

A familial cluster of infection associated with the 2019 novel coronavirus indicating potential person-to-person transmission during the incubation period

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Main point: In a familial cluster of four 2019-nCoV cases in Shanghai, the first case only exposed to his asymptomatic family members who developed symptoms later. The results suggest a potential transmission of 2019-nCoV during the incubation period.

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Abstract

An ongoing outbreak of pneumonia associated with 2019 novel coronavirus (2019-nCoV) was reported in China. It is unclear if the infectivity exists during the incubation period, although a person-to-person transmission has been reported in previous studies. We report the epidemiological features of a familial cluster of four patients in Shanghai, of which one was 88 years old man with moving difficulties and was only exposed to his asymptomatic family members who developed symptoms later. The epidemiological evidence has shown a potential transmission of the 2019-nCoV during the incubation period.

Key words: 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 Feb 12, 2020, confirmed cases were reported in 31 provinces, municipalities, and special administrative regions of China, a total of 59804 confirmed cases of 2019-nCoV have been detected in China, of whom 1367 have died and 5911 cases have recovered. Moreover, cases of 2019-nCoV are no longer limited to mainland China, infections have been reported in 24 countries, such as Singapore, Republic of Korea, Japan et.al up to this date [2].

The first clinical data from 41 individuals with a confirmed diagnosis of 2019-nCoV infection from Wuhan, China, has been published. Twenty-seven of the 41 cases had direct exposure to the Wuhan seafood market which is thought to be the initial infection site from an animal source [3]. Separately, the clinical and microbiological data from a family of six people who had travelled to Wuhan and later presented with viral pneumonia at a Shenzhen Hospital in Guangdong province was reported. Five of the 6 were identified as being infected with the 2019-nCoV, but none had been to the Wuhan market, and only two had visited a Wuhan hospital. These findings demonstrated a possible person-to-person transmission of this novel coronavirus in a hospital and family setting; this data followed the reports of other infected travelers in other geographical 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 SARS-CoV outbreak which started 17 years ago [6-8]. Thus,

to stop the spread of the disease, public health officials have to rely on placing those who may have been exposed to 2019-nCoV under quarantine and isolating those with suspected, probable, and confirmed cases of the 2019-nCoV, and require people wear masks in public place.

However, according to the updated version of new coronavirus pneumonia prevention and control program (version 4) published by Chinese National Health Commission, the close contacts are all those who have exposed to the cases with clinical symptoms [9]. At present, most of close contacts are isolated at their own homes and taken self-health monitoring, and the main monitoring indicators are fever or respiratory symptoms. To make the quarantine and isolation as effective as possible, knowing the infectivity of 2019-nCoV during the incubation period is essential.

Here, we report the epidemiological features of a family cluster involving four 2019-nCoV cases in Shanghai. Two cases were from Wuhan, whereas the other two cases have not left Shanghai recently. The evidence from our epidemiological investigation showed there is a potential infectivity of the 2019-nCoV during the incubation period.

Methods

On Jan 21, 2020, two patients from one family unit were taken to hospital A in Shanghai with fever, respiratory symptoms, and pulmonary infiltrates on their chest radiographs images. Considering the serious outbreak in Wuhan, both two cases were diagnosed as suspected cases of 2019-nCoV according to the epidemiological history and clinical features. Cases were immediately

isolated and reported to the local Center for Disease Control and Prevention (CDC).

Immediately, the investigators from the local CDC conducted a face to face epidemiological survey for case 1 and case 2, and collected the clinical and laboratory data including haematological, radiological and respiratory pathogen examinations. Case 3 and case 4 were investigated by telephone. Epidemiological information had been provided by the cases. All laboratory procedures for the clinical samples have been previously reported [10]. Nasopharyngeal and throat swabs were taken and put into viral transport mediums. Plasma was separated from EDTA bottles, and the serum was separated from clotted blood bottles.

This investigation was undertaken in response to a public health emergency declared following the Laws of the People's Republic of China on the Prevention and Treatment of Infectious Diseases (<http://www.nhc.gov.cn/fzs/s3576/201808/6d00c158844f42c5bcf94993bffa665a.shtml>), which was not carried out with formal ethical approval. All the patients were informed of their rights according to the laws outlined above. We obtained verbal consent from all the patients.

Respiratory samples of the patients were tested for influenza A and B viruses using the Xpert Xpress Flu/RSV assay (GeneXpert System, Cepheid, Sunnyvale, CA, USA) according to the manufacturer's instructions [11]. The 2019-nCoV nucleic acid test was conducted by real-time RT-PCR, and the detection reagents were from Zhuo Cheng Hui Sheng Biotechnology Co., Ltd and Berger Medical Technology Co., Ltd.

Results

Totally, there were 4 cases in our study who were from one family unit. We defined the case number from case 1 to case 4 according to the order of the onset. The relationship and demographic information are shown in [Figure 1](#).

Case 1

Case 1 was incapacitated, and had hypertension, heart disease, and chronic obstructive pulmonary disease. Case 1 was living in Shanghai all year round, only with case 4. He had not left home for at least two weeks before illness onset, and never contacted other people besides case 2 and case 3. Moreover, case 1 had neither contacted with wild animals or fever/pneumonia patients, nor visited a farmer's market or local hospitals in Shanghai during the certain time period.

Around 11 AM on Jan 20, case 1 showed a poor appetite and dry cough at home, then had a fever (body temperature 38.2°C). Case 1 was taken to hospital A by ambulance at 5PM on Jan 21 ([Figure 2](#)). Because of the serious illness, case 1 was admitted to the intensive care unit with support treatments including oxygen and fluids.

Pre-admission examination showed: a body temperature of 38.2°C, blood test was normal with white blood cell count of $7.16 \times 10^9/L$, and lymphocyte absolute value of $1.19 \times 10^9/L$. The C-reactive protein was also normal. CT scan showed interstitial hyperplasia with an infection in both 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 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 were negative.

Case 2

Case 2 and case 3 were living in Wuhan, and they visited case 1 and case 4 in Shanghai by high-speed train on Jan 15. From Jan 1 to Jan 19, about two weeks before illness onset, case 2 and case 3 lived as normal. They did not eat out, come into contact with wild animals, or visit a farmer's market, such as the Huanan seafood wholesale market. They did not be exposed to fever or pneumonia patients, or Wuhan local hospitals, either. Case 2 and case 3 were previously healthy, without a history of long-term use of immunosuppressive drugs, immunosuppressive diseases and recent vaccination history.

After arrival in Shanghai on Jan 15, case 2 and case 3 lived together with case 1 and case 4. None of them had any symptoms for the next 4 days. In particular, case 2 did not present any symptoms until 10PM on January 20. She started having chills and fever around 10PM on Jan 20, but did not measure the body temperature or take any drugs at that time. The next morning (Jan 21) at 7 AM, after her body temperature reached 37.6°C, case 2 took Oseltamivir phosphate by herself after lunch, but her symptoms showed no sign of improvement. In the afternoon, she also took Paracetamol and felt that the fever went down slightly. However, soon after, she had a fever again. Case 2 arrived at hospital A at 5PM with case 1 together, and was admitted to the fever clinic observation room (Figure 2).

Pre-admission examination showed that a body temperature of 38.5°C, the blood test was normal with white blood cell count of $4.37 \times 10^9/L$, and lymphocyte absolute value of $0.88 \times 10^9/L$. Two ground-glass opacities were found at the inferior lobe of the right lung on CT scans. Both influenza A and B antigen tests were negative.

Case 3 and case 4

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

Etiology test results

The Shanghai Center for Disease Control and Prevention (CDC) confirmed that the nasopharyngeal and throat swabs were 2019-nCoV positive for cases 1&2 on Jan 22, 2020, and cases 3&4 on Jan 24, 2020 according to the 2019-nCoV nucleic acid tests.

Discussion

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

It is worth noting that case 1 was an 88-year-old man with limited mobility. He had not left his apartment for at least two weeks prior to illness onset. Five days before case 1's illness onset, case 2 and case 3 came from Wuhan, where is the 2019-nCov epidemic focus. It was confirmed that case 2,

case 3, and case 4 had not any symptoms for at least two weeks before case 1's illness onset. Although the initial infection sources of case 1 were most likely case 2 or case 3 during their incubation period, there was also another possibility that case 4 may have been infected by case 2 or case 3 and then infected case 1 during her incubation period as they lived in one room with more contacts. Thus, the source infection of case 1 may be one or more of case 2, case 3 or case 4. The findings indicate that a person with 2019-nCoV might be infectious during the incubation period.

Zeng G and colleagues have reported that SARS cases are only infectious during their symptomatic period and are non-infectious during the incubation period [12]. Both SARS-CoV and MERS-CoV infect intrapulmonary epithelial cells more than cells of the upper airways [13,14]. Therefore, isolation for medical observation should be placed for individuals who are in close contact with symptomatic SARS patients. However, human airway epithelial cells were used to isolate 2019-nCoV, 2019-nCoV was declared as the seventh member of the family of coronaviruses that infect humans which is different from both MERS-CoV and SARS-CoV [6]. The nasopharyngeal and throat swabs of all the four cases were 2019-nCoV positive in our study which indicated 2019-nCoV can infect the upper respiratory tract. According to China National Health Commission's guideline for diagnosis and treatment of pneumonia caused by 2019-nCoV, isolation and in vitro culture of 2019-nCoV showed that it can be found in human respiratory epithelial cells in about 96 hours [15]. These results support that 2019-nCoV is more infectious as it is easily discharged through the respiratory tract.

The infectivity during the incubation period for the 2019-nCoV is a big challenge for controlling the disease, especially with the new considerations for the potential infectious sources, the recognition of close contacts, and the isolation of close contacts. Here are our recommendations. Firstly, 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. Secondly, the determination of close contacts should also include those who are exposed to the cases during their incubation. Thirdly, the research and development of high sensitivity rapid diagnostic reagent of 2019-nCoV should be accelerated, so as to facilitate the screening of infected persons among clinical and close contacts. Fourthly, health education should be further strengthened and protective equipment should be properly used in order to reduce the exposure of 2019-nCoV. Finally, if possible, the isolation and medical observation of close contacts should be centralized under the premise of the safely transport. It is important to establish a community supervision mechanism when home isolation and observation are needed.

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Figure 1

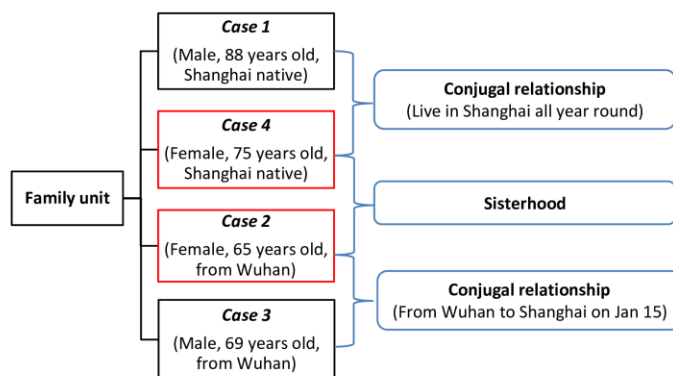


Figure 1: The relationship and demographics of cases

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Figure 2

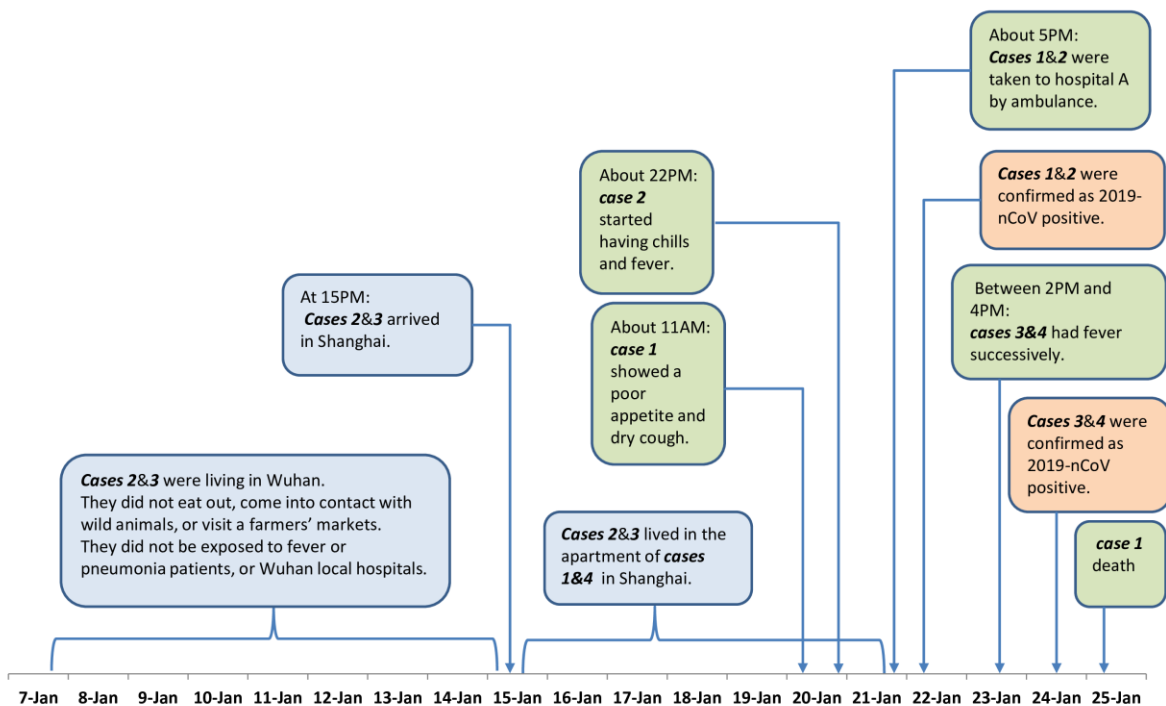


Figure 1: Chronology of illness onset of the family cluster cases

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