Global Veterinaria 21 (4): 215-224, 2019
ISSN 1992-6197

DOI: 10.5829/idosi.gv.2019.215.224

Review on Middle East Respiratory Syndrome: An Emerging Zoonosis

[1]Tsegaye Gebre, [2]Feyissa Begna and [1]Yitbarek Habtamu

[1]National Institute for Control and Eradication of Tsetsefly and Trypanosomosis, Addis Ababa, Ethiopia
[2]Jimma University College of Agriculture and Veterinary Medicine, Jimma, Ethiopia

Abstract: Middle East respiratory syndrome coronavirus (MERS-CoV) is among the genus *Betacoronavirus*, which was initially identified in Saudi Arabia in September 2012. MERS-CoV marks the second known zoonotic introduction of a highly pathogenic coronavirus next to SARS. Identification of neutralizing antibodies suggested that MERS-CoV appears to have been circulating in dromedary camels for over 20 years. Both on the Arabian Peninsula and in Africa, high percentages of adult dromedaries are seropositive for MERS-CoV. MERS-CoV uses the DPP4 (CD26) receptor to gain entry and effectively replicate in camels, bats and humans. Camel milk was investigated as a possible source of transmission, given the common practice of consuming camel milk in the Arabian Peninsula. However, respiratory transmission is currently considered as the most likely route of transmission. MERS-CoV has been detected by reverse transcription PCR (RT-PCR). Currently, the disease has no vaccine and treatment except supportive care. Therefore, developing an effective camel MERS-CoV vaccine and implementing appropriate infection control measures may control the continuing epidemic. Awareness of MERS-CoV infections should be raised among animal and human health professionals as well as people of the world. Understanding the role of dromedary camels and possibly other animals in transmission of MERS-CoV to humans remains a priority for future investigation to enable development of targeted control measures and prevent future cases and deaths from this emerging pathogen. This paper aimed to review the epidemiology and zoonotic importance of MERS.

Key words: Middle East · Camels · Bats · Respiratory · Corona Virus · Zoonosis

INTRODUCTION

Middle East Respiratory Syndrome (MERS) is often a lower respiratory tract disease associated with fever, cough, breathing difficulties, pneumonia that can progress to acute respiratory distress syndrome, multi-organ failure and death among more than a third of those infected. It is caused by MERS-Corona Virus (CoV). Severe disease is usually found in older males and co-morbidities are frequently present in cases of MERS. Compared to Sever Acute Respiratory Syndrome (SARS), MERS progresses more rapidly to respiratory failure and acute kidney injury, is more often observed as severe disease in patients with underlying illnesses and is more often fatal [1]. MERS occurred in more than 20 countries with about 38% fatalities. All cases reported outside of the Middle East have had a recent travel history to the Middle East or contact with a case travelled from the Middle East [2].

MERS-CoV is a novel virus among the genus *Betacoronavirus*, which was first reported in Saudi Arabia in September [3]. Multiple outbreaks of respiratory illness have been attributed to MERS-CoV and severe respiratory illness caused by this virus continues to be identified [4]. Prior to 2003, corona viruses were not considered serious human pathogens since they only caused mild Upper Respiratory Tract Infections (URTIs) [5]. In 2002, the first zoonotic implication of coronaviruses appeared in China known as severe acute respiratory syndrome coronavirus (SARS-CoV) which caused a global pandemic and left with 8,400 cases and 800 deaths (~10%) [6] and MERS is the second.

There is very close phylogenetic similarity with the bat Betacoronaviruses (BtCoV-HKU4 and BtCoV-HKU5) andgene sequences which have been recovered from bats [7]. MERS-CoV uses the evolutionary conserved dipeptidyl peptidase-4 (DPP4) (CD_{26}) protein in *Pipistrellus* bats [8] and camels [9] to gain entry and

Corresponding Author: Yitbarek Habtamu, National Institute for Control and Eradication of Tsetsefly and Trypanosomosis, Addis Ababa, Ethiopia P.O. Box: 19917, Cell: +251996860199.

effectively replicate in. In humans, it is abundantly expressed on the epithelial and endothelial cells of mostorgans, including lung, kidney, small intestine, liver and prostate, as well as immune cells and exists as a soluble form in the circulation [10].

MERS-CoV appears to have been circulating in dromedary camels for over 20 years [11]. This evidence was found after diagnoses of preserved samples from different countries collected at different times. It has been isolated from dromedaries, which are nearly identical to human MERS-CoV. Recent investigations showed high percentages of adult dromedaries are seropositive for MERS-CoV. Young dromedaries ($\leq$ 2 years) are more often acutely infected than adult camels [12].

Camel milk was investigated as a possible route of transmission, given the common practice of consuming camel milk in the Arabian Peninsula. The first reported case of MERS-CoV in Yemen occurred in a Yemeni pilot who consumed raw camel milk [12, 13] reported the finding of MERS-CoV in camel milk in Qatar. However, respiratory transmission is currently considered as the most likely route of transmission [14]. MERS-CoV has been detected by reverse transcription PCR (RT-PCR) from the nasal swabs of three camels in Qatar and was linked to two confirmed human cases with high similarity upon sequencing, suggesting a possible respiratory mode of transmission [15]. The objective of this review was to throw lighton the epidemiology and zoonotic importance of MERS.

ETHIOLOGY

Etiology and Genome Structure: Coronaviruses (CoVs) are large, enveloped, positive-sense RNA viruses that infect birds and a wide range of mammals, including humans. These viruses are composed of a few structural proteins that hold a relatively long (around 30 kb) genome [16]. MERS-CoV belongs to clade C of the genus Betacoronavirus (βCoV) in the family Coronaviridaeunder the order Nidovirales [10]. At present, six CoVs have been identified that infect humans: HKU1, NL63, 229E, OC43, SARS- CoV and MERS-CoV. The former two cause upper respiratory infection which is self-limiting while the last two are recently emerging causing pandemic worldwide characterized by severe lower respiratory infection [16]. Spike (S) glycoprotein on MERS-CoV surface binds cellular receptor dipeptidyl peptidase 4 (DPP4, CD26) (Fig. 1) for host cell entry [8]. On S glycoprotein, a receptor-binding domain (RBD) mediates this interaction [17].

Epidemiology

Geographical Distribution: The persistence of the epidemic of MERS-CoV is postulated to be related to repeated animal-to-human transmissions from at least one type of animal reservoir that is in frequent contact with residents in the region, which are amplified by non-sustained person-to-person transmission in multiple

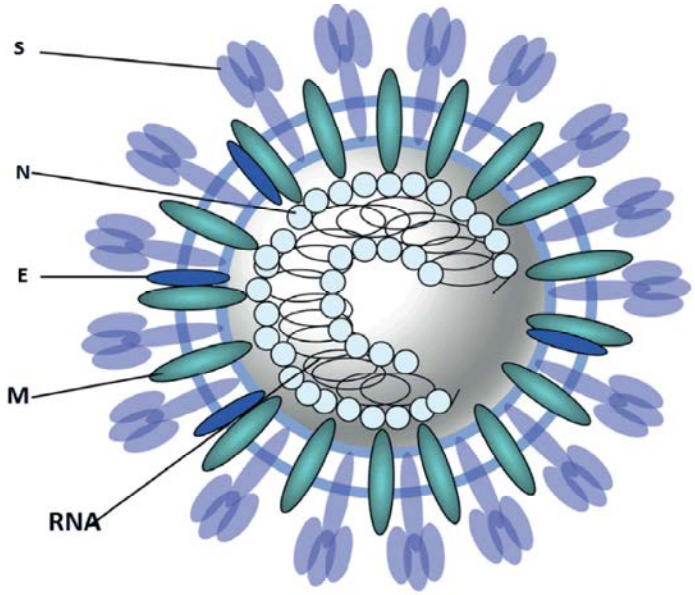

Fig. 1: The structure of a MERS-CoV: S=spike protein; M= membrane protein; E= envelope protein; N=nucleocapsid protein. Source: [16].

Table 1: Cases classified according to country where infection was acquired.

Country	Cases	Deaths
Saudi Arabia	1048	454
South Korea	150	16
United Arab Emirates (UAE)	75	8
Jordan	17	6
Qatar	15	6
Oman	6	3
Iran	6	2
Kuwait	3	1
Tunisia	2	0
United Kingdom	2	1
Yemen	1	1
France	1	0
Lebanon	1	0
Total	1,327	498

Source: (22).

large-scale health care-associated outbreaks and limited household clusters [10]. On the basis of epidemiologic studies, involvement of an animal host has been suggested [18]. Dromedary camels have been identified as a possible intermediate host on the basis of MERS-CoV antibodies and detection of MERS-CoV viral RNA in respiratory swab samples [15, 18, 19]. Furthermore, MERS-CoV genome sequences obtained from dromedary camels clustered with MERS-CoV sequences obtained from humans were linked to the same farm [15]. Nonetheless, most persons with MERS-CoV did not report any direct contact with dromedary camels; therefore, how MERS-CoV zoonotic transmission occurs is unclear [20]. Bats of different species have been also implicated as natural reservoir of the MERS-CoV virus because of the close similarity of gene sequences with human CoVs [10]. Detailed analysis of the molecular evolution and spatiotemporal distribution of genomes of human and animal strains of MERS-CoV provides useful information for detecting viral adaptation to animal-to-human and person-to-person transmissions, identifying zoonotic and other sources of human infections and assessing the pandemic potential of the virus. The virus shows temporal difference in prevalence being high in cooler months but lower during hot months [21].

MERS visited more than twenty countries in the world. A study carried out by WHO [22] showed that a total of 1,327 with 498 deaths (37.5%) from 13 countries wasrecorded (Table 1). These countries included Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, the United Arab Emirates and Yemen with the majority of cases occurred in Saudi Arabia. A limited number of cases have also been reported from Algeria, Austria, China, Egypt, France, Germany, Greece, Iran, Italy, Malaysia, the Netherlands, the Philippines, South Korea, Thailand, Tunisia, Turkey, the United Kingdom and the United States. In the European and Asian countries as well as in Algeria, Egypt, Tunisia and the United States, patients developed illness after returning from the Arabian Peninsula. In the United Kingdom, France, Italy and Tunisia, limited human-to-human transmission occurred among close contacts of the index cases [2].

Seroepidemiology of MERS in Camels

Arabian Peninsula: Saudi Arabia is the country most severely affected by the virus. Studies conducted in Qatar detected MERS-CoV in 4 (35.7%) of 14 [15] animals tested; in Saudi Arabia, 9 (22%) of 41 [23] in Oman, 5 (6.6%) of 76 [24] and in Egypt, 4 (3.6%) of 110 [25]. A study conducted in the United Arab Emirates showed from 376 dromedary camels screened 26% were found to be infected with MERS-CoV [26].

Africa: Serum samples were tested for the presence of IgG antibodies reactive with S_1 antigens against MERS-CoV in Ethiopia, Nigeria, Somalia, Kenya, Tunisia, Egypt and Sudan by using extensively validated protein-microarray technology. High percentages of camels were seropositive for MERS-CoV in Nigeria and Ethiopia. The overall seropositivity was 94% in adult dromedaries in Nigeria and 93% and 97% for juvenile and adults, respectively, in Ethiopia. All provinces in which dromedaries were sampled in both countries showed high rates of seropositivity. The overall seropositivity in dromedaries in Tunisia was 30% for $\leq$2 years of age and 54% for adult animals. Serum samples from 72%, 82% and 67% of the dromedaries from Nigeria, Ethiopia and Tunisia, respectively, reacted with the OC43 antigen, confirming common circulation of βCoV in camels [27]. Seropositivity of 81.4, 86.7 and 85.2% in Egypt, Sudan and Somalia, respectively wasrecorded [28].More than 90% of tested serum samples were seropositive for the virus in Ethiopia [27].

Methods of Transmission

Human to Human Transmission: MERS-CoV, like other coronaviruses, is thought to spread from an infected person's respiratory secretions, such as through coughing. However, the precise ways the virus spreads are not currently well understood. MERS-CoV has spread from ill people to others through close contact, such as caring for or living with an infected person. Infected people have spread MERS-CoV to others in healthcare settings, like hospitals [29]. Several clusters of MERS-CoV

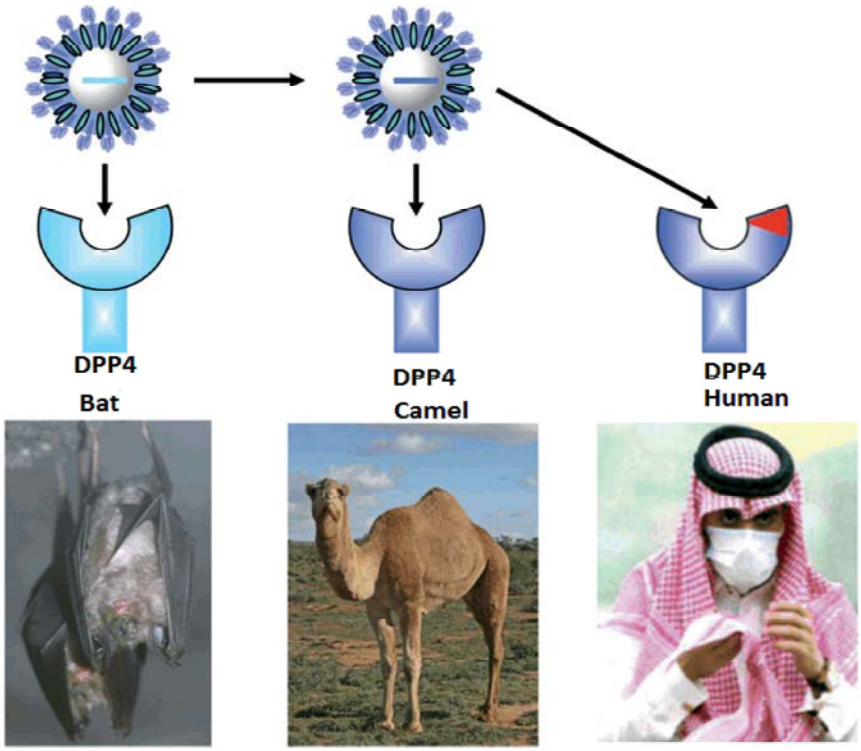

Fig. 2: Zoonotic transmission of MERS-CoV.Source:[16]

cases have been reported, mainly among household members and health care workers, suggesting that transmission is through close contact [30].

Camel to Human Transmission: The origin of MERS-CoV remains a mystery. Bats seem to be the reservoir host of the virus [31] but are probably not the source of the ongoing MERS-CoV outbreak because of limited contact with humans in the Arabian Peninsula. Early observations that some MERS-CoV-infected persons had been exposed to camels suggested a possible role of these animals as intermediate reservoir hosts [32]. MERS-CoV infection in dromedary camels was definitively proven by the detection of virus and virus sequences in respiratory specimens, feces and milkcollected from camels in different infected countries. Residents of the Arabian Peninsula commonly drink unpasteurized milk and it was proven that MERS-CoV virus, when introduced into milk, can survive for prolonged periods [20]. Serologic studies of domestic livestock in Jordan, Saudi Arabia, Qatar, United Arab Emirates and Egypt have found high seroprevalence to a MERS-like CoV in dromedary camels but not in other domestic animals [33]. The epidemiology of the disease so far is suggestive of multiple zoonotic transmissions from an animal reservoir leading to human infection [34]. A study to investigate the replicative capacity of MERS-CoV in livestock cell lines was conducted in goats, sheep, cattle, camelids (dromedary and alpaca), rodents, bats and human and nonhuman primates. The result showed cell lines originating from goats and camels showed efficient replication of MERS-CoV. These results provide direction in the search for the intermediate host of MERS-CoV [35]. MERS-CoV uses a common entry receptor, dipeptidyl peptidase 4 (DPP4), in humans, camels as well as bats which suggests the emergence of MERS-CoV in humans from dromedary camels and potentially earlier in time from bats [16].

As shown in Fig 2, the emergence of MERS-CoV from dromedary camels is facilitated by the presence of a highly similar viral receptor (DPP4) in humans. Hypothetically, MERS-CoV present in dromedary camels may have emerged from CoVs in bats that also use DPP4 as an entry receptor[16].

Incubation Period: The median incubation period of the virus is determined to be about 5.2 days [36].

Risk Factors for Severe Disease: Severe cases requiring hospitalization were more commonly seen among primary older patients with comorbidities. Younger patients and

health care workers without comorbidities were reported. Severe nosocomial infections among patients sharing contaminated equipment with improper barrier controls have also been reported. In Saudi Arabia with 47 severe cases requiring hospitalization, the median age of infection was 56 years with a male-to-female ratio of 3.3 to 1 [37]. The most common comorbidities include diabetes mellitus (68%), chronic renal disease (49%), hypertension (34%), chronic cardiac disease (28%) and chronic pulmonary disease (26%). Smoking (23%) and obesity (17%) were reported in those patients [38, 39].

Phylogenetic Study: Coronavirus of South African *Neoromiciacapensis* bat is called NeoCoV. NeoCoV and MERS-CoV share essential details with respect to genomic architecture. The full genome of an African bat virus was characterized and found closely related to MERS-CoV. This shows that human, camel and bat viruses belong to the same viral species [40]. The bat virus roots the phylogenetic tree of MERS-CoV, providing evidence for an evolution of MERS-CoV in camels that preceded humans. The revised tree suggests that humans are infected by camels rather than vice versa. The emergence of MERS-CoV likely involved exchanges of genetic elements between different viral ancestors. NeoCoV shared 85.5% to 85.6% overall nucleotide identity with MERS-CoVs from humans and camels [40]. The well-studied CoV host switches have probably occurred from bats to humans. The foremost example is the paradigmatic host switch of SARS-CoV from rhinolophid bats into humans or potentially civets [41].

Clinical Manifestations

Humans: Most people confirmed to have MERS-CoV infection have had severe acute respiratory illness with symptoms of fever, cough and shortness of breath [29]. The common presenting symptoms of MERS are nonspecific and include feverishness, chills, rigors, sore throat, nonproductive cough and dyspnea. Other symptoms of respiratory tract infections, including rhinorrhea, sputum production, wheezing, chest pain, myalgia, headache and malaise, may also be present. Rapid clinical deterioration with development of respiratory failure usually occurs within a few days after these initial symptoms [39]. Physical signs at the time of deterioration may include high fever, tachypnea, tachycardia and hypotension. Diffuse crepitations may be present on chest auscultation, but they may be disproportionately mild compared with radiological findings [42]. About 3 to 4 out of every 10 people reported with MERS have died. Most of the people who died had an underlying medical condition. Some infected people had mild symptoms (such as cold-like symptoms) or no symptoms at all [39]. The virus was detected from urine and blood of MERS patients which indicates systemic occurrence of the disease [43]. Potential risk factors for the development of severe disease include obesity, diabetes mellitus, end-stage renal disease, cardiac disease, hypertension, lung disease, including asthma and cystic fibrosis and any immunosuppressive condition [44].

Camels: Dromedary camels infected with MERS-CoV may not show disease but still may excrete MERS-CoV through nasal fluids, faeces and, potentially, in their milk and urine [12]. But, a study conducted in Saudi Arabia showed dromedary camels, naturally infected with MERS-CoV, showed nasal and lachrymal discharge. Samples collected from these discharges revealed positive result for the virus. In this studyit was confirmedthat upper and lower respiratory tract are the sites of viral replication [21].

Animal Models: Clinical signs varied between animals and were usually transient, lasting for only 3 days or less in most animals, which was consistent with the robust but self-limiting inflammatory response and leukocyte activation in blood and lungs of tested animals [45]. Recently, common marmosets were also found to be susceptible to MERS-CoV infection, which resembled moderate to severe MERS in humans with viremia and disseminated infection as evidencedby the presence of viral RNA in blood and multiple organs [46]. However, extrapulmonary manifestations that are commonlyseen in human cases of MERS, such as acute renal failureand diarrhea, were absent in both the rhesus macaque and common marmoset models. Goats were also found to be susceptible to MERS-CoV infection, but they developed predominantly upper respiratory tract symptoms without pneumonia [47]. Most small animal models that worked for SARS-CoV, including the BALB/c mouse, Syrian hamster and ferret, were not susceptible to MERS-CoV infection. Infected animals had minimal clinical signs, no detectable virus in respiratory tract and extra pulmonary specimens and no seroconversion. These findings suggest that MERS-CoV fails to enter these host cells because of variable DPP_4-binding affinities for MERS-CoV S RBD among different species [10].

Clinical Pathology in Humans: Laboratory analyses of blood from MERS patients have revealed mild to severe abnormalities. Haematological abnormalities included elevated leukocyte counts and lymphopenia, while a few

Table 2: Specimens suitable for testing for MERS-CoV.

Specimen type	Transport medium	Transport to laboratory
Sputum	No	4°c. If a delay in testing of > 48 hrs consider freezing, shipping with dry ice
Broncho-alveolar lavage	No	As for sputum
Tracheal aspirate	No	As for sputum
Nasopharyngeal aspirate	No	As for sputum
Combined Nasopharyngeal/ Oropharyngeal swabs	Virus transport Medium	As for sputum
Tissue from biopsy or autopsy Including lung	Virus transport medium or sterile saline if specimen is also for bacterial culture	As for sputum
Serum for serology tests	No	4°C or frozen, Shipped on dry ice

Source: (49).

cases showed lymphocytosis, thrombocytopenia and coagulopathy. Other laboratory findings included elevated creatinine, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase levels, suggestive of renal and liver disease or failure [38, 48].

Diagnosis

Specimen Collection: As shown in Table 2, lower respiratory tract specimens such asbroncho-alveolar lavage, sputum and tracheal aspirates contain the highest viral loads. Serum samples should also be collected. Paired sera samples are preferred but single samples are also of value. Paired serum samples should be collected 14-21 days apart, with the first being taken during the first week of illness. If only a single sample is to be collected, it should be done at least 14 days after onset of symptoms. When there is likely to be a delay in the laboratory receiving respiratory tract specimens, it is strongly recommended that the specimens be frozen, preferably to -80°C and shipped on dry ice. It is, however, important to avoid repeated freezing and thawing of specimens. Serum should be separated from whole blood and can be stored and shipped at 4°C or frozen to -20°C or lower and shipped on dry ice. The storage of respiratory and serum specimens in domestic frost-free freezers should be avoided, owing to their wide temperature fluctuations [50].

Molecular Tests: Molecular tests are used to diagnose active infection (presence of MERS-CoV) in people who are thought to be infected with MERS-CoV based on their clinical symptoms and having links to places where MERS has been reported [50]. A Molecular test such as Real-time reverse-transcription polymerase chain reaction (rRT-PCR) is currently used for diagnosing MERS-CoV using specific genomic targets. This technique uses specimens, including lower (bronchoalveolar lavage, sputum and tracheal aspirates) and upper (e.g., nasopharyngeal and oropharyngeal swabs) respiratory samples, serum and stool specimens [50].

Serological Tests: Serology testing is used to detect previous infection (antibodies to MERS-CoV) in people who may have been exposed to the virus.

ELISA (Enzyme-Linked Immunosorbent Assay): ELISA is a screening test used to detect the presence and concentration of specific antibodies that bind to a viral protein. ELISAs usually produce results within a few hours. If a clinical sample is determined to be antibody-positive by ELISA, the Center for Disease Control (CDC) then uses the immunofluorescence assay (IFA) assay and/or micro-neutralization assay to confirm the positive result [50].

IFA (Immunofluorescence Assay): IFA is a confirmatory test in which specific antibodies, if present in the person's blood, attach to virus-infected cells fixed on a glass slide. These attached antibodies are detected by adding a secondary antibody labeled with a compound that makes them glow an apple-green color when viewed under a special microscope. This secondary antibody will bind to any antibodies which are present in the blood and have attached to the virus-infected cells. Like the ELISA results, IFA results can also be obtained in a few hours. If a clinical sample is positive by both ELISA and IFA, the specimen is determined to be positive and if a clinical sample is positive by ELISA but indeterminate or negative by IFA, CDC then performs additional confirmatory testing [50].

Micro-Neutralization Assay: Micro-neutralization assay is a highly specific confirmatory test used to measure neutralizing antibodies, or antibodies that can neutralize virus. This method is considered the gold standard for

detection of specific antibodies in serum samples. However, compared with the ELISA and IFA, the micro-neutralization assay is labor-intensive and time-consuming, requiring at least 5 days before results are available [50]. If a clinical sample is positive by ELISA, indeterminate by IFA and positive by micro-neutralization, the specimen is determined to be positive. If a clinical sample is positive by ELISA, indeterminate or negative by IFA and negative by micro-neutralization, the sample is determined to be negative [50].

Control and Prevention: MERS-CoV binds to the DPP4 (CD26) surface receptor using the spike (S) surface protein with subsequent cell entry. The exact mechanism of entry after receptor binding is still unknown. The S surface protein is composed of a core subdomain that shares similarity with that of SARS-CoV and a Receptor Binding Subdomain (RBSD) that exhibits significant variation from the SARS-CoV RBSD. The development of vaccines targeting the RBSD of MERS-CoV is currently under investigation because they are thought to be safer and more effective than vaccines based on inactivated virus, DNA, or viral vectors [51]. Another potential therapeutic approach is the inhibition of the papain-like and/or 3C-like protease of MERS-CoV [52]. To date, no effective therapy or prophylaxis for MERS-CoV exists. Supportive therapy remains the cornerstone of management. Current treatment is based on previous experience with the SARS-CoV, in-vitro studies and case series. Various agents have been tried, including those that block virus entry, inhibit viral replication, or interfere with host immune response [39]. The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) suggested therapeutic options for treatment of MERS-CoV infection with various agents alongside continuous evaluation of efficacy and in the setting of clinical trials [52].

Based on experience with SARS-CoV, the use of convalescent plasma, hyper-immune globulin, or human monoclonal antibodies that contain neutralizing antibodies may be efficacious and is recommended as first-line treatment when available [54]. Ribavirin and interferon alpha-2b both showed promising results, especially when used in combination, both in vitro and in animal studies using rhesus macaques monkeys [55]. However, these positive results did not translate clinically in an observational study in five patients, all of whom succumbed to the infection [39, 56]. Repurposing of currently available agents may be an efficient approach. In the lab, Dyall *et al.* [56] screened various agents with potential therapeutic efficacy. Cyclosporin A, mycophenolic acid, interferon-beta, homoharringtonine, cycloheximide, anisomycin and emetine dihydrochloride hydrate were found to have the most potent in vitro activity against MERS-CoV [30].

CONCLUSIONS

Since the discovery of MERS-CoV in 2012, accumulating serologic and molecular evidence demonstrates that the virus in dromedaries is genetically very similar to MERS-CoV in humans and points to the conclusion that dromedary camels are reservoirs for human infection. Developing an effective camel MERS-CoV vaccine and implementing appropriate infection control measures may control the continuing epidemic. Awareness of MERS-CoV infections should be raised among health workers. Understanding the role of dromedary camels and possibly other animals in transmission of MERS-CoV to humans remains a priority for future investigation to enable development of targeted control measures and prevent future cases and deaths from this emerging pathogen.

Recommendations:

- Surveillance program for MERS-CoV in camels needs to be strengthened.
- Strengthening joint or collaborative investigations of confirmed and probable cases through multidisciplinary teams is valuable.
- Provide guidance in risk analysis on MERS-CoV threats to countries in the regions of the Arabian Peninsula, Middle East, North Africa, Horn of Africa and beyond.
- Avoid drinking raw camel milk.
- People working at camel farms, slaughterhouses, markets and camel-racing facilities and also veterinarians, are at risk and should practice good personal hygiene and wear facial protection and protective clothing.
- Protective vaccine development efforts should get prior emphasis to stop threats.

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