IJPSR (2018), Volume 9, Issue 7 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 20 October, 2017; received in revised form, 15 January, 2018; accepted, 27 January, 2018; published 01 July, 2018

MIDDLE EAST RESPIRATORY SYNDROME (MERS): A SYSTEMATIC REVIEW

Pathan Amanulla Khan, B. B. Sarah Nousheen *, Naseerah Maryam and Khateeja Sultana

Department of Pharmacy Practice, Anwarul Uloom College of Pharmacy, Hyderabad - 500001, Telangana, India.

Keywords:

Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS), upE assay, Real-time Reverse Transcription (rt-RT) PCR Assay

Correspondence to Author:
B. B. Sarah Nousheen

Pharm D,
Department of Pharmacy Practice,
Anwarul Uloom College of Pharmacy,
Hyderabad - 500001, Telangana,
India.

E-mail: sarahnousheen@gmail.com

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-α2b 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 2012 [1]. 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 2002 [5].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(7).2616-25

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(7).2616-25

The origin of coronaviruses dates back to the 1960s. These species of viruses have been known to cause several pulmonary infections [6], and are the fourth or fifth most commonly implicated viruses causing respiratory illnesses [7]. They are positive grade RNA viruses, categorized under the family Coronaviridae and subfamily Coronavirinae [3]. 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 Arabia [9], as it is the focal point for the

virus [10]. 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 family [12]. 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 males [15]. 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 recorded [17].

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 thence [18 - 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 May [24] - 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 demises [27].

Saudi Arabia is since then, continually witnessing smaller outbreaks of MERS-CoV; 22 cases were added between 16 and 18 June 2016 [28], 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 morbidities [29], shown in **Fig. 1**.

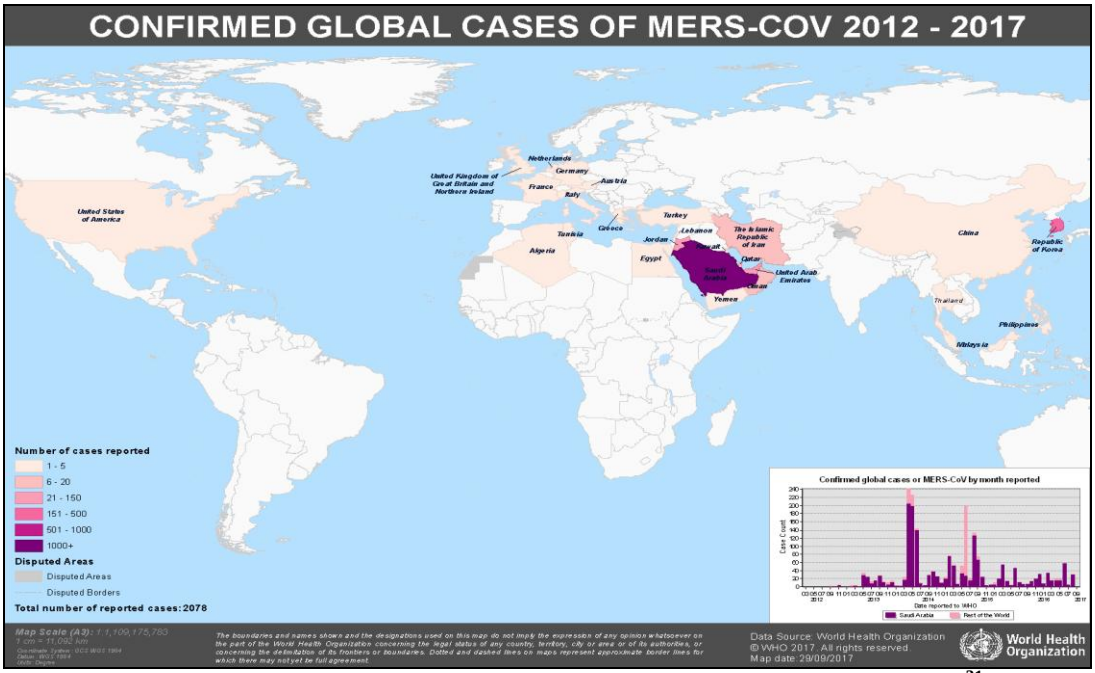

FIG. 1: GEOGRAPHIC DISTRIBUTION OF MERS-COV OUTBREAKS [31]

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 nations [30].

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 unfamiliar [16]. A crucial factor in governing the transmission route is the camel's milk, as the virus was observed in 41.7% of 12 samples examined [32]. Additional studies are required to procure information regarding secretion and handling of contaminated milk and its effect on the severity of the ailment [33]. 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 Peninsula [32].

Data on person to person dissemination of MERS-CoV though not adequate, are recorded in hospital outbreaks and in travellers coming from the Middle East [34]. This mode also constitutes the bulk of cases [35]. The virus is transmitted from diseased to healthy persons *via* close contact like caring for or living with an infected individual [36], likely to be due to the release of respiratory droplets while coughing or sneezing [34]. Many of the secondary transmitted cases, which have arisen from household settings [35, 37], remain asymptomatic and are more moderate than the primary ones [37]. 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 camels [38]. Apart from camels and bats, till now no other animal has been known [32].

Virology: Coronaviridae family contains four groups namely alpha-CoV, beta-CoV, gamma-CoV and delta-CoV [6]. Further, A, B, C and D are four lineages of beta coronavirus [39], with MERS-CoV falling under lineage C [40]. The novel coronavirus was first isolated by an Egyptian virologist, Dr. Ali M. Zaki in 2012 [12]. 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 arranged [42].

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 ORF1b [40], which were the first key diagnostic targets for recognition of coronaviruses [43]. 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 HR2 [45]. S protein also contains a transmembrane domain. Cell tropism and receptor interaction are determined by S1 domain binding to DPP4 receptors of the host cell [2]. For cell fusion and release of genomic RNA into the cytoplasm, protease cleft of S protein is required [1].

For governing the type of species and tissue tropism of coronaviruses, cellular receptors are required [46]. 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 sequestration [41].

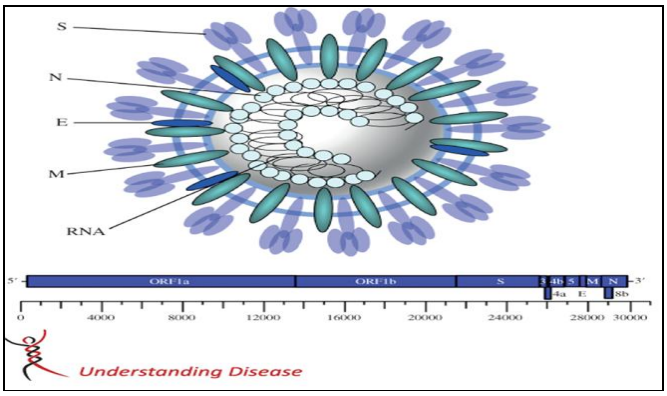

FIG. 2: SCHEMATIC DIAGRAM OF A MERS-COV PARTICLE AND MERS-COV GENOME ORGANIZATION [34]
S: spike protein; N: nucleocapsid protein; E: envelope protein; M: membrane protein; ORF 1a: Open Reading Frame 1a; ORF 1b: Open Reading Frame 1b.

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-CoV [34]. 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 LRT [56] explains the pathology of respiratory clinical features. MERS-CoV affects a number of immune cells such as macrophages, dendritic cells [57], T cells [54, 57], and other cells such as humans' hepatoma cells [34], type II alveolar cells [56], and spleen of common marmosets [54]. *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 host [57].

Organisms more prone to MERS-CoV are humans, pigs and bats [58]. 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 examination [1].

MERS can be intricate if the patient has acute pyelonephritis or Kawasaki disease [60]. 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 dysregulation [54]. 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 throat [51]. 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 apparent [51]. Lower respiratory tract revealed larger bulk of viruses [43], evidenced when isolation of the virus deemed to be much more convenient from LRT samples than the URT samples [61]. The incubation period was approximated to be 12 days [62] or 2-14 days [63]. Studies on MERS-CoV infected pregnant women remain limited. During the Jordanian outbreak of the disease in 2015 [64], 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 infant [65].

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 URT [66]. MERS may also be silent with asymptomatic carriers. Symptoms may progress to severe respiratory disorders and culminate in death of the individual [49]. 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 tissue [11]. CVS abnormalities such as pericarditis, and haematologic abnormalities such as DIC (Disseminated Intravascular Coagulopathy) were reported in 2 cases upto 2012 [48]. 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 patients [67].

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 procedures [68]. 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 obtained [70]. Serum [71, 72], faecal [69, 71] and urine samples should also be considered for diagnosis [69]. 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 performed [72].

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 infection [75]. The upE assay (specificity analogous to ORF1a assay) emerged as a better alternative [76 - 78], hence was utilized first in screening the viruses [77], confirmation was then made using the rt-RT PCR assay or the less sensitive ORF1b assay [78]. 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 infected [79].

ii. Serology Tests: Immunofluorescence assays specific for IgG antibodies tested positive in patients 10 and 11 days after admission [11]. Antibodies of the IgA and IgG types from serum and respiratory samples were identified using recombinant ELISA [61]. 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 persons [72].

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 personnels [72].

iv. Complete Blood Picture: Since MERS corresponds to an infection [73], 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 virus [11].

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 performed [80].

Treatment: Generally, viral respiratory infections are treated in a presentation oriented manner with medications to reduce fever and relieve symptoms [6]. However, no definitive treatment has yet been established for infections caused by corona viruses, peculiarly SARS and MERS [81]. Uncomplicated MERS treatment is symptom centered [35, 49] and focuses on preventing complications whilst providing relief to the patient [35]. Supportive care is the mainstay of treatment [82]. 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 regimens [84].

Adenosine deaminase, a natural antagonist, was found to diminish further infection by blocking viral attachment to the host [85], lopinavir and nelfinavir reduced viral counts through their cytotoxic effects [86], 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 proposed [88]. 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 expression [89].

Another study demonstrated that interferons, either when used alone or in combination (IFN-α2b 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 patients [90]. Interferon-β1b and MPA combination therapy [86] and administration of antibiotics and intravenous immunoglobulin also reduced the illness [80].

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 vaccine [44]. Complicated MERS leading to respiratory depression may require mechanical ventilation [35].

Prevention and Control: Close contact with affected individuals leading to disease transmission and spread has accounted for majority of MERS cases [52]. Potentially effectual methods of prevention and control that are centered on reducing infections include [82]:

- 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 planes [35].
- 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 infection [35]. 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 encouraged [94].

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 transmission [43]. 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 hamsters [46]. 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.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: All authors have none to declare.

FINANCIAL SUPPORT AND SPONSORSHIP: Nil

REFERENCES:

1. Zumla A, Hui DS and Perlman S: Middle East Respiratory Syndrome. Lancet 2015; 386: 995-1007.
2. Durai P, Batool M, Shah M and Choi S: Middle East respiratory syndrome coronavirus: transmission, virology and therapeutic targeting to aid in outbreak control. Experimental & Molecular Medicine 2015; 47: 181.
3. de Groot RJ, Baker SC, Baric RS, Brown CS, Drosten C, Enjuanes L, *et al*: Middle East Respiratory Syndrome Coronavirus (MERS-CoV): Announcement of the Coronavirus Study Group. Journal of Virology 2013; 87: 7790-7792.
4. Hui DS, Memish ZA and Zumla A: Severe acute respiratory syndrome vs. the Middle East respiratory syndrome. Current Opinion in Pulmonary Medicine 2014; 20: 233-241.
5. Centers for Disease Control and Prevention, CDC SARS Response Timeline; https://www.cdc.gov/about/history/sars/ timeline.htm.
6. Centers for Disease Control and Prevention, Coronavirus: About Coronavirus; https://www.cdc.gov/coronavirus/about/.
7. Geller C, Varbanov M and Duval RE: Human Coronaviruses: Insights into Environmental Resistance and Its Influence on the Development of New Antiseptic Strategies. Viruses 2012; 4: 3044-3068.
8. Mohd HA, Al-Tawfiq JA and Memish ZA: Middle East Respiratory Syndrome Coronavirus (MERS-CoV) origin and animal reservoir. Virology Journal 2016; 13: 87.
9. World Health Organization, Update on MERS-CoV transmission from animals to humans, and interim recommendations for at-risk groups; http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_RA_20140613.pdf?ua=1.
10. Khalafalla AI, Lu X, Al-Mubarak AI, Dalab AH, Al-Busadah KA and Erdman DD: MERS-CoV in Upper Respiratory Tract and Lungs of Dromedary Camels, Saudi Arabia, 2013–2014. Emerging Infectious Diseases 2015; 21: 1153-1158.
11. Zaki AM, Van Boheemen S, Bestebroer TM, Osterhaus AD and Fouchier RA: Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. New England Journal of Medicine 2012; 367: 1814-1820.
12. ProMED-mail, Novel coronavirus - Saudi Arabia: human isolate; http://www.promedmail.org/direct.php?id=20120920.1302733.
13. Acute respiratory illness associated with a new virus identified in the UK; http://www.wales.nhs.uk/sitesplus/888/news/24205.
14. Bermingham A, Chand MA, Brown CS, Aarons E, Tong C, Langrish C, *et al.:* Severe respiratory illness caused by a novel coronavirus, in a patient transferred to the United Kingdom from the Middle East, September 2012. Eurosurveillance 2012; 17: 1-5.
15. World Health Organization, Middle East respiratory syndrome coronavirus (MERS-CoV) summary and literature update – as of 22 November 2013; http://www.who.int/csr/disease/coronavirus_infections/Update12_MERSCoV_update_22Nov13.pdf.
16. World Health Organization, Middle East respiratory syndrome coronavirus (MERS‑CoV) summary and literature update–as of 9 May 2014; http://www.who.int/csr/disease/coronavirus_infections/MERS_CoV_Update_09_May_2014.pdf.
17. Oboho IK, Tomczyk SM, Al-Asmari AM, Banjar AA, Al-Mugti H, Aloraini MS, *et al*: 2014 MERS-CoV Outbreak in Jeddah - A Link to Health Care Facilities. New England Journal of Medicine 2015; 372: 846-854.
18. Centers for Disease Control and Prevention, MERS in the U.S; https://www.cdc.gov/coronavirus/mers/us.html.
19. Centers for Disease Control and Prevention, First Confirmed Cases of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Infection in the United States, Updated Information on the Epidemiology of MERS-CoV Infection, and Guidance for the Public, Clinicians, and Public Health Authorities - May 2014; https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6319a4.htm.
20. Centers for Disease Control and Prevention, CDC announces second imported case of Middle East Respiratory Syndrome (MERS) in the United States; https://www.cdc.gov/media/releases/2014/p0512-US-MERS.html.
21. Al-Tawfiq JA and Memish ZA: An update on Middle East respiratory syndrome: 2 years later. Expert Review of Respiratory Medicine 2015; 9: 327-335.
22. World Health Organization, Middle East respiratory syndrome coronavirus (MERS-CoV) – Saudi Arabia; http://www.who.int/csr/don/26-december-2014-mers/en/.
23. Park YS, Lee C, Kim KM, Kim SW, Lee KJ, Ahn J, *et al.:* The first case of the 2015 Korean Middle East Respiratory Syndrome outbreak. Epid. and Health 2015; 37: 1-5.
24. World Health Organization, Middle East respiratory syndrome coronavirus (MERS-CoV) – Republic of Korea; http://www.who.int/csr/don/24-may-2015-mers-korea/en/.
25. World Health Organization, Middle East respiratory syndrome coronavirus (MERS-CoV) – Republic of Korea; http://www.who.int/csr/don/14-july-2015-mers-korea/en/.
26. Cho SY, Kang JM, Ha YE, Park GE, Lee JY, Ko JH, *et al.:* MERS-CoV outbreak following a single patient exposure in an emergency room in South Korea: an epidemiological outbreak study. Lancet 2016; 388: 994-1001.
27. World Health Organization, Middle East respiratory syndrome coronavirus (MERS-CoV) - Saudi Arabia; http://www.who.int/csr/don/4-december-2015-mers-saudi-arabia/en/.
28. World Health Organization, Middle East respiratory syndrome coronavirus (MERS-CoV) - Saudi Arabia; http://www.who.int/csr/don/ 21- june- 2016- mers- saudi-arabia/en/.
29. World Health Organization, Middle East respiratory syndrome coronavirus (MERS-CoV) – Saudi Arabia; http://www.who.int/csr/don/06-july-2017-mers-saudi-arabia/en/.
30. Watson JT, Hall AJ, Erdman DD, Swerdlow DL and Gerber SI: Unraveling the Mysteries of Middle East Respiratory Syndrome Coronavirus. Emerging Infectious Diseases 2014; 20: 1054-1056.
31. World Health Organization, MERS-CoV maps and epicurves; http://www.who.int/csr/disease/coronavirus_infections/maps-epicurves/en/.
32. Al-Tawfiq JA and Memish ZA: Middle East respiratory syndrome coronavirus: epidemiology and disease control measures. Infection and Drug Resistance 2014; 7: 281-287.
33. Van Doremalen N, Bushmaker T, Karesh WB and Munster VJ: Stability of Middle East respiratory syndrome coronavirus in milk. Emerging Infectious Diseases 2014; 20: 1263-1264.
34. Van den Brand JM, Smits SL and Haagmans BL: Pathogenesis of Middle East respiratory syndrome coronavirus. The Journal of Pathology 2015; 235: 175-184.
35. World Health Organization, Frequently Asked Questions on Middle East respiratory syndrome coronavirus

(MERS-CoV); http://www.who.int/csr/disease/coronavirus _infections/faq/en/.
36. Centers for Disease Control and Prevention, Middle East Respiratory Syndrome (MERS): Transmission; https:// www.cdc.gov/coronavirus/MERS/about/transmission.html.
37. McIntosh K: Middle East respiratory syndrome coronavirus: Virology, pathogenesis, and epidemiology. Up-to-date 2016.
38. National Institute of Allergy and Infectious Diseases, Tracking MERS-CoV Transmission; https://www.niaid. nih.gov/ diseases- conditions/ tracking- mers- cov-transmission.
39. Woo PC, Lau SK, Lam CS, Lau CC, Tsang AK, Lau JH, *et al.:* Discovery of Seven Novel Mammalian and Avian Coronaviruses in the Genus *Delta coronavirus* Supports Bat Corona viruses as the Gene Source of Alpha corona virus and Beta corona virus and Avian Corona viruses as the Gene Source of Gamma corona virus *and* Delta corona virus. Journal of Virology 2012; 86: 3995-4008.
40. Van Boheemen S, de Graaf M, Lauber C, Bestebroer TM, Raj VS, Zaki AM, *et al.:* Genomic Characterization of a Newly Discovered Coronavirus Associated with Acute Resp.Distress Syndrome in Humans. mBio 2012; 3: 1-9.
41. Niemeyer D, Zillinger T, Muth D, Zielecki F, Horvath G, Suliman T, *et al*.: Middle East Respiratory Syndrome Coronavirus Accessory Protein 4a Is a Type I Interferon Antagonist. Journal of Virology 2013; 87: 12489-12495.
42. Wernery U, Lau SK and Woo PC: Genomics and zoonotic infections: Middle East respiratory syndrome. Revue Scientifique Et Technique 2016; 35: 191-202.
43. Mackay IM and Arden KE. MERS coronavirus: diagnostics, epidemiology and transmission. Virology Journal 2015; 12: 222.
44. Zhang N, Jiang S and Du L: Current advancements and potential strategies in the development of MERS-CoV vaccines. Expert Review of Vaccines 2014; 13: 761–774.
45. Weiss SR and Navas-Martin S: Corona virus Pathogenesis and the Emerging Pathogen Severe Acute Respiratory Syndrome Corona virus. Microbiology and Molecular Biology Reviews 2005; 69: 635-664.
46. Milne-Price S, Miazgowicz KL and Munster VJ: The emergence of the Middle East Respiratory Syndrome coronavirus (MERS-CoV). Pathogens and Disease 2014; 71: 119-134.
47. World Health Organization, Middle East respiratory syndrome coronavirus (MERS-CoV) summary and literature update–as of 11 June 2014; http://www.who.int/ csr/disease/coronavirus_infections/MERS-CoV_summary_ update_20140611.pdf?ua.
48. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, *et al*.: Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infectious Diseases 2013; 13: 752-761.
49. World Health Organization, Middle East respiratory syndrome coronavirus (MERS-CoV): Fact sheet; http://www.who.int/mediacentre/factsheets/mers-cov/en/.
50. Naeem Z: Middle East Respiratory Syndrome (MERS) – An update. International Journal of Health Sciences (Qassim) 2013; 7: 5-6.
51. Arabi YM, Arifi AA, Balkhy HH, Najm H, Aldawood AS, Ghabashi A, *et al*.: Clinical course and outcomes of critically ill patients with Middle East Respiratory Syndrome Coronavirus Infection. Annals of Internal Medicine 2014; 160: 389-397.
52. Centers for Disease Control and Prevention, Middle East Respiratory Syndrome (MERS): People Who May Be at Increased Risk for MERS; https://www.cdc.gov/corona virus/mers/risk.html#fever.
53. Reusken CB, Farag EA, Haagmans BL, Mohran KA, Godeke GJ, Raj VS, *et al*.: Occupational Exposure to Dromedaries and Risk for MERS-CoV Infection, Qatar, 2013–2014. Emerging Inf. Diseases 2015; 21: 1422-1425.
54. Chu H, Zhou J, Wong BH, Li C, Chan JF, Cheng ZS, *et al*.: Middle East Respiratory Syndrome Coronavirus Efficiently Infects Human Primary T Lymphocytes and Activates the Extrinsic and Intrinsic Apoptosis Pathways. Journal of Infectious Diseases 2016; 213: 904-914.
55. Raj VS, Mou H, Smits SL, Dekkers DH, Müller MA, Dijkman R, *et al*.: Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus - EMC. Nature 2013; 495: 251-254.
56. Coleman CM and Frieman MB: Emergence of the Middle East Respiratory Syndrome Coronavirus. PLoS Pathogens 2013; 9: 1-3.
57. Zhou J, Chu H, Chan JF-W and Yuen KY: Middle East respiratory syndrome coronavirus infection: virus-host cell interactions and implications on pathogenesis. Virology Journal 2015; 12: 1-7.
58. Zielecki F, Weber M, Eickmann M, Spiegelberg L, Zaki AM, Matrosovich M, *et al.:* Human Cell Tropism and Innate Immune System Interactions of Human Respiratory Coronavirus EMC Compared to Those of Severe Acute Respiratory Syndrome Coronavirus. Journal of Virology 2013; 87: 5300-5304.
59. Falzarano D, de Wit E, Feldmann F, Rasmussen AL, Okumura A, Peng X, *et al*.: Infection with MERS-CoV Causes Lethal Pneumonia in the Common Marmoset. PLoS Pathogens 2014; 10: 1-13.
60. Okamoto T, Sato Y, Yamazaki T and Hayashi A: Clinically mild encephalitis / encephalopathy with a reversible splenial lesion associated with febrile urinary tract infection. European Journal of Pediatrics 2014; 173: 533-536.
61. Muth D, Corman VM, Meyer B, Assiri A, Al-Masri M, Farah M, *et al*.: Infectious Middle East Respiratory Syndrome Coronavirus Excretion and Serotype Variability Based on Live Virus Isolates from Patients in Saudi Arabia. Jou. of Clin. Microbiology 2015; 53: 2951-2955.
62. Guery B, Poissy J, el Mansouf L, Séjourné C, Ettahar N, Lemaire X, *et al*.: Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome corona virus: a report of nosocomial transmission. Lancet 2013; 381: 2265-2272.
63. Centers for Disease Control and Prevention, Middle East Respiratory Syndrome (MERS): Symptoms and Complications; https://www.cdc.gov/coronavirus/mers/ about/symptoms.html.
64. World Health Organization, Middle East respiratory syndrome coronavirus (MERS-CoV) - Jordan; http://www.who.int/csr/don/18-sep-2015-mers-jordan/en/.
65. Payne DC, Iblan I, Alqasrawi S, Al Nsour M, Rha B, Tohme RA, *et al*.: Stillbirth during infection with Middle East Respiratory Syndrome Coronavirus. Journal of Infectious Diseases 2014; 209: 1870-1872.
66. de Wit E, Rasmussen AL, Falzarano D, Bushmaker T, Feldmann F, Brining DL, *et al*.: Middle East respiratory syndrome coronavirus (MERS-CoV) causes transient lower respiratory tract infection in rhesus macaques. Proceedings of the National Academy of Sciences USA 2013; 110: 16598-16603.

67. Cha R, Joh JS, Jeong I, Lee JY, Shin HS, Kim G, *et al*.: Renal complications and their prognosis in Korean patients with Middle East respiratory syndrome-coronavirus from the central MERS-CoV designated hospital. Journal of Korean Medical Science 2015; 30: 1807-1814.
68. World Health Organization, Infection prevention and control of epidemic-and pandemic prone acute respiratory infections in health care: WHO guidelines. http://www.who.int/csr/bioriskreduction/inf_control/publication/en/.
69. Drosten C, Seilmaier M, Corman VM, Hartmann W, Scheible G, Sack S, *et al*.: Clinical features and virological analysis of a case of Middle East respiratory syndrome coronavirus infection. Lan Inf Dis 2013; 13: 745-751.
70. Memish ZA, Al-Tawfiq JA, Makhdoom HQ, Assiri A, Alhakeem RF, Albarrak A, *et al*.: Respiratory tract samples, viral load and genome fraction yield in patients with Middle East respiratory syndrome. Journal of Infectious Diseases 2014; 210: 1590-1594.
71. Shahkarami M, Yen C, Glaser C, Xia D, Watt J and Wadford DA: Laboratory testing for Middle East respiratory syndrome coronavirus, California, USA, 2013–2014. Emerging Infectious Diseases 2015; 21: 1664-1666.
72. World Health Organization, Laboratory Testing for Middle East Respiratory Syndrome Coronavirus; http://www.who.int/csr/disease/coronavirus_infections/WHO_interim_recommendations_lab_detection_MERSCoV_092014.pdf.
73. Drosten C, Günther S, Preiser W, van der Werf S, Brodt H-R, Becker S, *et al*.: Identification of a novel corona virus in patients with severe acute respiratory syndrome. New England Journal of Medicine 2003; 348: 1967-1976.
74. Vijgen L, Moes E, Keyaerts E, Li S and Van Ranst M: A pancoronavirus RT-PCR assay for detection of all known coronaviruses. Methods in Mol. Biol. 2008; 454: 3-12.
75. Drosten C, Chiu LL, Panning M, Leong HN, Preiser W, Tam JS, *et al*.: Evaluation of advanced reverse transcription-PCR assays and an alternative PCR target region for detection of severe acute respiratory syndrome-associated coronavirus. J of Cli Mic 2004; 42: 2043-2047.
76. upE assay and ORF1b assay; https://virologie-ccm.charite.de/fileadmin/user_upload/microsites/m_cc05/virologie-ccm/Dateien_upload/BenchProtPCRupE_assay MERS-CoV.pdf.
77. Corman VM, Eckerle I, Bleicker T, Zaki A, Landt O, Eschbach-Bludau M, *et al*.: Detection of a novel human coronavirus by real-time reverse-transcription polymerase chain reaction. Eurosurveillance 2012; 17: 1-6.
78. Corman VM, Müller MA, Costabel U, Timm J, Binger T, Meyer B, *et al*.: Assays for laboratory confirmation of novel human corona virus (hCoV-EMC) infections. Eurosurveillance 2012; 17: 1-9.
79. U.S. Food and Drug Administration, Emergency Use Authorizations, https:// www.fda.gov/ Medical Devices/ Safety/EmergencySituations/ucm161496.htm.
80. Kapoor M, Pringle K, Kumar A, Dearth S, Liu L, Lovchik J, *et al*.: Clinical and laboratory findings of the first imported case of Middle East respiratory syndrome corona virus to the United States. Clinical Infectious Diseases 2014; 59: 1511-1518.
81. Falzarano D, de Wit E, Martellaro C, Callison J, Munster VJ and Feldmann H: Inhibition of novel β coronavirus replication by a combination of interferon-α2b and ribavirin. Scientific Reports 2013; 3: 1-6.
82. Centers for Disease Control and Prevention, Middle East Respiratory Syndrome (MERS): Prevention & Treatment; https://www.cdc.gov/coronavirus/mers/about/prevention.html.
83. World Health Organization, Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus (MERS-CoV) infection is suspected; http://www.who.int/csr/disease/coronavirus_infections/case-management-ipc/en/.
84. Al-Tawfiq JA and Memish ZA: What are our pharmacotherapeutic options for MERS-CoV? Expert Review of Clinical Pharmacology 2014; 7: 235-238.
85. Raj VS, Smits SL, Provacia LB, van den Brand JM, Wiersma L, Ouwendijk WJ, *et al*.: Adenosine deaminase acts as a natural antagonist for dipeptidyl peptidase 4-mediated entry of the Middle East respiratory syndrome coronavirus. Journal of Virology 2014; 88: 1834-1838.
86. Chan JF, Chan KH, Kao RY, To KK, Zheng B-J, Li CP, *et al*.: Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. Journal of Infection 2013; 67: 606-616.
87. de Wilde AH,Raj VS, Oudshoorm D, Bestebroer TM, van Nieuwkoop S, Limpens RW, *et al*.: MERS-coronavirus replication induces severe *in vitro* cytopathology and is strongly inhibited by cyclosporin A or interferon-α treatment. Jou. of General Virology 2013; 94: 1749-1760.
88. Hart BJ, Dyall J, Postnikova E, Zhou H, Kindrachuk J, Johnson RF, *et al*.: Interferon-β and mycophenolic acid are potent inhibitors of Middle East respiratory syndrome coronavirus in cell-based assays. Journal of General Virology 2014; 95: 571–577.
89. Pan Q, de Ruiter PE, Metselaar HJ, Kwekkeboom J, de Jonge J, Tilanus HW, *et al*.: Mycophenolic acid augments interferon-stimulated gene expression and inhibits hepatitis C Virus infection *in vitro* and *in vivo*. Hepatology 2012; 55: 1673-1683.
90. Loutfy MR, Blatt LM, Siminovitch KA, Ward S, Wolff B, Lho H, *et al*.: Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. JAMA 2003; 290: 3222-3228.
91. Almazán F, DeDiego ML, Sola I, Zuñiga S, Nieto-Torres JL, Marquez-Jurado S, *et al*.: Engineering a Replication-Competent, Propagation - Defective Middle East Respiratory Syndrome Coronavirus as a Vaccine Candidate. mBio 2013; 4: 1-11.
92. Du L, Zhao G, Kou Z, Ma C, Sun S, Poon VK, *et al*.: Identification of a Receptor-Binding Domain in the S Protein of the Novel Human Coronavirus Middle East Respiratory Syndrome Coronavirus as an Essential Target for Vaccine Development. J of Vir 2013; 87: 9939-9942.
93. Centers for Disease Control and Prevention, Interim Infection Prevention and Control Recommendations for Hospitalized Patients with Middle East Respiratory Syndrome Coronavirus (MERS-CoV); https://www.cdc.gov/coronavirus/mers/infection-prevention-control.html.
94. Khan A, Farooqui A, Guan Y and Kelvin DJ: Lessons to learn from MERS-CoV outbreak in South Korea. Journal of Infection in Developing Countries 2015; 9: 543-546.

How to cite this article:
Khan PA, Nousheen BBS, Maryam N and Sultana K: Middle east respiratory syndrome (mers): A systematic review. Int J Pharm Sci Res 2018; 9(7): 2616-25. doi: 10.13040/IJPSR.0975-8232.9(7).2616-25.