MERS-CoV INCIDENCE IN THE KINGDOM OF SAUDI ARABIA
AND WORLDWIDE: GENERAL REVIEW ARTICLE

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Abstract

In recent years, several outbreaks of the Middle East Respiratory Syndrome Corona Virus
(MERS-CoV) were reported to the WHO by Saudi Arabia (2014, 2015, and 2017) and the
Republic of Korea (2015). These large outbreaks indicate that MERS-CoV, if not adequately con-
trolled, can cause severe outbreaks and negative socio-economic consequences. The disease was
identified and reported in 27 countries around the world, particularly in the Middle East, Africa,
Asia, Europe, and North America. The total number of laboratory-confirmed MERS-CoV cases
reported to the WHO between 2012 and 21 July 2017 was 2040, of which 1672 (82%) were r
ported to the Kingdom of Saudi Arabia. Since the 5th December 2016, about 190 cases were
confirmed in Saudi Arabia, out of which 63 were reported in one outbreak and four different
clusters in the Riyadh region.

This review discusses the background of the disease along with its epidemiology, risk factors,
clinical features, diagnosis, treatment, vaccination, prevention and control. The review also co-
cludes with some future perspectives.

Key words: Saudi Arabia, MERS-CoV, Worldwide, General review

Background

The Middle East Respiratory Syndrome Corona Virus (MERS-CoV) was initially
identified in Middle Eastern countries, particularly Saudi Arabia, in September 2012
(Azhar et al, 2014). It belongs to the Nidovirals order, Coronaviridae family and the
Coronavirinae subfamily. It is of the Betacoronavirus genus, and the species is Mid-
dle East Respiratory Syndrome Coronavirus (MERS-CoV). It was a novel enveloped, po-
itive-sense, the single-stranded RNA genome as a large virus with a helical symmetry of a
genomic size ranging from 26 to 32 kilo-bases (Anand et al, 2003; Siddell et al, 1983).

Globally, since its discovery, more than 2,040 laboratory confirmed cases linked to
infectious MERS-CoV were reported to the WHO (2017a), resulting in a high mortality
rate (712 deaths). Therefore, serious consider-
erations of the increasing number of infected
cases, the high mortality rate as well as the
pandemic state of the virus during the Hajj
season are essential. Several questions re-
main open, even though there is invaluable
information available about the viral patho-
physiology, suggesting an “animal reservoir”, and revealing the intermediate host of
the virus (Azhar et al, 2014). To provide and
review the current knowledge about the in-
fected MERS-CoV, including its history,
the mode of transmission, epidemiology, clin-
cal symptoms, diagnostic approaches,
treatment options and, finally, future the
perspectives the target of the present study.

In September 2012, a novel Corona Virus
was isolated and identified by an Egyptian
virologist Dr. Ali Mohamed Zaki, then re-
ported on the Program for Monitoring Emer-
ing Diseases (ProMED-mail, 2012). In May
the Middle East Respiratory Syndrome Cor-
ona Virus (MERS-CoV) was launched by the
Corona Virus Study Group of the Interna-
tional Committee on Taxonomy of Virus-
es (ICTV) (De Groot et al, 2013). The isola-
tion of the MERS-CoV in Saudi patients showed that the virus’ genomic sequencing belongs to the lineage C of the Betacoronavirus genus, together with the bat corona Viruses Ty-BatCoV-HKU4 and Pi-BatCoV-HKU5, which have been detached from two different bats species, respectively: *Tylochirus pachypus* and *Pipistrellus abramus* (Woo et al., 2006; Khalil et al., 2013). Prior to 2003, it was assumed that human Corona Viruses were not serious infectious human pathogens, since they were represented by the viruses HCoV-OC43 and HCoV-229E, which can infect the upper respiratory tract system and cause mild flu-like symptoms, known as the common cold (Drosten et al., 2003). However, between 2002 and 2003, the initiation of an unknown infectious human corona virus was reported as the first zoonotic agent introduced by the corona virus into the human population, which was later named Severe Acute Respiratory Syndrome: Corona Virus (SARS-CoV) and led to the first Corona Virus-associated human epidemic and global pandemic viral infection, infecting approximately 8,400 cases and killing 800 people (WHO, 2003). Recently, the MERS-CoV proved to be a highly pathogenic, sporadic, and was ranked the second zoonotic viral disease after SARS-CoV. It was hypothesized that the MERS-CoV originates from natural reservoir animals, such as bats, and an intermediate host, such as palm civet (Guan et al., 2003).

There are three existing basic reasons that support the theory that MERS-CoV originated from bats, as follows: 1- it shares a highly similar phylogenetic similarity with the bat Betacoronaviruses; BatCoV-HKU4 & BatCoV-HKU5; 2- bats in Asia, Africa, the Americas and Eurasia have been found to possess closely-related Corona Virus sequences; and 3- it enters the cells by using the evolutionary conserved dipeptidyl peptidase-4 (DPP4) protein found in the *Pipistrellus pipistrellus* bats (Lau et al., 2010; Raj et al., 2013).

Epidemiology: During the summer of year 2012, in Jeddah, Saudi Arabian, an anonymous Corona Virus (CoV) was first isolated from the saliva of a patient who was suffering from acute pneumonia and renal atrophy. The virus was then named MERS-CoV by the ICTV (De Groot et al., 2013). MERS-CoV is known as one of the human corona viruses that consist of a further five strains, namely: SARS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL-63, and HCoV-HKU1. MERS-CoV is considered a zoonotic disease, and seems to have variety of dependent transmission patterns. Moreover, it can be transmitted by droplets or close contact (Fig. 1) between infected camels, chiefly dromedary camels, rhinorrhea and humans, as well as via human to human transmission (Cotten et al, 2013; Drosten et al., 2014).

On the other hand, the virus can be transmitted by touching contaminated surfaces (Chu et al, 2014). MERS have been mainly identified and reported in 27 countries around the world, particularly in the Middle East, Africa, Asia, Europe, and North America. These countries are distributed across four continents and areas, including (Fig. 2): Saudi Arabia, Kuwait, Qatar, Yemen, Oman, Bahrain, Jordan and Lebanon in the Middle East; Tunisia, Egypt and Algeria in Africa; Iran, South Korea, China, Thailand, the Philippines, Malaysia and Indonesia in Asia; Italy, France, Germany, Greece, Austria, Turkey, Netherlands and the United Kingdom in Europe; and in the United States (WHO, 2017b).

Since September 2012, WHO has reported 2,040 laboratory-confirmed cases of MERS-CoV, resulting in at least 712 MERS-CoV-related deaths?

Two thousands forty laboratory confirmed cases of MERS-CoV from 27 countries and the majority of cases (about 82%, e.g. 1672 cases) was reported from Saudi Arabia (Tab.1)
Table 1: No. of laboratory-confirmed MERS-CoV cases reported since September 2012 (WHO, 2017b).

<table>
<thead>
<tr>
<th>No. of Countries</th>
<th>Countries reporting</th>
<th>No. of laboratory-confirmed MERS cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Algeria</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Austria</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Bahrain</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>China</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Egypt</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>France</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>Germany</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>Greece</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>Iran</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>Italy</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>Jordan</td>
<td>28</td>
</tr>
<tr>
<td>12</td>
<td>Kuwait</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>Lebanon</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>Malaysia</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>Netherlands</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td>Oman</td>
<td>8</td>
</tr>
<tr>
<td>17</td>
<td>Philippines</td>
<td>17</td>
</tr>
<tr>
<td>18</td>
<td>Qatar</td>
<td>19</td>
</tr>
<tr>
<td>19</td>
<td>Republic of Korea</td>
<td>185</td>
</tr>
<tr>
<td>20</td>
<td>Saudi Arabia</td>
<td>1672</td>
</tr>
<tr>
<td>21</td>
<td>Thailand</td>
<td>3</td>
</tr>
<tr>
<td>22</td>
<td>Tunisia</td>
<td>3</td>
</tr>
<tr>
<td>23</td>
<td>Turkey</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>United Kingdom</td>
<td>4</td>
</tr>
<tr>
<td>25</td>
<td>United Arab Emirates</td>
<td>83</td>
</tr>
<tr>
<td>26</td>
<td>United States of America</td>
<td>2</td>
</tr>
<tr>
<td>27</td>
<td>Yemen</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>2,040</td>
</tr>
</tbody>
</table>

Furthermore, it is worthy to mention that since the 5th December 2016; about 190 cases were confirmed from Saudi Arabia, of whom 63 were reported from one outbreak and four different clusters in the Riyadh Region (Tab. 2).

Table 2: Outbreaks and clusters of MERS-CoV from the Kingdom of Saudi Arabia since 5th December 2016 (WHO, 2017b).

<table>
<thead>
<tr>
<th>City reporting</th>
<th>Data</th>
<th>No. of laboratory-confirmed MERS cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wadi-Aldwaser (a cluster at one hospital)</td>
<td>March 2017</td>
<td>10</td>
</tr>
<tr>
<td>Wadi-Aldwaser (a cluster at same hospital)</td>
<td>April 2017</td>
<td>5</td>
</tr>
<tr>
<td>Riyadh (a cluster at health care facility)</td>
<td>June 2017</td>
<td>5</td>
</tr>
<tr>
<td>Riyadh (a cluster at 1 hospital)</td>
<td>June 2017</td>
<td>9</td>
</tr>
<tr>
<td>Riyadh (an outbreak at a hospital)</td>
<td>1 June 2016 - 3 July 2017</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>63</td>
</tr>
</tbody>
</table>

The case mortality rate is exceedingly high and the fatality rate reaches up to 40% among older people (WHO, 2017b). MERS-CoV has an incubation period ranging between two days to two weeks (Lee, 2015). The human respiratory tract is considered the primary infection site for MERS-CoV. It was verified that MERS-CoV could apparently infect, target and robustly replicate within human respiratory epithelium tissues. MERS-CoV uses its Spike protein receptor to bind its tropism receptors, such as metalloprotease amino-peptidase N and dipeptidyl peptidase 4 (DPP4), in the surface molecules cells, which are mainly non-ciliated bronchial epithelial cells, alveolar epithelial cells, bronchiolar epithelial cells, and endothelial cells of the pulmonary vessels (Zhou et al., 2015). As the first line of host immune defense, human primary respiratory epithelial cells, human lung tissue, and respiratory epithelial cell lines are stimulated to produce antiviral and pro-inflammatory chemokines and cytokines to eradicate the invading virus. Also, MERS-CoV infection fails to elicit a strong pro-inflammatory cytokines response in human primary respiratory epithelial cells and respiratory tissues. Copulatively
MERS-CoV may have evolved various antagonistic mechanisms to attenuate or diminish the host immune defense, which might contribute to the high pathogenicity in humans (Zhou et al, 2015).

Risk factors conducive to MERS-CoV infections: Farmers, shepherds, abattoir workers or dromedary owners who are in close or direct contact with camels or dealing with animals or visiting farms, camel pens, barn areas or market environments where camels are sold are at a high risk of encountering the MERS-CoV (WHO, 2014). Moreover, persons who are at high risk of severe pattern of MERS-CoV include the immunocompromised hosts who are undergoing chemotherapy or radiation, smokers, the elderly and people who suffer from diabetes, chronic lung disease, renal failure or heart failure and/or hypertension (WHO, 2014).

It is also noticed from Saudi Arabia that workers at health-care settings are at high risk of encountering the MERS-CoV infection. This is in line with the report of the WHO (2017b) which stated that around 20% of the total confirmed cases from 2012 up to date have been among health-care practitioners.

Clinical features: People infected with the MERS-CoV present symptoms for a duration ranging from 2 to 14 days. It is unknown whether patients are infectious and capable of spreading the virus during this incubation period (IDSA, 2014). Clinically, MERS-CoV can infect the upper and lower respiratory systems and cause disease ranging from mild to severe clinical symptoms (IDSA, 2014). Therefore, the majority of infected cases remain asymptomatic, without the appearance of any severe symptoms, or normally present with signs and symptoms such as a high fever, chill, cough, shortness of breath, chest pain, headache, myalgia, sore throat and arthralgia (Al-Abdallat et al, 2014). Within one week, a few cases display dyspnea, which rapidly develops into pneumonia and shock (Arabi et al, 2014). Gastrointestinal symptoms such as abdominal pain, anorexia, vomiting, and severe diarrhea are present in some cases (Assiri et al, 2013). Co-infections, mainly related to nosocomial bacterial, fungi, and respiratory viruses, appear to be very common (Memish et al, 2014). Immunocompromised patients or those with "other co-morbidities" such as chemotherapy, radiotherapy, obesity, hypertension, diabetes, lung disease, cardiac disease, acute renal failure (ARF), and organ transplantation display high severity symptoms (Assiri et al., 2013). MERS-CoV is a highly fatal disease, particularly in lethal appearances during severe pneumonia with acute respiratory distress syndrome (ARDS) as well as in ARF due to kidney infection and renal tissue hypoxia. Additionally, severe neurologic syndrome associated with MERS-CoV was identified in three patients, resulting in a changed level of consciousness, confusion, ataxia, focal neurological deficits, and coma (Arabi et al, 2015). Besides, laboratory abnormality data recognized with MERS-CoV included disseminated intravascular coagulation (DIC), leukopenia, lymphopenia, thrombocytopenia, elevated serum level of lactate dehydrogenase (LDH), liver enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine levels (Assiri et al, 2013).

Diagnosis: A reliable diagnosis of MERS-CoV is a prerequisite for treating and preventing the infection. Therefore, MERS-CoV samples can be collected from either the upper respiratory tract system (such as by a nasopharyngeal swab taken from the nasopharynx or an oropharyngeal swab), or lower respiratory tract system (such as from sputum, bronchoalveolar lavage, lung tissue and tracheal aspirates), which constitute a significant body of evidence about the highest viral loads (Drosten et al, 2013; Guery et al, 2013). Whole blood and serum specimens are able to provide strong evidence during virus and immunity detection (Kraaij-Dirkzwager et al, 2014). A low level of viral load has been detected in urine
Several diagnostic techniques, as the chest radiography, electron microscope, Immunofluorescence microscopy, cell culture, enzyme linked immunosorbent assay (ELISA), and real-time polymerase chain reaction (RT-PCR) were utilized in viral identification and quantification (Corman et al, 2012a; Drosten et al, 2015). Chest X-rays are easy to perform, fast, and fairly inexpensive, producing data that were available in electronic format and so easily be archived, stored, and made widely available to hospitals and clinicians (Delrue et al, 2011). However, excessive exposure to radiation can cause malignancy in general and birth defects among pregnant women. Moreover, this technique cannot distinguish between different viral infections, and the interpretation of chest X-ray reports remains challenging (Delrue et al, 2011).

Electron microscope, meanwhile, relies on the isolation of the novel coronavirus from classic tissue-culture that is used to amplify the viral pathogen for the purpose of etiological identification. It is a widely-used, highly sensitive, and versatile technique that offers several advantages, including the used in clinical virology and histopathology research, not requiring specific reagents, and being able to recognize viral morphology's "unique nature" and distinguish among different microorganisms in the tested samples to help to connect them to the disease (Johnson et al, 1977; Hazelton and Gelderblom, 2003). Nevertheless, this technique requires expertise, it's availability was only in reference labs, very expensive, cannot classify a pathogen based on its appearance and morphogenesis, and is unsuitable for investigating a large number of samples during outbreaks (Hazelton and Gelderblom, 2003; Biel et al, 2004).

Moreover, an alternative diagnostic method is to use immunofluorescence microscopy to detect the antibody response to MERS-CoV. This labour- and materials-intensive approach has numerous applications, including genetically modifying and fluorescently staining biological molecules, a routinely feasible approach, detecting difficult, uncultured microbes, investigating outbreaks of respiratory disease, detecting antigens in the absence of viral infectivity, examining post-mortem specimens, controlling cross-infection, and diagnosing infectious agents of a distance samples from laboratories (Jenson et al, 1998). However, the specificity of this assay is doubtful, due to the cross reactivity between the Betacorona viruses genus, the ability to identify the infection only during the convalescent phase, the temporary nature of fluorescence dye activity, the occurrence of photo-bleaching, the necessity for the chemical fixation of fluorescence fadesAnti-body-labeled as well as treatment with detergents to prepare cell membrane permeability (Gardner, 1984).

Cell culture is generally a useful, less technically-demanding method that was effective for isolating a variety of viruses (Le land and Ginocchio, 2007). Notwithstanding, its disadvantages included the time-consuming incubation period and observation of the cytopathic effect (CPE), high cost, need for substantially skilled, experienced staff for the interpretations, and the high risk of viral contamination and danger of viral transmission (Hematian et al, 2016).

Another approach is ELISA, the greatest advantage of which is that it provides results faster than any of the previous techniques and utilized not only to quantify antibodies and discriminate between the early and end phases but also to detect antigens (Word Press, 2016). ELISA is a widely-distributed technique in developing and developed countries, and has been used as a sensitive and specific serological diagnosis approach for routinely detecting and monitoring several microbiological organisms in different med-
clinical fields (Izumi et al., 1991; WordPress, 2016). Also, due to being more cost effective, not requiring any skilled personnel and being easy to use, apply and prepare for large population screening, it is favored over other alternative methods (Balsam et al., 2013). Despite the benefits of using ELISA methods, they suffered from several drawbacks, including: the immobilization of antigens is not specific, cross-reactivity, time-consuming and less flexibility because of using a secondary antibody as well as the need for an inimitably conjugated primary antibody, respectively, to detect each protein of interest (Koenig, 1981; Oswald, 2014).

To sum up the technical aspects of MERS-CoV diagnosis at present, real-time reverse-transcription polymerase chain reaction (RT-PCR) assays are suitable for the quantitative and qualitative detection of the new infectious agents, (Corman et al., 2012b) because the quantitative technique can help to evaluate the height and period duration of the virus secretion, and can also be functional as an early, robust parameter for monitoring treatment outcomes, its benefits, and understanding the viral pathogenesis (Peiris et al., 2003; Corman et al., 2012b). Nucleic acid amplification methods also offer certain advantages, including rapid identification and clear differentiation between coronavirus sp. and disease levels (Sampath et al., 2005). PCR technique provides results very rapidly (within 60 minutes), which facilitated coronavirus monitoring and enabled avoidance of its clinical complications and pathogen distribution (Vos et al., 1995; Van de Pol et al., 2006). The method can be utilized to examine a high number of several types of specimens in a single run that decreased time required for viral detection and analysis (Cupić et al., 2006). Additional advantages of PCR include its higher sensitivity and specificity over conventional techniques, its ability to identify and detect difficult and uncultured viral and atypical pathogens, and its greater cost-effectiveness (Gruteke et al., 2004; Syrmis et al., 2004). Finally, without cross-reactivity is in a well-designed PCR with consequence of 100% primer sensitivity and specificity that led to reliable, accurate diagnoses (Thai et al., 2004).

Treatment and Vaccination: Two main clinical complications followed MERS-CoV (respiratory & renal atrophy), inspiring physicians, pharmacists and researchers to seek a drug treatment that is capable of eradicating the viral infection. Although no effective antiviral agents are suggested for treating patients with MERS-CoV infection, primarily supportive medicine, focusing on supporting the organs and reducing the virus transmission, is considered the current clinical management for MERS-CoV disease (De Wilde et al., 2013). The use of extracorporeal membrane oxygenation (ECMO) is recommended due to its characteristic ability to reduce fertility rates during acute respiratory failure (Zampieri et al., 2013). For renal atrophy, however, the use of continuous venovenous hemofiltration as well as a reduction in immunosuppressant drugs was thought to increase infected life expectancy (Villa et al., 2017). For secondary bacterial infection and other viral agents, beta-lactam broad-spectrum, such as Amoxicillin and Ampicillin, and antivirals against influenza infection, mainly zanamivir and ribavirin, have been endorsed (Akers et al., 2017; Bakaletz, 2017). Several potential therapeutic agents were assessed for targeting and curing MERS-CoV infection (Tab.3).

These candidate drugs’ activities promised to reduce or suppress viral replication, cytotoxic effect formation, viral genomic transcription and translation, and viral progeny release, and so alleviate the symptoms and complications associated with MERS-CoV disease (De Wilde et al., 2013; Giere et al., 2013). Although various drug measures and control procedures have been followed to prevent/reduce the virus’ effectiveness and dissemination, vaccinations remain the most powerful way to cure the disease (Hajj Hussein et al., 2015). Hence, numerous mechanisms to develop effective vaccines to eradi-
cating viral respiratory disease are ongoing; these mechanisms include neutralizing the antibody pathway, signaling processes, in-

Table 3: Therapeutic agents evaluated as promising drugs and vaccines candidates for opposing MERS-CoV infection (Doulkeridou, 2013).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanisms</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>INF-α</td>
<td>Reduction of MERS-CoV replication in pseudo-stratified HAE cultures</td>
<td>Kinderer et al. (2013)</td>
</tr>
<tr>
<td>pegylated IFN-α</td>
<td>Inhibition of MERS-CoV-induced CPE and reduction of viral RNA levels in human lung epithelial and monkey kidney cell lines</td>
<td>De Wilde et al. (2013)</td>
</tr>
<tr>
<td>INF-β</td>
<td>Reduction of viral load in MERS-CoV-infected human lung epithelial and monkey kidney cell lines</td>
<td>Zalecki et al. (2013)</td>
</tr>
<tr>
<td>INF-α3</td>
<td>Reduction of MERS-CoV replication in pseudo-stratified HAE cultures</td>
<td>Kinderer et al. (2013)</td>
</tr>
<tr>
<td>INF-α2b</td>
<td>Reduction of MERS-CoV-induced CPE &amp; viral protein levels in monkey kidney cell lines (more efficient combined with Ribavirin)</td>
<td>Falzarano et al. (2013)</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Reduction of MERS-CoV-induced CPE &amp; viral protein levels in monkey kidney cell lines (more efficient combined with INF-α2b)</td>
<td>Falzarano et al. (2013)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Significant improvement in respiratory condition of a MERS-CoV patient (no direct effect proved)</td>
<td>Gubernina et al. (2014)</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>Inhibition of MERS-CoV-induced CPE in monkey kidney &amp; human liver cell lines</td>
<td>De Wilde et al. (2013)</td>
</tr>
<tr>
<td>SB203580</td>
<td>Reduction of viral load in a human lung epithelial cell line</td>
<td>Josset et al. (2015)</td>
</tr>
<tr>
<td>ADS-J1</td>
<td>Inhibition of MERS-CoV pseudo-virus infection in human liver &amp; mink lung cell lines</td>
<td>Zhao et al. (2013)</td>
</tr>
<tr>
<td>HP-HAS</td>
<td>Inhibition of MERS-CoV pseudo-virus infection in human liver &amp; mink lung cell lines</td>
<td>Zhao et al. (2013)</td>
</tr>
<tr>
<td>MDL28170</td>
<td>Inhibition of MERS-CoV-S-mediated transduction of a human fetal lung fibroblast cell line</td>
<td>Gierer et al. (2013)</td>
</tr>
<tr>
<td>NH4Cl</td>
<td>Inhibition of MERS-CoV-S-mediated transduction of a human fetal lung fibroblast cell line</td>
<td>Burkard et al. (2014)</td>
</tr>
<tr>
<td>Camostat</td>
<td>Inhibition of MERS-CoV-S-mediated transduction of a human colon cell line</td>
<td>Gierer et al. (2013)</td>
</tr>
<tr>
<td>N3</td>
<td>Inhibition of proteolytic activity of MERS-CoV 3CLpro</td>
<td>Ren et al. (2013)</td>
</tr>
<tr>
<td>CE-10</td>
<td>Inhibition of proteolytic activity of MERS-CoV 3CLpro</td>
<td>Kilianska et al. (2013)</td>
</tr>
<tr>
<td>MERS-CoV RBD</td>
<td>Reduction of viral load in a MERS-CoV-infected monkey kidney cell line</td>
<td>Chen et al. (2013)</td>
</tr>
<tr>
<td>Chloroquine/ Hydrochloroquine</td>
<td>Prevent binding to receptor Endosome</td>
<td>Savarino et al. (2003)</td>
</tr>
<tr>
<td>Lopinavir/ Ritonavir/ Nelfinavir</td>
<td>Inhibition of viral replication</td>
<td>Gronenberg et al. (2005)</td>
</tr>
<tr>
<td>Interferon alfacon-1</td>
<td>Countering antiviral signaling by altering intracellular environment to restrict viral replication</td>
<td>Loutfy et al. (2003)</td>
</tr>
<tr>
<td>MERS-CoV S protein, Novavax</td>
<td>Inducing virus neutralizing antibodies (NAb)</td>
<td>Excler et al. (2016)</td>
</tr>
</tbody>
</table>

Prevention and control: Infection prevention and control are considered essential ways of preventing the transmitting of infection among patients, health care workers, visitors, companions, livestock, shepherd and slaughterhouses workers. Also, preparing health care facilities for early identification, avoiding antimicrobial dissemination or resistance and minimizing the negative impact of infectious agents are other essential aspects of disease prevention. Recommendations for disease prevention and control for patients with suspected or confirmed MERS-CoV infection in outbreaks have been implemented by the World Health Organization (WHO, 2017c). According to the WHO, while caring for patients with acute or chronic respiratory tract infection, the standard and droplet precautions must be followed to prevent viral transmission (WHO, 2017c). Consequently, several procedures in hospitals to avoid the spread of infectious agents include airborne and contact precautions, eye protection, medical masks, negative pressure rooms, hand hygiene, and remaining at least 1 metre away from the patient when controlling and managing probable and identified MERS-CoV cases as well as raising public awareness of MERS-CoV (WHO, 2017c).

WHO recommend that patients who are recovering from MERS-CoV infection and did not require hospitalization, isolated and cared at their home (WHO, 2017c). Besides, several risk factors associated with MERS-CoV must be considered, mainly avoiding camel contact, particularly dromedary camels, during two weeks before symptoms onset were recommended by WHO. Other recommendations included avoiding contact with animals such as bats and goats, following good hand hygiene through frequent hand-washing before and after touching animals, protective clothing and washing.
soiled clothing, plastic gloves, shoes and other items. Avoiding contact with camel urine or drinking raw camel milk, and only eating camel meat that has been cooked thoroughly. Eating food that may be contaminated with animal secretions or products should be avoided unless these have been appropriately cleaned, peeled or cooked (WHO, 2014). Also, heightening bio-security measures at farms, sharing information around camels, probable introduction of certificate/passports for racing camels and trade, engagement of private sector, e.g. breeding enterprises, meat packing operations and racing associations and finally closer coordination to avoid risks are compulsory for controlling of virus infections and diseases (Younan et al, 2016). Likewise, travelling to endemic countries must be avoided to reduce virus distribution and risk of infection becoming pandemic (Al-Tawfiq et al, 2014).

Future perspectives: MERS-CoV is a recently-discovered virus, about which further research and investigation is required. The environmental reservoir of MERS has been unclear for some time. It appears to have been transmitted from bats, camels and goats, but its precise origin remains unclear, as are the environmental factors that foster its sustained growth. So, the mode of transmission and risk factors among humans, camel herds and other animals such as bats remain questionable and require further research to decrease the global health threat posed by MERS-CoV. Also, scientific research must be conducted to uncover the exact modes of transmission in health-care settings. To date, older males constitute the majority of patients who have been reported as having MERS-CoV. Although MERS-CoV infection in humans has numerous risk factors, they are still not completely understood and require further investigation. The incubation period is a maximum of two weeks, but the delivery of the virus during the infectious stage remains unknown. To date, our understanding of the MERS-CoV pathogenesis remains unclear due to the lack of surgical and pathological details about the infected people. Actual mechanism and receptors binding MERS-CoV, humans and other susceptible hosts require further investigation. In spite of the ability of RT-PCR to detect and quantify MERS-CoV, this is not an optimal approach because of its high cost and considerable laboratory equipment demand. Nowadays, effective treatments or vaccines against MERS-CoV are not available, thus, more research are demanded.

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Fig. 1: Worldwide density of camel livestock with/without MERS-CoV (Miguel et al, 2015).

Fig. 2: Confirmed Global Cases of MERS-CoV (2012 - 2017)