Middle East Respiratory Syndrome Coronavirus and the One Health concept

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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. MERS-CoV is considered an ideal example of the One Health concept. Animals play important roles in the transmission and sustainability of the virus, and the virus can be transmitted through aerosols of infected patients into the environment. However, there is some debate regarding the origin of MERS-CoV either from bats or other unknown reservoirs. The dromedary camel is the only identified animal reservoir to date. These animals play important roles in sustaining the virus incertaincommunities and may act as an amplifier of the virus by secreting it in their body fluids, especially in nasal and rectal discharges. MERS-CoV has been detected in the nasal and rectal secretions of infected camels, and MERS-CoV of this origin has full capacity to infect human airway epithelium in both in vitro and ex vivo models (Chan et al. 2014). Other evidence confirms the direct transmission of MERS-CoV from camels to humans, though the role of camel meat and milk products has yet to be well studied. Human-to-human transmission is well documented through contact with an active infected patient or some silently infected persons. Furthermore, there are some significant risk factors of individuals in close contact with a positive MERS-CoV patient, including sleeping in the same patient room, removing patient waste (urine, stool and sputum), and touching respiratory secretions from the index case. Outbreaks within family clusters have been reported, whereby some blood relative patients were infected though their wives in the same house were not infected. Some predisposing genetic factors favor MERS-CoV infection in some patients, which is worth investigating in the near future. The presence of other comorbidities may be another factor. Overall, there are many unknown/confirmed aspects in the virus/human/animal network. Here, the most recent advances in this context are discussed, and the possible reasons behind the emergence and sustainability of MERS-CoV in certain regions are presented. Identification of the exact mechanism of transmission of MERS-CoV from camels to humans and

searching for new reservoir/s are of high priority. This will reduce the shedding of the virus into the environment, and thus the risk of human infection can be mitigated.

1   **Middle East Respiratory Syndrome Coronavirus and the One Health concept**

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

Abstract:

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26 healthcare systems in some countries, especially in the Arabian Peninsula. MERS-CoV is

27 considered an ideal example of the One Health concept. Animals play important roles in the

28 transmission and sustainability of the virus, and the virus can be transmitted through aerosols of

29 infected patients into the environment. However, there is some debate regarding the origin of

30 MERS-CoV either from bats or other unknown reservoirs. The dromedary camel is the only

31 identified animal reservoir to date. These animals play important roles in sustaining the virus

32 in certain communities and may act as an amplifier of the virus by secreting it in their body fluids,

33 especially in nasal and rectal discharges. MERS-CoV has been detected in the nasal and rectal

34 secretions of infected camels, and MERS-CoV of this origin has full capacity to infect human

35 airway epithelium in both in vitro and ex vivo models (Chan et al. 2014). Other evidence confirms

36 the direct transmission of MERS-CoV from camels to humans, though the role of camel meat and

37 milk products has yet to be well studied. Human-to-human transmission is well documented

38 through contact with an active infected patient or some silently infected persons. Furthermore,

39 there are some significant risk factors of individuals in close contact with a positive MERS-CoV

40 patient, including sleeping in the same patient room, removing patient waste (urine, stool and

41 sputum), and touching respiratory secretions from the index case. Outbreaks within family

42 clusters have been reported, whereby some blood relative patients were infected though their

43 wives in the same house were not infected. Some predisposing genetic factors favor MERS-CoV

44   infection in some patients, which is worth investigating in the near future. The presence of other

45   comorbidities may be another factor. Overall, there are many unknown/confirmed aspects in the

46   virus/human/animal network. Here, the most recent advances in this context are discussed, and

47   the possible reasons behind the emergence and sustainability of MERS-CoV in certain regions

48   are presented. Identification of the exact mechanism of transmission of MERS-CoV from camels

49   to humans and searching for new reservoir/s are of high priority. This will reduce the shedding

50   of the virus into the environment, and thus the risk of human infection can be mitigated.

51

52 1. Introduction

53 The main reason behind developing this article is to summarize the current understanding about

54 MERS-CoV in the context of the One Health concept. In this article, I highlight the known

55 information about the MERS-CoV infection and its pathogenesis in humans, the patterns of

56 MERS-CoV in dromedary camels, the potential roles of other animals in the transmission cycle

57 of MERS-CoV, and the interaction of MERS-CoV/humans/animals. I elaborate on how some

58 strategies can be used to stop or reduce the frequencies of MERS-CoV outbreaks based on the

59 One Health concept, identified some gaps in the literature, and drew conclusions.

60 SURVEY METHODOLOGY

61

62 For this review article, I conducted a literature search of the most up-to-date published articles on

63 MERS-CoV in the past 7 years. First, I focused the introduction section on the historical

64 background of coronaviruses and the One Health concept. Then, I highlighted the most up-to-

65 date literature from PubMed central, Google Scholar and ResearchGate on the interaction of

66 MERS-CoV/humans/animals. I identified some important gaps in the research dealing with

67 MERS-CoV/human/environment in the context of the One Health concept. I also summarized the

68 current acceptable theories on the emergence and evolution of MERS-CoV. Finally, I highlighted

69 progress to date in the control of MERS-CoV.

70 **2. Coronaviruses: the past, present, and future**

71   Coronaviruses are a large group of viruses causing many health problems (respiratory,

72 enteric, and nervous syndromes) in various species of animals and humans. Six human

73 coronaviruses that have been identified to date (HCoV-229E, HCoV-OC43, HCoV-NL-63,

74 HCoV-HUK-1, SARS-CoV, and MERS-CoV). Two of them emerged in the past 15 years (Lau

75 & Chan, 2015), namely, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the

76 Middle East respiratory syndrome coronavirus (MERS-CoV). SARS-CoV emerged in 2003 in

77 China and spread to many countries throughout the world (Peiris *et al.*, 2003). Approximately

78 8000 people were infected, and 10% of them died (Aronin & Sadigh, 2004). Only 9 years later,

79 MERS-CoV emerged in Saudi Arabia (Zaki *et al.*, 2012). This is a relatively short period for the

80 emergence of a new coronavirus. One of the main reasons behind the rapid emergence of new

81 coronaviruses is the poor proofreading capability of their RNA polymerases (Hofer, 2013). This

82 is in addition to the possibility of the recombination of different coronaviruses (Makino *et al.*,

83 1986), and it will not be surprising if new coronaviruses emerge in the near future. MERS-CoV

84 continues to pose great challenges to the healthcare system of some countries in the Middle East

85 and Arabian Peninsula. Since its discovery late in 2012 (Zaki et al., 2012), there are ongoing

86 reports to the World Health Organization (WHO) from some countries in the Middle East,

87 especially the Arabian Peninsula, with spread to other countries around the globe, especially

88   from the Middle East. According to the latest WHO statistics, there have been a total of 2,266

89   laboratory-confirmed cases of MERS-CoV infection including at least 804 deaths (reported case

90   fatality rate of 35.0 %) (WHO, 2018). The continuous ongoing reports on MERS-CoV

91   suggesting the presence of some factors favor its sustainability in certain regions. There are

92   many uncertain aspects of the virus evolution, pathogenesis, and transmission cycle.

93   Unfortunately, recently, there was a sharp decline in the rate of research on the virus from

94   different aspects. This hampered the production of new data about the MERS-CoV from

95   different aspects. Below, I summarize the current understanding of the virus in the context of the

96   One Health concept.

97   **3. Coronaviruses and the One Health concept**

98   The One Health concept is a new concept outlining the close interaction among humans, animals

99   and the environment (Destoumieux-Garzon *et al.*, 2018). Currently, there are two coronaviruses

100   candidates representing the One Health Concept, the SARS-CoV and the MERS-CoV. Animals

101   play important roles in the transmission cycle of both viruses (Alshukairi *et al.*, 2018, Wang *et*

102   *al.*, 2005). Both viruses were proven to be of zoonotic origin (Gao *et al.*, 2016).

103   **4. MERS-CoV in Humans**

104   MERS-CoV may infect a wide group of people ranging from very young ages, even infants

105   less than one year of age, to 109 years of age (CDC, 2016). However, children are less likely to

106   be infected with MERS-CoV when compared to adults, and if infected, they tend to have

107   asymptomatic or mild disease (Arwady *et al.*, 2016). The reason for this is still not entirely clear

108   and requires further study. The case fatality rate is always very high in case of the

109   immunocompromised infected patients especially those who are suffering from chronic diseases

110   such as cancer, diabetes, blood pressure, kidney problems, etc. (Arwady et al., 2016). Human-to-

111   human transmission is reported in many cases. MERS-CoV replicates efficiently in various in

112   vitro and ex vivo models (Chan *et al.*, 2014). Moreover, many family clusters and hospital

113   outbreaks were reported in the past 5 years (Arwady et al., 2016; Drosten *et al.*, 2014 Memish *et*

114   *al.*, 2013). This confirms the potential spread of MERS-CoV among those who are in close

115   contact in the population (Mollers *et al.*, 2015). The most at-risk groups are healthcare workers

116   including nurses, medical doctors and other hospital staff and the elderly with underlying chronic

117   diseases (Arabi *et al.*, 2014). The prevalence rate of MERS-CoV in primary cases among males

118   is relatively higher than that of females (Darling *et al.*, 2017), which may be because exposure to

119   infected dromedary camels is much higher in males than in females. The virus triggers some

120   unique interferons and cytokine gene expression profiles. The virus seems to be a poor interferon

121   inducer (Chan et al., 2014). This suggests the potential immune evasion strategies triggered by

122   the virus to hijack the host immune system and may be responsible for the high fatality rate, at

123   least in part. Viral spreading among people seems to not yet be very efficient. Those in close

124   contact are among the at-risk groups for infection (Drosten et al., 2014), as observed in many

125   hospital outbreaks as well as family clusters (Alfaraj *et al.*, 2018, Choi *et al.*, 2017, Xiao *et al.*,

126   2018). This suggests that transmission of the virus among people requires exposure to a high

127   viral load, which will sometimes produce active infection in people who are in close contact.

128   Several MERS-CoV family clusters have been reported (Drosten et al., 2014). Interestingly,

129   MERS-CoV is reported in the dromedary camels in many African countries (Egypt, Nigeria,

130   Tunisia, and Ethiopia), but no primary human cases have been reported in these countries to date

131   (Ali *et al.*, 2017; Roess *et al.*, 2016; van Doremalen *et al.*, 2017), which may be related to some

132   variation in the circulating Asian and African strains of MERS-CoV. Some important deletions

133 in the MERS-CoV currently circulating in dromedary camels from Africa were recently reported

134 (Chu *et al.*, 2018). These deletions may explain at least in part the reason behind the variations in

135 the pathogenesis among the Asian and African strains of MERS-CoV. MERS-CoV infection

136 varies from severe respiratory illness accompanied by a high fever and respiratory distress to

137 mild asymptomatic cases. Patients are usually admitted to the intensive care unit (ICU) and

138 provided with a source of oxygen. Most cases result in pneumonia, which is fatal in almost 40%

139 of the affected patients (Hong *et al.*, 2017; Rubio *et al.*, 2018). Some patients may develop renal

140 failure [13]. Several MERS-CoV travel-associated infections were in many cases associated with

141 the Middle East (Bayrakdar *et al.*, 2015, Rubio et al., 2018). Among these reported was the

142 Korean outbreak in early 2015 (Choi et al., 2017; Kim *et al.*, 2017; Xiao et al., 2018). One

143 Korean citizen visited some countries in the Middle East and then returned home ill. This person

144 visited several healthcare facilities in Korea. This resulted in the largest MERS-CoV human

145 outbreak outside the Arabian Peninsula (Xiao et al., 2018). This outbreak confirmed the human-

146 to-human transmission. During this outbreak, MERS-CoV was isolated from air samples from

147 the hallways of the healthcare facilities close to the hospitalized patients (Xiao et al., 2018). This

148 at least explains in part the rapid development of MERS-CoV hospital outbreaks.

149 **5. MERS-CoV in animals**

150 Since the discovery of MERS-CoV late in 2012 (Zaki et al., 2012), many research groups

151 have searched for its potential animal reservoir/s. Dromedary camels are the only currently

152 proven reservoir for MERS-CoV (Hemida *et al.*, 2014; Hemida *et al.*, 2017b; Reusken *et al.*,

153 2014; Reusken *et al.*, 2016). Interestingly, others were able to trace the virus back 30 years ago

154 in dromedary camel specimens in retrospective studies (Corman *et al.*, 2014; Hemida et al.,

155 2014; Reusken et al., 2014). All these data suggest that the virus has been circulating for decades

156   without it being recognized. Although the actual and typical clinical features of the MERS-CoV

157   natural infection in dromedary camels is not well documented to date, very few studies reported

158   these patterns under experimental infection approaches (Adney *et al.*, 2014). Based on these

159   findings, camels do not show any pathognomonic signs despite a subtle fever and mild nasal

160   discharge for up to 6 days post-infection (dpi) (Hemida et al., 2014). Meanwhile, shedding of the

161   infectious virus was reported in the experimentally infected camels started at 2 dpi up to the 7th

162   dpi (Adney et al., 2014). Interestingly, viral RNA was still detected at 35 dpi (Adney et al.,

163   2014), though it is not known whether the viral RNAs may act as potential sources of infection

164   similar to some other positive-sense RNA viruses. No viral shedding in the oral secretions, rectal

165   swabs, urine, or sera of these animals has been reported (Adney et al., 2014), in contrast to the

166   detection of the virus in the fecal specimens and swabs under natural viral field infection

167   (Hemida et al., 2014). This finding suggests differential patterns of MERS-CoV infection

168   between natural and experimental approaches. Further studies are required to understand the

169   natural MERS-CoV infection in dromedary camels, which may be achieved by conducting long-

170   term longitudinal studies as well as careful monitoring of the virus infection in large populations

171   of camels. On necropsy examination of MERS-CoV, experimentally infected dromedary camels

172   revealed only mild-to-moderate inflammatory reactions in the upper respiratory tract (Khalafalla

173   *et al.*, 2015). Detection of the viral antigens in the tissue sections of the turbinate bone and the

174   upper respiratory tract was reported (Adney et al., 2014). Interestingly, seroconversion of the

175   inoculated animals was reported to begin at 14 dpi (Hemida et al., 2014), indicating that MERS-

176   CoV induces a robust humoral immune response after infection. More recently, one longitudinal

177   study reported the possibility of MERS-CoV infection in seropositive animals. This raises

178   concern about the role of the antibodies in the protection of the MERS-CoV infection (Hemida *et*

179 *al.*, 2017a). It seems that all the members of the family Camelidae (dromedary, alpaca, and

180 llamas) are susceptible to MERS-CoV infection (Corman et al., 2014, Vergara-Alert *et al.*,

181 2017). David et al. (2018) reported the presence of antibodies against MERS-CoV in some

182 alpacas and llamas in Israel but only used commercial ELISA kits, and they did not address the

183 possibility of cross-reactivity with other coronaviruses especially BCoV. It had been previously

184 showed that there is clear cross-reactivity between MERS-CoV and BCoV in dromedary camels

185 (David *et al.*, 2018). Interestingly, one study showed an absence of any detectable antibodies of

186 MERS-CoV in the sera of Bactrian camels (Chan *et al.*, 2015), though this is the only study to

187 report this finding concerning the seronegativity of Bactrian camels to MERS-CoV. It is not well

188 known whether the absence of detectable MERS-CoV antibodies in the sera of Bactrians camels

189 is due to the geographical location of the tested animals in Mongolia, far from the Middle East

190 and Africa. This may be supported by similar findings in dromedary camels in Australia and the

191 Canary Islands (Crameri *et al.*, 2015). Another possibility is that this might be due to some

192 genetic factors, which contribute to the resistance of Bactrians to MERS-CoV infections; this

193 point is worthy of further investigation. Experimental MERS-CoV infection in both alpacas and

194 llamas showed a similar pattern to that of dromedary camels (Crameri *et al.*, 2016; Vergara-Alert

195 et al., 2017), which suggested that both animals might act as a model animal for the study of

196 MERS-CoV *in vivo*. However, the experimental infection of pigs with MERS-CoV did not

197 reveal as much infection as that reported in alpacas and llamas (Vergara-Alert et al., 2017).

198 Active MERS-CoV particles were neither retrieved from the experimentally infected animals nor

199 from the close contact non-infected animals during the duration of this study (Vergara-Alert et

200 al., 2017). This result suggested that pigs might not play an active role in the transmission of

201 MERS-CoV. Although bats are considered the main reservoir for many coronaviruses, their roles

202 in the MERS-CoV still need further clarifications. One study reported the presence of MERS-

203 CoV in one specimen collected from bats in Saudi Arabia. The genome sequence of this

204 particular virus showed almost 100% identity to a MERS-CoV index case (Memish et al., 2013).

205 More recently, Jamaican fruit bats were found to be permissible for MERS-CoV infection

206 (Munster *et al.*, 2016). However, MERS-CoV-infected bats did not show any apparent clinical

207 signs; however, viral shedding was reported in the swabs from bats up to 9 dpi. The clinical

208 profiles and viral shedding curve during the course of the MERS-CoV infection in these bats

209 look similar to that of dromedary camels (Munster et al., 2016), yet the amount of infectious

210 viral shedding in bats is less compared to that in dromedary camels. This species of bat is not the

211 most relevant for MERS-CoV infection, but this study offers some insights into the molecular

212 pathogenesis of MERS-CoV in bats. Interestingly, another study revealed the expression of

213 MERS-CoV receptors (dipeptidyl peptidase-4, DPP4) in the respiratory and digestive tracts of

214 some insectivorous bats (Widagdo *et al.*, 2017). An interesting study tested the potential roles of

215 other species in the transmission of MERS-CoV such as cattle, sheep, goats, donkeys, buffaloes,

216 mules, and horses from Egypt, Tunisia and Senegal (Kandeil *et al.*, 2019). This study revealed

217 the presence of neutralizing antibodies in the sera of some sheep and goats. Meanwhile, viral

218 RNA was detected in swabs collected from some sheep, goats and donkeys from these countries

219 (Kandeil et al., 2019). Several attempts were made to identify an appropriate experimental

220 animal model for MERS-CoV. The Syrian hamster was non-permissive to MERS-CoV infection

221 (de Wit *et al.*, 2013). Experimental infection of this animal neither develops any clinical signs or

222 pathology nor produces any cytokines after infection (de Wit et al., 2013). This was in contrast to

223 New Zealand white rabbits, which showed active infection after inoculation with the MERS-

224 CoV (Monchatre-Leroy *et al.*, 2017). Furthermore, both rhesus macaques and common

225   marmosets supported MERS-CoV infection (Yu *et al.*, 2017). Additionally, both the transgenic

226   and the transduced mice expressing the dipeptidyl peptidase 4 human receptors worked as a

227   model for MERS-CoV studies (Zhao *et al.*, 2015).

228   **6. MERS/human/animal interaction**

229   It is now well accepted that human exposure to MERS-CoV-infected dromedary camels is a

230   predisposing factor to human infection, particularly in immunocompromised people (Zumla *et*

231   *al.*, 2015). Based on the latest WHO reports, the prognosis of MERS-CoV infection is poor for

232   elderly patients who have chronic diseases such as cancer, diabetes, kidney failure, etc. (Arabi et

233   al., 2014). Transmission of MERS-CoV from dromedary camels to humans has been proven

234   indirectly in some recent reports (Azhar *et al.*, 2014). One study showed strong evidence of

235   direct transmission of MERS-CoV from an infected camel to its owner, which was confirmed by

236   comparing the viral genome sequencing of the virus isolated from the infected dromedary camel

237   to that isolated from its owner. Both viruses were almost a 100% match (Azhar et al., 2014).

238   Meanwhile, this study reported the detection of MERS-CoV nucleic acid in air samples from the

239   indicated dromedary camel barn during the active course of the viral infection (Azhar et al.,

240   2014).

241   There is a debate about the role of the dromedary camel's milk and meat products and by-

242   products in the transmission of MERS-CoV. Experimental introduction of MERS-CoV to raw

243   milk revealed little difference between the virus stock in milk and that kept in DMEM (van

244   Doremalen *et al.*, 2014). Due to their culture, some people in the Middle East would drink raw

245   camel milk in efforts to seek treatment for some diseases such as diabetes. The authors

246   acknowledge that MERS-CoV was introduced into the dromedary camel milk at a high dose and

247   that the viral RNA was detected in a limited concentration in the camel's milk (van Doremalen et

248   al., 2017). Thus, drinking the raw camel milk poses a great risk to the people consuming this

249   milk without any heat treatment or pasteurization (van Doremalen et al., 2014, Zhou *et al.*,

250   2017). One study connected the infection of some people to the drinking of the milk from one

251   infected camel (Memish *et al.*, 2015). However, another study was conducted in Qatar to assess

252   the possibility of acquiring the infection from contaminated teats and udders of infected she-

253   camels during the process of milking (Reusken et al., 2014), though no active MERS-CoV

254   shedding in milk has yet to be reported. Further studies are encouraged to come to a conclusion

255   about the potential role of raw camel milk in the transmission of MERS-CoV. Nonetheless, the

256   role of camel meat in the transmission of MERS-CoV has not been studied carefully to date.

257   Thus, special attention should be paid to the efficient cooking of camel meat and its products as

258   well as thorough boiling of camel milk. It is suggested that people not drink raw camel milk to

259   avoid any risk of infection not only with MERS-CoV but also with other pathogens such as

260   Brucella (Garcell *et al.*, 2016). Some studies reported that MERS-CoV is one of the occupational

261   zoonotic viral diseases, as was claimed based on some studies investigating the seroconversion

262   of some at-risk group of people to MERS-CoV. This study reported the presence of specific

263   MERS-CoV antibodies in approximately 3 % of the workers in some slaughterhouses in Qatar

264   (Farag *et al.*, 2015). On the other hand, some studies reported the absence of any detectable

265   antibodies in the sera of some herdsmen, veterinarians, and slaughterhouses in Saudi Arabia

266   (Hemida *et al.*, 2015). One possible explanation for the variations between the two studies is the

267   difference in the sensitivity of the techniques used. Those two studies used two different

268   techniques to report the presence/absence of the MERS-CoV antibodies in the sera of at-risk

269 people (Farag et al., 2015; Hemida et al., 2015). Regardless, further investigation on a large-scale

270 basis is required to solidify this conclusion about MERS-CoV.

271 **7. Gaps on the MERS-CoV-related research**

272 There is more to be known about the molecular biology of MERS-CoV. Identification of the

273 DPP-4 as viral receptors does not rule out the presence of other co-receptors or

274 transcription/translation factors that favor the virus infection in a certain host. There are many

275 immune evasion strategies triggered by MERS-CoV to hijack the host immune responses, and

276 the mechanisms of such strategies have not been well studied. Moreover, there are many

277 unknown aspects especially in the context of the MERS-CoV/human/animal interaction.

278 Meanwhile, some studies were conducted on a small scale or with low numbers of

279 animals/specimens and reported some important conclusion. These studies need further

280 confirmation, and refinement of some of these observations is urgently needed in the near future.

281 Here, we highlight some gaps in the research regarding the evolution and transmission of MERS-

282 CoV. Presumably, there might be an unidentified reservoir in the transmission cycle of MERS-

283 CoV. Although respiratory infection still is the main route of MERS-CoV infection, the exact

284 mechanism of transmission of MERS-CoV from dromedary camels to humans is still not well

285 understood. The possibility of another reservoir in the transmission cycle of MERS-CoV has not

286 been ruled out. Thus, there might be a missing link in the chain of the human/camel interaction.

287 Meanwhile, the exact modes of transmission of MERS-CoV from dromedary camels to humans

288 have not been well clarified, and the typical pattern of the natural MERS-CoV infection in

289 dromedary camels has not been well studied. Additionally, the potential role of most camel

290 secretions and excretions has not been fully understood. The seroprevalence of MERS-CoV was

291 reported in the dromedary camels from different countries in Africa and Asia (Ali et al., 2017;

Hemida et al., 2014), though feral camels in Australia and the Canary islands were found to be

293 seronegative (Crameri et al., 2015). The reason behind this phenomenon may be due to these

294 regions being isolated lands and away from the MENA region as described above; it may also be

295 due to the absence of an active camel movement between the Middle East and Africa and these

296 regions of the world. Very few studies reported the cross-reactivity between MERS-CoV and

297 other coronaviruses such as the bovine coronavirus (BCoV) that might infect dromedary camels.

298 It is unknown if this might be the reason behind the high seroprevalence of MERS-CoV among

299 the dromedary camel population. This may be due to the high frequency of exposure to the

300 MERS-CoV infection during the camel's life, the cross-reactivity of other coronaviruses, or an

301 unknown mechanism related to the dromedary camel's immune system. These considerations

302 require further studies. There is ongoing demand for the development of novel diagnostic assays

303 for coronaviruses, and special interest should be paid to those techniques that enable the

304 simultaneous detection of the viral nucleic acids and those that can simultaneously distinguish

305 between the antibodies for several coronaviruses. Furthermore, it is not well understood why

306 only the Bactrian camels among the family Camelidae did not seroconvert to MERS-CoV

307 infection (Chan et al., 2015). The genetic susceptibility of certain human populations, especially

308 blood-related people, is not clear in the context of MERS-CoV infection. There are several levels

309 of human exposure to dromedary camels, such as camel attendants, workers in camel abattoirs,

310 veterinarians inspecting their carcasses, and camel owners. Those groups of people are in close

311 contact with camels for various amounts of time and are considered to be a high-risk group of

312 people due to the long time they spend in close contact with the dromedary camels. Meanwhile,

313 there is an urgent need to develop a risk scoring system for human exposure to the dromedary

314 camels.

8. Current theories in the MERS-CoV/human/animals interaction

It is believed that there is some unidentified reservoirs in the context of MERS-CoV transmission presenting the virus to the community. This virus is able to infect dromedary camels, which act as an amplifier host for the virus, favoring the circulation of the virus in some camel herds. The virus has the ability to circulate among the animals in the same herd and the camel herds in close proximity to them (Figure 1). MERS-CoV in camels has the full potential to infect the human especially immunocompromised persons. Once the virus infects a human, there is always a possibility of infecting other people, especially closely-related individuals (figure 1), including household relatives and workers plus healthcare workers such as doctors and nurses. Infection depends on the level of exposure to the infected person, and MERS-CoV infection in humans ranges from very severe cases of pneumonia to death. Currently available data indicate that severely infected individuals can shed the infectious virus into the environment (Kim *et al.*, 2016), though there are few data regarding the capacity of mildly infected individuals to transmit the virus. Asymptomatic individuals, however, are unlikely to transmit the virus (Moon & Son, 2017).

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

There are many factors behind the emergence, sustainability and spread of MERS-CoV. The presence of an unidentified MERS-CoV reservoir in the transmission cycle is still considered, and this unknown reservoir may contribute substantially to the suitability of the virus in certain regions. Dromedary camels remain the amplifier of the virus; the close contact of these animals to the human population in certain regions of Africa and Asia may pose a great risk for human infection and indirectly contribute to the spread of the virus. Additionally, public animal markets,

337   especially for dromedary camels, may act as an amplifier of the virus. This poses a great risk to

338   the surrounding community. The lack of active surveillance programs for respiratory viruses,

339   especially coronaviruses, may result in many subclinical or mild cases of MERS-CoV being

340   missed in a certain population. These patients may shed the virus in their secretions and may act

341   as a source of infection to other persons in close contact with them. Although many MERS-CoV

342   vaccine and drug candidates are being researched, none are available yet. All these factors may

343   favor the sustainability of MERS-CoV in certain regions.

344   **10. Current progress on the control of MERS-CoV**

345   Interestingly, the case fatality rate of MERS-CoV among the affected population dropped from

346   almost 50% in 2012 to 34 % early 2019 (WHO, 2018), and we may relate this progress in the

347   control of MERS-CoV over the past 7 years to many factors. First, identification of the main

348   reservoir of the virus, namely, the dromedary camel (Hemida et al., 2014). Second, continuous

349   molecular and serological surveillance of MERS-CoV among the dromedary camel population in

350   the Arabian Peninsula and Africa (Corman et al., 2014; Farag et al., 2015; Hemida et al., 2017a;

351   Hemida et al., 2017b; Khalafalla et al., 2015; Reusken et al., 2014). Currently, testing the

352   population of camels in regional camel markets is associated with shutting down of the market in

353   case of positive shedding of MERS-CoV by the animals. I believe this will substantially

354   minimize the risk of community-acquired infections through these positive populations. Third,

355   vaccination of dromedary camels, especially animals under two years of age, will have a great

356   impact on the reduction of the viral shedding from these animals to the surrounding community.

357   This will also have a great positive impact on the reduction of the number of reported human

358   infections. Fourth, there has been progress in the current understanding of viral tropism,

359   pathogenesis, and mode of transmission in the past five years (Chan et al., 2014; Widagdo et al.,

360 2017). Fifth, new strategies have been adopted to reduce the spread of infection in health care

361 units (Rajakaruna *et al.*, 2017). Sixth, some therapeutic and control approaches for MERS-CoV

362 such as cyclosporine, ribavirin and interferon show promising trends for the treatment of MERS-

363 CoV-infected patients (Al-Tawfiq *et al.*, 2014; de Wilde *et al.*, 2013). Meanwhile, good progress

364 has been made in screening large numbers of drugs/therapies for the treatment of MERS-CoV

365 (Han *et al.*, 2018; He *et al.*, 2019; Niu *et al.*, 2018; Totura & Bavari, 2019). This may lead to the

366 development of some effective novel drugs against MERS-CoV infection in the near future.

367 **11. One Health-based interventions to stop MERS-CoV outbreaks**

368 To stop MERS-CoV outbreaks, there are several strategies to be adopted in the context of the

369 One Health concept. Some strategies are related to the animal, while others are related to human

370 health. The main objective is to minimize or stop the viral shedding from dromedary camels to

371 the environment (Figure 2). This may be achieved in many ways including regular monitoring of

372 the population of dromedary camels. Active animal shedders need to be identified, and

373 quarantine measures should applied until they stop shedding the virus. Vaccination of young

374 dromedary camel calves should occur during their first 6 months of life, which will minimize the

375 chances of these animals becoming infected and actively passing the virus to older animals and

376 then to the environment. Reorganization and reshaping of the camel industry includes allocating

377 the camel markets away from the cities. Global awareness concerning the necessity of thorough

378 boiling and cooking of the camel milk and meat products, respectively, should take place.

379 Animal abattoirs should be established far away from large cities. They should not use mixed-

380 animal platforms, and each platform should deal with one species of animal. Thorough

381 decontamination of animals' biological wastes in abattoirs should occur using the appropriate

382 standard protocols. Regular surveillance of MERS-CoV among the population especially during

383   the active peak of virus shedding by the animals should occur during November to April every

384   year. People who are in close contact with the camels should wear proper personal protective

385   equipment at all times.

386   **12. Conclusions**

387   At almost 7 years after its emergence, there are ongoing reports of MERS-CoV infection from

388   time to time. This may be related to many unknown aspects of the viral evolution and pathogenesis.

389   Some of these unknown aspects are the following. (1) Little is still known about virus/host

390   interactions and how MERS-CoV hijacks the host immune system. (2) Potential reservoirs in the

391   context of the MERS-CoV/human/animal network need to be identified. (3) Why do MERS-CoV-

392   infected dromedary camels not exhibit obvious clinical signs during active viral shedding? (4)

393   Does the presence of neutralizing antibodies in the sera of animals protect them against future

394   active infection by the virus? (5) Does vaccination of dromedary camels have a positive impact on

395   controlling the spread of MERS-CoV among dromedary camels? More research is urgently needed

396   to explore the unknown aspects of the MERS-CoV/human/animal network.

397   **Figure legends**

398

399   **Figure 1: Current acceptable theories in the MERS-CoV/human/animals interaction**

400   There might be an unknown reservoir in the transmission cycle of MERS-CoV. Bats play a

401   role in the context of MERS-CoV transmission. The virus is transmitted to dromedary camels

402   through an unknown mechanism. The dromedary camels act as amplifying hosts for the virus.

403   MERS-CoV is transmitted from dromedary camels to humans through the respiratory aerosols and

404   some other unknown mechanisms. The virus is then transmitted among the human population

405   through respiratory routes. The human-to-human transmission has been confirmed. The human-

406   to-camel transmission still needs further clarification. Question marks indicate the non-confirmed

407   phenomenon.

408

409   **Figure 2. Some interventions based on the One Health-based to stop MERS-CoV outbreaks**

410   **References**

411   Adney, D. R., N. van Doremalen, V. R. Brown, T. Bushmaker, D. Scott, E. de Wit, R. A. Bowen and V. J.
412   Munster, 2014: Replication and shedding of MERS-CoV in upper respiratory tract of inoculated
413   dromedary camels. *Emerg Infect Dis,* **20,** 1999-2005.
414   Al-Tawfiq, J. A., H. Momattin, J. Dib and Z. A. Memish, 2014: Ribavirin and interferon therapy in patients
415   infected with the Middle East respiratory syndrome coronavirus: an observational study. *Int J*
416   *Infect Dis,* **20,** 42-46.
417   Alfaraj, S. H., J. A. Al-Tawfiq, T. A. Altuwaijri, M. Alanazi, N. Alzahrani and Z. A. Memish, 2018: Middle
418   East respiratory syndrome coronavirus transmission among health care workers: Implication for
419   infection control. *Am J Infect Control,* **46,** 165-168.
420   Ali, M. A., M. M. Shehata, M. R. Gomaa, A. Kandeil, R. El-Shesheny, A. S. Kayed, A. N. El-Taweel, M.
421   Atea, N. Hassan, O. Bagato, Y. Moatasim, S. H. Mahmoud, O. Kutkat, A. M. Maatouq, A. Osman,
422   P. P. McKenzie, R. J. Webby and G. Kayali, 2017: Systematic, active surveillance for Middle East
423   respiratory syndrome coronavirus in camels in Egypt. *Emerg Microbes Infect,* **6,** e1.
424   Alshukairi, A. N., J. Zheng, J. Zhao, A. Nehdi, S. A. Baharoon, L. Layqah, A. Bokhari, S. M. Al Johani, N.
425   Samman, M. Boudjelal, P. Ten Eyck, M. A. Al-Mozaini, J. Zhao, S. Perlman and A. N. Alagaili,
426   2018: High Prevalence of MERS-CoV Infection in Camel Workers in Saudi Arabia. *MBio,* **9.**
427   Arabi, Y. M., A. A. Arifi, H. H. Balkhy, H. Najm, A. S. Aldawood, A. Ghabashi, H. Hawa, A. Alothman,
428   A. Khaldi and B. Al Raiy, 2014: Clinical course and outcomes of critically ill patients with Middle
429   East respiratory syndrome coronavirus infection. *Ann Intern Med,* **160,** 389-397.
430   Aronin, S. I. and M. Sadigh, 2004: Severe acute respiratory syndrome. *Conn Med,* **68,** 207-215.
431   Arwady, M. A., B. Alraddadi, C. Basler, E. I. Azhar, E. Abuelzein, A. I. Sindy, B. M. Sadiq, A. O.
432   Althaqafi, O. Shabouni, A. Banjar, L. M. Haynes, S. I. Gerber, D. R. Feikin and T. A. Madani, 2016:
433   Middle East Respiratory Syndrome Coronavirus Transmission in Extended Family, Saudi Arabia,
434   2014. *Emerg Infect Dis,* **22,** 1395-1402.
435   Azhar, E. I., A. M. Hashem, S. A. El-Kafrawy, S. S. Sohrab, A. S. Aburizaiza, S. A. Farraj, A. M. Hassan, M.
436   S. Al-Saeed, G. A. Jamjoom and T. A. Madani, 2014: Detection of the Middle East respiratory
437   syndrome coronavirus genome in an air sample originating from a camel barn owned by an
438   infected patient. *MBio,* **5,** e01450-01414.

439   Bayrakdar, F., A. B. Altas, G. Korukluoglu and S. Topal, 2015: [Molecular diagnosis and phylogenetic
440   analysis of the first MERS case in Turkey]. *Mikrobiyol Bul*, **49,** 414-422.
441   CDC, 2016: Coronavirus | Home | CDC. (2016). gov. *Retrieved 26 December 2016, from*
442   *https://www.cdc.gov/coronavirus/*.
443   Chan, R. W., M. G. Hemida, G. Kayali, D. K. Chu, L. L. Poon, A. Alnaeem, M. A. Ali, K. P. Tao, H. Y. Ng,
444   M. C. Chan, Y. Guan, J. M. Nicholls and J. S. Peiris, 2014: Tropism and replication of Middle East
445   respiratory syndrome coronavirus from dromedary camels in the human respiratory tract: an in-
446   vitro and ex-vivo study. *Lancet Respir Med*, **2,** 813-822.
447   Chan, S. M., B. Damdinjav, R. A. Perera, D. K. Chu, B. Khishgee, B. Enkhbold, L. L. Poon and M. Peiris,
448   2015: Absence of MERS-Coronavirus in Bactrian Camels, Southern Mongolia, November 2014.
449   *Emerg Infect Dis*, **21,** 1269-1271.
450   Choi, S., E. Jung, B. Y. Choi, Y. J. Hur and M. Ki, 2017: High reproduction number of Middle East
451   respiratory syndrome coronavirus in nosocomial outbreaks: mathematical modelling in Saudi
452   Arabia and South Korea. *J Hosp Infect*.
453   Chu, D. K. W., K. P. Y. Hui, R. Perera, E. Miguel, D. Niemeyer, J. Zhao, R. Channappanavar, G. Dudas, J.
454   O. Oladipo, A. Traore, O. Fassi-Fihri, A. Ali, G. F. Demissie, D. Muth, M. C. W. Chan, J. M.
455   Nicholls, D. K. Meyerholz, S. A. Kuranga, G. Mamo, Z. Zhou, R. T. Y. So, M. G. Hemida, R. J.
456   Webby, F. Roger, A. Rambaut, L. L. M. Poon, S. Perlman, C. Drosten, V. Chevalier and M. Peiris,
457   2018: MERS coronaviruses from camels in Africa exhibit region-dependent genetic diversity. *Proc*
458   *Natl Acad Sci U S A*.
459   Corman, V. M., J. Jores, B. Meyer, M. Younan, A. Liljander, M. Y. Said, I. Gluecks, E. Lattwein, B. J. Bosch,
460   J. F. Drexler, S. Bornstein, C. Drosten and M. A. Muller, 2014: Antibodies against MERS
461   coronavirus in dromedary camels, Kenya, 1992-2013. *Emerg Infect Dis*, **20,** 1319-1322.
462   Crameri, G., P. A. Durr, J. Barr, M. Yu, K. Graham, O. J. Williams, G. Kayali, D. Smith, M. Peiris, J. S.
463   Mackenzie and L. F. Wang, 2015: Absence of MERS-CoV antibodies in feral camels in Australia:
464   Implications for the pathogen's origin and spread. *One Health*, **1,** 76-82.
465   Crameri, G., P. A. Durr, R. Klein, A. Foord, M. Yu, S. Riddell, J. Haining, D. Johnson, M. G. Hemida, J.
466   Barr, M. Peiris, D. Middleton and L. F. Wang, 2016: Experimental Infection and Response to
467   Rechallenge of Alpacas with Middle East Respiratory Syndrome Coronavirus. *Emerg Infect Dis*,
468   **22,** 1071-1074.
469   Darling, N. D., D. E. Poss, M. P. Schoelen, M. Metcalf-Kelly, S. E. Hill and S. Harris, 2017: Retrospective,
470   epidemiological cluster analysis of the Middle East respiratory syndrome coronavirus (MERS-
471   CoV) epidemic using open source data. *Epidemiol Infect*, **145,** 3106-3114.
472   David, D., D. Rotenberg, E. Khinich, O. Erster, S. Bardenstein, M. van Straten, N. M. A. Okba, S. V. Raj, B.
473   L. Haagmans, M. Miculitzki and I. Davidson, 2018: Middle East respiratory syndrome
474   coronavirus specific antibodies in naturally exposed Israeli llamas, alpacas and camels. *One*
475   *Health*, **5,** 65-68.
476   de Wilde, A. H., V. S. Raj, D. Oudshoorn, T. M. Bestebroer, S. van Nieuwkoop, R. W. Limpens, C. C.
477   Posthuma, Y. van der Meer, M. Barcena, B. L. Haagmans, E. J. Snijder and B. G. van den Hoogen,

478   2013: MERS-coronavirus replication induces severe in vitro cytopathology and is strongly
479   inhibited by cyclosporin A or interferon-alpha treatment. *J Gen Virol,* **94,** 1749-1760.
480   de Wit, E., J. Prescott, L. Baseler, T. Bushmaker, T. Thomas, M. G. Lackemeyer, C. Martellaro, S. Milne-
481   Price, E. Haddock, B. L. Haagmans, H. Feldmann and V. J. Munster, 2013: The Middle East
482   respiratory syndrome coronavirus (MERS-CoV) does not replicate in Syrian hamsters. *PLoS One,*
483   **8,** e69127.
484   Destoumieux-Garzon, D., P. Mavingui, G. Boetsch, J. Boissier, F. Darriet, P. Duboz, C. Fritsch, P.
485   Giraudoux, F. Le Roux, S. Morand, C. Paillard, D. Pontier, C. Sueur and Y. Voituron, 2018: The
486   One Health Concept: 10 Years Old and a Long Road Ahead. *Front Vet Sci,* **5,** 14.
487   Drosten, C., B. Meyer, M. A. Muller, V. M. Corman, M. Al-Masri, R. Hossain, H. Madani, A. Sieberg, B. J.
488   Bosch, E. Lattwein, R. F. Alhakeem, A. M. Assiri, W. Hajomar, A. M. Albarrak, J. A. Al-Tawfiq, A.
489   I. Zumla and Z. A. Memish, 2014: Transmission of MERS-coronavirus in household contacts. *N*
490   *Engl J Med,* **371,** 828-835.
491   Farag, E. A., C. B. Reusken, B. L. Haagmans, K. A. Mohran, V. Stalin Raj, S. D. Pas, J. Voermans, S. L.
492   Smits, G. J. Godeke, M. M. Al-Hajri, F. H. Alhajri, H. E. Al-Romaihi, H. Ghobashy, M. M. El-
493   Maghraby, A. M. El-Sayed, M. H. Al Thani, S. Al-Marri and M. P. Koopmans, 2015: High
494   proportion of MERS-CoV shedding dromedaries at slaughterhouse with a potential
495   epidemiological link to human cases, Qatar 2014. *Infect Ecol Epidemiol,* **5,** 28305.
496   Gao, H., H. Yao, S. Yang and L. Li, 2016: From SARS to MERS: evidence and speculation. *Front Med,* **10,**
497   377-382.
498   Garcell, H. G., E. G. Garcia, P. V. Pueyo, I. R. Martin, A. V. Arias and R. N. Alfonso Serrano, 2016:
499   Outbreaks of brucellosis related to the consumption of unpasteurized camel milk. *J Infect Public*
500   *Health,* **9,** 523-527.
501   Han, H. J., J. W. Liu, H. Yu and X. J. Yu, 2018: Neutralizing Monoclonal Antibodies as Promising
502   Therapeutics against Middle East Respiratory Syndrome Coronavirus Infection. *Viruses,* **10**.
503   He, L., W. Tai, J. Li, Y. Chen, Y. Gao, J. Li, S. Sun, Y. Zhou, L. Du and G. Zhao, 2019: Enhanced Ability of
504   Oligomeric Nanobodies Targeting MERS Coronavirus Receptor-Binding Domain. *Viruses,* **11**.
505   Hemida, M. G., A. Al-Naeem, R. A. Perera, A. W. Chin, L. L. Poon and M. Peiris, 2015: Lack of middle
506   East respiratory syndrome coronavirus transmission from infected camels. *Emerg Infect Dis,* **21,**
507   699-701.
508   Hemida, M. G., A. Alnaeem, D. K. Chu, R. A. Perera, S. M. Chan, F. Almathen, E. Yau, B. C. Ng, R. J.
509   Webby, L. L. Poon and M. Peiris, 2017a: Longitudinal study of Middle East Respiratory
510   Syndrome coronavirus infection in dromedary camel herds in Saudi Arabia, 2014-2015. *Emerg*
511   *Microbes Infect,* **6,** e56.
512   Hemida, M. G., D. K. Chu, L. L. Poon, R. A. Perera, M. A. Alhammadi, H. Y. Ng, L. Y. Siu, Y. Guan, A.
513   Alnaeem and M. Peiris, 2014: MERS coronavirus in dromedary camel herd, Saudi Arabia. *Emerg*
514   *Infect Dis,* **20,** 1231-1234.

515 Hemida, M. G., A. Elmoslemany, F. Al-Hizab, A. Alnaeem, F. Almathen, B. Faye, D. K. Chu, R. A. Perera
516   and M. Peiris, 2017b: Dromedary Camels and the Transmission of Middle East Respiratory
517   Syndrome Coronavirus (MERS-CoV). *Transbound Emerg Dis,* **64,** 344-353.
518 Hofer, U., 2013: Viral evolution: fooling the coronavirus proofreading machinery. *Nat Rev Microbiol,* **11,**
519   662-663.
520 Hong, K. H., J. P. Choi, S. H. Hong, J. Lee, J. S. Kwon, S. M. Kim, S. Y. Park, J. Y. Rhee, B. N. Kim, H. J.
521   Choi, E. C. Shin, H. Pai, S. H. Park and S. H. Kim, 2017: Predictors of mortality in Middle East
522   respiratory syndrome (MERS). *Thorax.*
523 Kandeil, A., M. Gomaa, M. Shehata, A. El-Taweel, A. E. Kayed, A. Abiadh, J. Jrijer, Y. Moatasim, O.
524   Kutkat, O. Bagato, S. Mahmoud, A. Mostafa, R. El-Shesheny, R. A. Perera, R. L. Ko, N. Hassan, B.
525   Elsokary, L. Allal, A. Saad, H. Sobhy, P. P. McKenzie, R. J. Webby, M. Peiris, M. A. Ali and G.
526   Kayali, 2019: Middle East respiratory syndrome coronavirus infection in non-camelid domestic
527   mammals. *Emerg Microbes Infect,* **8,** 103-108.
528 Khalafalla, A. I., X. Lu, A. I. Al-Mubarak, A. H. Dalab, K. A. Al-Busadah and D. D. Erdman, 2015: MERS-
529   CoV in Upper Respiratory Tract and Lungs of Dromedary Camels, Saudi Arabia, 2013-2014.
530   *Emerg Infect Dis,* **21,** 1153-1158.
531 Kim, K., S. A. Andrew and K. Jung, 2017: Public Health Network Structure and Collaboration
532   Effectiveness during the 2015 MERS Outbreak in South Korea: An Institutional Collective Action
533   Framework. *Int J Environ Res Public Health,* **14.**
534 Kim, S. H., S. Y. Chang, M. Sung, J. H. Park, H. Bin Kim, H. Lee, J. P. Choi, W. S. Choi and J. Y. Min, 2016:
535   Extensive Viable Middle East Respiratory Syndrome (MERS) Coronavirus Contamination in Air
536   and Surrounding Environment in MERS Isolation Wards. *Clin Infect Dis,* **63,** 363-369.
537 Lau, S. K. and J. F. Chan, 2015: Coronaviruses: emerging and re-emerging pathogens in humans and
538   animals. *Virol J,* **12,** 209.
539 Makino, S., J. G. Keck, S. A. Stohlman and M. M. Lai, 1986: High-frequency RNA recombination of
540   murine coronaviruses. *J Virol,* **57,** 729-737.
541 Memish, Z. A., J. A. Al-Tawfiq, R. F. Alhakeem, A. Assiri, K. D. Alharby, M. S. Almahallawi and M.
542   Alkhallawi, 2015: Middle East respiratory syndrome coronavirus (MERS-CoV): A cluster analysis
543   with implications for global management of suspected cases. *Travel Med Infect Dis,* **13,** 311-314.
544 Memish, Z. A., N. Mishra, K. J. Olival, S. F. Fagbo, V. Kapoor, J. H. Epstein, R. Alhakeem, A. Durosinloun,
545   M. Al Asmari, A. Islam, A. Kapoor, T. Briese, P. Daszak, A. A. Al Rabeeah and W. I. Lipkin, 2013:
546   Middle East respiratory syndrome coronavirus in bats, Saudi Arabia. *Emerg Infect Dis,* **19,** 1819-
547   1823.
548 Mollers, M., M. Jonges, S. D. Pas, A. A. van der Eijk, K. Dirksen, C. Jansen, L. B. Gelinck, E. M. Leyten, I.
549   Thurkow, P. H. Groeneveld, A. B. van Gageldonk-Lafeber, M. P. Koopmans, A. Timen and M. E.-
550   C. O. I. T. o. t. Netherlands, 2015: Follow-up of Contacts of Middle East Respiratory Syndrome
551   Coronavirus-Infected Returning Travelers, the Netherlands, 2014. *Emerg Infect Dis,* **21,** 1667-1669.

552 Monchatre-Leroy, E., F. Boue, J. M. Boucher, C. Renault, F. Moutou, M. Ar Gouilh and G. Umhang, 2017:
553   Identification of Alpha and Beta Coronavirus in Wildlife Species in France: Bats, Rodents,
554   Rabbits, and Hedgehogs. *Viruses,* **9**.

555 Moon, S. Y. and J. S. Son, 2017: Infectivity of an Asymptomatic Patient With Middle East Respiratory
556   Syndrome Coronavirus Infection. *Clin Infect Dis,* **64,** 1457-1458.

557 Munster, V. J., D. R. Adney, N. van Doremalen, V. R. Brown, K. L. Miazgowicz, S. Milne-Price, T.
558   Bushmaker, R. Rosenke, D. Scott, A. Hawkinson, E. de Wit, T. Schountz and R. A. Bowen, 2016:
559   Replication and shedding of MERS-CoV in Jamaican fruit bats (Artibeus jamaicensis). *Sci Rep,* **6,**
560   21878.

561 Niu, P., G. Zhao, Y. Deng, S. Sun, W. Wang, Y. Zhou and W. Tan, 2018: A novel human mAb (MERS-
562   GD27) provides prophylactic and postexposure efficacy in MERS-CoV susceptible mice. *Sci China*
563   *Life Sci,* **61,** 1280-1282.

564 Peiris, J. S., S. T. Lai, L. L. Poon, Y. Guan, L. Y. Yam, W. Lim, J. Nicholls, W. K. Yee, W. W. Yan, M. T.
565   Cheung, V. C. Cheng, K. H. Chan, D. N. Tsang, R. W. Yung, T. K. Ng, K. Y. Yuen and S. s. group,
566   2003: Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet,* **361,** 1319-
567   1325.

568 Rajakaruna, S. J., W. B. Liu, Y. B. Ding and G. W. Cao, 2017: Strategy and technology to prevent hospital-
569   acquired infections: Lessons from SARS, Ebola, and MERS in Asia and West Africa. *Mil Med Res,*
570   **4,** 32.

571 Reusken, C. B., E. A. Farag, M. Jonges, G. J. Godeke, A. M. El-Sayed, S. D. Pas, V. S. Raj, K. A. Mohran, H.
572   A. Moussa, H. Ghobashy, F. Alhajri, A. K. Ibrahim, B. J. Bosch, S. K. Pasha, H. E. Al-Romaihi, M.
573   Al-Thani, S. A. Al-Marri, M. M. AlHajri, B. L. Haagmans and M. P. Koopmans, 2014: Middle East
574   respiratory syndrome coronavirus (MERS-CoV) RNA and neutralising antibodies in milk
575   collected according to local customs from dromedary camels, Qatar, April 2014. *Euro Surveill,* **19**.

576 Reusken, C. B., C. Schilp, V. S. Raj, E. De Bruin, R. H. Kohl, E. A. Farag, B. L. Haagmans, H. Al-Romaihi,
577   F. Le Grange, B. J. Bosch and M. P. Koopmans, 2016: MERS-CoV Infection of Alpaca in a Region
578   Where MERS-CoV is Endemic. *Emerg Infect Dis,* **22,** 1129-1131.

579 Roess, A., L. Carruth, S. Lahm and M. Salman, 2016: Camels, MERS-CoV, and other emerging infections
580   in east Africa. *Lancet Infect Dis,* **16,** 14-15.

581 Rubio, E., M. J. Martinez, V. Gonzalo, J. Barrachina, N. Torner, A. I. Martinez, M. Jane, A. Vilella, A. Del
582   Rio, N. Rodriguez-Valero, M. J. Pinazo, J. Munoz, A. Soriano, A. Trilla, J. Vila and M. A. Marcos,
583   2018: Definitive diagnosis in suspected Middle East Respiratory Syndrome Coronavirus cases. *J*
584   *Travel Med,* **25**.

585 Totura, A. L. and S. Bavari, 2019: Broad-spectrum coronavirus antiviral drug discovery. *Expert Opin Drug*
586   *Discov,* **14,** 397-412.

587 van Doremalen, N., T. Bushmaker, W. B. Karesh and V. J. Munster, 2014: Stability of Middle East
588   respiratory syndrome coronavirus in milk. *Emerg Infect Dis,* **20,** 1263-1264.

589 van Doremalen, N., Z. S. Hijazeen, P. Holloway, B. Al Omari, C. McDowell, D. Adney, H. A. Talafha, J.
590   Guitian, J. Steel, N. Amarin, M. Tibbo, E. Abu-Basha, A. M. Al-Majali, V. J. Munster and J. A.

591   Richt, 2017: High Prevalence of Middle East Respiratory Coronavirus in Young Dromedary
592   Camels in Jordan. *Vector Borne Zoonotic Dis,* **17,** 155-159.

593 Vergara-Alert, J., J. M. van den Brand, W. Widagdo, M. t. Munoz, S. Raj, D. Schipper, D. Solanes, I.
594   Cordon, A. Bensaid, B. L. Haagmans and J. Segales, 2017: Livestock Susceptibility to Infection
595   with Middle East Respiratory Syndrome Coronavirus. *Emerg Infect Dis,* **23,** 232-240.

596 Wang, M., M. Yan, H. Xu, W. Liang, B. Kan, B. Zheng, H. Chen, H. Zheng, Y. Xu, E. Zhang, H. Wang, J.
597   Ye, G. Li, M. Li, Z. Cui, Y. F. Liu, R. T. Guo, X. N. Liu, L. H. Zhan, D. H. Zhou, A. Zhao, R. Hai, D.
598   Yu, Y. Guan and J. Xu, 2005: SARS-CoV infection in a restaurant from palm civet. *Emerg Infect*
599   *Dis,* **11,** 1860-1865.

600 WHO, 2018: Middle East Respiratory syndrome cornavirus (MERS-CoV).
601   *http://www.who.int/emergencies/mers-cov/en/.*

602 Widagdo, W., L. Begeman, D. Schipper, P. R. V. Run, A. A. Cunningham, N. Kley, C. B. Reusken, B. L.
603   Haagmans and J. M. A. van den Brand, 2017: Tissue Distribution of the MERS-Coronavirus
604   Receptor in Bats. *Sci Rep,* **7,** 1193.

605 Xiao, S., Y. Li, M. Sung, J. Wei and Z. Yang, 2018: A study of the probable transmission routes of MERS-
606   CoV during the first hospital outbreak in the Republic of Korea. *Indoor Air,* **28,** 51-63.

607 Yu, P., Y. Xu, W. Deng, L. Bao, L. Huang, Y. Xu, Y. Yao and C. Qin, 2017: Comparative pathology of
608   rhesus macaque and common marmoset animal models with Middle East respiratory syndrome
609   coronavirus. *PLoS One,* **12,** e0172093.

610 Zaki, A. M., S. van Boheemen, T. M. Bestebroer, A. D. Osterhaus and R. A. Fouchier, 2012: Isolation of a
611   novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med,* **367,** 1814-1820.

612 Zhao, G., Y. Jiang, H. Qiu, T. Gao, Y. Zeng, Y. Guo, H. Yu, J. Li, Z. Kou, L. Du, W. Tan, S. Jiang, S. Sun and
613   Y. Zhou, 2015: Multi-Organ Damage in Human Dipeptidyl Peptidase 4 Transgenic Mice Infected
614   with Middle East Respiratory Syndrome-Coronavirus. *PLoS One,* **10,** e0145561.

615 Zhou, J., C. Li, G. Zhao, H. Chu, D. Wang, H. H. Yan, V. K. Poon, L. Wen, B. H. Wong, X. Zhao, M. C.
616   Chiu, D. Yang, Y. Wang, R. K. H. Au-Yeung, I. H. Chan, S. Sun, J. F. Chan, K. K. To, Z. A.
617   Memish, V. M. Corman, C. Drosten, I. F. Hung, Y. Zhou, S. Y. Leung and K. Y. Yuen, 2017:
618   Human intestinal tract serves as an alternative infection route for Middle East respiratory
619   syndrome coronavirus. *Sci Adv,* **3,** eaao4966.

620 Zumla, A., E. I. Azhar, Y. Arabi, B. Alotaibi, M. Rao, B. McCloskey, E. Petersen and M. Maeurer, 2015:
621   Host-directed therapies for improving poor treatment outcomes associated with the middle east
622   respiratory syndrome coronavirus infections. *Int J Infect Dis,* **40,** 71-74.

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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.
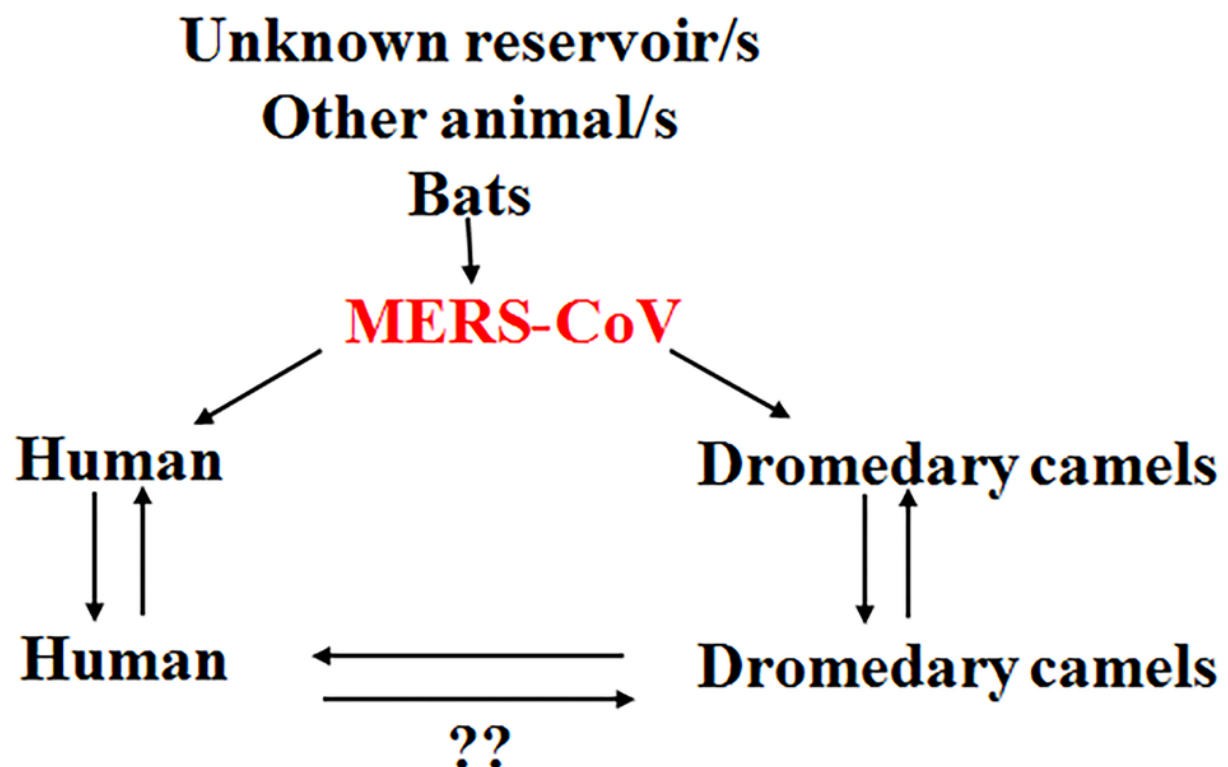
Figure 2

Some interventions based on the One Health-based to stop MERS-CoV outbreaks

Some control measures for the MERS-CoV based on the One Health concept.