses. In patients with SARS, innate immune responses characterized by an extended period of cytokine secretion (eg, IFNα and IFNβ) was correlated with delayed antibody responses and poor management outcomes; this prolonged innate response has not yet been shown in patients infected with MERS-CoV [48]. MERS-CoV productively infects activated human T cells and induces delayed cytokine responses after infection of human myeloid cells in vitro, both of which could impair virus clearance and the development of an effective immune response [49]. During the acute phase of MERS, robust virus-specific CD8 T-cell responses were detected in most patients with severe or moderate disease, with antibody and CD4 T-cell responses appearing later in the disease course [50] T-cell and antibody responses were reliably detected 2–3 weeks after diagnosis, although they were detected earlier in some patients [45]. Studies of MERS survivors showed that MERS-CoV-specific antibody responses tended to be lower and transient in patients with mild or subclinical disease when compared with patients with severe disease, in whom MERS-CoV-specific antibody responses were detected for at least 2 years [50]. In contrast, T-cell responses were detected in all MERS survivors for at least 2 years. The transitory nature of the antibody response in mild disease and greater stability of the T-cell response suggest that induction of both will be required for optimal long term protection; the measurement of both will enhance the accuracy of prevalence studies [38].

Clinical Features: The specific exposures that lead to sporadic MERS-CoV infections are unknown; therefore it is impossible to estimate the incubation period in primary cases. However, based on data from cases of human-to-human transmission, the incubation period is a median of 5–7 days, with a range of 2–14 days (median 5.2 day) [25, 51].

Immunocompromised patients can present with longer incubation periods of up to 20 days [16]. The clinical presentation of patients infected with MERS-CoV ranges from asymptomatic or mild upper respiratory illness to rapidly progressive pneumonitis, respiratory failure, acute respiratory distress syndrome, septic shock and multi-organ failure with fatal outcome [25, 51].

The signs and symptoms associated with MERS are non-specific, with or without multisystem involvement and thus could be mistaken for other causes of respiratory tract or gastrointestinal illnesses [25, 51]. Therefore, the clinical diagnosis of MERS can be easily missed. Patients with MERS can typically present with fever, chills, rigors, headache, a non-productive cough, sore throat, arthralgia and myalgia followed by dyspnea. Other associated symptoms include coryza, nausea, vomiting, dizziness, sputum production, diarrhea and abdominal pain. Some patients with MERS can present Figure 4: Chest imaging abnormalities in patients with Middle East respiratory syndrome (A) Chest x-rays showing bilateral extensive diffuse and focal opacities. (B) Chest CT scan showing bilateral extensive ground-glass reticulo-nodular shadowing with bronchiolar wall thickening with atypical symptoms of mild respiratory illness without a fever and a gastrointestinal illness that precedes the development of pneumonia[16]. Neuromuscular manifestations include hyper-somnolence, weakness and tingling in the extremities similar to Guillain-Barre syndrome or virus-related sensory neuropathy [16]. Co-infection of MERS-CoV with other respiratory viruses

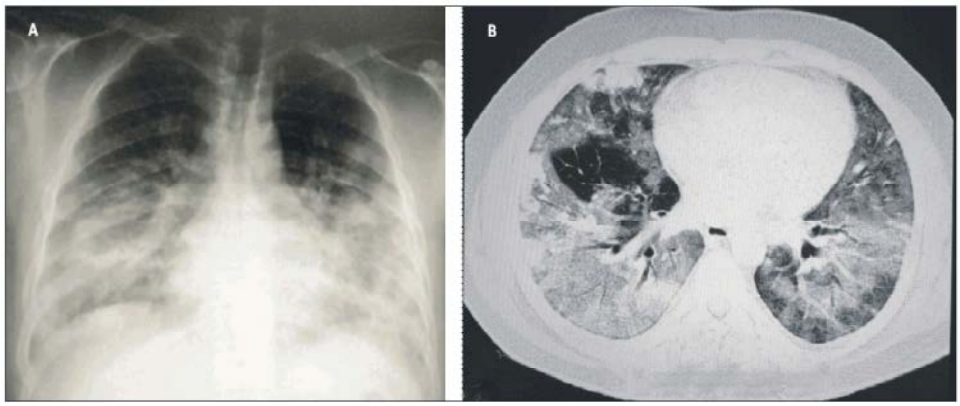

Fig. 4: Asymptomatic-to-mild infection rates of 25–50% have been reported
Source: [52].

such as parainfluenza virus, rhinovirus, influenza A or B virus, respiratory syncytial virus, enteroviruses and human meta-pneumonia virus and nosocomial bacterial infections has been reported in patients receiving intensive care [53]. Immunocompromised patients or those with co-morbidities Immunocompromised patients or patients with chronic heart, liver and kidney disease can present with atypical features, such as a longer incubation period, a longer period from initial PCR positivity to symptom onset, persistent prolonged viral shedding and increased mortality [16]. MERS-CoV causes more severe disease in people older than 60 years and those with chronic comorbid diseases such as renal disease, cancer, chronic lung disease, immune suppression and diabetes. In children younger than 5 years, MERS-CoV infection appears to be rare and usually presents as mild disease with cough as the predominant clinical symptom. Acute and severe respiratory illness (i.e, a fatal outcome after multi-organ failure) has been noted in only two of 38 reported pediatric cases and these were in boys aged 9 months and 2 years with co-morbidities (infantile nephritic syndrome and cystic fibrosis, respectively) [54]. Data on the prevalence of MERS-CoV in pregnant women are limited to case reports and the clinical presentations and mortality rates are similar to non-pregnant women [55]. MERS should be kept on the differential diagnosis list for ill travelers returning home from MERS-CoV leucopenia (white blood cell count <3.5 × 110?/L) and thrombocytopenia (platelets <150 × 10?/L) either with or without prominent respiratory symptoms [25, 51]. It is important that clinicians are alert to the possibility that patients could have MERS in all health-care settings where the virus is circulating so that an accurate diagnosis can be made and infection control measures implemented efficiently [10].

Diagnosis: The type and quality of the clinical specimen are important in the laboratory diagnosis of MERS-CoV infection. Both upper respiratory tract specimens (oropharyngeal or nasopharyngeal swabs) and lower respiratory tract specimens (sputum, endotracheal aspirate or lavage) should be analyzed whenever possible [10]. Patients with MERS might not shed the virus during the early stage of their illness; thus, initial negative results from upper respiratory samples do not rule out the possibility of MERS and patients should be retested using a lower respiratory tract sample. Several studies of MERS-CoV viral load measurements show that upper respiratory tract specimens have lower viral loads than lower respiratory specimens [56, 57]. MERS-CoV RNA has been detected in blood, urine and stool but at much lower viral loads than in the respiratory tract [55]. Clinical specimens must be collected by trained staff using appropriate personal protective equipment (eg, when taking nasopharyngeal and oropharyngeal specimens, Dacron or rayon swabs specifically designed for collecting specimens for virology must be used [10]. These swab kits should contain virus transport medium. A single negative test result does not exclude the diagnosis and repeat sampling and testing is strongly recommended [52]. A minimum of two samples, preferably from the lower respiratory tract, are needed to exclude MERS-CoV after initial assessment. To confirm clearance of the virus, respiratory samples should be collected sequentially (every 2 to 4 days) over ensuing days until there are two consecutive negative results at least 24 h apart in people who are clinically recovered WHO guidelines for testing should be followed [58]. MERS-CoV testing must be performed in appropriately equipped bio-safety laboratories by staff trained in the relevant technical and safety procedures.

National or WHO guidelines on the laboratory bio-safety should be followed in all circumstances[52]. Three real-time RT-PCR (rRT-PCR) assays for routine detection of MERS-CoV have been developed targeting upstream of the E protein gene (upE) and open reading frame (ORF)1b and ORF1a. The assay for the upE target is considered highly sensitive and is recommended for screening with the ORF1a assay in which ORF1a assay is considered more sensitive than ORF1b assay [58]. An updated roadmap for MERS-CoV product development lists all available diagnostics and other diagnostics in the developmental phase[59]. Several diagnostic tests are under development to accelerate turnaround times from sample analysis to result [60]. A 2018 rapid and specific assay for the detection of MERS-CoV combines the reverse transcription loop-mediated isothermal amplification technique and a vertical flow visualization strip (RT-LAMP-VF) to detect the nucleo-capsid gene of MERS-CoV. The RT-LAMP-VF assay provides detection of MERS-CoV within 35 min and is easier to perform than the WHO-recommended rRT-PCR method [61]. Several serological assays are available for detection of MERS-CoV: ELISA, recombinant spike immune-fluorescent assay and spike pseudo-particle neutralization and micro-neutralization assay [62, 63]. A case confirmed by serology requires evidence of sero-conversion in two samples, ideally taken at least 14 days apart, by a screening (eg, ELISA, immune-fluorescence assay) and neutralization assay [58, 64]. A range of abnormal but non-specific chest x-ray findings are seen in patients with MERS [65, 66]. These abnormalities include unilateral or bilateral bronchovascular shadowing, interstitial infiltrates, reticular opacities, reticulo-nodular shadowing, nodules, pleural effusions and patchy to confluent consolidation. Lower lobes tend to be affected more than upper lobes early in the course of MERS and rapid pacification of lungs and progression to acute respiratory distress syndrome can occur. High-resolution CT might show ground glass opacities (Figure 5B) in early CT findings (with or without consolidation) followed by interlobular septal and intra-lobular interstitial thickening with peripheral and lower lobe involvement within the first week of MERS-CoV infection [65, 67]. During subsequent weeks, a so-called crazy-paving lung abnormality, cavitation, tree-in-bud pattern and centri-lobular nodules, constrictive obliterate bronchiolitis, bronchiolitis obliterans, peri-bronchiolar air-trapping, thickened peripheral bronchioles and organizing pneumonia have been observed [68].

Treatment and Management: Currently, there are no specific anti-MERS-CoV therapies available for human use. The mainstay of clinical management of MERS cases is mostly symptom focused, providing supportive care [15, 53] with pain and fever management, treating concomitant or secondary bacterial infections and supporting vital organ functions. Mild MERS cases can be managed at home [58]. Predictive factors for development of pneumonia include older age (>56 years), high fever, thrombocytopenia, lymphopenia, C-reactive protein greater than or equal to 2 mg/dL and a high viral load in sputum (threshold cycle value of rRT-PCR <28.5) [15, 69]. Respiratory failure and acute kidney injury (with hematuria and proteinuria) are common among patients admitted for hospital care because of the severity of their disease and who require mechanical ventilation, extracorporeal membrane oxygenation and dialyses [15].Several empirical treatments have been studied in severely ill patients. Therapies used for severely ill patients with MERS have included convalescent plasma, corticosteroids, antiviral agents (e.g., interferons and ribavirin) and protease inhibitors, or combination of members from these groups. A systematic review of 30 publications on therapeutic agents used for MERS treatment in various outbreaks showed a complete absence of an accurate evidence base and emphasized the need for controlled trial [70]. Several antiviral agents have shown inhibitory effects against MERS-CoV in cell cultures, including interferons, ribavirin, cyclosporine and mycophenolic acid [15, 53]. Empirical lopinavir–ritonavir, PEGylated interferon alfa-2a and ribavirin have been used for serious cases, but no efficacy data are yet available. There is an ongoing randomized clinical trial in progress in Saudi Arabia (the MIRACLE trial; NCT02845843) comparing lopinavir–ritonavir, recombinant interferon beta and standard supportive care against placebo and standard supportive care in patients with laboratory-confirmed MERS requiring hospital admission. This recursive, multi-center, placebo controlled, double-blind, randomized controlled trial is designed to include two components, each consisting of two stages. The first two-stage component is designed to adjust sample size and determine futility stopping, but not efficacy stopping (n=34). The second two-stage component is designed to determine efficacy stopping and possibly readjustment of sample size. The use of plasma from patients with MERS who have made a full recovery (convalescent plasma) requires clinical trial evaluation. Preclinical animal data show that transfer of serum samples from MERS-CoV immune camels to infected mice resulted in reduced

weight loss and lung histopathology [71].Thus suggesting therapeutic potential in the 2015 Korean outbreak, three of 13 patients with MERS with respiratory failure were given four infusions of convalescent plasma [72] two of three showed neutralizing activity. Donor plasma with a plaque reduction neutralization test (PRNT) titer of 1/80had a meaningful serological response after convalescent plasma infusion, while that with a PRNT titer of 1/40 did not. The authors conclude that for effective convalescent plasma infusion in patients with MERS, donor plasma with a neutralization activity of a PRNT titer greater than or equal to 1/80 should be used. Antibiotic therapy is commonly started empirically in seriously ill patients. A retrospective study of 136 patients with MERS found that macrolide therapy resulted in no reduction in mortality or faster MERS-CoV RNA clearance compared with those who were not treated with macrolides [73]. For serious cases, hospital inpatient care is required to reduce the risk of complications such as organ failure and secondary infections. Non-invasive ventilation is associated with a high failure rate (92%) in patients with acute hypoxemic respiratory failure due to MERS-CoV infection [74].Patients with severe symptoms might need to be managed in an intensive care unit, where lung protective ventilator strategies for acute respiratory distress syndrome, inotropic support, antimicrobial therapy for co-infections and renal replacement therapy for acute renal failure can be provided. Studies show no benefit from the use of systemic corticosteroids. Systemic corticosteroids were shown to delay viral clearance in critically ill patients with MERS-CoV infection [75].

Prevention: The prevention of transmission of MERS-CoV in the community and in health-care settings is crucial to preventing outbreaks and further spread. Several substantive reviews and WHO guidelines are available on the subject [76, 75]. It is important to maintain good personal and environmental hygiene and to implement stringent contact and droplet precautions among health-care workers. To prevent community transmission, contact tracing, quarantine or isolation of close contacts and public education are important measures [29, 77]. In hospitals, early case detection followed by isolation is essential, ideally in negative pressure isolation rooms. The main infection prevention and control measures for managing patients with MERS are well documented from the SARS epidemic and from experiences from managing MERS outbreaks [13].

Advances in Vaccine Development: Advances in technology, vaccine platforms, clinical trial designs and bioinformatics are supporting MERS-CoV vaccine development. WHO target product profiles for MERS-CoV vaccines calls for the development of three types of MERS vaccines: a human vaccine for long-term protection of people at high exposure risk, such as health-care workers and those working with potentially infected camels; a human vaccine for reactive use in outbreak settings; and a dromedary camel vaccine to prevent zoonotic trans mission [24]. Multiple types of vaccine candidates are in development including inactivated whole virus, live attenuated virus, viral vectored vaccines, subunit vaccines and DNA vaccines [24, 78]. Most vaccines use the S protein or the domain of the S protein required for binding to host DPP4 as an immunogenic, since neutralizing antibodies are mostly directed to the receptor binding domain.WHO, FAO of the UN and World Organization for Animal Health, in consultation with global MERS community, identified knowledge gaps and priorities for MERS research, surveillance, management and control [33]. Several recent publications have highlighted the importance of a one-human-environmental-animal-health (One Health) approach to tackle and control the spread of MERS-CoV [24, 33, 79].

Public Health Response: Upon identification of these above-mentioned cases, anincident report, case investigation and contact tracing were initiated. The investigation included screening of all close contacts, including occupational contacts in the two farms, household contacts and healthcare workers at the health care facilities. All close contacts have been tested for MERS-CoV and the results are negative. All of them have been monitored on a daily basis for the appearance of respiratory or gastrointestinal symptoms for 14 days after the last exposure to the confirmed cases. The veterinary authorities have been notified and investigation in animals is ongoing [10].

Risk Assessment by WHO: Infection with MERS-CoV can cause severe disease resulting in high mortality. Humans are infected with MERS-CoV from direct or indirect contact with dromedary camels. MERS-CoV has demonstrated limited ability to transmit between humans. So far, the observed non-sustained human-to-human transmission has occurred mainly in health care settings. The notification of additional cases does not change the overall risk assessment. WHO expects that additional cases of MERS-CoV infection will be reported from the Middle East and that cases will continue to be exported to other countries by individuals who might acquire the infection after exposure to dromedary camels, animal

products (for example, consumption of camel's raw milk), or humans (for example, in a health care setting). WHO continues to monitor the epidemiological situation and conducts risk assessment based on the latest available information [10].

WHO Advice: Based on the current situation and available information WHO encourages all Member States to continue their surveillance for acute respiratory infections and to carefully review any unusual patterns. Infection prevention and control measures are critical to prevent the possible spread of MERS-CoV in health care facilities. It is not always possible to identify patients with MERS-CoV infection early because like other respiratory infections, the early symptoms of MERS-CoV infection are non-specific [10].Therefore, healthcare workers should always apply standard precautions consistently with all patients, regardless of their diagnosis. Droplet precautions should be added to the standard precautions when providing care to patients with symptoms of acute respiratory infection; contact precautions and eye protection should be added when caring for probable or confirmed cases of MERS-CoV infection; airborne precautions should be applied when performing aerosol generating procedures. Early identification, case management and isolation, together with appropriate infection prevention and control measures can prevent human-to-human transmission of MERS-CoV. MERS-CoV appears to cause more severe disease in people with underlying chronic conditions such as diabetes, renal failure, chronic lung disease and immune-compromised persons. Therefore, these people should avoid close contact with animals, particularly dromedary camels, when visiting farms, markets, or barn areas where the virus is known to be potentially circulating. General hygiene measures, such as regular hand washing before and after touching animals and avoiding contact with sick animals, should be adhered to. Food hygiene practices should be observed. People should avoid drinking raw camel milk or camel urine, or eating meat that has not been properly cooked. WHO does not advise special screening at points of entry with regard to this event nor does it currently recommend the application of any travel or trade restrictions [10].

CONCLUSIONS AND RECOMMENDATIONS

MERS-CoV is a pathogen with epidemic potential that continues to cause sporadic human disease and remains on the WHO Blue print 2020 priority. MERS-CoV appears to be highly endemic among dromedary camels from geographically widespread areas of the Middle East and Africa and thus zoonotic transmission with consequent risk of human epidemics will most likely continue for years to come. MERS-CoV endemic and at-risk countries must invest more in surveillance, in public health research and in medical interventions including human and camel vaccine development. The continued risk of human MERS-CoV outbreaks 7 years after its first discovery, effective human and camel MERS-CoV vaccines appear to be the ideal way to prevent continuing spread of MERS-CoV in dromedary camels in the Middle East and in humans at high risk of acquiring community and nosocomial MERS-CoV infection.

Therefore depending on above conclusions, the following recommendations should be forwarded:

- Strict regulation of camel movement, regular herd examination and isolation of positive camels.
- Similarly, urgent epidemiological studies and molecular detection like sequencing of viral RNA by RT-PCR of MERS-CoV are mandatory to better understand the transmission patterns of MERS-CoV both in human and camel samples.
- It is also important to raise awareness among travelers to regions affected by MERS-CoV about the signs and symptoms of the disease and to urge individuals to report any of these signs and symptoms so as to receive proper and timely care.
- Improved surveillance, epidemiological research for the development of new therapies and vaccine are important for both human and camels.

List of Abbrevations:

DIC	Disseminated Intravascular Coagulation
UPE	Upstream elements
MERS-COV	Middle East Respiratory Syndrome
GIT	Gastro Intestinal Tract
WHO	World Health Organization
RNA	Ribo nucleic acid
PPE	Personal Protective Equipment
SARS	Severe Acute Respiratory Syndrome
UAE	United Arab Emirate
RT-QPCR	Real-Time reverse-transcription Polymerase Chain Reaction
EMC	Erasmus Medical Center
RDRP	RNA-dependent RNA polymerase
PRO-MED	Program for Monitoring Emerging Disease
UK HPA	United Kingdom's Health Protection Agency
HCOV-EMC	Human Corona virus Erasmus Medical Center

KSA	Kingdom of Saudi Arabia
BAL	Broncho-Alveolar Lavage
EMCO	Extra-Corporeal Membrane Oxygenation
IFA	Immune-Fluorescence Assays
DNA	DeoxyriboNucleic Acid
ORF	Open Reading Frame
N	Number
PRNT	Plaque Reduction Neutralization Test (Reapted)

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