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MIDDLE EAST RESPIRATORY SYNDROME (MERS): A SYSTEMATIC REVIEW

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ABSTRACT: The first case of middle east respiratory syndrome (MERS) was identified in a mid-aged Saudi Arabian resident in 2012. The syndrome is analogous to severe acute respiratory syndrome (SARS) in its clinical course, with a male predominance in incidence. MERS virus is disseminated as a result of close proximity of people to camels, person to person transmission being uncommon and confined to hospital settings. The incubation period usually lasts for 2 - 14 days. MERS-CoV appears to be an enzootic virus, tracing its origin to bats, whereas camels may act as intermediate hosts. Typical flu-like symptoms are observed, which include pyrexia, myalgia, apnoea and cough. Symptoms advance over time leading to multiple organ failure, septic shock and eventually death. Diagnosis can be done with the aid of recombinant IgA and IgG ELISAs, and other specific assays such as upE and real-time Reverse Transcription (rt-RT) PCR assay. Currently, neither an authorized vaccine nor a definitive treatment is available for human use. However, adenosine deaminase, mycophenolic acid (MPA), cyclosporine A, nelfinavir, lopinavir, combination of IFN- α 2b and ribavirin are underway to attain recognition as specific therapies. The following review summarizes the pharmacotherapy and management options for healthcare workers and preventive strategies for susceptible groups. Our review demonstrates that there exists some relation of the virus with seasonal variability, peculiarly in months from May to September.

INTRODUCTION: Middle east respiratory syndrome coronavirus (MERS-CoV) was first recognized in a Saudi Arabian citizen in 2012¹. Formerly called the Human Coronavirus-Erasmus Medical Center / 2012 (HCoV-EMC/2012), it was later renamed by the International Committee on Taxonomy of Viruses as MERS-CoV^{2, 3}. It possesses symptoms similar to those of severe acute respiratory syndrome (SARS)⁴, which was first identified in 2002⁵.

The origin of coronaviruses dates back to the 1960s. These species of viruses have been known to cause several pulmonary infections⁶, and are the fourth or fifth most commonly implicated viruses causing respiratory illnesses⁷. They are positive grade RNA viruses, categorized under the family Coronaviridae and subfamily Coronavirinae³. The spike proteins on their exteriors impart a crown like impression, and hence the name. The coronavirus subgroup is further divided into four genera: alpha, beta, gamma and delta, where the human corona viruses constitute the former two^{6, 8}. A survey in Qatar displayed that abattoir house workers and veterinarians had greater risk of acquiring the infection. Travellers, visitors, and hajj and umrah pilgrims should be well educated prior to their visit to Saudi Arabia⁹, as it is the focal point for the

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virus¹⁰. The following review summarizes the pharmacotherapy and management options for healthcare workers and preventive strategies for susceptible groups.

Epidemiology: On 13 June 2012, a 60 year old resident of KSA presented with febrile acute respiratory disease and was admitted to a private hospital in Jeddah, who succumbed to the infection and expired on the 11th day of illness (24 June, 2012)¹¹. On 20 September 2012, the causative organism was identified as a new member belonging to the Coronaviridae family¹². Three months following discovery of the novel corona virus, a second case, seemingly in a traveller from the Middle East, with clinical manifestations of acute respiratory illness was reported in the U.K.^{13, 14}. Since then, WHO is being regularly notified on the annual updates of MERS. The organization reported a sum of 9 confirmed cases by 30 November 2012, and 157 confirmed and 19 apparent cases by 22 November 2013. From the 176 cases stated in 2013, 69 (39.2%) died, of which 65.3% were males¹⁵. The average age was 51 years (range: 9 or 14 months-94 years)^{15, 16}.

The source city witnessed the first outbreak of MERS from January to May 2014, constituting 255 patients, 174 of which were male, average age being 45 years. 93 deaths were recorded¹⁷.

Meanwhile, the first case in the U.S was reported on 1st May 2014, in a traveller from Saudi who arrived in the States^{18, 19}. This was followed by a second U.S case reported on 11 May 2014. Both the patients were successfully treated and discharged thence¹⁸⁻²⁰. By 26 December 2014, the WHO was notified of 941 morbidities and 347 mortalities from across 23 countries and 4 continents worldwide^{21, 22}. The Korean outbreak of MERS began with an infection in a 68 year old comorbid male who was a frequent visitor to the Middle East. On 18 May 2015, he was diagnosed as suffering from the nosocomial infection^{23, 24}. This outbreak (20 May²⁴ - 14 July 2015),²⁵ resulting from person to person contact^{23, 26}, was reported to have affected 186 individuals and taken 38 lives until a formal end was announced. By 4 December 2015, the WHO revealed 1,621 confirmed cases and 584 demises²⁷.

Saudi Arabia is since then, continually witnessing smaller outbreaks of MERS-CoV; 22 cases were added between 16 and 18 June 2016²⁸, and 56 cases from 1 to 23 June 2017. Affecting 27 countries and 4 continents across the globe, the data reported to the WHO as of 4 July 2017 are 2,040 confirmed cases associated with 712 deaths, while in September the number rose to 2,078 morbidities²⁹, shown in **Fig. 1**.

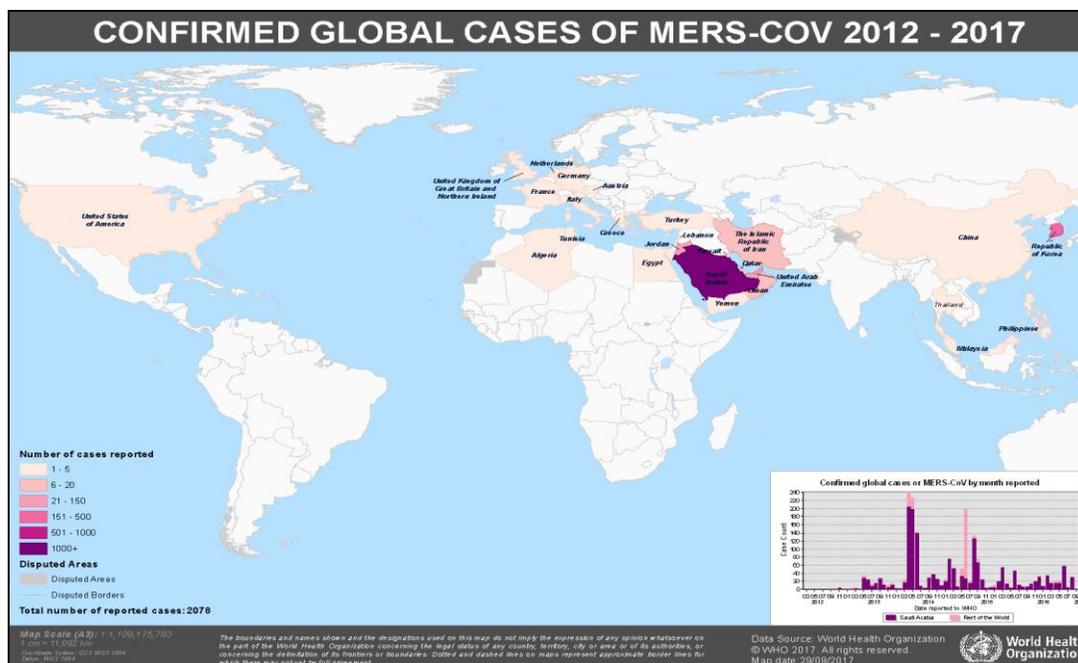


FIG. 1: GEOGRAPHIC DISTRIBUTION OF MERS-COV OUTBREAKS³¹

Saudi Arabia with the highest prevalence of the disease (more than 2000 confirmed cases) is shown in purple. A total of 2078 cases were notified to the WHO as of 29 September 2017.

However, contact transmission is not the only means of viral dissemination. This was evidenced in 2013 when no confirmed cases of infection were reported in the weeks following the Hajj pilgrimage, containing 1.37 million pilgrims from 188 nations³⁰.

Transmission: It is known that the virus is primarily zoonotic in nature, camels being the dominant sources of infection; the route of transmission whether direct or indirect is unfamiliar¹⁶. A crucial factor in governing the transmission route is the camel's milk, as the virus was observed in 41.7% of 12 samples examined³². Additional studies are required to procure information regarding secretion and handling of contaminated milk and its effect on the severity of the ailment³³. Affected animals may drop MERS-CoV in saliva, nasal and eye discharges, faeces and also in urine, all of which are speculated to play a role in transmission of the disease^{2, 9}. Food-borne transmission may be another means of spread, by drinking of raw or unprocessed milk and consuming half cooked meat, as practised by natives of the Arabian Peninsula³².

Data on person to person dissemination of MERS-CoV though not adequate, are recorded in hospital outbreaks and in travellers coming from the Middle East³⁴. This mode also constitutes the bulk of cases³⁵. The virus is transmitted from diseased to healthy persons *via* close contact like caring for or living with an infected individual³⁶, likely to be due to the release of respiratory droplets while coughing or sneezing³⁴. Many of the secondary transmitted cases, which have arisen from household settings^{35, 37}, remain asymptomatic and are more moderate than the primary ones³⁷. For determining the possible origin of the infection, researchers assessed for the presence of MERS antibodies in various animals such as Arabian camels, water buffaloes, cows, pigs, sheep and goats in Egypt. It was found that camels tested positive for these antibodies while other mammals tested negative. This indicated that either MERS-CoV or an analogous virus had infected the Arabian camels³⁸. Apart from camels and bats, till now no other animal has been known³².

Virology: Coronaviridae family contains four groups namely alpha-CoV, beta-CoV, gamma-CoV

and delta-CoV⁶. Further, A, B, C and D are four lineages of beta coronavirus³⁹, with MERS-CoV falling under lineage C⁴⁰. The novel coronavirus was first isolated by an Egyptian virologist, Dr. Ali M. Zaki in 2012¹². It was labelled by the Coronaviridae Study Group (CSG) of the ICTV as MERS-CoV^{3, 41}. 182 genomes of the virus have since been arranged⁴².

MERS-CoV is a single stranded RNA virus meticulously related to bat coronaviruses HKU4 and HKU5. The genome consists of 10 open reading frames (ORF) and is 30,119 nucleotides long. Three quarters of the genome from the 5' cap consists of ORF1a and ORF1b⁴⁰, which were the first key diagnostic targets for recognition of coronaviruses⁴³. Two polyproteins, polyprotein 1a (pp1a) and polyprotein 1ab (pp1ab) are generated during translation, that begins in ORF1a and sustains in ORF1b. These polyproteins are split by viral encoded proteases *i.e.* papain-like protease (PLpro) and 3C-like protease (3CLpro) into 16 putative nonstructural proteins (nsps). Two thirds of the ORFs encode for nsps while the remainder ORFs encrypt for structural and accessory proteins^{2, 40, 44} such as protein 3(p3), p4a, p4b, p5 and p8b^{41, 44}.

Advancement towards 3' end of the polycistronic genome reveals the spike (S), nucleocapsid (N), envelope (E) and membrane (M) proteins, encoded by a number of smaller genes^{2, 40, 44}, as shown in **Fig. 2**. The spike proteins (type I glycoproteins) are separated into two non-covalently coupled subunits; S1 and S2 in the golgi apparatus. S1 subunit encompasses a receptor binding domain (RBD) while the S2 subunit comprises of two heptad repeat domains HR1 and HR2⁴⁵. S protein also contains a transmembrane domain. Cell tropism and receptor interaction are determined by S1 domain binding to DPP4 receptors of the host cell². For cell fusion and release of genomic RNA into the cytoplasm, protease cleft of S protein is required¹.

For governing the type of species and tissue tropism of coronaviruses, cellular receptors are required⁴⁶. 4a proteins of MERS-CoV block the release of type I interferon (IFN). Hence these MERS-CoV 4a proteins are also called as interferon antagonists, which act by blocking

melanoma differentiation - associated protein 5 (MDA5) dependent type I IFN activation and by binding with ds RNA molecules, resulting in ds RNA sequestration⁴¹.

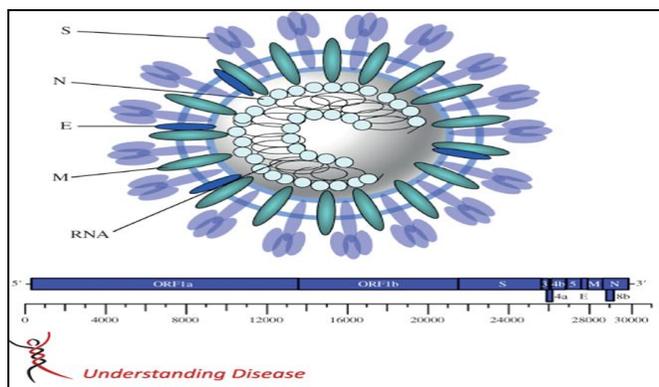


FIG. 2: SCHEMATIC DIAGRAM OF A MERS-COV PARTICLE AND MERS-COV GENOME ORGANIZATION³⁴

S: spike protein; N: nucleocapsid protein; E: envelope protein; M: membrane protein; ORF 1a: Open Reading Frame 1a; ORF 1b: Open Reading Frame 1b.

Risk Factors: Clinical researches for the determination of risk factors are still in progress. However, MERS-CoV is found to be more frequent in the geriatric population (65 years or above), immune compromised patients and those with comorbid conditions such as cancer, chronic lung diseases and diabetes^{47 - 51}. Other risk factors include, visitors to the Gulf *i.e.* countries including Saudi Arabia, Iraq, Iran, Bahrain, Gaza, Israel, Jordan, Kuwait, Lebanon, Oman, Qatar, Syria, UAE and Yemen; healthcare workers, and those who are in close contact with confirmed MERS cases; people working with animals^{52, 53}; and expecting mothers.

Pathogenesis: The pathogenesis of MERS-CoV, though not distinctly comprehended, is assumed to imitate that of SARS-CoV³⁴. Dipeptidyl peptidase-4 receptor (DPP4), also called CD26, is crucial in elucidating the pathogenesis of MERS-CoV^{54, 55}. The ability of the virus to replicate in the LRT⁵⁶ explains the pathology of respiratory clinical features. MERS-CoV affects a number of immune cells such as macrophages, dendritic cells⁵⁷, T cells^{54, 57}, and other cells such as humans' hepatoma cells³⁴, type II alveolar cells⁵⁶, and spleen of common marmosets⁵⁴. *Ex vivo* studies in humans have demonstrated that endothelial cells lining the blood vessels of lung tissue were susceptible to MERS-CoV. This data contributed to the evidence of viral dissemination in the host⁵⁷.

Organisms more prone to MERS-CoV are humans, pigs and bats⁵⁸. Studies in animals like macaques, marmosets and camels revealed that, upon infection, macaques and marmosets acquired systemic abnormalities^{1, 59}, while camels acquired rhinitis, with no systemic disease on examination¹.

MERS can be intricate if the patient has acute pyelonephritis or Kawasaki disease⁶⁰. Studies conclude that MERS-CoV infected and entered T cells more conveniently, contrary to SARS-CoV which failed to invade the cells. The virus also infected higher amplitude of CD4+ T cells compared to CD8+ cells. These factors contribute to the exorbitant pathogenicity of MERS. Further, a précis of the pathogenesis as summarized by Chu *et al.*, involves the progression of infection in the following manner: as the virus enters the host cell, it releases accessory proteins. These viral accessory proteins elude the host innate immune response, and expedite viraemia by causing infection of antigen presenting cells which include monocyte-derived macrophages (MDMs) and dendritic cells. Once infected by the pathogen, dendritic cells move to the lymph nodes and transfer the virus to T cells, which once affected, lead to more severe immunopathology, according to *ex-vivo* and *in-vivo* studies. MERS-CoV is also responsible for cytokine dysregulation⁵⁴. Overall, the pathophysiology of MERS replication in the host is much more complex, but a detailed description would be beyond the scope of this review.

Clinical Features: MERS-CoV infected patients present with a wide range of clinical features. Common symptoms include fever^{11, 48, 51} with chills and rigors^{11, 48}, cough, dyspnoea, myalgia or arthralgia^{11, 48, 51}, headache, weakness, wheezing, sputum production, rhinorrhoea, blood in sputum and sore throat⁵¹. Gastrointestinal manifestations such as vomiting, diarrhoea and abdominal pain^{11, 48}, and non-respiratory feature such as acute kidney injury (AKI) and acute abdomen were also apparent⁵¹. Lower respiratory tract revealed larger bulk of viruses⁴³, evidenced when isolation of the virus deemed to be much more convenient from LRT samples than the URT samples⁶¹. The incubation period was approximated to be 12 days⁶² or 2-14 days⁶³. Studies on MERS-CoV infected pregnant women remain limited. During the Jordanian outbreak of the disease in 2015⁶⁴, a 39

year old woman was tested positive for MERS-CoV antibodies. Further investigations traced back the disease to her unprotected exposure to two positive relatives and thus her cause for acquiring the same. Typical flu-like symptoms with vaginal bleeding and abdominal pain became prominent on the 7th day of illness following which she immediately delivered a stillborn infant⁶⁵.

The infection is more probable in patients with acute respiratory illness, acute respiratory distress syndrome (ARDS), pneumonia and in those with comorbidities^{48, 51}. An animal based evidence was considered crucial in determining the pathogenesis and symptoms of the disease; *Rhesus macaque* was hence used. Virus shedding was apparent from the nose and throat. The infection was most likely to occur in the LRT than the URT⁶⁶. MERS may also be silent with asymptomatic carriers. Symptoms may progress to severe respiratory disorders and culminate in death of the individual⁴⁹. Of the six corona viruses discovered up to date, SARS-CoV and MERS-CoV induce severe lower respiratory tract infections while the remainder cause mild respiratory tract infections^{6, 34}.

Complications: Renal failure is the most significant complication of the disease resulting from septicity of renal tissue¹¹. CVS abnormalities such as pericarditis, and haematologic abnormalities such as DIC (Disseminated Intravascular Coagulopathy) were reported in 2 cases upto 2012⁴⁸. In a study conducted in Korea, monitoring 30 MERS-CoV affected subjects, 8 patients (26.7%) developed AKI as a complication. Development of AKI, diabetes mellitus, continuous renal replacement therapy (CRRT), along with septic shock progression and multiple organ failure posed a risk of death in patients⁶⁷.

Diagnosis: If the medical history and physical exam are indicative of MERS-CoV infection, further investigations for confirmation of the disease are to be effectuated. Laboratory technicians and other healthcare workers are required to abide by the guidelines communicated by the WHO for performing the stated procedures⁶⁸. The highest virus titres were obtained from LRT specimens^{62, 69, 70} such as bronchoalveolar lavage (BAL), bronchial wash (BW), tracheal aspirate (TA) and sputum^{11, 71}, hence these should be

prioritized for testing. URT samples such as nasopharyngeal swabs (NPS) and oropharyngeal swabs (OPS)⁷¹ can then be obtained⁷⁰. Serum^{71, 72}, faecal^{69, 71} and urine samples should also be considered for diagnosis⁶⁹. The clinical specimens are to be obtained at intervals of 2 - 4 days or frequently in emergency situations. Samples from symptomatic patients can be tested with the application of PCR. In cases of negative sampling, retests with fresh samples are to be performed⁷².

i. Real-time Reverse Transcription Polymerase Chain Reaction (rt-RT PCR) Assay: The golden standard for diagnosing all kinds of corona viruses is the detection of nucleic acid by real time-RT PCR assay (rt-RT PCR)^{73, 74}. However, the assay remained limited due to its inability to identify the virus in the initial stages of infection⁷⁵. The upE assay (specificity analogous to ORF1a assay) emerged as a better alternative^{76 - 78}, hence was utilized first in screening the viruses⁷⁷, confirmation was then made using the rt-RT PCR assay or the less sensitive ORF1b assay⁷⁸. Under the authority of FDA, the 'CDC Novel Coronavirus 2012 Real time-RT PCR Assay' was regarded as being suitable for the speculative diagnosis of MERS in emergency situations, both in patients at risk and in those already infected⁷⁹.

ii. Serology Tests: Immunofluorescence assays specific for IgG antibodies tested positive in patients 10 and 11 days after admission¹¹. Antibodies of the IgA and IgG types from serum and respiratory samples were identified using recombinant ELISA⁶¹. Confirmation can then be made employing either the indirect fluorescent antibody (IFA) test or micro neutralization test (MNT)^{43, 72}. Asymptomatic patients' samples are to be collected within a fortnight of previous contact and are to be screened utilizing procedures analogous to the ones for symptomatic persons⁷².

iii. Virus Isolation: Virus isolation procedures are also a useful tool in detecting the presence of the agent but the operations are limited to well equipped laboratories with trained personnels⁷².

iv. Complete Blood Picture: Since MERS corresponds to an infection⁷³, blood analysis (*i.e.* complete blood picture) when performed, portrayed the following data: haematologic abnormalities

such as an increase in neutrophils and a fall in lymphocyte percentage on the second day of admission and a rise in blood urea nitrogen (BUN) and creatinine levels on the third day of admission. As the disease progressed, WBC levels up surged with neutrophilia, persistent lymphopaenia and thrombocytopaenia. However, blood or tracheal aspirate samples obtained 4 days after admission were negative for the virus¹¹.

v. Chest Radiography: Chest radiographic examination of affected patients revealed ARDS and multiple organ dysfunction syndrome (MODS)¹¹.

vi. CT Scan: CT scan of chest may also be performed⁸⁰.

Treatment: Generally, viral respiratory infections are treated in a presentation oriented manner with medications to reduce fever and relieve symptoms⁶. However, no definitive treatment has yet been established for infections caused by corona viruses, peculiarly SARS and MERS⁸¹. Uncomplicated MERS treatment is symptom centered^{35, 49} and focuses on preventing complications whilst providing relief to the patient³⁵. Supportive care is the mainstay of treatment⁸². Management of MERS should be in accordance with the guidelines laid by the WHO (see http://www.who.int/csr/disease/coronavirus_infections/InterimGuidance_ClinicalManagement_NovelCoronavirus_11Feb13.pdf)⁸³. Anti-MERS agents can be categorized based on their mechanism of action as: drugs halting invasion of virus, those terminating virus reproduction, drugs altering immune response of the host and combination regimens⁸⁴.

Adenosine deaminase, a natural antagonist, was found to diminish further infection by blocking viral attachment to the host⁸⁵, lopinavir and nelfinavir reduced viral counts through their cytotoxic effects⁸⁶, while mycophenolic acid (MPA)⁸⁴ and cyclosporine A inhibited virus multiplication^{84, 87}. However, the precise mechanism of action of MPA against MERS-CoV is not clear though many mechanisms have been proposed⁸⁸. It is a broad spectrum antiviral, presumed to exert its therapeutic action by 2 definite ways *i.e.* by blockage of inosine monophosphate dehydrogenase (IMPDH) pathway and by interferon stimulated gene expression⁸⁹.

Another study demonstrated that interferons, either when used alone or in combination (IFN- α 2b with ribavirin), were effective both in the treatment and prophylaxis of the disease^{81, 90}. IFNs with corticosteroids diminished immune reaction of the host in SARS patients⁹⁰. Interferon- β 1b and MPA combination therapy⁸⁶ and administration of antibiotics and intravenous immunoglobulin also reduced the illness⁸⁰.

MERS Vaccine: The widespread prevalence of MERS-CoV with an increase in fatality rate in several countries has been a matter of serious concern demanding the development of an effective MERS vaccine. Therefore, many attempts to develop vaccine against the virus have been made^{35, 91, 92}. The various kinds of vaccines as evaluated by Naru *et al.*, include inactivated and live attenuated virus vaccines, DNA vaccines, viral vector based vaccines and subunit vaccines. The subunit type offers a promising option for modelling an efficacious and potent MERS vaccine⁴⁴. Complicated MERS leading to respiratory depression may require mechanical ventilation³⁵.

Prevention and Control: Close contact with affected individuals leading to disease transmission and spread has accounted for majority of MERS cases⁵². Potentially effectual methods of prevention and control that are centered on reducing infections include⁸²:

- Maintaining hygiene, mainly by washing hands frequently with adequate amount of soap. Should soap be unavailable, a hand sanitizer may be substituted.
- Single-use tissues should be used while coughing or sneezing and must be properly disposed off.
- Frequent contact of impure hands with eyes, nose or mouth should be avoided.
- Sharing of utensils, cups or towels of affected individuals should be avoided.
- Awareness regarding infection prevention and control should be created among healthcare workers as well as the general population to prevent further spread of the disease.
- Healthcare professionals in close contact with affected patients must comply with the preventive measures laid by the CDC (see

<https://www.cdc.gov/coronavirus/mers/infection-prevention-control.html>)⁹³.

- Travellers to the Gulf region must be well educated regarding the infection and its associated complications. This can be made possible with the aid of patient education leaflets and posters in airports or while boarding planes³⁵.
- Special precautions should be taken for the geriatric population, immune suppressed, comorbid and those working with animals, as these categories of people portray a greater vulnerability to infection³⁵. The WHO does not presently restrict the consumption of pasteurized camel milk and cooked camel meat.
- Other health habits such as nutritional balance and physical activity, as well as taking adequate amount of sleep which aid in boosting the body's immunity should be practised.

An organized approach for prevention and control of the infection, with timely diagnosis, and exchange of information among healthcare officials is encouraged⁹⁴.

Future Outlooks: Six years since it was first identified, MERS-CoV continues to pose health threats globally with a case fatality rate of more than 30%⁵⁷. A closer approach to the understanding of MERS-CoV outbreaks reveals their greater frequency in the months from May to September. It can therefore be hypothesized from this observation that there exists some relation of the pathogen with seasonal variations (see: Epidemiology).

Further studies in view of this are to be effectuated. A male predominance in MERS cases was observed. The reason behind this gender variation, though not certain, is attributed to the face veil that women wear in KSA, presumed to protect the latter from the virus gaining entry into the body, thereby preventing infections. Despite the widespread epidemiology of the disease, it is debarred from being called a pandemic infection. This can be endorsed from the fact that the virus is confined to small gatherings in spite of being granted multiple opportunities to cause an epidemic. This is indicative of the rarity in human to human transmission⁴³. Continuous and ongoing clinical

trials to accelerate the establishment of a specific MERS therapy with promising outcomes and designation of MERS vaccine for prophylactic concerns are being carried out.

CONCLUSION: The year 2012 introduced an unfamiliar member into the Coronaviridae family, called MERS-CoV. It was found to be extensively present in *Camelus dromedarius* in Middle East and few areas of Africa. Zoonotic transmission started from animal species and is presumed to continue for long. Males are more likely to get affected. The coronavirus gains entry into the body by attaching to host cell receptors of humans *i.e.* dipeptidyl peptidase 4 (DPP-4) receptors, but fails to do so in mice, ferrets and hamsters⁴⁶. High quality supportive care is the keystone of management. Antiviral regimens specific to MERS-CoV remain to be entrenched. However, treatment with commercially available medications such as type-I IFNs, lopinavir, ribavirin (at high doses) along with corticosteroids, have shown to improve therapeutic response in patients. Vaccine clinical trials focusing on demonstrating prophylaxis of the disease are continually being conducted, the most efficacious being the subunit vaccine. Given the probability of MERS transmission from camels to humans, adequate precautions should be taken such as keeping away from slaughter houses and farm houses or wearing facial masks when working with animals.

Questions and queries such as the exact cause and route of transmission, the rationale behind seasonal variability, travel restrictions (if any) and limitation of the virus from widespread dissemination amongst mass congregations remain unanswered. Therefore, improved surveillance measures and investigations are required to predict the present epidemiology and to analyze the upcoming scenario of the infection. All healthcare agencies are required to be equipped with prior management planning in the case of an emergency situation.

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