



UPDATED RAPID RISK ASSESSMENT

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

Eleventh update, 21 August 2014

Main conclusions

Since the last ECDC rapid risk assessment, published on 31 May 2014, the number of incident cases has been steadily declining and from 10 July to 20 August 2014, only two cases of MERS-CoV were reported. The cases currently occurring seem to be sporadic. While the virus continues to circulate in the affected region at a lower frequency, uncertainties in the reservoir of the virus and possible community transmission remain. Following detection of imported cases in Europe, transmission chains have been very limited and appropriate infection control and contact tracing methods appear to be effective in limiting further transmission in a European setting. Extensive contact tracing efforts for flights on which probable or confirmed cases have travelled have so far not shown evidence of transmission to other passengers. Therefore the current risk of human infections and sustainable human-to-human transmission in Europe remains low.

The national healthcare providers and public health institutions should remain prepared for and able to respond to a possible imported case in the EU/EEA. The advice for travellers to affected areas remains the same as it was in the previous (tenth) ECDC risk assessment.

An increasing body of evidence points to dromedary camels as the direct or indirect source of infection for many of the human cases. Gene sequences from the recent camel and human MERS-CoV sequences show no significant mutations compared to previous sequences from this outbreak, and therefore provide no indication of further adaptation to humans as a host. The current pattern of disease appears to be the combination of repeated introductions of the virus from camels to people, resulting in limited, un-sustained, human-to-human transmission. Detection of viral RNA in the air of a camel barn where transmission took place suggests that airborne transmission could be considered as a possible route of transmission together with droplet, contact and fomite transmission.

In response to new available information on MERS-CoV infection, the World Health Organization (WHO) issued updates of surveillance, case definition and laboratory methods in order to achieve early detection of sustained human-to-human transmission and determine the geographic risk area for infection with the virus. More detail and analysis of the events in the Arabian Peninsula is urgently needed to define the source of the infection and to further define the risks posed by this event. The World Health Organization also recommends infection prevention precautions for management of probable and confirmed cases in healthcare facilities, and for care of patients with MERS-CoV infection presenting with mild symptoms as well as management of contacts in home care settings.

The risk-benefit profile of possible experimental or other treatment protocols have been reviewed by Public Health England (PHE) and the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC). Observational clinical studies are urgently needed to improve the existing knowledge base in these areas.

Source and date of request

ECDC internal decision, 30 July 2014.

Public health issue

This eleventh update of the rapid risk assessment of the MERS-CoV outbreak addresses whether the risk to EU citizens from the transmission of MERS-CoV in the Middle East has changed since the last update on 31 May 2014, considering:

- the updated epidemiological information showing a decrease of reported cases
- the recent cluster of cases in Iran
- the updated scientific evidence, including revised treatment guidelines
- the upcoming Hajj preparations.

Previous rapid risk assessments

ECDC has published [ten previous Rapid Risk Assessments](#) (one initial and nine updates) on MERS-CoV since the start of the outbreak [1].

Consulted experts

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Event background information

Descriptive epidemiology

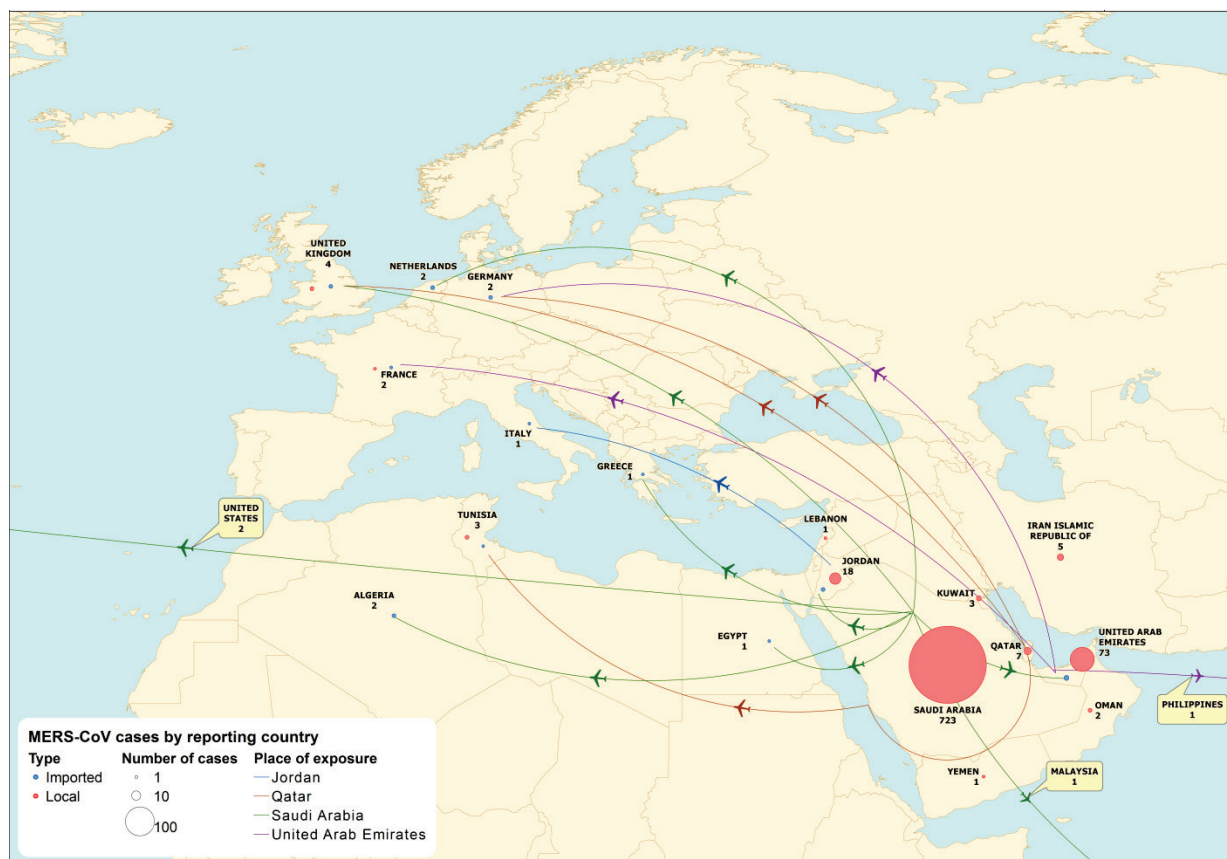
As of 20 August 2014, 855 laboratory-confirmed cases of MERS-CoV have been reported to public health authorities worldwide, including 333 deaths (Table 1). Most of the cases (97,5%) have occurred in the Middle East (Saudi Arabia, United Arab Emirates (UAE), Qatar, Jordan, Oman, Kuwait, Egypt, Yemen, Lebanon and Iran). All of the cases which have been reported outside of the Middle East have had recent travel history to the Middle East or contact with a case who travelled in the Middle East (Figure 1).

On 31 May 2014 the [WHO Regional Office for Africa](#) reported two cases from Algeria with travel history to Saudi Arabia, where they took part in Umrah. One of these cases died.

Table 1. Number of confirmed cases and deaths, by country of reporting, March 2012–20 August 2014

Reporting country	Cases	Deaths	Date of onset/reporting for most recent case
Saudi Arabia	723	300	06/08/2014
United Arab Emirates	73	9	11/06/2014
Qatar	7	4	04/11/2013
Jordan	18	5	23/05/2014
Oman	2	2	20/12/2013
Kuwait	3	1	07/11/2013
Egypt	1	0	22/04/2014
Yemen	1	1	17/03/2014
Lebanon	1	0	22/04/2012
Iran	5	2	25/06/2014
United Kingdom	4	3	06/02/2013
Germany	2	1	08/03/2013
France	2	1	08/05/2013
Italy	1	0	31/05/2013
Greece	1	1	08/04/2014
Netherlands	2	0	05/05/2014
Tunisia	3	1	01/05/2013
Algeria	2	1	24/05/2014
Malaysia	1	1	08/04/2014
Philippines	1	0	11/04/2014
United States of America	2	0	01/05/2014
Total	855	333	

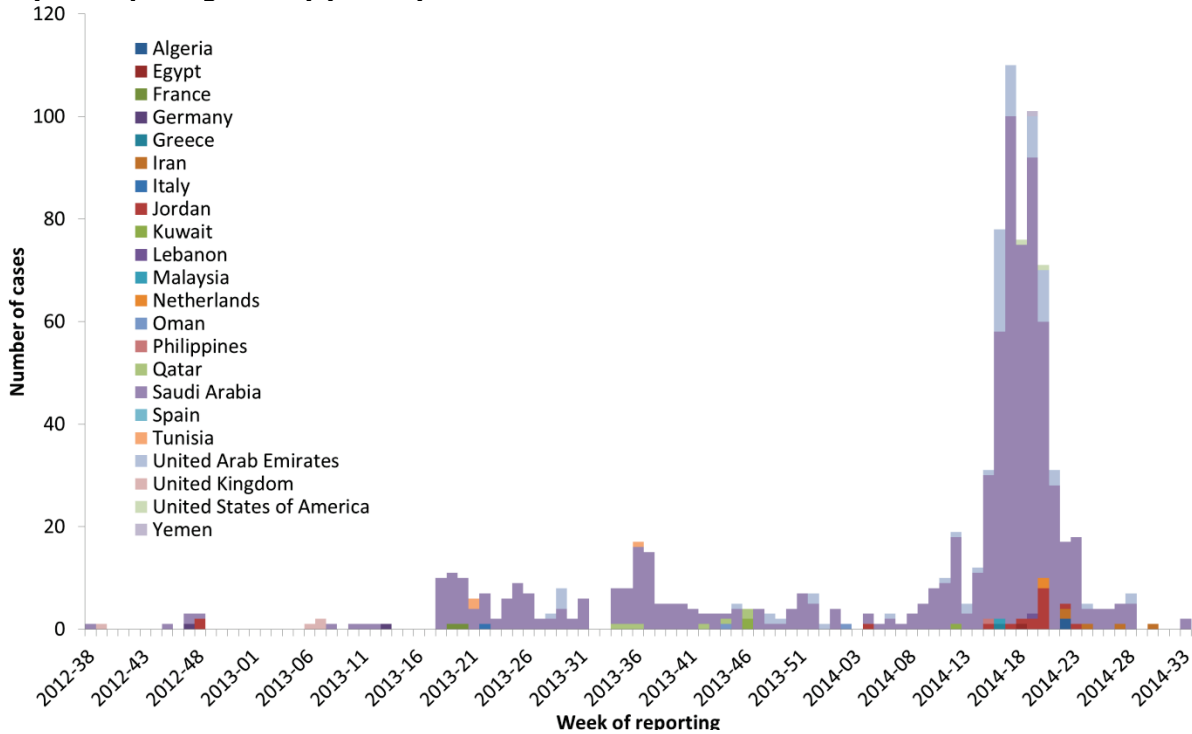
Figure 1. Geographical distribution of confirmed MERS-CoV cases and place of probable infection, worldwide, as of 20 August (n=855)



Epidemic curves

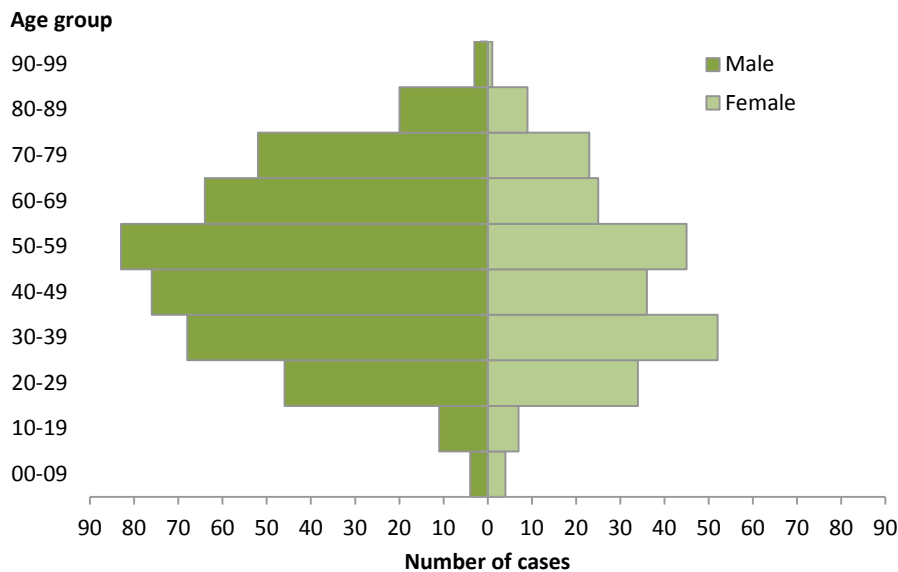
Since the last rapid risk assessment on 31 May 2014, 190 cases have been reported by health authorities in five countries (Saudi Arabia 175 (this includes 113 cases reported retrospectively), United Arab Emirates 6, Iran 5, Jordan 2 and Algeria 2)

Figure 2. Distribution of confirmed cases of MERS-CoV reported September 2012–20 August 2014, by day and reporting country (n=855)



Almost two thirds of the cases are male (male/female sex ratio of 1.8) for the 665 cases with documented gender. The median age for the 655 cases with documented age is 48 years (range 1 to 94). The cases are mostly middle-aged men aged 40 years and above (44.5 %). The median age is 50 for males and 46 for females.

Figure 3. Distribution of confirmed MERS-CoV cases by gender and age group (n=655), March 2012–20 August 2014



Cases since 31 May 2014

Since 31 May 2014, 175 cases have been reported in Saudi Arabia. The overview of the epidemiology in Saudi Arabia can be found on the Ministry of Health website.

This case count includes 113 cases reported by bulk to WHO on 3 June 2014. The detailed description of these cases can be found on the WHO website.

Saudi Arabia did not report cases between 10 July 2014 and 11 August 2014. However, on 11 and 12 August, the Ministry of Health issued separate notifications of two new confirmed cases and one fatal case in what appears to be a previously reported case.

Since 31 May 2014, six cases have been reported by the United Arab Emirates. Five cases had mild symptoms, while one was asymptomatic. Four of the cases were reported to have had animal contact, and three had direct contact with a camel. Of the three one drank camel milk.

Jordan reported two cases, where one of the cases was hospitalised prior to his illness for another condition. The second case was a healthcare worker who was a contact of another healthcare worker diagnosed with MERS-CoV on 11 May 2014.

Cases in the Iran

Iran recently reported its fifth MERS-CoV case and second death from the illness.

The MERS-CoV case in Iran involved a 67-year-old woman who became very ill after her release from a hospital following treatment for chronic obstructive pulmonary disease (COPD), as reported by the World Health Organization (WHO). She lived in Kerman province, the site of all of Iran's cases so far.

Cases in Algeria

Algeria has reported two cases in men who travelled to Saudi Arabia for the performance of Umrah. The date of onset of illness for both patients was 23 May 2013. The first case, a 66 year old man presented with fever and dyspnoea on 23 May 2014 upon arrival from Mecca the same day. The second case, a 59 year old man, also presented with Influenza like illness (ILI) and diarrhoea on May 23 2014 in Saudi Arabia, and was hospitalised on 29 May, and later died on 10 June 2014.

Source of infection and transmission

Based on the current reports, the disease is inefficiently transmitted from person to person. The current pattern of disease appears to be the combination of repeated introductions of the virus from camels to people, resulting in limited, un-sustained, human-to-human transmission [2].

There is growing evidence that the dromedary camel is a host species for the MERS-CoV and that camels play an important role in the transmission to humans [2,3], however the source of infection and transmission modes of MERS-CoV are still not completely understood.

Recently, researchers from Saudi Arabia detected MERS-CoV viral RNA in three air samples from a camel barn [3]. Previously, they had found the same strain of MERS-CoV in a camel from that barn and in its infected owner, who later died from the condition. However, virus isolation in cell culture was unsuccessful from the air sample collected in the study [3]. This finding and reports on the shedding of MERS-CoV into the environment by infected patients [4] indicate that airborne transmission might have to be considered as a possible route of transmission together with droplet, contact and fomite transmission.

A recent study [5] showed that viral RNA and antibodies against MERS-CoV could be detected in milk samples collected according to local customs from dromedary camels in Qatar in April 2014. This highlights the possibility of camel milk being infectious, although it does not confirm it. MERS-CoV remains infectious beyond 72 hours after introduction of an infectious dose in unpasteurised camel milk [6]. The consumption of camel milk is traditional in Arabic culture and sometimes among pilgrims visiting Saudi Arabia and may therefore play a role in transmission. However, information of exposure to camel milk is documented only in a very few cases.

MERS-CoV RNA has also been demonstrated in nasal and rectal swabs of infected camels [2,5].

Previous studies on abattoir workers involved in camel meat production in Saudi Arabia have not shown evidence of human infections. However, emerging evidence from analysis of studies in other countries of the region appear to suggest high rates of seroconversion among this occupationally heavily exposed group [2]. It is unclear what these discrepancies are due to, but the time of specimen collection in relation to time of virus circulation in the camel herds could be a possible explanation.

Surveillance

As MERS-CoV is an emerging pathogen not completely understood, surveillance recommendations including case definitions and finding, laboratory testing, reporting and contact tracing are being continuously revised in response to new information. [WHO](#) keeps an updated website with the latest guidance documents. An [ECDC factsheet](#) will compile the relevant information on the virus and the disease on the ECDC website.

Objectives of surveillance

The primary objectives of the enhancements described in the last WHO surveillance recommendations [7] are to:

- detect early, sustained human-to-human transmission
- determine the geographic risk area for infection with the virus.

Additional clinical and epidemiological investigations are needed to:

- determine key clinical characteristics of the illness, such as incubation period, spectrum of disease, and the natural history of the disease.
- determine key epidemiological characteristics of the virus, such as exposures that result in infection, risk factors, secondary attack rates, and mode of transmission.

Case definition

The [WHO case definition](#) for surveillance is based on the clinical picture, exposure and results of laboratory tests [8].

Case finding

Any person diagnosed with an acute respiratory infection and having been possibly exposed to MERS-CoV by visiting affected countries, working in an affected facility, having contact with dromedary camels or being part of an unexplained cluster of severe respiratory infections should be tested for MERS-CoV. For details see [WHO surveillance guidance](#).

Reporting

All cases diagnosed in the EU/EEA, including cases confirmed by serology only, should immediately be reported to the national authorities, who in turn are obliged to report to the EU Early Warning and Response System (EWRS) and to WHO under the International Health Regulations (IHR 2005). Patients still under investigation do not need to be reported internationally while awaiting confirmation.

The results of positive serology can now be considered as confirmatory tests for MERS-CoV.

Clinicians should also be familiar with the most recent WHO infection control guidelines, all of which can be found on the WHO Global Alert and Response webpage for coronavirus.

Patients who are evacuated from the Arabian Peninsula and neighbouring countries should be given special attention. Companies undertaking medical evacuations from the region should be reminded of their obligation to protect staff engaged in the transfer and the need to inform receiving hospitals and public health authorities 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 use of personal protective equipment until MERS-CoV infection has been ruled out.

Contact tracing

All close contacts of probable and confirmed MERS-CoV cases should be followed-up and monitored for symptoms until 14 days after the last exposure. Although no cases of infection with MERS-CoV on board aircraft have been documented, it is advisable for countries to trace contacts of confirmed MERS-CoV cases on flights in accordance with the Risk Assessment Guidelines for Infectious Diseases transmitted on Aircraft (RAGIDA) for severe acute respiratory syndrome (SARS) contact tracing. This should be done regardless of flight time.

Virological characteristics

MERS-CoV is a RNA virus belonging to lineage C within the Betacoronavirus genus (Coronavirinae subfamily), along with several viruses detected in bats in Europe, Africa and China [9]. Several different clades and subclades of MERS-CoV have been detected [10]. Data on virological characteristics including virus tropism, genome sequence, molecular and serological testing remain unchanged since the last RRA update.

The full-genome sequences of the MERS-CoV coronaviruses retrieved from the dromedary camels have shown to be very similar to previously found human genomes of clade B MERS-CoV [10,11] which supports the hypothesis that human infection may be acquired directly from camels.

Laboratory testing

MERS-CoV is confirmed by a real-time RT-PCR targeting two out of three available RNA targets or alternatively by sequencing [12].

Serological testing

Serology can be used to detect antibodies in patients or contacts when the direct detection (molecular methods) of MERS-CoV is negative in suitable specimens, as well as for human and animal surveys. However interpretation of MERS-CoV serological results can be hampered by the widespread circulation of other human coronaviruses such as HCoV-OC43, HCoV-HKU1, HCoV-NL63, and HCoV-229E. Different screening assays are used such as indirect immunofluorescence assay (IFA), ELISA, western blot, protein microarrays using the whole virus or recombinant spike and nucleocapsid proteins or a soluble S1 subunit of spike protein. A gold-standard neutralisation test should be used for confirmation (i.e. plaque reduction neutralisation test or micro neutralisation test or using pseudoparticle virus) [13].

In Germany, two cases tested using IFA had high titres of antibodies and this was also confirmed by microarray testing and neutralisation tests [14-16].

Treatment

An updated decision support tool for treatment of MERS-CoV was published by ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium) on 14 July 2014 [17]. Based on little available evidence, convalescent plasma, interferon and lopinavir may be considered for specific treatment. Mono- and polyclonal antibodies are currently in development. There is little or no clinical evidence for other therapies, in particular antiviral drugs.

Infection prevention and control

Standard, contact and droplet precautions for management of probable and confirmed cases in healthcare settings are recommended (WHO, CDC). For aerosol-generating procedures, including airway management, such as tracheal intubation, broncho-alveolar lavage and manual ventilation, given the MERS-CoV viability in experimentally aerosolised particles [16], airborne precautions are recommended. Additional infection prevention precautions or considerations may be needed if a MERS-CoV patient has other conditions or illnesses that warrant specific measures (e.g. tuberculosis, *Clostridium difficile*, multi-drug resistant organisms). The WHO advice on home care for patients with MERS-CoV infection presenting with mild symptoms and management of contacts is targeted towards public health and infection control professionals, health managers and healthcare workers.

Donation of substances of human origin

The absence of reported transmission through blood transfusion or transplantation and experience with related SARS coronavirus viraemia, which seemed largely confined to the symptomatic patients, suggest that the current risk of donor-derived MERS CoV transmission is very low. Thus specific deferrals of donors returning from affected countries are not considered necessary at this stage of the outbreak. Safety criteria for prospective donors presenting acute respiratory symptoms are sufficient to identify symptomatic MERS-CoV cases residing in or returning from affected countries and exclude them from the donation of blood, cells and tissues, and organs [18,19].

Additionally, travellers returning from Saudi Arabia and Yemen are temporarily deferred from blood donation due to malaria endemicity in those countries. The Netherlands applies universal deferral from blood donation for 28 days of all travellers abroad of Europe, and France introduced deferral for 28 days of prospective blood donors returning from the Arabian Peninsula and neighbouring countries in 2013.

ECDC threat assessment for the EU

The number of human MERS-CoV cases reported from the Arabian Peninsula has decreased rapidly during the last month. Considering the unknown reservoir of infection and the epidemiological pattern of outbreak, a continuous but diminished threat from MERS-CoV for the EU is still present. Experience from previous years shows that sporadic cases of primary, possibly zoonotic transmission, with small clusters of secondary nosocomial or family transmission, are likely to occur in affected areas. So the possibility of imported cases of travellers to affected areas cannot be excluded.

MERS-CoV has displayed mixed features of both an epidemic and an illness of a more sporadic nature. It seems that the outbreak is currently in the sporadic phase. Epidemic peaks might be explained by annual cyclicity of camel breeding in Saudi Arabia. However there is limited evidence to prove or discard this hypothesis. Infection in camels appears to occur in early life and then clears. Up to a third of young camels carry this infectious virus. Because camels are born in the spring, there may be an increased amount of virus circulating in camels in spring and summer months. This may contribute to a seasonal spike in the reported number of MERS-CoV cases [20].

The majority of cases reported so far are associated with healthcare settings, and WHO missions to assess these outbreaks have concluded that suboptimal implementation of infection control procedures have contributed to these outbreaks, although in at least one outbreak in Al-Hasa, genomic evidence suggested multiple introductions in the healthcare facility, rather than a single nosocomial outbreak. Many of the cases detected outside of the region have had healthcare exposures in the affected region during the assumed incubation period. More detailed information regarding the events surrounding healthcare-associated MERS-CoV infection would enable us to make a better assessment of the risk of the disease spreading through various modes of transmission. The majority of cases detected outside the region visited healthcare facilities in the region during the incubation period, suggesting an association between the infection and an exposure in healthcare settings. Studies are needed to identify risk and protective factors for infection in hospitals. Strict adherence to standard precautions (including hand hygiene) and additional contact and airborne transmission precautions continue to be recommended in order to prevent infection in the event of any suspected case of MERS-CoV.

The annual Muslim pilgrimage is expected to take place around the first week of October in 2014. Despite intensive surveillance in Saudi Arabia and in countries receiving pilgrims back from the Hajj in 2013, no cases of MERS-CoV were detected among the estimated two million pilgrims. In 2014, several cases detected outside of Saudi Arabia have been returning pilgrims from the minor pilgrimage, Umrah. Considering the large increase of detected and reported cases in 2014, the detection of cases in healthcare facilities in Mecca, the ongoing circulation of the virus in dromedary camels and large numbers of pilgrims expected in 2014, cases among pilgrims or in the healthcare facilities providing services to the pilgrims are to be expected. The establishment of a Ministry of Health Command and Control centre in Jeddah has clearly improved situational awareness and surveillance activities for MERS-CoV.

Assessment of risk for the EU

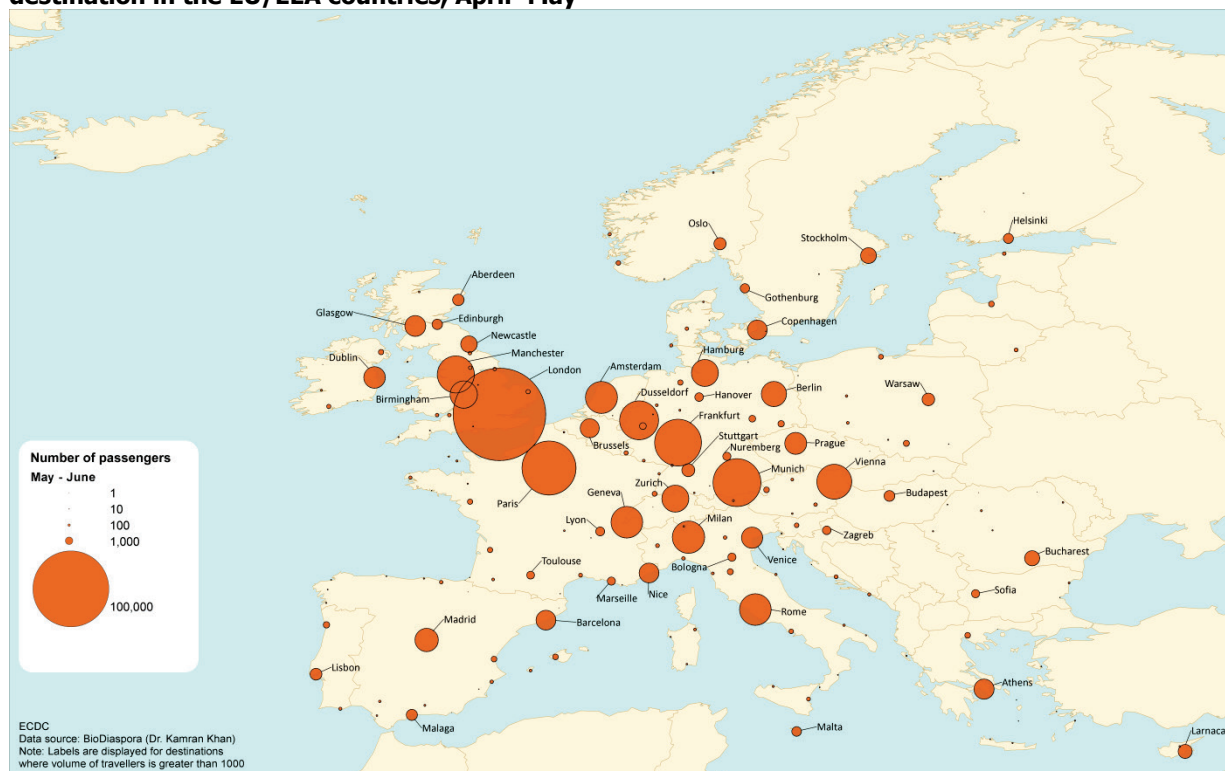
The assessment of the risk of MERS-CoV establishing itself in Europe is limited by gaps in our knowledge of the animal-human interface with camels and the epidemiology of the infection in animals and humans, particularly since the direct source of infection for humans has not yet been identified. Serological studies and case-control studies are needed to estimate risk factors and protective factors for infection and severe disease. This would improve the targeting of preventive measures and advice to EU citizens.

In the absence of additional information, there is a risk that individual EU citizens travelling to or residing in the Arabian Peninsula, and especially Saudi Arabia, may be infected through direct or indirect contact with camels. The magnitude of that risk is difficult to quantify in the absence of evidence.

Current epidemiology still relates the majority of the cases to the Arabian Peninsula and specifically to Saudi Arabia. Therefore the risk of sustainable human-to-human transmission in Europe is very low. However, the number of people travelling between the Arabian Peninsula and EU countries reaches hundreds of thousands every month. Therefore, while the epidemic phase of the 2014 outbreak appears to be over in the region, it is still possible that further imported cases will also be detected in Europe.

According to estimates from the International Air Transport Association (IATA) and BioDiaspora, the main final destinations of flight passengers from the region are currently the large air travel hubs of Europe (Figure 4).

Figure 4. Volume of passengers originating from Saudi Arabia and United Arab Emirates by final destination in the EU/EEA countries, April–May



Conclusions

Since the last ECDC rapid risk assessment was published on 31 May 2014, the number of incident cases has been steadily declining and from 10 July to 20 August 2014 only two cases of MERS-CoV were reported. Uncertainties remain in the reservoir of the virus and possible community transmission and it cannot be excluded that the virus continues to circulate in the affected region. After detection of imported cases in Europe, all transmission chains have been very limited and appropriate infection control and contact tracing methods appear to function in limiting further transmission in a European setting. National healthcare providers and public health institutions should remain prepared for and able respond to a possible imported case in the EU/EEA Member States.

An increasing body of evidence points to dromedary camels as the direct or indirect source of infection for many of the human cases. Camels are a host species for this virus, as confirmed by studies showing the same virus sequence in animal and human cases, and the fact that some of the primary cases in clusters have been infected through direct or indirect contact with camels. Full-genome sequences of MERS-CoV very similar to the sequences obtained from human cases have been retrieved from nasal specimens taken from dromedary camels. However, some earlier studies showed that camel farm workers did not have antibodies to MERS-CoV. No other animal species have been shown to be infected with this virus.

Gene sequences from the recent camel and human MERS-CoV sequences show no significant mutations compared to previous sequences from this outbreak and thus provide no indication of further adaptation to humans as a host. It should be noted that sometimes only minor polymorphisms can be associated with major changes in the properties of the virus.

Extensive contact tracing efforts for flights on which probable or confirmed cases have travelled have thus far not shown evidence of transmission to other passengers.

Epidemiological studies in the region have been called for to determine exposures and host factors related to increased risk of infection for primary cases in clusters. The World Health Organization has provided the affected countries in the region with a study protocol and questionnaire for an international case-control study.

The risk-benefit profile of possible experimental or other treatment protocols have been reviewed by PHE and ISARIC. Observational clinical studies are urgently needed to improve the existing knowledge base in these areas.

This event has had a serious public health impact in the region and has the potential to spread and have a wider geographical impact. At the moment there is no sustained human-to-human transmission documented. More detail and analysis of the cases on the Arabian Peninsula are urgently needed to define the source of the infection and to further define the risks posed by this event. Currently, the risk of human infections in Europe remains low.

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Sources of additional information

- WHO source page novel coronaviruses: [click here](#)
- University of Bonn – Diagnosis: [click here](#)
- ECDC MERS-CoV rapid risk assessments: [click 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](#)
- Kingdom of Saudi Arabia – Ministry of Health - Novel coronaviruses: [click here](#)