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Review

Public health risk and transmission route of Middle East respiratory syndrome (MERS): MERS coronavirus in dromedary camel

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Middle East respiratory syndrome corona virus (MERS-CoV) is a novel enzootic beta origin corona virus which was described in September 2012 for the first time. According to the reports of different researchers, the prevalence of MERS-CoV antibodies, during serological examination, is very high in dromedary camels of Eastern Africa and the Arabian Peninsula. However, the infection in camel is mostly asymptomatic. In contrast to the camel case, the clinical signs and symptoms of MERS-CoV infection in humans ranges from an asymptomatic or mild respiratory illness to severe pneumonia and multi-organ failure with an overall mortality rate of about 35%. Therefore, the objective of this paper was to review the public health risk, transmission routes of Middle East respiratory syndrome and to recommend the disease for further research. The identification of MERS-CoV RNA and viable virus from dromedary camels, including samples with respiratory symptoms by different studies have been detected especially in isolation of identical strains of MERS-CoV from epidemiologically linked humans and camels are the suggestive evidence for inter-transmission of the virus, primarily from camels to humans and its public health risks. Though inter-human spread within health care settings is responsible for the majority of reported MERS-CoV human cases, the virus is currently incapable of causing sustained human-to-human transmission (pandemic occurrence). Phylogenetic studies and viral sequencing results strongly suggest that MERS-CoV originated from bat ancestors after evolutionary recombination process, primarily in dromedary camels in Africa, before its exportation to the Arabian Peninsula through the camel trading routes. Currently, there is no specific drug or vaccine available for treatment and prevention of infections due to MERS-CoV in patients. The important measures to control MERS-CoV spread are strict regulation of camel movement, regular herd screening and isolation of infected camels, use of personal protective equipment by camel handlers and awareness creation on the public, especially in African pastoralists where consumption of unpasteurized camel milk is common. Therefore, urgent global epidemiological studies are required, especially in the poor camel rearing African countries to understand the transmission patterns and the human cases of MERS-CoV and also for the proper implementation of the above mentioned control measures.

Key words: Dromedary camel, epidemiology, MERS-CoV, public health**,** respiratory syndrome.

INTRODUCTION

Middle East respiratory syndrome coronavirus (MERS-CoV) is a novel lineage C beta corona virus derived from bats which can cause acute viral respiratory disease in humans (WHO, 2014a) and in camels (also known as camel flu) (Richard, 2015). Dromedary camels in the Middle East have high sero prevalence for MERS-CoV and MERS-CoV RNA has been consistently detected in these animals, especially in settings such as camel abattoirs, where camels from multiple origins are assembled, but the exact source of infection in camels has not been identified. More than 60% of the global population of dromedary camels is distributed in African countries and some of these countries are important camel exporters to the Arabian Peninsula (Faye and Bonnet, 2012). MERS-CoV antibodies were also found with high prevalence in dromedary camels in these African countries with positive rates higher than 80% for the animals in Egypt, Ethiopia, Nigeria and Sudan, and 30 to 54% in Tunisia (Reusken et al., 2014).

According to WHO (2015c), there were 1,618 laboratory-confirmed cases of MERS reported with 579 human deaths and camels are believed to be involved in its spread to humans but its way of transmission is unclear (Zumla et al., 2015). This disease in human is zoonotic in origin, although clusters of human-to-human transmission have been reported, especially in health care or family settings (WHO, 2015a). However, this human zoonotic disease has so far been reported only from countries in the Middle-East, the reason for the absence of zoonotic disease report from Africa is unclear (Chu et al., 2014) and it should be of great concern to researchers.

In humans, the virus is graver and opportunistic pathogen associated with the death rate of 40% from infection cases report. It is yet to be established whether infections thought to have been acquired from an animal origin produce a more severe outcome than those spread between humans (WHO, 2013a). Therefore, the objective of this paper was to review the public health risk, transmission routes of Middle East respiratory syndrome and to recommend the disease for further research.

PUBLIC HEALTH RISK AND DESCRIPTIONS OF MERS CORONA VIRUS

History and origin

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 (2003), SARS-CoV causes 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 of evidence currently support this theory: the very close phylogenetic similarity with the bat *Beta corona viruses* such as, BtCoV-HKU4 and BtCoV-HKU5 (van-Boheemen et al., 2012); 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 *Pipistrellus pipistrellus* bats for cell entry (Raj et al., 2013).

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 (Zaki et al., 2012), accordingly, most cases have occurred in the Arabian Peninsula (Zumla et al., 2015). HCoV-EMC/2012 is a strain of MERS-CoV that is detected in the first infected person in London in 2012, which was found to have a 100% identical viral sequencing to the strain identified in Egypt from tomb bats (Zaki et al*.,* 2012); this result is suggestive that bats are the primary origin of MERS-CoV.

Etiology

Middle East respiratory syndrome is caused by the newly identified MERS corona virus (MERS-CoV), with single-stranded RNA belonging to the genus beta corona virus which is distinct from SARS corona virus and the common-cold corona virus (Saey, 2013). According to Eckerle et al*.* (2014), 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 (Milne- Price et al*.*, 2014).

Different studies suggested that the mean incubation period of the virus is 5 to 6 days, it will take 13 to 14 days to show clinical illness in infected person and to subsequently spread to another person. In progressively diseased patients, death can occur within 11 to 13 days, sometimes it will range from 5 to 27 days (Chan et al., 2014; Ki, 2015).

Pathogenesis and clinical sign

The disease in human initially showed simple respiratory problem with mild fever, chills, muscle ache and respiratory stress (shortness of breath). Then it leads to severe pneumonia within 2 to 3 days after infection progressively after some period of time it will develop into severe acute respiratory syndrome (SARS) or acute corona virus, probably originating from bats. Three lines

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respiratory distress syndrome (ARDS). In later cases, MERS-CoV causes clinical symptoms of upper and lower respiratory tract infections specific signs and symptoms including high-grade fever, non-productive cough, dyspnea, headache, myalgia, nausea, vomiting, and diarrhea that may precede the respiratory symptoms (Guery et al., 2013). Finally, death may occur in almost half of the cases, especially in unmanaged patients, more death rate will occur (Abdullah et al., 2013).

Laboratory result on admission of patients indicates leukopenia, lymphopenia, thrombocytopenia, and elevated lactate dehydrogenase levels (Assiri et al., 2013). MERS-CoV can also cause severe pneumonia with acute respiratory distress syndrome (ARDS), requiring mechanical ventilation and intensive care admission (Drosten et al., 2013). Incontrast to the human cases, camel showed minor clinical signs of the disease, including of rhinorrhea and a mild increase in body temperature but no other clinical signs were observed (Ahsa, 2013) and the nasal discharge drained from both nostrils varied in character from serous to purulent (Daniella et al., 2014)

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 (WHO, 2013b). 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 (Memish et al., 2014).

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 (Memish et al., 2013).

EPIDEMIOLOGY OF THE DISEASE

Distribution

According to WHO (2014b) official report, 707 infected patients were identified in 21 countries from three continents of the world. From those detected human cases, 252 patients have died due to MERS-CoV, indicating the case fatality rate of the disease to be about 35% (Drosten et al., 2013). The infection so far has been acquired either directly through a probable zoonotic source, or as a result of human to human transmission through close contacts (Hijawi et al., 2012). An unexplained observation has shown the seasonal variation in the number of reported cases, with a peak occurrence from April to June of each year. The number of cases reported during April, 2014 alone was alarming, because it was greater than the cumulative number of cases reported since the outbreak began (http://coronamap.com, 2014). The possible justification for the seasonal variation of camel case reports may be that it coincides with camel breeding season, and younger camels seem to be more often infected than older camels in the herds (Holmes et al., 2014). Human cases have also been reported in Kuwait, Yemen, Oman, Iran, Lebanon, Tunisia, Algeria, Bangladesh, Malaysia, even in non-camel rearing countries like France, Italy, Germany, the Netherlands, United Kingdom, Greece, Italy and United States (WHO, 2014c), which is suggestive of the presence of other probable intermediate hosts in addition to camel. Furthermore, sero positive camels for MERS-CoV antibodies were identified in Egypt, Kenya, Nigeria, Tunisia and Ethiopia (Figure 1), suggesting that there may be MERS-CoV human cases that are undetected in Africa (Reusken et al., 2014).

Species affected, reservoirs and route of transmission

The disease due to MERS-Cov is thought to be zoonotic because of its close genetic similarity to bat corona viruses (Karesh et al*.*, 2012). Identical strains with human MERS-Cov have been isolated from camels in Egypt, Qatar and Saudi Arabia and MERS-CoV antibodies have also been detected in camels of Africa and the Middle East (Memish et al*.,* 2014). According to Reusken et al. (2013), camels are thought to be a source of human infection, this is because genetic sequence similarities have been determined between human and camel corona viruses (Memish et al., 2014). Transmission from dromedary camels to humans has been shown with RT-PCR and viral genome sequence analysis, molecular detection and phylogenetic analysis have been also performed to investigate transmission (Azhar et al., 2014). 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 (Reusken et al., 2013). Bats are known natural reservoirs for several

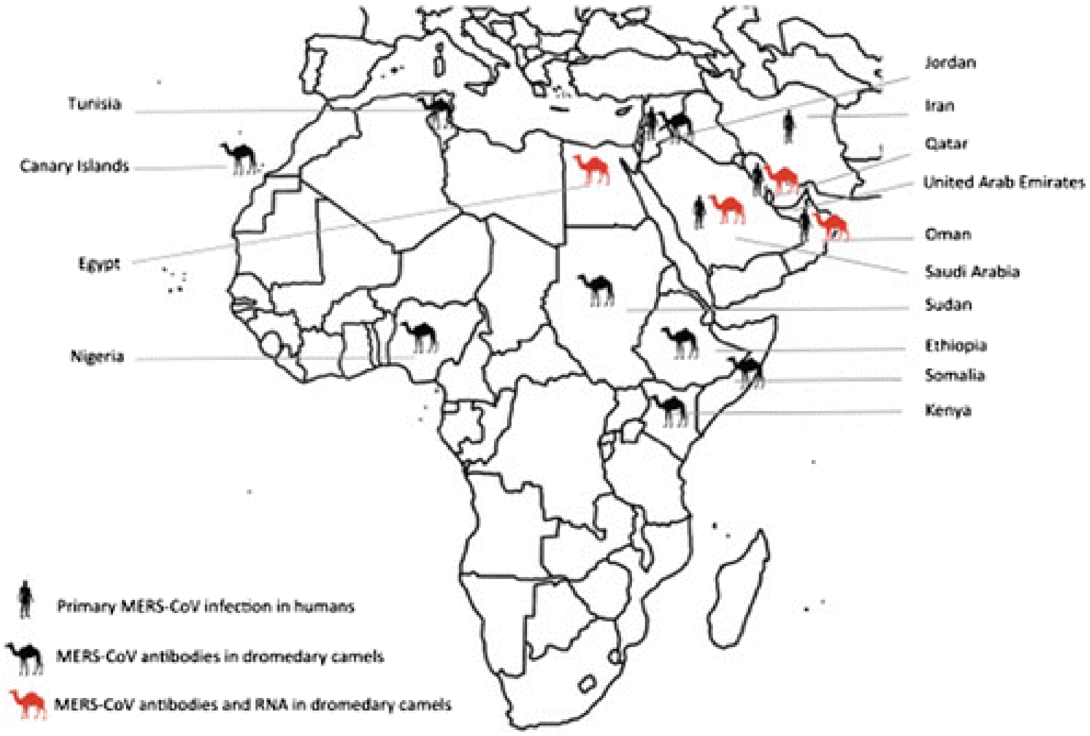

Figure 1. Distribution of human MERS-CoV cases and prevalence of MERS-CoV based on serological and RNA detection in dromedary camels (Source: Taylor and Francis, 2016).

emerging viral infections in humans including rabies, Nipah virus, Hendra virus and Ebola virus (Han et al., 2015). Due to their extremely diverse species with a long evolutionary history, bats have co-evolved with a variety of viruses and due to their lack of B-cell-mediated immune responses which allows them to carry viruses without showing overt clinical signs of viral infections (Dobson, 2005; Karesh et al., 2012). As a result of their low metabolic rate and suppressed immune response during bats' hibernation time, there is delayed viral clearance, which make them the potential reservoirs for different viruses (George et al., 2011). Generally, species affected by Middle East respiratory syndrome and used as source of infection are *Homo sapiens* (human), camels and bats (Augustina et al*.,* 2013).

MERS-CoV is a zoonotic virus that is transmitted from animals to humans (WHO, 2015b). The route of transmission from animal to human is not fully understood(Zumla and Memish, 2014), but researchers hypothesize that camels are a likely reservoir host for MERS-CoV (Figure 2) and most likely, camels are the animal which is source of infection for humans (Saad and Said, 2011).

In some areas of the Arabian Peninsula, the consumption of unpasteurized milk is common and, in some cultural practices of the region, camel milk and urine are consumed for their believed medicinal effects (Saad and Said, 2011). Researchers have proved that MERS-CoV in milk can survive for prolonged periods (van-Doremalen et al., 2014). Contact with a MERS-CoV-infected animal, such as a dromedary, or its bodily fluids may be responsible for zoonotic transmission to humans, but investigations continue to better clarify this question (Aburizaiza et al., 2014).

Transmission of MERS-CoV from human-to-human occurs similarly to other corona viruses. It is believed that it is transmitted by contact with the respiratory secretions of an infected individual that are aerosolized by coughing or sneezing (WHO, 2015a). Many of those infected with MERS-CoV were associated with healthcare settings such as hospitals, but the virus does not have a chance to pass easily from human to human if there is not direct close contact with the infected individual (Oboho et al., 2014).

Group at risk

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 human in the same geographic area.

These and other studies also have found MERS-CoV antibodies in camels in Africa and the Middle East and also, preliminary results from an ongoing investigation in Qatar show that people working closely with camels (e.g. farm workers, slaughterhouse workers and veterinarians)

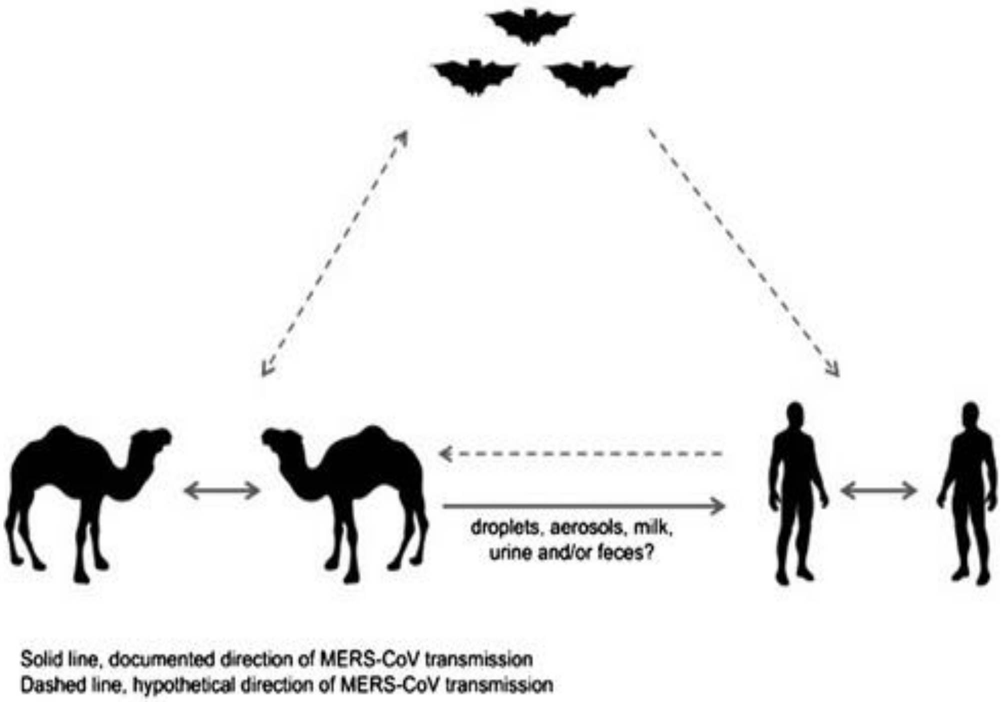

Figure 2. Reported Infection sources and transmission routes of MERS-CoV between bats, camels and human (Source: Taylor and Francis, 2016).

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 (WHO, 2014d).

MERS coronavirus in dromedary camel

According to Informer East Africa (2016), many outbreak cases of MERS in camels of Kenya is reported and more than 500 camels died due to the disease. An investigation, using real time polymerase chain reaction (RT-PCR) identified MERS-CoV prevalence rate of 3.6% in apparently healthy camels in a slaughterhouse of Egypt. Other research report also indicate that 92% of examined sera collected from camels were reactive to MERS-CoV antibodies and the camels that tested positive were all imported from either Sudan or Ethiopia (Chu et al., 2014).

Studies conducted from 2010 to 2013, in which incidence of MERS was examined in 310 dromedary camels, indicate high titers of neutralizing antibodies to MERS-CoV in the collected serum sample of these animals (Hemida et al*.,* 2013).

A further investigation was conducted on sequenced MERS-CoV on nasal swabs of dromedary camels in Saudi Arabia, result indicate that, MERS-CoV in camels had sequenced exact similarity with previously sequenced human isolates (Briese et al., 2014). The prevalence of MERS-CoV antibodies is significantly higher in older camels when compared with those aged two years or less (Alagaili et al., 2014), which indicates MERS-CoV have been found circulating in dromedary camels for more than 20 years in camel rearing in middle east and African countries (Corman et al., 2014). In addition to the high total prevalence of MERS CoV serum antibody in dromedary camels from Kenya and other African countries, 14.28% of MERS-CoV sero prevalence in dromedary camels from the Canary Islands were also reported by Hemida et al*.* (2014), this result also included three positive camels that were imported from Morocco to the Canary Islands even though there is no current report from Morocco on the disease.

In contrast to the Middle East and African camel infection prevalence report, currently, there is no published report on MERS-CoV antibodies detection in dromedary camels from Australia, Canada, the United States of America, Germany, the Netherlands or Japan, which will be a research question for researchers indicating that further global epidemiological study on the disease is mandatory.

The investigated high sero prevalence of MERS-CoV in dromedary camel of Africa and the Middle East (Table 1) suggests that animal movement has facilitated the transmission and circulation of MERS-CoV (Briese et al*.*, 2014).

Which is also suggestive of the risk of emerging new outbreak in those countries currently free from MERS-CoV.

Table 1. Sero prevalence of MERS-CoV antibodies in dromedary camel in different countries reporting the disease.

Country	Number of camel tested	Prevalence (%)	Year
Saudi Arabia	9	100	2013
UAE	8	100	2015
Oman	50	100	2015
Jordan	11	100	2013
Qatar	105	97	2014
Egypt	110	98.2	2013
Tunisia	158	54	2009
Ethiopia	31	93	2010-2011
Nigeria	358	94	2010-2014
Somalia	86	83.7	1983-1984
Sudan	60	86.7	1984
Kenya	774	29.5	1992-2013
Canary Island	105	14.3	2013

Source: (Taylor and Francis, 2016).

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. Currently, as mentioned above, the pattern of the disease transmission will dictate the methods for prevention (Figure 2). 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 (WHO, 2014a). 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 (WHO, 2014b).

Currently, there is no specific drug or vaccine available for treatment of infection caused by MERS-CoV. Therefore, medical care is focused on supportive treatment. Even though, a number of antiviral medicines are currently under study (Zumla et al*.,* 2015), there is no licensed vaccine to prevent MERS-CoV infection. However, one company has developed an experimental candidate MERS-CoV vaccine (Novavax, 2013). Almazán et al. (2013) also developed other candidate vaccines which are being studied as full-length infectious cDNA clone of the MERS-CoV genome in a bacterial artificial chromosome.

CONCLUSION

MERS-CoV is a zoonotic emerging disease with bats and dromedary camels as the important animals mainly involved as source for its emergence, outbreak and epidemiological pattern. Transmission of MERS-CoV from camel to human is well documented and studied by different researchers but is generally not very efficient because transmission route of the virus back from human to camel is still hypothetical. The exact mechanism of transmission is not clear, including whether other intermediate hosts are involved, which will be a risk for new incidence of the disease, especially for those countries in which infection cases were not reported. Currently, the most applicable and commonly used control measures of MERS-CoV spread are strict regulation of camel movement, regular herd examination and isolation of positive camels. Thus, case-control studies of humans with MERS-CoV infection are needed to identify important risk factors and possible chains of transmission from camels and other animals and animal products which are sources of human infections. Similarly, urgent epidemiological studies and molecular detection like sequencing of viral RNA by real-time reverse-transcriptase polymerase chain reaction of MERS-CoV are mandatory to better understand the transmission patterns of MERS-CoV both in human and camel samples, in camel rearing African countries like Ethiopia where camel dependent poor pastoral communities are found, even though current human cases are not reported.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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