

Middle east respiratory syndrome coronavirus and the one health concept

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The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is one of the major threats to the healthcare systems in some countries, especially in the Arabian Peninsula. There is some debates about the origin of MERS-CoV either from bats or from other unknown reservoirs. Dromedary camel has only identified animal reservoir so far. Dromedary camels play important roles in sustaining the virus in certain community. They may act as an amplifier of the virus by secreting it in their body fluids especially the nasal and rectal discharges. MERS-CoV was detected in the nasal and rectal secretions of infected camels. MERS-CoVs from dromedary camel origins has the full capacity to infect human airway epithelium in both in vitro and ex vivo models (Chan et al. 2014). Some other evidence confirmed the direct transmission of MERS-CoV from camels to human. Furthermore, the roles of the camel meat and milk products are not well studied yet. Human-to-human transmission is well documented through contact of an active infected patient or through the contact of some silently infected persons. There are some significant risk factors of individuals came in close contacts with a positive MERS-CoV patient. These factors include sleeping in the same patient room, removing patient waste: urine, stool and sputum and touching respiratory secretions from index case. Outbreaks within family clusters were reported since some blood relative patients infected despite their wives in the same house were not infected. This suggesting some predisposing genetic factors favor the MERS-CoV infection. This worth investigation in the near future. There are many unknown/confirmed aspects in the virus/human/animal network. Here, we discussed the most recent advances in this context. We presented the possible reasons behind the emergence and the sustainability of MERS-CoV in certain regions. Identification of the exact mechanism of transmission of MERS-CoV from camels to human and searching for new reservoir/s are of high priority. This will reduce the shedding of the virus to the environment thus; the risk of human infection can be mitigated.

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ABSTRACT:

Background. The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) emerged late 2012 in the Arabian Peninsula. Whether MERS-CoV originated from bats or from an unknown reservoir has been debated. Dromedary camels are the only identified animal reservoir thus far. Dromedary camels play important roles in sustaining the virus in certain communities. They may amplify the virus by secreting it in their bodily fluids, especially in their nasal and rectal discharges, where it has been detected. MERS-CoVs originating from dromedary camels can fully infect the human airway epithelium in both in vitro and ex vivo models. Other evidence has confirmed the direct transmission of MERS-CoV from camels to humans. Furthermore, the roles of camel meat and milk products remain unclear. Human-to-human transmission via contact with either actively infected patients or silently infected persons is well documented. Infected individuals who have close contact with MERS-CoV-positive patients exhibit some potential risk, which include sleeping in the same room, removing the patient's waste (urine, stool and sputum) and touching respiratory secretions from an index case. Outbreaks within family clusters have been reported since some blood relatives have been infected despite their spouses living in the same house and being uninfected. This suggests that some predisposing genetic factors favor MERS-CoV infection and require further study. Many unknown/unconfirmed aspects exist in the virus/human/animal network. Herein, we discuss the most recent advances in this context and present the possible reasons behind the emergence and sustainability of MERS-CoV in certain regions. Identifying the exact mechanism of MERS-CoV transmission from camels to humans

and searching for new reservoirs are of high priority. This will reduce viral shedding into the environment thus mitigating the risk of human infection.

Subjects: One Health, Zoonosis and public health, Epidemiology, Infectious Diseases

Keywords: MERS-CoV; One Health, dromedary camel; human; reservoir; transmission.

SURVEY METHODOLOGY

In this review article, I used to do literature search of the most up-to-date published articles on MERS-CoV in the past 7 years. First, I focused the introduction section on the historical background of coronaviruses and the One Health concept. Then, I highlighted the most up-to-date literature from the PubMed central, Google scholar and Researchgate on the relationship between the MERS-CoV/human/ animal interaction. I identified some important gaps in the research dealing with MERS-CoV/human/environment in the context of the One Health concept. Meanwhile, I summarized the current acceptable theories on the emergence and evolution of MERS-CoV. Finally, I highlighted the progress made for the control of MERS-CoV.

1. Coronaviruses: the past, present, and future

Coronaviruses are a large group of viruses that cause many health problems (respiratory, enteric, and nervous) and syndromes in various animal species, including humans. Currently, six human coronaviruses have been identified (HCoV-229E, HCoV-OC43, HCoV-NL-63, HCoV-HUK-1, SARS-CoV, and MERS-CoV), two of which emerged in the past 15 years (Lau & Chan 2015): the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). SARS-CoV emerged in 2003 in China and spread to many countries worldwide (Peiris et al. 2003). Approximately 8000 people were

infected, and 10% of these died (Aronin & Sadigh 2004). Nine years later, MERS-CoV emerged in Saudi Arabia (Zaki et al. 2012). This is a relatively short period for the emergence of new coronaviruses. One of the main reasons behind the rapid emergence of new coronaviruses is the poor proofreading capability of their RNA polymerases (Hofer 2013) in addition to the possibility of corona viral recombination (Makino et al. 1986). New coronaviruses will likely emerge soon. Several sporadic MERS-CoV cases continue to be reported in the Middle East and Arabian Peninsula. Since the discovery of MERS-CoV in late 2012 (Zaki et al. 2012), reports to the World Health Organization (WHO) are ongoing from some countries in the Middle East, especially in the Arabian Peninsula. The virus then spreads to other countries around the globe, especially in the Middle East. As per the latest WHO statistics, 2,279 cases of MERS-CoV infection have been confirmed, including at least 806 deaths (reported case fatality rate of 35.0%; (WHO 2018). Continuous reports of MERS-CoV suggest the presence of factors favoring its sustainability in certain regions. Despite some available data from recent research, many aspects of the virus remain uncertain, including its evolution, pathogenesis, and transmission cycle. It seems the rate of research on the virus has recently gradually declined. This hampers the production of new data on MERS-CoV. Below, we summarize our current understanding of the virus in the context of the “One Health” concept.

2. Coronaviruses and the One Health concept

The One Health concept is a new concept outlining the close interaction between humans, animals and the environment (Destoumieux-Garzon et al. 2018). Currently, two coronavirus candidates represent the One Health concept: SARS-CoV and MERS-CoV. Animals play important roles in the transmission cycles of both viruses (Alshukairi et al. 2018; Wang et al. 2005), which are both of zoonotic origin (Gao et al. 2016).

3. MERS-CoV in humans

MERS-CoV can infect people of all ages and has been documented in patients less than one year old up to 109 years old (CDC 2016). However, children are less likely to be infected with MERS-CoV than are adults, and when infected, children are often asymptomatic or have a milder form of the disease (Arwady et al. 2016). The reason for this remains unclear and requires further study. The case fatality rate remains very high in immunocompromised infected patients, especially those with chronic diseases such as cancer, diabetes, hypertension, and kidney problems (Arwady et al. 2016). Human-to- human transmission has been reported in many cases, and many family clusters have been reported over the past 5 years (Arwady et al. 2016; Drosten et al. 2014; Memish et al. 2013). This confirms the potential spread of MERS-CoV among close-contact populations (Mollers et al. 2015). The most at risk groups for MERS-CoV infection are healthcare workers, camel workers, and the elderly with underlying chronic diseases (Arabi et al. 2014). The prevalence rate of MERS-CoV primary cases is higher in men than in women (Darling et al. 2017), possibly because men are more likely to be exposed to infected dromedary camels than are women. MERS-CoV replicates efficiently in various in vitro and ex vivo models (Chan et al. 2014). The virus triggers unique interferon and cytokine gene expression profiles. The virus seems to be a poor interferon inducer (Chan et al. 2014), suggesting potential immune evasion strategies triggered by the virus to hijack the host's immune system. This may be partly responsible for the high case fatality rate. Viral spreading among humans appears highly inefficient at present. People in close contact are among the at-risk groups for infection (Drosten et al. 2014) as has been observed in many family clusters (Alfaraj et al. 2018; Choi et al. 2017; Xiao et al. 2018). This suggests that viral transmission among humans often requires exposure to high viral loads to produce active infections in people in close contact. Several MERS-CoV

family clusters have been reported (Drosten et al. 2014). Interestingly, MERS-CoV has been reported in dromedary camels in many African countries (Egypt, Nigeria, Tunisia, and Ethiopia); however, no human cases have been reported in these countries thus far (Ali et al. 2017; Roess et al. 2016; van Doremalen et al. 2017). This could be related to variations in the circulating Asian and African strains of MERS-CoV. Some important deletions were recently reported in the MERS-CoV currently circulating in dromedary camels from Africa (Chu et al. 2018), which may partly explain the reason for the variations in pathogenesis among the Asian and African strains of MERS-CoV. MERS-CoV infection varies from severe respiratory illness to inducing high fevers and respiratory distress to mild and asymptomatic cases. Severe patients are usually admitted to the intensive-care unit (ICU) and provided with an oxygen source. Most patients end up with pneumonia, which is fatal in nearly 40% of affected patients (Hong et al. 2017; Rubio et al. 2018). Some patients may develop renal failure [13]. Most MERS-CoV travel-associated infections have been associated with the Middle East (Bayrakdar et al. 2015; Rubio et al. 2018); among these was the Korean outbreak in early 2015 (Choi et al. 2017; Hong et al. 2017; Xiao et al. 2018). A Korean citizen visited some countries in the Middle East, then returned home ill. This person visited several healthcare facilities in Korea, resulting in the largest MERS-CoV human outbreak outside the Arabian Peninsula (Xiao et al. 2018). This outbreak confirmed that human-to-human transmission is possible. During this outbreak, MERS-CoV was isolated from air samples from contaminated surfaces, objects, fomites as well as from the hallways of the healthcare facilities near where the patients were hospitalized (Xiao et al. 2018).

4. MERS-CoV in animals

Since the discovery of MERS-CoV in late 2012 (Zaki et al. 2012), many research groups have looked for its potential animal reservoir/s. Dromedary camels are the only currently known

reservoir of MERS-CoV (Hemida et al. 2014; Hemida et al. 2017b; Reusken et al. 2014; Reusken et al. 2016). Interestingly, we and others traced the virus back 30 years in dromedary camel specimens via retrospective studies (Corman et al. 2014; Hemida et al. 2014; Reusken et al. 2014), and the data suggest that the virus have been circulating for decades unnoticed. Although the actual and typical clinical features of MERS-CoV natural infection in dromedary camels has not been well documented, a few studies have reported these patterns under experimental infection conditions (Adney et al. 2014). These studies found that camels showed no pathognomonic signs despite their having subtle fevers and runny noses for up to 6 days postinfection (dpi) (Hemida et al. 2014). Meanwhile, shedding of the infectious virus was reported in experimentally infected camels from 2 to 7 dpi (Adney et al. 2014). Interestingly, viral RNA was still detected at 35 dpi (Hemida et al. 2014). The RNA may act as a potential source of infection since MERS-CoV is a positive-sense RNA virus. No viral shedding was reported in these animals' oral secretions, rectal swabs, urine, or sera (Adney et al. 2014), which contradicted the virus being previously detected in fecal specimens and swabs during a natural viral field infection (Hemida et al. 2014). This may suggest different MERS-CoV infection patterns between natural and experimental approaches. Further studies are required to establish a MERS-CoV infection model in dromedary camels. This may be achieved by conducting long-term longitudinal studies and careful monitoring of the viral infection in large camel populations. Necropsy of the MERS-CoV experimentally infected dromedary camels revealed only mild to moderate inflammatory reactions in the upper respiratory tract (Khalafalla et al. 2015), and viral antigens were detected in tissue sections of the turbinate bone and upper respiratory tract (Khalafalla et al. 2015). Interestingly, seroconversion of the inoculated animals was reported starting at 14 dpi (Hemida et al. 2014). This indicates that MERS-CoV induces a robust humoral

immune response after infection. More recently, one longitudinal study reported the possibility of MERS-CoV infection in seropositive animals. This raises concerns regarding the roles of antibodies in protecting against MERS-CoV infection (Hemida et al. 2017a). Only some members of the *Camelidae* family (dromedary camels, alpacas, and llamas) appear susceptible to MERS-CoV infection, which occurs naturally in dromedary camels and experimentally in alpacas and llamas (Corman et al. 2014; Vergara-Alert et al. 2017). Interestingly, one study showed an absence of detectable antibodies against MERS-CoV in the sera of Bactrian camels (Chan et al. 2015). This was the only study to report this finding of MERS-CoV seronegativity in Bactrian camels. Whether the absence of detectable MERS-CoV antibodies in Bactrian camel sera is due to the tested animals' geographical location in Mongolia far from the Middle East and Africa remains unknown. This may be supported by similar findings in dromedary camels in Australia and the Canary Islands (Crameri et al. 2015). Another possibility is that this might be due to genetic factors that contribute to the resistance of Bactrians to MERS-CoV infections, which requires further investigation but suggests that genetic factors play roles in susceptibility to the viral infection. Experimental MERS-CoV infection in both alpacas and llamas showed a similar pattern to that of dromedary camels (Vergara-Alert et al. 2017), suggesting that both animals might serve as models to study MERS-CoV in vivo. Experimentally infecting pigs with MERS-CoV revealed a lesser infection than that reported in alpaca and llamas (Vergara-Alert et al. 2017). No active MERS-CoV particles were retrieved from the experimentally infected animals nor from close contact with uninfected animals during the study duration (Vergara-Alert et al. 2017). This suggested that pigs might not play active roles in transmitting MERS-CoV. Although bats are considered the main reservoir for many coronaviruses, their roles in MERS-CoV require further clarification. One study reported the presence of small fragment of MERS-

CoV sequences in one specimen collected from bats in Saudi Arabia. The genome sequence of this virus showed nearly 100% identity to a MERS-CoV index case (Memish et al. 2013). However, this study was not confirmed by other studies. Investigating the potential roles of bats in the Arabian Peninsula is one of the most important missing research directions. and require further investigation. More recently, Jamaican fruit bats tested positive for MERS-CoV experimental laboratory infection (Munster et al. 2016). MERS-CoV-infected bats showed no apparent clinical signs; however, viral shedding was reported in swabs from the bats up to 9 days postinoculation. Meanwhile, the clinical profiles and viral shedding curve during the course of the MERS-CoV infection in these bats was highly similar to that in dromedary camels (Munster et al. 2016). Although this bat species is not the most relevant for studying MERS-CoV, this study provided insights on the molecular pathologies of MERS-CoV in bats. Interestingly, another study revealed that MERS-CoV receptors (dipeptidyl peptidase-4, DPP4) were expressed in the respiratory and digestive tracts of some insectivorous bats (Vergara-Alert et al. 2017). Several attempts have been made to look for an appropriate experimental animal model of MERS-CoV. The Syrian hamster is nonpermissive to MERS-CoV infection (de Wit et al. 2013). Experimentally infecting this animal yields no clinical signs or pathology and produces no cytokines after infection (de Wit et al. 2013). This was in contrast to results in New Zealand white rabbits, which showed signs of an infection after being inoculated with MERS-CoV (Monchatre-Leroy et al. 2017). Furthermore, both rhesus macaques and common marmosets supported the MERS-CoV infection (Yu et al. 2017). Additionally, both transgenic and transduced mice expressing human dipeptidyl peptidase-4 receptors served as models for MERS-CoV studies (Zhao et al. 2015).

5. MERS/human/animal interaction

Human exposure to MERS-CoV-infected dromedary camels is a predisposing factor to human infection, particularly in immunocompromised people (Zumla et al. 2015). Based on the latest WHO reports, the prognosis of MERS-CoV infection is poor for elderly people with chronic diseases such as cancer, diabetes, and kidney failure (Arabi et al. 2014). MERS-CoV transmission from dromedary camels to humans has been demonstrated indirectly in recent reports (Azhar et al. 2014). One study strongly evidenced direct transmission of MERS-CoV from an infected camel to its owner. This was confirmed by comparison via genome sequencing of the virus isolated from the infected dromedary camel to that isolated from its owner. Both viruses shared nearly 100% identity (Azhar et al. 2014). This study also reported the detection of MERS-CoV nucleic acid in air samples from the infected dromedary camel barn during the active course of the viral infection (Azhar et al. 2014). The roles of dromedary camel milk, meat products and byproducts in MERS-CoV transmission is debatable. Experimentally introducing MERS-CoV into raw milk revealed little difference between the viral stock in the milk and that maintained in Dulbecco's modified Eagle's medium (DMEM) (van Doremalen et al. 2014). As a cultural tradition, some Middle Eastern citizens used to drink raw camel milk to seek treatment for diseases such as diabetes. Thus, drinking raw camel milk poses a great risk to those who consume it without heat treatment or pasteurization (van Doremalen et al. 2014; Zhou et al. 2017). One study connected an infection in some people to their drinking the milk of one infected camel (Memish et al. 2015). Another study was conducted in Qatar to determine the possibility of becoming infected from the contaminated teats and udder of an infected female camel during milking (Reusken et al. 2014). However, no active MERS-CoV shedding in milk has been reported this far. Further studies are encouraged to conclude the potential roles of raw camel milk in transmitting MERS-CoV. Meanwhile, the role of camel meat in MERS-CoV

transmission requires further study. Thus, special attention should be paid to efficiently cooking camel meat and its products as well as thoroughly boiling the camel milk. People are advised not to drink raw camel milk to avoid the risk of infection not only with MERS-CoV but also with other pathogens such as Brucellosis (Garcell et al. 2016). In conclusion, consumption of raw milk is a health risk for various known reasons, but that there is currently no evidence for infection by MERS-CoV via ingestion. Some studies have reported that MERS-CoV is an occupational zoonotic viral disease based on investigating the seroconversion of some at-risk groups to MERS-CoV. This study reported the presence of specific MERS-CoV antibodies in approximately 3% of workers in some slaughterhouses in Qatar (Farag et al. 2015). Conversely, our studies reported an absence of detectable antibodies in the sera of some herdsmen, veterinarians, and slaughterhouse workers in Saudi Arabia (Hemida et al. 2015). One possible explanation for the variations between the two studies is the difference in the sensitivities of the techniques used. The studies used two different techniques to report the presence/absence of MERS-CoV antibodies in the sera of people at risk (Farag et al. 2015; Hemida et al. 2015). However, these studies require further replications on a larger scale to confirm this conclusion.

6. Gaps in the MERS-CoV related research

As mentioned above, research on MERS-CoV has sharply declined, especially in the last couple years, and much information on the molecular biology of MERS-CoV remains to be determined. Identifying DPP-4 viral receptors does not exclude the presence of other coreceptors or transcription/translation factors that favor the viral infection in specific hosts. MERS-CoV triggers many immune evasion strategies to hijack host immune responses. The mechanisms of such strategies are unclear. Many unknown aspects exist, especially in the context of MERS-CoV/human/animal interactions. Meanwhile, some studies have been conducted on a small scale

or with few animals/specimens and have reported some important conclusions, which require further confirmation. Further refining some of these observations is needed. Here, we highlight some gaps in the research on MERS-CoV evolution and transmission. Presumably, there may be an unidentified reservoir/s in the MERS-CoV transmission cycle. Although respiratory infection remains the main route for MERS-CoV infection, the exact mechanism of transmission of MERS-CoV from dromedary camels to humans remains to be clarified. Other reservoir/s may exist in the MERS-CoV transmission cycle; thus, there may be a missing link in the chain between humans and camels. Meanwhile, the exact modes of MERS-CoV transmission from dromedary camels to humans remain unclear, and the pattern of natural MERS-CoV infection in dromedary camels requires further study. The potential roles of most camel secretions and excretions are also unclear. Seroprevalence of MERS-CoV was reported in dromedary camels from different countries in Africa and Asia (Ali et al. 2017; Hemida et al. 2014); however, feral camels from Australia and the Canary islands were found to be seronegative (Crameri et al. 2015). The reasons behind this phenomenon are unclear. Very few studies have reported cross reactivity between MERS-CoV and other coronaviruses, such as the bovine coronavirus (BCoV), which may infect dromedary camels (Wunschmann et al. 2002). Whether this is the reason behind the high MERS-CoV seroprevalence in dromedary camels is unknown. Whether this is due to the high frequency of exposure to MERS-CoV infection during the camel's life or the crossreactivity of other coronaviruses or due to an unknown mechanism related to the dromedary camel's immune system remains to be determined and requires further study. Demand is ongoing for the development of novel diagnostic assays for coronaviruses. Special interest should be paid to techniques that enable simultaneous detection of the viral nucleic acids and that can distinguish between antibodies for several coronaviruses in the field. Meanwhile, the reason that

only Bactrian camels among the *Camelidae* family do not seroconvert to MERS-CoV infection is unclear. The genetic susceptibility of some human populations, especially of blood relatives is unclear in the context of MERS-CoV infection. Meanwhile, development of a risk scoring system for human exposure to dromedary camels is urgently needed.

7. Current theories on the MERS-CoV/human/animal interaction

Unidentified reservoirs that present the virus to the community are thought to exist in the context of MERS-CoV transmission (Figure 1). This virus can infect dromedary camels, which maintain the virus and favor viral circulation in some camel herds. The infected animal sheds the virus in its body secretions specially the nasal and rectal secretions. The virus can circulate among animals in the same herd and nearby herds. MERS-CoV in camels can potentially infect humans, especially those who are immunocompromised. Once infected, a person can possibly infect others, especially close relatives. This includes household relatives, employees and health care workers, including doctors and nurses, and depends on the level of exposure to the infected person. MERS-CoV infection in humans ranges from mild respiratory syndrome to very severe cases of pneumonia that end in the infected patient's death. Current data indicate that severely infected individuals can shed infectious viruses into the environment (Kim et al. 2016), although few data exist regarding the capacities of mildly infected individuals to transmit the virus. Asymptomatic individuals, however, are unlikely to transmit the virus (Moon & Son 2017).

8. Potential reasons for the emergence and spread of MERS-CoV

Many factors are behind the emergence, sustainability and spread of MERS-CoV. Presence of an unidentified MERS-CoV reservoir in the transmission cycle is possible. This unknown reservoir may contribute at least in part to the viral suitability in certain regions. Dromedary

camels amplify the virus. Close contact between these animals and humans in some regions in Africa and Asia may pose a great risk for human infection and indirectly contribute to spreading the virus. Additionally, public animal markets, especially for dromedary camels, may act as viral amplifiers, which pose great risks to the surrounding community. Lack of active surveillance programs for respiratory viruses, especially coronaviruses, may result in missing many subclinical or mild cases of MERS-CoV in certain populations. These patients may shed the virus in their secretions and may act as a source of infection to persons with whom they are in close contact. Many MERS-CoV vaccines and drug candidates are being studied, but none is available yet. These factors may favor the sustainability of MERS-CoV in certain regions.

9. Current progress on the control of MERS-CoV

Interestingly, the case fatality rate of MERS-CoV among the affected population dropped from almost 50% in 2012 to 34 % early 2019 (Alqahtani et al. 2018; WHO 2018). We may relate this progress in the control of MERS-CoV over the past 7 years to many factors. First, identification of the main reservoir of the virus; the dromedary camel (Hemida et al. 2014). Second, Continuous molecular and serological surveillances of MERS-CoV among dromedary camel population in the Arabian Peninsula and Africa (Corman et al. 2014; Farag et al. 2015; Haagmans et al. 2014; Hemida et al. 2017a; Hemida et al. 2017b; Khalafalla et al. 2015; Nowotny & Kolodziejek 2014; Reusken et al. 2014). Currently, testing the population of camels in regional camel markets are associated with shutting down of the market in case of positive animal shedding MERS-CoV. I believe this will substantially minimize the risk of community acquired infections through these positive population. Third, more progress in our understanding about the viral tropism, pathogenesis, mode of transmission have been made in the past five years (Chan et al. 2014; Widagdo et al. 2017; Widagdo et al. 2016). Fourth, Development of

some novel, rapid and sensitive methods for the early diagnosis of MERS-CoV in human and dromedary camels (Baek et al. 2018; Huang et al. 2018; Perera et al. 2013; Shirato et al. 2018). Fifth, development of some novel therapeutic and control approaches for MERS-CoV (Arabi et al. 2019; Dawson et al. 2019; Wang et al. 2019; Zhou et al. 2019).

10. Conclusions

Nearly 6 years after its emergence, reports of MERS-CoV infection are ongoing. This may be related to the many unknown aspects of the viral evolution and pathogenesis. More research is urgently needed to explore the unknown aspects of the MERS-CoV/human/animal network.

Figure legends

Figure 1: Current theories regarding the MERS-CoV/human/animal interaction

An unknown reservoir may exist in the MERS-CoV transmission cycle. Bats play roles in the context of MERS-CoV transmission, and the virus is transmitted to dromedary camels through an unknown mechanism. The dromedary camels act as viral amplifying hosts. MERS-CoV is transmitted from dromedary camels to humans through respiratory aerosols and other unknown mechanisms. The virus is then transmitted among humans via respiratory routes, and human-to-human transmission has been confirmed. Human-to-camel transmission requires further clarification. Question marks indicate the unconfirmed phenomena.

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Figure 1

Current theories regarding the MERS-CoV/human/animal interaction

An unknown reservoir may exist in the MERS-CoV transmission cycle. Bats play roles in the context of MERS-CoV transmission, and the virus is transmitted to dromedary camels through an unknown mechanism. The dromedary camels act as viral amplifying hosts. MERS-CoV is transmitted from dromedary camels to humans through respiratory aerosols and other unknown mechanisms. The virus is then transmitted among humans via respiratory routes, and human-to-human transmission has been confirmed. Human-to-camel transmission requires further clarification. Question marks indicate the unconfirmed phenomena.

