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REVIEW

# Is the discovery of the novel human betacoronavirus 2c EMC/2012 (HCoV-EMC) the beginning of another SARS-like pandemic?

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**Summary** Fouchier et al. reported the isolation and genome sequencing of a novel coronavirus tentatively named "human betacoronavirus 2c EMC/2012 (HCoV-EMC)" from a Saudi patient presenting with pneumonia and renal failure in June 2012. Genome sequencing showed that this virus belongs to the group C species of the genus betacoronavirus and phylogenetically related to the bat coronaviruses HKU4 and HKU5 previously found in lesser bamboo bat and Japanese Pipistrelle bat of Hong Kong respectively. Another patient from Qatar with similar clinical presentation and positive RT-PCR test was reported in September 2012. We compare and contrast the clinical presentation, laboratory diagnosis and management of infection due to this novel coronavirus and that of SARS coronavirus despite the paucity of published information on the former. Since 70% of all emerging infectious pathogens came from animals, the emergence of this novel virus may represent another instance of interspecies jumping of betacoronavirus from animals to human similar to the group A coronavirus OC43 possibly from a bovine source in the 1890s and the group B SARS coronavirus in 2003 from bat to civet and human. Despite the apparently low transmissibility of the virus at this stage, research preparedness against another SARS-like pandemic is an important precautionary strategy.


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## Introduction and the evolution of events

In 2003, the world witnessed the first pandemic of the new millennium. Instead of the anticipated influenza virus, the pandemic was caused by, for the first time, a novel coronavirus which was subsequently named the severe acute respiratory syndrome (SARS) coronavirus (CoV).[1–6] Within a few months, the virus caused a total of 8422 cases of SARS with 916 deaths in over 30 countries among five continents, with a crude fatality rate of around 11%.[7] The outbreak had left a lasting impact not only in the lives of those who were infected, but also the frontline healthcare workers, public health officials, and even general public. To many, the slightest hint of the potential re-emergence of SARS would be the beginning of another nightmare. On 23 September 2012, less than a decade after the SARS pandemic, the World Health Organization (WHO) reported two cases of severe community-acquired pneumonia which bear significant reminisce with SARS (Table 1).[8–13] Subsequent laboratory tests revealed a novel human coronavirus, the human betacoronavirus 2c EMC/2012 (HCoV-EMC).[14,15]

The emergence of these two cases of HCoV-EMC infection at this stage may represent one of the four possible scenarios. Firstly, HCoV-EMC may be similar to the seasonal human coronavirus HKU1 which was detected in less than 5% of samples from those with respiratory tract infections while 22%–59.2% of the general population is seropositive due to mild or asymptomatic infections in the past.[16–22] Even human coronavirus HKU1 was occasionally associated with mortality in those with underlying multiple comorbidities who presented with acute community-acquired pneumonia.[23] Therefore these two severe cases of HCoV-EMC may just represent the tip of an iceberg due to another previously unknown seasonal coronavirus. Secondly, it may be analogous to the situation of avian influenza H5N1 in which there are occasional transmissions of the virus from poultry to humans manifesting with severe disease and a mortality of over 50%.[24–36] Thirdly, this is a rare instance of a few isolated zoonotic infections which are dead-ends. The fourth situation, the most dangerous one, is that this is the beginning of another SARS-like pandemic in which there will be increasing animal-to-human and subsequent human-to-human transmissions. When the suitable environmental conditions and opportunities for transmission associated with lapse in biosafety and infection control measures are present, the virus may cause an explosive outbreak as in the case of SARS. It would therefore be important to review the current knowledge on the clinical features, epidemiology, virology, and laboratory diagnosis of this novel coronavirus, and most importantly, to formulate possible treatment options and infection control measures based on comparisons made with other coronaviruses including SARS CoV.

## Taxonomy and virology

There are four genera in the family *Coronaviridae* within the order *Nidovirales* (Fig. 1A).[37] The genus alphacoronavirus contains the human coronavirus 229E and NL63 which are associated with common cold, and the genera gammacoronavirus and deltacoronavirus which contain viruses that affect only animals especially the avian species. The genus betacoronavirus contains four groups. Group A contains human coronavirus OC43, which is associated with respiratory tract infections. Group B contains SARS-CoV, which is associated with severe pneumonia. HCoV-EMC belongs to the group C betacoronavirus. Group D betacoronavirus contains the Rousettus bat coronavirus HKU9. Members of *Coronaviridae* are known causes of respiratory, intestinal, hepatic and neurological diseases of varying severity in humans and animals. Similar to other coronaviruses, HCoV-EMC is an enveloped positive-sense single-stranded RNA virus with a genome size of about 30 kb. It is classified as a group 2c coronavirus by previous nomenclature, and was named as such by the Erasmus Medical Center in Rotterdam, the Netherlands, which was the first institution to sequence the viral genome. It is most closely related to the bat coronaviruses HKU4 and HKU5 found in the lesser bamboo bats (*Tylonycteris pachypus*) (Fig. 2A and B) and Japanese Pipistrelle bat (*Pipistrellus abramus*) (Fig. 2C and D) respectively as shown in the phylogenetic tree (Fig. 1A).[38,39] As expected, their genome arrangements are also similar to those of the members of group C betacoronavirus but different from other groups.[40] The gene order from 5′ to 3′ is Orf1ab containing the highly conserved polymerase and helicase genes, followed by the highly variable gene encoding Spike, five other accessory proteins, and then the more conserved Envelope, Membrane and Nucleoprotein (Fig. 1B). The polymerase gene (RdRp) of HCoV-EMC has 90–92% amino acid identity with that of bat coronaviruses HKU4 or 5 while its spike gene (S) has only 64–67% amino acid identity with that of bat coronaviruses HKU4 or 5. The environmental stability of the virus is not known at this stage but might be important in determining its potential for further dissemination. In the case of SARS CoV, the virus had a higher degree of stability in the environment than other human coronaviruses, and could survive for at least two to three days on dry surfaces at room temperature and two to four days in stool.[41,42] Further studies should be conducted to obtain the key basic virological information including its life cycle and molecular evolution in order to understand its clinical and epidemiological significance.

## Clinical features and disease spectrum

The clinical presentation of both laboratory-confirmed cases of infection associated with HCoV-EMC is an acute severe community-acquired pneumonia with acute renal failure (Table 1). In case 2, a preceding period of mild respiratory symptoms of fever and rhinorrhoea (from 14 August 2012 to 21 August 2012) was followed by a period of clinical stability (from 21 August 2012 to 3 Sept 2012) prior to the re-emergence of symptoms including cough, arthralgia, myalgia, and deterioration with severe pneumonia with acute renal failure. It is currently unknown whether the initial mild symptoms were caused by this novel virus, or related to another mild viral infection as no microbiological diagnosis was made. Of note, some friends of case 2 who travelled on the same trip also developed the initial mild symptoms, but all recovered without subsequent deterioration. It remains to be seen whether this novel coronavirus

**Table 1** Sequence of important events related to human betacoronavirus 2c EMC/2012 (HCoV-EMC).[8–15]

| | Important events |
|---|---|
| 19 Apr 2012 | Ministry of Health in Jordan reported an outbreak (11 patients: 7 nurses & 1 doctor) of severe respiratory disease in a hospital ICU in Zarga, Jordan<br>One nurse died; no virological confirmation yet |
| 26 Apr 2012 | The ECDC reported the outbreak in Jordan |
| 6 Jun 2012 | Case 1: M/60 in Jeddah, KSA, presented with acute community-acquired pneumonia |
| 13 Jun 2012 | Case 1: Admitted to a regional hospital for severe pneumonia, and later developed acute renal failure |
| 24 Jun 2012 | Case 1: The patient died. Post-mortem lung tissue was negative for flu A/B, PIF, enteroviruses, adenoviruses; positive for coronavirus by pancoronavirus RT-PCR. EMC: sequencing showed evidence of a novel betacoronavirus |
| 13 Jul-18 Aug 2012 | Case 2: M/49 in Qatar, good past health, travelled to KSA, had self-limiting respiratory illness (rhinorrhoea and fever) along with his friends. Kept camels and sheep in a farm in Qatar |
| 21 Jul-3 Aug 2012 | Case 2: Remained clinically well after recovering from the mild respiratory illness |
| 3 Sep 2012 | Case 2: Developed cough, myalgia and arthralgia |
| 8 Sep 2012 | Case 2: Admitted to an ICU in Doha, Qatar, for fever and hypoxia, CXR: bilateral lower zone consolidation; Rx: ceftriaxone, azithromycin, oseltamivir |
| 11 Sep 2012 | Case 2: Required mechanical ventilation and was transferred to ICU in UK by air ambulance. Cr 353umol/L on admission. Deterioration despite broad-spectrum antimicrobials and corticosteroids |
| 14 Sep 2012 | Case 2: HPA (UK) Imported Fever Service notified. Haemofiltration started |
| 17—20 Sep 2012 | Case 2: URT and LRT samples were negative for flu A/B, hMPV, RSV, human coronaviruses OC43, NL63, 229E, and SARS CoV |
| 20 Sep 2012 | Case 1: Reported to the WHO through ProMED-mail. Case 2: ECMO started |
| 21 Sep 2012 | Case 2: 2 LRT samples were positive for coronavirus by pancoronavirus RT-PCR with amplicon sequence almost identical to case 1 |
| 22 Sep 2012 | Case 2: Reported to the WHO by the HPA (UK) |
| 23 Sep 2012 | The WHO reported 2 laboratory-confirmed cases of severe respiratory disease associated with a novel coronavirus. The nucleotide BLAST search: 80% homology to bat coronaviruses HKU-4 and HKU-5. Their 250 bp PCR fragment showed 99.5% sequence homology (1 nucleotide difference) |
| 24 Sep 2012 | ECDC recommendation on the rapid risk assessment of severe respiratory disease associated with a novel coronavirus published<br>Case 2: The HPA (UK) reported no illness among contacts of case 2, including healthcare workers and the medical evacuation company personnel who managed case 2 on their follow up |
| 25 Sep 2012 | WHO issued an interim case definition for severe respiratory disease associated with the novel coronavirus (Table 2) |
| 26 Sep 2012 | The HPA (UK) issued infection control advice for suspected or confirmed novel coronavirus cases |
| 27 Sep 2012 | Complete genome of the novel coronavirus, human betacoronavirus 2c EMC/2012, was available in the GenBank (accession number: JX869059) |
| 28 Sep 2012 | The HPA (UK) issued algorithms for investigation and management of possible cases and close contacts of confirmed cases of severe acute respiratory illness associated with the novel coronavirus |
| 29 Sep 2012 | The WHO issued a revised interim case definition for severe respiratory disease associated with the novel coronavirus (Table 2) |
| 2 Oct 2012 | Case 2: Remained stable but fully dependent on ECMO |

CXR, chest radiograph; Cr, creatinine; ECDC, European Centre for Disease Prevention and Control; ECMO, extracorporeal membrane oxygenation; EMC, Erasmus Medical Center; flu, influenza; hMPV, human metapneumovirus; HPA, Health Protection Agency; ICU, intensive care unit; KSA, the Kingdom of Saudi Arabia; LRT, lower respiratory tract; M, male; PIF, parainfluenza; RSV, respiratory syncytial virus; RT-PCR, reverse transcription-polymerase chain reaction; Rx, treatment; SARS CoV, severe acute respiratory syndrome coronavirus; UK, the United Kingdom; URT, upper respiratory tract.

can cause mild infections especially as specific virological diagnostic tests are not performed routinely in most places.

From the limited clinical information released up to this stage, their clinical presentation of HCoV-EMC infection is unusual among the human coronaviruses 229E, NL63, OC43, and HKU1 which cause predominantly an acute self-limited upper respiratory tract infection without renal failure. The only exception is SARS CoV which causes an acute

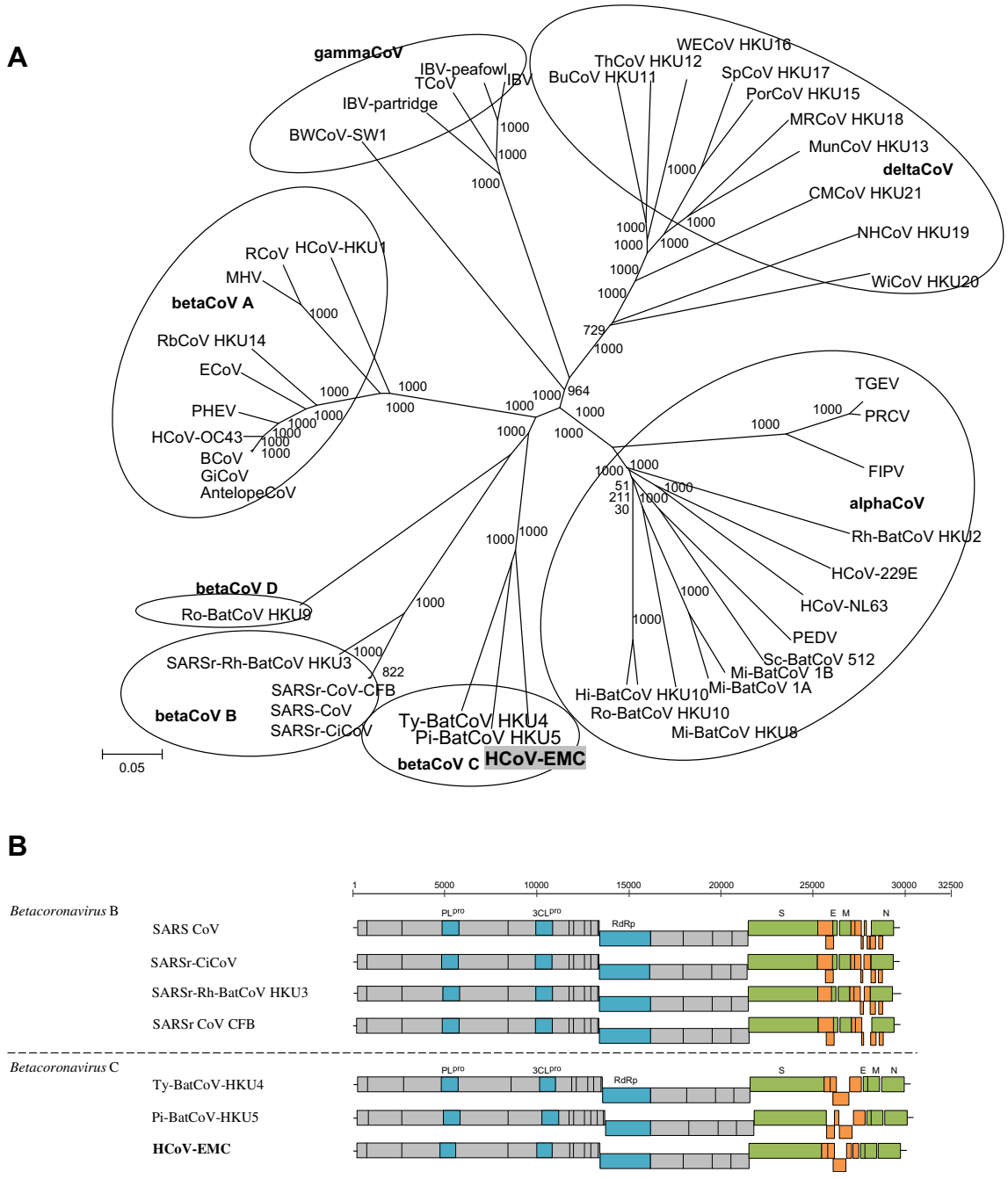


**Figure 1** (A) Phylogenetic tree of the novel human betacoronavirus 2c EMC/2012 (HCoV-EMC) and other coronaviruses. The tree was constructed by the neighbour-joining method using clustalX 2.0.12. The scale bar indicates the estimated number of substitutions per 20 nucleotides. ALCCoV, Asian leopard cat coronavirus (EF584908); AntelopeCoV, sable antelope coronavirus (EF424621); BCoV, bovine coronavirus (NC_003045); BuCoV HKU11, bulbul coronavirus HKU11 (FJ376619); BWCoV-SW1, beluga whale coronavirus SW1 (NC_010646); CCoV, canine coronavirus (GQ477367); CMCoV HKU21, common moorhen coronavirus HKU21 (NC_016996); ECoV, equine coronavirus (NC_010327); FIPV, feline infectious peritonitis virus (AY994055); GiCoV, giraffe coronavirus (EF424622); HCoV-EMC, human betacoronavirus 2c EMC/2012; HCoV-229E, human coronavirus 229E (NC_002645); HCoV-HKU1, human coronavirus HKU1 (NC_006577); HCoV-NL63, human coronavirus NL63 (NC_005831); HCoV-OC43, human coronavirus OC43 (NC_005147); Hi-BatCoV HKU10, *Hipposideros* bat coronavirus HKU10 (JQ989269); IBV, infectious bronchitis virus (NC_001451); IBV-partridge, partridge coronavirus (AY646283); IBV-peafowl, peafowl coronavirus (AY641576); MHV, murine hepatitis virus (NC_001846); Mi-BatCoV 1A, *Miniopterus* bat coronavirus 1A (NC_010437); Mi-BatCoV 1B, *Miniopterus* bat coronavirus 1B (NC_010436); Mi-BatCoV HKU8, *Miniopterus* bat coronavirus HKU8 (NC_010438); MRCoV HKU18, magpie robin coronavirus HKU18 (NC_016993); MunCoV HKU13, munia coronavirus HKU13 (FJ376622); NHCoV HKU19, night heron coronavirus HKU19 (NC_016994); PEDV, porcine epidemic diarrhoea virus (NC_003436); PHEV, porcine haemagglutinating encephalomyelitis virus (NC_007732); Pi-BatCoV-HKU5, *Pipistrellus* bat coronavirus HKU5 (NC_009020); PorCoV HKU15, porcine coronavirus HKU15 (NC_016990); PRCV,

community- or hospital-acquired pneumonia with rapid respiratory deterioration. Besides the presenting symptoms of fever, chills, myalgia, malaise, and nonproductive cough, clinical deteriorations typically occurred one week after the onset of symptoms in SARS and were usually accompanied by watery diarrhoea.[5,6,43–53] Physical findings were indiscriminative from other causes of atypical pneumonia. Common chest radiograph findings included ground-glass opacities, focal consolidations with a predilection for involvement of the periphery and subpleural regions of the lower zones, progressive involvement of bilateral lung fields, and spontaneous pneumomediastinum.[44,54–58] The most prominent histopathological features in SARS patients who died before and after the tenth day of symptom onset were acute diffuse alveolar damage with air space oedema, and mixture of acute changes with organizing phase of diffuse alveolar damage respectively.[59–61] Less commonly, haemophagocytosis in the alveolar exudates, thrombosis of venules, secondary bacterial and fungal pneumonia,[62] and systemic vasculitis involving the walls of small veins have also been reported.[63] Unfortunately, the post-mortem histopathological findings in case 1 are not available for comparison at this stage.

The other unusual clinical feature observed in both cases of infection associated with HCoV-EMC was the presence of acute renal failure. Acute renal failure with histological evidence of acute tubular necrosis was present in 6.9% of patients with SARS which is possibly due to hypoxic kidney damage,[64] and was a poor prognostic factor.[65] However, 28.8% of SARS patients' urine had viral load detectable by quantitative reverse transcription-polymerase chain reaction (RT-PCR) which correlated with abnormal urinalysis.[66] It would be important to know the relative contribution of the direct HCoV-EMC induced cytolysis and the indirect pneumonia-related hypoxic damage to the severity of the renal pathology. In broiler chickens suffering from infection by the avian nephropathogenic infectious bronchitis virus, severe renal swelling and accumulation of urate in the tubules were commonly seen.[67] Histological findings included lymphoplasmacytic interstitial nephritis with characteristic tubular epithelial degeneration and sloughing. Minimal respiratory involvement was noted with this nephropathogenic coronavirus. Important differential causes of viral pneumonia with acute renal failure which should be considered when the initial sepsis work-up of a compatible case is unrevealing include hantaviruses, agents of viral haemorrhagic fever, and influenza viruses. Other extrapulmonary manifestations of SARS including lymphopenia, diarrhoea, hepatic dysfunction, diastolic cardiac impairment, pulmonary arterial thrombosis, bleeding diathesis, myositis, neuromuscular abnormalities, and epileptic fits should also be looked for in the two cases of HCoV-EMC infection.[43,68–74]

Because of the lack of knowledge on the spectrum of disease severity, the WHO's interim case definitions for case finding may only be appropriate for notification but not for frontline clinical management and triage because the initial presentation may be a milder form of acute respiratory infection with or without subsequent deterioration (Table 2). In elderly and young children with SARS, atypical presentation with the absence of fever and respiratory symptoms, and mild form of infection were occasionally reported.[77–82] Furthermore, co-infection with other causative agents of community-acquired pneumonia may lead to a false sense of security when other agents of acute respiratory disease were found as in the case of SARS when co-infection by human metapneumovirus was reported in 12.5%—66.7% of such patients.[53,83] Therefore, applying the WHO interim case definitions in the investigation of patients without individualized risk assessment may lead to a significant proportion of patients with atypical presentation, mild disease, or co-infections being missed. In order to better understand the full spectrum of clinical features, to promptly provide the necessary treatment, and to apply the appropriate infection control measures to stop further dissemination of this novel coronavirus, a working algorithm with less stringent criteria for investigation in areas where resources are available can be considered (Fig. 3). In Hong Kong, we recommend to investigate patients based on an individualized risk assessment approach, in which immunocompetent adult patients who have travelled to or resided in an area where infection with HCoV-EMC has been reported, or who are close contact within the last 10 days before the onset of illness with a probable or confirmed case while the case was ill, and who present with fever and respiratory symptoms, should receive a baseline chest radiograph for assessment of lower respiratory tract involvement, urinalysis and renal function tests to detect renal impairment. In immunocompromised, elderly, and paediatric patients who may have atypical or mild forms of the infection, the decision for further investigations should be more liberal.

## Laboratory diagnosis and gene targets

Definitive diagnosis of infection associated with HCoV-EMC requires laboratory confirmation as its clinical features are

porcine respiratory coronavirus (DQ811787); RbCoV HKU14, rabbit coronavirus HKU14 (NC_017083); RCoV, rat coronavirus (NC_012936); Rh-BatCoV HKU2, *Rhinolophus* bat coronavirus HKU2 (EF203064); Ro-BatCoV-HKU9, *Rousettus* bat coronavirus HKU9 (NC_009021); Ro-BatCoV HKU10, *Rousettus* bat coronavirus HKU10 (JQ989270); SARS CoV, SARS-related human coronavirus (NC_004718); SARSr-CiCoV, SARS-related palm civet coronavirus (AY304488); SARSr CoV CFB, SARS-related Chinese ferret badger coronavirus (AY545919); SARSr-Rh-BatCoV HKU3, SARS-related *Rhinolophus* bat coronavirus HKU3 (DQ022305); Sc-BatCoV 512, *Scotophilus* bat coronavirus 512 (NC_009657); SpCoV HKU17, sparrow coronavirus HKU17 (NC_016992); TCoV, turkey coronavirus (NC_010800); TGEV, transmissible gastroenteritis virus (NC_002306); ThCoV HKU12, thrush coronavirus HKU12 (FJ376621); Ty-BatCoV-HKU4, *Tylonycteris* bat coronavirus HKU4 (NC_009019); WECoV HKU16, white-eye coronavirus HKU16 (NC_016991); WiCoV HKU20, wigeon coronavirus HKU20 (NC_016995). (B) Genome organizations of members of group B and group C betacoronaviruses showing that the novel HCoV-EMC has similar genome arrangements to other group C betacoronaviruses but different from other group B betacoronaviruses. PL, papain-like protease; 3CL, chymotrypsin-like protease; RdRp, RNA-dependent RNA polymerase; Hel, helicase; S, spike; E, envelope; M, membrane; N, nucleocapsid.


**Figure 2** (A) and (B) Lesser bamboo bat (*Tylonycteris pachypus*), often found dwelling in hollows of bamboo plants in South East Asia, from which bat coronavirus HKU4 was first discovered. (C) and (D) Japanese Pipistrelle (*Pipistrelle abramus*), often found at ceilings and roof tops of residential houses in South East Asia, from which bat coronavirus HKU5 was first discovered.

not pathognomonic. Similar to SARS CoV, a positive viral culture from respiratory, faecal, urine, or tissue specimens, or a fourfold rise in the neutralizing antibody titre in serum samples taken at 14—21 days apart should be the most definitive evidence of infection. However, their uses during the acute stage of the illness are limited by the long turnaround time, absence of access to designated biosafety level 3 laboratories for viral culture, or the need for convalescent samples. HCoV-EMC can be cultured by Zaki et al. on monkey kidney cells such as the Vero and LLC-MK cell lines.[11]

In both cases, the laboratory diagnosis was made by nucleic acid detection by a pancoronavirus RT-PCR followed by viral genome sequencing. The development of specific quantitative real-time RT-PCR, with a turnaround time of a few hours, is expected soon but the low number of cases will impede the validation of such tests. Taking the experience from SARS CoV diagnostics, two specific gene targets, namely the polymerase gene and the nucleoprotein gene, should be considered as they are both well conserved in coronaviruses and less subject to variation with different clinical strains.[84—93] However the use of the accessory protein gene sequence upstream the Envelope gene (E) present only in HCoV-EMC was reported to be highly specific.[14] The nucleoprotein gene has the theoretical advantage of being more sensitive as its subgenomic RNA copy number is more abundant in infected cells, but clinical studies with SARS CoV did not definitively prove this advantage. Since the timing of the peak viral load of HCoV-EMC has not been determined, repeating the test in suspected cases with an initial negative result is necessary to avoid a false-negative result because the viral load of SARS CoV in nasopharyngeal aspirate (NPA) peaked at day 10 of symptom onset.[44,84] Since the implications of a positive case are significant, positive test results from a single sample should be confirmed by a second test which detects a different region of the viral genome on the same sample in order to avoid false-positive results due to amplicon carryover.

As the two cases both presented with severe pneumonia with lower respiratory tract involvement, lower tract specimens including sputum, bronchoalveolar lavage, endotracheal aspirate, and even lung tissue as in case 1, are the preferred specimen types to be collected and put into viral transport medium. However, in suspected cases where only upper respiratory tract involvement is clinically apparent, NPA, nasopharyngeal swab, throat swab and/or expectorated sputum should be obtained, and if initially negative, should be repeated with deterioration of symptoms and at day 7 to day 10 of symptom onset (Fig. 3). As in the case of SARS and other coronaviruses, feces,[66,94] urine,[64,66] and sera[95] might be useful and should be collected for further testing as clinically indicated.

Besides RT-PCR, serum antigen detection with monoclonal antibodies or monospecific polyclonal antibody

**Table 2** Interim case definitions for case finding and reporting of infection associated with human betacoronavirus 2c EMC/2012 by the World Health Organization and Health Protection Agency of the United Kingdom.[75,76]

| | WHO (29 September 2012) | HPA (26 September 2012) |
|---|---|---|
| *Case finding* | | |
| Clinical | 1. A person with acute respiratory infection, which may include fever (≥38 °C, 100.4 °F) and cough; AND<br>2. Suspicion of pulmonary parenchymal disease (e.g.: pneumonia or ARDS) based on clinical or radiological evidence of consolidation; AND<br>3. Travel to or residence in an area (Qatar or KSA) where infection with human betacoronavirus 2c EMC/2012 has recently been reported or where transmission could have occurred; AND<br>4. Not already explained by any other infection or aetiology, including all clinically indicated tests for community-acquired pneumonia according to local management guidelines | 1. Any person with acute respiratory syndrome which includes fever (≥38 °C) or history of fever and cough; AND<br>2. Requiring hospitalization; OR<br>3. With suspicion of lower airway involvement (clinical or radiological evidence of consolidation) not explained by another infection or aetiology |
| Epidemiological | | 1. Close contact during the 10 days before onset of illness with a confirmed or probable case while the case was ill; OR<br>2. Travel to or residence in an area (Qatar or KSA) where infection with human betacoronavirus 2c EMC/2012 has recently been reported or where transmission could have occurred in the ten days before onset of illness |
| *Case reporting* | | |
| Possible | | Any person meeting the clinical and epidemiological criteria |
| Probable | 1. A person fitting the definition above for case finding with clinical, radiological, or histological evidence of pulmonary parenchyma disease (e.g.: pneumonia or ARDS) but no possibility of laboratory confirmation either because the patient or samples are not available or there is no testing available for other respiratory infections, OR<br>2. Close contact with a laboratory confirmed case, OR<br>3. Not already explained by any other infection or aetiology, including all clinically indicated tests for community-acquired pneumonia according to local management guidelines | 1. Any person meeting the possible case criteria; AND<br>2. Negative results for seasonal respiratory virus screen |
| Confirmed | A person with laboratory confirmation of infection with human betacoronavirus 2c EMC/2012 | Any person with positive laboratory confirmation of infection with human betacoronavirus 2c EMC/2012 |
| Closed contact | 1. Anyone who provided care for the patient including a healthcare worker or family member, or had other similarly close physical contact; OR<br>2. Anyone who stayed at the same place (e.g.: lived with, visited) as a probable or confirmed case while the case was symptomatic<br><br>Closed contacts who developed symptoms within the first 10 days after the last contact should be investigated | From date of illness onset in index case and throughout their symptomatic period.<br>1. Health and social care workers: provided direct care or examination of a symptomatic confirmed case or within close vicinity of an aerosol generating procedure (<3 feet) AND not wearing full PPE at the time (correctly fitted high filtration mask, gown, gloves, and eye protection)<br>2. Household: prolonged face-to-face contact (>15 min) with the confirmed case(s) any time during the illness after onset in a household setting<br>3. Other close contact: prolonged face-to-face contact (>15 min) with a confirmed case in any other enclosed setting and not wearing a mask (e.g.: school, visitor to the hospital to the bed side) |

ARDS, acute respiratory distress syndrome; PPE, personal protective equipment.

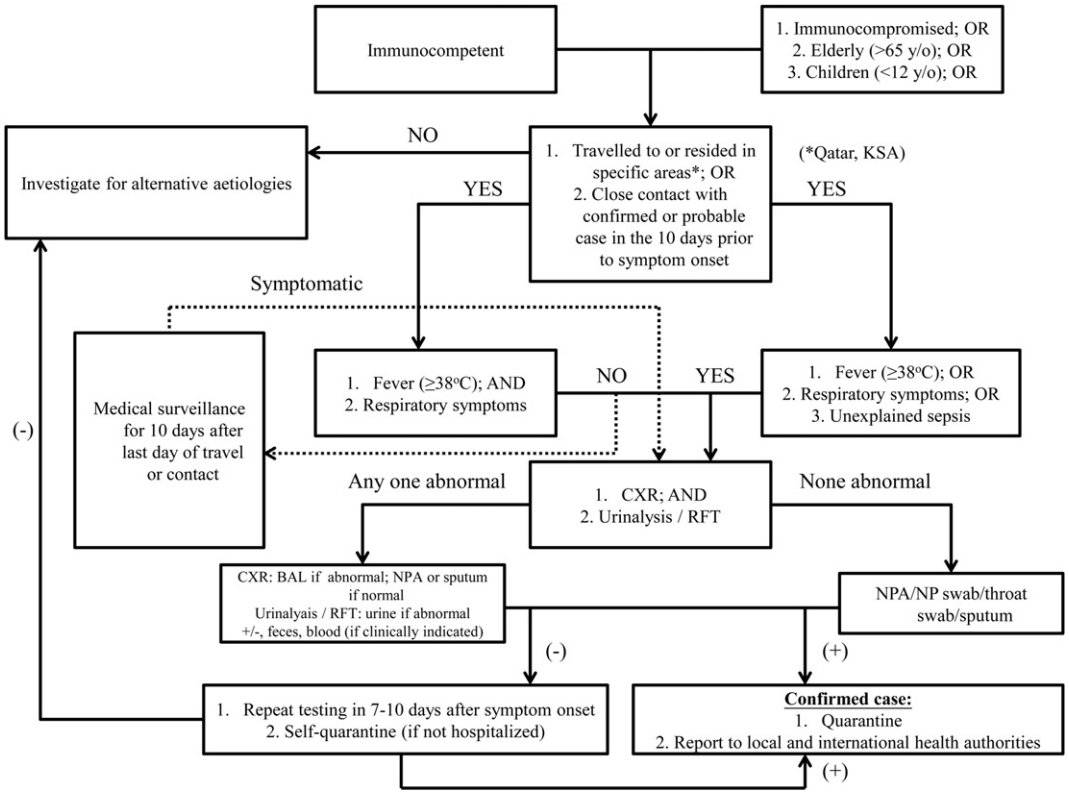


**Figure 3** Proposed working algorithm for the diagnosis, management, and infection control of suspected and confirmed cases of HCoV-EMC infection.

against the viral N protein was also shown to be a sensitive and specific test in the sero-diagnosis of SARS before the onset of neutralizing antibody response,[96–98] and might also be useful for infections associated with HCoV-EMC especially in areas where RT-PCR is not available. As the spectrum of clinical manifestations, epidemiology, and potential for further dissemination of this new disease are still poorly understood, antibody detection assays would be useful for seroepidemiological studies which would be highly useful in determining the exact situation and in planning of the relevant infection control strategies to contain the infection at an early stage.

## Epidemiology and animal contact

The information on the epidemiology of infections associated with HCoV-EMC is mainly derived from the sequence of important events which is summarized in Table 1. The most important epidemiological linkage at present seems to be the travelling to or the residence in areas where the infection has been reported, namely Qatar and the Kingdom of Saudi Arabia, in the preceding 10 days prior to the onset of illness. Case 2 had history of contact with camels and sheep.[10] Given the close phylogenetic relationships between HCoV-EMC and the bat coronaviruses HKU4 and HKU5 (Fig. 1A), our speculation is that wild animals including bat may serve as the natural reservoir of many group B or C betacoronaviruses which jump into one or more intermediate hosts of food or game animals dwelling closely to human as in the case of infection due to SARS CoV (civet), Hendra (horses), Nipah (swine), and Ebola (primates) viruses.[99,100] While pipistrelles, the natural reservoir of bat coronavirus HKU5, can be found in the Kingdom of Saudi Arabia, they are also seen in many other parts of the world. One possible reason why cases of infection associated with HCoV-EMC have not been reported in other areas may be explained by drawing an analogy to SARS CoV, whose transmission from the horseshoe bat (*Rhinolophus sp.*) to human was enhanced by intermediate animal hosts in palm civets and raccoon dogs. In Hong Kong, the regular surveillance of coronaviruses in patients' specimens or non-bat animal specimens in the past 5 years did not reveal a single case of infection by group C betacoronaviruses using consensus coronavirus primers and amplicon sequencing.[101] This might be related to the absence of the necessary intermediate hosts for amplifying the novel virus in our locality and the high level of biosecurity measures adopted at our farms and markets. Further studies are required to prove these postulations concerning animal-to-human transmission.

In contrast to SARS, person-to-person transmission has so far not been observed in infections associated with HCoV-EMC. In case 2, no clinically apparent infection was seen in the healthcare workers and personnel of the medical escort company involved in the care and transfer of the patient from Qatar to the United Kingdom. Furthermore, the two confirmed cases were separated by three months temporally, and had no specific epidemiological linkage except for both having been in the Kingdom of Saudi Arabia prior to the onset of illness. There have been no further cases reported which might signify the absence of ongoing transmission in the community. However, if the outbreak of severe respiratory

illness that occurred in a Jordanian hospital in April 2012, which involved a total of 11 people with eight of them being healthcare workers and one fatal case, was subsequently confirmed to be associated with HCoV-EMC, then person-to-person transmission, and particularly nosocomial transmission, would be possible (Table 1). In the case of SARS, person-to-person transmission by direct or indirect contact of the mucosae with infectious respiratory droplets or fomites was considered to be the primary mode of spread, although airborne transmission under special circumstances has been reported.[102] Nosocomial transmission, facilitated by the use of nebulizers, suction, intubation, bronchoscopy, and cardiopulmonary resuscitation, was also well documented.[49,103,104] Importantly, unlike those with influenza, patients with SARS were most infectious on or after the fifth day after the onset of symptoms, and the viral load in nasopharyngeal secretions usually peaked on the tenth day.[44] Therefore, if the novel virus was truly capable of causing person-to-person spread, the optimal infection control strategies might need to be further reviewed. As the Hajj is approaching, recommendations on whether travel restrictions or additional infection control measures are required are urgently needed. It would be disastrous if the phenomenon of super-spreading events observed in SARS was also encountered in infections associated with HCoV-EMC. An example was the large community outbreak that occurred in Amoy Garden of Hong Kong in which dried U traps of sewage drains facilitated the contaminated aerosols generated in toilets by exhaust fans to ascend the light well connecting different floors and resulted in a massive outbreak affecting hundreds of residents.[105,106]

In terms of the hosts at risk of developing severe disease, no conclusion could be made at present. Both patients were reported to be free of chronic medical conditions prior to the infection.[107] Another poorly defined characteristic of the infections associated with the novel virus is the incubation period. Neither case gave an accurate account of the incubation period prior to the onset of symptoms as they were both considered to be sporadic cases. In general, the incubation period of human non-SARS coronaviruses is 2—5 days and that of SARS CoV is 2—14 days.[108,109] A well documented incubation period of this novel infection is critical for setting up the appropriate case definition for case finding, optimizing the timing of laboratory tests and number of tests required, and deciding on the necessary periods of medical surveillance and quarantine required for contact and confirmed cases respectively.

## Treatment and ECMO

There is no proven effective antiviral agent against coronaviruses including SARS and HCoV-EMC.[3,110] No animal model for satisfying Koch's postulates or for testing antiviral treatment or immunization is yet reported for HCoV-EMC. Clinical management is therefore mainly supportive, with particular emphasis on organ support for respiratory and renal failure. The recent advances made in the use of extracorporeal membrane oxygenation (ECMO) in the intensive care unit has been shown to improve survival rates to up to 50—70% in cases of acute respiratory failure.[111—114] As for renal failure, continuous venous—venous haemofiltration is commonly used in the intensive care unit with the aim of tiding the patient over the initial critical stage. Broad-spectrum antimicrobial coverage against typical and atypical agents of severe community-acquired pneumonia, such as a regimen consisting of a β-lactam, a macrolide, and an antiviral against influenza, should be instituted while awaiting the laboratory diagnosis. The antimicrobial treatment should be stopped when the diagnosis of HCoV-EMC associated pneumonia is made, unless in situations where nosocomial infections or immunosuppressive states coexist.[115]

Specific antiviral agents including interferons (interferon-alfacon-1), ribavirin, and lopinavir-ritonavir with or without high-dose corticosteroid have been used in patients with SARS.[3] But their use was limited by a lack of evidence from randomized control trials and their potential side effects especially for ribavirin and steroid. Many other agents have shown in-vitro activities against SARS CoV, and included protease inhibitors such as nelfinavir and others, angiotensin-converting enzyme 2 analogues, helicase inhibitors and nucleoside analogues. However, their in-vivo activity and clinical utility for SARS and other coronaviruses remain elusive.[3] Corticosteroid should no longer be considered since patients with severe pneumonia and respiratory failure can be supported by ECMO till the cytokine storm is over.

Immunomodulating therapy with IgM-enriched immunoglobulin or convalescent plasma with neutralizing antibodies has been used in a small number of patients with SARS.[116—119] The data generated from these studies were limited by the small number of patients involved and the lack of randomized control trials conducted. Convalescent plasma is relatively free of side effect and might be considered should the novel virus continue to cause severe infections in a larger number of patients. However, if there were only a few convalescent patients, the preparation of convalescent plasma would not be feasible.

## Infection control and viral load

There is currently no specific international guideline for the infection control of HCoV-EMC. The WHO recommends strategies discussed in the WHO interim guideline for "infection prevention and control of epidemic- and pandemic-prone acute respiratory diseases in heath care".[120] These include the practice of Standard, Contact, and Airborne Precautions before the route of transmission is better defined. The HPA of the United Kingdom recommends a similarly stringent approach.[76] Besides these recommendations, a second virological test should be considered as the patient deteriorates or at day 7 to day 10 of symptom onset in symptomatic contacts who have an initial negative test result because the viral load may peak at day 10 as in the case of SARS CoV. While there is no travel restrictions imposed at present, the subsequent development of events associated with HCoV-EMC must be closely monitored especially as the Hajj is approaching. There is no recommendation on the infection control measures regarding animal contact. Simple personal hygienic measures such as hand hygiene after contact with animals and their excreta should be taken.

## Conclusion

One of the major reasons why the SARS CoV successfully caused a devastating pandemic was the lack of anticipation by the global health community. Although the currently available information about HCoV-EMC seems to suggest that it has a lower transmissibility than that of SARS CoV, many important epidemiological, clinical and scientific questions remain unresolved. Healthcare authorities should not discard the potential of this novel virus to cause another SARS-like pandemic before such answers are available. While over-reactions are unnecessary, appropriate preparations and collaborations by international and local health agencies are important.

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