Transmissibility of SARS-CoV-2 during incubation period: Epidemiologic evidence from 178 confirmed clusters in China

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Abstract

An outbreak of novel coronavirus (SARS-CoV-2) was identified in China in December 2019, and has spread rapidly to more than 200 countries and areas in four months. A few studies have reported that transmissibility exists during the late incubation period based on one single infection cluster caused by SARS-CoV-2. Here based on 178 SARS-CoV-2 clusters confirmed in Zhejiang Province, we analyzed the epidemic link between all 212 secondary cases with their previous cases, and found 49 secondary cases (from 26 clusters), which were 23.11% (49/212) of the total secondary cases infected from previous cases during the latter's incubation period. The median days from the last exposure of secondary cases to the onset of previous cases was 2.0 days (IQR: 1.00~5.00 days, 90th percentile: 9.00 days) .This study has shown transmission of the SARS-CoV-2 during the incubation period and indicated that some cases might be infectious soon after they were exposed to a prior transmitter. The results highlight the importance of extending the contact group for medical observation and isolation to those in contact with the index case nine (90th percentile) or more days before the latter's illness onset, when medical resources were sufficient.

Introduction

In December 2019, an outbreak of unexplained pneumonia developed in Wuhan, China and Chinese scientists confirmed that this was caused by a novel coronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV-2), on January 7, 2020 [1-7]. Although the majority of cases (55%) with onset before January 1, 2020 were associated with the Huanan Seafood Wholesale Market, more evidence indicates that human-to-human transmission of SARS-CoV-2 is occurring [8-11]. As of Apr 22, 2020, a total of 2 475 723 confirmed cases have been reported, of which 84 288 confirmed cases were identified in China [12].

Estimation of transmissibility during the incubation period of SARS-CoV-2 infection is crucial for understanding the mechanisms of transmission and for control measure recommendations [4,8,13]. However, there are limited data on this issue. Germany reported a case of SARS-CoV-2 infection acquired outside of Asia in which transmission appears to have occurred during the incubation period in the index patient based on one SARS-CoV-2 cluster [8].

We conducted epidemiological analysis based on 178 clusters with SARS-CoV-2 in Zhejiang Province, one of the severely affected locations, where 800 000 persons returned from Hubei Province. We aimed to collect detailed exposure history data and to provide a more accurate estimate of the transmissibility during the incubation period for SARS-CoV-2.

Methods

Sources of data

According to the Chinese Notifiable Infectious Diseases Surveillance System, COVID-19 was classified as a class-B infectious disease, with class-A management since January 20, 2020. It is mandatory that any medical staff or health facility report to the National Public Health Emergency Reporting System within two hours when any clustered COVID-19 is identified. The local Centers for Diseases Control and Prevention (CDCs) initiate detailed field investigations within 24 hours. Local health workers interview the confirmed case(s) and/or their relatives to determine the exposure history two weeks before onset, basic information, onset date and confirmed date, as well as contacts. All available medical records are provided by local clinical healthcare workers. This study extracted cluster data from the National Public Health Emergency Reporting System between 20th January and 11th February 2020.

Case definitions

In accordance with the Chinese guidelines for the diagnosis and treatment of humans infected with SARS-CoV-2 (5th edition), a laboratory-confirmed case with SARS-CoV-2 was defined as either detection of two targets (open reading frame 1a or 1b, nucleocapsid protein) tested positive by real time reverse-transcription-polymerase chain-reaction (RT-PCR) assay or a genetic sequence that matches SARS-CoV-2 [14].

A cluster was defined as a group of one or more confirmed cases of SARS-CoV-2 infection and additional confirmed or asymptomatic cases associated with a specific setting, such as a classroom, workplace, household, extended family, hospital, or other residential institution, or with onset of cases occurring within 14 days by person-to-person transmission, or co-exposure to a contaminated environment.

Incubation period of patients was defined as days from last exposure to confirmed cases or a contaminated environment to onset of symptoms.

Days from the exposure of secondary cases to the onset of index cases were defined as days from the last exposure of secondary cases from index cases to the onset of the latter.

Specimen Collection and Diagnostic Testing

Clinical specimens for SARS-CoV-2 diagnostic testing were obtained in accordance with Chinese guidelines [15]. Throat swab specimens and sputum were collected with synthetic fiber swabs; each swab was inserted into a separate sterile tube containing 2 to 3 ml of viral transport medium. Specimens were stored between 2°C and 8°C until ready for shipment to the Zhejiang CDC. Clinical specimens were tested with an rRT-PCR assay that was provided by China CDC.

Statistical analysis

Analyses of the incubation period and serial interval were performed with the use of SPSS (version 16.0) and R software (R Foundation for Statistical Computing). We present continuous measurements as mean±SD if they are normally distributed or median (IQR) if they are not, and categorical variables as count (%).

Ethics Approval

The study was approved by the Zhejiang Provincial Health Commission of China to be part of a continuing public health outbreak investigation. All initial information identifying patients was anonymized in this study, thus we applied ethics exemption, which was supported by Zhejiang Provincial Corona Virus Disease 2019 Ethics Committee (approval number 2020-005).

Results

A total of 178 clusters were collected between 20th January and 11th February 2020 in Zhejiang province, China. These clusters were classified as follows: family clusters (158, 88.76%), workplace clusters (5, 2.80%), entertainment place clusters (3, 1.69%), clusters because of religious gathering (2, 1.12%), flight cluster (1, 0.56%), banquet clusters (2, 1.12%) and others (7, 3.93%). The 178 clusters covered a total of 543 confirmed cases, including 331 first-generation and 212 secondary cases. Among 331 first-generation cases, 221 (66.77%) cases were citizens ever lived (181, 54.68%) or travelled (40, 12.08%) to Wuhan or its neighbouring regions like Xiaogan city in Hubei province within 14 days before onset; 58 (17.52%) cases had ever contacted confirmed people came from epidemic regions in Hubei province and 17 (5.14%) cases ever contacted confirmed cases from other provinces of China expect Hubei when they were travelling outside Zhejiang within 14 days before onset; 21 (6.34%) cases had unclear source of infection, and the last 14 (4.23%) cases' epidemic information was insufficient to infer their source of infection.

After examining the epidemic link between 212 secondary cases with their previous cases, we extracted the data from 49 secondary cases with clear epidemic link with their previous cases within 26 clusters; all 49 cases were exposed to a previous generation of patients during the latter's incubation period. These cases accounted for 23.11% (49/212) of the total secondary cases. There were 22 males and 27 females. The average age of the patients was 50.70 years (SD 15.78) (Table 1). According to available information of 47 of these secondary cases, we found the median incubation period was 5.00 (IQR: 3.00-7.00) days, and 82.98% of patients had incubation shorter than 7 days (Table 1).

Table 1. Demographic characteristics and incubation period of COVID-19 cases infected during incubation period of previous cases between 20 January and 11 February 2020.

Characteristic	Number of cases	
	(N=49)	%
Average age*(SD, range)-yr	50.70(15.78,7-96)	
<15 yr	1	2.17
15-44 yr	14	30.43
45-64 yr	23	50.00
>=65 yr	8	17.39
Male sex	22	44.90
Incubation period – days		
<3 days	8	17.02
3-7 days	31	65.96
8-13 days	8	17.02

*Age was not available for three cases, which were not included in the mean calculation for total cases.

The median days from the last exposure of secondary cases to the onset of their previous generation of cases were -2.00 days (IQR: -1.00~-5.00 days), ranging from -0.00 to -12.00 days, with a 90th percentile of -9.00 days. This lag was more than -10 days among 8.16% (4/49) of the secondary cases (Figure 1).

We selected six index and seven secondary cases with clear exposure date and illness onset date from six of the 26 above clusters. For index cases, their median incubation period was 4.00 (range: 2.00 ~ 8.00 days) days, while the median days between the last exposure of the index case and the last exposure of the secondary case was 1.00 day. In further investigation of the exposure history, two of the secondary cases (case 3 and case 7 in Figure 2) lived together with their index cases during the incubation period, and the other five secondary cases had continued exposure to their index cases at least half a day with eating, chatting or shopping together.

Cluster 5 and cluster 6, with clear transmission chains, were further examined to analyze the epidemic links. The index case in cluster 5 had lived in Wuhan and came back to Zhejiang on January 15. She fell ill on January 19, and was confirmed by RT-PCR on January 24. On January 16 and 18, her sister (patient 1 in cluster 5) came to visit her home. They ate and shopped together on both days. Patient 1 went back to her own home in the afternoon of January 18, began to feel ill on January 20, and was confirmed by PCR on January 26. On January 19, a banquet was held at patient 3's home. Patient 1 (patient 3's aunt) and patient 2 (patient 3's brother in law) came to visit. They ate and chatted together till nighttime. Both patient 2 and patient 3 in cluster 4 became ill on January 22, and were confirmed on January 26. For details, see Figure 2.

The index case in cluster 6 had lived in Wuhan and came back to Zhejiang on January 20. Her illness onset occurred on January 21 and was confirmed by RT-PCR on January 27. In the nights of January 22 and January 23, her friend (patient 1 in cluster 6) came to visit. They played cards together till the next morning on both nights. On January 28, patient 1 in cluster 6 was isolated as a close contact of the index patient, and fell ill on January 30 (confirmed on January 31). On January 23, patient 1's daughter (patient 2 in cluster 6) came back home from school because of winter vacation. During January 23-28, they lived together, till her mother was isolated. She also fell ill on January 30, and was confirmed on January 31 (Figure 2).

Discussion

There is a substantial amount of uncertainty regarding the infections during the incubation period for SARS-CoV-2. This study conducted an in-depth, epidemiological investigation for 26 confirmed clusters involved in 49 cases in the Zhejiang Province outbreak and obtained a more detailed and accurate estimate of the infections during the incubation period. This suggests that transmission exist during asymptomatic incubation period, and some cases might become infectious soon after they were exposed to a prior transmitter.

Zeng G and his colleges have reported that SARS cases are only infectious during their symptomatic period and are non-infectious during the incubation period [16]. By contrast, our study suggests that 49 secondary confirmed cases (23.11%) have been exposed to index cases during the latter's incubation period. The median days from the last exposure of secondary cases to the onset of previous cases was 2.0 days (IQR: 1.00~5.00days, 90th percentile: 9.00 days). This raises the important suggestion that the isolation for individuals who have been in close contact with SARS-CoV-2 patients should be expanded to include contacts from at least two days before the index case's symptom onset. The early diagnosis and isolation of the potential cases will decrease the transmission of SARS-CoV-2, and control the size of SARS-CoV-2 clusters. This is consistent with the measures recommended by the WHO on February 2020, who recommended individuals who had contact with patients four days before the latter's symptom onset should be isolated. However, when medical resources were sufficient, expansion to nine days before onset is necessary to isolate 90% of potentially infected persons.

We further analyzed the six clusters and covered six index cases and seven secondary cases with a clear exposure history. The secondary cases received infection from the index cases 1.00 day after the index cases were exposed to a prior transmitter. The median incubation period of the index cases was 4.00 (range: 2 ~ 8 days) days. This indicates that some cases with short incubation period might become infectious soon after they were exposed, which highlights the importance of early isolation of contact group. The short time interval between the exposure of two generations of cases greatly increased the difficulty of COVID-19 prevention and control. Another example came from three third-generation cases involved in two clusters above, who became ill after contact with the primary case patient's contacts (the secondary cases). Our results are consistent with other reports [9,17,18]. This is proof indicating the infectivity of COVID-19 cases during the incubation period on one hand, and on the other hand, suggests measures which should be taken to control COVID-19, namely that the second-level close contacts should also be paid attention. We suggest that close contacts should be centrally isolated and the second-level close contacts should be isolated in their own home for 14 days. Once close contacts have illness onset, the second-level close contacts should be centrally isolated, and their contacts should in turn be home-isolated, and so on. Moreover, samples of close contacts could be collected and tested for SARS-CoV-2 to identify positive carriers or patients in their incubation period.

The age and sex distribution of the study population (46 secondary cases in table 1) seemed to be different from those reports from the whole China [4]. More cases in people 45-64 years old, and more female cases were found in this study. It might be attributed to small sample size on one hand, on the other hand, most first-generation cases in this study were citizens coming back from Wuhan, Hubei province, among whom most were labor output (mainly young or mid-aged men). When they came back home because of the Spring Festival, their wives and parents might be the most persons they met and infected. In this study, days from the last exposure of secondary cases to the onset of index cases were calculated, which has been a conservative estimate for the time interval between infection of secondary cases and the previous cases' illness onset.

In conclusion, our findings suggest that transmission exist during asymptomatic incubation period, and some cases might become infectious soon (one day) after they were exposed to a prior transmitter. This highlights the necessity for public health authorities to isolate contact group early and extend the period of medical surveillance from contacts after the onset of an index patient's illness to those during the latter's incubation period. Our results contribute to a better understanding of novel COVID-19 infection and provide important information that will aid in the surveillance and control of this emerging infectious disease with high person-to-person transmission.

Declarations

Acknowledgement

Author contributions

Competing interests

The author(s) declare no competing interests.

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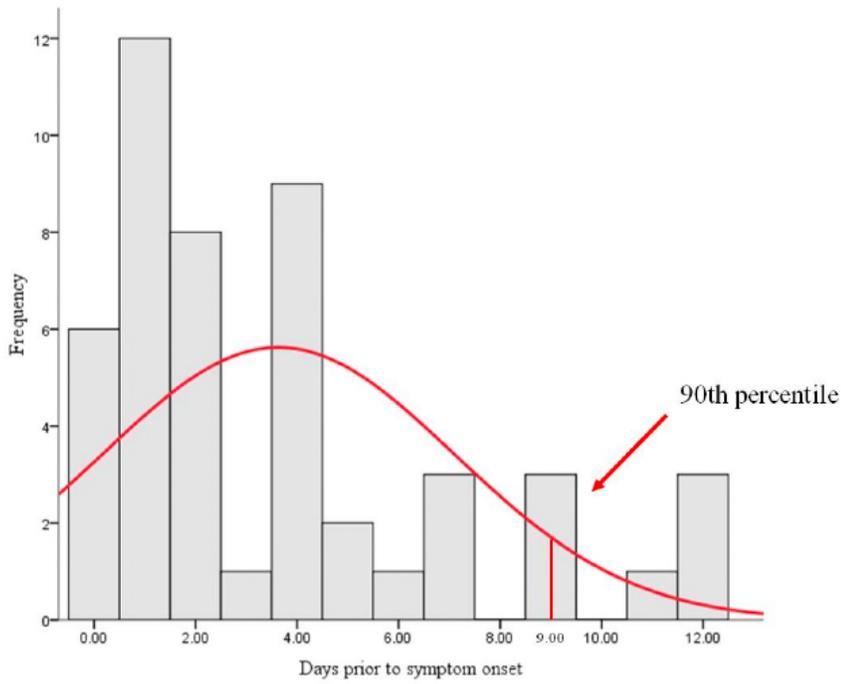
Figures

Figure 1

Infectivity of incubation period in COVID-19 cases (days prior to symptom onset of previous-generation cases)

Figure 2

Timeline of infection of COVID-19 in incubation period in successive generation of cases and their onset of symptoms