



Assessment of Pre-symptomatic transmission of COVID-19

Questions for NERVTAG:

1. Does NERVTAG consider that there is sufficient evidence for transmission from a laboratory confirmed index case of COVID-19 to others, during the pre-symptomatic period?
2. If NERVTAG does consider there be to sufficient evidence for pre-symptomatic transmission:
 - a. what is NERVTAG's opinion in relation to how significant pre-symptomatic transmission to others is, compared to transmission during the symptomatic period
 - b. should contact tracing include the pre-symptomatic period and if so, what time period prior to the development of symptoms should be used for contact tracing?

Background

In this document, the term “pre-symptomatic transmission” refers to transmission from a laboratory confirmed COVID-19 case to others in the time before an individual becomes symptomatic. For clarity, this is different to the use of the term “asymptomatic transmission” which refers to any suggestion of onward transmission from laboratory confirmed cases who do not appear to develop symptoms. This is outside the scope of this paper.

The assessment of these risks is informed by reports of laboratory confirmed detections of SARS-CoV2 in individuals in the absence of symptoms with associated descriptions of putative transmissions to others. Most reports have been identified from individual cluster and outbreak reports in publications or pre-prints.

Approach

Identified cluster and outbreak reports were assessed according to the criteria below:

- **Temporal relationship:** does the timing of the exposure and onset of symptoms in the cases support the conclusion that transmission has occurred?
- **Route of exposure:** is there a feasible route of exposure?
- **Evidence of infection:** How strong is the laboratory evidence to support the conclusion that transmission occurred?
- **Exclusion of alternative sources:** Have other potential sources been considered/addressed?

Description of reports

1. Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ. Presymptomatic Transmission of SARS-CoV-2 — Singapore, January 23–March 16, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:411–415.

Temporal relationship: This report describes seven clusters of what is described as “suggesting pre-symptomatic transmission”. For one cluster, the route of exposure between one index case and secondary case pair was not contemporaneous suggesting the possibility of fomite transmission; this individual had onset of symptoms 15 days after the exposure. For four of the transmission pairs published in this report, the interval between onset in the index and secondary cases was zero days; of these, three were in household settings. When household exposures are excluded, the pre-symptomatic exposure period ranges between 1 and 5 days (median 3 days), although this includes an overlapping exposure from 2 cases.

Route of exposure: The reported transmission settings included 1 singing class, 2 churches, 3 household settings and 1 daytime meeting

Evidence of infection: For each of the clusters, the index and secondary cases were laboratory confirmed but direct communication with Singapore determined there was insufficient sequencing information available to support review of the transmission events.

Exclusion of alternative sources: Possibility of unknown source acknowledged.

2. **Preprint:** Böhmer M et al. Outbreak of COVID-19 in Germany resulting from a single travel-associated primary case

This preprint appears to be a more comprehensive investigation of the German cluster described by Rothe et al in the *New England Journal of Medicine*. This later paper identified one transmission in the pre-symptomatic period.

Temporal relationship: The transmission occurred two days prior to onset in the index case. The exposure involved both individuals sitting back to back in a canteen, with the secondary case borrowing a salt shaker from the table of case 4.

Route of exposure: Sitting in close proximity and potential fomite spread.

Evidence of infection: A nonsynonymous nucleotide substitution (G6446A) was found in virus from both these individuals but not in earlier cases. Later cases with this substitution traced back to the secondary case in this pair.

Exclusion of alternative sources: Other contact between the two individuals denied. Sequencing information as above.

3. Li P, Fu JB, Li KF, et al. Transmission of COVID-19 in the terminal stage of incubation period: a familial cluster [published online ahead of print, 2020 Mar 16]. *Int J Infect Dis.* 2020;S1201-9712(20)30146-6. doi:10.1016/j.ijid.2020.03.027

This article profiles a case from Zhoushan who had travelled between Hunan province, Wuxi City and Zhoushan, tested positive through contact tracing on 6th February and developed symptoms on 7th February 2020. There were four secondary cases highlighted by the authors, who had household-level contact with the case between the 31st January 2020 and 3rd February 2020. Of these 4, one remained asymptomatic, another was asymptomatic but developed changes on chest CT and the remaining two had a cough and chest CT changes.

Temporal relationship: The transmission is considered by the authors to have occurred between 4 and 7 days before onset of symptoms in the case. The onset date of symptoms in the two symptomatic contacts is unclear from this publication.

Route of exposure: Household-level exposure.

Evidence of infection: Laboratory confirmed but no sequencing information available

Exclusion of alternative sources: Not specifically addressed

4. Tong Z, Tang A, Li K, Li P, Wang H, Yi J, et al. Potential Presymptomatic Transmission of SARS-CoV-2, Zhejiang Province, China, 2020. *Emerg Infect Dis.* 2020;26(5):1052-1054.

This article describes an individual who was reportedly laboratory confirmed as a case, outside the jurisdiction of the authors but travelled from Wuhan to attend a conference. The individual attended a dinner with two others, 2 days before the index case developed symptoms.

The 2 other individuals then developed symptoms 4 and 6 days, respectively, after the dinner and due to delays in presentation and recognition of the risk of SARS-CoV2 infection, were eventually laboratory confirmed 13 days after their exposure.

Temporal relationship: The onset of symptoms was occurred within a timeframe compatible with what is known about COVID-19 infection.

However, the diagnosis was delayed in both these contacts so there remains a possibility that another unidentified exposure could have caused this infection.

Route of exposure: The authors report that the index case and secondary cases shared a dinner and served dinner from common serving plates. There is not specific information about distances between individuals, so an assumption based on serving from the same plate is that this was close contact.

Evidence of infection: The authors report laboratory confirmed infection in the secondary cases and some of their household contacts but the infection in the index case was based on the individual's own report and this is specifically acknowledged in the article.

Exclusion of alternative sources: The index case travelled from Wuhan for the purpose of a conference and the authors acknowledge that they cannot exclude another source of infection from the conference which was organised by the employer of the 2 secondary cases. The delay in diagnosis of the secondary cases and their mild symptoms prior to diagnosis, raises the possibility of alternative source of infection.

5. Huang L, Zhang X, Zhang X, et al. Rapid asymptomatic transmission of COVID-19 during the incubation period demonstrating strong infectivity in a cluster of youngsters aged 16-23 years outside Wuhan and characteristics of young patients with COVID-19: A prospective contact-tracing study [published online ahead of print, 2020 Apr 10]. *J Infect.* 2020;S0163-4453(20)30117-1. doi:10.1016/j.jinf.2020.03.006

This paper reports an individual who travelled from Wuhan to Hefei on January 19th 2020, four days prior to the restrictions placed on the former. This individual developed symptoms initially on 22nd January 2020, and was laboratory confirmed as a case on 23rd January 2020.

Temporal relationship: Among the individual's contacts, there were 7 who later became laboratory confirmed cases. One of these was a relative who had exposure to the case in his pre-symptomatic and symptomatic periods and developed symptoms 7 and 3 days later respectively. These secondary cases represented 40% of the contacts of the index case.

The remaining six contacts who became cases and had exposure to the index during his pre-symptomatic period, developed symptoms between 1 and 4 days after exposure. Two of the cases reported symptoms on the same day as the index case.

Route of exposure: Apart from the relative who had discrete close contacts with the index case when the latter was pre-symptomatic and also symptomatic, the remaining secondary contacts were exposed to the index case in social settings including sharing meals with others and spending time in a Karaoke room for 2.5 hours.

Evidence of infection: All the cases were laboratory confirmed but no sequencing information as apparent.

Exclusion of alternative sources: History of travel to Wuhan was also excluded from the secondary cases as was attendance at live markets. However, it is unclear if other potential sources were excluded.

Comment

A common limitation of many of the papers is that these tend not to exclude alternative sources of infection such as other cases in the local community; in the case of mainland China, these papers tend to assume that there has not been any spread outside of Wuhan.

In addition, the temporal relationships between index cases and secondary cases have demonstrated that onset dates of the latter have been reported to have occurred prior to, or at the same time, as onset in the index cases.

The Singaporean report indicated that the pre-symptomatic transmissions they had profiled accounted for 6.4% (10/157) of locally acquired infections during the period of study (up to 16th March 2020).

In the German investigation, sixteen cases were identified following the initial index case who travelled from mainland China. However, only one of these cases was proposed by the authors to have been infected during pre-symptomatic transmission; the other transmission events were considered to have occurred on the day of symptom onset or during the prodromal phase.