RAPID RISK ASSESSMENT

Severe respiratory disease associated with a novel coronavirus

19 February 2013

Main conclusions and recommendations

- As of 16 February 2013, twelve laboratory confirmed cases of respiratory illness caused by the novel coronavirus (novel CoV) have been reported to the World Health Organization (WHO). Six of the cases have been fatal and two others remain very ill. Onset of disease was between April 2012 and February 2013.
- Three new confirmed cases have been diagnosed in the UK in the last ten days. The second and third cases were infected through human-to-human transmission although the exact route of transmission is still under investigation by the UK authorities. Human-to-human transmission may also have happened in two instances in the Middle-East. However, no sustained transmission or expanding clusters of infection have been identified in any country.
- Close follow-up of approximately 200 health care workers (HCWs), family and other contacts of cases in Europe and the Middle-East have not yet found other demonstrated instances of human-to-human transmission.
- The most recent UK case, a relative of the other two UK cases, had only a mild disease and has recovered quickly. The Health Protection Agency (HPA) is undertaking intensive follow-up of close contacts of these three recent cases to determine if there have been any further mildly symptomatic or asymptomatic infections. No further secondary cases had been detected by 18 February 2013. Depending upon these findings, case-finding strategies may need to be reviewed, which ECDC is currently considering.
- ECDC supports recommendations of laboratory investigation for novel-CoV of patients with severe acute respiratory infection returning from the Arabian Peninsula and neighbouring countries as defined in the current WHO guidance.
- Healthcare workers should be alerted to the need to identify patients requiring investigation following current WHO guidance.
- 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 novel-CoV.
- Healthcare workers caring for patients under investigation for novel-CoV should exercise infection control measures following national or international guidance.
- Contacts of confirmed cases must be monitored for symptoms for 10 days following the last exposure and informed what to do if they become ill. 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.

Main conclusions and recommendations (continued)

- WHO and ECDC re-emphasise the importance of timely and thorough investigation and reporting of clusters of severe acute respiratory infections in the community or in HCWs regardless of where in the world they occur. Such cases should be investigated rapidly and managed according to WHO recommendations or national guidance documents.
- 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). The evidence to date continues to support WHO travel advice that recommends no travel or trade restrictions in relation to novel coronaviruses.

Source and date of request

ECDC Internal Decision, 12 February 2013.

Public health issue

This third update of the rapid risk assessment of 'severe respiratory disease associated with a novel coronavirus' is produced in relation to three more laboratory-confirmed infections reported from the UK in the past 10 days. Two resulted from human-to-human transmission and one of the two was much milder than any previous confirmed cases [1–3]. These cases have added to the limited knowledge about 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 December. The document should be seen in the light of the many uncertainties remaining at this stage of the investigation of cases

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

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Recent developments

On 11 February 2013, the HPA published details of a male UK resident (Case 10) with confirmed novel coronavirus infection who had travelled to Pakistan and the Middle-East, developed respiratory symptoms on 24 January 2013 and then had arrived unwell in the UK on 28 January 2013 [1]. While staying with his family at home his condition deteriorated and he was admitted to hospital where he is in intensive care. On 6 February 2013, a male household member (Case 11) who had contact with Case 10 from his arrival until hospital admission fell unwell. This patient had an existing medical condition that may have made him more susceptible to a severe respiratory infection. His respiratory condition deteriorated and he was admitted to hospital, where he was in intensive care but subsequently died.

The third confirmed case is a younger female family member, who only had exposure to the original index case while he was in hospital. She became ill on 5 February 2013 with a typical flu like illness, which did not require hospital admission and from which she has now fully recovered. Unlike the source case (Case 10), neither Case 11 nor 12 have travelled abroad recently. HPA is actively investigating the possible route of infection. Infection control measures around the three cases are following national UK guidance and case-finding is on-going for those who may have been exposed. Active follow-up of contacts of the three confirmed cases had not detected any further confirmed secondary cases by 18 February 2013.

Background information

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 [4]. 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 [5]. A virus was isolated from this case, sequenced and the genetic code put in the public domain. It was almost identical to the virus from the case in Saudi Arabia[1] . In November 2012, additional cases with similar symptomatology were diagnosed in Qatar and Saudi Arabia (Table 1), including a family cluster of three confirmed cases and one probable case [6]. 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 cases fit the WHO definition for 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.

The retrospective finding of two cases in Jordan raises the issue of whether this is a new infection in humans or one that has been occurring for some time. Equally, although the first cases were all connected with the Middle-East, it is noticeable that they came from widely separated places. Since similar animal coronaviruses can be found in bats in all regions of the world, it is possible that these infections are to be found sporadically in many countries [7–12]. This makes a strong case for further studies of animal coronaviruses and prospective and retrospective searches for cases in other regions. 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 (Cases 4, 6 & 10) [13, 5, 14].

Only the most recent case (Case 12) has shown mild influenza-like symptoms. All other confirmed patients have presented with severe lower respiratory tract infection such as pneumonia. A number of cases have also developed renal failure during the course of illness. The proportion of deaths is high; six out of twelve with two others still receiving high level care. The age range is from 25 to 60 years and a noticeable feature is that only two cases are female.

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

Table 1. Confirmed cases of novel coronavirus infection, April 2012 to 13 February 2013, in order of onset of disease.

Case No.	Date of Onset	Age (years)	Sex	Probable place of infection	Date reported	Outcome	Part of a cluster	Initial Source of information
1	Apr-2012	45	F	Jordan	30/11/2012	Dead	Yes – hospital A	WHO/IHR
2	Apr-2012	25	M	Jordan	30/11/2012	Dead	Yes – hospital A	WHO/IHR
3	13/06/2012	60	M	Saudi Arabia	20/09/2012	Dead	No	ProMed/Publication [4]
4	03/09/2012	49	M	Qatar/ Saudi Arabia	23/09/2012	Alive/Hospitalised	No - patient transferred to the UK	HPA/publication/publication [15, 5]
5	10/10/2012	45	M	Saudi Arabia	04/11/2012	Alive	No	ProMed/Publication [6]
6	12/10/2012	45	M	Qatar	23/11/2012	Alive	No - patient transferred to Germany	RKI
7	3-5/11/2012	31	M	Saudi Arabia	20/11/2012	Alive	Yes – family A	ProMed
8	28/10/2012	39	M	Saudi Arabia	23/11/2012	Dead	Yes – family A	WHO/IHR
9	Oct-2012	Adult	M	Saudi Arabia	28/11/2012	Dead	Yes – family A	WHO/IHR
10	24 /1/2013	Adult	M	Pakistan/ Saudi Arabia	11/02/2013	Alive/Hospitalised	Yes – family B	HPA
11	06/02/2013	Adult	M	United Kingdom	12/02/2013	Dead	Yes – family B	HPA
12	05/02/2013	Adult	F	United Kingdom	13/02/2013	Alive/Recovered only mild disease	Yes – family B	HPA

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, and SARS-CoV belong to the genus Betacoronavirus. 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 Rousettus bat coronavirus HKU9 (BtCoV-HKU9) (lineage D), Tylonycteris bat coronavirus HKU4 (BtCoV-HKU4), and Pipistrellus bat coronavirus HKU5 (BtCoV-HKU5) (both lineage C). The novel coronavirus belongs to lineage C, and is thus the first Betacoronavirus lineage C member isolated from humans. The novel coronavirus is sufficiently distinct from the bat coronaviruses HKU4 and HKU5 to be classified as a new species but similar to coronaviruses often found in bats. No animal reservoir or mode of zoonotic transmission has yet been identified for the novel coronavirus 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 be through environmental contamination or via intermediary animal hosts [11]. 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 [16]. The new 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) [17].

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 according to this diagnostic guidance. Screening by controlled upE-RT-PCR assay was available in 19 of 30 EU and 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, even in those eighteen countries it does not follow that there is the capacity for large scale or rapid testing with what are non-commercial and technically demanding tests. Additional molecular assays for sensitive and specific case confirmation have been described [18]. Serological tests have been developed but they are labour-intensive and although they are starting to be used, are not yet suitable for use outside of a few highly specialised laboratories. Specifically, there is a high probability of false-positive serological results due to cross-reaction of NCoV with any of the four common-cold CoV co-circulating in humans. Two parallel approaches are being employed for second-stage serological investigation in specialised laboratories: first, presence of anti-NCoV antibodies is confirmed by virus neutralisation tests. Second, presence of cross-reactive antibodies reacting with any common-cold virus is investigated using virus-specific recombinant tests. For this reason, it is not recommended to screen asymptomatic patients by simple serological tests such as immunofluorescence, if the possibility is not given to conduct immediate second-stage serology. More information about diagnostic procedures can be found in the following articles [19, 18, 15, 13] and on the University of Bonn website.

Interim case definitions – case-finding strategy and surveillance recommendations

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 [20]. 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 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. There is a pressing need for seroepidemiological studies using protocols like those of the CONSISE partnership [21]. In light of this, a new case-finding strategy may need to be developed and ECDC is working to review this with Member States and international partners. At present, following-up all contacts of confirmed cases is recommended. 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 [13]

Routes of transmission, human-to-human transmission, incubation period and infection risk

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. With the exception of the three UK cases, there has been little information available in the public domain. As of now, there are two instances when documented human-to-human transmission has taken place. Case 11 represents human-to-human transmission from Case 10 who had returned unwell from abroad, while Case 11 had not travelled recently. A complicating factor is Case 11 had an underlying health condition which may have made him more susceptible to infection and developing disease.[2] The second human-to-human transmission, Case 10 to 12, is potentially of more concern as the time in proximity to Case 10 was less and the possibility of an intermediary case or fomite spread are possible. However, the investigation and intensive case finding around the three cases remains on-going and the results cannot be prejudged. [3]

There remains insufficient information from the Jordanian hospital cluster to comment on the possibility of transmission in the hospital as even though there were two confirmed cases, the other cases are without virological and serological confirmation, and could represent infections due to other causes. A family cluster of three confirmed male cases and a probable case in Saudi Arabia looks more indicative of human-to-human spread. Although there was extended exposure of more than twenty family members to an index case, common environmental exposure in the family home cannot be excluded.

Therefore, human-to-human transmission has almost certainly taken place twice in the UK and maybe also in the Middle-East. However, it is important to quantify infectivity and there is also evidence suggesting low infectivity at a population level. 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 [5, 14]. Additionally, although there have been human infections for at least 10 months, there does not seem to have been the super-spreading events seen with SARS in 2003 [22]. Neither have there been any chains of transmission. A less reassuring finding is the ability of the virus in controlled laboratory experiments to infect a wide range of mammalian cells [16].

The two UK transmission cases represent the first opportunity to estimate the incubation period from exposure to disease. However with only two secondary cases and investigations not yet completed, it is too early to come to conclusions.

Threat assessment for the EU

The recent three cases detected in the UK have changed the assessment of the situation regarding this novel coronavirus. The fact that an infection has come to Europe on a commercial flight and then resulted in two probable human-to-human transmission episodes has increased the threat, although the cluster has been restricted to one family. The appearance of a milder secondary case has a more mixed impact. As already highlighted, despite extensive contact tracing amongst previous contacts, this is the first mildly symptomatic secondary case detected. However it is concerning that milder cases could be present and potentially spread the infection but be missed in case-finding. This highlights the need for further work to document the spectrum of illness. It is possible it is an infection that can lead to both severe disease of uncommon zoonotic origin, and also cause a milder disease and maybe even aymptomatic infection. Though it is somewhat reassuring that there are no detected expanding clusters of cases, chains of transmissions or SARS-like super-spreading events to date, the fact remains that there is a lot more that we do not know than we know about this virus. ECDC is currently discussing public health orientated research and development priorities with its Advisory Forum, after which it will issue some guidance on this topic.

A particular issue remains around patients transferred for tertiary care to Europe and within Europe via air ambulance. Patients presenting with acute lower respiratory tract infections will probably continue to be referred to hospitals in the EU for care.

Recommendations

- The current epidemiological information supports the WHO recommendations for investigation of patients with severe acute respiratory infection returning from the Arabian Peninsula and neighbouring countries.
- Healthcare workers in the EU should be alerted to identifying patients requiring investigation following the current WHO guidance (December 12 2012)[2] . Such cases should be investigated rapidly and managed as recommended by WHO or national guidance.
- 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.
- 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 novel-CoV.
- Healthcare workers caring for patients under investigation for novel-CoV 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 Health Protection Agency (HPA) 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 at this present time consider there is any need for testing individual patients with unexplained pneumonias or other respiratory symptoms unless they fall under one of the above categories.
- Clusters of severe acute respiratory infections in the community or in health care settings, either among patients or health care workers, should always be rapidly investigated 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 [13].
- The evidence to date continues to support WHO travel advice that recommends no travel or trade restrictions in relation to novel coronaviruses.

- **Concerning research:** It should be considered that he reservoir of infection and the modes of transmission to humans remain unknown. Though it has been noted that similar coronaviruses are found commonly among bats, the involvement of intermediary animal hosts and infection through contamination of the environment cannot be excluded. Other important questions remain to be investigated and answered concerning these infections including the spectrum of disease, the routes of transmission, incubation period, the true distribution in animals and humans and how best to manage the patients. Robust and deployable specific serological tests urgently needed to investigate the possibility of more mild and even asymptomatic infections. Due to a high probability of false-positive serological results due to cross-reaction of novel CoV with any of the four common-cold CoV co-circulating in humans, it is not recommended to screen asymptomatic patients by serological tests such as immunofluorescence, unless there is a possibility to conduct immediate second-stage serology tests. Once validated these tests should be deployed in further seroepidemiological studies employing prior agreed protocols such as those from the CONSISE consortium [22]. In order to provide information on the distribution of this seemingly new infection applied epidemiological and laboratory research studies should be undertaken testing patients with severe lower respiratory tract infection either using retrospective contemporaneous archives of suitable stored specimen or as prospective planned studies.

[2] Check the WHO novel coronavirus web-site for the most recent information on case-finding, surveillance and case definition.

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Sources of additional information

- WHO Source Page Novel Coronaviruses: Link Here
- Health Protection Agency – Coronaviruses Source Page: Link Here
- Health Protection Agency: Questions and answers: Link Here
- Health Protection Agency: Information for Healthcare Professionals: 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