

Epidemiological features of COVID-19 family clusters, Beijing, China

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0. Abstract

Background. Since its discovery, SARS-CoV-2 has been spread throughout China before becoming a global pandemic. In Beijing, family clusters are the main mode of human-human transmission accounting for 57.6% of the total confirmed cases.

Method. We present the epidemiological and clinical features of the clusters of three large and one small families.

Result. All family clusters except one had an index case who was exposed in Wuhan. Among the 4 families, a total of 22/24 members were diagnostic with COVID-19. Among those infected, mostly (20/22) had mild symptoms and only two had severe clinical manifestation. And children in the family generally showed milder symptoms. The duration for virus incubation period varied from 2 to 18 days, and the shedding of virus in upper respiratory tract lasted from 5 days to over 30 days. In 8/24 cases, virus shedding preceded the onset of disease. And long period of virus shedding (>30 days) in upper respiratory tract was observed in 5/24 cases, who remains SARS-CoV-2 positive even after all disease symptoms disappear.

Conclusion. SARS-CoV-2 is transmitted quickly in the form of family clusters. While the infection rate is high within the cluster, the symptoms are generally mild out of Wuhan. The disease manifestation, incubation

period, and virus shedding period varied greatly among individual cases or clusters. Long period virus shedding should be considered as the main public health problem. We need to chase the patients even though they don't have any clinic manifestation.

Keywords. Coronaviurs disease-19 (COVID-19); epidemiological features, family clusters

1. Introduction

As of Feb 11, 2020, a total of 43,103 laboratory-confirmed human cases of SARS-CoV-2 infections had been reported to the World Health Organization[1], and the case number has been growing. Among these cases, 7333 were regarded as severe and 1017 resulted in death. The disease has now spread to more than 60 countries, with a potential to become a global pandemic [2]. The new virus is highly infectious and has strong ability to transmit from human to human [3]. On Feb 10th, 2020, 73 clusters of COVID-19 transmission had been identified in Beijing, of which 66 were family clusters in Beijing [4]. The family clusters involved 197 confirmed cases, comprising 57.6% of the total confirmed cases in Beijing (Feb 10th). Therefore, family clusters became the main mode of human-human transmission [5]. In Beijing, the Beijing Ditan Hospital is the designated hospital for the COVID-19 patients. Here we report 4 family clusters of COVID-19 infection cases in Beijing, which highlights the epidemiological features of COVID-19 circulating in China.

2. Methods

2.1 Cluster investigation

We interviewed four families recruited from Jan 16 to Jan 29, 2020 at Beijing Ditan hospital, one of the designated hospital for COVID-19 in Beijing. All patients were diagnosed as SARS-CoV-2 positive according to “Guidelines for the Diagnosis and Treatment of Novel Coronavirus (SARS-CoV-2) Infection by the National Health Commission (Trial Version 5)”[6]. The study was approved by the ethics committee of Beijing Ditan Hospital. Informed consent to the therapeutic regimen was obtained from each patient prior to the study.

2.2 Epidemiologic and clinical characteristics and laboratory testing

Epidemiological, demographic, clinical, and laboratory testing data were collected through a review of medical records. Clinical data and laboratory testing results were closely monitored until February 26, 2020. Laboratory confirmation of SARS-CoV-2 was carried out by Beijing CDC and the Beijing Ditan Hospital. Briefly, throat-swab specimens from the upper respiratory tract that were obtained from all patients at admission were maintained in viral-transport medium. SARS-CoV-2 was confirmed by RT-PCR using the protocol described previously[7]. Their blood samples were collected as part of routine care. All patients had chest radiography at admission.

3. Results

3.1 Epidemiologic and demographics characteristics

Four families are included in this study; altogether there were twenty-four family members. Each family had one index case, who had direct or indirect contact to Wuhan, which is the epicenter of the COVID-19 outbreak. To reveal the transmission of disease within these families, the relationship, contact time-line, and nucleic acid test are shown in Table 1 and Figure 1.

Table 1 The epidemiologic and demographic characteristics

Family member#	Age (years)	Gender	Relation to index case	Date of nucleic acid test positive	Latent period&	Date of nucleic acid test negative	nucleic acid last time (days)*	generations of case
FA1	36	M	Index case	Jan 21	5	28-Jan	7	1st
FA2	36	F	wife	Jan 21	5	30-Jan	9	2nd
FA3	60	F	mother	Jan 21	2	NA	NA	2nd
FA4	10	F	daughter	Jan 27	10	11-Feb	15	2nd
FA5	7	M	son	ND	N/A	ND	ND	Negative
FA6	9m	F	daughter	Jan 26	8	5-Feb	10	2nd
FB1m	60	F	Index case	28-Jan	12	NA	NA	2nd
FB1f	58	M	husband	28-Jan	9	NA	NA	3rd
FB1	33	F	daughter	1-Feb	16	positive now	>16	3rd
FB2	86	F	son-in-law's grandma	30-Jan	14	positive now	>29	3rd
FB3	64	F	son-in-law's mother	31-Jan	15	positive now	>28	3rd
FB4	65	M	son-in-law's father	30-Jan	14	25-Feb	26	3rd
FB5	37	M	son in law	30-Jan	14	positive now	>28	3rd
FB6	6	F	Granddaughter	29-Jan	13	12-Feb	14	3rd
FB7	10m	M	Grandson	2-Feb	17	7-Feb	5	3rd
FC1	33	M	Index case	29-Jan	15	18-Feb	20	1st
FC2	59	M	Father-in-law	31-Jan	12	7-Feb	7	2nd
FC3	56	F	Mother-in -law	31-Jan	12	15-Feb	15	2nd
FC4	32	F	wife	3-Feb	18	positive now	>26	2nd
FC5	5	F	senior daughter	2-Feb	17	19-Feb	17	2nd
FC6	3	F	junior daughter	2-Feb	17	19-Feb	17	2nd
FD1	52	M	Index case	31-Jan	6	positive now	>28	1st
FD2	46	F	wife	ND	NA	NA	ND	Negative
FD3	2	F	daughter	2-Feb	12	Positive again	>30	2nd

#FA: family A; FB: family B; FC: family C; FD: family D; NS: no symptom; N/A: not applicable; ND: not detected;

&Latent period: from the onset to test positive day.

*The number with a “>” on the left show that these cases remain positive when this study ended (Feb 28).

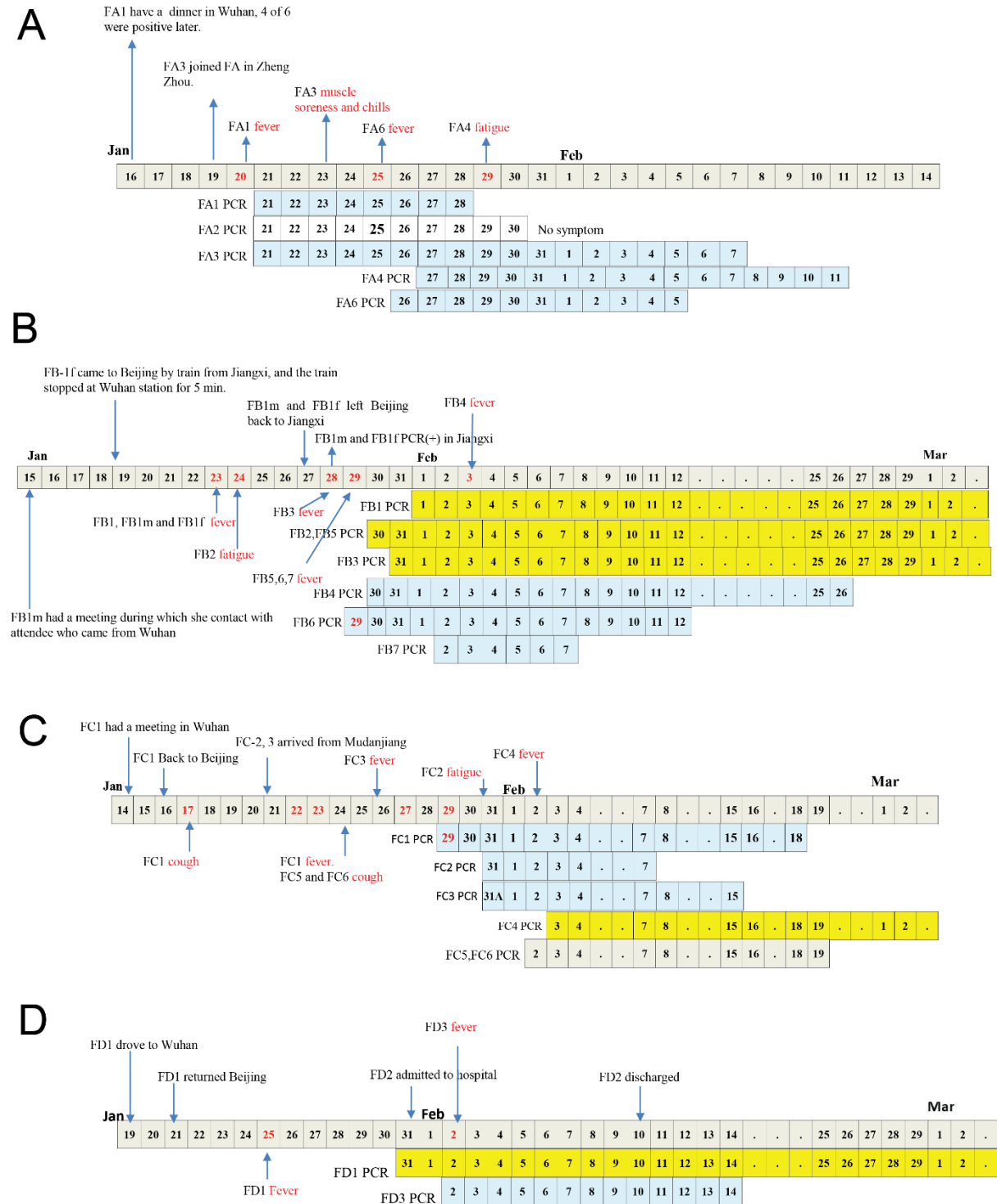


Figure 1: Description of family cases (Figure 1A,1B,1C,1D). The index case and the family members infectious ways and the period for the onset and PCR.

Yellow: The yellow bars showed those patients who were still positive till the paper finished.

Family A On Jan 16th 2020, the index case (FA1) had a reunion dinner in Wuhan (4 out of 6 at that dinner were later diagnosed with COVID-19) and returned home at midnight to join his wife (FA2) and three children (FA4, FA5 and FA6). FA1 shared the same bedroom with F2 and F6. On Jan 19th, the four members of the family joined the FA1's mother (FA3) at Zhengzhou, Henan Province, and the entire family took the train and arrived at Beijing on Jan 20th at noon. On the afternoon of Jan 20th, FA1 started to show symptoms of a fever and dry cough, while other members of the family hadn't shown any symptoms. On Jan 21st, all the elders within the family (i.e. FA1, FA2, FA3) were tested positive for SARS-CoV-2. FA2 never showed any symptoms during the whole course of disease, but a CT chest scan suggested pathological changes in both lungs. FA3 had muscle soreness and chills between Jan 23rd and 31st, and a chest CT scan performed on Feb 3rd showed resolving inflammation in both lungs. The family had three children, all of whom were said to be infected with 'flu' in mid-December. As for SARS-CoV-2, one child (FA5) tested negative and remained symptom free for the whole period of this study. On the other hand, FA4 was PCR positive before the onset of disease (headache), whereas FA-6 had a fever the same day that she tested PCR positive. Neither FA4 nor FA6 showed any abnormality in their chest CT scans. All members of the family were released from hospital by Feb 14th.

Family B. Family B had 4 generations living in two different cities. FB1's mother (FB1m) is an employee at public health institutes in Nanchang who came to Beijing for a meeting on Jan 15th 2020 during which she had contact with attendees from Wuhan. In Beijing, she stayed in her daughter's (FB1) house. FB1's father (FB1f) lived in Jiangxi province - he came to Beijing by train on Jan 19th to stay in FB1's house, and the train had stopped at Wuhan station for 5 min. FB1m and FB1f left Beijing for Nanchang on Jan 27th. The rest of the family, which include FB1, FB2 (mother-in-law), FB3 (husband), FB4 (father-in-law), FB5 (husband's grandmother), FB6 (daughter), and FB7 (son), stayed in Beijing the whole time in the same apartment and had no contact history with people from Wuhan. All the above-mentioned family members contracted COVID-19. The earliest onset of disease occurred on Jan 23rd and included FB1 and her mother (FB1m) and father (FB1f), and the latest was FB4 on Feb 3rd. Meanwhile, PCR assays were performed frequently after the index case and all family members became PCR positive between the period Jan 28th and Feb 2nd. Importantly, FB1 had been sick for 10 days before she was tested positive for SARS-CoV-2. On the other hand, FB4 (father-in-law) was first tested positive by PCR (Jan 30th) before he became sick on Feb 3rd, indicating virus shedding long before the onset of disease. FB4 PCR turned negative Feb 26. From the incubation of the index case to becoming PCR negative, there was a period of just over one month. As of Feb 28th, four of the family members were still hospitalized.

Family C. Family C had 3 generations living together. The index case FC1 (husband) had a meeting in Wuhan: he arrived on Jan 14th 2020 and came back to Beijing on Jan 16th. He had cough and expectoration the next day (Jan 17th), fever on Jan 22nd, and abnormality on his chest CT scan on Jan 27th. He had positive PCR results on Jan 29th when he clinically deteriorated and required critical care. FC2 and FC3 are parent-in-laws of FC1, who visited their home on Jan 19th, and later developed symptoms on Jan 27th and 23rd, respectively; however, they were both PCR confirmed only on Jan 31st. Similarly, the children (FC5 and FC6), who stayed with FC1 the whole time, developed symptoms on Jan 22nd, and were PCR confirmed on Feb 2nd. The wife (FC4), who stayed with her husband and daughters in the same bedroom, developed symptoms last, on Jan 29th and was PCR positive on Feb 3rd. She was still in hospital as of Feb

28th. In this family cluster, PCR results all became positive much later than the initial onset of disease symptoms. Furthermore, all family members had CT scans, but only the adults showed abnormalities.

Family D. Family D is a small family with three members. The father (FD1) drove to Wuhan on Jan 19th 2020, and stayed in his brother's home, who later was also diagnosed with COVID-19. FD1 returned to his family on Jan 21st, became sick on Jan 25th, and was tested PCR positive for SARS-CoV-2 on Jan 31st. The same day, his wife (FD2) was admitted to hospital for observation only, but she never developed any symptoms other than an occasional cough and remained PCR negative the whole time. On the other hand, their daughter ((FD3) became ill on Feb 1st, and was PCR positive two days later. The child was released on Feb 14th, but returned again to hospital on Mar 4th because of the PCR test became positive again. Nevertheless, no symptom was observed.

All families except Family B had an index case who was exposed in Wuhan. Family B didn't have the direct exposure in Wuhan, but index case had a meeting with an individual who had come from Wuhan to Beijing. The index cases in the other three families were diagnosed as the 1st generation contact with the disease, while the other family members were diagnosed as the 2nd generation cases. The FB index case were the 2nd generation, and the FB family members were diagnosed as the 3rd generation.

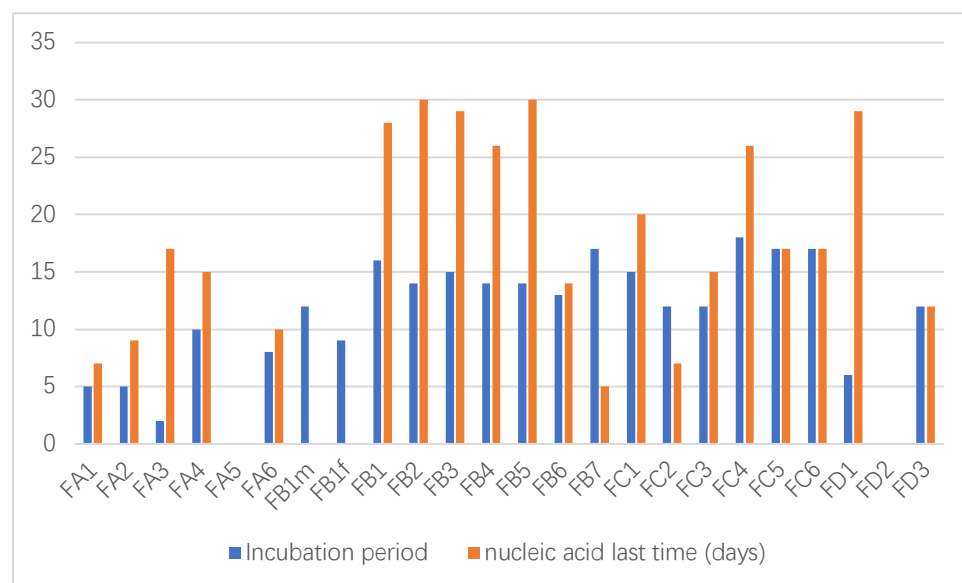


Figure 2 The duration of incubation period (blue bar), PCR positive days (orange bar), and an addition of two (grey bar). Latent period is from the contact to the index case to the PCR positive or symptom onset days

From our study of these four families it is obvious that the latent period from the contact with the index case to viral detection or symptom onset was highly variable, ranging from 2 to 17 days. Similarly, the shedding of virus in upper respiratory tract (i.e. viral nucleic acid detected in throat swabs) was also variable; it ranged from 5 days to over 30 days (figure 2). There were 8 cases who remained PCR positive for over 3 weeks, including 5 cases in the family B, 2 cases in Family C and 1 case in Family D, regardless

of symptoms. The virus shedding from the upper respiratory tract usually followed the onset of symptoms, but in some cases preceded any symptoms. Before we report this paper, the FD3 became positive again on 4th mar without any symptoms.

3.2 Clinical characteristics and laboratory assessment

Case FA2 had no clinical symptoms, but her PCR was positive. She also had a chest CT scan that showed bilateral infiltration (figure 3A1, A2). Case FA3, was PCR positive just 2 days after exposure to the index case FA1. She had no fever or cough, and only felt slight fatigue 4 days later. This symptom lasted a few days. All the patients had mild symptoms except case FB5 and case FC1 who developed more severe symptoms. Indeed, the CT scans of FB5 and FC1 showed progressive interstitial infiltrates and confluent consolidation. (figure 3B1, B2)

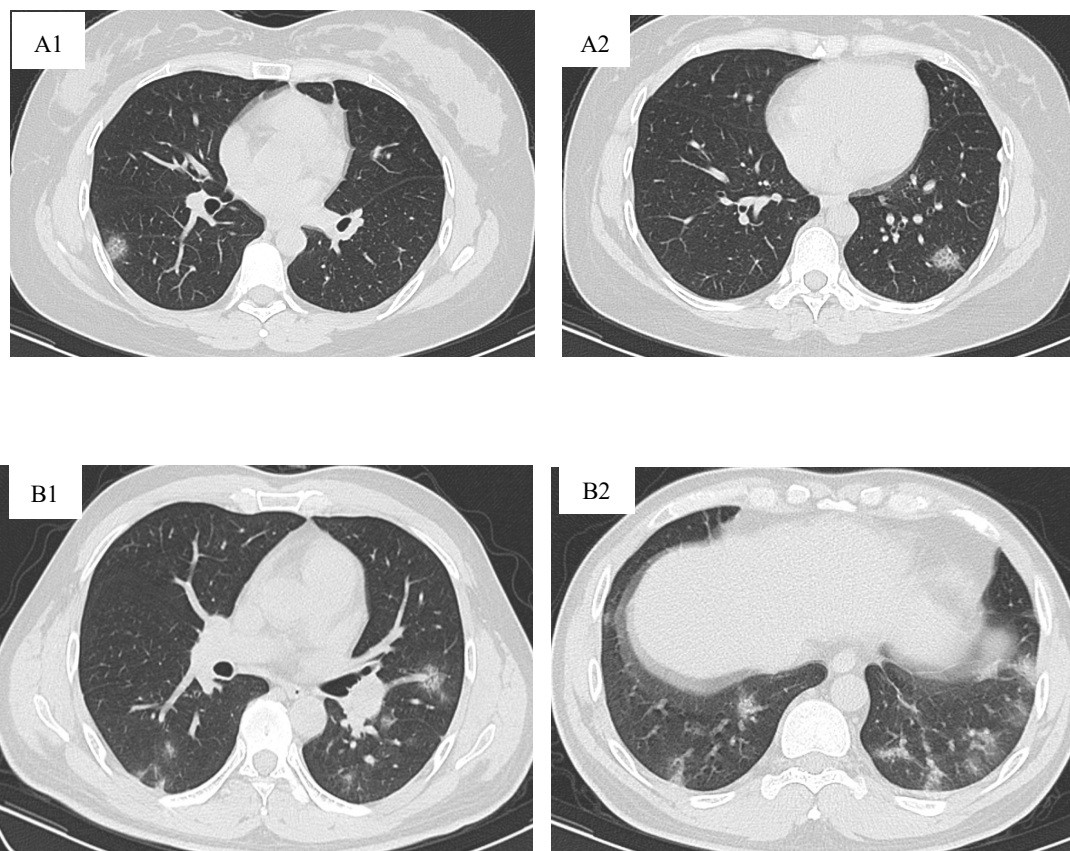


Figure 3(A, B). The Chest CT images of FA2 and FB5

(A1, A2): Chest CT image of FA2 showing bilateral ground glass changes.

(B1, B2): Chest CT image of FB5 showing ground glass changes and some consolidation in both lungs.

There were 13 cases with fever at presentation but none of them developed after hospitalization. Some of these had radiologic abnormalities, but none of them had ARDS. Most of the clinical test results were normal except one patient had lymphocytes below the normal.(table 2).

Table 2 Laboratory findings

Variable	normal value	Children (Media) (n=6)	Adults (Media) (n=9)
Laboratory findings			
WBC:10 ⁹ /L	4-10	6.685 (4.76-10.48)	4.96 (3.36-10.55)
NE: 10 ⁹ /L	2-8	1.945 (1.2-3.03)	2.69 (2.30-7.57)

LY: 10 ⁹ /L	1-5	4.53 (2.68-6.59)	1.24 (0.90-3.06)
HGB: g/L	120-160	130 (106-145)	137 (129-150)
PLT: 10 ⁹ /L	100-300	312.5 (223-406.1)	181 (94-276)
CRP: mg/L	0-5	1 (0.4-6.5)	19.65 (3.4-39.6)
ALT: U/L	15-40	13 (12-14.5)	20.5 (10.8-36)
CREA: umol/L	57-97	29.55 (14-37.1)	61 (49.9-301)
CK: U/L	50-310	92.5 (67.2-131)	86.05 (61-301)
ALB: g/L	40-55	50 (40.1-51.1)	46 (41.2-47)
LDH: U/L	120-250	262.5 (227-298.9)	193.3 (192-236.3)
PT: s	9.4-12.5	10.8 (10.5-12.3)	11.75 (10-14.4)
APTT: s	25.1-36.5	36 (34.8-42.9)	35 (26.8-59.6)
TT: s	10.3-16.6	18 (16-20.7)	16.25 (14-17.2)
FIB: ug/ml	200-400	204 (183-386)	216.5 (178-453)

Most of the children were asymptomatic or only mildly symptomatic. Only 2 of them had a fever. Two of the adults were mild to moderate in terms of symptoms. Most had fever, cough and radiographic changes in the lungs. However, all patients, including the oldest lady (84 years old) who had several co-morbidities, recovered in the end. Those who were still in the hospital because of the PCR positive, had no symptoms at all. Their examinations were within normal range. All of the patients received basic supportive care, along with some anti-viral medication according to local guidelines [3].

4. Discussion

This study documents how COVID-19 spreads within families and suggests adults are more likely to be symptomatic compared to children[8]. Eight children were included in this study. The youngest was aged 9-months and the oldest was ten years old. The symptoms of the disease varied from asymptomatic to mild. One child didn't have symptoms and the nuclear acid test for SARS-CoV-2 virus remained negative. Previous studies showed that children appeared to have milder infections than adults[9]. All the children with positive RT-PCR results became negative between 5-17 days). For the adults, the PCR remained positive much longer, some for over 28 days. In addition, we have shown that viral shedding can precede the onset of symptoms, suggesting the patient could carry the virus for over 40 days in some cases (i.e FB family members) which may contribute to the spread of this virus. Other interesting observation is, there are seems to be different in latent and viral shedding period between family clusters, suggesting the potential difference in virulence of the infecting virus as suggested that original virus (S type) has evolved outside of Wuhan and some with reduced virulence (L type) (REF) which merits further investigation.

The index case had no exposure to the Huanan Seafood Market. Not all family members had a cough so it is possible that much of the transmission was via saliva. Kelvin [10] et al. have detected and cultured the COVID-19 in saliva. Our data indicate close contact (e.g., sleeping in the same room as an index patient) and even casual contact or simple proximity (e.g., eating in the same room as an index patient), increases the risk for transmission. This transmission route seems similar to the MERS [11], but more effective. As with MERS-CoV infection control, some authors advise stringent control standards to minimize the emergence of new generations of virus[12].

We can see that some cases examined nucleic acid positive for prolonged periods. This, plus the recognition of subclinical infection, decreases the probability of fully controlling the outbreaks as both sorts of individuals are probably important sources of infection. It might be necessary to ensure a patient has a negative PCR results before stopping isolation measures. The latent patient should be traced. They are the main infectious sources.

Our study had several limitations. First, the small sample size did not enable multivariable risk factor analysis and collinearity could not be evaluated. Second, we need more virologic and serologic testing to evaluate the possible risk factors for the COVID-19. Thirdly, specimens were not available for detailed sequencing analysis, which might help us to clarify the transmission chains within the families.

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