

Middle east respiratory syndrome coronavirus and the one health concept

Maged Gomaa Hemida ^{Corresp. 1}

¹ Microbiology and Parasitology, King Faisal University, Al-Hufuf, Al-Hasa, Saudi Arabia

Corresponding Author: Maged Gomaa Hemida
Email address: mhemida@kfu.edu.sa

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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4 **Maged Gomaa Hemida**^{1, 2*}

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7 ¹ Department of Microbiology and Parasitology, College of Veterinary Medicine, King Faisal

8 University, Saudi Arabia. mhemida@kfu.edu.sa

9 ² Department of Virology, Faculty of Veterinary Medicine, Kafrelsheikh University, Egypt.

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11 Corresponding author*

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14 *Maged Hemida: mhemida@kfu.edu.sa; Tel.: +966-53027-0662

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17 **Running title:** MERS-CoV/human/animal interaction

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24 **ABSTRACT:**

25 **Background.** The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) emerged late
26 2012 in the Arabian Peninsula. Whether MERS-CoV originated from bats or from an unknown
27 reservoir has been debated. Dromedary camels are the only identified animal reservoir thus far.
28 Dromedary camels play important roles in sustaining the virus in certain communities. They may
29 amplify the virus by secreting it in their bodily fluids, especially in their nasal and rectal
30 discharges, where it has been detected. MERS-CoVs originating from dromedary camels can
31 fully infect the human airway epithelium in both in vitro and ex vivo models. Other evidence has
32 confirmed the direct transmission of MERS-CoV from camels to humans. Furthermore, the roles
33 of camel meat and milk products remain unclear. Human-to-human transmission via contact with
34 either actively infected patients or silently infected persons is well documented. Infected
35 individuals who have close contact with MERS-CoV-positive patients exhibit some potential risk,
36 which include sleeping in the same room, removing the patient's waste (urine, stool and sputum)
37 and touching respiratory secretions from an index case. Outbreaks within family clusters have
38 been reported since some blood relatives have been infected despite their spouses living in the
39 same house and being uninfected. This suggests that some predisposing genetic factors favor
40 MERS-CoV infection and require further study. Many unknown/unconfirmed aspects exist in the
41 virus/human/animal network. Herein, we discuss the most recent advances in this context and
42 present the possible reasons behind the emergence and sustainability of MERS-CoV in certain
43 regions. Identifying the exact mechanism of MERS-CoV transmission from camels to humans

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

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

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

48 **SURVEY METHODOLOGY**

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

58 **1. Coronaviruses: the past, present, and future**

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

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

83 **2. Coronaviruses and the One Health concept**

84 The One Health concept is a new concept outlining the close interaction between humans,
85 animals and the environment (Destoumieux-Garzon et al. 2018). Currently, two coronavirus
86 candidates represent the One Health concept: SARS-CoV and MERS-CoV. Animals play
87 important roles in the transmission cycles of both viruses (Alshukairi et al. 2018; Wang et al.
88 2005), which are both of zoonotic origin (Gao et al. 2016).

89 3. MERS-CoV in humans

90 MERS-CoV can infect people of all ages and has been documented in patients less than one
91 year old up to 109 years old (CDC 2016). However, children are less likely to be infected with
92 MERS-CoV than are adults, and when infected, children are often asymptomatic or have a
93 milder form of the disease (Arwady et al. 2016). The reason for this remains unclear and requires
94 further study. The case fatality rate remains very high in immunocompromised infected patients,
95 especially those with chronic diseases such as cancer, diabetes, hypertension, and kidney
96 problems (Arwady et al. 2016). Human-to- human transmission has been reported in many cases,
97 and many family clusters have been reported over the past 5 years (Arwady et al. 2016; Drosten
98 et al. 2014; Memish et al. 2013). This confirms the potential spread of MERS-CoV among close-
99 contact populations (Mollers et al. 2015). The most at risk groups for MERS-CoV infection are
100 healthcare workers, camel workers, and the elderly with underlying chronic diseases (Arabi et al.
101 2014). The prevalence rate of MERS-CoV primary cases is higher in men than in women
102 (Darling et al. 2017), possibly because men are more likely to be exposed to infected dromedary
103 camels than are women. MERS-CoV replicates efficiently in various in vitro and ex vivo models
104 (Chan et al. 2014). The virus triggers unique interferon and cytokine gene expression profiles.
105 The virus seems to be a poor interferon inducer (Chan et al. 2014), suggesting potential immune
106 evasion strategies triggered by the virus to hijack the host's immune system. This may be partly
107 responsible for the high case fatality rate. Viral spreading among humans appears highly
108 inefficient at present. People in close contact are among the at-risk groups for infection (Drosten
109 et al. 2014) as has been observed in many family clusters (Alfaraj et al. 2018; Choi et al. 2017;
110 Xiao et al. 2018). This suggests that viral transmission among humans often requires exposure to
111 high viral loads to produce active infections in people in close contact. Several MERS-CoV

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

132 **4. MERS-CoV in animals**

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

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

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

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

203 **5. MERS/human/animal interaction**

204 Human exposure to MERS-CoV-infected dromedary camels is a predisposing factor to
205 human infection, particularly in immunocompromised people (Zumla et al. 2015). Based on the
206 latest WHO reports, the prognosis of MERS-CoV infection is poor for elderly people with
207 chronic diseases such as cancer, diabetes, and kidney failure (Arabi et al. 2014). MERS-CoV
208 transmission from dromedary camels to humans has been demonstrated indirectly in recent
209 reports (Azhar et al. 2014). One study strongly evidenced direct transmission of MERS-CoV
210 from an infected camel to its owner. This was confirmed by comparison via genome sequencing
211 of the virus isolated from the infected dromedary camel to that isolated from its owner. Both
212 viruses shared nearly 100% identity (Azhar et al. 2014). This study also reported the detection of
213 MERS-CoV nucleic acid in air samples from the infected dromedary camel barn during the
214 active course of the viral infection (Azhar et al. 2014). The roles of dromedary camel milk, meat
215 products and byproducts in MERS-CoV transmission is debatable. Experimentally introducing
216 MERS-CoV into raw milk revealed little difference between the viral stock in the milk and that
217 maintained in Dulbecco's modified Eagle's medium (DMEM) (van Doremalen et al. 2014). As a
218 cultural tradition, some Middle Eastern citizens used to drink raw camel milk to seek treatment
219 for diseases such as diabetes. Thus, drinking raw camel milk poses a great risk to those who
220 consume it without heat treatment or pasteurization (van Doremalen et al. 2014; Zhou et al.
221 2017). One study connected an infection in some people to their drinking the milk of one
222 infected camel (Memish et al. 2015). Another study was conducted in Qatar to determine the
223 possibility of becoming infected from the contaminated teats and udder of an infected female
224 camel during milking (Reusken et al. 2014). However, no active MERS-CoV shedding in milk
225 has been reported this far. Further studies are encouraged to conclude the potential roles of raw
226 camel milk in transmitting MERS-CoV. Meanwhile, the role of camel meat in MERS-CoV

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

242 **6. Gaps in the MERS-CoV related research**

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

250 or with few animals/specimens and have reported some important conclusions, which require
251 further confirmation. Further refining some of these observations is needed. Here, we highlight
252 some gaps in the research on MERS-CoV evolution and transmission. Presumably, there may be
253 an unidentified reservoir/s in the MERS-CoV transmission cycle. Although respiratory infection
254 remains the main route for MERS-CoV infection, the exact mechanism of transmission of
255 MERS-CoV from dromedary camels to humans remains to be clarified. Other reservoir/s may
256 exist in the MERS-CoV transmission cycle; thus, there may be a missing link in the chain
257 between humans and camels. Meanwhile, the exact modes of MERS-CoV transmission from
258 dromedary camels to humans remain unclear, and the pattern of natural MERS-CoV infection in
259 dromedary camels requires further study. The potential roles of most camel secretions and
260 excretions are also unclear. Seroprevalence of MERS-CoV was reported in dromedary camels
261 from different countries in Africa and Asia (Ali et al. 2017; Hemida et al. 2014); however, feral
262 camels from Australia and the Canary islands were found to be seronegative (Crameri et al.
263 2015). The reasons behind this phenomenon are unclear. Very few studies have reported cross
264 reactivity between MERS-CoV and other coronaviruses, such as the bovine coronavirus (BCoV),
265 which may infect dromedary camels (Wunschmann et al. 2002). Whether this is the reason
266 behind the high MERS-CoV seroprevalence in dromedary camels is unknown. Whether this is
267 due to the high frequency of exposure to MERS-CoV infection during the camel's life or the
268 crossreactivity of other coronaviruses or due to an unknown mechanism related to the dromedary
269 camel's immune system remains to be determined and requires further study. Demand is ongoing
270 for the development of novel diagnostic assays for coronaviruses. Special interest should be paid
271 to techniques that enable simultaneous detection of the viral nucleic acids and that can
272 distinguish between antibodies for several coronaviruses in the field. Meanwhile, the reason that

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

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

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

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

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

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

304 **9. Current progress on the control of MERS-CoV**

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

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

322 **10. Conclusions**

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

326 **Figure legends**

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

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

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336 paper.

337 **Conflicts of Interest:** The author declares no conflicts of interest.

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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.

