



UPDATED RAPID RISK ASSESSMENT

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

Tenth update, 31 May 2014

Main conclusions and options for action

Currently, the risk of human infections and sustainable human-to-human transmission in Europe remains low. However, the number of human MERS cases reported from the Arabian Peninsula has increased rapidly in the past few months. Specifically, several healthcare associated clusters in Saudi Arabia and UAE have been reported which have been responsible for large numbers of cases. Given the current increase in nosocomial infections and travel-associated cases of MERS in the Arabian Peninsula, and the large number of people travelling between the Arabian peninsula and Europe, it is likely that more cases will be imported and detected in the EU/EEA. Continued vigilance in assessing patients with travel history to the affected region is warranted.

Since the previous (ninth) ECDC rapid risk assessment on MERS-CoV was published, it has become clear that false negative results cannot explain the increase in cases and it is unlikely that mutations have led to increased human-to-human transmission. Three other scenarios likely to play a part in the current epidemiology are:

- increased zoonotic transmission leading to increased introductions to community and healthcare facilities;
- suboptimal infection control in hospitals;
- a more sensitive case detection algorithm used in some areas that has led to the current increase in number of cases.

In addition, there is an increasing body of evidence that dromedary camels are the direct or indirect source of infection for many of the human cases.

This updated rapid risk assessment contains options for action in the following areas:

Travel advice: there are no travel restrictions in place, however those travelling to the region should consult a doctor if suffering from a severe medical condition; avoid travelling if ill with an infectious disease; ensure good hygiene practices; avoid contact with animals, especially camels, and not consume unpasteurised milk or undercooked meat.

The international public health community could consider providing further outbreak assessment support to better understand modes and sources of transmission, determine optimal management of patients and encourage serological surveys.

EU/EEA Member States could review their preparedness in the event of a large MERS cluster; sensitise public health professionals and healthcare workers to the possibility of MERS presenting in returning travellers and increase awareness of the available testing, infection control, surveillance and reporting guidance.

Source and date of request

ECDC Internal Decision, 16 May 2014.

Public health issue

This tenth update of the rapid risk assessment of the MERS-CoV outbreak addresses the following public health question:

Has the risk to EU citizens from the transmission of MERS-CoV in the Middle East changed since the last update of the risk assessment on 24 April 2014, considering:

- the updated epidemiological information;
- the findings of increased number of infections in April 2014 through primary cases and nosocomial transmission, and among returning travellers from the Arabian Peninsula and neighbouring countries;
- the updated scientific evidence on the virus and the suspected animal reservoir (dromedary camels)?

Previous rapid risk assessments

ECDC has published [nine previous Rapid Risk Assessments](#) (one initial and eight updates) on Middle East respiratory syndrome coronavirus since the start of the outbreak. [1]

Consulted experts

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External experts: Christian Drosten (University of Bonn, Germany), Maria Zambon (Health Protection Agency, UK), Marion Koopmans (Netherlands), Aura Timen (RIVM, Netherlands), Ziad Memish (Saudi Arabia) and Susan Gerber (US CDC). ECDC is grateful for input from the World Health Organization (WHO) however the views expressed in this document do not necessarily represent the views of WHO. The experts were consulted as individuals on the basis of their specialist knowledge and experience rather than as representatives of their institutions or countries. Responsibility for the content of this risk assessment rests with ECDC.

Event background information

Descriptive epidemiology

As of 22 May 2014, 665 laboratory-confirmed cases of MERS-CoV had been reported to public health authorities worldwide, including 205 deaths (Table 1.) Most of the cases have occurred in the Middle East (97%) (Saudi Arabia, United Arab Emirates (UAE), Qatar, Jordan, Oman, Kuwait, Egypt, Yemen and Lebanon). 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).

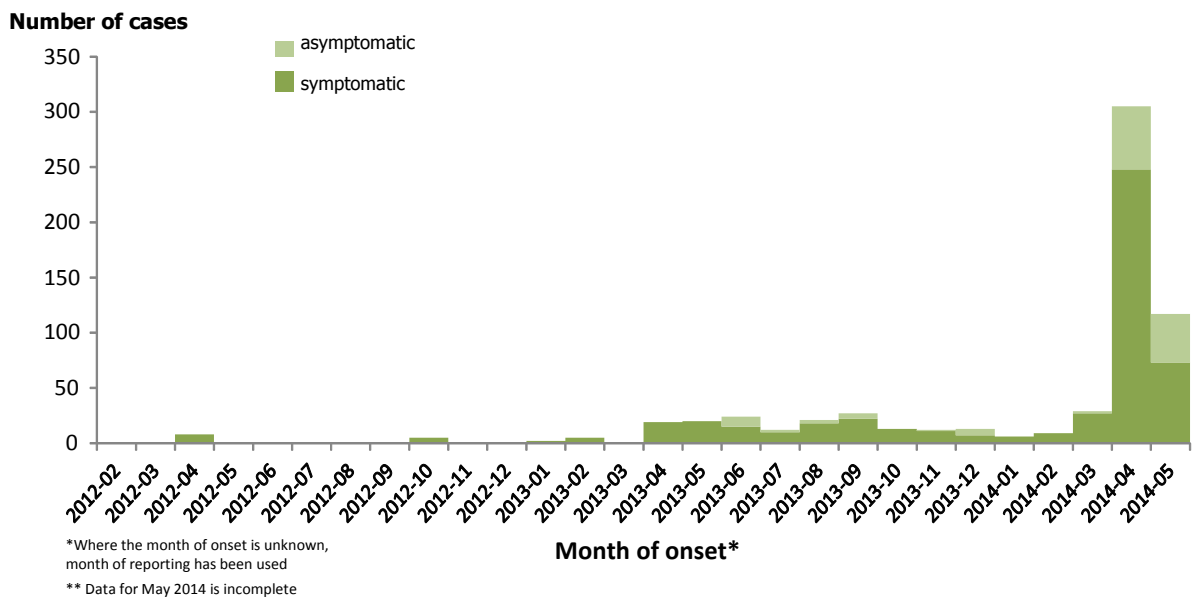
On 26 May 2014, health authorities in Iran reported two confirmed cases that had had contact with a traveller returning from Saudi Arabia one of which has died. These cases are not yet reflected in the analysis below.

On 31 May 2014 the [WHO Regional Office for Africa](#) reported two cases with recent travel history to Saudi Arabia, where they took part in Umrah. These cases are not included in the analysis below.

Table 1. Number of confirmed cases and deaths, by country of reporting, March 2012– 22 May 2014

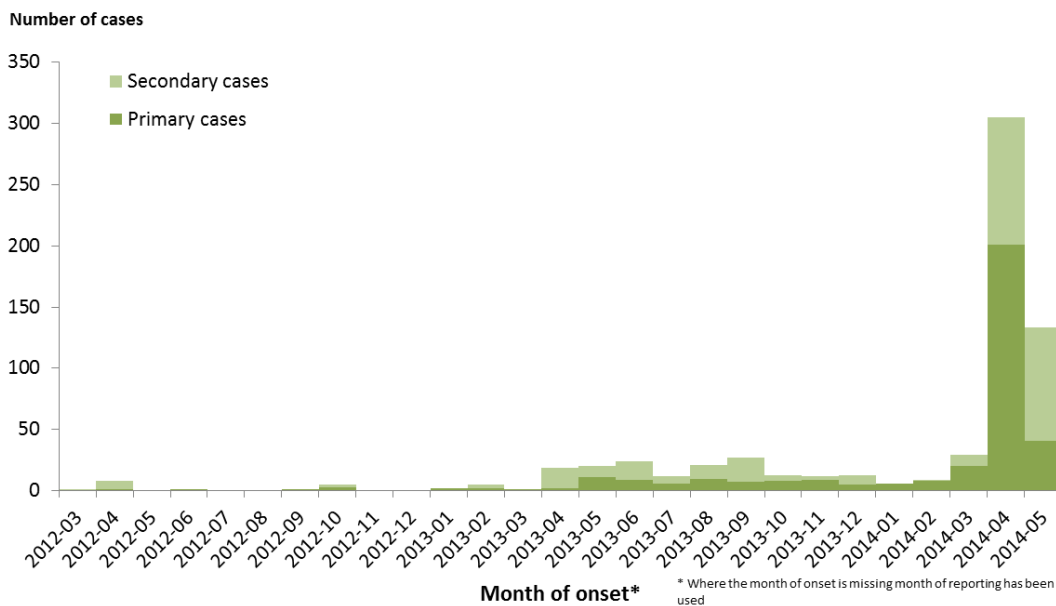
Reporting country	Cases	Deaths
Saudi Arabia	548	177
United Arab Emirates	67	9
Qatar	7	4
Jordan	16	4
Oman	2	2
Kuwait	3	1
Egypt	1	0
Yemen	1	1
Lebanon	1	0
United Kingdom	4	3
Germany	2	1
France	2	1
Italy	1	0
Greece	1	0
Netherlands	2	0
Tunisia	3	1
Malaysia	1	1
Philippines	1	0
United States of America	2	0
Total	665	205

Figure 3. Distribution of confirmed cases of MERS-CoV by month of onset and symptom status, March 2012 – 22 May 2014 (n=665*)



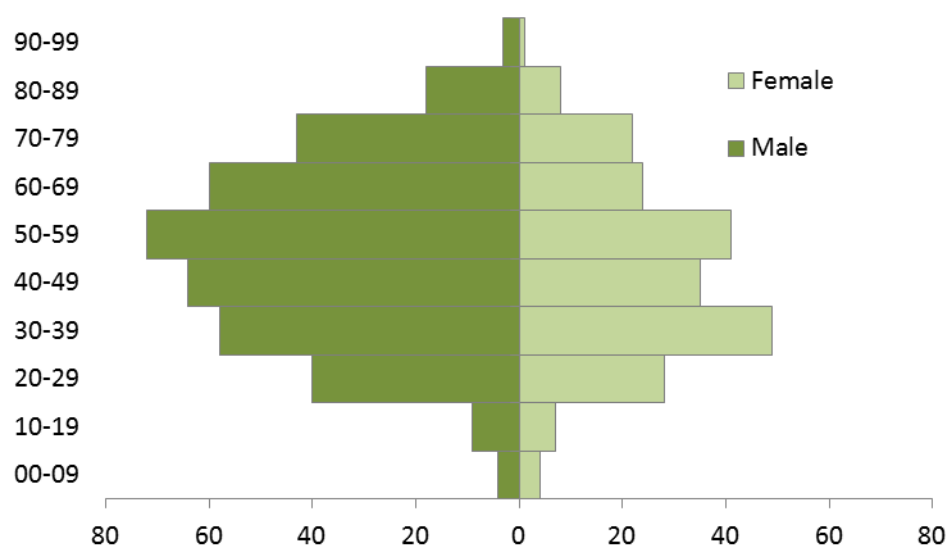
Of the 665 cases since the beginning of the outbreak, 354 (53%) have been identified as primary cases, meaning that these cases have no link to previously confirmed cases based on the publicly available information. The remaining 311 cases (47%) have been identified as secondary cases (with contact with a confirmed case prior the onset of the illness) (Figure 4).

Figure 4. Distribution of primary and secondary confirmed cases of MERS-CoV by month of onset, March 2012 – 22 May 2014 (n=665*)



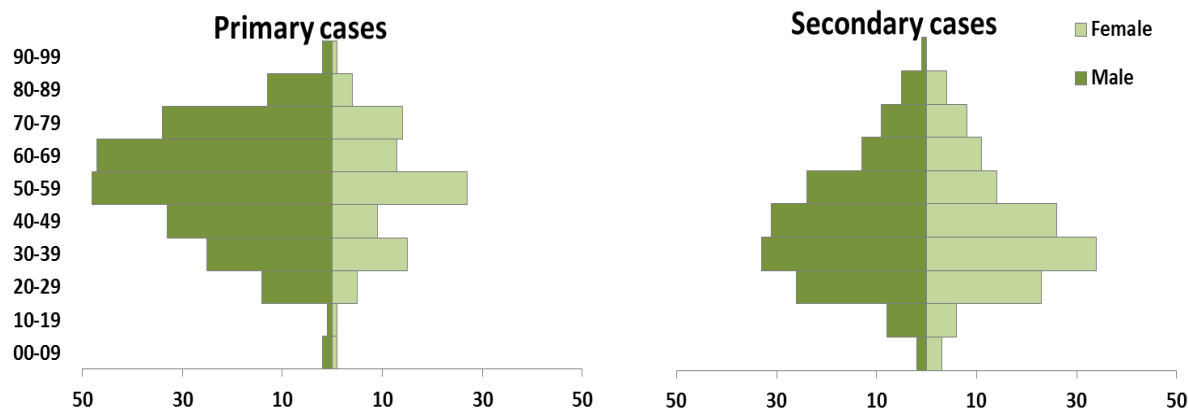
Almost two thirds of the cases are among males (male/female sex ratio of 1.7) for the 595 cases with documented gender. The median age for the 654 cases with documented age is 49 years (range 1 to 94). The cases are mostly middle-aged men aged 40 years and above (39%).The median age is 50 for males and 46 for females. (Figure 5).

Figure 5. Distribution of confirmed MERS cases by gender and age group (n=595), March 2012–22 May 2014



A difference in age and sex distribution can be seen between primary and secondary cases (Figure 6).

Figure 6. Distribution of confirmed MERS cases by gender and age group, primary (n=309*) and secondary cases (n=281), March 2012–22 May 2014**



*45 primary cases where age or sex was missing have been excluded.

**30 secondary cases where age or sex was missing have been excluded.

The slight over-representation of males among secondary cases may be due to the fact that primary cases are predominantly males, and patient-to-patient transmission in a healthcare setting will tend to affect more males due to segregation by gender in hospitals.

The age and gender distribution has changed since the increase in cases seen in April 2014. (Figure 7)

Figure 7. Distribution of confirmed cases of MERS-CoV by gender and age group by first available date (n= 595)

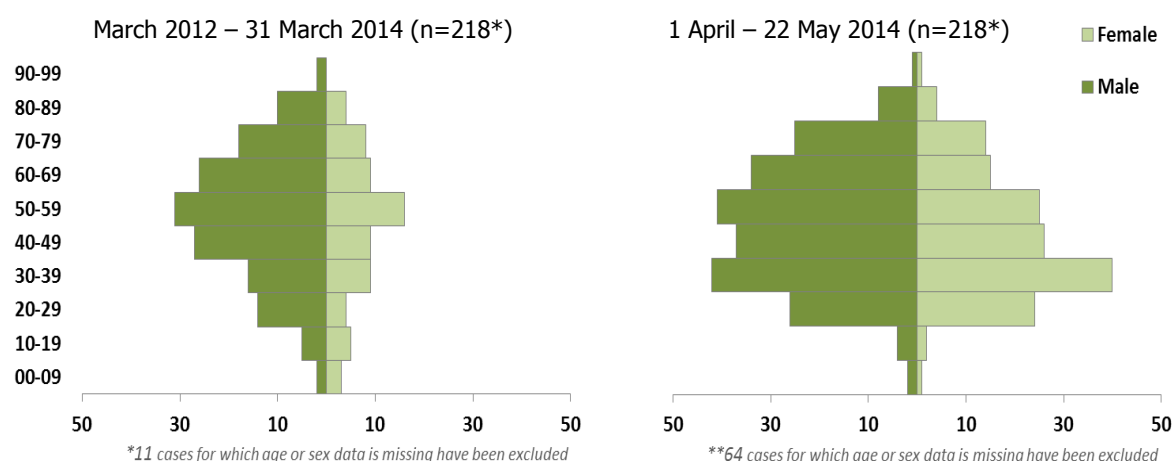


Table 2 indicates that during the last two months monitored there has been a higher proportion of asymptomatic cases and a seemingly lower case fatality ratio.

The percentage of healthcare workers has not changed in the two periods. Among healthcare workers, the gender distribution is almost even, with the age groups 20– 39 year being the most affected.

Table 2. Profile of confirmed cases of MERS before and after 1 April 2014 by date of reporting

Indicator	1 March 2012 to 31 March 2014	1 April 2014 to 22 May 2014	Total
Months monitored	25	2	27
Symptomatic cases	178	353	531
Asymptomatic cases	28	106	134
Total cases	206	459	665
% of asymptomatic	14%	23%	20%
Deaths	86	119	205
CFR among symptomatic cases	48%	34%	35%
Sex ratio (M/F)	2.2	1.5	
Median age	53 years	45 years	
Healthcare workers			
Healthcare workers n (%)	33/206 (16%)	78/459 (17%)	111/665 (17%)
HCW asymptomatic n (%)	14/28 (50%)	33/106 (31%)	47/134 (35%)
Median age	39 years	39 years	
Sex ratio (M/F) (n=92)	0.4	1.9	1.2

Healthcare workers

Since 2012, 111 cases have been reported among healthcare workers, 78 of them since April 2014. Seventy of the healthcare workers were reported from Saudi Arabia, 29 from the United Arab Emirates, eight from Jordan two from USA and one each from Lebanon and the Philippines. The healthcare workers are younger than the other cases (median age 39 years). The male/female ratio among healthcare workers is less skewed than the general one; among the 93 healthcare workers with known gender, 51 were male and 42 female (sex ratio 1:2). However, while the sex M/F ratio was only 0:4 before April 2014, it has been 1.9 since, with significantly more male health care workers being reported.

Autochthonous cases since 24 April 2014

Since 24 April 2014, 263 cases have been reported in Saudi Arabia: Riyadh (101 cases), Jeddah (96), Mecca (23), Medina (23), Tabuk (9), Taif (7), Najran (2), Hafr Al Batin (1) and Kufudha (1).

Of these 263 cases, 68 (26%) have been asymptomatic or mild, while 188 (71%) have died or been reported as being in a critical but stable condition. For seven cases the condition was not indicated.

Among the 263 cases 19 (7%) were healthcare workers. Ten of the healthcare workers were reported as asymptomatic or having mild symptoms, while eight were in a critical or stable condition. For one the condition was unknown. The median age for the healthcare workers was 37 years. Eleven (78%) of the 14 cases with known gender were female.

Since 24 April 2014 25 cases have been reported by the United Arab Emirates. Among these cases 15 had mild symptoms or were asymptomatic, five were reported to be in a critical condition and for the others there were no clinical details. All the healthcare workers are either asymptomatic or presented with mild symptoms. At least one case reported from UAE had travelled to Jeddah, Saudi Arabia.

Exported cases since last update

Cases in the Netherlands

On 14 May 2014, the Netherlands notified the first laboratory confirmed MERS-CoV infection in a 70-year-old male citizen of the Netherlands, with recent travel history to Saudi Arabia between 26 April 2014 and 10 May 2014. The patient had begun feeling ill on 1 May 2014 while in Medina, Saudi Arabia. He was evaluated at an emergency care unit in Mecca on 6 May and given antibiotics. He did not present with respiratory symptoms while in Saudi Arabia. On the return flight to the Netherlands on 10 May, his condition deteriorated and he developed respiratory symptoms. He was admitted to hospital the same day. On 13 May, he tested positive for MERS-CoV. On 15 May 2014, the Netherlands notified a second laboratory-confirmed MERS case. The second case was in a 73 year-old female citizen of the Netherlands who was a close family member of the first case.

Both cases travelled together as part of a travel group from the Netherlands and shared a hotel room throughout the entire journey. The second case developed respiratory symptoms on 5 May 2014 in Mecca, Saudi Arabia. On her return to the Netherlands on 10 May, she presented with mild respiratory symptoms and fever. Her MERS-CoV infection was confirmed through the investigation of the first MERS case contacts in the Netherlands.

Neither of the cases reported contact with animals or consumption of raw animal products while travelling in Saudi Arabia. Contact has been made with members of the travel group, close contacts and passengers on the group's return flights and investigation is ongoing.

Cases in the USA

On 2 May 2014, the United States of America reported the first laboratory confirmed MERS case in the United States in a male US citizen in his 60s who lives and works in Riyadh, Saudi Arabia. The case travelled from Riyadh to Chicago on 24 April 2014 via London Heathrow with travel from Chicago to Indiana by bus. He began feeling unwell around 14 April 2014 with a low-grade fever but no respiratory symptoms. On 28 April 2014, he was admitted to a hospital.

On 11 May 2014, the US reported a second laboratory-confirmed MERS case in a male healthcare worker in his 40s, living and working in Jeddah, Saudi Arabia. The case travelled to the US from Jeddah on 1 May 2014 on commercial flights via London Heathrow with travel from London to Boston, Massachusetts, from Boston to Atlanta, Georgia and from Atlanta to Orlando, Florida. He began feeling unwell on 1 May 2014 on the flight from Jeddah to London with a low-grade fever, chills, and a slight cough. On 9 May 2014, he was seen in an emergency room and hospitalised.

While investigating contacts of the first confirmed case, one contact initially tested negative for MERS-CoV by PCR based on respiratory tract samples taken ten days after contact with the first case. However, on 16 May, this contact tested positive for MERS-CoV antibodies in a blood sample taken 14 days after contact. This individual, a 70-year-old male with co-morbidities and no history of travel to countries outside the United States, is currently asymptomatic.

The initial antibody test result suggested this individual may have been infected with MERS-CoV. However, confirmatory serologic tests were negative, and the case was therefore discarded.

Source of infection and transmission

Zoonotic transmission

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]. The first evidence of the implication of dromedary camels in transmission was the detection of high rates of MERS-CoV antibodies in dromedary camels on the Arabian Peninsula [4,5]. Evidence of infection in camels precedes the first evidence of human infection [6,7]. Recently, viral RNA has been detected in different specimens from camels and the virus has been isolated from nasal and faecal samples [6,8-12].

The detection of MERS-CoV in dromedary camels imported from Sudan and Ethiopia for slaughter in Egypt [9], as well as serological evidence of previous MERS-CoV infection in dromedaries in Ethiopia, Kenya [13], Nigeria [14], Tunisia [14] and the Canary Islands (Spain; some originating from Morocco) [5] suggests that the virus could be geographically widespread in the dromedary camel populations on the African continent and that previously undetected transmission to humans may occur outside of the Arabian Peninsula [14].

However, in two studies, the absence of MERS-CoV antibodies was reported respectively in 226 and 179 abattoir workers in Saudi Arabia (from Jeddah and Makkah sampled in October 2012) and in Egypt (June–December 2013), suggesting that the virus is not easily transmitted from camels to humans [9,15]. Among the primary cases reported from Saudi Arabia, only a minority have documented camel contact.

A recent study showed that the MERS-CoV remains infectious beyond 72 hours after introduction in unpasteurised camel milk [16]. The consumption of raw camel milk is traditional in the Arabic culture. So far, to our knowledge, no study has looked at the excretion rate of MERS-CoV in camel milk and urine. Raw camel milk may therefore play a role in transmission.

In a prospective study of two camel herds in Saudi Arabia from November 2013 to February 2014, nasal, oral, or rectal swabs and blood samples were collected up to five times. The study showed that acute MERS-CoV infections diagnosed with PCR resulted in increased anti MERS-CoV titers. The infection of very young animals (<one month) indicates that maternal antibodies may not fully protect very young animals from infection. There was no evidence of prolonged virus shedding or viraemia among the tested animals [10].

Human-to-human transmission

While the source or reservoir of MERS-CoV is unknown, the disease is transmitted from person to person, for example by close contacts or in healthcare facilities [17-24]. Based on information related to the first 77 cases, the basic reproduction number of the infection (R_0) was estimated to be 0.69 (95% CI 0.50–0.92) at the time [25], indicating a low pandemic potential [26]. For comparison, the R_0 was estimated to be 0.80 (95% CI 0.54–1.13) for SARS-CoV, using the same methodology [25]. However, the small number of confirmed cases used for this calculation, the increasing detection of asymptomatic cases and the potential evolution of the virus will probably modify these figures [27]. An investigation of community transmission among household contacts of 26 clusters with 280 contacts over six months in 2013 showed nine positive cases by serology and PCR revealing an R_0 of 0.35 (Memish, personal communication).

Nosocomial transmission has been a hallmark of MERS-CoV [28] [29] and has resulted in an upsurge of cases during spring 2014 [30]. A large outbreak was previously documented in Al-Ahsa, Saudi Arabia in 2013. Twenty-three confirmed and 11 probable cases were diagnosed as part of a single outbreak that involved four healthcare facilities [17]. The majority of cases were hospitalised 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. Sequencing of viral isolates from this outbreak suggested multiple introductions to the facility rather than a single one [17] [30]. Strict infection control measures allowed the containment of outbreaks when implemented e.g. in Al-Ahsa.

Virus shedding in urine has been observed in a human case up to 13 days after symptom onset, in stool up to 16 days and from oronasal swabs up to 16 days after onset of symptoms [31]. In another study, a tracheal aspirate sample was shown to be viral nucleotide positive 20 days after onset of disease [21]. However, this does not yet confirm for how long the infectious virus is shed. The detection of MERS-CoV in a sample is obviously affected by the time of sampling with regard to the onset of disease; type of sample; sensitivity and specificity values of the laboratory tests available, and the prevalence of the MERS-CoV in the population to which the test is applied.

There is no information available about virus shedding among infected camels. The shedding in urine among humans makes it plausible that this also applies to camels. Therefore, taking into account the occasional use of camel urine as traditional medicine in the Arabic culture, the possibility of urine as a source of infection should not be disregarded [55]. However, to date, no urinary route secondary case has been confirmed.

Faecal transmission was indicated as the most likely route for the nosocomial case in France [28].

Asymptomatic and mildly symptomatic healthcare workers have been identified. One study reported seven MERS cases in Saudi Arabia (two asymptomatic and five symptomatic) confirmed by RT-PCR. All were women, six had no pre-existing conditions. All had contact with a known MERS case and most were linked to lapses in infection control while taking care of the patients. No secondary cases were identified from these healthcare workers [32]. In Germany and the United Kingdom [20,22,31], a follow-up screening exercise of nearly 200 personal contacts and healthcare workers exposed to two imported confirmed cases found no evidence of human-to-human transmission [20,22,31]. No tertiary cases were identified from these healthcare workers [32].

Limited clusters of close contacts (one or two secondary cases among close contacts) were identified in Tunisia and Saudi Arabia [31]. The risk of community transmission has increased as more human-to-human transmission has been observed.

Surveillance

Case finding

On 27 June 2013, WHO revised their '[Interim surveillance recommendations for human infection with Middle East respiratory syndrome coronavirus](#)' [33]; the 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 \(MERS-CoV\)](#)' [34]. A confirmed case is a laboratory-confirmed case as defined in '[Laboratory testing for novel coronavirus: Interim recommendations](#)' [35]. The revised case definition identifies three categories of probable cases based on clinical presentation, exposure, and level of testing.

Clinicians should be familiar with the most recent WHO [surveillance guidance](#) [36], [case investigation guidelines](#) [37], WHO [case definitions for MERS-CoV](#) [34] and 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 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.

Reporting

All cases diagnosed in the EU/EEA, including cases confirmed by serology only, should immediately 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 until 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 case in any closed setting. Close contacts should have a baseline serum sample collected and stored, which can be used for comparison of paired sera if required later. Where local epidemiology allows, it is also advisable to collect airway specimens for PCR testing. When collecting specimens, it should be considered that lower respiratory specimens generally have a higher viral load than upper respiratory specimens [38].

In the Netherlands, a tiered approach has been taken to contact tracing. High risk and low risk contacts have been defined. All contacts were required to monitor their temperature twice a day for up to 14 days. The high risk contacts were determined as close family members of cases; other close contacts who meet the criterion of prolonged face-to-face contact; the airplane passengers at risk according to RAGIDA guidelines, and those in the same group that travelled to Saudi Arabia. The low risk contacts were healthcare staff who wore appropriate personal protective equipment when taking care of the cases and other community contacts. The Dutch public health authorities have collected molecular (t= seven and 14 days after contact) and serological samples (t= seven and 21 days) from both, high and low risk contacts.

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 cases on flights in accordance with 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 case
- passengers seated two rows in front or behind the case
- all crew members
- passengers providing care for the case
- passengers having had >15 minutes of face-to-face contact with the case
- passengers having had contact with respiratory secretions of the case
- passengers living in the same household as the 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 to possibly include all passengers and crew members. If firm evidence of on-board MERS-CoV transmission is lacking, efforts should be made to undertake 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 of the flight (in order to facilitate contact tracing).

Virological characteristics

MERS-CoV belongs to lineage C within the *Betacoronavirus* genus (*Coronavirinae* subfamily), along with several viruses detected in bats in Europe, Africa and China [39].

An analysis of virus tropism has indicated that these viruses can infect a variety of cell lines, including human cells, via surface receptors distinct from SARS coronavirus receptors [40]. MERS-CoV seems to be able to infect human bronchial epithelia cultures [41].

MERS-CoV uses its spike protein to bind to the cellular receptor dipeptidyl peptidase 4 (DDP4; CD26) for entry to host cells [42]. As DDP4 has been evolutionarily conserved across different species, MERS-CoV has a broad hypothetical host range. In humans, DPP4 is expressed particularly in lung and kidney cells. In cells originating from livestock, the best production of infectious MERS-CoV particles has been seen in goat lung and kidney cells and in camelid kidney cells [43]. This would indicate urine as a possible source of infectious material for humans [43]. However, urine has not been sampled or studied for the presence of MERS-CoV in any of the livestock studies, including those on camels.

Several virus sequences are available in GenBank including complete genome sequences from both humans and camels [44]. Preliminary genome sequences from the current outbreak in Jeddah, Saudi Arabia have been determined by the Ministry of Health in Riyadh and the University of Bonn and have been published at www.virology-bonn.de (GenBank submission currently awaiting curation). These human sequences suggest no relevant changes in important functional domains such as the receptor binding site when compared with MERS-CoV sequences found earlier and elsewhere. All sequences belong to one contiguous clade, suggesting a uniform source compatible with a hospital-associated outbreak.

The full-genome sequences of the MERS coronaviruses retrieved from the dromedary camels have shown themselves to be very similar to human isolates of clade B MERS-CoV [10,45] which supports the hypothesis that human infection may be acquired directly from camels.

Molecular testing

An external quality assessment was recently conducted by ENIVD (European network for viral imported diseases: www.enivd.de) for coronavirus detection focusing on MERS-CoV. The panel included MERS-CoV, seasonal coronavirus and negative specimens. Preliminary results from 87 laboratories, including 46 laboratories from 23 EU/EEA countries and 12 laboratories from the Arabian Peninsula, showed that the participating countries had a good capability of detecting MERS-CoV and that there were no false positive results (e.g. due to cross-reaction from seasonal coronaviruses). The sensitivity of the assays and the typing of the seasonal coronaviruses may need improvement in some laboratories.

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) [46]. Serological testing has confirmed human cases in Germany as well as the current asymptomatic infection in the US. In Germany, two cases tested using IFA had high titers of antibodies and this was also confirmed by microarray testing and neutralisation tests [22,31,47].

According to the interim WHO case definition [34] a person with an acute febrile respiratory illness of any severity and a direct epidemiological link with a confirmed MERS case and an inconclusive MERS-CoV laboratory test (i.e. serology including neutralisation) is presently classified as a probable case.

Treatment

A decision support tool for treatment of MERS [48] was published by ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium) on 29 July 2013. This reviews the available evidence on treatment of MERS patients and is largely based on the experience of treating SARS.

Infection control

According to international WHO guidance [49], the prevention and control of transmission in healthcare settings requires the implementation of control measures, organised hierarchically according to their effectiveness in the form of administrative measures, engineering/environmental measures and the use of personal protective equipment.

WHO recommends that probable and confirmed cases requiring admission are admitted in adequately ventilated single rooms or airborne precaution rooms. Healthcare workers caring for probable or confirmed cases of MERS-CoV infection should apply standard precautions (including hand hygiene and use of PPE to avoid direct contact with patients' blood, body fluids and secretions) and in addition, contact and droplet precautions (medical mask, eye protection - goggles or a face shield - gown and gloves).

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. The procedure should be performed in an adequately ventilated room with the number of persons in the room limited to a minimum.

All persons present should wear:

- a well-fitted FFP2 or FFP3 respirator
- tight-fitting eye protection
- gloves and a long-sleeved impermeable protective gown.

Further information on infection control can be obtained from the WHO interim guidance document [49].

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. Additional references are available from WHO [50] 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 is targeted towards 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 metre from cases. Strict hand and respiratory hygiene is stressed, and all exposed materials should be disposed of appropriately. 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 (H1N1)pdm and remained viable for up to 48 hours on plastic and metal surfaces [16]. 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 problems (including coughing and shortness of breath) or diarrhoea. Discussions are currently underway on revising guidance for appropriate management of mild or asymptomatic cases, based on recent developments.

Donation of substances of human origin

Safety criteria for prospective donors presenting acute respiratory symptoms are sufficient to identify symptomatic MERS cases residing in or returning from affected countries and exclude them from the donation of blood, cells and tissues [51,52]. Organ donors should be assessed individually in combination with the recipient, taking into account the current epidemiological situation. However, the possibility of asymptomatic viraemia and potential transmission through transfusion and transplantation cannot be excluded.

Nevertheless, 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.

Additionally, travellers returning from Saudi Arabia and Yemen are temporary 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 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 cases reported from the Arabian Peninsula has increased rapidly in recent months. Specifically, several healthcare-associated clusters in Saudi Arabia and UAE have been reported with large numbers of cases. Cases of MERS reported from the Philippines, Malaysia, Greece and the US in recent weeks may be linked to healthcare settings.

Since describing five possible scenarios in the ninth ECDC rapid risk assessment on 24 April 2014, it has become clear that false negative results cannot explain the increase in cases and it is quite unlikely that mutations leading to increased human-to-human transmission outside healthcare settings are taking place. It is probable that the remaining three scenarios: increased zoonotic transmission leading to increased introductions to healthcare facilities, amplified by suboptimal infection control in hospitals and a more sensitive case detection algorithm used in some areas has led to the current epidemiology.

Increased zoonotic transmission

Dromedary camels are a host species for MERS-CoV. Juvenile animals have a higher virus load, indicating a higher likelihood of transmission. Transmission could potentially occur via respiratory or faecal shedding, or other types of contact. Reinfection of animals appears to be possible and pre-existing antibodies are not fully protective. Therefore, a higher circulation could be assumed after the calving period in the winter months, when a larger number of animals is susceptible.

Camel farming has progressively changed in Saudi Arabia over the last ten years with an increased number of farms near cities [53]. Intensive camel farming could be at the origin of an increased zoonotic risk.

A good understanding of the epidemiology of camels (e.g. seasonal calving periods and diarrheal outbreaks) is needed to fully assess the zoonotic risk. Many gaps remain in our knowledge of the epidemiology of coronavirus infections in dromedary camels, including exact contact patterns with humans, both in the population generally and in MERS cases. Though we know that MERS-CoV is circulating widely among the camel herds in the Arabian Peninsula, we do not know what has triggered the apparent outbreak in humans and why such outbreaks have not occurred in other geographical regions where serological evidence exists for infection of dromedary camels.

Importation of live dromedary camels, raw camel meat and unsterilized camel milk from the Arabian peninsula to the EU is prohibited.

Increased nosocomial transmission because of suboptimal infection control measures

The reports of hospital-associated clusters of MERS provide further evidence of the risk of nosocomial transmission and call into question the effectiveness of the precautionary measures used in the affected healthcare facilities. The recent WHO mission to Jeddah concluded that infection-control practices in the affected hospitals were suboptimal, thus providing support to the notion that transmission in hospitals is a key, but not the only, driving factor behind the recent increase in cases [54].

More sensitive case detection, improved surveillance

To the best of our knowledge, the screening protocol in Saudi Arabia recommended testing cases with severe acute respiratory infections admitted to intensive care for MERS and testing all close contacts of cases, including healthcare workers, for the virus. However practices might differ at the facility level. These samples have been tested according to WHO protocols with PCR testing of two target genes (e.g. upE specific and ORF-1a). Only cases confirmed using this technique have been reported to WHO.

A recent change in the screening protocol, even if only at affected hospitals, such as testing of patients presenting with milder symptoms or wider contact tracing could contribute to the recent increase in reported cases and would indicate wider transmission of the virus in the community than previously estimated. This is known to have happened in Jeddah, and is supported by the finding that more asymptomatic and mild cases appear to have been detected in recent weeks. Asymptomatic or subclinical infections were also documented in SARS-exposed healthcare workers using RT-PCR.

Improved surveillance and/or more sensitive case detection contributing for the increase would indicate that cases might have been missed in the past, particularly in highly-exposed individuals such as healthcare workers employed in settings where infection control measures are insufficient. If a majority of those were mild, the human epidemiology for MERS would be quite different to what was previously thought. On the one hand, the case-fatality would be lower, and on the other hand, human-to-human transmission might have been underestimated. In this scenario is it likely that more cases, but less severe ones, could also be detected in the EU/EEA in the future.

Assessment of risk for the EU

Our assessment of the overall 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 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.

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.

A better understanding of the current case detection and contact tracing procedures implemented in countries within the region, and any recent changes to these procedures would be useful in order better characterise the current epidemiology.

More detailed information is needed on the risk factors underlying the recent increase in cases in order to assess the risk of human-to-human transmission.

Risk for importation of MERS coronavirus

Current epidemiology still relates the majority of the cases to the Arabian Peninsula, and thus 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 outbreak is not being controlled in the region, it is likely that further imported cases will also be detected in Europe.

According to estimates from IAEA and BioDiaspora the main final destinations of flight passengers from the region are currently the large air travel hubs of Europe (Figure 8).

Figure 8. 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 24 April 2014, an additional increase in human cases of MERS infection has been reported. Since the first detection of this virus, six EU countries have reported confirmed cases of MERS to date: France, Germany, Greece, Italy, the Netherlands and the UK, all with travel connections to the Arabian Peninsula. Given the current increase in nosocomial infections and travel-associated cases of MERS on the Arabian Peninsula and associated with that region, it is likely that more cases will be imported and detected in EU Member States. Further vigilance is therefore warranted in assessing patients with travel history to the affected region.

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 of the earlier studies showed that camel farm workers did not have antibodies to MERS-CoV.

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.

Access to information on the recent events in Saudi Arabia has improved as a result of WHO missions but it is still difficult to draw firm conclusions on the risks posed by the nosocomial outbreaks. Increasing numbers of primary cases are being reported, however, there is no evidence of wider secondary community transmission taking place.

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.

Little is known of the effectiveness and safety of appropriate experimental or other treatment protocols and the effectiveness of available antiviral medications. 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 evolving 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. Currently, the risk of human infections in Europe remains low.

Options for action

Travellers from the EU/EEA to the Arabian Peninsula and its neighbouring countries need to be aware of the presence of MERS-CoV in this area and of the small risk of infection.

Travellers from the EU to the Arabian Peninsula should:

- Consult their doctor before travelling if suffering from serious or severe medical conditions (such as diabetes, chronic lung, renal disease or immunodeficiency) that may increase the likelihood of illness including MERS-CoV infection, or the likelihood of contact with healthcare facilities while in the region.
- Avoid travelling if ill with an infectious disease.

Pilgrims planning to attend the Hajj or Umrah should comply with the Saudi Arabian Ministry of Health's [health regulations from 2013](#). They recommend that the elderly (over 65 years), pregnant women, children (under 12 years), those with chronic diseases (e.g. heart disease, kidney disease, respiratory disease, diabetes) and pilgrims with immune deficiency postpone the performance of the Hajj and Umrah for their own safety.

All EU/EEA visitors to, and EU/EEA citizens residing in the Arabian Peninsula should:

- Follow general health travel precautions to lower the risk of infection:
 - wash hands often with soap and water and use antibacterial hand gel regularly;
 - maintain good personal hygiene;
 - avoid consuming undercooked meat and unpasteurised milk, especially from camels;
 - avoid consuming food prepared in an unsanitary environment;
 - wash fruits and vegetables before eating;
 - use appropriate precautions when in close contact with people who are ill, especially those with flu-like symptoms (respiratory illness), diarrhoea (and other gastrointestinal illness) or other potentially infectious diseases.

The measures above are especially important when visiting or staying in healthcare facilities in the region, where most of the transmission to humans appears to be occurring.

- Avoid unnecessary contact with farms, domestic and wild animals, especially camels.
- Avoid any animal excretions, especially urine and faeces, particularly from camels and bats.
- Seek medical attention if developing flu-like illness or severe respiratory illness while travelling or within 14 days after returning from the Arabian Peninsula and advise healthcare providers of any travel history, possible contact with animals or other sick individuals.
- If ill with a potentially infectious disease:
 - use appropriate cough etiquette (coughing and sneezing into your elbow and using disposable tissues);
 - avoid close contact with other people to keep from infecting them;
 - avoid participating in food production or preparation;
 - wash hands often with soap and water and use antibacterial hand gel regularly;
 - maintain good personal hygiene.

Possible action for the international public health community and affected countries

- Urgently provide support for further respiratory disease outbreak assessments to minimise the possibility of widespread human-to-human transmission in the community.
- Encourage and support as urgent, studies to describe and determine modes and sources of transmission for MERS-CoV, in particular in the animal (camel)-human interface, among primary cases of clusters and in healthcare facilities. Epidemiological studies, such as cohort or case-control studies are well suited to such assessments.
- Encourage, and support as urgent, observational clinical studies of MERS cases to determine optimal management of patients in order to improve outcomes.
- Ensure that appropriate serum samples (positive and negative controls) of MERS cases are available for international standardisation of serological tests.
- Encourage serological surveys among close contacts of cases of MERS and in affected settings.
- Ensure that adequate numbers of MERS-CoV isolates are sequenced and submitted to publicly available databanks, such as GenBank throughout the epidemic.
- Monitor risk perception and impact of measures in close contacts of MERS-CoV cases in order to provide optimal support.
- Improve timely and transparent risk communication practices in affected areas.

Possible action for EU/EEA Member States

- Support WHO efforts to coordinate assessment and response to this outbreak.
- Review laboratory and healthcare preparedness for large clusters of MERS cases presenting in their healthcare systems.
- Sensitise healthcare workers to the possibility of MERS cases presenting in EU hospitals.
- Familiarise public health professionals, healthcare workers and risk communication experts with available guidance on MERS-CoV.
- Support healthcare facilities to implement the infection control measures recommended by WHO (see Infection Control Section). Member States may consider recommending airborne precautions for routine patient care of probable and confirmed cases, due to the remaining uncertainty in the mode of human-to-human transmission.
- Follow up on all close contacts of probable and confirmed MERS cases and monitor them for symptoms for 14 days after the last exposure (see Contact tracing section).

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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](#)