

A Familial Cluster of Infection Associated With the 2019 Novel Coronavirus Indicating Possible Person-to-Person Transmission During the Incubation Period

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An ongoing outbreak of pneumonia associated with 2019 novel coronavirus was reported in China. It is unclear whether the virus is infective exists during the incubation period, although person-to-person transmission has been reported elsewhere. We report the epidemiological features of a familial cluster of 4 patients in Shanghai, including an 88-year-old man with limited mobility who was exposed only to asymptomatic family members whose symptoms developed later. The epidemiological evidence has shown possible transmission of 2019 novel coronavirus during the incubation period.

Keywords. 2019-nCoV; family cluster; incubation period; infectivity.

In December 2019, a series of viral pneumonia cases of an unknown cause appeared in Wuhan, Hubei, China [1]. Deep sequencing analysis from lower respiratory tract samples indicated a novel coronavirus, which was named 2019 novel coronavirus (2019-nCoV). As of 12 February 2020, a total of 59 804 confirmed cases of 2019-nCoV infection have been detected in China, in 31 provinces, municipalities, and special administrative regions. Of the persons infected, 1367 have died and 5911 have recovered. Moreover, cases of 2019-nCoV are no longer limited to mainland China; at this writing, infections have been reported in 24 countries, including Singapore, the Republic of Korea, and Japan [2].

The first clinical data from 41 individuals with a confirmed diagnosis of 2019-nCoV infection in Wuhan, China, have been published. Of the 41 patients, 27 had direct exposure to the

Wuhan seafood market, which is thought to be the initial infection site from an animal source [3]. Separately, clinical and microbiological data were reported from a family of 6, who had travelled to Wuhan and later presented with viral pneumonia at a Shenzhen Hospital in Guangdong province. Five of those 6 were identified as being infected with the 2019-nCoV, but none had been to the Wuhan market, and only 2 had visited a Wuhan hospital. These findings suggested possible person-to-person transmission of this novel coronavirus in a hospital and family setting; they followed the reports of other infected travelers in other geographic regions [4]. As the outbreak progressed, more relative studies with bigger population have been reported [5].

The ongoing 2019-nCoV outbreak has undoubtedly brought back memories of the severe acute respiratory syndrome (SARS)-coronavirus (CoV) outbreak, which started 17 years ago [6–8]. With this experience in mind, to stop the spread of the disease, public health officials have to rely on placing under quarantine those who may have been exposed to 2019-nCoV, and isolating those with suspected, probable, or confirmed cases of infection, and requiring everyone to wear masks in public places.

However, according to the updated version (version 4) of a new coronavirus pneumonia prevention and control program published by China's National Health Commission [9], close contacts are defined as those who have been exposed to case patients with clinical symptoms. At present, most close contacts are isolated in their homes and performing self-monitoring; the main monitoring indicators are fever or respiratory symptoms. To make the quarantine and isolation as effective as possible, it is essential to know the infectivity of 2019-nCoV during the incubation period.

Herein, we report the epidemiological features of a family cluster involving 4 2019-nCoV cases in Shanghai. Two case patients were from Wuhan, but the other 2 had not left Shanghai recently. The evidence from our epidemiological investigation suggests that 2019-nCoV may be infectious during the incubation period.

METHODS

On 21 January 2020, 2 patients from the same family unit were taken to hospital A in Shanghai with fever, respiratory symptoms, and pulmonary infiltrates on their chest radiographs. Considering the serious outbreak in Wuhan, both cases were diagnosed as suspected 2019-nCoV infection, according to the epidemiological history and clinical features. The patients were immediately isolated and reported to the local Center for Disease Control and Prevention.

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The investigators from the local center immediately conducted a face-to-face epidemiological survey for patients 1 and 2, and they collected clinical and laboratory data, including results of hematological, radiological, and respiratory pathogen examinations. On 23 January 2020, another 2 patients from this family unit were also taken to hospital A with fever. Cases 3 and 4 were investigated by telephone. Epidemiological information had been provided by the patients. All laboratory procedures for the clinical samples have been reported elsewhere [10]. Nasopharyngeal and throat swab samples were obtained and placed into viral transport medium. Plasma was separated using ethylenediaminetetraacetic acid bottles, and serum using clotted blood bottles.

This investigation was undertaken in response to a public health emergency declared according to the laws of the People's Republic of China on the prevention and treatment of infectious diseases [11], and it was not carried out with formal ethical approval. All patients were informed of their rights according to the laws cited above, and we obtained verbal consent from all patients.

Respiratory samples from the patients were tested for influenza A and B viruses using the Xpert Xpress Flu/RSV assay (GeneXpert System; Cepheid), according to the manufacturer's instructions [12]. The 2019-nCoV nucleic acid test was conducted by means of real-time reverse-transcription polymerase chain reaction, using detection reagents from Zhuo Cheng Hui Sheng Biotechnology and Berger Medical Technology.

RESULTS

In total, there were 4 patients in our study from 1 family unit. We numbered the cases from 1 to 4 according to the order of illness onset. The relationships and demographic information are shown in Figure 1.

Patient 1

Patient 1, an 88-year-old man, was incapacitated, and had hypertension, heart disease, and chronic obstructive pulmonary disease. He lived in Shanghai year-round, with only his wife, patient

4. He had not left home for at least 2 weeks before illness onset, and had no contact with any other people except patients 2, 3, and 4. He had had no contact with wild animals or persons with fever or pneumonia, nor had visited a farmers market or local hospitals in Shanghai 2 weeks before illness onset.

At about 11 AM on 20 January, patient 1 had a poor appetite and dry cough at home, and then a fever (body temperature, 38.2°C). He was taken to hospital A by ambulance at 5 PM on 21 January (Figure 2). Because of his serious illness, he was admitted to the intensive care unit with supportive treatment, including oxygen and fluids.

Preadmission examination showed a body temperature of 38.2°C and normal blood test results, with a white blood cell count of $7.16 \times 10^9/L$ and an absolute lymphocyte count value of $1.19 \times 10^9/L$; the C-reactive protein level was also normal. Computed tomography showed interstitial hyperplasia with infection in both of the patient's lungs, especially the posterior segment of the upper lobe of the right lung and the posterior basal segment of the lower lobe of the left lung, chronic bronchitis, emphysema, pulmonary bullae of lingual segment of the left lung, pulmonary hypertension in both lungs, increased heart shadow, and calcification of the aorta and aortic wall. Both influenza A and B antigen tests had negative results.

Patient 2

Patients 2 and 3, married and living in Wuhan, visited patients 1 and 4 in Shanghai by high-speed train on 15 January. (Patient 2 was patient 4's sister.) From 1 to 19 January, about 2 weeks before illness onset, patients 2 and 3 lived as they normally did. They did not eat out, come into contact with wild animals, or visit a farmers market, such as the Huanan seafood wholesale market. They were not exposed to patients with fever or pneumonia and did not visit local hospitals in Wuhan. They were both previously healthy, without a history of long-term use of immunosuppressive drugs or immunosuppressive diseases and with a history of recent vaccinations.

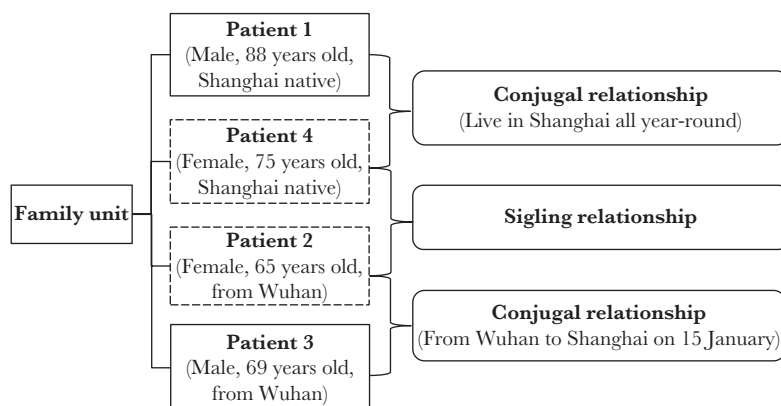


Figure 1. Relationships and demographics of the 4 case patients.

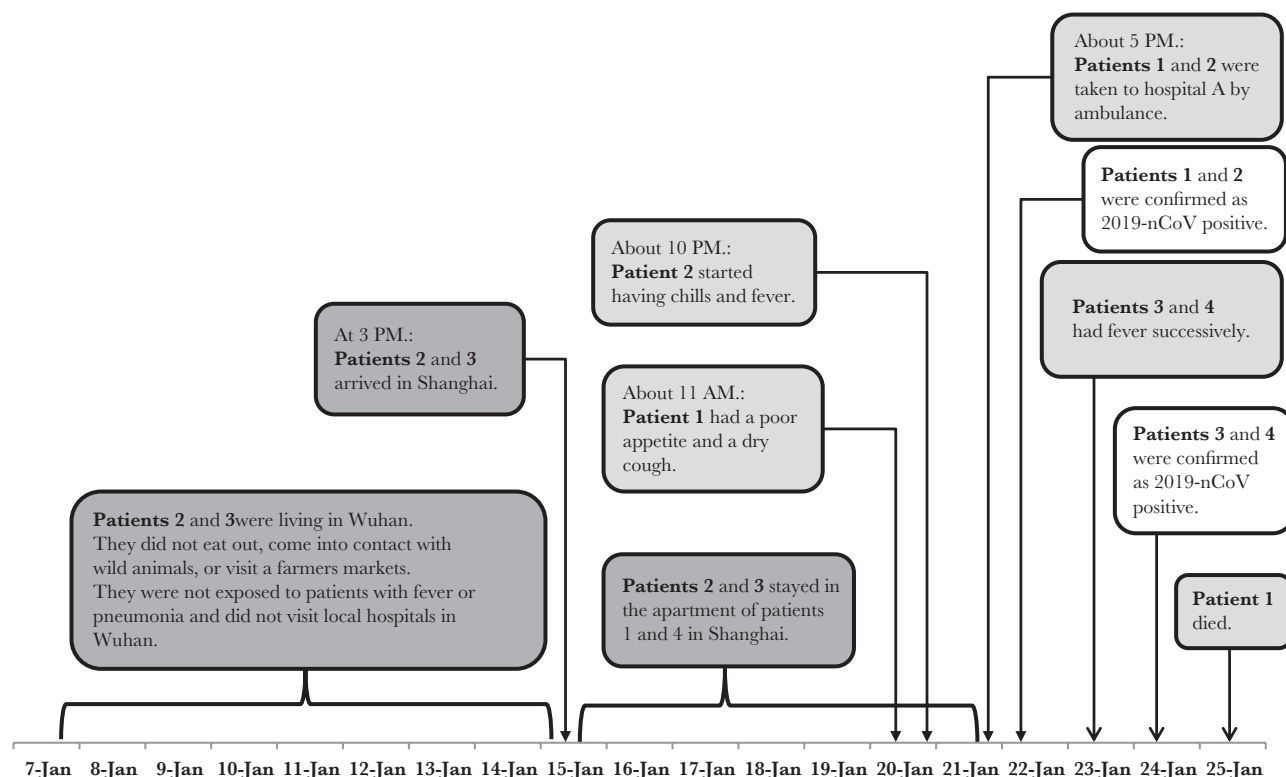


Figure 2. Chronology of illness onset in the family cluster cases. Abbreviations: 2019-nCoV, 2019 novel coronavirus; Jan, January 2020.

After arrival in Shanghai on 15 January, patients 2 and 3 stayed in the home of patients 1 and 4. None of them had any symptoms for the next 4 days. Patient 2 began to experience chills and fever around 10 PM on 20 January but did not measure her body temperature or take any drugs at that time. The next morning, 21 January, her body temperature was 37.6°C at 7 AM. She self-administered oseltamivir phosphate after lunch, but her symptoms showed no sign of improvement. In the afternoon, she also took acetaminophen and thought that her fever went down slightly. However, soon after that, she had a fever again. Patient 2 arrived at hospital A at 5 PM on 21 January, together with patient 1, and was admitted to the fever clinic observation room (Figure 2).

Preadmission examination showed that patient 2 had a body temperature of 38.5°C and normal blood test results, with white blood cell count of $4.37 \times 10^9/L$ and an absolute lymphocyte count of $0.88 \times 10^9/L$. Computed tomographic scans showed 2 ground-glass opacities on the inferior lobe of the right lung. Both influenza A and B antigen tests had negative results.

Patients 3 and 4

One day after patients 1 and 2 were admitted to hospital A, patients 3 and 4 had fever successively on 23 January. They were also admitted to hospital A, and nasopharyngeal and throat swab samples were collected for nucleic acid detection of 2019-nCoV.

Etiology Test Results

The Shanghai Center for Disease Control and Prevention confirmed that the nasopharyngeal and throat swab samples were 2019-nCoV positive for patients 1 and 2 on 22 January and for patients 3 and 4 on 24 January 2020, according to the 2019-nCoV nucleic acid tests.

DISCUSSION

In this familial cluster of 2019-nCoV infection, 4 patients were tested and confirmed as 2019-nCoV positive, according to nucleic acid detection. Two of them had radiological changes showing viral pneumonia.

It is worth noting that patient 1 was an 88-year-old man with limited mobility. He had not left his apartment for at least 2 weeks before onset of his illness. Five days before that onset, patients 2 and 3 came from Wuhan, the focus of the 2019-nCoV epidemic. It was confirmed that patients 2, 3, and 4 had not any symptoms for at least 2 weeks before the onset of illness in patient 1. Although the initial infection sources in patient 1 were most likely patient 2 or 3 during their incubation period, it is also possible that patient 4 was infected by patient 2 or 3 and then infected patient 1 during her incubation period. Because they lived in one bedroom. Thus, the infection source for patient 1 may have been patients 2, 3 and/or 4. The findings indicate that a person with 2019-nCoV might be infectious during the incubation period.

Zeng and colleagues [13] have reported that SARS cases are infectious only during their symptomatic period and are non-infectious during the incubation period [13]. Both SARS-CoV and Middle East respiratory syndrome (MERS)-CoV infect intrapulmonary epithelial cells more than cells of the upper airways [14, 15]. Therefore, individuals in close contact with symptomatic patients with SARS should be isolated for medical observation. However, human airway epithelial cells were used to isolate 2019-nCoV, which was declared to be the seventh member of the family of coronaviruses that infect humans, different from both MERS-CoV and SARS-CoV [6]. The nasopharyngeal and throat swab samples from all 4 patients were 2019-nCoV positive in our study, indicating that 2019-nCoV can infect the upper respiratory tract. According to the National Health Commission's guideline for diagnosis and treatment of pneumonia caused by 2019-nCoV, isolation and in vitro cultures showed that 2019-nCoV can be found in human respiratory epithelial cells in about 96 hours [16]. These results support the hypothesis that 2019-nCoV is more infectious than MERS-CoV and SARS-CoV, as it is easily discharged through the respiratory tract.

The infectivity during the incubation period for 2019-nCoV is a big challenge for controlling the disease, especially with the new considerations for the possible infectious sources and the recognition and isolation of close contacts. Here are our recommendations. First, the epidemiological exposure history should be taken as the most important reference for judging the potential source of infection, and isolation and protection measures should be further strengthened for the relevant persons with clear risk factors for exposure history. Second, the determination of close contacts should also include those who are exposed to case patients during their incubation. Third, research into and development of a high-sensitivity rapid diagnostic reagent for 2019-nCoV should be accelerated, to facilitate the screening of infected persons among clinical and close contacts. Fourth, health education should be further strengthened, and protective equipment should be properly used to reduce the exposure to 2019-nCoV. Finally, if possible, the isolation and medical observation of close contacts should be centralized under the premise of the safely transport, such as masks, single-person transfer and transport vehicle disinfection, et al. It is important to establish a community supervision mechanism when home isolation and observation are needed.

Notes

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