



## Editorial article

The Middle East respiratory syndrome coronavirus<sup>☆</sup>

## El coronavirus causante del síndrome respiratorio de Oriente Medio

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The coronavirus (CoV) causes the Middle East respiratory syndrome (MERS). This virus is the first human CoV, taxonomically belonging to genus *Betacoronavirus* lineage C, within the *Coronaviridae* family.<sup>1,2</sup> Before having been described, only 2 CoV were known in this lineage, detected in African wild bats.<sup>3–5</sup> The natural reservoir of this new CoV consists of several species of wild bats. Up to 25% of the studied specimens have been detected in the feces of these bats.<sup>4,5</sup> This reservoir is the same as the one using not only the MERS-CoV, but also the previous, the severe acute respiratory syndrome (SARS) and many other CoV have no recognized human infective capacity yet.<sup>6,7</sup>

Since its first detection in September 2012, in a patient from Saudi Arabia who died of severe pneumonia and multiple organ failure, the MERS-CoV has already caused more than 1500 cases, with an average mortality of about 40%.<sup>7–10</sup> All primary cases are epidemiologically linked to the Middle East, where it remains as an endemic infection. This geographical area, which consists of 18 countries and multiple ethnic groups, presents customs and direct relationship with camels, which seem to be the intermediate or amplifier host. The epidemic has been spread secondarily to different countries in Europe, Africa, Asia and the USA, but always after contact with a case of the area involved.<sup>7–10</sup> Also, from this original focus, there has been a major outbreak in South Korea with more than 180 cases, which was epidemiologically controlled.<sup>11</sup>

As if Nature were cyclical, in the first decade of the new millennium (21st century) the world suffered a respiratory epidemic caused by a new CoV, the SARS-CoV.<sup>6,7</sup> In the second decade a new CoV reappears (MERS-CoV), with a very similar pathological behavior, although with higher mortality. Both viruses are very similar in origin, source of animal reservoirs (bats), use of intermediate hosts and their ability to cross the interspecies barrier and infect humans.<sup>7</sup> As it happened with SARS-CoV, the MERS-CoV is considered a major threat to global public health, because it might become a potential pandemic virus, since it has the ability to spread from person to person and, currently, effective therapeutic measures are not available. WHO appointed it in 2014 as the fourth horseman of

the apocalypse, after avian influenza viruses A(H5N1) and A(H7N9) and ebola virus, considering its high mortality (30–50%), human-to-human transmission capacity and scarce therapeutic measures available. This virus might finish, in the case of becoming pandemic phenomena, with a significant part of the global population.<sup>12</sup>

The persistence of the current epidemic is believed to be due to the existence of a continuous animal to human transmission from at least one type of animal reservoir frequently in contact with people from the epidemic geographical area. This epidemic is spread sporadically by a non-maintained human-to-human transmission, occurring as outbreaks associated with health caregivers (hospitals) and intrafamily contact.<sup>8,13</sup>

Most human infections have been linked to direct contact with camels and dromedaries (25% primary infection) or other patients previously infected with MERS-CoV (45% secondary infection). However, there is still a large group of patients where no relationship with these two sources of infection has been proven. To date no case of neonatal or vertical transmission has been reported.<sup>7,13,14</sup>

From the more than 700 confirmed initial cases of MERS-CoV it has been observed that 63.5% of those infections have occurred in men (the male:female ratio ranges from 2.8:1 to 3.3:1), with an average age of 47 years (range 9 months–94 years). There have been very few cases reported in children aged under 15.<sup>7–9</sup> The average incubation period of the infection has been estimated at 5.2 days (range 1.9–14.7 days); 95% of patients report clinical symptoms before day 12. The series interval, which represents the time between the onset of symptoms of a case and the onset of symptoms of a contact, has been estimated at about 7.6 days (range 2.5–23.1 days) being below 19 days in 95% of all cases. The primary transmission rate (R0) has been set at 2–6.7 in hospital outbreaks and secondary cases. In intrafamily contacts, transmission has been estimated by 4%.<sup>14–16</sup> The average time between the onset of symptoms and death is about 23.7 days (range 22–25.3).<sup>15,16</sup> The epidemic appears to have a certain seasonal distribution, predominating between the months of April and May (spring) and it might be associated with the time of birth and rearing of new camels.<sup>7,9</sup>

The first cases were reported as severe pneumonia with respiratory difficulty and extrapulmonary manifestations. Initial symptoms are nonspecific and include fever, chills, sore throat, nonproductive cough and dyspnea. In cases of poor prognosis, the patient has a significant respiratory impairment in 3–4 days. Radiographic images usually show local or systemic pneumonia, similar to acute respiratory distress syndrome. One of the main

<sup>☆</sup> Please cite this article as: Reina J, Reina N. El coronavirus causante del síndrome respiratorio de Oriente Medio. Med Clin (Barc). 2015;145:529–531.

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extrapulmonary manifestations is acute renal failure, which occurs in about 50% patients infected with MERS-CoV and appears within 10 days after onset of process, which involves the need for a kidney transplant in over 15% cases.<sup>14–19</sup> This severe renal impairment is a unique or very specific clinical feature of MERS-CoV infection, since in the SARS epidemic only 6.7% of patients developed renal failure and only 5% required kidney transplant.<sup>6,7</sup> The presence of the virus in urine might imply the direct participation of this renal condition, although it is postulated that systemic hypoxia is the main cause.<sup>18,19</sup>

25% of patients with MERS-CoV have intestinal symptoms; and from 6 to 25% serious cases suffer from diarrhea, nausea and vomiting. It has been possible to detect the virus in feces, but no conclusive data are available about its meaning and possible route of dissemination.<sup>15,17</sup>

Most (62%) of serious cases require hospitalization, being mainly primary cases in elderly patients with comorbidities (96%). The main identified comorbidities have been: diabetes (68%), chronic renal disease (49%), hypertension (34%), chronic heart disease (28%) and chronic lung disease (26%). Smoking and obesity have been reported in 23 and 17% cases, respectively. Although the average fatality rate is 40%, the highest levels were reported in men aged over 50 with multiple comorbidities.<sup>6,7,18,19</sup>

Epidemiological studies in the environment of family and hospital outbreaks have shown the existence of completely asymptomatic cases or with little obvious symptomatology which would have not been reported in case of no outbreak. Most asymptomatic cases are youngsters, children and healthy women being health caregivers (27%).<sup>7,20,21</sup> Therefore, it seems clear that the cases reported so far only include severe and complicated cases requiring hospitalization. Most likely, the number of people infected with MERS-CoV is much higher in accordance with seroprevalence data and asymptomatic infection (from 1.1 to 3.6% of healthy population),<sup>6,7</sup> the epidemic being much more widespread than as initially expected (endemicity).

From the epidemiological point of view it has been postulated that MERS-CoV infection is very similar to that observed in SARS-CoV; that is, a very prevalent disease among the general population (many asymptomatic or mild cases) and few serious cases, only elderly or immunosuppressed patients.<sup>6–8</sup> Retrospective serological studies have shown that the MERS-CoV had not been in circulation 2 years before the first clinical case in 2012.<sup>22</sup> Nor seropositive cases have been detected in people who work in direct contact with animals, such as slaughterhouses.

Due to the sudden emergence of MERS-CoV without definitive evidence of past exposure in the general population, the emergence of a new episode of interspecies transmission of a new virus of animal origin (zoonotic event) has been postulated. In accordance with the studies on genetic concordance conducted in bats, the MERS-CoV might have been present in this animal reservoir for more than 40 years.<sup>23,24</sup> Because the contact or transmission between bats and humans is rare, we should think of an intermediate host to amplify the infective process. *In vitro* studies on cell lines have shown that MERS-CoV is able to replicate efficiently in cells of many animal species, including camels, goats, pigs, rabbits, horses and civets.<sup>22,24</sup>

To this virus, the ability to infect cells (species tropism) depends on the expression of dipeptidyl peptidase-4 receptor (DPP4) in these cells, which is well preserved and present in many cells of mammals.<sup>25</sup> Glycoprotein S in MERS-CoV is the glycoprotein specifically binding the DPP4 receptor located on the surface of epithelial and endothelial cells of human beings, including lung, kidney, intestine and liver as well as in the T lymphocytes. In lung, these receptors are located in pneumocytes type 1 and 2 and alveolar macrophages which are located in the deepest parts of the lung parenchyma, determining difficulty and respiratory failure.<sup>7,25</sup>

Alveolar cell destruction due to rapid viral replication and the immune response induced (cytokine cascade) determine the deterioration of respiratory function and systemic manifestations.<sup>6,7</sup>

The first evidence supporting the presence of an intermediate animal host for MERS-CoV emerged when the presence of specific neutralizing antibodies was verified in a group of native camels.<sup>26</sup> Subsequent studies confirmed this finding and the wide areal distribution of infected camels not only in the Arabian Peninsula, but also in African countries. Therefore, camels have been regarded as potential asymptomatic carriers or reservoirs for this new virus. A retrospective serological analysis reported that from 1983 to 1992 there were already seropositive camels in some areas from Africa and that the virus might have arrived later to current areas through their imports.<sup>23,24,26</sup> It seems confirmed that the MERS-CoV originally came from African bats and then it crossed the first interspecies barrier infecting camels in the Horn of Africa. Afterwards, the virus arrived in the countries of the Arabian peninsula in these hosts and eventually it crossed a second interspecies barrier and infected humans.<sup>4,5,7,26</sup>

The screening analysis of MERS-CoV genome in different samples of seropositive camels showed their nonconstant presence in nasal secretions, but not in feces.<sup>7,27</sup> Thus, it was thought that airborne transmission might be through droplets from the infected camels to humans in direct contact with them. Confirmation of the camel to human transmission could be demonstrated definitively through genetical analysis of a MERS-CoV strain from a patient with severe pneumonia and from the nasal aspirate of a camel with rhinorrhea owned by this patient.<sup>7,26,27</sup> Thus it was established that the virus could persist in the air around the infected camels or even humans with respiratory symptoms for at least 24 h. However, since culture is not possible, their actual infectivity is unknown, but evident airborne transmission is presupposed.<sup>28</sup>

Seropositive camels would show intermittent or sporadic episodes of replicative activity that would be associated with the respiratory excretion, but most of the time they would remain as active nonexcreta. The presence of antibodies in these animals and transmission to their newborns would not have a definite protective effect on the virus to prevent reactivation processes or potential reinfection.<sup>27,28</sup>

It remains unclear whether camels are simply intermediate amplifier hosts or actual natural reservoirs of MERS-CoV. It seems clear that the actual natural reservoir are bats (primary reservoir). However, the detection of antibodies in African camels over 28 years ago, the high genetic stability of the virus in camel populations (low genetic divergence is suspicious of adaptation to the host) and the high genetic identity between human and camel strains, evidences that the MERS-CoV is perfectly adapted and has been spread freely among the camels for a long time. Therefore, it may have become a natural secondary reservoir.<sup>6–9</sup> It cannot be ruled out the existence of another viral source, since about 30% confirmed cases lack contact with animals or humans.<sup>7</sup> The potential infective routes from the camel should also be re-evaluated. Respiratory route appears to be most likely, due to the presence of the virus in nasal and conjunctival secretions, but direct contact with other fluids might have some epidemiological role. Thus, it has been suggested that the intake of raw camel milk might be a hidden source of infection, because the virus is able to survive in it for at least 48 h at 4–22 °C.<sup>29</sup>

Despite the time elapsed since the diagnosis of the first case of MERS-CoV infection, no specific antiviral treatment is available that has proven significant clinical efficacy.<sup>7,8</sup> A large number of clinical trials are being conducted with different drugs, but the available data do not provide definitive or conclusive results yet. Thus, *in vitro* studies have shown that the MERS-CoV appears to be much more sensitive to pegylated interferon compared to SARS-CoV. However, no clinical data are available on human

effectiveness. Nevertheless, the combination of interferon with ribavirin provides future therapeutic hope.<sup>7,30</sup> In this perspective, the only possible treatment for patients is life support measures and the prevention of complications.<sup>7,8</sup>

Similarly, a specific vaccine is not available yet for human or animal intermediates (camels) that can be applied as a preventive measure. As it happened with SARS-CoV, it appears that the use of surface glycoprotein molecule will be the candidate for the vaccine.<sup>7–9</sup> However, how soon it is obtained depends on the evolutionary future of the current epidemic, the cost-benefit analysis and preventive vaccine targets.

It is very important to monitor the evolution and spread of the current MERS-CoV epidemic as well as genetic variations of the new CoV to know and understand its adaptability to human population and, particularly, its transmission capacity among individuals. The epidemic lethality will probably decrease if specific diagnoses and support treatments are initiated early. Therefore, this fourth horseman of the apocalypse will become a local endemic zoonosis.

### Conflict of interests

The authors report no conflict of interest.

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