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Current Opinion in Virology

Unresolved questions in the zoonotic transmission of MERS

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The Middle East Respiratory Syndrome-coronavirus (MERS-CoV) is the second of three zoonotic coronaviruses to infect humans since 2002, causing severe pneumonia. Unlike SARS-CoV-1 and SARS-CoV-2, the causes of the severe acute respiratory syndrome and Covid-19, respectively, MERS-CoV is enzootic in dromedary camels, a domestic/companion animal present across Africa, the Middle East and Central or South Asia and is sporadically transmitted to humans. However, it does not transmit readily from human to human except in hospital and household settings. Human MERS disease is reported only from the Arabian Peninsula (and only since 2012 even though the virus was detected in camels from at least the early 1990's) and in travelers from this region. Remarkably, no zoonotic MERS disease has been detected in Africa or Asia, even in areas of high density of MERS-CoV infected dromedaries. Here, we review aspects of MERS biology and epidemiology that might contribute to this lack of correlation between sites of camel infection and human zoonotic disease. Since MERS-CoV or MERS-like CoV have pandemic potential, further investigations into this disparity is critical, to forestall pandemics caused by this virus.

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Current Opinion in Virology 2022, **52**:258–264

This review comes from a themed issue on **Viral pathogenesis**

Edited by **Michaela Gack** and **Susan Baker**

For complete overview about the section, refer Viral Pathogenesis (2022)

Available online 6th January 2022

https://doi.org/10.1016/j.coviro.2021.12.013

MERS coronavirus (MERS-CoV) was first reported from a patient with fatal viral pneumonia in Saudi Arabia in 2012 and identified as a novel group C betacoronavirus [1•]. Camels were identified as the source of zoonotic infection [2]). Most zoonotic infections remain undetected or self-limited but can lead to outbreaks resulting from chains of limited human-to-human transmission, particularly in health care facilities, sometimes in excess of 150 individuals [3]. An infected traveler returning to South Korea resulted in an outbreak affecting 186 individuals [4]. This single source infection provided insight into MERS-CoV evolution, in the absence of repeated introduction from camels (see below). As of 20th October 2021, there have been 2580 confirmed human MERS infections reported from 27 countries leading to 927 deaths https://www.fao.org/ag/againfo/programmes/en/empres/mers/situation_update.html. Given its potential to cause limited human-to-human transmission, MERS-CoV is regarded as one of the eight pathogens of greatest concern for global public health [5].

Many MERS-CoV infections remain unrecognized and are mild [6] and disease is often clinically apparent mainly when older individuals with co-morbidities are infected or when outbreaks in health care facilities occur [3]. Many of these older individuals do not have camel contact so the source of their infection remains obscure. Camel workers, who are young, healthy males, are exposed to camels and likely become infected [7,8], but how this would result in infection of susceptible people is not known.

MERS-CoV poses a number of additional enigmas. Seroepidemiological studies reveal that adult dromedary camels in most of the world have evidence of past infection [9] with the exception of dromedaries in Australia and Kazakhstan [10,11]. Bactrian camels can be infected with MERS-CoV experimentally but are not found to be infected in their natural habitat [12,13].

The prototype HCoV-EMC/2012 strain (abbreviated EMC herein) and a few others from the Arabian Peninsula form clade A, the majority of contemporary viruses from the Arabian Peninsula are classified as clade B, while all viruses from Africa are designated clade C viruses [14••]. Viruses from West (Nigeria, Burkina Faso) and North Africa cluster together as clade C1.1, those from Ethiopia and Kenya as Clade C2 while those from Egypt, Sudan or Djibouti cluster as clade C1.2 or clade 2. Although MERS-CoV exhibits region-dependent genomic diversity, all known MERS-CoVs have >99% identity at the nucleotide level. Some clade C viruses in West Africa have developed progressive deletions in accessory proteins ORF4b and ORF3. ORF3 and ORF4b are believed to contribute to immune evasion in humans

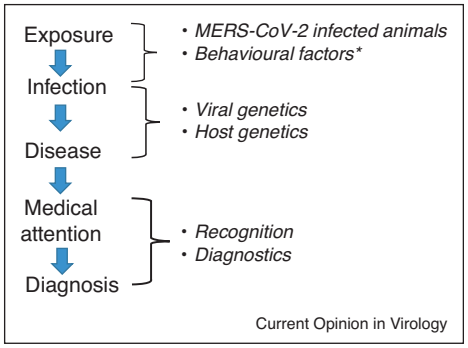
but its role in camels (or a putative natural reservoir) is unclear. With a few sporadic exceptions, such deletions are not seen in clade B viruses currently in the Arabian Peninsula. The continued emergence of deletions in accessory proteins may indicate that MERS-CoV is still not fully adapted to the dromedary host. The contention that dromedaries may not be the natural reservoir of MERS-CoV is also supported by the lack of infection in dromedaries in regions such as Kazakhstan and Australia. Time resolved phylogeny and the use of molecular clocks of evolution place the emergence of MERS-CoV in dromedaries to a few decades before its initial detection in 2012 but such studies with coronaviruses may be unreliable and also does not take account of sweeps of extinction of some virus lineages which may falsely reduce the estimates of time of emergence. Serological evidence of infection from archived serum samples provides conclusive evidence of MERS-CoV circulation dating from 1993 in the Arabian Peninsula and 1984 in Africa [15,16]. These represent the earliest archived sera tested; MERS-CoV may have emerged in dromedaries at even earlier times. But whether dromedaries are the natural reservoir and how long the virus has been enzoonotic in dromedaries remains unclear. Infection in dromedaries leads to a mild coryzal upper respiratory disease.

The apparent paucity of human MERS disease in Africa

Although cases of MERS acquired through travel to the Arabian Peninsula have been reported in Africa (https://www.fao.org/ag/againfo/programmes/en/empres/mers/Situation_update.html), no locally acquired zoonotic clinically apparent MERS has been described, even though over 75% of the global dromedary population is found in East, West and North Africa [17,18]. The extent of virus activity as judged by prevalence of antibody or virus RNA detection rates were comparable in dromedaries in Africa or the Arabian Peninsula [9]. Possible explanations for the lack of locally acquired zoonotic MERS reported from Africa may include the following: a) behavioral or cultural differences that may result in differences in camel exposure, b) human genetic polymorphisms that reduce susceptibility to MERS-CoV, or higher incidence of co-morbid conditions that increase susceptibility to MERS-CoV, c) viral genetic and phenotypic differences in MERS-CoV found in Africa versus Arabian Peninsula, d) lack of awareness or laboratory testing of suspected cases in Africa (Figure 1).

Studies in a camel abattoir in Kano, Nigeria and in camel exposed populations in Morocco have confirmed very close interactions between humans and dromedaries in those parts of Africa [19,20]. They also found high prevalence of drinking fresh (unboiled) camel milk, drinking camel urine and using camel urine for medicinal purposes. These factors may enhance the likelihood of zoonotic infection [21]. On the other hand, possible differences from the Arabian Peninsula are the lack of large organized events such as camel racing and beauty pageants (e.g. El Mazzaien) in Africa. Taken overall, it seems unlikely that social factors by themselves would explain the lack of human infection in Africa.

Figure 1



Possible explanations for the lack of locally acquired zoonotic MERS reported from Africa.
**Note*: Behavioural factors refer to cultural, dietary or other activities that affect the exposure of humans to dromedary camels.

Serological evidence of MERS-CoV infection in camel exposed populations can provide a clue whether MERS-CoV infections are indeed taking pace in Africa. As seen in Table 1, serological evidence for MERS-CoV infection in camel exposed populations in Africa is largely lacking. It should be noted however, that given the high prevalence of virus infection, especially in abattoir settings in both the Arabian Peninsula and Africa, and the implied high levels of exposure to such infected camels, the sero-prevalence in camel workers is still lower that expected, even in the Arabian Peninsula. Studies of cohorts of RT-PCR confirmed MERS-CoV infections have shown that sero-conversion is commonly seen in patients with severe disease but is not always seen in patients with mild or asymptomatic infection [22,23]. Furthermore, as seen with SARS-CoV-1 infection in 2003, waning antibody may result in sero-negative status even in those who did develop antibody in the past although T cell responses remained detectable over 15 years later [24]. Thus, it is very likely that serology underestimates the prevalence of mild infections. It has been shown that some individuals with mild or asymptomatic infection may have undetectable antibody responses but have detectable specific T cell responses to MERS-CoV [8,25••]. Studies carried out in camel abattoir workers and controls in a camel abattoir in Kano, Nigeria, which had been shown to have evidence of MERS-CoV infected camels, revealed that approximately 1/3rd of camel exposed workers (but not controls) had detectable CD4 and/or CD8 T cell responses to MERS-CoV, although

Table 1

Sero-epidemiological studies in humans using neutralization assays for confirmation of results

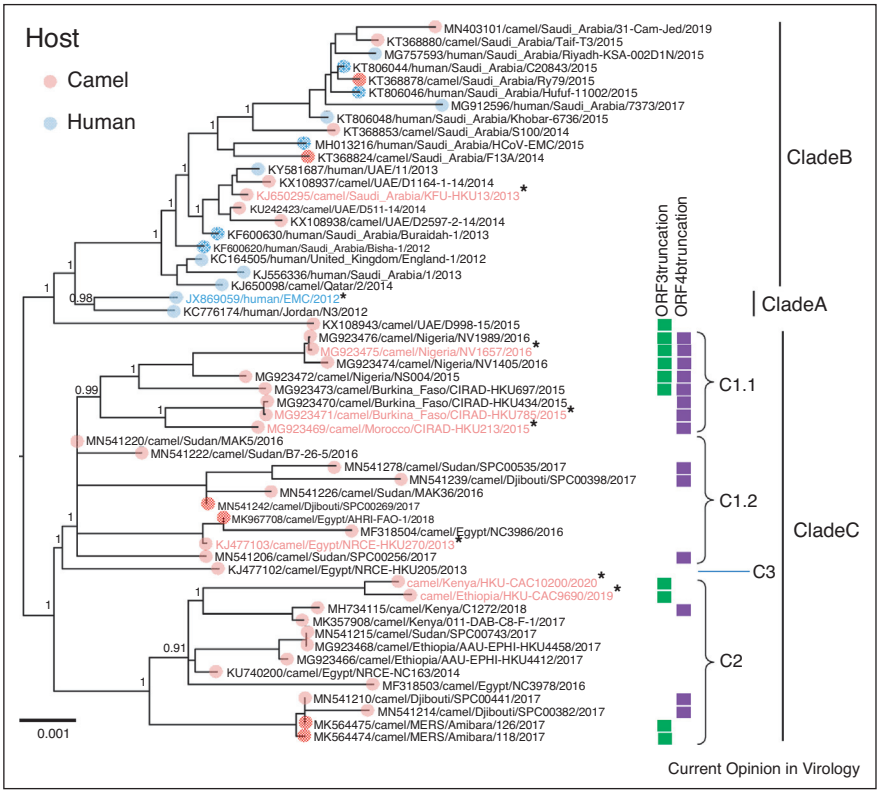
Location (reference)	Camel exposed	Control
Arabian Peninsula		
Kingdom of Saudi Arabia [41]	2 (2.3%) of 87 camel herders 5 (3.6) of 140 camel abattoir workers	15 (0.15%) of 10 009 general population
Kingdom of Saudi Arabia [42]	0 of 300 camel workers	0 of 50
Kingdom of Saudi Arabia [43]	0 of 12 camel workers exposed to an infected herd 0 of 30 veterinarians in a camel hospital 0 of 3 camel abattoir workers	0 of 146
Kingdom of Saudi Arabia [44]	2 (0.9%) of 226 slaughterhouse workers	0 of 130 blood donors
Qatar [45]	2 (40%) of 5 camel abattoir workers 2 (9%) of 22 camel barn workers	
Kingdom of Saudi Arabia [8]	15 of 30 camel workers	0 of 30 controls
United Arab Emirates [46]	3 sampling rounds: 6 (6%) of 100; 29 (19%) of 151; 40 (17%) of 235 positive.	
Qatar [47]		0 of 4719
Total Arabian Peninsula	**103 (7.7%) of 1338**	**15 (0.1%) of 15,214**
Southern Asia		
Pakistan [48]		0 of 2409 general population in camel herding areas
Pakistan [49]	12/100 camel handlers + families	
Africa		
Egypt [50]	0 of 179 camel abattoir workers	
Egypt [51]		0 of 815 general population
Kenya [52]	0 of 760 camel exposed people	
Kenya [53]		2 (0.18%) of 1122 general population
Nigeria [20]	0 of 261 camel abattoir workers	0 of 50 abattoir workers not working with camels
Morocco [19]	2 (1.5%) of 137 camel abattoir workers 0 of 156 camel herders	1 (0.5%) of 186 general population
Sudan [54]	0 of 56 camel workers	
Total Africa	**2 (0.13%) of 1549**	**3 (0.6%) of 4582**

none of these individuals had detectable antibody to MERS-CoV [26••]. Such T cell responses were even detectable to accessory proteins that are unique in amino acid sequence to MERS-CoV and not similar to those in endemic human common cold coronaviruses. The complete absence of seropositivity in the face of a low but detectable T cell response is surprising. Studies from COVID-19 patients have demonstrated the presence of pre-existing T cells that recognize SARS-CoV-2 proteins [27]; whether this is a factor in the Kano study is not known. This study documenting MERS-CoV specific T cell responses in camel exposed populations urgently needs to be replicated in other camel exposed populations in Africa, but suggests that camel-exposed populations are being infected, albeit mildly, with MERS-CoV. The question remains why such infections are not being recognized. A recent prospective study of dromedary camel-herders in Kenya with repeated swab and serum sampling detected two asymptomatic individuals who were transiently RT-PCR positive for MERS-CoV in nasal swabs [28••]. This may suggest asymptomatic infection, although contamination of nares with virus from infected camels cannot be ruled out.

Host genetic polymorphisms that may predispose to MERS-CoV infection or disease have not been well investigated. Polymorphisms of the virus receptor DPP4 which reduce MERS-CoV virus entry have been reported but it is unclear if these have any significant relevance to the lack of MERS-CoV in Africa [29]. The incidence of co-morbidities that predispose to severe MERS include obesity, diabetes, hypertension, chronic cardiac, chronic renal and older age [3,30]. The presence of these co-morbidities is more frequent in affluent individuals in the Arabian Peninsula, who are those most often diagnosed with MERS. Although camel herders from East Africa commonly serve to tend camel herds in the Arabian Peninsula, they are rarely diagnosed with MERS.

Viruses from Africa (clade C) are genetically distinct from those in the Arabian Peninsula (clade A or B) although all MERS-CoV share over 99% genetic identity at the nucleotide level (Figure 2). Virus isolates from Nigeria and Burkina Faso in West Africa (clade C1.1), Morocco (clade C1.1) in North Africa, Egypt in North East Africa (clade C1.2), Ethiopia and Kenya (clade C2) in East Africa were phenotypically compared with EMC (clade A) an AH13 (clade B) viruses from Saudi Arabia [14••]. All six viruses from Africa had significantly lower replication competence than those from Saudi Arabia in Calu-3 cells, a human alveolar epithelial cell line, and in *ex vivo* culture fragments of human lung parenchyma. All six African viruses also had significantly lower titers in the lungs of

Figure 2



Phylogenetic relationships of MERS-CoV strains circulating in the Arabian Peninsula and Africa (reproduced from Ref. [14••]). The tree was constructed by the maximum likelihood method usingPhyML. Scale bar indicates the pairwise nucleotide substitutions per site. The virus clade designations are denoted. Taxa labelled with blue and red at the branch tips represents MERS-CoV sequences from human and camels, respectively. ORF3 and ORF4b deletions in the virus genomes are indicated as green and purple boxes respectively. Prototype virus strain EMC is denoted in blue font and other strains from the Arabian Peninsula and Africa that were phenotypically characterized in Ref. [14••] are denoted with *.

human DPP4 knockin mice (mice genetically manipulated for sensitization to MERS-CoV infection) at day 3 post infection. To identify factors important for this diminished replicative competence, the role of the virus spike protein in virus entry of EMC (clade A) and Burkina Faso or Nigerian (clade C1.1) viruses into Calu-3 cells was compared. Reduced virus entry was associated with viruses pseudotyped with the clade C1.1 spikes. These findings were confirmed using isogenic EMC (clade A) virus with spike of EMC or Burkina Faso MERS-CoV spike generated using reverse genetics. The Burkina Faso virus spike was associated with reduced virus entry and replication competence in Calu-3 cells and reduced replication competence in *ex vivo* cultures of human bronchus and in the lungs of human DPP4 knockin mice [14••]. In another study, the EMC S protein was replaced by the S protein from a clade C2 (Ethiopia, Amihara) virus [31]. In agreement with the previous study, the resulting chimeric viruses replicated less well than the parental EMC strain in Vero cells.

The EMC virus causes very mild infection in human DPP4 knockin mice but on serial passage through mouse lungs, the virus becomes more virulent [32]. Chimeric viruses expressing S proteins from clades C1 (Burkina Faso, Nigeria, Morocco) and C2 (Ethiopia) were introduced into the background of this mouse-adapted virus. The resulting viruses entered cells less efficiently than the parental mouse adapted virus, but the parental and chimeric viruses caused equivalent mortality and morbidity in human DPP4 knockin mice [33]. Of note, there are only 6 amino acid differences in the spike proteins of the viruses from Burkina Faso and Saudi Arabia. It would be of interest to identify which amino acid residues are critical for reduced entry, both for mechanistic understanding and for public health implications, that is, what amino acid change/s may enhance entry and thereby potentially convert African clade C viruses to a more pathogenic phenotype. Together, these studies suggest that virus entry is compromised in African isolates, but that other factors are also involved.

Since clade C1.1 viruses also have deletions in ORF4b, which may impact the immune evasion competence of MERS-CoV [34,35], chimeric viruses with intact or deleted ORF4b were engineered [36,37]. Deletion of ORF4b was associated with increased induction of interferon β, interferon λ1, CXCL-10, ISG15 and MX1 in Calu-3 cells and modestly reduced replication competence in Calu-3 cells. It should be noted that ORF4 deletions are not invariably found in clade C2 or C1.2 MERS-CoV from East Africa and thus this cannot be the only reason for reduced MERS-CoV replication competence in Africa. Overall, these findings suggest that African camel MERS-CoV genetic determinants contribute to reduced replicative capacity in human respiratory epithelial cells, which may contribute to the lack of human zoonotic MERS in Africa.

Irrespective of any possible differences in pathogenic potential for humans, clade C viruses appear well adapted to transmit in camels because almost all adult camels in different regions of Africa are sero-positive for MERS-CoV. However, it is of note that clade C viruses have not been yet reported from dromedaries in the Arabian Peninsula. This is surprising because there is continued importation of dromedaries from the Horn of Africa to Saudi Arabia, mainly as a source of camel meat and these camels may be infected with clade C MERS-CoV [38]. In contrast, at the time of slaughter in abattoirs in Saudi Arabia distant from the port of importation, camels are infected with clade B rather than clade C viruses [39]. This implies that the camels are infected or re-infected in KSA and may indicate that clade B viruses are outcompeting clade C viruses introduced into Saudi Arabia. However, this may also reflect the force of the founder-effect of established clade B, and the paucity of virus genetic surveillance in the Arabian Peninsula. Nevertheless, if it is true that clade B viruses outcompete clade C viruses, it implies that the introduction of clade B viruses into the African Continent may result in them gradually out-competing clade C, with potentially grave consequences for public health.

The perception that human MERS is not acquired in Africa has resulted in a lack of testing for MERS in patients with severe respiratory disease. Outside of a few limited studies [40], there have not been reports of large numbers of patients with severe respiratory disease without recent travel history being tested for MERS-CoV in Africa. Even when such studies are done, it is likely to be in major population centers and cities, which are not the areas where camel herding or camel abattoirs are located. This perception very likely leads to a self-reinforcing outcome that MERS remains undetected in Africa, even if transmission occurs. Irrespective of whether MERS-CoV in Africa is less pathogenic for humans, given the findings of specific T cell responses in camel abattoir workers in Nigeria, it is important that systematic surveillance of severe acute respiratory infections (SARI) in camel herding regions of Africa be strengthened and that such surveillance includes testing for MERS-CoV.

Conflict of interest statement

Nothing declared.

Acknowledgements

The work was funded in part by the Commissioned Research on Control of Infectious Diseases (Phase III and IV) from the Health and Medical Research Fund, Hong Kong SAR, Health and Medical Research Fund grant 19181032, and the US National Institutes of Health grants AI151810, (MP), AI060699 (SP) and AI129269 (SP).

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