



**RAPID RISK ASSESSMENT - UPDATE**

# Severe respiratory disease associated with a novel coronavirus

8 May 2013

## Summary

- The reporting of 17 new infections in the Kingdom of Saudi Arabia in the past week and two more imported severe infections with the novel coronavirus in Europe indicate that there is an ongoing source of infection and risk of transmission to humans in the Arabian Peninsula and neighbouring countries.
- More than seven months on from the emergence of these infections being appreciated as an important public health event of international concern there are very few of the analyses needed to inform ECDC's risk assessment from the countries where most of the transmission have taken place.
- Hence ECDC is having to consider a wide range of epidemiological scenarios with quite different implication for Europe. Resolving which of these is the true scenario should be a global priority.
- The latest cases support existing ECDC and national recommendations for investigation of patients with severe acute respiratory infection returning from the Arabian Peninsula and neighbouring countries.

## Recommendations

- Healthcare workers in the EU should continue to be vigilant in identifying patients requiring investigation following the ECDC and national guidance. Hence patients with severe respiratory infections and who have been in the Arabian Peninsula and neighbouring countries in the preceding 10 days should be investigated rapidly as recommended in ECDC and national guidance.
- Health professionals engaged in receiving medical evacuated patients from the Arabian Peninsula and neighbouring countries with any infectious respiratory condition should be reminded to be particularly vigilant concerning the possibility of infection with nCoV.
- Given the experience of a case with dual influenza and novel coronavirus infections the possibility of co-infection should also be considered, and identification of one causative agent should not exclude testing for novel coronavirus where that is indicated.

## Recommendations (continued)

- Healthcare workers caring for patients under investigation for nCoV should exercise infection control measures following national or international guidance.
- Contacts of confirmed cases must be monitored for symptoms for the 10 days following last exposure and should be tested and informed what to do if they become ill, according to guidance, such as that developed by the Public Health England UK (See Sources of Additional Information).
- 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 in this period.
- 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.
- Mapping of international routes of medical evacuation or emergency medical care from the Middle East to the EU should be undertaken in order to determine the most vulnerable centres in the EU where these cases might arrive.
- Clusters of severe acute respiratory infections in the community or in health care settings, either among patients or healthcare workers, should always be rapidly investigated for a range of pathogens and reported, regardless of where in the world they occur.
- Any probable or confirmed case being diagnosed in the EU/EEA area 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 in order of inform international understanding of the geographical extent of these infections.
- ECDC supports the WHO travel advice that advises no travel or trade restrictions in relation to novel coronaviruses. However, EU citizens travelling to the Arabian Peninsula and neighbouring countries need to be made aware of the presence of nCoV in this geographical area and of the small risk of infection.

## 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 is produced in relation to 19 additional cases of laboratory-confirmed infections reported in the last two months. Seventeen of these were reported by the Kingdom of Saudi Arabia in the past week and the other two were from European countries: the first case reported from in France (May 7<sup>th</sup>) that was most likely infected in Dubai but presented for care after return to France. Prior to that another case was reported from Germany on March 25<sup>th</sup> in a man infected in the Middle East transferred for care. These cases have added some information to the still very limited understanding of these coronaviruses and the infections and disease they cause. The aim of this risk assessment is to document the important changes and their implications and to summarise other knowledge gained since the [update in February](#). The document should be seen in the light of the many uncertainties that still continue with the investigation of cases in the Middle East.

Additional information can be found on the [ECDC novel coronavirus web-site](#), on the WHO and the Public Health England (UK) web-sites listed below under 'sources of additional information'.

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## Consulted experts

None for this update.

## Background information

At the date of the last rapid risk assessment of 19 February 2013, 12 cases of confirmed nCoV had been identified worldwide.

The first case confirmed with this novel coronavirus 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 second case, a 49 year old male living in Qatar, presented with symptoms similar to the first case. He was transferred for care in Europe [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<sup>1</sup>. It was the then appreciation that this was a novel coronavirus cause severe respiratory disease in humans and occurring in two separate parts of the Arabian Peninsula that led to [notifications through the International Health Regulations and EWRS systems on September 22<sup>nd</sup> 2012](#).

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

Subsequently, two fatal cases were confirmed retrospectively in Jordan from within a cluster of 11 people with severe lower respiratory infections that were associated with a hospital in April 2012. Although the nine other persons fit the WHO definition for having probable novel coronavirus infections they were less severe than the 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 having a travel history to Saudi Arabia and Pakistan. These included the first two transmissions in Europe [4]. These cases result in a total of four cases identified and reported by UK to date.

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<http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/NovelCoronavirus2012/respPartialgeneticsequenceofnovelcoronavirus/>

## Recent developments

Between 13 February (when the last ECDC risk assessment was published) and 5 May 2013, 19 additional confirmed cases of nCoV have been reported worldwide, including 11 deaths.

These are:

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

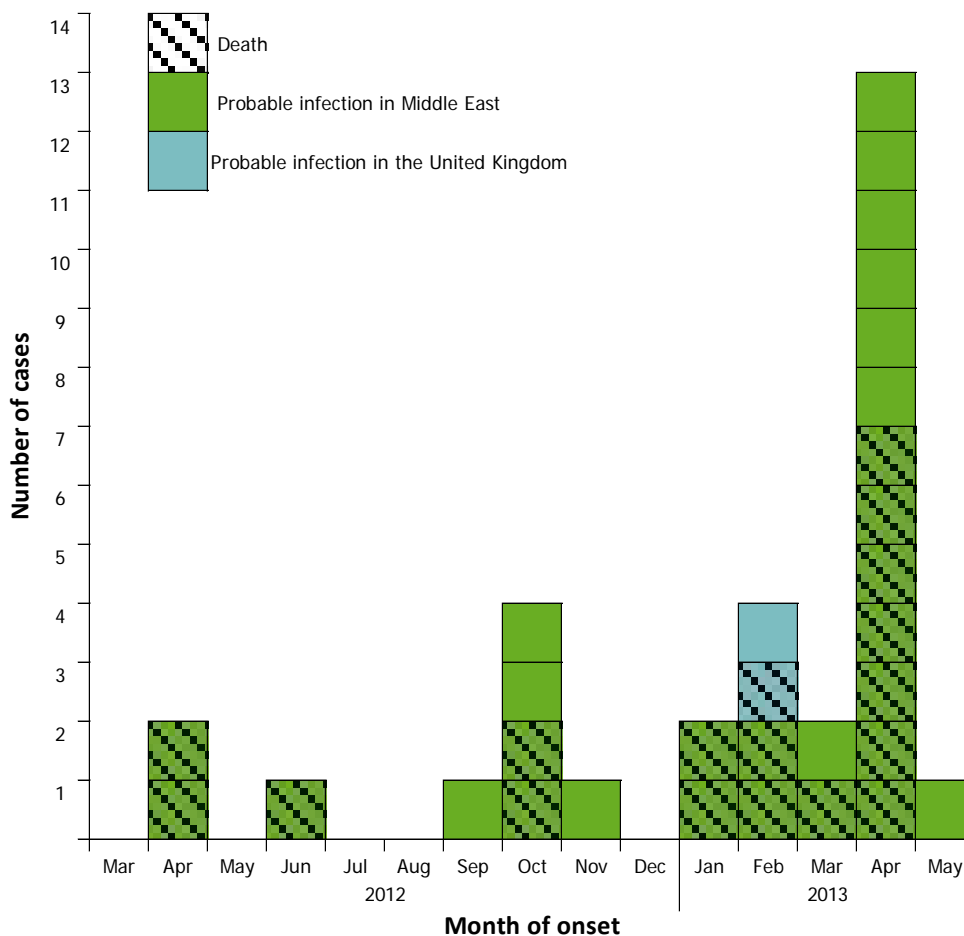
**Seventeen cases from the Kingdom of Saudi Arabia:** 17 cases have been detected and reported by the Kingdom of Saudi Arabia in the last week and started to be reported by WHO on [May 2<sup>nd</sup> 2013](#). Thirteen of these cases seem to be part of a recently detected cluster in Al-Ahsa in the Eastern Province of Saudi Arabia, which may be linked to the same health care facility and have onset dates over a 3 week-period (14 April-1 May 2013) [6]. Though investigations are stated to be on-going by the Saudi Arabian authorities, no additional information or analysis from investigations have been is available to ECDC as of 8 May 2013.

**A 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 sought medical care in France for fever, diarrhoea and lumbar pain on 23 April. Though he did not have a history of 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 nCoV on 3 May. A bronchoalveolar lavage (BAL) specimen taken on 26 April arrived to the Reference Laboratory on 7 May and tested positive for nCoV. The patient is on mechanical ventilation [Communication by France, EWRS message 7 May 2013] [7].

## Epidemiological summary

As of 8 May, 31 cases have been reported worldwide, including 18 deaths. An epicurve of the month of onset of reported cases by clinical outcome and probable place of infection is shown in Figure 1.

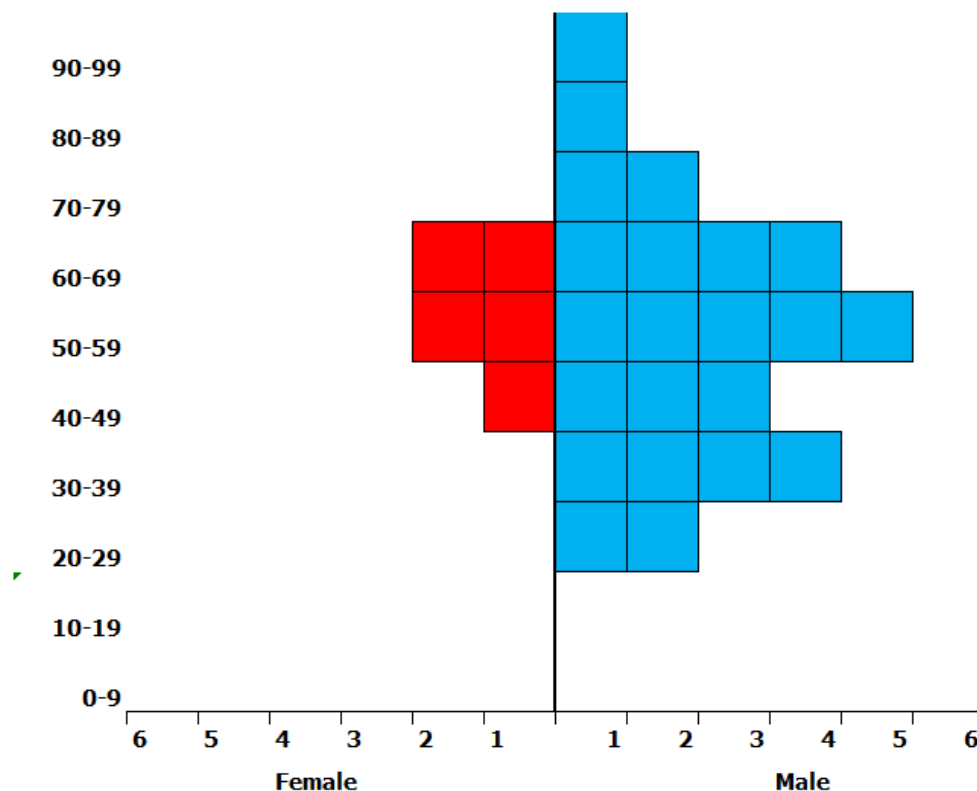
**Figure 1: Number of cases of novel coronavirus reported worldwide by month of disease onset, outcome and probable place of infection, data as of 7 May (n=31)**



All 31 cases worldwide remain associated (including indirectly following secondary person-to-person transmission in the UK) with transmission in the Middle-East, and though the majority of cases are from Saudi Arabia, transmission are reported to have taken place in a number of locations across the Arabian Peninsula and Middle East.

The majority of reported cases continue to be associated with severe disease (lower respiratory tract infection such as pneumonia and/or renal failure). A few cases were reported to present with an underlying disease. Only one case in Europe (part of the family cluster identified in the UK) presented with mild influenza-like symptoms.[4] Eighteen of the 31 cases were reported to have died, resulting in a case-fatality ratio of 58%. The age of cases ranges from 24 to 94 years (n=27 cases) with fewer females (23%) affected than males (Figure 2).

**Figure 2: Distribution of cases of novel coronavirus by gender and age, April 2012 – 8 May 2013 (n=27)**



## Virological information

The novel virus 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 the novel coronavirus 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 HCoVHKU1, and lineage B the SARS-CoV, all of which belong to different species.

Lineages C and D include viruses detected only in bats, such as:

- in China *Rousettus* bat coronavirus HKU9 (BtCoV-HKU9) (lineage D), *Tylonycteris* 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].

The novel coronavirus 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 nCoV although the similarities to bat coronaviruses make them a likely source, specifically insectivorous bats 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 that of the SARS coronaviruses [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 nCoV replication in cell culture and nCoV was found to be 50-100 times more sensitive to interferon-alpha (IFN- $\alpha$ ) treatment than SARS-CoV [12].

[Interim laboratory testing guidance](#) for screening and confirmation of NCoV infection was issued by WHO in December 2012. A survey by ECDC and 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 that in these 18 countries, there is the capacity for large scale or rapid testing with such non-commercial technically demanding tests. 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](#).

Serological tools for detection of specific NCoV IgM and IgG antibodies based on protein microarray technology have been recently developed and validated with limited number of specimens [17]. These assays, presently in 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.[18]

## 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 has included 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. Special attention was paid to persons in or coming recently from Middle-Eastern countries. Secondly, looking vigorously for cases among the contacts of confirmed cases both for control purposes and to assess whether human-to-human transmission was taking place.

The features of the last three UK cases, especially the one with only moderate symptoms plus the fact that an infected person travelled in a commercial airliner (albeit he was unwell) suggest that case-finding strategies for the EU/EEA countries may need to be reviewed based on findings of the public health investigations. Certainly it emphasises the importance of testing close contacts of confirmed cases. There is a pressing need for sero-epidemiological studies using protocols like those of the CONSISE partnership [18,20] and the UK has published a protocol of this purpose that is suitable for use in other countries [21]. Following up all contacts of confirmed cases is recommended in Europe as described in the HPA protocol. If those numbers increase and it becomes apparent that more are presenting milder symptoms, a more selective approach will be needed. 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 December 12th 2012](#). There will need to be particular emphasis on capturing the results of case finding, negative as well as positive, as was undertaken in the



ECDC-WHO laboratory survey as this will help inform the true geographical extent of these infections globally [13, 18].

## Routes of transmission and possible sources

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, 22-25], 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 highlighted in ECDC's risk assessment in February. 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, 26].

No reservoir or source of infection for the novel Coronavirus 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 Middle East.

The routes of transmission to humans have not yet been determined. This is a common problem with emerging zoonoses where there is often simultaneous possibilities including environmental, animal and human exposures. There is very little information available to ECDC and the rest of Europe either in the public domain or from other sources, which contrasts with the situation during the SARS outbreak ten years ago.[27-29]

In Germany and the UK, follow-up of nearly 200 personal contacts and health care workers 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 both Germany and the UK developed mild respiratory infections, virological investigations showed this represented expected background mild respiratory virological infections rather than being due to the novel coronavirus [2,25].

However there have been one cluster where person-to-person transmission is certain to have taken place. These are two transmission in the family cluster of three cases in the UK.[4] The information from the earlier clusters in homes and hospitals the Middle East and now the most recent cases are insufficient for ECDC to comment on the routes of transmission or the underlying pattern of infection and disease.

## Threat assessment for the EU

The additional coronavirus cases reported by the Saudi Arabian authorities in the past week and the recent imported cases reported by Germany and France indicate clearly an on-going source of human infections is present in the Arabian Peninsula.

The recent cases reported by Germany and France of imported infections following respectively medical evacuation and travel indicate that more cases may be expected to be identified in the EU in the immediate future.

Despite extensive contact tracing amongst previous contacts, only one mild symptomatic secondary case has been detected to date in the EU. However it remains concerning that milder cases could be present in exposed populations in the Middle East. Further work to document the spectrum of illness and the route of transmission is still needed.[18]

## Conclusions

The reporting of 17 new infections in the Kingdom of Saudi Arabia in the past week and two more imported severe infections with the novel coronavirus in Europe indicate that there is an ongoing source of infection and risk of transmission to humans in the Arabian Peninsula and neighbouring countries.

More than seven months on from the emergence of these infections being appreciated as an important public health event of international concern there are very few of the analyses needed to inform ECDC's risk assessment from the countries where most of the transmission have taken place.

Hence ECDC is having to consider a wide range of epidemiological scenarios with quite different implications for Europe. Resolving which of these is the true scenario should be a global priority.

The latest cases support existing ECDC and national recommendations for investigation of patients with severe acute respiratory infection returning from the Arabian Peninsula and neighbouring countries.

## Recommendations

1. Healthcare workers in the EU should continue to be vigilant to identify patients requiring investigation following the existing ECDC and [the earlier WHO guidance \(December 12<sup>th</sup> 2012\)](#). That is patients with severe respiratory infections and who have been in the Arabian Peninsula and neighbouring countries in the preceding 10 days should be investigated rapidly as recommended in ECDC and national guidance.
2. Health professionals engaged in receiving medical evacuated patients from the Arabian Peninsula and neighbouring countries with any infectious respiratory condition should be particularly vigilant concerning the possibility of infection with nCoV.
3. Given the experience of a case with dual influenza and novel coronavirus infections the possibility of co-infection should also be considered, and identification of one causative agent should not exclude testing for novel coronavirus where that is indicated.
4. Healthcare workers caring for patients under investigation for nCoV should exercise infection control measures following national or international guidance.
5. Contacts of confirmed cases must be monitored for symptoms for the 10 days following last exposure and should be tested and informed what to do if they become ill, according to guidance, such as that developed by the Health Protection Agency (HPA) UK (See Sources of Additional Information).
6. 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 in this period.
7. 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.
8. Mapping of international routes of medical evacuation or emergency medical care from the Middle East to the EU should be undertaken in order to determine the most vulnerable centres in the EU where these cases might arrive.
9. Clusters of severe acute respiratory infections in the community or in health care settings, either among patients or healthcare workers, should always be rapidly

investigated for a range of pathogens and reported, regardless of where in the world they occur.

10. Any probable or confirmed case being diagnosed in the EU/EEA area 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 in order to inform international understanding of the geographical extent of these infections. [13].
11. ECDC supports the WHO travel advice that advises no travel or trade restrictions in relation to novel coronaviruses. However, EU citizens travelling to the Arabian Peninsula and neighbouring countries need to be made aware of the presence of nCoV in this geographical area and of the small risk of infection.

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[http://www.hpa.org.uk/webc/HPAwebFile/HPAweb\\_C/1317136300809](http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317136300809)
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## Sources of additional information and Resources

- WHO Source Page Novel Coronaviruses: [Link Here](#)
- Public Health England (previously the Health Protection Agency – Coronaviruses Source Page: [Link Here](#)
- Robert Koch Institute – Coronaviruses Source Page (in German): [Link Here](#)
- University of Bonn Website – Diagnosis [Link Here](#)
- ECDC Coronaviruses – Source Page: [Link Here](#) and [Here](#)
- CONSIZE Website [link here](#) and the CONSIZE protocols [link here](#)
- ISARIC and WHO SARI and Natural History Protocols [link here](#)