

Middle East Respiratory Syndrome Coronavirus

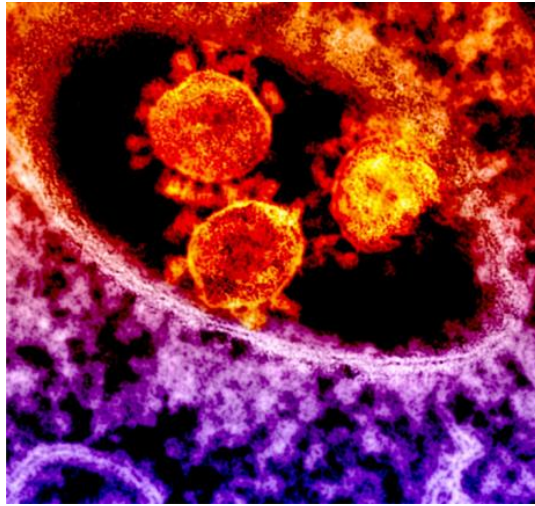


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MERS-CoV

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Introduction

A novel coronavirus distantly related to the SARS virus appears to have first emerged into human populations in the Middle East during 2012. As of 10 June 2016, WHO reported a total of 1733 confirmed human MERS-CoV cases including 628 deaths from 27 countries worldwide (Figure 1, Figure 2).

In September 2012, a novel coronavirus was isolated almost simultaneously from a patient with pneumonia in Saudi Arabia, and a patient from Qatar in the intensive care unit of a hospital in the United Kingdom. During the subsequent year, another 136 cases of MERS-CoV including 58 deaths were confirmed from patients hospitalized in 10 countries in Europe and the Middle East, including a previously unrecognized cluster of 2 confirmed fatal cases and 11 probable non-fatal cases of MERS-CoV in Jordan during March-May 2012 (WHO 2013). The retroactively-identified initial MERS-CoV outbreak in Jordan was especially notable because the cluster involved cases treated at three different hospitals, and apparent human-to-human transmission between and among the putative index case, family members, and health care workers (WHO 2014).

Over the two years subsequent to the retroactively detected index outbreak in Jordan (March 2012 - March 2014), WHO reported a total of 184 confirmed human cases including 80 fatalities caused by the MERS-CoV. A major

resurgence of new MERS-CoV cases during April 2014 brought the total number of reported confirmed MERS cases worldwide to more than 360 cases, with more than 100 new cases reported from Saudi Arabia alone during the first three weeks of April 2014. As of April 2014, the geographic distribution of reported confirmed MERS-CoV cases included 15 countries in the Middle East (Jordan, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, Yemen), Europe (France, Germany, Greece, Italy, United Kingdom), Africa (Tunisia), and Asia (Malaysia, Philippines). All persons with confirmed MERS-CoV infections had been individuals who were either residents of Middle Eastern countries, persons with a recent history of travel to the Arabian Peninsula, or persons having close contact with individuals having a recent history of travel to the Middle East, and there had been no evidence to indicate indicating any sustained human-to-human transmission or community-level transmission of MERS-CoV.

A major new development in the epidemiology of MERS-CoV occurred during May-July 2015, in conjunction with the proliferation of mass nosocomial outbreak in South Korea involving 15 separate health facilities, with a reported total of 186 confirmed cases including 36 deaths. All cases appear to have been derived from with a single index patient infected in the Middle East who developed symptoms after returning to Korea. One case associated with this cluster was reported from China, in a traveler from Korea who developed symptoms while travelling to China (ECDC 2015). It is important to recognize that that the Korea MERS-CoV outbreak of May-July included more confirmed human cases **than the total number of human recorded worldwide during the first two years following the first documented emergence of MERS-CoV into human populations.**

In January 2016, two apparent cases of human infection were serologically confirmed from archived serum specimens collected from two individuals in eastern Kenya during 2013 and 2014 who were known to have had exposure to livestock in a region where camels are common and consumption of camel milk and or meat likely, but no actual documented exposure to camels. These were the first reported autochthonous cases of human infection from MERS-CoV in Sub-Saharan Africa (Liljander et al. 2016).

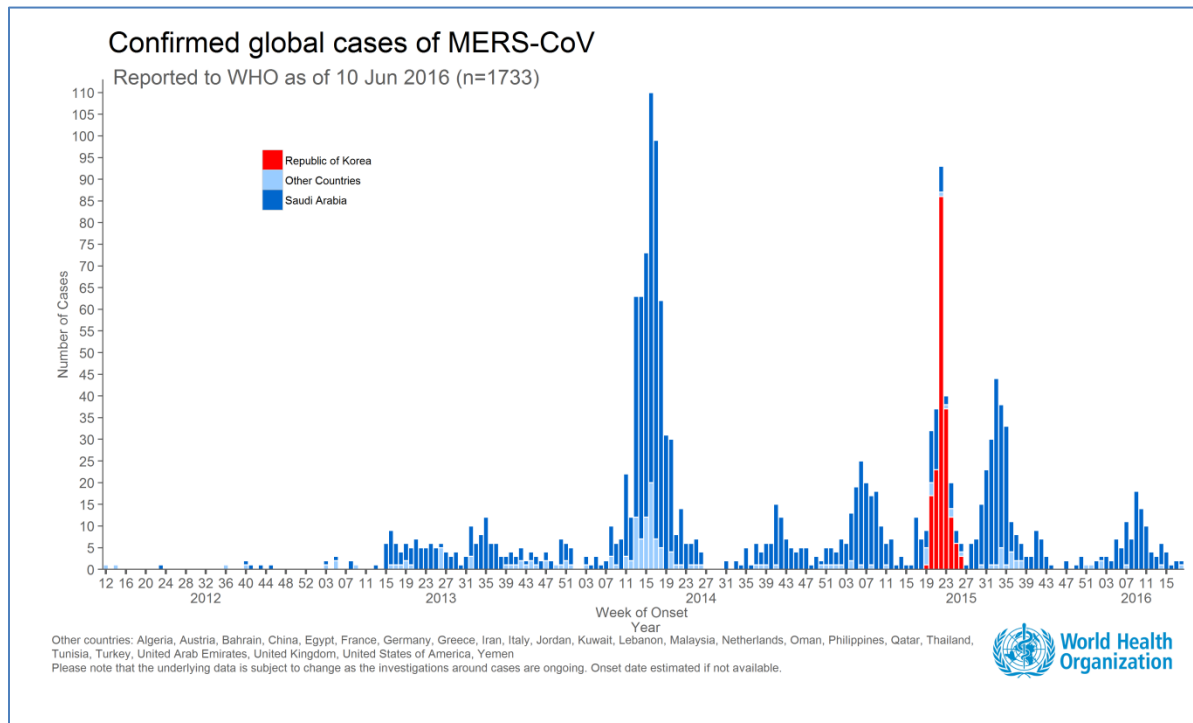


Figure 1. WHO graph showing incidence of confirmed human MERS-CoV cases from March 2012-May 2016.

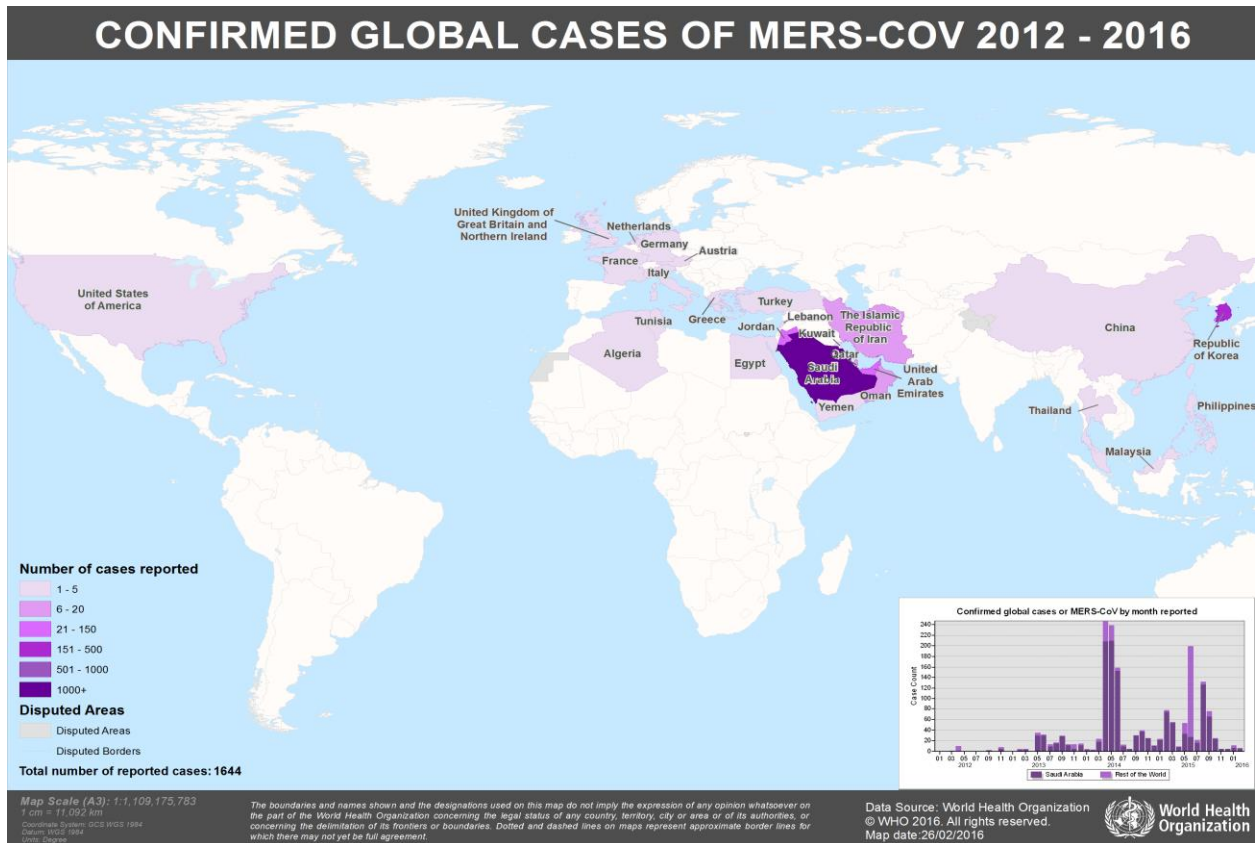


Figure 2. WHO map showing distribution of reported confirmed human MERS-CoV cases worldwide during period from March 2012 - February 2016.

Epidemiology

The typical clinical features of MERS-CoV disease are similar to those associated with the Severe Acute Respiratory Syndrome coronavirus (SARS): an acute lower respiratory disease syndrome (ARDS) with fever and dyspnea. Other common presenting symptoms include chills, rigor, headache, myalgia, malaise, and diarrhea. Unlike the related SARS coronavirus which emerged in China about a decade earlier, the MERS-CoV has been associated with a relatively high rate of deaths among confirmed cases (>35%).

The fatality rate among patients who develop severe respiratory disease symptoms typical ARDS symptomatic cases has been very high, about 60%, with the majority of fatal cases occurring in men >60 years old. Extensive outbreak clusters involving human-to-human transmission from patients to health care workers, family members, and other patients have been reported from hospitals in the Middle East, Europe, and South Korea (Hijawi et al. 2013; Memish et al 2013; ECDC 2015). Mild disease and atypical presentations associated with gastrointestinal presentations have also been reported, and appear to be most frequently associated with infections acquired through apparent human-to-human transmission. There is evidence that there may be multiple routes for human-to-human transmission of the MERS-CoV.

There are four distinct epidemiological patterns associated with human MERS-CoV cases

- isolated cases in persons with recent history of travel to the Middle East;
- isolated sporadic cases within communities (presumably from zoonotic infections);
- clusters of infections within families;
- clusters of infections within health care facilities (healthcare workers, patients, visitors)

Most reported MERS-CoV index cases have involved individuals with pre-existing medical conditions, and among the 1,201 cases for which data is available from WHO, the overwhelming majority of cases (84.2%) presented with severe illnesses (ARDS, pneumonia), approximately 10% of cases exhibited mild illness, while 6% were asymptomatic. The median age of confirmed cases for which data are available is 54 years (range 9 months - 109 years), with the highest rates of morbidity and mortality occurring among men \geq 50 years old. Among primary or index cases, 65% have been male, and men outnumber women by a factor of more than 2 to 1 among cases $>$ 60 years of age.

There has been a trend towards a lower median age and case fatality rate caused by the increased detections of mild cases or asymptomatic infections among health care workers, children, and young adults. Among the relatively few MERS-CoV cases documented from children and adolescents, the majority have been mild or asymptomatic infections. The largest numbers of cases have been those associated with hospital-related nosocomial transmission clusters, the most important of these being the epidemic of 186 cases in South Korea and China linked to a single index patient with a recent history of travel to the Middle East who has been treated at multiple hospitals in South Korea.

Genomic and Phylogenetic Analyses

The genetic diversity of available sequences in public bioinformatics databases indicates multiple introductions from a presumed zoonotic source, with subsequent human-to-human transmission. Genetic sequence analyses have estimated that the MERS-CoV probably first emerged into human populations sometime between 2007 and 2012. Studies have identified the period during June-July 2011 as a probable date for the first emergence of MERS-CoV into human populations (Cotton et al. 2013; Cauchemez et al 2014).

Recent studies of MERS-CoV sequences indicated that the novel "Lineage 5" recombinant subclade of MERS-CoV which appears to have first emerged in camels during 2014 became the dominant strain among human and camel populations in Saudi Arabia during 2015 (Sabir et al. 2016; Assiri et al. 2016). Most importantly, the available data from human cases collected during mid-2015 suggest that this new MERS-CoV Lineage 5 strain may have a potential for transmission by asymptomatic individuals (Assiri et al. 2016). These new findings highlight the need for increased epidemiologic and laboratory surveillance for MERS-CoV in human and camel populations.

Zoonotic Reservoir

The available evidence indicates that the dromedary camel is the principal animal reservoir for MERS-CoV, and the proximate source for most zoonotic human infections (Sabir et al. 2016). Retrospective serum analyses of samples from camels demonstrate that MERS-CoV or a genetically similar precursor virus has been circulating among camel populations in northern Africa and the Arabian Peninsula for several decades. Serological investigations have identified antibodies to MERS-CoV virus from dromedary camels in numerous countries in the greater Africa and the Middle East region, including Saudi Arabia, Jordan, Oman, Egypt, Sudan, Ethiopia, Kenya and the Canary Islands. Antibodies to a MERS-CoV-like virus have been detected in serum specimens collected from camels from Saudi Arabia and Kenya during 1992, and Somalia in 1983 (Aligali et al 2013; Müller et al. 2014).

Potential mechanisms for zoonotic transmission to humans include exposure to milk, urine, feces, nasal secretions, uncooked meat or internal organ tissues from infected camels (Memish et al. 2014; Hemida et al. 2015).

Experimental studies have demonstrated that the MERS-CoV can survive for prolonged periods in fresh camel milk at ambient temperatures of between 4⁰C and 22⁰C (van Doremalen et al 2014). The detection of MERS-CoV in nasal swab specimens from camels indicates the potential for respiratory transmission of the MERS-CoV from camels to humans (Hemida et al. 2014).

Several lines of evidence support the hypothesis that camels are the principal reservoir host for the MERS coronavirus. Human MERS cases in the Arabian Peninsula tend to be higher during winter and early spring periods when virus circulation in camel herds reaches at their highest levels (Hemida et al. 2015). A similar pattern of correlated peak outbreak cycles in humans and domesticated animal reservoir hosts (poultry) has been observed for the H5N1 avian influenza virus (Dudley 2008; Durand et al. 2015). Many confirmed MERS-CoV cases reported by WHO reportedly had recent contact with camels, or had consumed camel milk (WHO 2014).

Essentially identical MERS-CoV genetic sequences have been confirmed from dromedary camels in contact with confirmed human cases in Qatar and Saudi Arabia (Qatar Supreme Council of Health 2013; Alagaili et al 2014; Omrani et al. 2015; Hemida et al. 2015). A seroepidemiological investigation of MERS-CoV infection in an area of Saudi Arabia with sustained zoonotic transmission detected MERS-CoV antibodies in 0.15% of samples of adults over 15 years of age. Men had a significantly higher proportion of infections (0.25%) than women (0.05%), and with higher prevalences among individuals with direct exposure to camels. The seroprevalence of MERS-CoV among individuals with intensive occupational exposures to camels (shepherds, slaughterhouse workers) was 15–23 times higher than in the general population (Müller et al. 2015).



Figure 3. Dromedary camel (*Camelus dromedarius*) <http://en.wikipedia.org/wiki/File:Camelcalf-feeding.jpg>

Although it is clearly evident that MERS-CoV is a zoonotic disease that can be transmitted from camels to humans, the principal route(s) for camel to human transmission are not fully understood. Humans with regular and heavy exposure to infected camels do become seropositive, but even camel abattoir workers and farm workers who are exposed daily to camels who are regularly shedding MERS-CoV are not uniformly infected and rarely get overt disease (Hemida et al. 2015). Some investigators have suggested that there may be another unidentified zoonotic reservoir for the MERS-CoV virus which could serve as the original reservoir host, or as an intermediate host for transmission between camels and humans (Hemida et al. 2015). The identification of the principal route(s) of MERS-CoV transmission between camels and humans remains critical to preventing the spread of MERS-CoV into human populations.

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