



UPDATED RAPID RISK ASSESSMENT

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

17 May 2013

Summary

- As of 14 May 2013, 38 cases of Middle East respiratory syndrome coronavirus (MERS-CoV) have been reported worldwide, including 20 deaths. All cases remain associated (including indirect association following secondary person-to-person transmission in the UK and France) with transmission in the Arabian Peninsula and Jordan. The age of cases ranges from 24 to 94 years (N=34 cases), with a mean of 55.5 years and a male/female ratio of 1:0.2.
- The report of 19 new infections in Saudi Arabia in the past two weeks – including one infection with the novel coronavirus acquired in the United Arab Emirates and later imported to Europe – indicate that there is an ongoing source of infection and risk of transmission to humans in the Arabian Peninsula and Jordan.
- The most recent imported case, which resulted in a nosocomial transmission, originated in the United Arab Emirates and then moved to France. Both patients had underlying conditions and a degree of immunosuppression. One of the transmissions in the UK also affected an immunosuppressed person. These underlying conditions may be increasing vulnerability and the risk of transmission.
- The first French case raises the possibility that presentations may not include respiratory symptoms initially, especially in those with immunosuppression or underlying chronic conditions. This needs also to be taken into account when revising case-finding strategies.
- The confirmed infection in France of a patient who shared a hospital room with a patient returning from the United Arab Emirates indicates the risk of nosocomial transmission. This is the second nosocomial transmission in Europe. The first one took place when an imported case in the UK visited a relative in the hospital in February 2013.
- These conclusions should be seen in the light of the many uncertainties that still continue with the investigation of cases in the Arabian Peninsula and Jordan. It is unusual to have such a degree of uncertainty at this stage in an outbreak.

Recommendations

- Healthcare workers in the EU should be vigilant in identifying patients that may require further investigation; they should also follow ECDC and national guidance for case finding. Patients developing severe respiratory infections and who have been in the Arabian Peninsula or neighbouring countries in the preceding 10 days should be investigated rapidly. Special attention should be given to medical evacuated patients from the Arabian Peninsula and neighbouring countries.
- Patients with chronic underlying conditions who develop severe infections (not just respiratory infections) should also be investigated rapidly for novel coronavirus if they have been in the Arabian Peninsula or neighbouring countries in the preceding 10 days.
- Since routine microbiological sampling (nasopharyngeal swabs) may give misleading negative results in persons later shown to be infected with the coronavirus, tests should be repeated with deeper respiratory sampling if a person fits into a category that requires investigation, especially if their condition is worsening.
- As demonstrated by a case with dual influenza and novel coronavirus infections, there is a possibility of co-infection and this should be considered by healthcare personnel. Identification of one causative agent should not exclude testing for novel coronavirus where indicated.
- Mapping of international routes of medical evacuation or emergency medical care from the Arabian Peninsula and neighbouring countries to the EU could be considered in order to determine the most vulnerable centres in the EU where these cases might arrive.
- Companies undertaking medical evacuations from affected areas should be reminded of the risk of transferring infections across borders and of their obligations to protect staff engaged in the transfer; the same holds true for the staff of institutions which receive patients.
- Healthcare workers caring for patients under investigation for MERS-CoV should exercise standard infection control measures following national or international guidance.
- Close contacts of confirmed cases must be monitored for symptoms for 10 days after the last exposure, and should be tested, and should be informed what to do should they become ill. This should be carried out according to guidance, such as that developed by Public Health England UK (See 'Sources of additional information' below).
- Healthcare workers caring for confirmed cases should be monitored for early symptoms of infection and advised to seek testing and thereafter self-isolate if they become unwell.
- Clusters of severe acute respiratory infections in the community or in healthcare settings, either among patients or healthcare workers, should always be reported rapidly and investigated for a range of pathogens, regardless of where in the world these infections occur.
- ECDC does not currently consider a need for testing individual patients with unexplained pneumonias or other respiratory symptoms unless they fall under one of the above categories.
- Any probable or confirmed case being diagnosed in the EU/EEA should be reported to national authorities through the Early Warning and Response System (EWRS) and to WHO under the International Health Regulations (2005). Reporting through EWRS qualifies as IHR notification and avoids double reporting. Patients still under investigation do not need to be reported internationally before confirmation, but information on outcome of such testing exercises should be shared with ECDC.
- ECDC supports the WHO travel advice which imposes no travel or trade restrictions in relation to novel coronaviruses. However, EU citizens travelling to the Arabian Peninsula and neighbouring countries need to be aware of the presence of MERS-CoV in this geographical area and of the small risk of infection. Member States may consider active information efforts for travellers to areas most at risk.
- Although the reservoir of infection in the Middle East is unknown, other novel coronaviruses are zoonoses and have come from animal sources. Travellers should therefore follow standard good hygiene practise and avoid contact with animals or their waste products.

Source and date of request

ECDC internal decision, 6 May 2013.

Public health issue

This fourth update of the rapid risk assessment of severe respiratory disease associated with a novel coronavirus (MERS-CoV) was produced in relation to 22 additional cases of laboratory-confirmed infections reported in the last two months. The aim of this updated risk assessment is to review changes since the [February update](#) and assess the implications of change on ECDC's recommendations for EU/EEA countries.

ECDC internal response team

Paloma Carrillo-Santistevé, Denis Coulombier, Alastair Donachie, Assimoula Economopoulou, Kaja Kaasik Aaslav, Angus Nicoll, Lara Payne, Marc Struelens, Hervé Zeller (in alphabetical order).

Consulted experts

ECDC acknowledges the valuable contributions from the members of the ECDC Advisory Forum (all have submitted Declarations of Interest). It should be noted that opinions expressed by individual experts do not necessarily represent the opinion of their institutions.

Background information

On 19 February 2013, the date of the [last ECDC rapid risk assessment](#), 12 cases of MERS-CoV had been confirmed worldwide.

The first confirmed case was reported in a 60-year-old male who lived in Saudi Arabia. He died from severe pneumonia complicated by renal failure in Jeddah on 24 June 2012. The genome of the new coronavirus was isolated from this case, sequenced and the genetic code put in the public domain [1]. In September 2012, a 49-year-old male living in Qatar presented with symptoms similar to the first case. He was transferred to Europe for further care [2]. A virus was isolated from this case, sequenced and the genetic code put in the public domain by the UK authorities. It was found to be almost [identical to the virus from the case in Saudi Arabia](#). The emergence of a novel coronavirus causing severe respiratory disease in two separate parts of the Arabian Peninsula led to notifications through the International Health Regulations (IHR) and the EU Early Warning and Response System (EWRS) on 22 September 2012.

In November 2012, four additional cases with similar symptomatology were diagnosed in Saudi Arabia, including a family cluster of three confirmed cases, one probable case [3] and a second imported case to Europe (from Qatar to Germany) reported on 23 November.

Two fatal cases were confirmed retrospectively in Jordan. Both cases came from a cluster of 11 people with severe lower respiratory infections associated with a hospital in April 2012. Although the other nine persons also matched the WHO definition for probable novel coronavirus infections, the cases were less severe than the two confirmed cases. It has not yet been possible to undertake confirmatory virological or serological testing for these probable cases.

Three additional cases were diagnosed in February 2013 in the UK in a family cluster associated with an index case who has a travel history to Saudi Arabia and Pakistan. These cases included the first two transmissions in Europe [4]. These cases resulted in a total of four cases identified and reported by the UK to date.

Recent developments

Between 13 February, when the last ECDC risk assessment was published, and 12 May 2013, 26 additional confirmed cases of MERS-CoV were reported worldwide, including 12 deaths:

Single case imported into Germany: one case was diagnosed and reported by Germany on 25 March. The person arrived from the United Arab Emirates to receive medical care in Germany. It was the second imported case to be reported by this EU Member State. The patient, a 73-year-old male with underlying clinical conditions, had been hospitalised in United Arab Emirates and was transferred to a hospital in Germany for specific clinical care where the diagnosis of MERS-CoV infection was confirmed. Despite intensive-care treatment the patient died on 26 March [5].

Twenty-three cases from Saudi Arabia: 23 cases were detected and reported by Saudi Arabia in the last two weeks; WHO started reporting these case on [2 May 2013](#). Nineteen of these cases seem to be part of a recently detected cluster in Al-Hasa in the Eastern Province of Saudi Arabia, which may be linked to the same healthcare facility. Onset dates are from 6 April to 1 May 2013 [6]. Although investigations are stated to be ongoing by the Saudi Arabian authorities, no additional information or analyses have been made available to ECDC as of 14 May 2013.

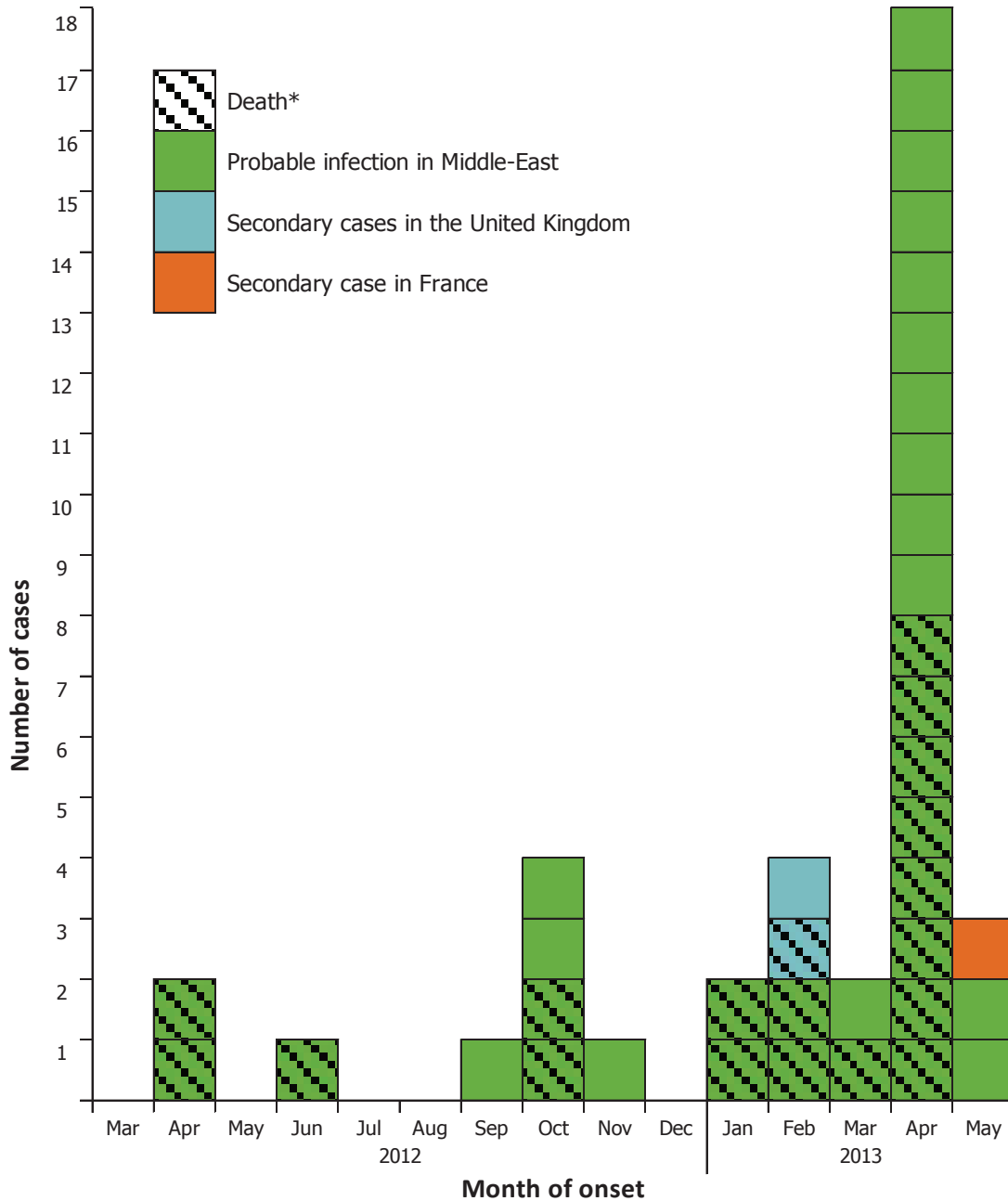
Single case imported into France: This first case reported by France on 7 May 2013 was in a French resident with a history of travel to Dubai, United Arab Emirates, in the two weeks prior to onset of illness in France (9–17 April). The 65-year-old man had a history of renal impairment and had sought medical care in France for fever, diarrhoea and lumbar pain on 23 April. Though he did not initially present with respiratory symptoms, pneumonia was subsequently diagnosed and laboratory tests were undertaken for novel coronavirus infection, as recommended by national and ECDC guidance. A naso-pharyngeal specimen was negative for MERS-CoV on 3 May. A bronchoalveolar lavage (BAL) specimen taken on 26 April arrived at the Reference Laboratory on 7 May and tested positive for MERS-CoV. The patient is on mechanical ventilation [communication by France, EWRS message, 7 May 2013] and investigations are underway concerning the possible exposure in Dubai [7].

Single nosocomial transmission in France: [On 12 May](#), France informed ECDC of an additional laboratory-confirmed case. The case is an immunosuppressed male in his fifties who, from 27 to 29 April 2013, shared a hospital room with the first laboratory-confirmed patient in France. This patient was identified as part of the epidemiological investigation initiated by the French authorities, following laboratory confirmation of the first case on 7 May 2013. The patient is currently hospitalised. An epidemiological investigation and contact identification is ongoing.

Epidemiological summary

As of 14 May, 38 cases have been reported worldwide, including 20 deaths. An epicurve of the month of onset of reported cases by clinical outcome and probable place of infection is shown in Figure 1.

Figure 1: Distribution of cases of MERS-CoV reported worldwide by month of disease onset, outcome and place of infection, as of 14 May (N=38)



* Month of onset is not available for one death

All 38 cases worldwide remain associated (including indirect association following secondary person-to-person transmission in the UK and France) with transmission in the Arabian Peninsula; the majority of cases are from Saudi Arabia.

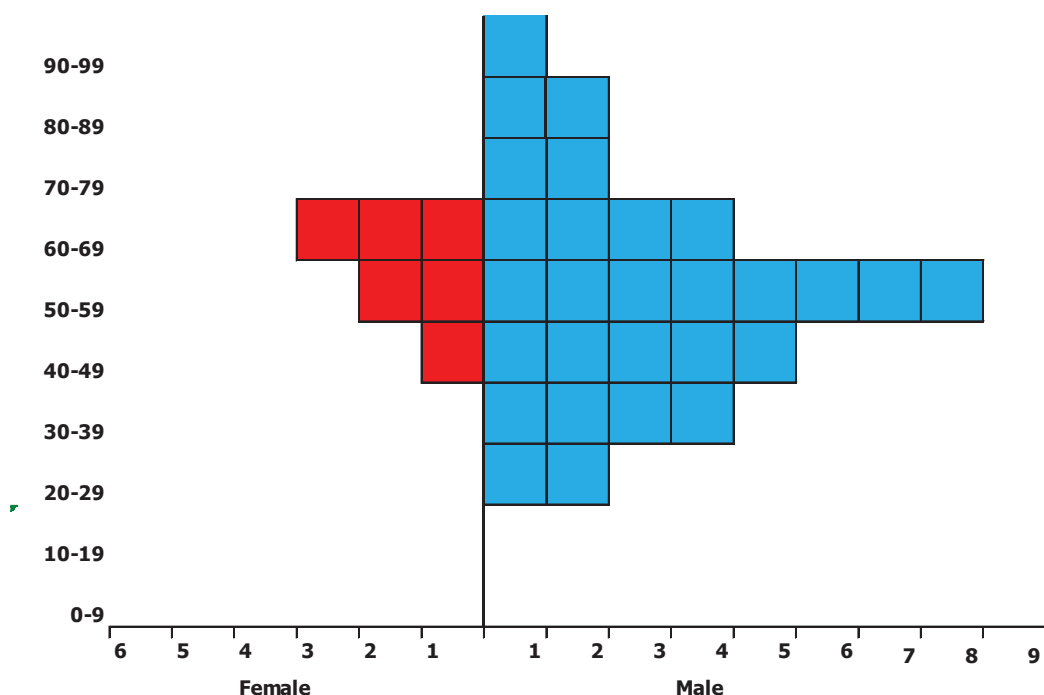
Eight cases were initially diagnosed in three European countries: three came to Europe as a result of medical transfers, two developed illness after returning from the Middle East, and three were the result of limited non-sustained person-to-person transmission in Europe (two of them were nosocomial infections).

Figure 2: Cases of MERS-CoV reported in the Arabian Peninsula and Jordan, April 2012 to 15 May 2013 (n=35)



The majority of reported cases continue to be associated with severe disease (lower respiratory tract infection such as pneumonia and/or renal failure). In those cases in which more detailed information is available, the majority is reported to have a history of underlying disease or immunosuppression. Only one case – part of the UK family cluster – presented with mild influenza-like symptoms [4]. Nineteen of the 38 cases are reported to have died, resulting in a case-fatality ratio of 50%. The age of cases ranges from 24 to 94 years (N=34 cases, information not available for four cases), with a mean of 55.5 years and a male-female ratio of 1:0.2 (Figure 3).

Figure 3: Distribution of cases of MERS-CoV by gender and age, April 2012 – 13 May 2013 (N=34)



Virological information

MERS-CoV is distinct from the coronavirus which caused the SARS outbreaks in 2003, and distinct from the endemic human coronaviruses (HCoV) OC43, 229E, HKU1, and NL63. The International Committee on Taxonomy of Viruses (ICTV) has recognised four genera within the *Coronavirinae* subfamily: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*.

HCoV-229E and HCoV-NL63 are viruses belonging to the genus *Alphacoronavirus*, while HCoV-OC43, HCoV-HKU1, SARS-CoV, and MERS-CoV belong to the genus *Betacoronavirus* [8]. Within the genus *Betacoronavirus*, four monophyletic lineages, A through D, are commonly recognised. Lineage A includes HCoV-OC43 and HCoV-HKU1, and lineage B the SARS-CoV, all of which belong to different species.

Lineages C and D include viruses detected only in bats, for example:

- In China: *Rousettus* bat coronavirus HKU9 (BtCoV-HKU9) (lineage D), *Tylosycteris* bat coronavirus HKU4 (BtCoV-HKU4), and *Pipistrellus* bat coronavirus HKU5 (BtCoV-HKU5) (both lineage C).
- In Europe: *Pipistrellus* bat coronaviruses 8-691 from Romania, UKR-G17 from Ukraine, or VM314 from the Netherlands [8].

MERS-CoV belongs to lineage C, and is thus the first *Betacoronavirus* lineage C member isolated from humans. It appears most closely related to several European bat coronaviruses [8].

No animal reservoir or mode of zoonotic transmission has yet been identified for MERS-CoV although the similarities to bat coronaviruses make bats a likely source, specifically insectivorous species such as *Pipistrellus*. However, experience with SARS indicates that the exposure may not be directly from bats but can result from environmental contamination or via intermediary animal hosts [9].

Analysis of virus tropism indicates that these viruses can infect a variety of cell lines, including human cells via surface receptors distinct from SARS coronavirus receptors [10]. Novel coronavirus seems to be fully able to penetrate human bronchial epithelia cultures. At the same time, like SARS-CoV, it appears to be sensitive to treatment with interferons (types I and III) [11]. Cyclosporin A has been shown as an inhibitor of MERS-CoV replication in cell culture and MERS-CoV was found to be 50 to 100 times more sensitive to interferon-alpha (IFN-α) treatment than SARS-CoV [12].

Interim laboratory testing guidance for screening and confirmation of MERS-CoV infection was issued by WHO in December 2012. A survey by ECDC and the WHO Regional Office for Europe ascertained the availability of national reference laboratory testing as of November 2012. Screening by controlled upE-RT-PCR assay was available in 19 of 30 EU/EEA countries [13]. Confirmation of positive-screened samples by either ORF1b – RT-PCR, or other target RT-PCR assays with sequence analysis or whole-genome sequence analysis, was available in 18 of 30 EU/EEA countries [13]. However, this does not imply the capacity for large-scale or rapid testing with such non-commercial technically demanding tests in these 18 countries. Additional molecular assays for sensitive and specific-case confirmation have been described [14]. More information about diagnostic procedures can be found in other articles [13-16] and on the [University of Bonn website](#).

Since routine microbiological sampling through nasopharyngeal swabs may give initial negative results in persons later shown to be infected with the coronavirus, tests should be repeated on deeper respiratory samples if a person meets the criteria for investigation, especially if their condition is worsening.

Serological tools for the detection of specific MERS-CoV IgM and IgG antibodies based on protein microarray technology have been recently developed and validated with a limited number of specimens [17]. 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 Arabian Peninsula and Jordan [18].

Following the identification and analysis of the viruses obtained from the first identified cases, the flow of viruses to specialised laboratories, especially from the Middle East cases, has slowed down, limiting the possibility to determine the full virological picture and making it difficult to assess whether the viruses are evolving.

Epidemiological surveillance

On 16 January 2013, WHO re-published its earlier case-definition for the novel coronavirus in humans, along with its interim surveillance recommendations for human infection of December 2012 [19]. This publication also includes a category for 'patient under investigation'. A confirmed case is a case in which novel coronavirus has been identified in a biological sample from the patient. Interim laboratory testing guidance for screening and confirmation of infection was issued by WHO in December 2012.

The initial case-finding strategy was based on two approaches:

- Firstly, looking for the virus in people with severe lower respiratory tract infection, especially in those with no other microbiological diagnosis. WHO recommends that special attention should be paid to persons who report onset of symptoms ten days (or less) after arriving from the Arabian Peninsula and Jordan.
- Secondly, contact tracing should be performed among all close contacts¹ of confirmed cases, both for control purposes and to assess whether human-to-human transmission occurred. If numbers increase and it becomes apparent that more are presenting with milder symptoms, a more selective approach will be needed.

The first French case raises the possibility that presentations may not initially include respiratory symptoms, especially in those with immunosuppression or other underlying chronic conditions and, as a result, delay the detection and implementation of measures.

The number of cases with immunosuppression or other underlying conditions, and the transmission to and from them, as in the two French cases, suggest that such persons may be at increased risk of acquiring or transmitting infections.

Protocols on the standardisation of influenza seroepidemiology have already been published [18, 20]. Drawing on these and in-country protocols, the UK has published a protocol specifically for the purpose of investigating cases of MERS-CoV infections. This protocol is suitable for use in other EU countries [21]. Most recently, the CONWISE group has published specific coronavirus protocols [20]. Seroepidemiological studies of close contacts are being undertaken in France, similar to studies already performed in Germany [27].

¹ A standard definition for 'close contact' is available online at <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20427>

- Aeroplane setting: the aircraft passengers in the same row and the two rows in front and behind a symptomatic case.
- Household setting: any person who had prolonged (>15 minutes) face-to-face contact with the confirmed case(s) any time during the illness in a household setting.
- Healthcare setting: either (i) a worker who provided direct clinical or personal care to or examined a symptomatic confirmed case or was within close vicinity of an aerosol-generating procedure AND who was not wearing full personal protective equipment (PPE) at the time; or (ii) a visitor to the hospital who was not wearing PPE at the bedside of a confirmed case; full PPE was defined as correctly fitted high filtration mask (FFP3), gown, gloves and eye protection.
- Other setting: any person who had prolonged (>15 minutes) face-to-face contact with a confirmed symptomatic case in any other enclosed setting.

The epidemiological pattern of the infections is unusual, with an excess of male cases and of cases presenting with co-morbidities, as well as an underrepresentation of children [22]. This is different from SARS, where there was a small female excess, co-morbidities were less marked, and cases were younger.

Applied epidemiological and laboratory studies will be of assistance here, and opportunistic and retrospective case-finding will be invaluable, focusing on severe cases for which there are suitable samples as defined by the [WHO laboratory guidance of 12 December 2012](#). Particular emphasis should be on capturing the results of case finding operations, negative as well as positive. The ECDC-WHO laboratory survey could serve as an example, as it helped to inform about the true geographical extent of these infections [13, 18].

Possible sources and routes of transmission

The retrospective finding of two cases in Jordan raised the issue of whether this is a new infection in humans or one that has been occurring for some time. Since similar animal coronaviruses can be found in bats in all regions of the world [8-9, 23-26], it is possible that these infections are to be found sporadically in many countries. This makes a strong case for further studies of animal coronaviruses and prospective and retrospective searches for cases in other regions – as was already pointed out in ECDC's risk assessment in February 2013. The testing of people with respiratory tract infections among those coming to Europe between September and November 2012 did not reveal any additional infections to the three already mentioned [2, 13, 27].

No reservoir or source of infection for MERS-CoV has been identified so far in Saudi Arabia, the country reporting most indigenous cases to date. The same is true for other cases and clusters in the other reporting countries of the Arabian Peninsula and Jordan. For a number of cases, contact with animals, in particular camels in herds or in camel markets has been mentioned. However, this information is not available for many of the primary cases.

The routes of transmission to humans have not yet been determined. This is a common issue with emerging zoonoses where there are often simultaneous possibilities, including environmental, animal and human exposures. There is very little information in the public domain, which contrasts with the situation during the SARS outbreak ten years ago [28-31].

In Germany and the UK, a follow-up of nearly 200 personal contacts and healthcare workers who were exposed to the first two imported confirmed cases has been completed and did not find evidence of human-to-human transmission. Although some contacts in Germany and the UK developed mild respiratory infections, virological and serological investigations did not link these infections to MERS-CoV [2, 26]. In France, the epidemiological investigation and contact tracing are ongoing.

There have been at least three instances in Europe where person-to-person transmission is certain to have taken place. Two of these transmissions were in a small family cluster of three cases in the UK. One transmission took place from an imported case to a healthy relative paying a hospital visit [4]. Person-to-person transmission also took place in the most recent French cases.

Threat assessment for the EU

Information on many of the basic epidemiological indicators required for determining effective control measures is still missing for most cases that occurred in the Middle East, e.g. the reservoir of infection, risk groups, incubation period, period of infectivity, settings where infection has occurred – despite the requirements formulated in Article 6.2 of the 2005 International Health Regulations [18]. In particular, information from the earlier clusters in private homes, from hospitals in the Arabian Peninsula, and from the recent cases in Saudi Arabia is insufficient, which makes it difficult to comment on the routes of transmission or the underlying pattern of infection and disease. Consequently, it is not possible to estimate the disease risk. As a result, ECDC has to consider a number of underlying scenarios that are compatible with the information available. At this stage, it is not possible to exclude a SARS-like scenario, especially in the light of the hospital-related outbreaks in Jordan and Al-Hasa, Saudi Arabia.

The additional coronavirus cases reported by the Saudi Arabian authorities in the past two weeks and the recent imported cases reported by Germany (related to medical evacuation) and France (travel related) indicate that an ongoing source of human infections remains present in the Arabian Peninsula and Jordan and that more cases may be identified in the EU in the immediate future.

Medical evacuations represent a potent introduction of cases in the European Member States. Numbers 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 with in hospitals in the area.

The three person-to-person transmissions that have been documented in Europe, two of which are nosocomial, indicate that the risk of onward transmissions in Europe is significant, in particular in healthcare settings.

In those cases from the Middle East in which more detailed information is available, the majority have a history of underlying disease and/or immunosuppression. However, given a median age of 55.5 years, this may be normal for these age groups [22]. Hence, it needs to be investigated whether the elderly may be at increased risk of acquiring MERS-CoV infection and/or transmitting it.

The reason for the strong male predominance among the cases is unexplained. This is different from SARS, and it needs to be investigated whether this represents a difference in care-seeking behaviour or care receiving in the Middle East [22].

Despite extensive contact tracing amongst previous contacts, only one secondary case with mild symptoms has been detected to date in the EU. It is, however, a reason for concern that milder cases could be present in exposed populations in the Arabian Peninsula and Jordan.

Further work to document the spectrum of illness and the route of transmission is still needed. A seroepidemiological approach might be useful once the available tests are validated in the Middle East [18].

Conclusions

- As of 14 May 2013, 38 cases of MERS-CoV have been reported worldwide, including 20 deaths. All cases remain associated (including indirect association following secondary person-to-person transmission in the UK and France) with transmission in the Arabian Peninsula and Jordan. The age of cases ranges from 24 to 94 years (N=34 cases), with a mean of 55.5 years and a male/female ratio of 1:0.2.
- The report of 19 new infections in Saudi Arabia in the past two weeks – including one infection with MERS-CoV acquired in the United Arab Emirates and later imported to Europe – indicate that there is an ongoing source of infection and risk of transmission to humans in the Arabian Peninsula and Jordan.
- The most recent imported case, which resulted in a nosocomial transmission, originated in the United Arab Emirates and then moved to France. Both patients had underlying conditions and a degree of immunosuppression. One of the transmissions in the UK also affected an immunosuppressed person. These underlying conditions may be increasing vulnerability and the risk of transmission.
- The first French case raises the possibility that presentations may not include respiratory symptoms initially, especially in those with immunosuppression or underlying chronic conditions. This needs also to be taken into account when revising case-finding strategies.
- The confirmed infection in France of a patient who shared a hospital room with a patient returning from the United Arab Emirates indicates the risk of nosocomial transmission. This is the second nosocomial transmission in Europe. The first one took place when an imported case in the UK visited a relative in the hospital in February 2013.
- These conclusions should be seen in the light of the many uncertainties that still continue with the investigation of cases in the Arabian Peninsula and Jordan. It is unusual to have such a degree of uncertainty at this stage in an outbreak.

Recommendations

- Healthcare workers in the EU should be vigilant in identifying patients that may require further investigation; they should also follow ECDC and national guidance for case finding. Patients developing severe respiratory infections and who have been in the Arabian Peninsula or neighbouring countries in the preceding 10 days should be investigated rapidly. Special attention should be given to medical evacuated patients from the Arabian Peninsula and neighbouring countries.
- Patients with chronic underlying conditions who develop severe infections (not just respiratory infections) should also be investigated rapidly for MERS-CoV if they have been in the Arabian Peninsula or neighbouring countries in the preceding 10 days.
- Since routine microbiological sampling (nasopharyngeal swabs) may give misleading negative results in persons later shown to be infected with the coronavirus, tests should be repeated with deeper respiratory sampling if a person fits into a category that requires investigation, especially if their condition is worsening.
- As demonstrated by a case with dual influenza and MERS-CoV infections, there is a possibility of co-infection and this should be considered by healthcare personnel. Identification of one causative agent should not exclude testing for MERS-CoV where indicated.
- Mapping of international routes of medical evacuation or emergency medical care from the Arabian Peninsula and neighbouring countries to the EU could be considered in order to determine the most vulnerable centres in the EU where these cases might arrive.
- Companies undertaking medical evacuations from affected areas should be reminded of the risk of transferring infections across borders and of their obligations to protect staff engaged in the transfer; the same holds true for the staff of institutions which receive patients.
- Healthcare workers caring for patients under investigation or confirmed for MERS-CoV should exercise infection control measures following national and international guidance [32].

- Close contacts of confirmed cases must be monitored for symptoms for 10 days after the last exposure, and should be tested, and should be informed what to do should they become ill. This should be carried out according to guidance, such as that developed by Public Health England UK (See 'Sources of additional information' below).
- Healthcare workers caring for confirmed cases should be monitored for early symptoms of infection and advised to seek testing and thereafter self-isolate if they become unwell.
- Clusters of severe acute respiratory infections in the community or in healthcare settings, both among patients or healthcare workers, should always be reported rapidly and investigated for a range of pathogens, regardless of where in the world these infections occur.
- ECDC does not currently consider a need for testing individual patients with unexplained pneumonias or other respiratory symptoms unless they fall under one of the above categories.
- Any probable or confirmed case being diagnosed in the EU/EEA should be reported to national authorities through the Early Warning and Response System (EWRS) and to WHO under the International Health Regulations (2005). Reporting through EWRS qualifies as IHR notification and avoids double reporting. Patients still under investigation do not need to be reported internationally before confirmation, but information on outcome of such testing exercises should be shared with ECDC.
- ECDC supports the WHO position of no travel or trade restrictions in relation to MERS-CoV. However, EU citizens travelling to the Arabian Peninsula and neighbouring countries need to be aware of the presence of MERS-CoV in this geographical area and of the small risk of infection. Member States may consider active information efforts for travellers to areas most at risk.
- Although the reservoir of infection in the Middle East is unknown, other novel coronaviruses are zoonoses and have come from animal sources. Travellers should therefore follow standard good hygiene practise and avoid contact with animals or their waste products.

References

- [1] Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012 8 November;367(19):1814–20. Available at: <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1211721>
- [2] Pebody RG, Chand MA, Thomas HL, Green HK, Boddington NL, Carvalho C et al. The United Kingdom public health response to an imported laboratory confirmed case of a novel coronavirus in September 2012. *Euro Surveill.* 2012;17(40):pii=20292. Available at: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20292>
- [3] AlBarrak,AM, Stephens GM, Hewson R, Memish, ZA Recovery from severe novel coronavirus infection. *Saudi Med J.* 33; 12: 1265–1269
- [4] The Health Protection Agency (HPA) UK Novel Coronavirus Investigation team. Evidence of person-to-person transmission within a family cluster of novel coronavirus infections, United Kingdom, February 2013 . *Euro Surveill.* 2013;18(11):pii=20427. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20427>
- [5] RKI. Aktualisierung der Risikoeinschätzung des RKI zu Erkrankungsfällen durch das neuartige Coronavirus (hCoV-EMC) 26 March 2013 <http://www.rki.de/DE/Content/InfAZ/C/Corona/Risikoeinschaetzung.html>
- [6] ProMed. Novel coronavirus – Eastern Mediterranean (18): Saudi Arabia <http://www.promedmail.org/direct.php?id=20130505.1693290>
- [7] Ministère des Affaires sociales et de la Santé, France. Premier cas confirmé de coronavirus en France. Accessed 8 May 2013. Available from: <http://www.sante.gouv.fr/premier-cas-confirme-de-coronavirus-en-france,13048.html>
- [8] Annan A, Baldwin HJ, Corman VM, Klose SM, Owusu M, Nkrumah EE, et al. Human betacoronavirus 2c EMC/2012–related viruses in bats, Ghana and Europe. *Emerg Infect Dis* [Internet]. 2013 Mar. Available at: <http://dx.doi.org/10.3201/eid1903.121503>
- [9] Li W, Shi Z, Yu M, Ren W, Smith C, Epstein JH. Bats are natural reservoirs of SARS-like coronaviruses. *Science.* 2005;310:676–9. DOI: 10.1126/science.1118391. Available at: <http://www.sciencemag.org/content/310/5748/676>
- [10] Müller M, Raj V, Muth D, et al. Human Coronavirus EMC Does Not Require the SARS-Coronavirus Receptor and Maintains Broad Replicative Capability in Mammalian Cell Lines. *America Society for Microbiology.* 11 December 2012 doi:10.1128/mBio.00508-12
- [11] Kindler E, Jónsdóttira HR, Muthb D, Hammingc OJ, Hartmannc R, Rodriguezc R et al. Efficient replication of the novel human betacoronavirus EMC on primary Human Epithelium Highlights Its Zoonotic Potential *mBio* doi: 10.1128/mBio.00611-12 19 February 2013 *mBio* vol. 4 no. 1 e00611-12.
- [12] de Wilde AH, Ray VS, Oudshoorn D, Bestebroer TM, van Nieuwkoop S, Limpens RW, Posthuma CC, van der Meer Y, Bárcena M, Haagmans BL, Snijder EJ, van den Hoogen BG. Human coronavirus-EMC replication induces severe in vitro cytopathology and is strongly inhibited by cyclosporin A or interferon-alpha treatment. *J Gen Virol.* 2013 Apr 25. [Epub ahead of print]
- [13] Palm D, Pereyaslov D, Vaz J, Broberg E, Zeller H, Gross D et al on behalf of the Joint ECDC-WHO Regional Office for Europe Novel Coronavirus Laboratory Survey participants; ECDC National Microbiology Focal Points, WHO European Region EuroFlu Network and European Network for Diagnostics of "Imported" Viral Diseases (ENIVD). Laboratory capability for molecular detection and confirmation of novel coronavirus in Europe, November 2012. *Euro Surveill.* 2012;17(49):pii=20335. Available at: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20335>
- [14] Corman VM, Müller MA, Costabel U, Timm J, Binger T, Meyer B et al. Assays for laboratory confirmation of novel human coronavirus (hCoV-EMC) infections. *Euro Surveill.* 2012;17(49):pii=20334. Available at: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20334>
- [15] Corman VM, Eckerle I, Bleicker T, Zaki A, Landt O, Eschbach-Bludau M et al. Detection of a novel human coronavirus by real-time reverse-transcription polymerase chain reaction. *Euro Surveill.* 2012;17(39):pii=20285. Available at: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20285>
- [16] Bermingham A, Chand MA, Brown CS, Aarons E, Tong C, Langrish C et al. Severe respiratory illness caused by a novel coronavirus, in a patient transferred to the United Kingdom from the Middle East, September 2012. *Euro Surveill.* 2012;17(40):pii=20290. Available at: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20290>
- [17] Reusken C, Mou H, Godeke GJ, van der Hoek L, Meyer B, Müller MA, Haagmans B, de Sousa R, Schuurman N, Dittmer U, Rottier P, Osterhaus A, Drosten C, Bosch BJ, Koopmans M. Specific serology for emerging human coronaviruses by protein microarray. *Euro Surveill.* 2013;18(14):pii=20441. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20441>

- [18] Nicoll A. Public health investigations required for protecting the population against novel coronaviruses. *Eastern Mediterranean Health Journal* 2013 (in press).
- [19] Danielsson N, on behalf of the ECDC Internal Response Team, Catchpole M. Novel coronavirus associated with severe respiratory disease: Case definition and public health measures. *Euro Surveill.* 2012;17(39):pii=20282. at: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20282>
- [20] Van Kerkhove M, Broberg E, Engelhardt OG, Wood J, Nicoll A on behalf of the CONSISE steering committee. The consortium for the standardization of influenza seroepidemiology (CONSISE): a global partnership to standardize influenza seroepidemiology and develop influenza investigation protocols to inform public health policy *Influenza and Other Respiratory Viruses* DOI: 10.1111/irv.12068. Available at: <http://onlinelibrary.wiley.com/doi/10.1111/irv.12068/full>
- [21] HPA. Epidemiological Protocols for Comprehensive Assessment of Early Novel Coronavirus Cases and their close contacts in the United Kingdom "The First Few Hundred (FF100)" Enhanced Case and Contact Protocol v4.0 http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317136300809
- [22] Peiris JM, Yuen KY, Osterhaus ADME, Stohr K. The Severe Acute Respiratory Syndrome *N Engl J Med* 2003;349:2431-41. Available from: <http://www2.medicine.wisc.edu/home/files/domfiles/infectiousdisease/SARS.pdf>
- [23] Drexler JF, Gloza-Rausch F, Glende J, Corman VM, Muth D, Goettsche M, et al. Genomic characterization of severe acute respiratory syndrome-related coronavirus in European bats and classification of coronaviruses based on partial RNA-dependent RNA polymerase gene sequences *J Virol.* 2010;84(21):11336-49. Available at: <http://jvi.asm.org/content/84/21/11336.abstract>
- [24] Anderson LJ, Tong S. Update on SARS research and other possibly zoonotic coronaviruses. *Int J Antimicrob Agents.* 2010;36 Suppl 1:S21-5.
- [25] Anthony S, Ojeda-Flores R, Rico-Chávez O, Navarrete-Macias I, Zambrana-Torrel C, Rostal M et al. Coronaviruses in Bats from Germany. Published online ahead of print January 30, 2013, doi: 10.1099/vir.0.049759-0 *J Gen Virol* January 2013 vir.0.049759-0 Available at: <http://vir.sgmjournals.org/content/early/2013/01/29/vir.0.049759-0.short>
- [26] Shi Z, Hu Z. A review of studies on animal reservoirs of the SARS coronavirus. *Virus Res.* 2008;133(1):74-87
- [27] Buchholz U, Nitsche A, Sanewski A, Bauer-Balci T, Bonin F et al Contact investigation of a case of human coronavirus infection treated in a German hospital, October-November 2012. *Euro Surveill.* 2013;18(8):pii=20406. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20406>
- [28] Heymann D, Mackenzie J, Peiris M. SARS legacy: outbreak reporting is expected and respected *Lancet*, 2013; 381: 779 - 781, 9 March 2013. doi:10.1016/S0140-6736(13)60185-3
- [29] WHO Consensus document on the epidemiology of severe acute respiratory syndrome WHO May 2003 <http://www.who.int/csr/sars/en/WHOconsensus.pdf>.
- [30] Anderson RM, Fraser C, Ghani A, Donnelly C, Riley S, Ferguson NM et al Epidemiology, transmission dynamics and control of SARS: the 2002-2003 epidemic *Philos Trans R Soc Lond B Biol Sci.* 2004 July 29; 359(1447): 1091-1105. doi: 10.1098/rstb.2004.1490. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1693389/>
- [31] WHO Press Statement Related to the Novel Coronavirus Situation May 12 2013. http://www.who.int/mediacentre/news/statements/2013/Novel_Coronavirus_12052013/en/index.html
- [32] WHO Infection prevention and control during health care for probable or confirmed cases of novel coronavirus (nCoV) infection Interim guidance.6 May 2013. Available at: http://www.who.int/csr/disease/coronavirus_infections/IPCnCoVguidance_06May13.pdf

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](#)
- CONWISE Website: [click here](#); CONWISE 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](#)