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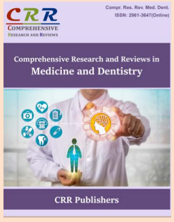

(REVIEW ARTICLE)

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Review on middle east respiratory syndrome corona virus in camel: Its public health importance and economic impact

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Abstract

Middle East respiratory syndrome corona virus (MERS-CoV) is a novel lineage C beta corona virus derived from bats which can cause acute viral respiratory disease in humans and in camels. According to a WHO report, MERS cases have been reported from 27 countries and there have been 2,428 confirmed cases, resulting in 838 deaths. MERS-CoV is transmitted to humans through close contact with dromedaries and it causes asymptomatic or mild-to-severe illness in the human population. MERS-CoV uses dipeptidyl peptidase-4 (DPP4) protein in *Pipistrelluspipistrellus* bats for cell entry. Dromedary camels are a host reservoir species for the MERS-CoV. It is suspected that nasal mucous, sputum, saliva, milk or uncooked meat of infected camels are the main sources of transmission. Several factors such as being male and comorbid pre-existing illnesses are associated with severe disease and high mortality rates in patients with MERS. Studies in Ethiopia, Burkina Faso and Morocco reported that the prevalence of MERS-CoV sero-positivity ranges between 85.1- 99.4%, 73.2-89.9% and 48.3-100%, respectively. The clinical presentation of infected patients often indicate the presence of hemoptysis, sore throat, fever, cough, shortness of breath, and other gastrointestinal symptoms such as diarrhea and vomiting. The average incubation period of MERS-CoV is 6-7 days. No vaccine or treatment is currently available for MERS-CoV. Supportive therapy necessitates respiration and circulatory support, preservation of renal and hepatic function, and prevention of secondary infections. This seminar paper is therefore, intended to highlight the public health and economic importance of the MERS-CoV.

Keywords: Dromedary Camel; FAO; MERS-CoV; OIE; One Health; WHO

1 Introduction

Middle East respiratory syndrome corona virus (MERS-CoV) is a novel lineage C beta corona virus derived from bats which can cause acute viral respiratory disease in humans [1] and in camels (also known as camel flu) [2]. Middle East respiratory syndrome (MERS) is an emerging respiratory disease caused by the MERS corona virus (MERS-CoV), which has been endemic to Saudi Arabia since 2012 [3]. As of May 22, 2019, there have been 2,428 confirmed cases in 27 countries, resulting in 838 deaths [4]. MERS-CoV is transmitted to humans through close contact with dromedaries, suggesting that MERS is a zoonotic disease [3]. Middle East respiratory syndrome corona virus (MERS-CoV) is a zoonotic respiratory infection that is endemic in dromedary camels (*Camelus dromedarius*) and causes asymptomatic or mild-to-severe illness in the human population [5].

Middle East respiratory syndrome corona virus (MERS-CoV) is a serious zoonotic pathogen associated with severe respiratory infection, renal failure and multi organ damage in infected patients [6]. The single-humped, Arabian dromedary camel (*Camelus dromedarius*) has been strongly implicated as the MERS-CoV reservoir in which the disease is either asymptomatic or manifested as mild respiratory infection [7]. Occupational MERS-CoV zoonosis from infected dromedaries was extensively documented in the Arabian Peninsula [8].

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Studies on MERS-CoV genetic sequences from humans and camels in Egypt, Oman, Qatar and Saudi Arabia point out a close similarity between the virus identified in camels and that detected in humans. Although dromedaries usually remain asymptomatic, or develop only mild symptoms due to MERS-CoV infection, it has been shown that they can shed considerable amount of virus. Studies on Bactrian camels (*Camelus bactrianus*), hybrid camels, alpacas (Vicugnapacos), llamas (Lama glama), and even pigs (Susscrofa), have revealed that these animals are also susceptible to MERS-CoV infection [9]. In contrast, studies on sheep, goats, cattle, horses, and chickens have indicated that, although sheep and goats may produce antibodies to MERS-CoV, none of these species effectively shed the virus [10]. Camel milk and urine are consumed for their believed medicinal effects [11]. Camel milk has been reportedly used to treat dropsy, jaundice, tuberculosis, and diabetes while camel urine is used to treat diarrhea and cancer [12]. Researchers have proved that MERS-CoV in milk can survive for prolonged periods [13].Camels infected with MERS-CoV can develop rhinitis or show no signs of infection and might shed virus through nasal and eye discharge and faeces. Suckling camel calves aged up to 1 year represent the most important source for MERS-CoV in dromedary camel populations of the KSA (kingdom of Saudi Arabia) [14].

As we know Middle East respiratory syndrome corona virus (MERS-COV) is a zoonotic disease, and thus, having a potential to be transmitted to humans causing disastrous health and economic effect. Moreover, it is well conceived that our pastoral community life is dependent on livestock and their products, and especially, the role of camels in family growing is very high in pastoral area. Despite these facts, in Ethiopia much attention is not being given to diseases like MERS-CoV and there is no routine surveillance and prevention strategies to limit the disease from reaching the public.

Therefore, the objectives of this seminar paper are to:

- Review the public health importance and economic impacts of Middle East Respiratory Syndrome and
- Highlight the major risk factors associated to the occurrence of Middle East Respiratory Syndrome.

2 Historical Background of Mers-Cov Disease

The first zoonotic introduction of a corona virus into the human population occurred by the severe acute respiratory syndrome corona virus (SARS-CoV) in 2002. According to WHO SARS-CoV caused a world pandemic, outbreak with 8,400 recorded infection cases and 800 deaths, similarly MERS-CoV marks the second known zoonotic introduction of a highly pathogenic microorganism of evidence currently support this theory [15]. Phylogenetically, MERS-CoV is close to the bat *Beta corona viruses* such as, BtCoV-HKU4 and BtCoV-HKU5 [16].

Closely related corona virus sequences have been recovered from bats in Africa, Asia, the Americas and Eurasia. Therefore, MERS-CoV uses the evolutionary conserved dipeptidyl peptidase-4 (DPP4) protein in *Pipistrelluspipistrellus*bats for cell entry [17]. Middle East respiratory syndrome in human was first identified in 2012, in Saudi Arabia and more than 1000 infection cases of the disease have been reported in May, 2015 and about 40% of those who were infected died due to the disease [18].

2.1 Etiology

Middle East respiratory syndrome (MERS) is caused by a type of coronavirus named Middle East respirator syndrome coronavirus (MERS-CoV) [19] with single-stranded RNA belonging to the genus beta corona virus which is distinct from SARS corona virus and the common-cold corona virus [20]. According to Eckerle *et al*.[21], MERS-CoV uses the DPP4 (CD26) receptor to gain entry and effectively replicate in camel cell lines and neutralizing antibodies for MERS-CoV have been detected in dromedary camels from Africa and Middle East [22].

2.2 Virology of MERS-CoV

Coronaviruses are a group of enveloped RNA viruses of the family *Coronaviridae*. Their surface appearance resembles that of a crown under the electron microscopy, which has given rise to their scientific name (Latin “corona” meaning “crown” or “halo”). Coronaviruses able to infect humans are shown to emerge via cross-host transmission from animals. MERS-CoV is a lineage C *beta coronavirus* that is found in humans and camels. This virus is different from the other human *beta corona viruses* (such as SARS-CoV). It is closely linked to some bat corona viruses (such as BtCoV-HKU4 or BtCoV-HKU5). This is why it is believed that MERS-CoV (like a plethora of other coronaviruses) originated in bats [23].

2.3 Epidemiology of MERS-CoV disease

2.3.1 Geographic distribution

According to WHO report, MERS cases were reported from 27 countries including Arabian Peninsula (Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, the United Arab Emirates, Iran, and Yemen), Europe (Austria, France, Germany, Greece, Italy, Netherland Turkey and UK), Asia (China, Philippines, Malaysia, Thailand, and Republic of Korea), Africa (Algeria, Egypt, and Tunisia) and USA. 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 [24]. In the United Kingdom, France, Italy, South Korea and Tunisia, limited human-to-human transmission occurred among close contacts of the index cases [25]. All of the cases outside of the Middle East have had a direct or indirect connection to the Middle East.

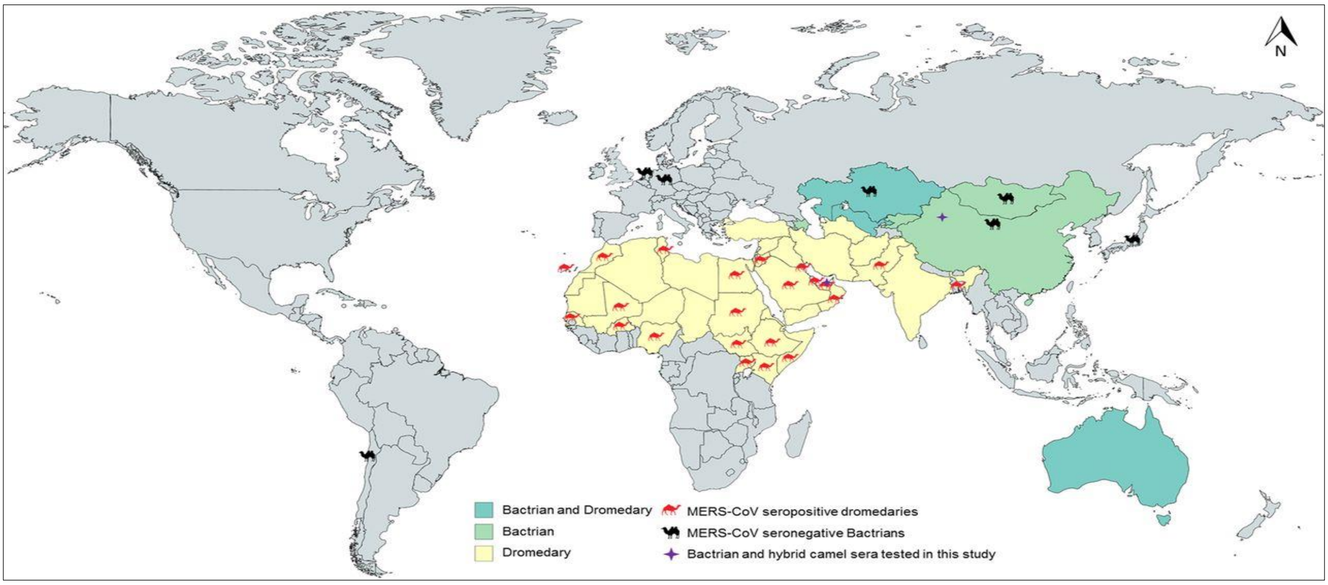

Figure 1 Geographical distribution of dromedaries and Bactrians Source: [26]

2.3.2 Sources of infection

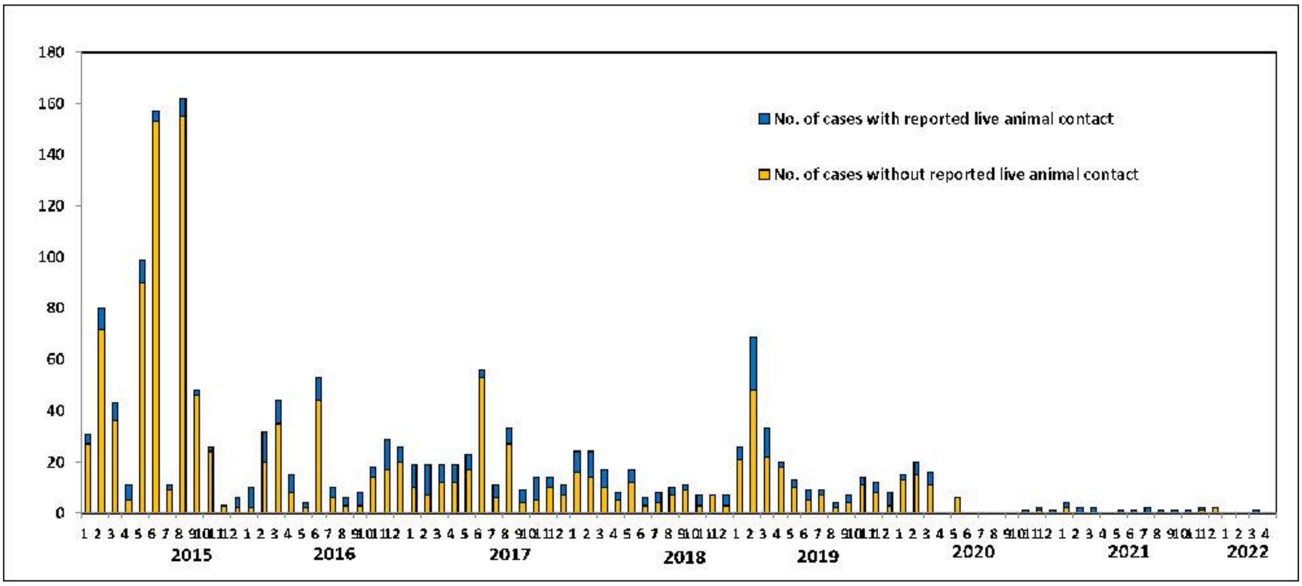

Figure 2 Human epidemiological timeline (with cases reporting animal exposure in blue), by month of disease onset since January 2015 [28]

The origin of all primary human MERS-CoV infections remains unknown. Dromedary camels are a host reservoir species for the MERS-Cov. Humans can acquire MERS-CoV through direct or indirect contact with infected dromedary camels or infected patients. Sources of MERS-CoV in camel could be camel nasal secretions, camel excreta (urine, saliva and faeces), camelid birth products (amniotic fluid, fetal membranes and placenta) and camel food products (milk, meat). In humans, both symptomatic and subclinical MERS-positive individuals inthe community, family householdsor compounds, hostels, health-care facilities and camel farms could be also ascribed to the occurrence of the infection with the agent [27].

2.3.3 Modes of MERS-CoV Transmission

It is suspected that nasal mucous, sputum, saliva, milk or uncooked meat of infected camels are the main sources of transmission. However, the secondary infection can be through droplets or direct contact, and the virus may spread through the air or fomites[29]. Camels have been confirmed by several studies to be the reservoir of the MERS-CoV infection in humans. Zoonotic transmissions of MERS-CoV from dromedary camels to humans were reported in multiple occasions. MERS-CoV has never been reported as a disease in camels though in experimental infections MERS-CoV has been associated with mild upper respiratory signs. Positive PCR results for MERS-CoV or isolation of the virus from camels is notifiable to the OIE because MERS is an emerging disease with a significant public health impact [30].

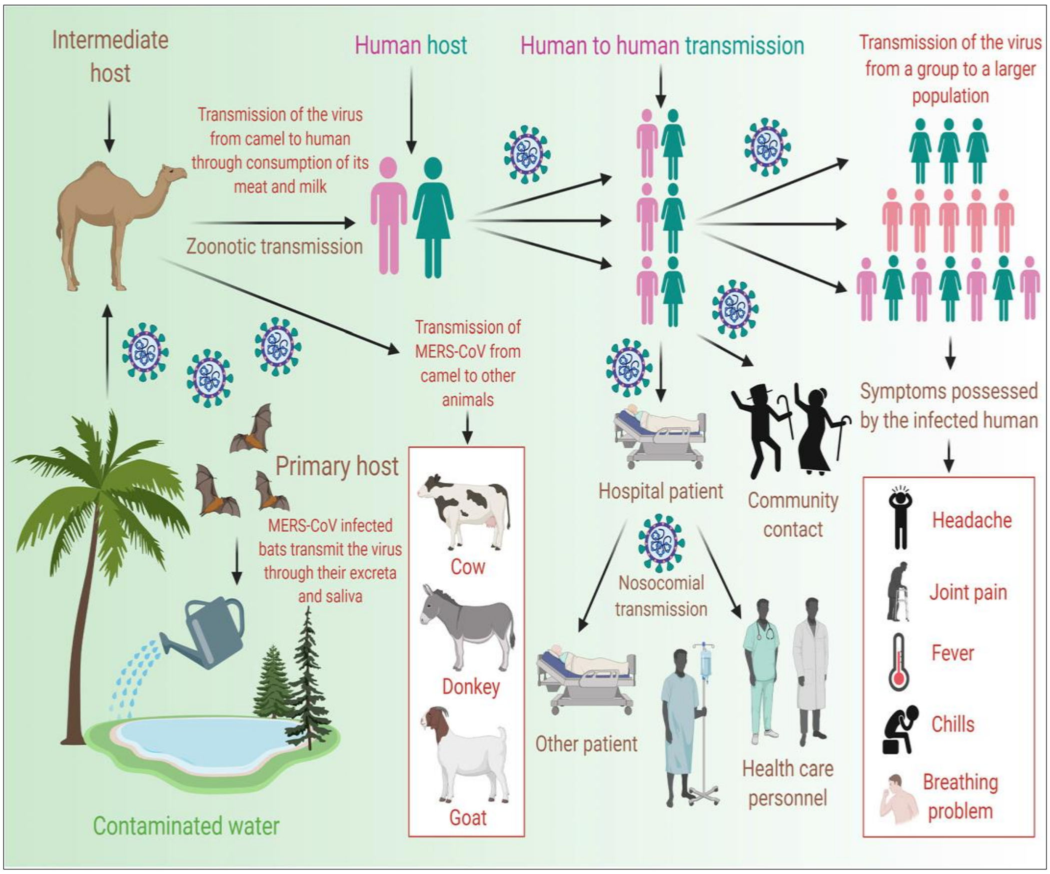

Figure 3 The transmission pattern of MERS-CoV and symptoms [33]

Camels as noted above, are likely to serve as hosts for MERS-CoV. The strongest evidence of camel-to-human transmission of MERS-CoV comes from a study in Saudi Arabia in which MERS-CoV was isolated from a man with fatal infection and from one of his camels; full-genome sequencing demonstrated that the viruses isolated from the man and the camel were identical [3].Other animals, such as goats, cows, sheep, buffalo, pigs and wild birds have been tested for MERS-CoV antibodies, but no positive findings have been reported. These investigation results provide evidence that camels are a primary probable source of the MERS-CoV zoonotic infection for humans [31]. Bats are also known natural reservoirs for several emerging viral infections in humans including rabies, Nipah virus, Hendra virus and Ebola virus,and could serve as reservoir for MERS-CoV too [32].

2.3.4 Risk Factors

Known risk factors for MERS-CoV acquisition, transmission and outbreaks are noted. MERS exposure data include travel history to endemic countries, direct or indirect contact with dromedary camels or their products, contact with humans with MERS-CoV infection and visits to health care facilities containing patients infected with MERS CoV are risk factors for acquiring MERS-CoV infection [34]. MERS-CoV has been detected in camel products (e.g., raw milk, meat, blood, urine, or birth products) evidencing that drinking raw camel milks, especially from suspected camels could be a risk for developing the disease. Transmission via contact with contaminated hospital environments is possible during outbreaks although genomic studies providing an evidence base are lacking. Factors such as age, being male and immunocompromised due to obesity, diabetes mellitus, cancer, chronic heart, lung and other disease states are associated with severe disease and high mortality rates in patients with MERS. DPP4 receptors are up regulated in the lungs of smokers and patients with chronic obstructive pulmonary disease, which might explain why patients with co-morbid lung diseases are prone to severe illness [35; 36; 37].

2.4 Pathogenesis of MERS-CoV

MERS-CoV pathogenicity is based on the extent pathogen-host interaction. It elicits maximum pathogenic potential especially in humans. This is due to the fact that MERS-CoV shows a strong tropism for bronchial non-ciliated epithelia. Furthermore, the virus arrests host bronchial interferon synthesis. It should be noted that most of other viruses causing respiratory diseases attack and damage epithelial cilia, including Influenza type A. Extensive investigations showed that another functional cellular receptor called DDP4 was also involved in the severity of MERS-CoV disease spread into the lungs [38]. Of note, receptors for DDP4 are also located in nephrons of kidneys and heart.

During the acute stage of the MERS-CoV infection, there is a severe viremia, leading o spread of MERS-CoV viral particles in the bloodstream. Hence, MERS-CoV leads not only to the damage of lungs but also kidneys and heart, thereby resulting in respiratory, renal and cardiac failure, ultimately ending to coma and death [16].

2.5 Signs and symptoms

The clinical presentation of MERS-CoV compasses from severe respiratory diseases to subclinical infections [6]. Infected patients often indicate the presence of hemoptysis, sore throat, fever, cough, shortness of breath, and other gastrointestinal symptoms such as diarrhea and vomiting [39]. A low range of lower pulmonary infiltrate associated with viral pneumonia was observed in the radiograph of patients infected with MERS-CoV [40]. It was observed that greater than 60% of the initially reported cases of MERS-CoV infection, the patients experienced severe disease which demanded intensive care treatments like extracorporeal membrane oxygenation and mechanical ventilation. Neuromuscular manifestations include hyper-somnolence, weakness and tingling in the extremities similar to Guillain-Barre syndrome or virus-related sensory neuropathy [41]. The average incubation period for MERS-CoV is 6-7 days [42].

2.6 Prevalence of MERS-Cov

During the MERS-CoV outbreak, cases of MERS-CoV infection were reported in 27 countries, among which 12 were located in the Eastern Mediterranean region [43].

Table 1 Summary on prevalence and distribution of MERS-COV in dromedary camels

Author (s)	Country	Prevalence	Year
[44]	Egypt	58.75%	2020
[45]	Saud Arabia	92.7%	2020
[46]	Tunisia	80.4%	2021
[11]	Djibouti	97.9%	2020
[35]	Ethiopia	99.4%.	2017
[11]	UAE	100	2017
[47]	Morocco	100	2015

2.7 Diagnosis

The definitive diagnosis of cases of coronavirus infection basically rely on advanced diagnostic perceptions like the detection of unique sequences of viral RNA by real-time reverse-transcriptase polymerase chain reaction (RTPCR) and immunofluorescence because the disease has no pathognomonic clinical manifestation both in human and in camel [48]. However, antibodies against beta coronaviruses are identified to cross-react within the other species of the genus due to their characteristic antigenic similarity. Therefore, immunofluorescence antibody tests effectively limit their use to confirmatory diagnosis of the disease [49].

Throat swabs, urine, faeces and serum samples were collected from wild bats in Saudi Arabia including the area where the first MERS-CoV patient had reported and worked, this study result indicate that, 227of the samples was found positive for nucleotide fragment of the RNA-dependent RNA polymerase region of MERS-CoV genome from the examined different 1003 samples; this result suggest that bats are the evolutionary origin of the virus for camel and human infections [40].

2.8 Treatment

No vaccine or treatment is currently available for MERS-CoV [50]. A great challenge exists in developing MERS-CoV infection models for several reasons. For one, small and larger animal models that aid in initial screening do not express the DPP4 receptor [51]. In addition, pharmaceutical companies have meager incentive for producing MERS-CoV vaccine as clinical trials are very costly and the timeline to approved vaccine use is 10 years or longer. However, sustained human-to-human MERS-CoV transmissions were to occur, the benefit of developing a safe and effective vaccine would outweigh any cost [52]. Supportive therapy necessitates respiration and circulatory support, preservation of renal and hepatic function, and prevention of secondary infections [53]. Administration of both ribavirin and interferon-α2b had shown decreasing viral load, as it has been demonstrated that they decrease the multiplication of MERS-CoV in Vero as well as LLC-MK2 cells [54].

2.9 Prevention and control

Understanding the route of transmission of MERS-CoV and its pattern of transmission is important for proper implementation control and prevention of the disease. The WHO advises people at risk of MERS-CoV infection to avoid contact with camels, to practice good hand hygiene, and to avoid drinking raw milk or eating contaminated food unless it is properly washed, peeled or cooked [55]. Since most of the cases occur in the health care setting, it is thoughtful that all health care workers practice appropriate infection control measures when taking care of patients with suspected or confirmed MERS-CoV [55]. Strict regulation of camel movement with imposition of requirement for MERS-CoV clearance prior to importation and transport of camels, including those that are presented for slaughter.

Camels with detectable MERS-CoV RNA should be quarantined and tested at regular intervals, Enforcing the use of personal protective equipment while handling dromedary camels, Efforts to increase awareness amongst camel owners and the general public of the risks of consuming unpasteurized camel milk and urine though challenging, given the depth of customs and beliefs in some areas [56]. Camel farm workers, slaughterhouse workers, market workers, veterinarians and those handling camels at racing facilities should practice good personal hygiene [57].

2.10 Advances in vaccine development

Advances in clinical trial designs, vaccine platforms, technology and bioinformatics are helping with the development of a vaccine for MERS-CoV [50]. Development is going on for various types of vaccine candidates, including viral vectored vaccines, inactivated whole virus, live attenuated virus, inactivated subunit vaccines and DNA vaccines. A large number of such vaccines use the S protein, or the domain of S protein needed for binding to host DPP4 as an immunogen, as neutralising antibodies are primarily driven towards the receptor-binding domain [58].

2.11 One health approach and its impact on controlling of MERS-CoV

Controlling MERS-CoV requires interdisciplinary efforts with the One Health concept focusing on human, animal and environmental health, intimately in order to understand the exact dynamics of MERS-CoV. Multidisciplinary teams with collaboration between public health officers and veterinarians ought to be primarily organized. This must include ranges of expertise such as academic researchers, physicians, ecologists, microbiologists/virologists, and phylogenetics cooperating and investigating valuable information on MERS-CoV [59]. It is questionable if camels and bats are the only reservoirs of MERS-CoV, this is why surveillance particularly towards wildlife is essential, and considerable gaps in the knowledge of MERS-CoV demands better case definitions, and this might be another point where One Health approach really impacts. Geographic Information Systems can serve for evaluating spatialized risk and identifying high risk areas. Lastly, education and raising awareness must be promptly carried out on topics of hygiene and food safety, and all these needs the convergence of many disciplines and expertise in the form of One Health approach for the common goal [60].

As one part, WHO continues to support field-based epidemiological and anthropological studies at the animal-human interface to evaluate the extent of spill-over and human infection in countries outside of the Arabian Peninsula towards the prevention and control of the disease worldwide? These studies are being planned or currently being implemented in Algeria, Egypt, Ethiopia, Pakistan, Somalia and Sudan in collaboration with Ministries of Health and other technical partners. WHO has also established an informal working group to advance the development of MERS-CoV vaccine candidates for dromedary camels and high-risk human population [24].

On the other hand, WHO is working closely with its partner organizations FAO and WHO to collate and share data to gain a better understanding about the disease situation in animals and to assess implications for animal and human health, The WAHO is also working closely with its Ad hoc groups and member countries to provide technical support and to encourage reporting of MERS-CoV detections in animals, The WAHO has updated the case definition for reporting confirmed MERS-CoV cases in dromedary camels and also develops and publishes international standards and guidelines on the prevention, control and surveillance of animal diseases including zoonosis [61].

Moreover, FAO also playing important role in providing technical assistance and guidance to countries to improve understanding of the disease situation, help filling existing gaps in epidemiological knowledge, and supporting national laboratories to develop capacity in serology and PCR diagnostic for MERS-CoV. The organization continues assisting different countries and stakeholders in developing communication strategies to ensure appropriate information reaches the public on MERS-CoV and avoid possible negative impacts of the crisis on the livestock industry [62]. It also supports regional technical working group on MERS-CoV such as in the IGAD region /Greater Horn of Africa with regard to preparedness and response assisting in the creation/strengthening of national One Health platforms and reinforce net-works by running simulation exercises for different scenarios [63].

2.12 Public health and economic importance of Mers-Cov

MERS-CoV can cause severe acute respiratory disease, mainly in immunocompromised patients due to other underlying diseases including diabetes, heart disease, renal failure or recently received organ transplants (e.g., kidney transplants), hypertension, chronic lung disease, including asthma and cystic fibrosis. Also history of travel in at risk countries and smoking might have considered as a risk factors of severe disease [64]. Consumption and handling of meat, milk and urine of infected camel has been claimed for human infection [6; 65].

People working closely with camels (e.g. farm workers, slaughterhouse workers and veterinarians) and health care workers may be at higher risk of MERS-CoV infection than people who do not have regular close contacts with camels and also health care workers [56; 66]. Male gender has higher incidence rate of infection as compared to the female gender in most outbreaks; especially in the Arab peninsula male gender can be linked with its culture and customs that made males having more exposure to camels as compared to females [41]. The exposure of contaminated equipment without proper barrier control risks healthcare workers being infected [7].

Some efforts in estimating the impact of MERS-CoV outbreak on selected sectors of the economy in some countries like South Korea have been made [67]. The direct medical costs of managing the epidemic that struck more than 24 countries and the costs associated to implementation of the infection control policies are among the major costs affecting the economy of affected countries [24; 68].

2.13 Status of Mers-Cov in Ethiopia

Camels sera collected from a number of countries have been found to have antibodies to MERS-CoV and African countries are considered as a possible source for the establishment of MERS-CoV. In Ethiopia, high sero-prevalence of MERS-CoV has been reported in camel population. In the country, a study conducted by Reusken *et al* [69] showed an overall MERS CoV sero- positivity of 93% and 97% in juvenile and adult animals, respectively. Another study by Miguel *et al.* [35] showed MERS-CoV RNA detection of up to 15.7% and sero-positivity as high as 99.4%. Fekadu *et al*. [70] also revealed 92.3 – 93.9% sero-prevalence and 7% viral detection in the country. In spite of high seropositivity, only few studies were carried out in Ethiopia on viral isolation and molecular characterization of the virus from camel. Recently published study confirmed that unlike the West African MERS-CoV virus reported from Burkina Faso and Nigeria, the Ethiopian camel MERS-CoV showed a genetic and phenotypic similarity with isolates from camel of Arabian Peninsula [71]; suggesting a potential significance for zoonotic transmission to high risk human population of Ethiopia

3 Conclusion and recommendations

MERS-CoV is a pathogen with epidemic potential that continues to cause sporadic human disease and remains on the WHO Blue print 2022 priority. MERS-CoV appears to be highly endemic among dromedary camels from geographically widespread areas of the Middle East and Africa and thus zoonotic transmission with consequent risk of human epidemics will most likely continue for years to come. MERS-CoV endemic and at-risk countries must invest more in surveillance, in public health research and in medical interventions including human and camel vaccine development. The continued risk of human MERS-CoV outbreaks 7 years after its first discovery signifies the need for effective human and camel MERS-CoV vaccines to prevent continuing spread of MERS-CoV in camels and in humans at high risk of acquiring community and nosocomial MERS-CoV infection.

Therefore, up on the above conclusion, the following recommendations can be forwarded:

- Strict regulation of camel movement, regular herd examination and isolation of positive camels.
- Robust molecular epidemiological studies are needed, mainly in countries like Ethiopia to better understand the transmission patterns of MERS-CoV both in human and camel.
- It is also important to raise awareness among camel herders, community and travelers to or from regions affected by MERS-CoV about the virus and signs and symptoms of the disease so as to manage the disease outbreak at its infant stage.
- Efforts need to be made to develop vaccines for both human and camels.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest.

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