

Short communication

Enhanced surveillance and investigation of coronavirus: what is required?

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تعزيز الترصد والتقصّي للفيروس التاجي: ما هو المطلوب؟

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الخلاصة: بعد اكتشاف مريضين لها صلة بإقليم شرق المتوسط، مصابين بالمرض التنفسي الوخيم الناجم عن الفيروس التاجي Coronavirus الجديد في أيلول/سبتمبر 2012، عززت جميع البلدان أنشطة الترصد والمختبرات اللازمة لكشف المزيد من الحالات، إلى جانب اتخاذ تقصّيات مركّزة للمخالطين للحالات من أجل التأكّد المختبري من الحالات. وبلغ العدد الكلي للحالات 30، منها 18 انتهت بالوفاة، مع اكتشاف ثلاث مجموعات عنقودية على الأقل حتى الآن (مجموعة عنقودية واحدة بين العاملين في الرعاية الصحية، ومجموعتان عنقوديتان بين أعضاء الأسرة) وحتى يومنا هذا، أظهرت الدراسات المجراة على انتقال العدوى اختطّاراً منخفضاً للانتقال من الإنسان للإنسان في المستقبل، مع سمات سريرية لاتزال وخيمة في معظم الحالات. ولا تزال هناك أسئلة عديدة، من بينها المصدر الحيواني للعدوى، والمدى الجغرافي للعدوى. وقد تم توسيع نطاق الترصد ليشمل المجموعات العنقودية للحالات أو العاملين في الرعاية الصحية المصابين بمرض تنفسي وخيم غير مشخص بغض النظر عن تاريخ السفر. وسوف يكون للدراسات البيئية والترصد المستمر والتقصّيات المستمرة للمخالطين للحالات المرتبطة بها دور حاسم في الإجابة عن بعض تلك الأسئلة.

ABSTRACT Following the discovery in September 2012 of 2 patients, both with links to the Eastern Mediterranean Region, with serious respiratory illness due to novel coronavirus, all countries have instigated surveillance and laboratory activities to detect further cases, with intensive case–contact investigations undertaken on laboratory confirmation of cases. A total of 30 cases, of whom 18 have died, and at least 3 clusters have been detected to date (1 cluster among health-care workers and another 2 clusters among family members). To date, transmission studies have shown a low risk of onward human transmission, with clinical presentation remaining severe for the majority. Many questions remain including the zoonotic source and geographical extent of infection. Surveillance has been extended to include clusters of cases or health-care workers with severe, undiagnosed respiratory illness regardless of travel history. Environmental studies, on-going surveillance and linked case–contact investigations will provide a critical role in answering some of these issues.

Surveillance et recherche renforcées pour le coronavirus : quels sont les besoins ?

RÉSUMÉ Suite à la découverte en septembre 2012 de deux patients atteints d'une maladie respiratoire sévère imputable à un nouveau coronavirus, tous deux ayant des liens avec la Région de la Méditerranée orientale, tous les pays ont initié des activités de laboratoire et de surveillance afin de dépister d'autres cas, et notamment des recherches de cas-contacts intensives pour les cas confirmés en laboratoire. Sur 30 cas au total, 18 sont décédés, et au moins trois groupes ont été identifiés à ce jour (un groupe chez des agents de soins de santé et deux autres groupes chez les membres des familles). À ce jour, les études de transmission ont démontré que le risque de future transmission interhumaine était faible, mais que le tableau clinique demeurait sévère pour la majorité des cas. Il reste de nombreuses questions en suspens, notamment la source zoonotique et la propagation géographique de l'infection. La surveillance a été élargie à ces groupes de cas ou aux agents de soins de santé atteints de maladies respiratoires sévères non diagnostiquées indépendamment de leurs voyages passés. Des études environnementales, une surveillance continue et des recherches reliant des cas-contacts seront essentielles pour répondre à certaines de ces questions.

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Introduction

The discovery of a novel coronavirus (nCoV) in a patient hospitalized with severe respiratory illness reported in September 2012 in Saudi Arabia [1] was shortly followed by the laboratory confirmation of nearly identical virus in a second individual in a hospital in London, United Kingdom [2]. This further, unlinked case had been transferred for medical care from Qatar following onset of a severe respiratory illness [3]. The detection of these 2 cases, both infected with a novel respiratory virus from the same genus as severe acute respiratory syndrome (SARS)-CoV, led to a global alert about the emergence of a new virus with possible SARS-like properties, with the experience of SARS at the forefront of response planning.

The appearance of a previously unrecognized virus, most closely related to beta coronaviruses in bats and which resulted in severe respiratory illness in humans, raised a series of important public health questions. These are summarized in the accompanying article by Nicoll et al. [4]. What was the likely animal reservoir of this virus? What were the risk factors for animal-to-human infection? What was the ability of the virus to spread from person-to-person? What was the extent of infection in the human population? And what was the spectrum of illness associated with infection in humans? The answers to all of these questions were unknown based on the experience of only 2 cases, 1 of which was fatal.

What role can surveillance play in helping to answer these questions? Surveillance was originally described by Langmuir as “the systematic collection, collation, analysis of data and dissemination of information on a specific disease to inform public health action” [5]. Latterly the epidemic intelligence role of surveillance, with timely alerting, analysis and dissemination of information, has gained greater prominence and is enshrined in the 2005 revision of the

World Health Organization (WHO) *International Health Regulations* [6,7].

The detection of the 2 initial cases, both of whom required intensive care support and who acquired their infection in the Eastern Mediterranean Region, together with the rapid development and availability of a sensitive and specific polymerase chain reaction (PCR) diagnostic tool for the detection of viral genetic material while virus shedding was still occurring [8], allowed the development of surveillance strategies to find further nCoV cases [9]. Relatively specific clinical case definitions were developed initially to provide a moderately good predictive value and ensure an efficient use of limited public health and laboratory capacity. The hierarchical case definitions developed by WHO and national organizations such as the Centers for Disease Control in the United States, Public Health England (formerly the Health Protection Agency) in England, the Robert Koch Institute in Germany and the European Centre for Disease Prevention and Control for the European Union [9–13] focused on the detection of individuals with severe undiagnosed respiratory illness with a history of travel from countries where indigenously acquired cases had been detected during the putative incubation period of nCoV. Such “patients under investigation” were recommended for nCoV testing (Table 1). Detailed laboratory algorithms needed to be established with a first-line sensitive assay to detect the virus, followed by a second-line assay to confirm virus detection, to avoid false conclusions about the incidence of disease.

Early detection and isolation of laboratory-confirmed cases of symptomatic illness allows the rapid implementation of measures to limit potential spread of infection to close contacts. Case ascertainment also provides an opportunity for an in-depth epidemiological, clinical and virological investigation of the first cases and their close

contacts using approaches developed during the 2009 influenza pandemic [11]. Collection of detailed information from cases (or their families when cases have died or were seriously unwell) allows a description of the demographic and clinical characteristics of cases and the development of hypotheses about risk factors for human infection from an as yet unknown reservoir. Describing laboratory-confirmed cases by time and place enables the epidemic curve and geographical distribution of this apparent emerging public health problem to be elaborated. Finally, the identification and follow-up of close contacts of confirmed cases provides the opportunity for detailed case-contact investigations that may provide clues to key epidemiological questions. These investigations involve intensive prospective follow-up of contacts for evidence of respiratory disease, together with virological and serological sampling. The availability of newly developed virological and serological assays provides the ability to detect secondary infections [14] and to measure the full disease spectrum among infected contacts [15].

These surveillance approaches, together with follow-up of an increasingly large number of close contacts, has resulted in 30 laboratory confirmed cases of nCoV being reported globally in the 6 months to 8 May 2013 [16]. Of the 30 confirmed cases, the majority have had severe respiratory disease, with 18 cases having died to date, a high case fatality rate. There is, however, a suggestion of a wider disease spectrum, with a small number of milder cases, detected through intense contact tracing activities [14], although active virological and serological follow-up of case-contacts regardless of symptoms has to date failed to uncover a significant hidden “iceberg” of mild or asymptomatic cases. The majority (24/30) of cases have been detected in the Eastern Mediterranean Region, with 6 cases diagnosed in Europe (the United Kingdom and Germany). Four of these latter 6 cases

Table 1 Definitions of patients and situations requiring public health investigation and testing for novel coronavirus (nCoV)

Organization [reference]	Patient under investigation	Other situations under investigation
World Health Organization [9]	<p>A person with an acute respiratory infection, which may include history of fever or measured fever $\geq 38^{\circ}\text{C}$ (100.4°F) and cough; AND Suspicion of pulmonary parenchymal disease (e.g. pneumonia or acute respiratory distress syndrome), based on clinical or radiological evidence of consolidation; AND Residence in or history of travel to the Arabian peninsula or neighbouring countries^a within 10 days before onset of illness; AND Not already explained by any other infection or etiology, including all clinically indicated tests for community-acquired pneumonia according to local management guidelines. It is not necessary to wait for all test results for other pathogens before testing for nCoV.</p>	<p><i>Ill contacts</i> Individuals with acute respiratory illness of any degree of severity who, within 10 days before onset of illness, were in close physical contact with a confirmed or probable case of nCoV infection while the case was ill. Any person who has had close contact with a probable or confirmed case while the probable or confirmed case was ill should be carefully monitored for the appearance of respiratory symptoms. If symptoms develop within the first 10 days after contact, the individual should be considered a "patient under investigation", regardless of the severity of illness, and investigated accordingly. <i>Clusters</i> Any cluster of severe acute respiratory infection, particularly clusters of patients requiring intensive care, without regard to place of residence or a history of travel; AND Not already explained by any other infection or etiology, including all clinically indicated tests for community-acquired pneumonia according to local management guidelines. <i>Health-care workers</i> Health-care workers who care for patients with severe acute respiratory infections, particularly patients requiring intensive care, who develop unexplained pneumonia without regard to place or residence or history of travel.</p>
Centers for Disease Control [10]	<p>A person with an acute respiratory infection, which may include fever $\geq 38^{\circ}\text{C}$ (100.4°F) and cough; AND Suspicion of pulmonary parenchymal disease (e.g. pneumonia or acute respiratory distress syndrome based on clinical or radiological evidence of consolidation); AND History of travel from the Arabian peninsula or neighbouring countries^a within 10 days; AND Not already explained by any other infection or etiology, including all clinically indicated tests for community-acquired pneumonia^b according to local management guidelines.</p>	<p>Persons who develop severe acute lower respiratory illness of known etiology within 10 days after travel from the Arabian peninsula or neighbouring countries^a but do not respond to appropriate therapy; OR Persons who develop severe acute lower respiratory illness who are close contacts of a symptomatic traveller who developed fever and acute respiratory illness within 10 days after travel from the Arabian Peninsula neighbouring countries^a. Close contact is defined as providing care for the ill traveller (e.g. a health-care worker or family member), or having similar close physical contact; or stayed at the same place (e.g. lived with, visited) as the traveller while the traveller was ill. <i>Clusters of severe acute respiratory illness</i> In addition, any clusters of severe acute respiratory illness in health-care workers in the United States should be thoroughly investigated. Occurrence of a severe acute respiratory illness cluster of unknown etiology should prompt immediate notification of local public health for further notification and testing.</p>
Health Protection Agency [11]	<p>Any person with severe acute respiratory infection: Symptoms of fever $\geq 38^{\circ}\text{C}$ or history of fever and cough; AND With evidence of pulmonary parenchymal disease (e.g. pneumonia or acute respiratory distress syndrome) based on clinical or radiological evidence; AND Not already explained by any other infection or etiology; AND History of travel to or residence in an area where infection with nCoV 2012 has recently been reported or where transmission could have occurred in the 10 days before onset of illness.</p>	<p>Health-care worker based in intensive care unit (ICU) caring for patients with severe acute respiratory infection; OR Close contact (i.e. prolonged face-to-face contact) during the 10 days before onset of illness with a confirmed case of nCoV infection while the case was ill. <i>Cluster</i> Two or more cases of severe acute respiratory infection requiring ICU admission, regardless of history of travel; AND Not already explained by any other infection or etiology.</p>

Table 1 Definitions of patients and situations requiring public health investigation and testing for novel coronavirus (nCoV) (concluded)

Organization [reference]	Patient under investigation	Other situations under investigation
Robert Koch Institute [12]	<p>Patient with respiratory symptoms independent of its severity; AND “epidemiological exposure A” (close contact); OR Patient with “clinical picture” and “epidemiological exposure B”.</p> <p><i>Clinical picture</i> Patients with acute respiratory syndrome (with or without fever ≥ 38 °C) and (with or without cough) for whom based on clinical or radiological signs of an inflammatory infiltrate it is suspected that the lower respiratory tract is affected (e.g. pneumonia or acute respiratory distress syndrome); AND Symptoms not explained by another cause of infection or disease including causes of community-acquired pneumonia (e.g. <i>Streptococcus pneumoniae</i>, <i>Haemophilus influenzae</i> type B, <i>Legionella pneumophila</i>, other bacterial, pneumonia virus, influenza virus type A or B, respiratory syncytial virus). <i>Epidemiological exposure</i> Within the last 10 days before onset of illness: (A) Close contact: With a patient, in particular by medical personnel, or family members; OR Stay in the same place (e.g. living together, visit) as a case, while they were symptomatic. (B) Stay (travel or residence) in the Arabian peninsula or in adjacent countries^c.</p>	<p>Medical personnel meeting the clinical picture after close contact with ICU-treated patients meeting the clinical picture and needing intensive care INDEPENDENT of epidemiological exposure.</p> <p>Two or more persons treated in ICU meeting the clinical picture, with onset of symptoms within the same 2 -week period and within the same classroom, workplace, household, extended family, hospital, other residential facility, barracks or camps INDEPENDENT of epidemiological exposure.</p>
European Centre for Disease Prevention and Control [13]	<p>A person with an acute respiratory infection, which may include history of fever and cough and indications of pulmonary parenchymal disease (e.g. pneumonia or acute respiratory infection), based on clinical or radiological evidence of consolidation, who requires admission to hospital; AND Has exposure in the Middle East within 10 days before onset of illness, unless another aetiology has been identified^d.</p>	<p>A person with an acute respiratory infection, which may include history of fever and cough and indications of pulmonary parenchymal disease (e.g. pneumonia or acute respiratory infection), based on clinical or radiological evidence of consolidation, who requires admission to hospital; AND any of the following:</p> <ul style="list-style-type: none"> • Is in a cluster that occurs within a 10-day period, without regard to place of residence or history of travel, unless another aetiology has been identified^d. • Occurs in a health-care worker who has been working in an environment where patients with severe acute respiratory infections are being cared for, particularly patients requiring intensive care, without regard to place of residence or history of travel, unless another aetiology has been identified^d.

^aCountries considered in the Arabian peninsula and neighbouring include: Bahrain, Iraq, Islamic Republic of Iran, Israel, Jordan, Kuwait, Lebanon, Oman, Palestinian territories, Qatar, Saudi Arabia, Syrian Arab Republic the United Arab Emirates and Yemen.

^bExamples of respiratory pathogens causing community-acquired pneumonia include influenza A and B, respiratory syncytial virus, *Streptococcus pneumoniae* and *Legionella pneumophila*.

^cYemen, Qatar, Kuwait, Oman, Saudi Arabia, United Arab Emirates and Iraq, Jordan, Bahrain, Syrian Arab Republic, Lebanon, Islamic Republic of Iran, Palestinian Territories, Israel.

^dNotes that dual infection has been demonstrated in at least 1 case and so that detection of another pathogen should not exclude testing for nCoV where the first pathogen is unlikely to explain the clinical presentation).

had travelled from the Eastern Mediterranean Region during the 10-day putative incubation period. The remaining 2 cases were both family members of one of the imported cases, who were infected following contact in the UK, one in a household setting, the other seemingly in a hospital setting [14]. Although the majority of cases have been sporadic, follow-up and investigation of close contacts of cases has identified likely evidence of non-sustained person-to-person transmission of virologically confirmed infection on at least 3 occasions. One cluster (of 2 confirmed cases and 11 probable cases) of severe respiratory illness among health care workers in a hospital in Jordan was identified based on retrospective testing; a second cluster (of 3 confirmed and 1 probable case) was identified in a family in Saudi Arabia and a third cluster (of 2 confirmed cases plus the index case) was found among family contacts of one of the confirmed cases imported to the UK. Investigation of each cluster did not demonstrate evidence of on-going person-to-person transmission. In May 2013, 13 confirmed cases were reported from Saudi Arabia to WHO and are currently under investigation [16].

The current picture is thus most likely of a severe, zoonotic infection with occasional transmission to humans, with limited person-to-person transmission. These preliminary and limited data suggest that the surveillance strategies implemented following the detection of the initial 2 cases are generally appropriate, with a focus on severe rather than mild disease to maintain optimum

specificity and sensitivity, although many gaps in knowledge remain. Although onward infection in the human population has been limited to date, experience with SARS illustrated the possibility for super-spreading events to take place [17], highlighting the importance of ensuring timely detection of new cases through physician awareness and early testing and implementation of prevention and control measures. The ongoing detection of new cases linked (directly or indirectly) to the Eastern Mediterranean Region, highlights the importance of continuing surveillance for cases of severe respiratory disease with a history of travel from countries where sporadic cases have been reported (Table 1). Global and national nCoV surveillance and investigation activities have evolved based on the emerging epidemiological picture. WHO has adapted nCoV surveillance guidelines with a focus on detecting the full geographical extent of cases and to detect evidence of person-to-person transmission. Key changes to the case definition will allow the full geographical "reach" of the infection in the human population to be better delineated by extending previous surveillance case definitions to include clusters of severe undiagnosed respiratory disease and severe undiagnosed respiratory disease in health-care workers regardless of history of travel (Table 1). Continuing to undertake case-contact transmission studies of new cases and follow-up of contacts of newly confirmed cases is essential to detect evidence of person-to-person transmission. Investigation

protocols and guidelines for these case-contact investigations have been developed [11] and should be deployed for future confirmed cases [11,18]. The emergence of nCoV has also highlighted the importance of international collaboration between laboratories and countries where suspect cases have occurred. This has allowed the technology transfer of real-time PCR diagnostic tools. The serological diagnostics for nCoV remain technically challenging, and the importance of a global reference laboratory will remain vital.

Such surveillance activities need to be supported by applied epidemiological studies to answer more specific questions and which should be undertaken in a standardized fashion to allow global pooling of results [13]. Other studies include: environmental and animal studies to identify the source of the infection; serological studies in a range of potentially exposed populations; case-control studies to identify and quantify risk factors for animal-to-person transmission and retrospective testing of sample repositories from cases of severe undiagnosed respiratory illness in a range of geographical settings. These studies should provide answers to the source of nCoV, whether nCoV is occurring in other settings, how long it has been around and what burden of illness it is responsible for. Such information is key to informing the revision and optimization of public health prevention and control measures to reduce the burden of disease due to this novel infection.

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