

REVIEW ON CORONAVIRUS, A MIDDLE EAST RESPIRATORY SYNDROME (MERS-CoV)

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➤ Supporting Information

ABSTRACT: Human coronaviruses (HCoVs) have long been considered in consequential pathogens, causing the “common cold” in otherwise healthy people. However, in the 21st century, 2 highly pathogenic HCoVs—severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)—emerged from animal reservoirs to cause global epidemics with alarming morbidity and mortality. In December 2019, yet another pathogenic HCoV, 2019 novel coronavirus (2019-nCoV), was recognized in Wuhan, China, and has caused serious illness and death. The ultimate cope and effect of this outbreak is unclear at present as the situation is rapidly evolving. Middle East respiratory syndrome coronavirus (MERS-CoV) is zoonotic diseases causing severe respiratory illness emerged in 2012 in Saudi Arabia. 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. The prevalence of MERS-CoV antibodies, the identification of MERS-CoV RNA and viable virus from dromedary camels of Eastern Africa and the Arabian Peninsula are the suggestive evidence for inter-transmission of the virus, primarily from camels to humans and its public health risks. 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%. 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). Currently, there is no specific drug or vaccine available for treatment and prevention of MERS-CoV. 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 where consumption of unpasteurized camel milk is common. Therefore, urgent global epidemiological studies are required, to understand the transmission patterns and the human cases of MERS-CoV and also for the proper implementation of the above-mentioned control measures.

Keywords: Bats, Dipeptidyl peptidase 4, Dromedary camels, MERS-CoV, SARS-CoV, Transmission

Abbreviations

COV	Coronavirus
MERS-CoV	Middle East respiratory syndrome coronavirus
SARS-CoV	Severe respiratory syndrome corona virus
DPP4	Dipeptyl peptidase 4
WHO	World Health Organization
ICTV	International Committee on Taxonomy of Virus
PCR	Polymerase Chain Reaction
Rt-PCR	Real Time Polymerase Chain Reaction
Hcov	Human Coronaviruses
ORF	Open Reading Frame
CDC	Centers for Disease Control and Prevention
ECDC	European Centre for Disease Prevention and Control
ELISA	Enzyme-linked immune sorbent assay
UpE	Upstream of the envelope gene
BtCOV	Bat coronaviruses

INTRODUCTION

Coronaviruses (CoV) are enveloped, positive-sense RNA viruses with large genomes (29–32 kb) packaged in particles with corona-like morphology (Lai et al., 2007). They can infect humans, as well as a variety of animals, such as bats, mice, birds, dogs, pigs, and cattle, causing mainly respiratory and enteric diseases (Perlman and Net land, 2009).

Before the 21st century, it was believed that human corona viruses, represented by the virus's hCoV-OC43 and hCoV-229E, can only cause mild respiratory symptoms (Saif, 2004). This notion changed after the outbreak of the severe acute respiratory syndrome (SARS) in 2002-2003, when a previously unknown human corona virus, named severe acute respiratory syndrome corona virus (SARS-CoV), caused the first corona virus-associated human epidemic, infecting approximately 8000 and killing 774 people (Peiris et al., 2004). In the years that followed, two additional human corona viruses were discovered, namely hCoV-NL63 and hCoV-HKU1 (Woo et al., 2005). All known human corona viruses are believed to have a zoonotic origin, with bats playing a major role in the interspecies transmission (To et al., 013).

MERS-CoV is the second newly discovered Beta corona virus lineage 2C and initially recognized in the Kingdom of Saudi Arabia in June 2012, when an elderly Saudi Arabian man was admitted to a local hospital with acute pneumonia and later died of progressive severe respiratory illness and renal failure (Zaki et al., 2012). The World Health Organization (WHO) global case count for MERS was 1952 laboratory-confirmed cases, including at least 693 deaths (case fatality rate 36%) from September 2012 to 3 April 2017 (WHO, 2017).

MERS-CoV previously called human corona virus-Erasmus Medical Center was discovered by Zaki et al. (2012) in Saudi Arabia in 2012. In May 2013, the Corona Virus Study Group of the International Committee on Taxonomy of Viruses renamed the virus "Middle East respiratory syndrome corona virus (Murphy et al., 2012; Degroot, 2013). MERS-CoV marks the second known zoonotic introduction of a highly pathogenic corona virus, probably originating from bats (Sharif and Kanj, 2014). Three lines of evidence currently support this theory: Firstly, the very close phylogenetic similarity with the bat Beta corona viruses: BtCoV-HKU4 and BtCoV-HKU5 (Van boheemen et al., 2012). Secondly closely related corona virus sequences have been recovered from bats in Africa, Asia, the Americas, and Eurasia; and thirdly MERS-CoV uses the evolutionary conserved dipeptidylpeptidase 4 (DPP4) protein in *Pipistrellus pipistrellus* bats for cell entry (Raj et al., 2013).

Since human-bat contact is limited, camels have been implicated as probable intermediate hosts. MERS-CoV appears to have been circulating in dromedary camels for over 20 years (Corman et al., 2014). Many studies have now identified dromedary camels (*Camelus dromedarius*) as a natural host for MERS-CoV, and there appears to be ample evidence of wide spread infection in dromedaries in the Middle East and in many parts of Africa (Reusken et al., 2014a, Hamid et al., 2015). MERS-CoV strains isolated from dromedaries are genetically and phenotypically very similar or identical to those infecting humans (Farang et al., 2015).

While corona viruses affect wide animal species (Woo et al., 2012a), MERS-CoV have affects limited host ranges. In the last few years, a large spectrum of domestic species has been negative after MERS-CoV serology tests, including horses, cattle, water buffalo, chickens, goats, and Bactrian camels (hemida et al., 2013). An exception was published recently when antibodies were detected in Alpaca (*Vicugna pacos*) in Qatar (Reusken et al., 2016) and susceptibility of pigs and llamas to MERS-CoV infection (Vergera et al., 2017).

In the case of MERS-CoV transmission, there is a large uncertainty about the various exposure pathways associated with new dromedary camel or human cases, and, although published research on MERS-CoV is actively increasing (Zyoud et al., 2016), few transmission risks have yet been quantified.

Therefore, the objective of this paper was to review the public health risk and transmission of Middle East Respiratory Syndrome.

ETIOLOGY AND TAXONOMY

Middle East respiratory syndrome (MERS), an emerging infectious disease, is caused by the MERS-corona virus (MERS-CoV) (Zaki et al., 2012). CoVs taxonomically belong to the subfamily Coronavirine, family Coronaviridae, in the order Nidovirales, and can be further classified into four genera: Alpha corona virus, Beta-corona virus, Gamma corona virus and Delta corona virus (De Groot, 2011).

The genus Beta corona virus contains four different lineages, A, B, C and D. The human corona virus's hCoV-229 and hCoV-NL63 belong to the genus Alpha corona virus, while hCoV-OC43 and hCoV-HKU1 belong to the lineage A of the genus Beta corona virus. SARS-CoV belongs to the genus Beta corona virus of lineage B while MERS-CoV grouped under lineage C beta corona virus. The genera Gamma and Delta corona virus contain only viruses that infect animals (ICTV, 2012).

Phylogenetic analysis performed by Zaki et al. (2012) after the isolation of MERS-CoV from the Saudi patient suggested that the virus belongs to the lineage C of the genus Beta coronavirus, together with the bat coronaviruses BtCoV-HKU4 and BtCoV-HKU5, which have been isolated from the species *Tylonycteris pachypus* and *Pipistrellus abramus*, respectively (Woo et al., 2012a).

As stated by the ICTV, viruses that present greater than 90% sequence identity in their replicase domains belong to the same species. To investigate whether the newly identified virus is the prototype of a novel virus species, the amino acid sequence of the replicase gene obtained by sequencing of the PCR fragments that the pan-coronavirus PCR yielded was aligned with the respective sequences of its closest relatives, BtCoV-HKU4 and BtCoV-HKU5 (ICTV, 2012).

The comparison showed that the identity the viruses shared was greater than 80%, suggesting that the discovered virus represents a novel Beta corona virus species, the first human coronavirus described in lineage C of this genus. These results were repeated by the study of Van Boheemen et al. (2012), after they obtained the complete genome sequence of the the virus.

EPIDEMIOLOGY OF THE DISEASE

Geographic distribution

According to WHO report, MERS cases reported from 27 countries including Arabian peninsula (Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, the United Arab Emirates, Iran, Yemen), Europe (Austria, France, Germany, Greece, Italy, Netherlands Turkey and UK), Asia (China, Philippines, Malaysia, Thailand, Republic of Korea), Africa (Algeria, Egypt, 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 (WHO, 2019). In the United Kingdom, France, Italy, and Tunisia, limited human-to-human transmission occurred among close contacts of the index cases (WHO, 2015). MERS outbreak is ongoing in South Korea since May 2015; the index case was a man who had traveled to Bahrain, the United Arab Emirates, Saudi Arabia, and Qatar. All of the cases outside of the Middle East have had a direct or indirect connection to the Middle East.

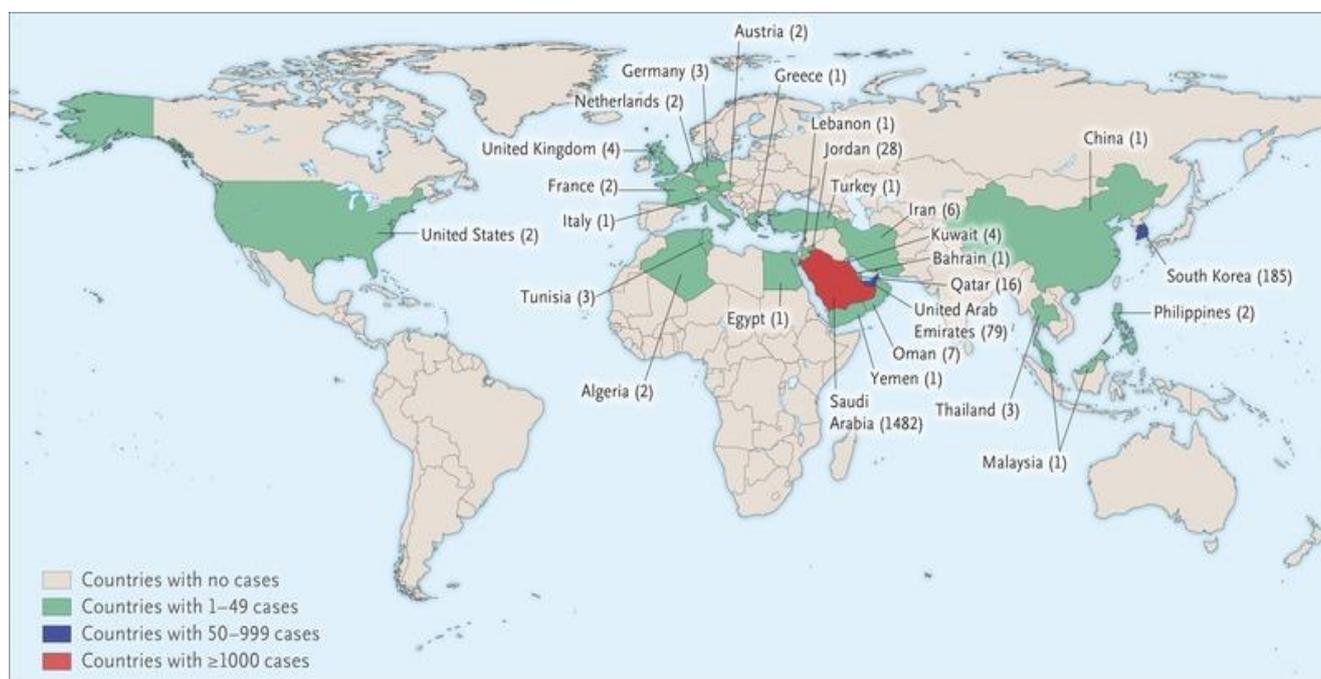


Figure 1 - Map showing confirmed global cases of MERS-CoV. Source: WHO (2017).

Virus replication on cyclophilin A

CypA is one of the most abundant cytosolic proteins constituting 0.1–0.4% of the total cellular protein content (Harding et al., 1986). Data from different labs suggest that relatively low levels of CypA may suffice to support efficient coronavirus replication. Cyclophilins were initially implicated as host factors in coronavirus replication during studies with general Cyp inhibitors such as cyclosporine A (CsA). In cell culture, the replication of a variety of coronaviruses was found to be strongly inhibited by low micromolar concentrations of cyclosporine A and the non-immunosuppressive Cs A analogs Alisporivir. The cyclosporine A dependence of the replication corona viruses in the same cell line (Huh7), in which CypA expression was knocked-out using CRISPR/Cas9 gene editing technology (de wilde et al , 2017).

Reservoirs and host susceptibility

Dipeptidyl peptidase 4 (DPP4; also, known as CD26) has been identified as the receptor for the MERS-CoV spike protein and is required for viral binding and entry into host cells (Raj et al., 2013). DPP4 is a type II Transmembrane glycoprotein that is expressed on epithelial and endothelial cells throughout the body (Lambeir et al., 2003). Although DPP4 is evolutionarily conserved, differences in the amino acids present in its extracellular domain, which interacts with MERS-CoV spike protein, have been noted among various animal species and humans. Specifically, 14 amino acids in DPP4 appear to be critical in determining whether the MERS-CoV spike protein can bind to DPP4 (Wang et al., 2013).

Bats

Bats are known natural reservoirs for several emerging viral infections in humans including rabies, Nipah virus, Hendra virus and Ebola virus (Han et al., 2015). Several features enable bats to be efficient sources of emerging human viral infections. As an extremely diverse species with a long evolutionary history, bats have co-evolved with a variety of viruses. Their lack of B-cell-mediated immune responses allows them to carry viruses without showing overt signs of illness (Brook and Dobson, 2015). Low metabolic rate and suppressed immune response during bats' hibernation result in delayed viral clearance (George et al., 2011). Bats live closely together in extremely large numbers facilitating stable circulation of viruses amongst them (Calisher et al., 2008).

Furthermore, bats are capable of flying and hence carrying potentially infectious pathogens over considerable distances (Drexler et al., 2014). A pertinent feature of bats is that they chew fruits to absorb their sugars and spit out the remains. The discarded fruits can be contaminated with viruses from the oral cavity, urine and feces providing a ready source for transmission to other potential hosts such animals and humans (Brook and Dobson, 2015).

Bats have been implicated as the main reservoir of members of the genera Alpha corona virus and Beta corona virus (Woo et al., 2012b) and play pivotal roles in interspecies transmission of CoVs. This is best exemplified by SARS-CoV, which was shown to originate from Chinese horseshoe bats (Lau et al., 2005), and was probably transmitted directly to humans (Ge et al., 2013) or through an intermediate host, such as the palm civet (Guan et al., 2004). MERS-CoV, together with bat CoV-HKU4 and HKU5, phylogenetically belongs to lineage C in the genus Beta corona virus (Van Boheemen et al., 2012). Thus, it is suspected that the emerging MERS-CoV might also originate from bats.

A large screening study for beta corona viruses was conducted on fecal specimens taken from 4758 bats of ten different species in Ghana, and 272 *Pipistrellus* bats from four European countries showed that a bat derived corona virus that has a very close phylogenetic relationship to MERS-CoV (Annan et al., 2013).

A report from South Africa and Saudi Arabia identified a bat derived corona virus that has a very close phylogenetic relationship to MERS-CoV (Ithete et al., 2013; Memish et al., 2013c). An experimental study conducted on Jamaican fruit bat (*Artibeusja maicensis*) showed evidence of infection as they shed the virus from their respiratory and intestinal tract (Munster et al., 2014). Therefore MERS-CoV, like many other coronaviruses, originated in bats. This is based on the isolation of other lineage C beta-corona viruses that are very closely related to MERS-CoV on phylogenetic analysis (De Benedicts et al., 2014).

Dromedary camels

The close phylogenetic relationship of human MERS-CoV isolates with those obtained from bats initially suggested that MERS-CoV might have originated from bats. However, bats were unlikely to be the direct source of the MERS outbreak, since MERS cases were rarely found to have a history of contact with bats. Therefore, other animals were searched as direct sources of zoonotic transmission of MERS-CoV (Han et al., 2016). Multiple lines of evidence implicate dromedary camels in the emergence and transmission of MERS CoV.

MERS-CoV antibodies are highly prevalent in dromedary camels from across the Arabian Peninsula, North Africa and Eastern Africa (Nowotny and Kolodziejek, 2014). The high prevalence of MERS-CoV seropositivity in Africa and the Middle East suggests that animal movement has facilitated the transmission and circulation of MERS-CoV amongst dromedary camels in these regions. MERS-CoV antibodies have neither been found in Mongolian or Dutch Bactrian camels nor in South American camelids such as llamas, alpacas and guanacos (Reusken et al., 2013a).

MERS-CoV reported by RT-PCR in oro-nasal and faecal samples from dromedary camels in multiple locations in the Arabian Peninsula (Hemida et al., 2013). The four of 110 dromedary camels in which MERS-CoV RNA was detected in Egypt were all imported from Sudan or Ethiopia for slaughter (Chu et al., 2014). MERS-CoV was also detected by RT-PCR in symptomatic camels. Dromedaries with active MERS-CoV infection exhibited symptoms such muco-purulent nasal and lachrymal discharge, cough, sneezing, fever and loss of appetite (Memish et al., 2013b).

The potential infectiousness of MERS-CoV recovered from dromedary camels was evident its capability to cause ex-vivo infection in human respiratory cells and human hepatoma cells. Successful MERS-CoV cultures usually coincide with corresponding high viral loads in the same specimens (Chan et al., 2014). Experimental MERS-CoV infection of dromedary camels with result mild clinical infection manifesting as fever and rhinorhea also implicate dromedary camels in the emergence and transmission of MERS CoV (Adney et al., 2014a,b).

Other animal species

Differences in virus susceptibility and pathogenicity between animals of different species could be explained by a distinct tissue distribution of DPP4, the MERS-CoV receptor. Species with few or no differences in the 14 amino acids seem to be susceptible to MERS-CoV, including rhesus macaques, common marmosets and result cytopathic cellular changes and mild to severe respiratory illness (Munster et al., 2013; Falzarano et al., 2014). Macaques and marmosets have already proved useful animal models for the investigation of MERS-CoV (Eckerle et al., 2014).

Dromedary camels seems to be the only domestic animal reservoir for MERS-CoV until a recent study by Reusken et al. (2016) and Vergera et al. (2017). Reusken et al. (2016) investigated the MERS-CoV infection status of 15 healthy alpacas (*Vicugna pacos*) in a herd of 20 that shared a barn complex with dromedaries. All tested alpacas were seropositive to MERS-CoV.

Recent study on livestock susceptibility conducted in 2017 indicate that pigs and llamas are susceptible to MERS-CoV infection (Vergera et al., 2017), but the level of MERS-CoV excreted in the nose of dromedaries seems to be much higher than that of other animal species described so far (Adney et al., 2014a,b). On the other hands the study showed that sheep did not show clinical sign. These results are in concordance with those reported by Adney et al. (2016) that MERS-CoV experimentally inoculated sheep showed no clinical disease and that only small amounts of virus were detected in nasal swab samples. Even though the receptor binding domain, and in particular key amino acids on the docking site are identical in horses and human (Van Doremalen et al., 2014), horses were not susceptible to MERS-CoV (Vergera et al., 2017). Screening study on equids including horses, donkeys and mules from UAE and Spain result in sero-

negative for MERS-CoV (Meyer et al., 2015). These results highlight that other mechanisms, such as epithelial cell permissibility or strong innate immune responses, may influence the establishment of infection. Differences in the number of goblet cells in the lining epithelium and mucus covering epithelial surfaces, which may have impeded the binding of the virus to the respiratory epithelium of horses (Vergera et al., 2017). Serological study, conducted in Saudi Arabia and Europe from sheep, goats, cattle, and chickens representing different geographical areas within the country were resulted sero negative for MERS-CoV (Hemida et al., 2013; Reusken et al., 2013a). In addition ferrets, hamsters, and mice are resistant to infection (Van et al., 2014).

Source of infection and transmission

There is growing evidences that the dromedary camel is host species for MERS-CoV and plays an important role in the transmission of the viruses to human (Azhar et al., 2014). In August 2013, for the first time, dromedary camels were implicated as a possible source of virus causing human infection because of the presences of MERS-CoV specific neutralizing antibodies in dromedary camels from Oman and other countries in the Arabian Peninsula and North Africa.

An analysis of an outbreak of MERS-CoV infection in humans in Qatar in October 2013 found that dromedary camels and humans were infected with a nearly identical strain of MERS-CoV (Hemida et al., 2013). Widespread circulation of different genetic variants of MERS-CoV has been found in camels and the presence of MERS-CoV specific antibodies in samples taken from camels, years earlier. Although dromedary camels are suspected to be the primary source of MERS-CoV leading to human infections, the true routes of zoonotic transmission remain to be determined (Azhar et al., 2014).

Chu et al. (2014) reported that Middle East respiratory syndrome corona virus from Egypt has been fully genetically sequenced and biologically characterized. While this virus was genetically diverse from viruses causing zoonotic infections in the Arabian Peninsula, the receptor binding domain of the Egyptian viruses is conserved, indicating that these viruses would be able to infect the human respiratory tract. This contention is supported by the finding that tropism and virus replication competence of MERS-CoV from Egypt in ex vivo cultures of the human bronchial and lung is comparable to that of camel of human virus isolates in the Arabian Peninsula (Chu et al., 2014).

Camel to human transmission

Whole MERS-CoV genome sequences obtained from viral cultures of the human and camel isolates were 100% identical. Importantly, 4-fold rise in MERS-CoV antibody titres was documented in the camels, indicating that active MERS-CoV infection was probably circulating in the dromedary herd. Later, rising MERS-CoV antibodies were documented in the patient, suggesting that MERS-CoV infection was transmitted from the camels to the human and not vice versa (Azhar et al., 2014). MERS-CoV was detected in eight asymptomatic dromedary camels at entry into UAE from Oman. Two asymptomatic men, aged 29 and 33 years, who were in contact with the camels, were found to be positive for MERS-CoV RNA in their respiratory samples. Partial sequences of MERS-CoV spike and nucleocapsid regions from the human and linked camels were identical. Within 4–8 days from diagnosis, both patients had undetectable MERS-CoV RNA (Al Hammadi et al., 2015).

MERS-CoV sequences have been detected more commonly in nasal swabs than in rectal specimens of camels (Hemida et al., 2014). Infection of camels in the laboratory also confirmed susceptibility, with a large quantity of virus shedding from the upper respiratory tract (Adney et al., 2014a,b). Therefore, droplet transmission or direct contact with infected camels may be the most likely mode of camel-to-human transmission of MERS-CoV. Direct contact with camels can only explain some of the primary cases, since some MERS cases did not report any direct contact with camels (Han et al., 2016).

Other possible routes for camel-to-human transmission include food-borne transmission through consumption of unpasteurized camel milk, raw meat and the camel urine. Camels are an important source of milk in some Middle East countries and parts of Africa, and more than half of the camel milk is sold as unpasteurized fresh or fermented milk to local and urban consumers in Saudi Arabia (Faye et al., 2014). A survey found the presence of MERS-CoV RNA in the milk of camels actively shedding the virus (Reusken et al., 2014b).

An experimental study of the stability of MERS-CoV in milk showed that viable viruses could still be recovered after 48 h regardless of reduction in virus titre, indicating that infection could happen by consumption of unpasteurized fresh raw milk (Van Doremalen et al., 2014). Consumption of undercooked meat from infected camels and handling of infected raw camel meat without proper protective equipment may also pose risks for getting MERS CoV from camel. An oral-faecal transmission mode was also suspected. Using protein intrinsic disorder prediction, MERS-CoV was placed into disorder group C and was likely to persist in the environment for a rather long period of time, and showed high oral-faecal transmission chances (Goh et al., 2013).

The single study, by Van Doremalen et al. (2013), on Plastic or steel surfaces inoculated with MERS-CoV at different temperature and relative humidity (RH) shows that the virus remained viable for 24 h. The study reported that MERS-CoV was more stable under low-temperature/low-humidity conditions, suggesting the potential for MERS-CoV to be transmitted via contact or fomite transmission due to prolonged environmental presence. By comparison, a well-known and efficiently transmitted respiratory virus, influenza A virus, could not be recovered in culture beyond four hours under any conditions. Aerosol experiments found MERS-CoV viability only decreased 7% at low relative humidity at 20 °C. In comparison, influenza A virus decreased by 95 % (Van Doremalen et al., 2013).

Enter-human transmission

While the introduction of MERS-CoV to the human species from an animal reservoir seems to be the reason for the initial infections, the occurrence of clusters suggests that the virus has adapted to human-to-human transmission. Person-to-person transmission of MERS-CoV has been documented in several human clusters associated with healthcare facilities, households and workplace (Assiri et al., 2013a; Memish et al., 2013a).

Nosocomial outbreak is a distinct hallmark in MERS-CoV transmission involving hospitalized patients, healthcare workers and close family contacts in healthcare facilities in affected countries in the Middle East and in some countries where the disease had been exported to, the most recent being the Republic of Korea (RoK). Droplet spread between humans is considered the mechanism of human-to-human transmission and the need for droplet precautions was emphasized after the Al-Ahsa hospital, the KSA (Khalafalla et al., 2015) and the South Korean outbreaks (Assiri et al., 2013a).

MERS-CoV's ability to remain viable over long time periods gives it the capacity to thoroughly contaminate a room's surfaces when occupied by an infected and symptomatic patient (Van Doremalen et al., 2013). Whether MERS-CoV can remain a drift and infectious for extended periods (truly airborne) remains unknown. Such findings expand our understanding of the possibilities for droplets to transmit respiratory viruses in many settings, including hospital waiting rooms, emergency departments, treatment rooms, open intensive care facilities and private patient rooms. The nature and quality of air exchange, circulation and filtration are important variables in risk measurement and reduction as is the use of negative pressure rooms to contain known cases (Assiri et al., 2013a).

Furthermore, given the high concentration of the virus in the lower respiratory tract of infected patients, airway suction or use of bronchoscopes could also serve as a source of transmission (Guberina, 2014). The infectiousness of urine and stool is currently under investigation, since the virus has been detected in urine and stool samples of patients and based on the fact that cluster patients had been sharing toilet rooms during hospitalization. Transmission via blood should also be considered a possible route, since scientists claim that the virus might be present in blood (Guery, 2013). This could be correlated to the reported person-to-person transmission in hemodialysis units of a hospital in Saudi Arabia (Assiri et al., 2013b).

Generally, corona viruses are transmitted among humans via aerosol droplets and/or through direct contact with other secretions (stool, urine etc.) (Danielsson, 2012). Currently, the pathways used by MERS-CoV for inter human transmission remain unknown. Several case investigations have suggested that airborne transmission seems to be the most likely route (Memish et al., 2013a).

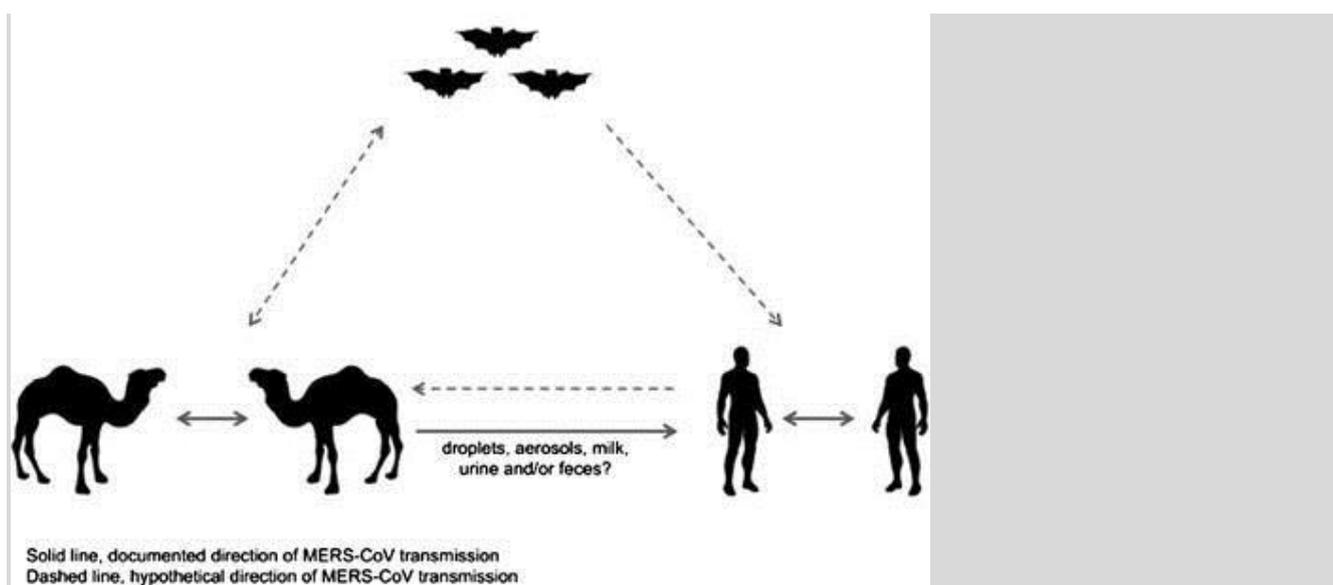


Figure 2 - Reported Infection sources and transmission routes of MERS-CoV between bats, camels and human (Source: Omrani et al., 2015).

Public health importance

This novel virus can cause severe acute respiratory disease, mainly in patient with immunosuppressant condition and underlying disease including diabetes, heart disease, renal failure, hypertension, chronic lung disease, including asthma and cystic fibrosis. Moreover, history of travel in at risk countries and smoking might have considered as a risk factors of severe disease (Al Barrak et al., 2012). Washing hands, face and hair in camel urine is a traditional custom among Bedouins and camel-herding peoples in the Arabian Peninsula and East Africa. There are currently no published data about MERS-CoV in the urine of infected camels, but the virus has been found in low concentration in human urine samples (Drosten et al., 2013), and therefore, consumption of camel urine may represent a risk factor for infection.

Dromedary camel meat represents 0.45% of the red meat produced worldwide (Faye, 2013). While there is no evidence of MERS-CoV in camel meat, by analogy with what is known about other viruses like Rift Valley fever virus, we can assume that the fall in pH of meat with maturation could inactivate the virus (Food and Agriculture Organization) and that proper cooking would kill the virus. However, handling of raw meat and slaughtering of animals should not be excluded as a risk factor. The list of at-risk countries, as defined in European Centre for Disease Prevention and Control (ECDC) rapid risk assessment included Iraq, Israel, Jordan, Qatar, Saudi Arabia, Syria, Kuwait, Lebanon, Palestine, Oman, UAE, Yemen, Bahrain and Iran (ECDC, 2013). People working closely with camels (e.g. farm workers, slaughterhouse workers and veterinarians) 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, 2014).

PATHOGENESIS

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.

Molecular studies revealed that cellular receptors for MERS-CoV are exopeptidase (angiotensin converting enzyme 2) (Coleman et al., 2014). Moreover, it was found that neutralization of angiotensin converting enzyme 2 by specific antibodies did not arrest the spread of infection into bronchus and lung alveolus. Extensive investigations showed that another functional cellular receptor called DDP4 was also involved in the severity of MERS-CoV disease spread into the lungs (de Wit et al., 2013). 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 to 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 (Van Boheemen et al., 2012). The severity is worsened by concurrent secondary bacterial infections. Recent research showed that bacterial infections due to *Staphylococcus aureus*, Group A *Streptococcus*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b augment the pathogenic potential of MERS-CoV, particularly in humans. These bacteria particularly dwell in the oral cavities, tonsils and pharynx of humans (Lau et al., 2013).

CLINICAL FEATURES

The median incubation period of a MERS-CoV infection is 5 days. The clinical manifestations in patients of MERS-CoV range from subclinical infection to severe respiratory disease. Symptomatic patients often present with fever, myalgia, and sore throat, shortness of breath, cough, and occasionally hemoptysis. Gastrointestinal symptoms such as diarrhea and vomiting are also common. Hematological abnormalities reported for clinical cases include thrombocytopenia, lymphopenia, lymphocytosis, and neutrophilia (Assiriet al., 2013a; Gueryet al., 2013). Radiographs with a spectrum of lower pulmonary infiltrates and consolidation consistent with viral pneumonia (Zakiet al., 2012; Assiriet al., 2013b).

In contrast 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 (Khalafalla et al., 2013) and the nasal discharge drained from both nostrils varied in character from serous to purulent (Daniella et al., 2014). In humans, after the entry of MERS-CoV viral particles in to lung alveoles, alveolar macrophages fail to contain the spread of infection. The strong host cellular immune response and cytokine release leads to inflammation and fluid accumulation in lungs.

DIAGNOSIS

Sputum from lower respiratory tract, nasopharyngeal swab, whole blood, tissue from biopsy or autopsy including from lung and serum for serology are important for virus detection. Lower respiratory tract specimens (such as tracheal aspirates and Broncho alveolar lavage) appear to have the highest virus titre. Upper respiratory tract specimens are also recommended, especially when lower respiratory tract specimens cannot be collected (Guery et al., 2013).

Rapid verification of cases of novel corona virus infection will be based on detection of unique sequences of viral RNA by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) and immune fluorescence. However, antibodies against beta corona viruses are identified to cross react within the genus. Therefore, immunofluorescence effectively limits their use to confirmatory applications (Corman et al., 2012b). However, for detection of MERS-CoV in particular, alternative RT-PCR assays are required, detecting certain targets that have been described to be specific for the virus (Van Boheemen et al., 2012).

Corman (2012a) proposed two RT-PCR assays for the detection of the virus, each one targeting different parts of the viral genome. The first assay targets a region upstream of the envelope (E) gene (upE assay), while the second assay targets part of ORF1b (ORF1b assay), which does not overlap with the target of pan-coronavirus assay. The upE assay was found to be more sensitive in comparison to the ORF1b assay. Thus, the use of the upE assay is recommended for screening, while the ORF1b assay can be used for confirmation (Corman et al., 2012b). The specificity of both assays was

confirmed by excluding cross-reactivity with the other known human corona viruses. A third assay, optimized for sensitivity, was described by the same group, this time targeting ORF1a. Overall, a combination of the upE and ORF1a assay seems to be the optimal approach for MERS-CoV detection (Corman et al., 2012a).

Several serology assays have been developed for the detection of MERS-CoV antibodies, including immunofluorescence assays and a protein microarray assay (Reusken et al., 2013b). The Center of Disease Control and Prevention (CDC) has developed a two-stage approach, which uses an enzyme-linked immune sorbent assay (ELISA) for screening followed by an indirect immunofluorescence test or micro neutralization test for confirmation.

PREVENTION AND CONTROL

Since there are currently no effective drug therapies to treat or prevent the infection, clinical management of patients with severe disease largely relies on meticulous intensive care support and prevention of complications. This includes hydration, antipyretic, analgesics, respiratory support, and antibiotics, if needed, for bacterial super infection. Current treatment is based on previous experience with the Severe Acute Respiratory Syndrome-Coronavirus (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 (Al-Tawfiq and Memish, 2014).

Monoclonal antibodies that efficiently block the interaction between the MERS-CoV envelope spike glycoprotein and a human protein DDP4 have been developed using a humanized mouse (transgenic mouse). These researchers are now working to move the antibodies into human trials. 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 (Jiang et al., 2014).

Understanding the zoonotic sources of MERS-CoV might guide 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 (WHO, 2014). 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, 2015). Currently, there is no specific drug or vaccine available for treatment of infection caused by MERS-CoV. 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). It also developed other candidate vaccines which are being studied as full-length infectious DNA clone of the MERS-CoV genome in a bacterial artificial chromosome.

CONCLUSION

Middle East respiratory syndrome is zoonotic diseases causing severe lower respiratory illness and now considered a threat to global public health. The current knowledge about virus is limited, since many important epidemiological and clinical aspects remain unknown. 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. Although MERS-CoV displays lower transmissibility among humans than SARS-CoV, the possibility that future mutations will render the virus highly transmittable, with a devastating outcome, cannot be discarded.

In the light of aforementioned conclusions the following general and specific points are recommended.

- Urgent epidemiologic investigations through surveillance on environmental, animal and testing around sporadic unexplained cases are needed to find other animal reservoirs.
- Extensive efforts are required to speed up the development of an effective therapy and vaccine.
- Camels may play important role in transmission of the virus, and the common practices in pastoral areas of consuming unpasteurized camels' milk and raw meat should be avoided.
- Health care workers caring for patients under investigation for MERS-CoV or confirmed cases should exercise standard precautions including hand hygiene, as well as contact or air borne precautions.

DECLARATION

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Authors' contribution

Dr. Birhanu and Dr. Kassahun participate in design the topic of the review. Dr. Damtew performed by gathering the data. In addition, Dr. Kassahun carefully revised and write the manuscript. Finally, all authors read and approved the final manuscript.

Availability of data

The data can be availed to the journal upon request.

Conflict of interest

The authors declare they have no competing of interests.

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