

REVIEW ARTICLE

Dromedary Camels and the Transmission of Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

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Summary

Middle East respiratory syndrome coronavirus (MERS-CoV) is an existential threat to global public health. The virus has been repeatedly detected in dromedary camels (*Camelus dromedarius*). Adult animals in many countries in the Middle East as well as in North and East Africa showed high (>90%) seroprevalence to the virus. Middle East respiratory syndrome coronavirus isolated from dromedaries is genetically and phenotypically similar to viruses from humans. We summarize current understanding of the ecology of MERS-CoV in animals and transmission at the animal–human interface. We review aspects of husbandry, animal movements and trade and the use and consumption of camel dairy and meat products in the Middle East that may be relevant to the epidemiology of MERS. We also highlight the gaps in understanding the transmission of this virus in animals and from animals to humans.

Introduction

Middle East respiratory syndrome coronavirus (MERS-CoV) was first detected in 2012 in respiratory specimens of a patient from Saudi Arabia with severe viral pneumonia leading to acute respiratory distress syndrome and death (Zaki et al., 2012). As of 19 June 2015, 1338 laboratory confirmed cases of MERS have been reported to the World Health Organization (WHO) leading to at least 475 deaths (WHO, 2015). Saudi Arabia is the most affected country with 1030 laboratory confirmed patients. Middle East respiratory syndrome patients have also been reported from Jordan, Kuwait, Lebanon, Oman, Qatar, United Arab Emirates (UAE), Iran and Yemen. MERS has been reported from travellers arriving from these countries into Europe (Austria, France, Germany, Greece, Italy, Netherlands,

Turkey, UK), Africa (Algeria, Egypt, Tunisia), Asia (China, Malaysia, Philippines; Republic of Korea, Thailand) and North America (USA). Some limited secondary transmission has been associated with some travel-associated patients with MERS but one large outbreak in the Republic of Korea led to over 160 human MERS infections (WHO, 2015). Large clusters of human cases have been identified in Saudi Arabia, Jordan and UAE, most of these being associated with human-to-human transmission within health-care facilities (Assiri et al., 2013; Oboho et al., 2015; WHO, 2015). While some of these case clusters are large, human-to-human transmission remains inefficient and sustained community transmission has not been documented so far (Majumder et al., 2014; WHO, 2015). However, it is relevant to note that the emergence of SARS in 2002 was heralded by repeated self-limited outbreaks of human disease,

but that virus finally adapted to transmission in humans, spreading to 25 countries across five continents, infecting approximately 8000 individuals and leading to almost 800 deaths (Peiris et al., 2004). Thus, it is important to understand the ecology and epidemiology of MERS so that zoonotic disease can be prevented and epidemic or pandemic threats mitigated.

Source of Zoonotic Infection

Zoonotic infections may arise from domestic animals as well as wild life. Seroepidemiological studies have been carried out in domestic livestock (cattle, sheep, goats, horses and poultry) in the Arabian Peninsula and the Middle East, but dromedary camels were the only species from which antibodies specific to MERS-CoV have been detected (Hemida et al., 2013; Perera et al., 2013; Reusken et al., 2013a,b; Meyer et al., 2014). Serological evidence of MERS-CoV infection of dromedaries has been reported from the Arabian Peninsula including Saudi Arabia, United Arab Emirates (UAE), Oman, Qatar and Jordan with seroprevalence in adult animals generally being >90% (Hemida et al., 2013, 2014; Reusken et al., 2013a,b; Alexandersen et al., 2014; Nowotny and Kolodziejek, 2014b). Serological evidence of MERS-CoV infection has also been demonstrated in dromedaries from Africa, including Egypt, Ethiopia, Nigeria, Tunisia, Sudan and the Canary Islands, with similarly high seroprevalence except Tunisia and Canary Islands, where adult seroprevalence was 54% and 14%, respectively (Perera et al., 2013; Reusken et al., 2013a, 2014; Corman et al., 2014b). In general, seroprevalence in adult animals was higher than in juveniles. Testing of archived dromedary sera has revealed that MERS-CoV has been circulating in camels in the Arabian Peninsula for at least three decades and is not a newly emerged virus from camels (Alagaili et al., 2014; Hemida et al., 2014; Meyer et al., 2014). The only region where dromedaries have been seronegative so far is Australia (Hemida et al., 2014). Data from dromedaries in Central Asia are lacking. Bactrian camels in Mongolia appear seronegative (Chan et al., 2015).

MERS-CoV viral RNA has been detected in nasal swabs of dromedaries in Qatar, Oman, Saudi Arabia, Egypt and UAE. In camel abattoirs where animals from multiple sources are mixed together prior to slaughter, positive rates range from 1.9% to 34.6% (Alagaili et al., 2014; Chu et al., 2014; Haagmans and Osterhaus, 2014; Hemida et al., 2014; Nowotny and Kolodziejek, 2014a; Raj et al., 2014; Wernery et al., 2015). In a dromedary camel herd where virus transmission was tracked for over 1 month, the virus remained genetically unchanged, suggesting that MERS-CoV is well adapted to this species (Hemida et al., 2014). Full-genome sequences of dromedary camel MERS-CoV from Saudi Arabia and Qatar revealed that the camel virus is very simi-

lar to viruses detected in humans, including in the virus spike protein, suggesting that the virus in dromedaries can potentially infect humans (Hemida et al., 2014; Raj et al., 2014). Virus isolation of dromedary MERS-CoV has been reported in Vero cells (Chu et al., 2014; Raj et al., 2014). Middle East respiratory syndrome coronavirus from humans and dromedaries have comparable capacity to infect and replicate in *ex vivo* cultures of the human respiratory tract, providing phenotypic evidence for the competence of dromedary viruses to infect humans (Chan et al., 2014). Temporal relationship between camel infection and development of human disease has been reported (Memish et al., 2014a). Virus genetic sequences from a person with MERS-CoV disease and from a camel with whom this person had recently been in close contact were very similar suggesting camel-to-human transmission does occur (Azhar et al., 2014).

Data from experimental camel infections suggest that MERS-CoV is a mild respiratory infection in camels (Adney et al., 2014), although this study was carried out with a cell culture adapted human MERS-CoV isolate rather than with the camel isolate. However, camel calves found shedding MERS-CoV in natural field settings also do not have overt clinical symptoms (Hemida et al., 2014; Wernery, 2014). Furthermore, camels sampled at abattoirs later shown to be shedding MERS-CoV did not have overt clinical symptoms (Chu et al., 2014).

With the ubiquitous nature of MERS-CoV infection of dromedaries the lack of antibodies in Bactrian camels in Mongolia, as assessed by seroprevalence studies (Chan et al., 2015), it is likely that dromedaries are a natural host for this virus, but whether they are natural reservoir remains to be established. As an analogy, swine have high seroprevalence to Japanese encephalitis and are an amplifier host for transmission to humans, but wild birds are the natural reservoir for this virus. Similarly, dromedary camels are a natural host and source of human infection but they may or may not be the natural reservoir for the virus.

While travel-associated MERS-CoV infections have been recognized in Egypt and Tunisia, no zoonotic transmission has been reported in East or North Africa in spite of virus being ubiquitous in camels. One possible explanation may be the lack of awareness that MERS may occur outside the Arabian Peninsula without a history of travel. A second possibility is that the MERS-CoV strains circulating in Africa are different in zoonotic potential. There is limited information on the genetic diversity or biological phenotype of MERS-CoV from Africa. Middle East respiratory syndrome coronavirus 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 (Chu et al., 2014). 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).

Seroepidemiology of humans in contact with camels

In a large countrywide seroepidemiological study of over 10 000 people older than 15 years carried out during 2012–2013 in KSA, an overall seroprevalence of 0.15% was detected while 5 of 140 (3.6%) of slaughterhouse workers were seropositive (Muller et al., 2014). The population-based seroprevalence suggests that tens of thousands of MERS-CoV infections have gone unrecognized in Saudi Arabia (Figs 1 and 2). This suggests that some patients with clinically overt MERS who have no obvious exposure to animals may well have acquired infection from such asymptomatic or mild infections, making the identification of true zoonotic infections a challenge. In a study in Qatar, 2% of camel farm workers, 14% of camel barn workers at an international racing track and 2 of 5 camel slaughterhouse workers were seropositive while none of 204 people with no camel contact were seropositive. In this slaughterhouse, virus RNA-positive rate in camels was as high as 60% on some sampling occasions indicating massive levels of human exposure (Reusken et al., 2013b, 2015). In other studies of some human with exposure to camels, there has been no evidence of seropositive to MERS-CoV (Aburizaiza et al., 2014; Memish et al., 2014b). Humans regularly exposed to a dromedary herd known to be infected for at least a month had no clinical or serological evidence of infection (Hemida et al., 2015). In summary, humans with

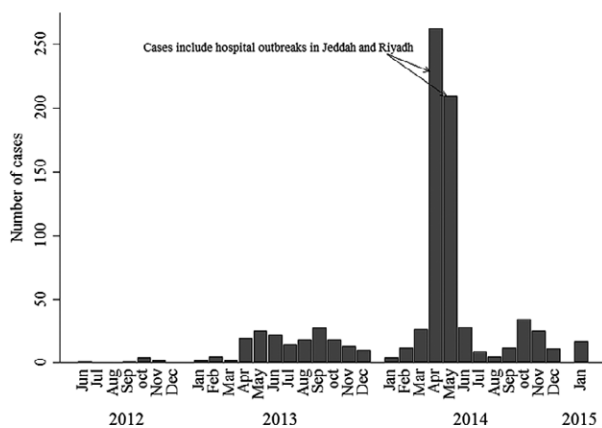


Fig. 1. Epidemic curve of MERS-CoV human infection in Saudi Arabia from June 2012 to December 2014 (Data used for generating epidemic curve were retrieved from the official Saudi Ministry of health quarterly reports).

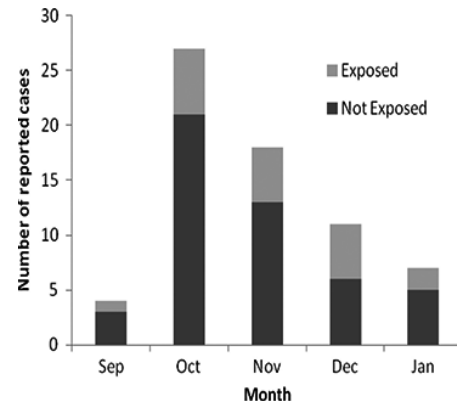


Fig. 2. Monthly human patients with MERS-CoV distributed by history of animal exposure (dark grey = not exposed, light grey = exposed) after exclusion of patients with hospital, community or healthcare personnel contact. Animal exposure (camels and other species) data were available from (September 2014 to January 2015), Saudi Ministry of Health.

regular and heavy exposure to infected camels do become seropositive but casual exposure to infected camels does not lead to efficient human infection. Even camel abattoir workers who are exposed daily to animals who are regularly shedding MERS-CoV are not uniformly infected and rarely get overt disease. Hardly any of the patients diagnosed with MERS so far are workers in these high-risk occupations. In many respects, the epidemiology of human MERS shares similarities with that of avian influenza A H5N1 where the virus can be ubiquitous in poultry but human disease is stochastic and rare. This highlights the many questions that remain to be understood about the susceptibility and epidemiology of human MERS (Fig. 3). It is possible that unusual routes of exposure or heterogeneity of host susceptibility to MERS-CoV are important determinants of human disease. The possibility of a hitherto unidentified animal host or vector also remains to be more intensively investigated. Nevertheless, given the key role that dromedaries play as a natural host in the ecology of MERS-CoV and the potentially important role that dromedaries may play in zoonotic MERS infection, it is important to review the ecology and animal husbandry of dromedary camels in the Arabian Peninsula.

Distribution of Dromedary Camels in the Arabian Peninsula

The global population of camels is estimated to be approximately 30 million, 95% of these being dromedary camels (reviewed in Gossner et al., 2016). Dromedary camels inhabit the Middle East region, North and East Africa and north-western parts of Asia (Farah, 2001). Bactrian camels (*Camelus bactrianus*), on the other hand, are native to the

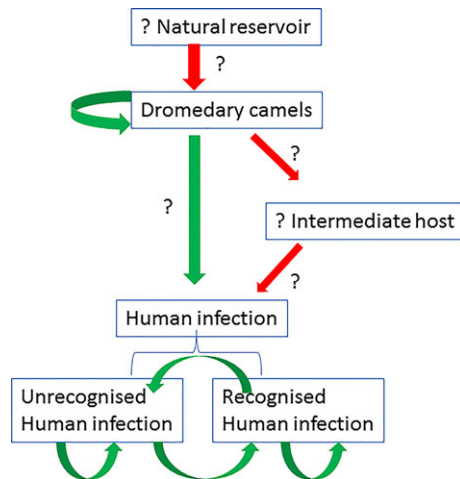


Fig. 3. Hypothesis of MERS-CoV transmission to humans. Green arrows represent confirmed transmission pathways. Red arrows represent potential transmission pathways, which may be confirmed in a few instances (for example, camel-to-human transmission in specific case reports) but not confirmed as main transmission pathways as yet. [Colour figure can be viewed at wileyonlinelibrary.com].

steppes of Central Asia and more adapted to regions with cooler climates. The dromedary and Bactrian camels share a common evolutionary origin with llamas, which originate from South America. Of the total of 28.5 million dromedary camels worldwide, 77% are in Africa, the largest camel populations being found in Somalia (6.2 million), Sudan (4.8 million), Kenya (3 million) and Ethiopia (2.3 million). Only approximately 4% are in the Arabian Peninsula. The highest density of camels by land area or by human population in the Arabian Peninsula is found in Qatar and UAE (Gossner et al., 2016). Table 1 shows the numbers of camels in countries in the Arabian Peninsula. There is a strong positive correlation ($r = 0.95, P < 0.001$) between the total number of camels and the reported MERS-CoV cases across the Arabian Peninsula. Saudi Arabia and UAE which have the largest populations of camels are also the ones with the highest number of confirmed cases of MERS. Although there are differences between the camel census data proposed by FAO and the data from the different Ministries of Agriculture, especially in Saudi Arabia (Table 1), the overall correlation of camel numbers and human MERS remains high.

In the Middle East, dromedary camels are indispensable to the traditional nomadic lifestyle, providing milk, meat, wool, leather, medicinal purposes as well as for transport, trade and racing. Thus, they are an important source of income and social prestige. More recently, camel husbandry in the Middle East has undergone significant changes. For example, the human population in Saudi Arabia has changed from being predominantly (80%) rural in the 1960s to currently being predominantly urbanized (87%) leading to associated changes in patterns of camel husbandry. In Saudi

Table 1. Camel population and confirmed MERS-CoV cases in Arabian Peninsula

N	Country	Camel population reported by ministries of Agriculture in respective countries*	Camel populations as reported by FAOstat 2014**	Confirmed MERS-CoV cases***
1	Saudi Arabia	810 000	266 000	977
2	UAE	360 000	364 000	50
3	Qatar	70 000	64 551	7
4	Oman	45 000	36 500	4
5	Kuwait	10 000	11 500	3
6	Bahrain	1000–2500	1025	0
	TOTAL	1 296 000–1 297 500	743 576	1041

*Camel Population as per the Ministry of Agriculture per each country 2010.

**Source: FAOstat, 2014.

***MERS-CoV laboratory confirmed cases (WHO, 2015).

Arabia, six types of camel farms and husbandry have been described; commercial farms, racing farms, use of camels for leisure for urban dwellers (weekend farms), traditional camel farms, camels for renting and camels for prestige (Abdallah and Faye, 2013). More recently, a more detailed typology study of camel husbandry in Saudi Arabia identified the following categories: (i) those who are purely camel farmers, some grazing in the desert with more or less integration into the market systems and with variable levels of application of modern animal management methods; (ii) retired people keeping camels for recreational and other purposes; (iii) camel farmers with good integration to the market and with good health management systems; and (iv) multi-active owners practicing camel rearing as a hobby. There was a distinction between farmers living in the desert together with moving animals as a primary source of livelihood and those living in cities, having camels in peri-urban or sometimes in desert locations but for mainly social satisfaction rather than for economic reasons. Integration to the market for milk and meat drives owners to an increasingly peri-urban setting with improved supplemental diet and better health management (Faye, 2013). Some highly intensive farms are also emerging all over the Arabian Peninsula both for milk production (including milk processing with forms of pasteurized milk) and meat production (feed-lot farms of young male camels (*hachi*) often imported from the Horn of Africa).

Camel Movement Across the Arabian Peninsula and its Implications for the Transmission of MERS-CoV

Camel herds frequently move across the Arabian Peninsula for many reasons such as grazing, participation in camel

aces and camel shows. They move across Saudi Arabia and cross the borders of many Gulf countries including UAE, Oman, Kuwait and Qatar every year during the winter season. For example, the Ministry of Environment in Qatar has banned grazing over their land for 2 years starting 24 August 2011, and this has led to different livestock species from Qatar, especially camels, sheep and goats, crossing into Saudi pasture sites. However, given the lack of official national identification procedures or of obligatory vaccination campaigns focused on camels, it is difficult to quantify the extent of these movements. Camels from both UAE and Qatar travel every year during the winter seasons (November–February) for grazing in the Eastern region of Saudi Arabia.

Recently, camel shows called Mazayin al-Ibl (meaning ‘best of camels’) have been annually held in many Gulf countries. One of the largest camel shows is usually held in November in Um al-Rughaiya in the Eastern Saudi Arabia, a region about 329 km from Riyadh and 160 km from Hafra al Batin city. More than 100 camel herds representing over 160 000 camels from all over the Arabian Peninsula travel

every year to participate in this international festival and over than 160 000 people attend this event every year (Harrigan, 2008). Camel movement usually runs parallel to the common highways during their journey from each country or within Saudi Arabia to their destination Um al-Rughaiya, passing cities such as Dhahran and Buraydah (Fig. 4). A major racing and show competition is held annually in February in an area at the suburb of Riyadh called Janadriyah. Other festivals are held in other Gulf countries such as in UAE, the Abu Dhabi Authority of Culture and Heritage (ADACH) international festival in April (Harrigan, 2008). Similar festivals are held annually in other Gulf countries including Oman, Qatar and Kuwait. This is in addition to the local festivals held in each county throughout the year. This regular movement of camels crossing borders of many countries may contribute to the transfer, amplification and evolution of MERS-CoV. For example, previous studies documented high degree of relatedness between MERS-CoV sequences obtained from camel herds in Al-Ahsa and MERS-CoV from humans in UAE and Burydah (Hemida et al., 2014). We speculated that the



Fig. 4. Map showing the active camel movement across Arabian Peninsula. Camel movements across the Arabian Peninsula and through Saudi Arabia are mainly for many purposes, importation, grazing, show, race and business. Arrows are showing the camel movement for the above indicated activities. Stickpins are showing the dry ports (Salwa, Albatha and Khafji) where animals cross the borders of Gulf countries including Qatar, UAE and Kuwait, respectively, as well as from Oman. Pushpins are showing the wet ports (Jeddah and Jizan), and dotted lines are showing the routes of camel importation from the African horn through Port Sudan and Aden from Sudan and Somalia, respectively. We inserted blue circles, the size of these circles is proportional to the number of reported human cases for each geographical location. The number of human cases reported from 2 March 2012 to 23 July 2014. This data are obtained from Fig. 4 in the review by Gossner et al., 2014. This map was produced by Esri, ArcGIS® and ArcMap™ software. [Colour figure can be viewed at wileyonlinelibrary.com].

movement of camels between these locations may spread the virus during their journey. Middle East respiratory syndrome coronavirus has been detected in camels crossing borders from Saudi Arabia into the UAE (Yusof et al., 2015). These journeys are bidirectional as camel herds actively move between places indicated on the map.

One of the main aspects regarding the camel economy worldwide is the importance of camel regional markets, mainly for providing animals to the meat market. In this context, important flows of live camels are reported from the Horn of Africa (exporting countries are Somalia, Ethiopia, Sudan, Kenya and Djibouti) to the North of the continent (Egypt, Libya) and to the countries of the Arabia Peninsula (Faye, 2013). These movements could be important in understanding the epidemiology and viral evolution of MERS-CoV. For example in Saudi Arabia, 131 932 camels were officially imported in 2013 representing more than 70% of the animals slaughtered in the Kingdom (Mackay, 2014). This camel trade through importation and exportation may affect the epidemiology of MERS-CoV and the introduction of viruses. The mixing of camels of different origins and immune status to MERS-CoV potentially provides opportunities for amplification and dissemination of MERS-CoV, analogous to what has been described for bovine coronaviruses in cattle where a high percentage of cattle, some of whom are already seropositive, actively shed bovine coronavirus nasally and in faeces shortly after mixing of animals or like in feed-lot cattle infected with BCov (Saif, 2010). A similar situation also occurs with avian influenza in live poultry markets (Sims and Peiris, 2013). There is anecdotal evidence in camels that prior MERS-CoV seropositivity does not preclude re-infection (Hemida et al., 2014).

Importation of livestock, including camels, from the Horn of Africa led to the outbreak of Rift Valley Fever (RVF) that started in Saudi Arabia in 2000–2001 associated with zoonotic infections and death of several dozen humans. Indeed, some of these camels imported for meat production are fattened within the country of importation for several months before slaughter, providing ample opportunity for interaction with local camel herds and exchange of viruses. Animals imported from some of these countries imported camels proved to be seropositive to MERS-CoV (Perera et al., 2013). Middle East respiratory syndrome coronavirus isolated from dromedaries in the abattoirs in Egypt, animals potentially sourced from Sudan or Ethiopia, were phylogenetically diverse (Chu et al., 2014), providing a glimpse of the potential overall diversity of MERS-CoV. Some countries also import animals and then export them to the other neighbouring countries. Camel movements across the Arabian Peninsula and from the Horn of Africa to the Arabian Peninsula could contribute to or predispose to the introduction and amplifica-

tion of MERS-CoV and be associated with an increase of human MERS cases. Further studies are required to confirm this hypothesis. A detailed, spatiotemporal understanding of camel movement patterns may explain the spread of disease and highlight high-risk areas. Furthermore, studies to genetically and phenotypically characterize the diversity of MERS-CoV in Africa are urgently needed.

Camel Calving Seasons and the Epidemiology of MERS-CoV Infections in Humans and Camels

In the past few years, seasonal increase of human MERS cases in the Middle East, especially in Saudi Arabia and UAE during winter and early spring has been noted. Camels are seasonal breeders with the male rutting only during the winter months. The gestation period is 12–13 months, and thus, calving season is also limited to the winter period and early spring. By providing new naïve hosts into the population in a seasonal manner, this reproductive cycle of dromedary camels could be associated with seasonal patterns of human MERS. The duration of passive maternal antibody and its role in suppressing infection by MERS-CoV remains to be fully defined. In addition, camel movement across the Arabian Peninsula during these times may also contribute to increased human disease. Several viral infections are common during the early life of different animal species such as coronaviruses and rotaviruses. Coronaviruses other than MERS affect newborn animals such as calves, lambs, foals and piglets (Torres-Medina et al., 1985; Dea et al., 1995; Munoz et al., 1996; Davis et al., 2000). The camel calving season usually occurs during the period late October to late February. Our studies and those of others have noted the association of dromedary MERS-CoV infection in camels and the calving season (Hemida et al., 2014; Wernery, 2014). In a follow-up of one camel herd, we detected the initial MERS-CoV infection by RT-PCR as early as late November with the peak of infection at late December, predominantly in calves (Hemida et al., 2014). By the end of February, the infection has been cleared from the herd. A study of a camel herd in Dubai found that virus shedding was more common in calves and that virus shedding in calves was of relatively short duration (Wernery et al., 2015). As calves appear to have the highest risk of MERS-CoV infection, it has been suggested that delayed weaning of calves may reduce the opportunity for humans being exposed to calves.

There was a large increase in human MERS occurring in Saudi Arabia during the period March–May 2014 (Majumder et al., 2014; Oboho et al., 2015). This was largely related to amplification of transmission within healthcare facilities. However, it is possible that the calving patterns of camels may seed these large human outbreaks.

Potential Roles of Raw Milk, Improperly Cooked Meat and Raw Internal Organs of Camels in the Transmission of MERS-CoV

Consumption of raw non-pasteurized milk has been proposed as a source of infection in one human MERS case (Memish et al., 2014a,b). The transmission of Hepatitis A virus, rabies virus and foot-and-mouth disease virus to humans through consumption of contaminated cow milk has been reported (Centers for Disease Control and Prevention, USA 1999; Headrick et al., 1998). Some other viruses such as tick-born encephalitis virus can be shed in milk during the active infection (Caini et al., 2012). Despite the potential risk of infection associated with drinking raw camel milk (Mousa et al., 1988), desert nomads in Arabian Peninsula often use raw camel milk as a whole meal for long periods which may last from days to months. They also drink raw milk because of the widespread belief that camel milk has prophylactic and therapeutic properties against many diseases and that boiling the milk destroys its nourishment and medicinal value (Shamsia, 2009). Stability of MERS-CoV (strain Jordan-N3/2012) at different temperatures in camel, cow and goat milk was investigated. The infectivity of MERS-CoV in camel milk was greatly reduced at 22°C compared to that stored at 4°C (van Doremalen et al., 2014). It should be noted, however, that this milk was sourced from seronegative camels for MERS-CoV. It is known that MERS-CoV-neutralizing antibody is secreted to camel milk and this may neutralize infectivity of any virus that may be present (Reusken et al., 2014). This study also found evidence of MERS-CoV RNA in samples of camel milk collected by traditional milking practices where the flow of milk ('letting') is initiated by allowing a calf to suckle the dam. Once the flow of milk is initiated, the herdsman will continue manual milking. As calves are at high risk of acquiring MERS-CoV infection, it is possible that the milk may get contaminated with virus in the nasal secretions or saliva of calves. In the study which reported detection of MERS-CoV RNA in camel milk, it is unknown whether the virus entered milk through contamination from an infected calf or whether the udder was infected via systemic dissemination of the virus through the blood stream. Irrespective of the routes by which the virus can enter the camel milk, the facts support the possibility that raw camel milk could be a source of MERS-CoV infection. Heat treatment or pasteurization may reduce the risk of infection from milk to a minimum (van Doremalen et al., 2014). Further epidemiological studies are needed to investigate the possibility of MERS-CoV shedding in camel milk.

Camel meat is the most popular type of meat in the Arabian Peninsula and is widely consumed. In addition, some consume raw internal organs of camels, particularly liver and spleen and sometimes the lung. Both the Saudi Min-

istry of health and the Centers for Disease Control and Prevention in the USA had reported that eating the raw camel liver caused human bubonic plague in Saudi Arabia in 2005 (Bin Saeed et al., 2005). From the limited data from experimentally infected animals (Adney et al., 2014), it appears unlikely that camel meat and internal organs will have MERS-CoV through virus dissemination through a viremia. However, contamination of such organs with respiratory tissues may occur during the process of slaughter, potentially leading to infection via this route. Further studies are needed to investigate the potential roles of these types of meat in MERS-CoV transmission.

Camel urine is also used for medicinal purposes and is consumed alone or mixed with camel milk. However, experimental infections of dromedaries with MERS-CoV did not reveal evidence of viremia or evidence of virus in the urine (Adney et al., 2014). Thus, camel urine is an unlikely source of virus transmission to humans.

MERS-CoV is relatively more stable in the environment than other enveloped viruses such as influenza (van Doremalen et al., 2014). Thus, fomites and dust may also be a route of transmission to humans.

Role of Other Animal Sources of MERS-CoV

Bats are incriminated in the origins of many known mammalian coronaviruses (Lau et al., 2013). SARS and the human coronavirus 229E appear to have arisen from precursor viruses in bats (Pfefferle et al., 2009; Drexler et al., 2014). There was one report that a short fragment (around 200 nucleotides) of viral RNA identical to that of MERS-CoV was detected in a *Taphozous perforates bat* in Saudi Arabia (Memish et al., 2013). However, this finding remains unconfirmed and this report needs to be regarded with caution.

Coronavirus closely related to but not identical with MERS-CoV has been detected in *Neoromicia capensis* bats, but the spike protein in particular is very divergent, and this virus is unlikely to be the precursor of MERS-CoV (Corman et al., 2014a,b). However, these findings highlight the possibility that the MERS-CoV precursor may indeed be found in bats. In a recent study, we documented introduction of MERS-CoV into a camel farm which was in a closed compound without much intermingling with other animals. The source of introduction of this virus was unclear (Hemida et al., 2014). Whether another animal host (bats, or other) was responsible for the introduction of the virus remains to be ascertained. Mechanical transmission by feed and manure removal trucks is another possibility.

Concluding Remarks

Dromedary camels are likely to be a natural host of MERS, and transmission between camels is clearly documented.

However, it is still unclear whether camels are the natural reservoir of the virus and the only source of human infection. Clearly, transmission from camels to humans does take place, and camel exposure is a risk factor for human infection but such transmission is not efficient and infection is not directly proportional to exposure. Heterogeneity of human susceptibility to MERS-CoV infection may be one possible explanation, as also proposed for avian influenza H5N1. Many thousands of people in the Arabian Peninsula appear to have evidence of unrecognized past MERS-CoV infection. On the other hand, many patients with clinically diagnosed MERS do not have an obvious history of direct exposure to camels or their products. This may be because such individuals are being infected from other humans who are infected with MERS unrecognized (asymptomatically or with mild illness). Thus, the true primary zoonotic infections may be difficult to identify. Alternate possibilities of other intermediate or reservoir hosts in the transmission of infection to humans also remains possible, and Fig. 3 illustrates the many 'known unknowns' that remain to be elucidated.

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Author Contributions

MGH, MP and AE collected and analysed the data, and all the authors wrote the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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