UPDATED RAPID RISK ASSESSMENT

Severe respiratory disease associated with Middle East respiratory syndrome coronavirus (MERS-CoV)

Seventh update, 24 September 2013

Main developments in this update

- As of 24 September 2013, 133 confirmed cases of MERS-CoV have been reported worldwide, 60 of which have been fatal. The age range is from 2 to 94 years, with a median age of 50 years. Sixty-two per cent of cases with gender information are male. To date, all cases have either occurred in the Middle East or have had direct links to a primary case infected in the Middle East. Saudi Arabia has reported 111 cases, including 49 deaths; Jordan reported two fatal cases, Qatar three (including two deaths), and the United Arab Emirates reported five cases, including one death.
- Twelve cases were reported outside of the Middle East: United Kingdom (4), Italy (1), France (2), Germany (2), and Tunisia (3). These 12 cases resulted from six separate chains of transmission. The primary case for each chain had been infected in the Middle East and local secondary transmission was reported from the United Kingdom, France, and Tunisia.
- All new cases reported since the 18 July update were reported by Saudi Arabia and Qatar.
- The number of new cases per month in Saudi Arabia increased tenfold since April 2013.
- The skewed age and gender distribution – with a higher incidence in older men – has become less accentuated since the last update because more mild and asymptomatic cases were detected through contact tracing.
- Nosocomial transmission currently accounts for 24% of all reported cases.
- Three studies were published related to the potential animal reservoir of MERS-CoV: two of them describe the identification of MERS-CoV-neutralising antibodies in a high proportion of dromedary camels from Oman, Egypt, and, to a lesser extent, from the Canary Islands. In none of these countries human cases of MERS-CoV were reported. The other study describes the possible identification of MERS-CoV in a single faecal sample from a bat sampled in Bisha, Saudi Arabia, a town in the vicinity of the index case's residence. The implications of these findings are still unclear. The reservoir, the potential hosts, and the route of transmission remain unknown.
- WHO issued three new documents:
  - Advice on home care for patients with MERS-CoV infection presenting with mild symptoms and management of contacts [3].
  - Interim travel advice [4] related to MERS-CoV for pilgrimages to the Kingdom of Saudi Arabia for Umrah and Hajj.
  - Interim recommendations for laboratory testing [5] for Middle East respiratory syndrome coronavirus.
- The International Severe Acute Respiratory and Emerging Infection Consortium published a decision support tool for treatment of MERS-CoV [7].

- The largest genetic analysis to date on MERS-CoV was published in May 2013 [18]. Phylogeographic analyses suggest that the MERS-CoV zoonotic reservoir is geographically disperse and that MERS-CoV has been introduced into the human population multiple times. This study suggests that the Al-Ahsa hospital outbreak might have had more than one virus introduction, and suggests that the R_0 in this event may be lower than previously estimated. The investigators estimated that the time of the most recent common ancestor was July 2011, which is consistent with other studies [19].
- Based on a recent survey carried out by ECDC in collaboration with WHO, all EU/EEA Member States have either the capacity to detect and confirm MERS-CoV or have arranged for cross-border referral for these services. Nineteen EU/EEA Member States have tested human specimens for MERS-CoV between September 2012 and June 2013.

Key conclusions

- The risk of importation of MERS-CoV to the EU is expected to continue and may increase as a result of possible increasing transmission in Saudi Arabia and the increasing number of visitors from the EU to Saudi Arabia during the Hajj in October 2013. The precise risk of importation is difficult to estimate as long as the source of the virus and the mode of transmission are unknown.
- Twenty-four per cent of MERS-CoV infections have occurred from nosocomial transmission in healthcare settings, both in Europe and in the Middle East.
- The risk of secondary transmission in the EU remains low and could be reduced further through screening for exposure among patients presenting with respiratory symptoms; strict implementation of infection prevention and control measures for patients under investigation would also reduce the risk of secondary transmission.
- Although studies indicate that animals are the probable source of infection, or intermediate hosts, the virus reservoir remains unknown. The transmission pattern in Saudi Arabia, with many sporadic cases distributed over a large geographical area, points to repeated introductions of the virus from a continuous non-human source. Finding the source of the virus is key to formulating advice on how to reduce the risk of exposure.
- All EU/EEA Member States have adequate capacity or provisions to detect MERS-CoV.

Key recommendations

- Travellers to the Middle East who develop respiratory disease within 14 days after their return to Europe should seek medical attention and immediately communicate their travel history to the healthcare provider. They should practice cough etiquette, avoid contact with others, and avoid public transport until assessed by a healthcare worker. Clinicians should consider MERS-CoV infection in those patients.
- Patients presenting with severe acute respiratory infections in the EU should be screened for travel history to Saudi Arabia and the Middle East and for contact with MERS-CoV patients at first contact with the health system.
- Clinicians and public health professionals should consult the WHO case definition to determine which patients should be tested. In addition to testing for MERS-CoV, patients should also be tested for community-acquired pneumonia as per local management guidelines.
- National authorities should report all cases diagnosed in the EU/EEA to the Early Warning and Response System (EWRS).
- All close contacts of probable and confirmed MERS-CoV cases should be followed-up and monitored for symptoms for 14 days after last exposure.
- Possible and confirmed cases requiring hospital admission should be admitted directly to negative-pressure single rooms. If this is not possible, a single room with en-suite facilities should be used.
- Healthcare workers caring for patients under investigation for MERS-CoV or confirmed cases should exercise standard precautions (including hand hygiene) as well as contact and airborne precautions.
- Travellers to the Middle East should:
  - avoid contacts with animals and their waste products;
  - limit contacts with others and practise cough etiquette (maintain distance, cover coughs and sneezes with disposable tissues or clothing, and wash hands) if they develop respiratory illness;
  - avoid close contact with sick people, especially with those suffering from acute respiratory infections;
  - practise good hand hygiene, especially after direct contact with ill people or their environments.
- Travellers from the EU who plan to visit Saudi Arabia for the Hajj pilgrimage should consult the recommendations made by the Saudi Arabian Ministry of Health/WHO and should consider deferring their travel if they are above 65 or below 12 years of age, pregnant, suffer from chronic disease (e.g. heart disease, kidney disease, respiratory disease, diabetes), immune deficiency (congenital and acquired), malignancy or terminal illnesses.

Source and date of request

ECDC internal decision, 13 September 2013.

Public health issue

This seventh update of the rapid risk assessment of the MERS-CoV outbreak reviews information that has become available since the 18 July update and its implications for EU/EEA countries.

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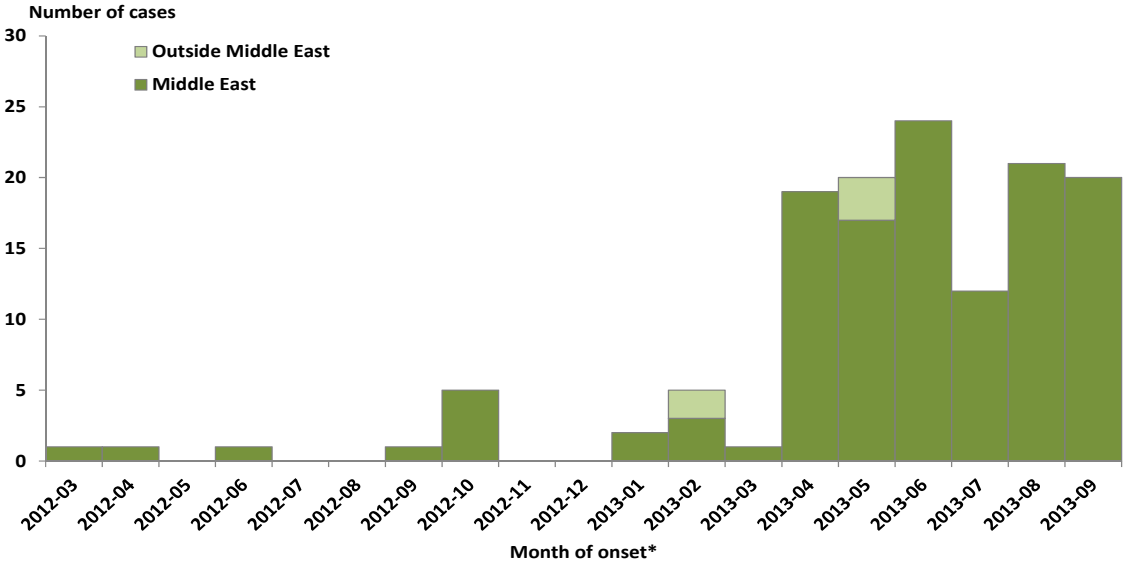
Event background and epidemiology

In June 2012, a case of fatal respiratory disease in a previously healthy 60-year-old man was reported from Saudi Arabia [1]. The cause was subsequently identified as a new coronavirus that has been named Middle East respiratory syndrome coronavirus (MERS-CoV). Retrospective investigations revealed that the first cases of the disease had occurred previously in a cluster of hospital-associated cases in Jordan in April 2012 [2]. By 23 September 2013, 133 cases of MERS have been reported. All cases have either occurred in the Middle East or have direct links to a primary case infected in the Middle East.

Saudi Arabia has reported 111 cases, including 49 deaths; Jordan reported two cases, including two deaths. Qatar reported three cases, including two deaths, and the United Arab Emirates reported five cases, including one death. Twelve cases were reported outside of the Middle East: in the United Kingdom (4), Italy (1*), France (2), Germany (2), and Tunisia (3). The primary case for each chain was infected in the Middle East, and local secondary transmission following importation was reported from the United Kingdom, France, and Tunisia.

* Two patients earlier reported as laboratory-confirmed with MERS-CoV infection in Italy were reclassified as probable cases. The reclassification follows a further analysis of the laboratory tests performed in May 2013, which has shown that the two cases do not fulfil the current WHO case definition for a 'confirmed case' of MERS-CoV. The two cases are the two-year-old girl and a 42-year-old woman who were identified as close contacts of the index case who travelled from Jordan.

Figure 1. Distribution of confirmed cases of MERS-CoV reported worldwide, by month of disease onset* and probable place of infection, March 2012 – 24 September 2013 (n=133)



** If unknown, month of reporting was used.*

An analysis of the first 47 cases of MERS hospitalised in Saudi Arabia documented a 60% case-fatality rate, which increased with age. The male to female ratio was >3:1. Almost all of the patients were adults (46 of 47, 98%), and the vast majority had chronic conditions (46 of 47, 98%), including diabetes, hypertension, chronic cardiac and chronic renal disease. In addition to fever (98%) and cough (83%), gastrointestinal symptoms were also frequent, including diarrhoea (26%), vomiting (21%), and abdominal pain (17%). All patients had abnormal chest radiography, and almost half (49%) had elevations in lactate dehydrogenase[6].

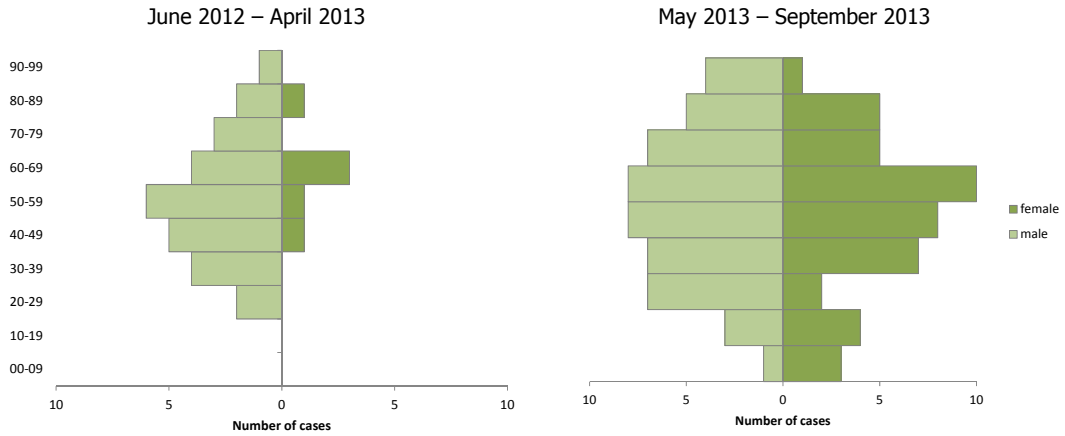
Based on officially reported data, a review of scientific articles, and epidemic intelligence information, 133 confirmed cases of MERS-CoV infections have been reported worldwide as of 24 September 2013; 60 (45%) cases have been fatal. The age range is from 2 to 94 years; the median age is 50 years.

Since April 2013, a tenfold increase of new cases per month was observed in Saudi Arabia, compared to previous months (Figure 1).

The following developments are noteworthy:

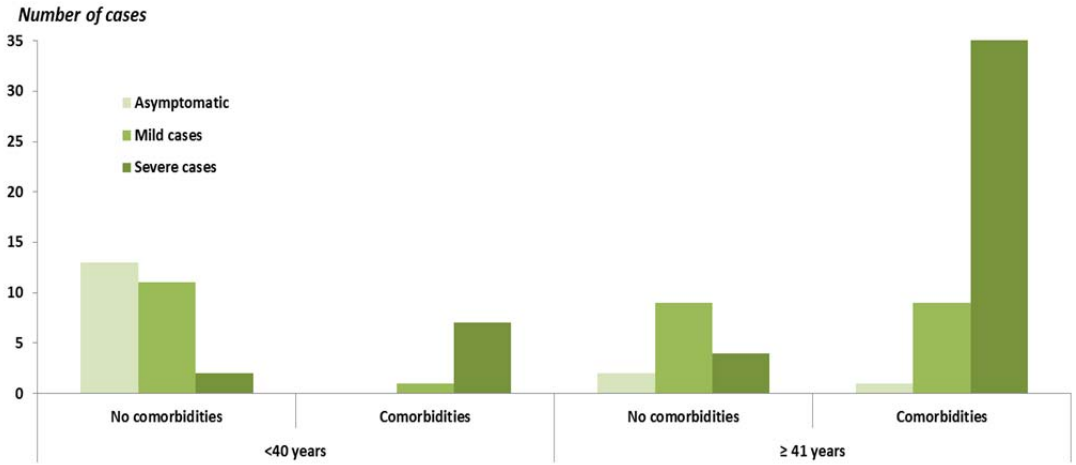
- The cumulative case–fatality rate (CFR) decreased from 60% (based on the first 47 cases in Saudi Arabia) to 45%, calculated from the beginning of the outbreak until 24 September 2013.
- The proportion of males among the cases is 62% (as of 24 September). In the beginning of the outbreak, the majority of the age groups had more male than female cases; between May 2013 and September 2013, a larger proportion of younger female cases was reported (Figure 2).
- The ratio of asymptomatic to symptomatic confirmed cases is increasing. Eighteen asymptomatic cases were reported since June 2013, compared with no asymptomatic cases in the first five months of the year. Five of these asymptomatic cases were reported in September 2013.

Figure 2. Distribution of confirmed cases of MERS-CoV by age, gender and period of reporting (128 cases with known age and gender)



Among the reported confirmed cases, comorbidity is associated with severe disease or fatal outcome (prevalence ratio=6.4, exact 95% CI 3.9 – 10.8). Among 18 with available information, only one healthcare worker was reported to have underlying disease .

Figure 3. Distribution of confirmed cases of MERS-CoV reported worldwide, by comorbidity, severity, and age group (as of 24 September 2013)



Seventy-seven per cent of healthcare workers were reported to be female. The proportion of asymptomatic cases among healthcare workers is higher (36%) compared with cases among non-healthcare workers (10%, p=0.005).

The reason for the strong male predominance in the beginning of the outbreak remains unexplained. However, there are indications that the gender distribution is becoming more balanced over time as contact tracing improves and more mild and asymptomatic cases are being detected, possibly because carers tend to be more female. It is important to note that there are more men than women in the Saudi population (M:F 1.21) and that this slightly skewed gender distribution is most accentuated in the 25–54-year age group (M:F 1.36). It is possible that gender-based care-seeking and care-receiving behaviour in the Middle East plays a role [8].

Overall, a decreasing CFR, a more balanced gender ratio, a less skewed age distribution, and the recognition of more mild and asymptomatic cases all indicate the influence of improved case-finding due to raised awareness, increased clinical suspicion, improved diagnostic capacity, and more effective surveillance and contact tracing.

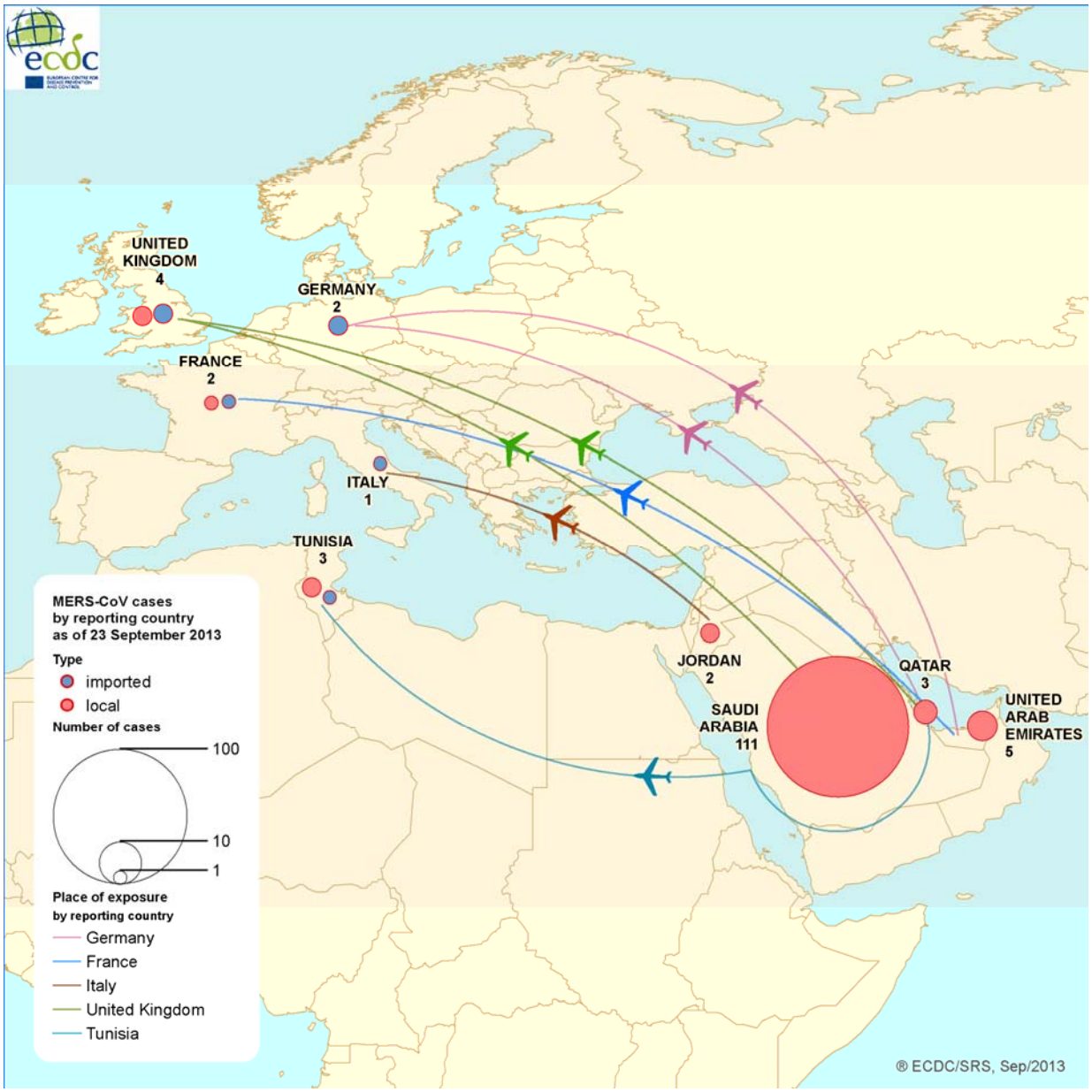
A serological study analysing human samples from Egypt and Hong Kong did not find any MERS-CoV-neutralising antibodies [9]. In addition, sero-epidemiological studies of close contacts are being undertaken in France, similar to studies already performed in Germany, which did not find evidence of MERS-CoV antibodies [9, 10]. It should be noted that the applied serological tests have not been sufficiently validated, and results should be interpreted with caution.

MERS-CoV in Europe

All nine European cases can be traced to contacts in the Middle East (Jordan, Saudi Arabia, and the United Arab Emirates) (Figure 4). Three primary cases were medically evacuated from the Middle East for specialised treatment in Europe; three others were patients who had been traveling in the Middle East and were hospitalised after

developing symptoms while in Europe, one case was a nosocomial contact of a hospitalised patient, and the last two cases were close contacts of primary patients [11-14]. Of the nine cases, five died.

Figure 4. Distribution of confirmed cases of MERS-CoV by place of reporting and place of exposure, April 2012 – 24 September 2013*



Virological information

MERS-CoV is distinct from the coronavirus which caused the SARS outbreaks in 2003; it is also distinct from the endemic human coronaviruses (HCoV) OC43, 229E, HKU1, and NL63. It belongs to lineage C within the *Betacoronavirus* genus (*Coronavirinae* subfamily), along with several viruses detected in bats in Europe and China [15].

An analysis of virus tropism indicated that these viruses can infect a variety of cell lines, including human cells, via surface receptors distinct from SARS coronavirus receptors [16]. MERS-CoV seems to be fully able to penetrate human bronchial epithelia cultures [17].

Several strains are available in GenBank as of 20 September 2013 [18, 19]. More data about recent cases are needed to allow comparative genomic studies of MERS-CoV. Genomic information on a larger panel of strains will likely shed light on the evolutionary rate of the virus and on the relationship between animal and human strains and make it possible to test alternative hypotheses on the transmission events underlying the emergence of MERS-CoV human infections.

A recently published descriptive genomic study about the transmission and evolution of MERS-CoV describes the genomic variation of 21 MERS isolates from Saudi Arabia, 20 of which from patients from a cluster in Al-Ahsa, Saudi Arabia [19]. The authors suggest that the Al-Ahsa outbreak was due to multiple zoonotic transfers, which contributed to the human-to-human transmission. The study identified at least two different lineages circulating in Riyadh in October 2012. They conclude that the transmission patterns are consistent with both human-to-human transmission and sporadic zoonotic events [19].

A recent study assessed the environmental viability of MERS-CoV. MERS-CoV remained viable for a longer duration on plastic and metal surfaces (viable at 48 hours in 20 °C and 40% relative humidity, comparable to an indoor environment) than influenza A (H1N1)pdm09. Using aerosol experiments, it was found that MERS-CoV also retained most of its viability in 20 °C and 40% relative humidity. Viability decreased at higher temperatures or higher levels of relative humidity. The authors concluded that the prolonged survival of MERS-CoV on surfaces increases the likelihood of contact and fomite transmission and that the ability to remain viable in an airborne state means that MERS-CoV may acquire the ability to be transmitted by aerosols [20].

These findings underscore the need for excellent infection control in healthcare settings and at home when taking care of MERS-CoV cases.

Based on a recent survey, all EU/EEA Member States have either the capacity to detect and confirm MERS-CoV or have arranged for cross-border referral for these services. Nineteen EU/EEA Member States have tested samples for MERS-CoV between September 2012 and June 2013 .

Source of infection

Unfortunately, there are not enough data from the hospitalised case series from Saudi Arabia or from the WHO-Saudi Arabia joint mission in June 2013 to make an authoritative statement on risk factors for acquiring MERS-CoV [21]. Key questions remain, including the source of MERS-CoV exposure and infection outside of healthcare settings. Case-control studies are urgently needed to identify risk factors for MERS-CoV, and serological studies are needed to determine the extent of MERS-CoV infection in the community.

No animal reservoir or mode of zoonotic transmission has yet been identified for MERS-CoV, although the similarities to bat coronaviruses make bats a possible source [22]. However, experience with SARS indicates that the exposure need not be directly from the animal source, but may result from environmental contamination or via intermediary animal hosts [15]. This hypothesis of bats being the possible source of infection is underlined by a study where bats were captured or their faeces were collected during two samplings in October 2012 and April 2013 in regions of Saudi Arabia where cases were reported. Of a total of 1 003 samples, 227 were positive for alpha and beta coronaviruses, isolated from faecal pellets or roost faeces, but not blood, wing punch biopsies, or throat swap samples. The only positive sample of MERS-CoV was identified in October 2012 in a faecal pellet of the bat species *Taphozous perforates* from Bisha, a town in the vicinity the index case's place of residence (the patient had died in September 2012) [22]. An amplification product was retrieved from a newly established generic MERS-CoV assay within a short highly conserved region; however, the recommended WHO MERS-CoV specific assay remained negative [22]. The fact that no other sequence information could be generated from this animal might indicate a very low virus load in the sample, but this does not rule out higher divergence within other genomic regions.

Two independent studies identified MERS-CoV-neutralising antibodies in dromedary camels from Oman, the Canary Islands, and Egypt, suggesting that these animals had previous contact with MERS-CoV or a very closely related virus (MERS-CoV-like) [9, 23]. Sera from other animals such as sheep, goats, cattle and other camelids did not show such antibodies. Cross-reactivity with human CoV OC43, SARS-CoV and bovine CoV was considered not to be relevant. No serologic data on animals from countries which reported human MERS-CoV are (yet) available. The high prevalence in Oman (all 50 tested sera from dromedary camels were positive) and Egypt (between 94% and 98% of a total of 110 camels tested positive, depending on the test used) suggests that the distribution of a MERS-CoV-like virus is widespread within the dromedary population in the Middle East and, to a lesser extent, in other regions (14% of a total of 105 camels tested positive in the Canary Islands) [23]. So far, no genetic information about the MERS-CoV-like virus infecting dromedary camels is available.

Routes of transmission

Zoonotic transmission

Animal and genetic studies provide some evidence that MERS-CoV might be a zoonotic disease, but it is still not clear how the disease transmits from animals to humans. The possibility of transmitting virus from bat excreta to humans has been discussed for other viruses such as bat rabies or *Hantavirus,* where humans can be infected by inhaling infectious viral particles present in dust. The route of transmission from dromedary camels to humans, if this is indeed the case, should be investigated in more detail if dromedary camels are confirmed as a source, or intermediate host, of MERS-CoV. Contact with animals, in particular camels, has been reported for some of the

cases, but this is anecdotal evidence which needs to be validated in case-control studies. To date, no epidemiologic studies documenting animal exposure have been published.

In order to identify the host/reservoir and source of infection, further studies are needed, including studies which provide data from animal sampling conducted in the Middle East.

Human-to-human transmission

While the source or reservoir of MERS-CoV is unknown, it is clear that the disease can be passed on from person to person, for example by close contacts or in healthcare facilities [10-13, 24-27]. Based on information on the first 77 cases, the basic reproduction number of the infection (R_0) has been estimated at 0.69 (95% CI 0.50–0.92) [28], indicating a low pandemic potential [29]. For comparison, the R_0 was estimated to be 0.80 (95% CI 0.54–1.13) for SARS-CoV, using the same methodology [28]. However, the small number of confirmed cases, the increasing detection of asymptomatic cases, and the potential evolution of the virus should be taken into account when interpreting these results [30].

Nosocomial transmission has been a hallmark of MERS-CoV. A large outbreak was documented in Al-Ahsa, Saudi Arabia: 23 confirmed and 11 probable cases were diagnosed as part of a single outbreak that involved four healthcare facilities [24]. The majority of cases were patients, but five family members and two healthcare workers were also affected. The haemodialysis unit was the most heavily affected, with nine confirmed cases, but transmission also occurred in the intensive care unit and the medical ward. Based on the epidemiology, one of the patients in the haemodialysis unit appears to have transmitted the infection to seven persons; another patient apparently infected three persons, and four patients transmitted the infection to two persons each. The median incubation period was 5.2 days, with a range of 1.9–14.7 (95% CI) [24]. The outbreak was reminiscent of SARS, with seven secondary cases transmitted in a haemodialysis unit. Despite a thorough investigation, questions remain, including whether person-to-person transmission occurred through airborne, respiratory droplets, or direct contact. Based on the currently available data, airborne transmission of MERS-CoV cannot be excluded, but there is no indication that it plays an important role in the transmission of the virus. Once strict infection control measures were implemented, the outbreak was contained.

Asymptomatic and mildly symptomatic healthcare workers have also been identified: one study reported seven cases in Saudi Arabia (two asymptomatic and five symptomatic) of MERS-CoV, confirmed by RT-PCR. All were women, six had no pre-existing conditions. All had some contact with a known MERS-CoV patient, and most were linked to some lapses in infection control while taking care of the patients. No secondary cases were identified from these healthcare workers [31]. In Germany and the United Kingdom [10, 11, 32], a follow-up screening exercise of nearly 200 personal contacts and healthcare workers who were exposed to two imported confirmed cases found no evidence of human-to-human transmission [10, 11, 32]. No secondary cases were identified from these healthcare workers [31].

Limited clusters of close contacts (1–2 secondary cases among close contacts) were identified in Tunisia and Saudi Arabia [32].

ECDC risk assessment for the EU

The increasing number of cases reported since April 2013 (Figure 1) appears to be the result of improved case finding, improved surveillance/contact tracing, and continued transmission in the Middle East. In any emerging disease outbreak, it is anticipated that raised awareness, increased clinical suspicion, improved diagnostic capacity, more effective surveillance, and contact tracing will result in higher case numbers, even if the actual transmission numbers remain stable. A higher case detection rate should also increase the proportion of mild and asymptomatic cases among new cases, as currently observed in the MERS-CoV outbreak.

At the moment there is no evidence of a change in infectiousness of MERS-CoV. The pandemic potential of MERS-CoV remains low. The basic reproduction number (R_0) was estimated to be 0.69, lower than for pre-pandemic SARS-CoV (0.80) and well below the epidemic threshold of 1 [28]. The ability of coronaviruses to evolve, make it likely that certain traits of MERS-CoV will change, for example pathogenicity, transmissibility, or detectability by current tests.

EU citizens may be at risk for contracting MERS-CoV either through travel to the Middle East or via nosocomial infection or through close contact with a case returning from the Middle East.

In the absence of information about the source of infection, routes of transmission, and behavioural risk factors, the risk of transmission to travellers in the Middle East is difficult to estimate. However, the risk of importation of MERS-CoV cases to the EU is also determined by the number of EU visitors to the Middle East and their length of stay. In 2007, Saudi Arabia received around 46 000 visitors from EU Member States. The number of visitors to Saudi Arabia is expected to increase significantly when the Hajj pilgrimage begins (13–18 October 2013). Around four million pilgrims from 180 countries went on the Hajj pilgrimage in 2012. Over 50% of the pilgrims arrive from outside Saudi Arabia, with around 45 000 from the EU [33, 34]. Saudi Arabia imposed a quota restricting the number of pilgrims from each country to 1 000 pilgrims per million Muslim population. The Ministry of Health in

Saudi Arabia has issued health recommendations for travellers to Saudi Arabia for the pilgrimage to Mecca (Hajj and Umrah) [35], stating that persons should consider deferring their travel if they are above 65 years of age or below 12 years of age, pregnant, suffer from chronic disease (e.g. heart disease, kidney disease, respiratory disease, diabetes), immune deficiency (congenital and acquired), malignancy or terminal illnesses.

Countries have a quota of 1 000 pilgrims per million Muslim population who can attend the Hajj. Therefore specific advice should be drawn up (in regional languages) and circulated through travel and religious organisations where appropriate and as recommended by WHO. The Saudi Arabian Ministry of Health has issued health recommendations for travellers to Saudi Arabia for the pilgrimage to Mecca (Hajj and Umrah) [38] stating that persons should consider deferring their travel if they are above 65 years of age or below 12 years of age, pregnant, suffer from chronic disease (e.g. heart disease, kidney disease, respiratory disease, diabetes), immune deficiency (congenital and acquired), malignancy or terminal illnesses.

The highest risk of transmission in the EU is likely to be from undiagnosed imported cases; efforts to rapidly identify cases in need of investigation are critical to prevent the spread of the disease.

Medical evacuations pose a particularly high risk of importation of cases to the EU. However, no secondary transmission has been associated with long-haul medical evacuations, suggesting that appropriate infection measures were applied and effective [10, 36]. The number of transfers may increase as concerns arise among clinicians and the public in the Middle East that there is a risk of MERS-CoV infection associated within hospitals in the area.

Due to the large number of guest workers in the Middle East, attention must also be drawn to the possible importation of MERS-CoV to southeast Asia and Pacific Asia, although so far no confirmed cases have been reported from this region [37].

Conclusions

The risk of importation of MERS-CoV to the EU is expected to continue, and it is possible that the risk of importation will increase as a result of increasing transmission in Saudi Arabia and an increasing number of visitors from the EU to Saudi Arabia during the Hajj from 13 to 18 October 2013. The precise risk of importation is difficult to estimate as long as the source of the virus and the mode of transmission remain unknown.

No cases were reported outside the Middle East since May.

The risk of secondary transmission in the EU remains low and could be further reduced through screening patients presenting which show suggestive respiratory symptoms and are linked to travel to the Middle East in the two weeks prior to presenting; the strict implementation of infection prevention and control measures for patients under investigation would be equally positive.

Limited human-to-human transmission has occurred in several clusters, among household or close contacts, and within healthcare facilities, both in Europe and in the Middle East [10-13, 24-26, 38]. The Al-Ahsa outbreak, with 23 confirmed cases in four facilities, the transmission in France between two people who shared a room and toilet, and the transmission in London from an intubated case to a visiting relative, indicate a significant risk for nosocomial transmission. The Al-Ahsa cluster is a significant event, which could have been caused by lack of appropriate infection prevention measures in the health facilities but also raises concerns about the possibility of a 'superspreading' event, a phenomenon that played an important role for the spread of the SARS-CoV pandemic.

Probably due to enhanced contact tracing activities, the proportion of cases associated with healthcare settings has increased substantially and now accounts for 24% of all reported cases. However, with the exception of the cluster in Al-Ahsa, the number of confirmed secondary cases per cluster has remained low, and there is no convincing evidence of the virus becoming more infective over time.

Although studies indicate that animals are the probable source of infection or intermediate hosts, the virus reservoir remains unknown. The transmission pattern in Saudi Arabia, with many sporadic cases distributed over a large geographical area, points to infrequent introductions of the virus from a continuous non-human source. However, no epidemiologic studies have been published that document animal exposure investigations.

Recommendations

Surveillance

Case finding

On 27 June 2013, WHO published revised their 'Interim surveillance recommendations for human infection with Middle East respiratory syndrome coronavirus' [39]; the recent update strongly recommends that specimens should be collected both from the upper and lower respiratory tract (see laboratory section).

On 3 July 2013, WHO published a 'Revised interim case definition for reporting to WHO – Middle East respiratory syndrome coronavirus (MERS-CoV)' [40]. A confirmed case is a laboratory-confirmed case as defined in 'Laboratory testing for novel coronavirus: Interim recommendations' [5]. The revised case definition identifies four categories of probable cases based on clinical presentation, exposure, and level of testing.

Travellers to the Middle East who develop respiratory disease within 14 days after their return to Europe should seek medical attention and immediately communicate their travel history to the healthcare provider. They should practice cough etiquette, avoid contact with others and avoid public transport until assessed by a healthcare worker. Clinicians should consider MERS-CoV infection in those patients. Clinicians should be familiar with the most recent WHO surveillance guidance [41], case investigation guidelines [42], WHO case definitions for MERS-CoV [40] and infection control guidelines, all of which can be found at the WHO Global Alert and Response page for coronavirus.

Patients who are evacuated from the Middle East deserve special attention. Companies undertaking medical evacuations from the Middle East should be reminded of their obligation to protect staff engaged in the transfer and the need to inform receiving hospitals of the risk of MERS-CoV infection. Receiving hospitals in the EU should screen patients for MERS-CoV infection and apply strict infection prevention and control measures, including administrative and environmental controls and personal protective equipment until MERS-CoV infection has been ruled out.

Laboratory testing

Clinicians and public health professionals should consult the WHO case definition [40] to determine which patients should be tested. In addition to testing for MERS-CoV, patients should also be tested for community-acquired pneumonia as per local management guidelines.

WHO updated their 'Interim recommendations for laboratory testing' [5] for screening and confirmation of MERS-CoV infection in September 2013 [5].

Recently published reports provide evidence that viral loads are higher in lower respiratory tract specimens (bronchoalveolar lavage, sputum, tracheal aspirates) compared with nasopharyngeal/oropharyngeal samples [32, 43]. Consequently, routine microbiological sampling through nasopharyngeal/oropharyngeal swabs may give negative results in persons later shown to be infected with the coronavirus; if a person meets the criteria for investigation, tests should be repeated on lower respiratory samples, especially if their condition is worsening [6]. The importance of continued multiple sampling from multiple sites will add knowledge about the duration of virus shedding and is strongly encouraged by WHO [5].

All specimens collected for laboratory investigation should be regarded as potentially infectious, and healthcare workers who transport clinical specimens should adhere rigorously to standard precautions to minimise the possibility of exposure to pathogens.

For shipping and transport purposes, diagnostic specimens should be treated as category B biological substances. Transport of specimens within national borders should comply with applicable national regulations. International transport of MERS-CoV specimens should follow applicable international regulations as described in the WHO publications 'Guidance on regulations for the transport of infectious substances 2013–2014' and 'Laboratory testing for Middle East respiratory syndrome coronavirus 2013' [5].

There are specific polymerase chain reaction (PCR) tests used to confirm the presence of MERS-CoV. At least two tests, using different methods, must be positive in order to confirm a case of MERS-CoV. A case with a positive PCR result for a single specific target without further testing but with a history of potential exposure and consistent clinical signs is considered a probable case. The recent publication describing MERS-CoV diversity does not interfere with the published assays for laboratory screening and confirmation (personal communication with Christian Drosten, Institute of Virology, University of Bonn) [44-46].

Serological tests have not been standardised and no ready-to-use kits are currently commercially available for serological testing. However, different serological tools for the detection of specific MERS-CoV IgM and IgG antibodies based on ELISA, protein microarray technology, and virus neutralisation have been developed recently. Validation is based on a limited number of specimens. These assays, presently in the hands of some specialised laboratories, can be used to aid diagnosis in individual patients, for confirmatory testing of positive tests, and for (large-scale) contact studies. These tests will need to be validated for use in the Middle East [46] [24]. The

availability of serological assays enables the performance of population-based serological studies on general prevalence or the investigation of frequency of seroconversion in exposed persons or risk groups.

Furthermore, protocols on the standardisation of influenza sero-epidemiology have been published. Drawing on these and in-country protocols, the United Kingdom has published a protocol for investigating cases of MERS-CoV infections which is suitable for use in other EU countries [7]. The CONSISE group has published specific coronavirus protocols [47].

More information about diagnostic procedures can be found in other journal articles [23, 27, 44, 45, 48-50] and on the University of Bonn website.

Reporting

All cases diagnosed in the EU/EEA should be reported by the national authorities to the Early Warning and Response System (EWRS) and to WHO under the International Health Regulations (IHR) (2005). Reporting in EWRS qualifies as IHR notification and avoids double reporting. Patients still under investigation do not need to be reported internationally while awaiting confirmation.

Contact tracing

All close contacts of probable and confirmed MERS-CoV cases should be followed-up and monitored for symptoms for 14 days after the last exposure. A close contact is defined as a healthcare worker or family member providing direct patient care or anyone who had prolonged (>15 minutes) face-to-face contact with a probable or confirmed symptomatic cases in any closed setting. Close contacts should have a base-line serum sample collected and stored, which can be used for comparison of paired sera if required later. Airway specimen should be tested with PCR if a contact develops symptoms. When collecting specimens, it should be considered that lower respiratory specimens generally have a higher viral load than upper respiratory specimens [7] [Guidance PHE, United Kingdom].

Countries should trace contacts of confirmed MERS-CoV cases on aircrafts according to the guidelines for SARS contact tracing in RAGIDA. This should be done regardless of flight time.

Priority for contact tracing efforts should be given to:

- passengers seated in the same row as the index case;
- passengers seated three rows in front or behind the index case;
- all crew members;
- passengers providing care for the index case;
- passengers having had >15 minutes of face-to-face contact with the index case;
- passengers having had contact with respiratory secretions of the index case; and
- passengers living in the same household with the index case.

Depending on the clinical presentation of the case during the flight and feasibility, Member State officials may consider extending the tracing of contacts beyond three rows, possibly including all passengers and crew members. Lacking firm evidence of on-board MERS-CoV transmission, efforts should be made for extensive contact tracing in order to inform future public health decisions. If a crew member is the index case and if all passengers cannot be contacted, contact tracing efforts should concentrate on passengers seated in the area where the crew member was working during the flight; in addition, all other members of the crew should be traced.

If a passenger is suspected of having MERS-CoV infection during a flight, the potentially infectious passenger should – as with any other respiratory infection – be isolated and provided with a surgical face mask. Flight attendants should follow the IATA guidelines for infection control. Captains should radio ahead to the destination airport, informing officials of a suspected MERS-CoV case on board (Article 28 of the International Health Regulation 2005). Contact passengers should provide identification and contact details (locator cards) to the health authorities within 14 days after the flight (in order to facilitate contact tracing).

Treatment

A decision support tool for treatment of MERS-CoV [7] has been published by the ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium) on 29 July 2013 and reviews the available evidence regarding treatment of MERS-CoV patients, which is largely based on the experience of treating SARS. The most important recommendation remains the general supportive care. Different plausible options such as treatment with convalescent plasma, intravenous immunoglobulin, interferon, HIV protease inhibitors, ribavirin, corticosteroids, nitazoxanide and combination therapy are discussed. Apart from convalescent plasma, which is hardly available, the evidence for any other treatment is minimal. The document also refers to the generic sampling protocol (http://www.prognosis.org/isaric) and case report form (http://www.prognosis.org/isaric/crf.php) developed by ISARIC.

Prevention

Infection control

In accordance with international WHO guidance [51], the prevention and control of transmission in healthcare settings requires the implementation of control measures, organised hierarchically according to their effectiveness in administrative measures, engineering/environmental measures, and the use of personal protective equipment [51].

Possible and confirmed cases requiring admission should be admitted directly to negative-pressure single rooms. If this is not possible, a single room with en-suite facilities should be used.

Healthcare workers caring for patients under investigation for MERS-CoV or confirmed cases should exercise standard precautions (including hand hygiene) as well as contact and airborne precautions. This entails the use of personal protective equipment consisting of a well-fitted single use FFP2 or FFP3 respirator, gloves, eye protection and gown. It should be noted that the EU recommendation specifying a FFP2 or FFP3 mask to be used when caring for patients under investigation differs from the WHO recommendation (medical/surgical mask). Further information on infection control can be obtained from a WHO interim guidance document [51]. A recent study demonstrated MERS-CoV viability in experimentally aerosolized particles [19]. Therefore, medical procedures require particular protection measures, particularly aerosol-generating procedures and all airway management, such as tracheal intubation, broncho-alveolar lavage, manual ventilation, and other diagnostic airway procedures. The number of persons in the room should be limited to a minimum during such procedures; all persons present should wear:

- a well-fitted FFP3 respirator;
- tight-fitting eye protection; and

gloves and long-sleeved impermeable protective gowns.All specimens collected for laboratory investigation should be regarded as potentially infectious, and healthcare workers who transport clinical specimens should adhere rigorously to [52] to minimise the possibility of exposure to pathogens. Additional references are available from WHO [53] and the European Committee for Standardisation.

The WHO advice on home care for patients with MERS-CoV infection presenting with mild symptoms and management of contacts [3] is targeted to public health and infection control professionals, health managers and healthcare workers. It states that evidence of transmission from mild cases is limited and that currently there is no evidence of transmission from asymptomatic cases. Confirmed and probable symptomatic cases should be admitted to hospital whenever possible, but if inpatient care is unavailable or unsafe, or if hospitalisation is refused, home care of mild cases in younger people without underlying conditions (e.g. chronic heart, kidney or lung disease, diabetes, immunosuppression, and blood diseases) needs to be considered. If home care is chosen, the patient needs to remain under close medical observation. Contact with the patient should be limited as much as possible, and caregivers should stay in a different room or keep a distance of at least one meter from cases.

Strict hand and respiratory hygiene is stressed, and all exposed materials should be appropriately discarded. Protective equipment should be used whenever possible. A recent article documented the relative stability of MERS-CoV at indoor conditions. MERS-CoV was found to be more stable than influenza A H1N1pdm and remained viable for up to 48 hours on plastic and metal surfaces [19]. Therefore, healthcare facilities and home environments should ensure appropriate environmental cleaning.

Quarantine or isolation for asymptomatic contacts is not recommended, but contacts are advised to monitor their health for at least 14 days after the last possible contact with an infected person. They should immediately seek medical attention if they develop symptoms such as fever, respiratory symptoms (including coughing and shortness of breath), or diarrhoea.

Travel advice

ECDC endorses the WHO travel advice for MERS-CoV, which does not impose any travel or trade restrictions. In view of the forthcoming Hajj (13–18 October 2013) and the large number of European Muslims who visit Saudi Arabia at all times of the year, Member States should consider disseminating specific advice through dedicated travel agencies and religious organisations.

Travellers to the Middle East should:

- avoid contacts with animals and their waste products;
- limit contacts with others and practise cough etiquette (maintain distance, cover coughs and sneezes with disposable tissues or clothing, and wash hands) if they develop respiratory illness;
- avoid close contact with sick people, especially with those suffering from acute respiratory infections;
- practise good hand hygiene, especially if respiratory symptoms develop and after direct contact with ill people or their environments.

Travellers from the EU who plan to visit Saudi Arabia for the Umrah and Hajj pilgrimage should consult the recommendations made by the Saudi Ministry of Health. The Health regulations for travellers to Saudi Arabia

regarding MERS-CoV [54] recommends that the elderly (above 65 years of age) and those with chronic diseases (e.g. heart disease, kidney disease, respiratory disease, diabetes) and pilgrims with immune deficiency (congenital and acquired), malignancy and terminal illnesses, pregnant women and children (under 12) should postpone the Hajj and Umrah for their own safety.

General travel health advice, including avoiding unsafe water, undercooked meats, and raw fruits and vegetables unless freshly peeled and washed, remain important for travel in the Middle East.

Sources of additional information and further resources

- WHO source page novel coronaviruses: click here
- Public Health England (previously Health Protection Agency) – coronaviruses source page: click here
- Robert Koch Institute – coronaviruses source page (in German): click here
- University of Bonn – Diagnosis: click here
- ECDC coronaviruses – source page: click here and here
- CONSISE website: click here; CONSISE protocols: click here
- Protocols for novel coronaviruses: click here
- ISARIC and WHO SARI and natural history protocols: click here
- Kingdom of Saudi Arabia – Ministry of Health: click here
- Novel coronaviruses: click here

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