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6 Article type : Short Article

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9 Pre-symptomatic transmission of novel coronavirus in community settings

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as [doi: 10.1111/IRV.12773](https://doi.org/10.1111/IRV.12773)

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36

37 **Funding**

38 This work was supported by the Shanghai Municipal Science and Technology
39 Commission (Epidemiological Study on COVID-19 in Shanghai, grant number
40 20411950100) and the Fudan University (Fudan University Research Project on
41 COVID-19 Emergency, grant number IDF201007).

42

43 **Acknowledgement**

44 We thank all the investigators at the Shanghai Municipal Center for Disease Control
45 and Prevention and all the District Centers for Disease Control and Prevention in
46 Shanghai for their contribution to the control and prevention of the COVID-19
47 epidemic. Furthermore, we thank all the cases of COVID-19 and their families for
48 their understanding and facilitation of our investigation.

49

50 **Potential conflicts of interest.** All authors: No reported conflicts of interest.

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54 **Abstract**

55 We used contact tracing to document how COVID-19 was transmitted across 5
56 generations involving 10 cases, starting with an individual who became ill on January
57 27. We calculated the incubation period of the cases as the interval between

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58 infection and development of symptoms. The median incubation period was 6.0 days
59 (interquartile range, 3.5 – 9.5 days). The last two generations were infected in public
60 places, 3 and 4 days prior to the onset of illness in their infectors. Both had certain
61 underlying conditions and comorbidity. Further identification of how individuals
62 transmit prior to being symptomatic will have important consequences.

63 **Keywords:** COVID-19; contact tracing; China; comorbidity

64
65 Novel coronavirus disease 2019 (COVID-19) was declared a pandemic on March 11,
66 2020.¹ Transmission chains have been difficult to identify in routine investigations.
67 Notable cases in Italy² and the US³ had no known source of infection. These cases
68 have raised the concern that there is transmission of the novel coronavirus
69 (SARS-CoV-2) in asymptomatic individuals (who never express symptoms) or in
70 pre-symptomatic individuals (prior to any symptoms).

71
72 Many public actions so far, including quarantine measures, body temperature
73 measurement, and fever symptom surveillance, have prioritized identification of
74 possible infected cases. However, these all depend on active expression of
75 symptoms and are not able to identify asymptomatic transmission or
76 pre-symptomatic transmission.⁴

77
78 Better understanding of transmission parameters, including the serial interval and
79 incubation period, can also help determine the possible progression of the outbreak.
80 The serial interval is defined as the interval between a primary case of COVID-19
81 developing symptoms and a secondary case developing symptoms, whereas the
82 incubation period is the timelag between infection and the start of symptoms. The
83 Chinese Center for Disease Control and Prevention (CDC) has estimated that the
84 mean serial interval for COVID-19 is 7.5 days, which is slightly longer than the
85 estimated incubation period of 5.2 days.⁵ However, the serial interval has varied in
86 other studies, such as a median of 4.6 days⁶, which is shorter than the incubation
87 period.

88

89 The challenge for controlling COVID-19 is to determine at what point an individual
90 becomes infectious, which can have implications for contact tracing and other
91 epidemiological investigations. In addition, one study in China showed that 12.1% of
92 transmission was likely to be pre-symptomatic.⁷ On February 24, 2020, the China
93 CDC revised the definition of the start date for close contact from “at the illness
94 onset of a confirmed case” to “2 days before the illness onset”⁸, as increased
95 evidence suggests pre-symptomatic transmission might be plausible.

96

97 Many previous studies of the transmission dynamics of COVID-19 have relied on
98 publicly available data or large surveillance datasets. It is difficult to discover
99 asymptomatic or pre-symptomatic cases in these datasets, and overall there is
100 limited information on how to determine when an individual becomes infectious.
101 This study describes a transmission chain of 5 generations involving 10 COVID-19
102 cases, and tracks whether infection occurred from asymptomatic or
103 pre-symptomatic individuals.

104

105 **Methods**

106 An index case (i.e., the last case) was first identified in our study who had no obvious
107 previous contact with a symptomatic case of COVID-19. For the index case we
108 identified 3 close contacts in the 14 days prior to disease onset, none of which had
109 COVID-19 at the time of contact. We worked backward to identify several
110 generations of transmission. We used contact tracing to identify possible people who
111 could have exposed the case. Close contacts were defined as people who live, study,
112 work, or otherwise have close contact with the case; medical personnel, family
113 members, or other people who have similarly had close contact with the case and
114 who did not take effective protective measures; other patients and their
115 accompanying staff in the same ward of the case; persons in the same vehicle as the
116 case and who had close contact with the case; and other persons who were deemed
117 close contacts by the field investigator.

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118

119 We retrospectively summarized the journey and visited places of the cases within 14
120 days before the illness onset in each generation. In this way, we identified possible
121 source cases and we worked backward to identify cases, which were
122 epidemiologically linked with each other, and which constituted a complete
123 transmission chain. Information about symptoms and date of illness onset was
124 provided directly by the cases. We acknowledge recall bias: cases may not have been
125 able to remember every contact they had.

126

127 All of the investigations were conducted by experienced investigators at Centers for
128 Disease Control and Prevention in the Shanghai Municipality and Zhejiang Province.
129 This study involved the use of existing, routinely-collected data from a public health
130 outbreak investigation, under the National Health Commission of the People's
131 Republic of China. Thus, this study is exempt from ethical review and informed
132 consent was not obtained.

133

134 **Results**

135 ***Initiation of investigation*** The index case was a 74-year old female who developed
136 symptoms on January 27. She lived alone and had very limited contact with foreign
137 people. She was found to have met with a 75-year old male, in a real estate trade
138 center for 3 hours on January 21, six days prior to the onset of her symptoms. The
139 male was recognized as an existing confirmed case (case 1) of COVID-19, who
140 developed symptoms only on January 25. Subsequently, case 2 was identified, who
141 was a friend of case 1 and had met him for 2.5 hours at a gym on January 19. Case 2
142 developed symptoms on January 22. The timeline of possible infection and illness
143 onset is illustrated in Figure 1.

144

145 ***Identification of two occasions of pre-symptomatic transmission*** We determined
146 the epidemiological linkages between index case, case 1, and case 2, after excluding
147 all of their close contacts who remained healthy throughout a 14-day medical

148 observation. It is noted that the infectees (index case and case 1) were possibly
149 infected with SARS-CoV-2 by infectors (case 1 and case 2) during the incubation
150 periods of the infectors (Figure 1).

151
152 To confirm the finding, we further checked if there was previous contact between
153 these cases. Cases 1 and 2 had not met for about one month, and did not meet after
154 January 19. Thus, the transmission was likely to occur on January 19 in the gym. The
155 index case and case 1 had also met on January 18. However, case 1 was not infected
156 on that day, and thus was likely to have occurred on January 21. Through an
157 examination of case 1 and 2's clinical symptoms, we inferred both transmitted
158 infection while pre-symptomatic.

159
160 **Source of transmission chain** We worked backward to further investigate the chain
161 of transmission. Case 2 and case 3 had not met before; however, they possibly
162 became infected by a common friend (case 4) at dinners on January 13 and 14.
163 Similarly, cases 4-7 became infected at dinners with a common friend (case 8).
164 During the dinners, case 8's daughter (case 9) could have been the common source
165 of infection, and she was infected by her co-worker who had traveled back from the
166 city of Wuhan, Hubei Province. Across these cases, we did not recognize any
167 evidence of pre-symptomatic transmission.

168
169 **Incubation period and serial interval** In this study, all the cases had an incubation
170 periods less than 14 days, with a median of 6.0 days (interquartile range, 3.5 – 9.5
171 days). Comparatively, we calculated the median serial interval to be 5.0 days
172 (interquartile range, 3.0 – 5.0 days). For the two instances of pre-symptomatic
173 transmission, the infectees' contact with the infectors occurred 3 or 4 days prior to
174 the infectors' illness onset, which suggests a shorter latent period than an incubation
175 period.

176
177 **Co-morbidities** To identify differences between pre-symptomatic transmission and

178 symptomatic transmission, we examined the health conditions of all cases. The index
179 case underwent a surgery for stomach cancer and had been receiving chemotherapy
180 for 1.5 years. Case 1 suffered from pneumonia and recovered late December 2019.
181 No other cases had underlying conditions and comorbidity.

182

183 **Discussion**

184 In this study, we traced the spread of coronavirus across five generations in
185 Shanghai, China, back to a case who had previously traveled to Wuhan, the original
186 source of the outbreak. The serial interval was estimated to be a little shorter than
187 the incubation period, and there were no known symptoms among suggested
188 possible pre-symptomatic transmission. However, two infector-infectee pairs with
189 pre-symptomatic transmission were identified out of 9 pairs. The index case and case
190 1 may have been more susceptible to pre-symptomatic infection due to their health
191 conditions, compared to other cases.

192

193 That the latent period may be shorter than the incubation period could affect
194 recommendations for contact tracing and case definitions. We found evidence of
195 pre-symptomatic transmission 3-4 days prior to the infectors' illness onset. Thus, we
196 suggest advancing the upper time limit of close contact to 4 days prior to illness
197 onset of a COVID-19 case, which is greater than the China CDC and WHO guidelines
198 of 2 days.^{8,9} We note that guidelines in Beijing use a time limit of 4 days as of May
199 18, 2020.¹⁰ One another study in China reported only 2-day lead time between
200 infectee's contact with the infector and infector's illness onset¹¹, and we have not
201 found any information that this could be longer. We recognize that increasing the
202 duration of a possible time of infection can add to the workload of routine
203 epidemiological investigations during the epidemic of COVID-19. Consequently, we
204 recommend it should be applied to cases with an unknown source of infection, such
205 as the index case in our study. Contact tracing guidelines should also rely on the
206 capacity of contact tracing and on updated information on when pre-symptomatic
207 transmission can occur. For example, a study of COVID-19 cases in Taiwan also

208 started investigations of COVID-19 up to 4 days before symptom onset, although this
209 was not consistently done.¹² Evidence from more chains of transmission can better
210 delineate the borderline between the latent period and infectious period.

211
212 Asymptomatic transmission has been documented among returned Japanese
213 citizens from China ¹³. However, it might be misunderstood due to short duration of
214 observation; that is to say, if we extend the duration of observation, we might
215 observe the occurrence of symptoms. Consequently, pre-symptomatic transmission
216 may be misunderstood as asymptomatic transmission. So far, asymptomatic
217 transmission and pre-symptomatic transmission have not been well documented
218 and further study of natural history of SARS-CoV-2 infection is urgently warranted.

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271

272 **Figure legends**

273 Figure 1. Timeline of contact and illness onset of novel coronavirus disease 2019
274 (COVID-19) cases in late January 2020. The persons involved in transmission venues
275 are listed, including four dinners (on January 9 and 10, January 13 and 14) and two
276 meetings in public places (on January 19 and 21). Not shown are additional close
277 contacts (with individuals who remained symptom-free after a 14-day quarantine): 3
278 for the index case, 1 for case 1, 1 for case 2, 11 for case 3, 12 for case 5, 1 for case 8,
279 and 1 for case 9.

Symbol	Meaning
●	1 st generation case
●	2 nd generation case
●	3 rd generation case
●	4 th generation case
⊗	Index case
●	Individual without symptoms

Day of symptom onset	Date	Day of exposure
9	January 8	
	January 9	9 8 7 6 5 4 ● ● ● ● ● ●
	January 10	
	January 11	
8	January 12	
6 4	January 13	4 3 2 ● ● ● ● ● ●
	January 14	
	January 15	
3	January 16	
	January 17	
	January 18	
5	January 18	2 1
	January 20	
	January 21	1 ⊗
2	January 22	
7	January 23	
	January 24	
1	January 25	
	January 28	
⊗	January 29	

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