



## UPDATED RAPID RISK ASSESSMENT

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

Ninth update, 24 April 2014

## Main conclusions and options for action

The seventh update of the rapid risk assessment on 24 September 2013 provides options for actions on case finding, laboratory testing, reporting, contact tracing, infection control and travel advice. These options for actions remain valid and can be found in the annex.

In addition:

### Visitors to and EU residents of the Arabian Peninsula should:

- Follow general travel health precautions that lower the risk of infection in general, including illnesses such as influenza and traveller's diarrhoea. This includes:
  - Wash hands often with soap and water. When hands are not visibly dirty, a hand rub can be used.
  - Adhere to good food-safety practices, such as avoiding undercooked meat and unpasteurised milk (especially from camels) or food prepared under unsanitary conditions, and properly washing fruits and vegetables before eating them.
  - Maintain good personal hygiene.
  - Avoid unnecessary contact with farm, domestic, and wild animals, especially camels.
  - Use appropriate precautions when in close contact with case-persons presenting with acute respiratory illness, diarrhoea or other potentially infectious diseases.
- Consult their physician if suffering major medical conditions (e.g. chronic diseases such as diabetes, chronic lung or renal disease, immunodeficiency) that can increase the likelihood of illness including MERS-CoV infection, or contact with healthcare facilities during travel.

### Returning travellers to EU/EEA Member States should:

- If developing acute illness with severe respiratory symptoms or diarrhoea, advise the healthcare providers in advance of the possibility of exposure to Middle East respiratory syndrome coronavirus (MERS-CoV) on the Arabian Peninsula in order to ensure appropriate measures are taken and if needed, testing considered.
- Not travel if acutely ill with an infectious disease.

### The international public health community and affected countries could:

- Urgently provide support for an outbreak assessment 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 the

healthcare facilities. Epidemiological studies, such as cohort or case-control studies are well suited for such assessments.

- Encourage and support as urgent, observational clinical studies to determine optimal management of patients in order to improve outcomes.
- Ensure that appropriate serum samples (positive and negative controls) are available for international standardisation of serological tests.
- Encourage serological surveys among close contacts of cases and in affected settings.
- Ensure that adequate numbers of virus isolates are sequenced and submitted to publicly available databanks, such as GenBank throughout the evolving epidemic.
- Improve timely and transparent risk communication practices in affected areas.

### EU/EEA Member States could:

- Review laboratory and healthcare preparedness for large clusters of MERS-CoV presenting in their healthcare systems;
- Sensitise healthcare workers to the possibility of MERS-CoV presenting in EU hospitals;
- Familiarise public health professionals, healthcare workers and risk communication experts with available guidance (see annex and seventh rapid risk assessment update).

## Source and date of request

ECDC Internal Decision, 15 April 2014.

## Public health issue

This ninth 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 of 6 November 2013, considering:

- the updated epidemiological information
- the recent findings of increased number of infections in healthcare workers (HCW) and suspicion of nosocomial transmission, and asymptomatic infections in close contacts
- the updated scientific evidence on the virus and the animal reservoir (camels).

## Previous rapid risk assessments

ECDC has published [nine previous Rapid Risk Assessments](#) (1 initial and 8 updates) on Middle East respiratory syndrome coronavirus since the start of the outbreak. [1]

## Consulted experts

**ECDC (alphabetically):** Kaja Kaasik-Aaslav, Cornelia Adlhoch, Sergio Brusin, Denis Coulombier, Niklas Danielson, Romit Jain, Josep Jansa, Daniel Palm, Pasi Penttinen, Diamantis Plachouras, Emmanuel Robesyn, René Snacken, Joanne Tay, Herve Zeller.

**External experts:** Marion Koopmans, Netherlands; the World Health Organization (WHO) was consulted on this document. The views in this document do not necessarily represent the views of WHO.

## Event background information

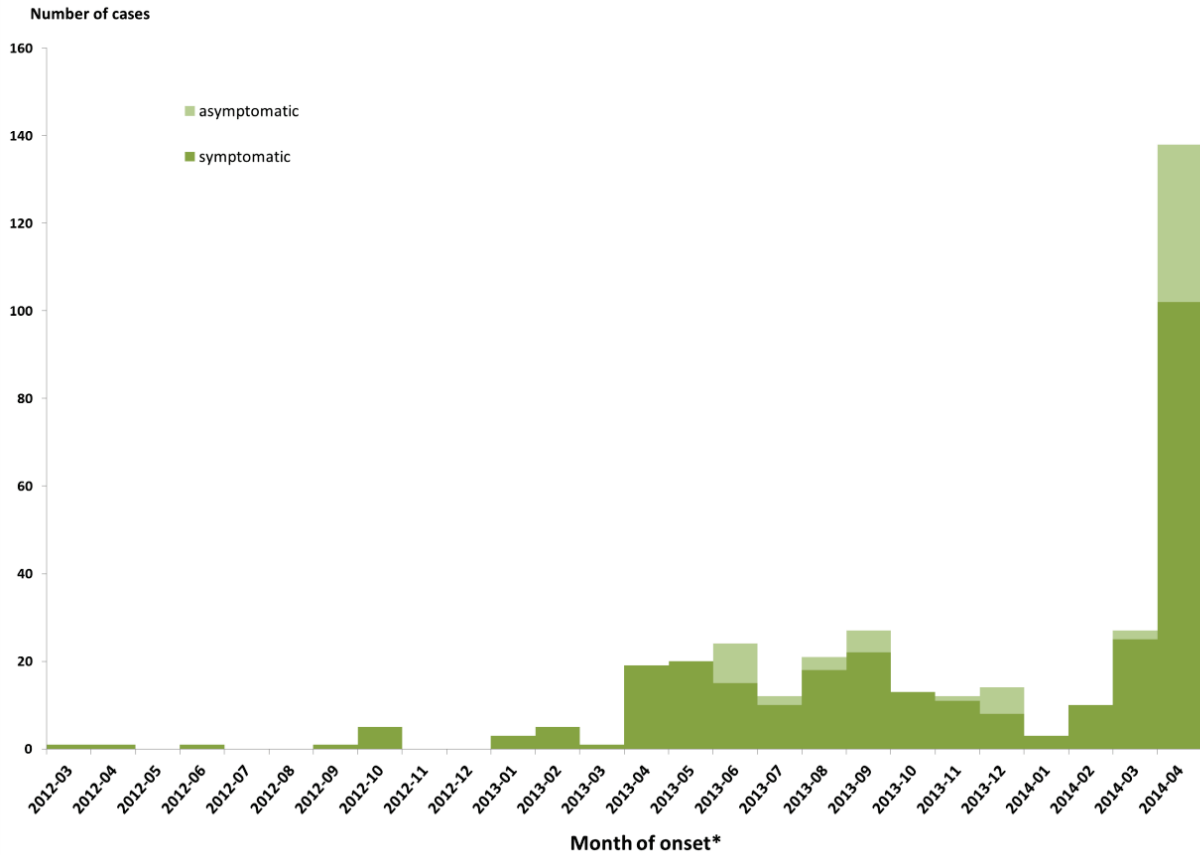
As of 23 April 2014, 345 laboratory-confirmed cases of MERS-CoV have been reported to public health authorities worldwide, including 107 deaths. Seventy-two of the 345 cases have been healthcare workers. The following countries have reported MERS-CoV cases.

Reporting country	Cases	Deaths
Saudi Arabia	272	81
United Arab Emirates	42	9
Qatar	7	4
Jordan	4	3
Oman	2	2
Kuwait	3	1
United Kingdom	4	3
Germany	2	1
France	2	1
Italy	1	0
Tunisia	3	1
Malaysia	1	1
Philippines	1	0
Greece	1	0
<b>Total</b>	<b>345</b>	<b>107</b>

Local person-to-person transmission has occurred outside of the Middle East in France, Tunisia and the UK after a primary case was imported. In France, the virus was transmitted from an imported case to a contact in a hospital before the infection was recognised. In Tunisia, transmission occurred to one close contact of a primary case. A second close contact who had accompanied the primary case in Saudi Arabia also developed confirmed infection but it is not clear when transmission occurred. In the UK, one imported case transmitted the virus to two family contacts.

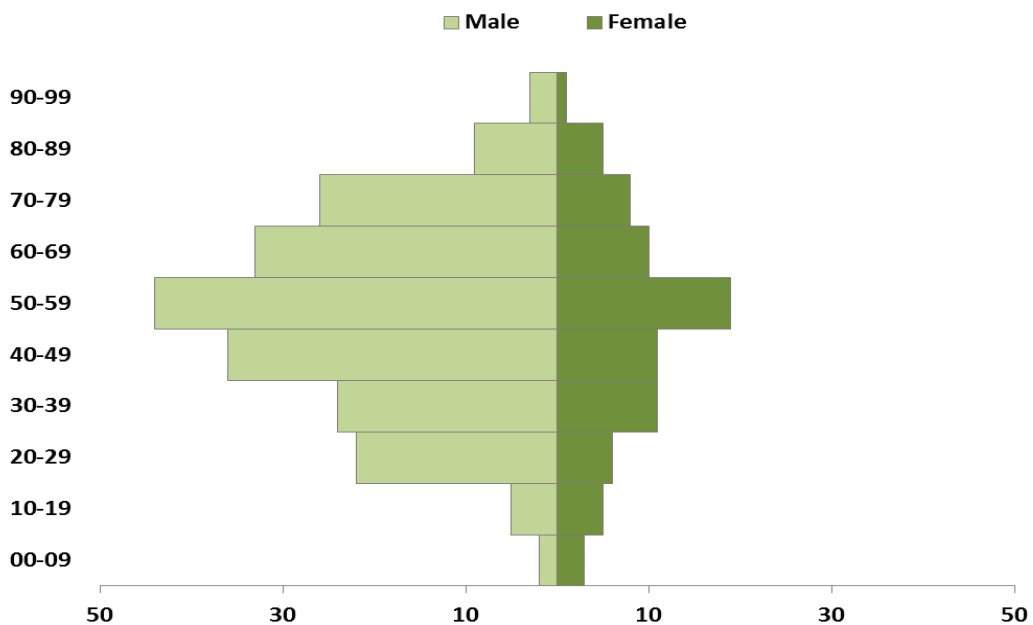
In November 2013, Spain reported two suspected imported case with exposure in Saudi Arabia, the first of whom triggered an update of the ECDC rapid risk assessment. The suspected cases imported to Spain could not be laboratory confirmed and were discarded. The cases have been deleted from the case count.

**Figure 1. Distribution of confirmed cases of MERS-CoV by month of onset and symptom status, March 2012–23 April 2014 (n=345\*)**



The cases are mostly in middle-aged men of the age group 50 to 59 years. (Figure 2).

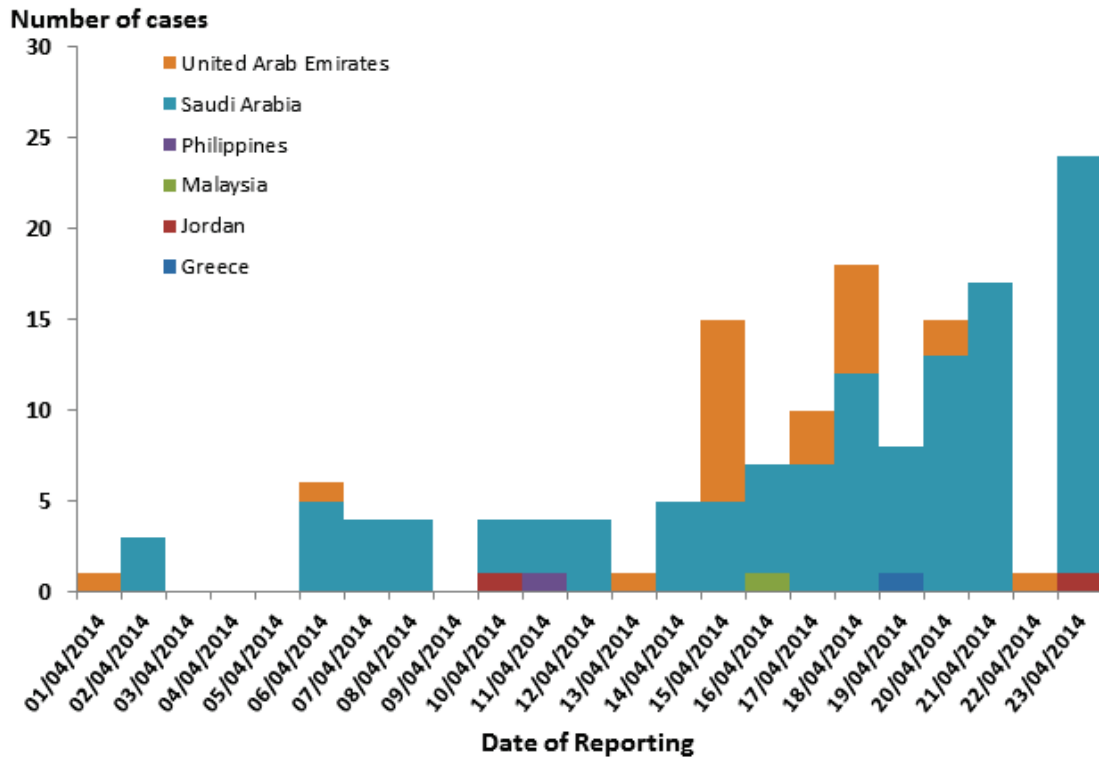
**Figure 2. Distribution of confirmed cases of MERS-CoV by gender and age group, March 2012–23 April 2014 (n=294)**



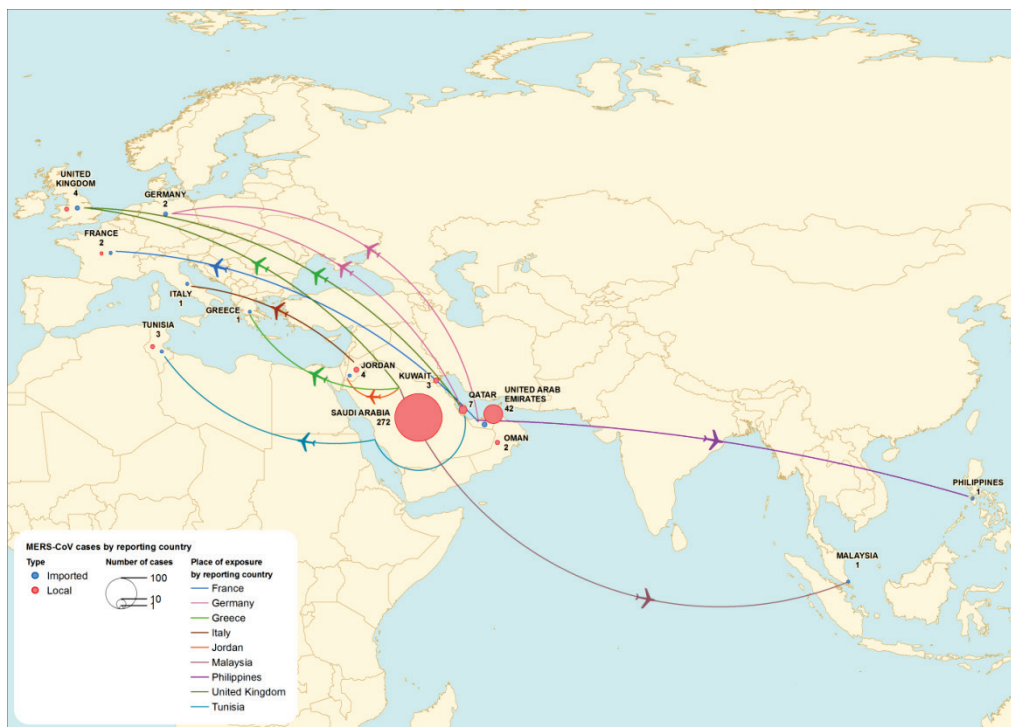
\*51 cases for which age or sex data is missing have been excluded

Recently the number of cases reported has increased substantially, leading to this updated rapid risk assessment. Between 13 and 23 April 2014, 108 cases have been reported by the respective Ministries of Health in the following countries: Saudi Arabia 83, United Arab Emirates (UAE) 23, one from Malaysia and one from Greece.

**Figure 3. Distribution of confirmed cases of MERS-CoV reported between 1 and 23 April 2014 by day and place of reporting (n=151)**



**Figure 4. Geographic distribution of confirmed MERS-CoV cases, worldwide, as of 23 April 2014 (n=345)**



Most of the latest cases reported from the UAE are linked to a cluster in a hospital in Al Ain where 16 healthcare workers (including one case exposed in UAE and reported by the Philippines) have tested positive for MERS-CoV. All these cases are linked to a previously reported case, who died on 10 April 2014.

Of the 23 cases in UAE, 10 had mild symptoms or were asymptomatic, two were reported to be in critical condition, one died, and there are no clinical details for the others. Only one of the healthcare workers is in critical condition and all the others are either asymptomatic or have mild symptoms. At least one case reported from UAE had travelled to Jeddah, Saudi Arabia. The average age of the latest cases in UAE is 41.

Of the 83 cases reported in Saudi Arabia since 13 April 2014, 57 are from Jeddah (one additional case exposed in Jeddah has been reported by the UAE), 20 are from Riyadh, four are from Medina, and one each are from Najran and Tabuk. The case reported in Malaysia had recently performed Umrah in Saudi Arabia.

The four cases in Medina are a family cluster with one death and three asymptomatic cases.

The 20 cases in Riyadh are all in serious condition, hospitalised or having died. Two are healthcare workers linked to known cases whose clinical condition is described as stable. The average age of these cases is 62 years.

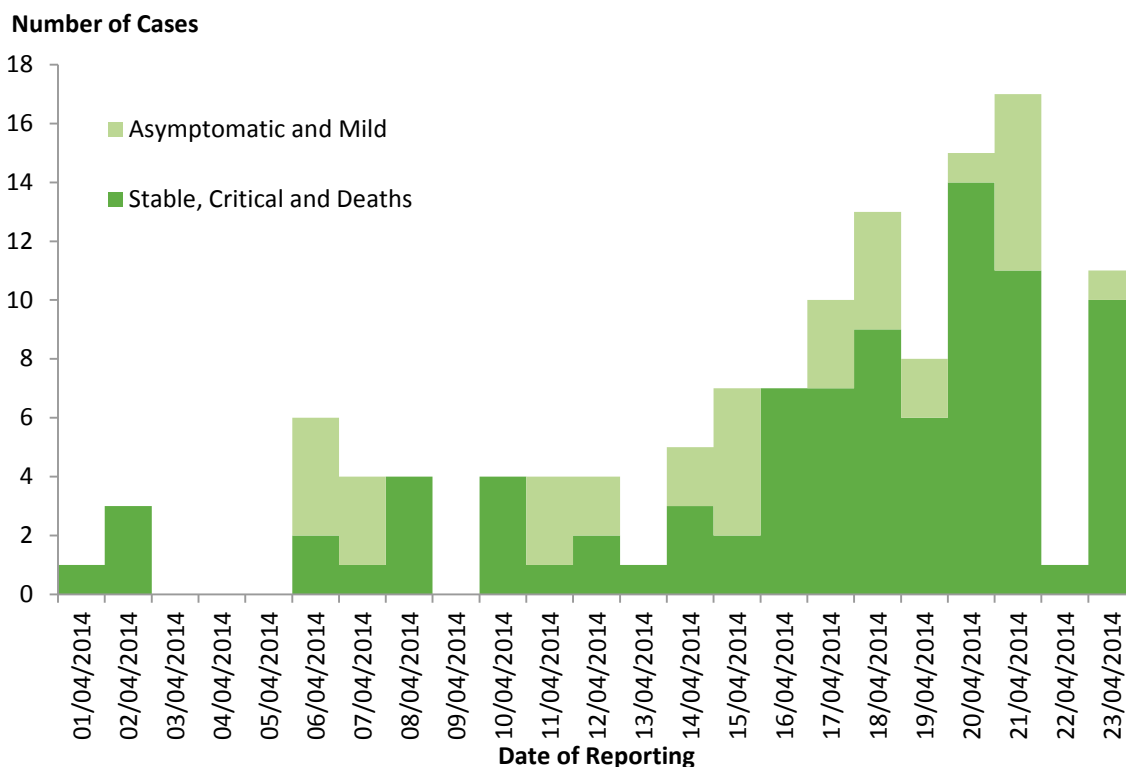
The 57 cases reported from Jeddah are presenting an age distribution similar to the other groups. However, 13 (23%) are reported as healthcare workers, and, for the others, the occupation is not specified, but assumed not to be in the health sector. Six (46%) of the healthcare workers are asymptomatic, four (31%) are described as stable, two are critical and one is unknown. The average age of the healthcare workers is 41.

Of the 44 non healthcare workers, seven (16%) are asymptomatic. The asymptomatic cases are thought to be contacts of hospitalised cases and on average are much younger, 24 years, compared to an average of 55 year in the symptomatic. Fourteen (32%) are reported in stable condition, 15 (34%) are critical, eight (18%) are dead, and for the remaining cases the clinical description is unclear.

The average age of the cases not reported as healthcare workers is 50 years.

The reporting process does not allow us to have a clear picture of the clustering of the cases although, from the media reports, it seems that there are clusters in at least two hospitals in Jeddah one of which is King Fahad Hospital. Currently, it is not possible to identify primary cases of the possible clusters with the information available.

**Figure 5. Distribution of confirmed cases of MERS-CoV reported between 1 and 23 April 2014 by severity (n= 138)**



*Fifteen cases with unknown outcome are not included in the graph*

On 18 April 2014, Greece reported its first case of MERS-CoV infection [2,3]. The case is a 69 year old male Greek citizen resident in Jeddah, Saudi Arabia. The patient arrived in Athens from Jeddah via Amman, Jordan, on 17 April 2014. He sought medical care on the same day for fever and diarrhoea at a large tertiary care centre. Laboratory testing of a throat swab at the national reference laboratory for influenza, Hellenic Pasteur Institute, confirmed the infection with MERS-CoV by polymerase chain reaction (PCR) for the Upstream E gene (screening test) and ORF-1A gene.

The Hellenic Centre for Disease Control and Prevention has identified 73 close contacts in Greece, including potentially exposed healthcare workers. Twelve contacts of the patient during the two flights with Royal Jordanian Airlines from Jeddah via Amman to Athens on 17 April 2014 are being contacted for screening of symptoms and are being offered laboratory testing.

## Scientific developments

### Source and route of infection

There is growing evidence that the dromedary camel is a host species for the MERS-CoV and that they play an important role in the transmission to humans.[4,5]

The first evidence of dromedary camels being part of the transmission chain was the detection of high rates of antibodies against MERS-CoV in dromedary camels on the Arabian Peninsula [6,7]. Evidence of infection in camels precedes the first evidence of human infection [8]. Recently, viral RNA has been detected in different specimens from camels and the virus has been isolated from nasal and faecal samples.[8-11]

The detection of MERS-CoV in dromedary camels imported from Sudan and Ethiopia for slaughter in Egypt [10], as well as serologic evidence of previous MERS-CoV infection in dromedaries in Nigeria, Ethiopia and Tunisia, suggest that the virus could be geographically widespread in the dromedary camel populations on the African continent, and that hitherto undetected transmission to humans may occur outside of the Arabian Peninsula [12].

A recent study showed that when MERS-CoV is added to unpasteurised camel milk stored at 4 degrees centigrade, the virus remains infectious beyond 72 hours but that infectious viruses could not be found after pasteurisation [13].

### Virological characteristics

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 (<1 months) indicate that maternal antibodies may not fully protect very young animals from infection. There was no evidence of prolonged virus shedding or viremia among the tested animals [11].

The full-genome sequences of the MERS coronaviruses retrieved from the dromedary camels in the above study were highly homologous to human isolates of clade B MERS-CoV [11,14].

No gene sequences of MERS-CoV have been published from the cases reported in 2014 [15].

### Virological testing

An external quality assessment was recently conducted by ENIVD (European network for viral imported diseases: [www.enivd.de](http://www.enivd.de)) for coronavirus detection focusing on MERS-CoV. The panel included 12 specimens. Preliminary results from 45 laboratories from 23 EU/EEA countries showed that:

- There were no false positive test results
- 100% of the laboratories detected the MERS-CoV samples for the two samples with the highest viral loads but only 73% of the laboratories correctly detected the specimen with a low viral load
- Only 24% of the laboratories correctly identified the four other coronaviruses included in the panel. However 38% of the laboratories correctly identified three out of the four other coronaviruses included in this panel.

In addition, results were also received from 47 laboratories worldwide including four laboratories in four affected countries in the Middle East. Data analyses for these results are still in process.

## ECDC threat assessment for the EU

The number of human MERS-CoV cases reported from the Arabian Peninsula has increased rapidly in the past weeks. Specifically, two healthcare associated clusters in Jeddah and Abu Dhabi have been reported with large number of cases. Cases of MERS-CoV reported from the Philippines, Malaysia and Greece in the past week may be linked to these healthcare associated clusters.

The cause of the rapid increase in cases is unknown. Possible scenarios include:

- A. More sensitive case detection through more active case finding and contact tracing or changes in testing algorithms.
- B. Increased zoonotic transmission with subsequent transmission in healthcare settings.
- C. Breakdown in infection control measures or otherwise increased transmission in the local healthcare setting.
- D. Change in the virus resulting in more effective human-to-human transmission, resulting in both nosocomial clusters, cases among travellers and increased numbers of asymptomatic community acquired cases.
- E. False positive lab results.

### Scenario A: More sensitive case detection, improved surveillance

To the best of our knowledge, the screening protocol in Saudi Arabia recommended testing of severe acute respiratory infections admitted to intensive care for MERS-CoV and testing of all close contacts of cases, including HCWs for the virus, however practices might differ at the facility level. These samples presumably have been tested according to WHO protocols with PCR of two target genes (e.g. upE specific and ORF-1a). Only cases confirmed by two tests 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 could explain the recent increase in reported cases and would indicate wider transmission of the virus in the community than previously estimated. ECDC does not have any evidence to suggest that screening practices have changed. A recent change of sensitivity in laboratory methods might also explain the recent increase of notified cases. During the past year, Saudi Arabia has rolled-out the PCR assays for MERS-CoV to at least five laboratories in the country, including Jeddah, but we are not aware of recent changes in laboratory assays used in Saudi Arabia for confirmation of cases.

The limited information about current and past testing practices in Saudi Arabia does not allow conclusions to be made about the extent of changes in practices and its impact on the number of reported cases. However, the fact that the proportion of asymptomatic to symptomatic confirmed cases has remained stable during the increase in cases in April indicates that increased testing alone is unlikely to explain the increase, as increased testing of contacts is expected to increase the proportion of asymptomatic cases.

If improved surveillance and/or more sensitive case detection are at the basis of the increase, it may indicate that many cases were missed in the past. If a majority of those were mild, the epidemiology would be quite different from what has previously been 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 it is likely that more cases, but likely less severe ones, could be detected in the EU/EEA in the future.

### Scenario B: Increased zoonotic transmission

Dromedary camels are a host species for MERS-CoV. Juvenile animals have 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 completely protective. Therefore, a higher circulation can 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 in the last ten years with an increased number of farms near cities [16]. Intensive camel farming could be at the origin of an increased zoonotic risk, similar to what was observed in the Q-fever outbreak in the Netherlands, although the mode of transmission would be different [17].



A good understanding of the epidemiology in camels, e.g. about seasonal calving periods and diarrheal outbreaks, is needed to fully assess the zoonotic risk. There currently remain many gaps in our knowledge on the epidemiology of coronavirus infections in dromedary camels, including the exact contact patterns with humans, both in the population in general and MERS-CoV cases. Though we know that MERS-CoV is widely circulating among the camel herds in the Arabian Peninsula, we do not know what triggers the apparent outbreak in humans and the absence of such outbreaks from other geographical regions where serological evidence exists for infection of dromedary camels.

## Assessment of risk for the EU

Our assessment of the risk is limited by gaps in our knowledge about the animal-human interface with camels and the epidemiology of the infection in animals and humans. Serological studies and case-control studies are needed to estimate risk factors for infection and risk factors for severe disease. This would allow better targeting of preventive measures and advice to EU citizens.

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

## Scenario C: Increased nosocomial transmission because of ineffective infection control measures

The reports of hospital associated clusters of MERS-CoV infections provide further evidence for the risk of nosocomial transmission and question the effectiveness of the precautionary measures used in the affected healthcare facilities. A full evaluation of the precautionary measures applied at the healthcare facilities involved in the outbreak would be useful to assess the effectiveness of hospital hygiene measures and possibly provide much needed information on the mode of transmission. If no important gaps were identified at the respective hospitals, it could indicate an increased risk for human-to-human transmission. The latter could be indicative of an important change in the risk for further spread of the outbreak.

## Assessment of risk for EU

More detailed information regarding the events of healthcare-associated MERS-CoV infection would allow better assessment of the risk for spread of the disease through various modes of transmission. With the information currently available, strict adherence to standard precautions (including hand hygiene) and additional contact and airborne transmission precautions remain the recommended infection prevention and control measures for any suspected case or case under investigation of MERS-CoV.

## Scenario D: More effective human-to-human transmission

Most asymptomatic or mild cases tend to be younger and do not have pre-existing illnesses. In recent clusters, secondary cases tend to be milder than previously reported.

The increased number of cases reported could be a result of more effective human-to-human transmission, even if the main source of infection is still zoonotic as indicated by the fact that cases are still associated with stay in the Arabian Peninsula. If the case-finding procedures are not more sensitive than before, the fact that more asymptomatic infections have been reported, more close contacts infected, and that there is more nosocomial transmission, could indicate more effective transmission. However, the absence of more detailed information about transmission risks, does not allow us to draw more significant conclusions.

## Assessment of risk for EU

More detailed information is needed about the risk factors at the basis of the recent increase of cases to assess the risk of human-to-human transmission. 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.

## Scenario E: Laboratory artefact

Laboratories performing PCR assays need to ensure that samples do not get cross-contaminated. A rapid scale-up of laboratory capacity for MERS-CoV in local laboratories in response to the outbreak might compromise stringent quality standards, increasing the possibility of cross-contamination. ECDC is not aware of the regional laboratory capability, laboratory standards or recent scale-up activities and it is therefore difficult to assess the likelihood of this scenario.

## Assessment of risk for EU

If laboratory contamination is shown to explain the reported cases even partially, this would decrease the current risk to populations in the affected area as well to European citizens to levels before April 2014. Considering the recent outbreaks have occurred simultaneously in three different cities in two countries, it is unlikely that laboratory contamination would be the only explanation of the evolving outbreak.

## Conclusions

The first confirmed case in Greece increased to five the number of EU countries that have reported confirmed cases of MERS-CoV infection: France, Germany, Greece, Italy and the UK. Given the current epidemiology on the Arabian Peninsula, it is likely that more cases will be imported and detected in EU Member States. Further vigilance in assessing patients with travel history to the affected region is warranted.

The quality of verified information on the recent events in Saudi Arabia and United Arab Emirates is insufficient to draw firm conclusions on the risks posed by the outbreaks. It is not clear what role nosocomial transmission is playing in these clusters or whether wider community transmission is taking place. However, unless these recent detections are due to laboratory contaminations, the epidemiological evidence from Saudi Arabia and UAE seems to suggest increased circulation of the virus or increased case detection among humans. More cases have recently been reported in individuals travelling out of the region, which might indicate increased transmissibility of the virus and perhaps longer human transmission chains than have been seen in the past. An apparent increase in the size of nosocomial clusters also supports this hypothesis.

Camels are a host species for this virus and it is likely that at least some of the primary cases in clusters have been infected through direct or indirect camel contact. Dromedary camels could be the direct or indirect source of human MERS-CoV infection. Full-genome sequences of MERS-CoV with very high homology have been retrieved from nasal specimens from dromedary camels with respiratory symptoms. However, many of the cases detected or treated outside of the Arabian Peninsula could have been healthcare acquired.

Gene sequences from the recent human cases have not been submitted to GENBANK or other publicly available databases, therefore it is impossible to verify whether significant mutations have appeared.

Extensive contact tracing efforts on board flights, on which cases have travelled, have thus far not shown evidence of transmission to other passengers.

No case control-studies or other epidemiological studies have been done 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.

Important gaps remain in appropriate treatment protocols and 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 geographic impact, if the virus is transmitting among humans. This unusual and unexpected disease has already been detected outside of the Middle East in Asia, Africa, Europe. More details and analysis of the evolving events in UAE and Saudi Arabia are urgently needed to further define the risks posed by this event.

## Options for action

The seventh update of the rapid risk assessment on 24 September 2013 provides options for actions on case finding, laboratory testing, reporting, contact tracing, infection control and travel advice [18]. These options for actions remain valid and can be found in the annex.

In addition:

### Visitors to and EU residents of the Arabian Peninsula should:

- Follow general travel health precautions that lower the risk of infection in general, including illnesses such as influenza and traveller's diarrhoea. This includes:
  - Wash hands often with soap and water. When hands are not visibly dirty, a hand rub can be used.
  - Adhere to good food-safety practices, such as avoiding undercooked meat and unpasteurised milk (especially from camels) or food prepared under unsanitary conditions, and properly washing fruits and vegetables before eating the.
  - Maintain good personal hygiene.
  - Avoid unnecessary contact with farm, domestic, and wild animals, especially camels.
  - Use appropriate precautions when in close contact with case-persons presenting with acute respiratory illness, diarrhoea or other potentially infectious diseases.
- Consult their physician if suffering major medical conditions (e.g. chronic diseases such as diabetes, chronic lung or renal disease, immunodeficiency) that can increase the likelihood of illness including MERS-CoV infection, or contact with healthcare facilities during travel.

### Returning travellers to EU/EEA Member States should:

- If developing acute illness with severe respiratory symptoms or diarrhoea, advise the healthcare providers in advance of the possibility of exposure to MERS-CoV on the Arabian Peninsula, in order to ensure appropriate measures are taken and if needed, testing considered.
- Not travel if acutely ill with an infectious disease.

### The international public health community and affected countries could:

- Urgently provide support for an outbreak assessment 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 the healthcare facilities. Epidemiological studies, such as cohort or case-control studies are well suited for such assessments.
- Encourage and support as urgent, observational clinical studies to determine optimal management of patients in order to improve outcomes.
- Ensure that appropriate serum samples (positive and negative controls) are available for international standardisation of serological tests.
- Encourage serological surveys among close contacts of cases and in affected settings.
- Ensure that adequate numbers of virus isolates are sequenced and submitted to publicly available databanks, such as GenBank throughout the evolving epidemic.
- Improve timely and transparent risk communication practices in affected areas.

### EU/EEA Member States could:

- Review laboratory and healthcare preparedness for large clusters of MERS-CoV presenting in their healthcare systems.
- Sensitise healthcare workers to the possibility of MERS-CoV presenting in EU hospitals.
- Familiarise public health professionals, healthcare workers and risk communication experts with available guidance (see annex and 7th RRA update).

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# Annex: Options for actions from seventh updated rapid risk assessment, 24 September 2014

Note that the literature references in this annex are referring to the original document references that are available at [18]

## Surveillance

### Case finding

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

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

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

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

### Laboratory testing

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

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

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

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

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

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

Serological tests have not been standardised and no ready-to-use kits are currently commercially available for serological testing. However, different serological tools for the detection of specific MERS-CoV IgM and IgG antibodies based on ELISA, protein microarray technology, and virus neutralisation have been developed recently. Validation is based on a limited number of specimens. These assays, presently in the hands of some specialised laboratories, can be used to aid diagnosis in individual patients, for confirmatory testing of positive tests, and for (large-scale) contact studies. These tests will need to be validated for use in the Middle East [46] [24]. The availability of serological assays enables the performance of population-based serological studies on general prevalence or the investigation of frequency of seroconversion in exposed persons or risk groups. Furthermore, protocols on the standardisation of influenza sero-epidemiology have been published. Drawing on these and in-country protocols, the United Kingdom has published a protocol for investigating cases of MERS-CoV infections which is suitable for use in other EU countries [7]. The CONSISE group has published specific coronavirus protocols [47].

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

## Reporting

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

## Contact tracing

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

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

Priority for contact tracing efforts should be given to:

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

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

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

## Treatment

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

## Prevention infection control

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

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

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

The number of persons in the room should be limited to a minimum during such procedures; all persons present should wear:

- a well-fitted FFP3 respirator;
- tight-fitting eye protection; and
- gloves and long-sleeved impermeable protective gowns.

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

The WHO advice on home care for patients with MERS-CoV infection presenting with mild symptoms and management of contacts [3] is targeted to public health and infection control professionals, health managers and healthcare workers. It states that evidence of transmission from mild cases is limited and that currently there is no evidence of transmission from asymptomatic cases. Confirmed and probable symptomatic cases should be admitted to hospital whenever possible, but if inpatient care is unavailable or unsafe, or if hospitalisation is refused, home care of mild cases in younger people without underlying conditions (e.g. chronic heart, kidney or lung disease, diabetes, immunosuppression, and blood diseases) needs to be considered. If home care is chosen, the patient needs to remain under close medical observation. Contact with the patient should be limited as much as possible, and caregivers should stay in a different room or keep a distance of at least one meter from cases. Strict hand and respiratory hygiene is stressed, and all exposed materials should be appropriately discarded. Protective equipment should be used whenever possible. A recent article documented the relative stability of MERS-CoV at indoor conditions. MERS-CoV was found to be more stable than influenza A H1N1pdm and remained viable for up to 48 hours on plastic and metal surfaces [19]. Therefore, healthcare facilities and home environments should ensure appropriate environmental cleaning.

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

## Travel advice

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

Travellers to the Middle East should:

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

Travellers from the EU who plan to visit Saudi Arabia for the Umrah and Hajj pilgrimage should consult the recommendations made by the Saudi Ministry of Health. The Health regulations for travellers to Saudi Arabia regarding MERS-CoV [54] recommends that the elderly (above 65 years of age) and those with chronic diseases (e.g. heart disease, kidney disease, respiratory disease, diabetes) and pilgrims with immune deficiency (congenital and acquired), malignancy and terminal illnesses, pregnant women and children (under 12) should postpone the Hajj and Umrah for their own safety.

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

## Sources of additional information and further resources

- WHO source page novel coronaviruses: [click here](#)
- University of Bonn – Diagnosis: [click here](#)
- ECDC MERS-CoV rapid risk assessments: [click here](#)
- CONSIZE website: [click here](#); CONSIZE 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](#)