

## APPENDIX

### Asymptomatic transmission SARS-COV-2

#### ***“What is the current evidence on asymptomatic transmission of COVID-19?” (Asymptomatic transmission and tracing of close contacts 48h before onset of symptoms)***

2020-03-24

1. As pointed out by medical advisors, transmissibility of viral infections 24-48 hours prior to the development of symptoms is common in viral infections, although transmission is most likely to occur after symptoms develop.
2. Both WHO and Chinese guidelines for case ascertainment, particularly during the period of identifying the first few cases assume asymptomatic transmission can occur up to 4 days before symptoms (China CDC, 2020; WHO, 2020).
3. The viral load in symptomatic, mild symptoms and asymptomatic cases was similar in study of a cluster of cases (Zou et al., 2020) and high in an asymptomatic healthy infant (Kam et al., 2020). This suggests the transmission potential of asymptomatic or minimally symptomatic patients is similar to those that are clinical.
4. The studies listed in Table 1 describe the evidence (mainly epi tracing) of SARS-COV-2 asymptomatic transmission occurring. A few of these studies have provided the likely timing of transmission relative to symptoms occurring in the **last 3 days of incubation**, but possibly up to 8 days.

*Table 1: List of studies that describe evidence of asymptomatic transmission occurring. Where reported the timing of asymptomatic transmission prior to clinical symptom onset is reported.*

REFERENCE	DESCRIPTION	LIKELY TIMING OF ASYMPTOMATIC TRANSMISSION
(XIA ET AL., 2020) <b>(GOOD PAPER)</b>	<p>This study describes 50 cluster investigations that include 124 cases where the secondary case contact with the first generation case occurred before symptom onset. The infectious curve showed that in 73.0% of the secondary cases, their date of getting infected was before symptom onset of the first-generation cases, particularly in the last three days of the incubation period.</p> <ul style="list-style-type: none"><li>• Mean (SD) incubation period 4.9 days (95% CI, 4.4 to 5.4 days, range: 0.8 to 11.1 days (2.5th to 97.5th percentile).</li><li>• Mean (SD) serial interval 4.1±3.3 days, 2.5th and 97.5th percentiles at -1 and 13 days.</li></ul>	The last 3 days of incubation
(ROTHER ET AL., 2020)	The cluster from Germany provided evidence that transmission before the development of symptoms is	

	possible. The index case had symptoms prior to meeting contacts 1 and 2. However, contacts 3 and 4 only had contact with contact 1 and 2 (the people who met with the index case) prior to symptom development	
(YU, ZHU, ZHANG, HAN, & HUANG, 2020)	Shanghai family cluster – 4 cases, Case 1 had not left his apartment within the 2 weeks before hospitalization and was only exposed to case 2 and 3 before the onset of anyone’s symptoms. Case 2 and 3 were from Wuhan and visited Case 1 and 4 from Jan 15 (no high risk exposures noted in Wuhan for case 2,3). Case 1 and 2 were admitted to hospital Jan 21, 3 and 4 Jan 23. All cases were RT-PCR positive by nasopharyngeal and throat swab.	NR
(BAI ET AL., 2020)	Family cluster (Anyang, China) patient 1 was asymptomatic and lived in Wuhan. Her first RT-PCR was negative and second positive, incubation period reported as 19 days. Patient 2-6 were relatives of patient 1 that she visited and they all developed COVID-19 including a hospitalized relative in a hospital where no COVID-19 had been diagnosed yet. There were no other plausible exposures. Exposure Jan 10-13 with relatives showing symptoms Jan17-26.	NR
(HU ET AL., 2020)	This study identified 24 asymptomatic infections (nucleic acid confirmed) identified via close contact screening in Nanjing, China Jan 28-Feb 9. The median communicable period (1st day test positive to test negative) was 9.5 days (up to 21 days). Epidemiological investigation for some of these asymptomatic infections indicates it is highly likely these asymptomatic infected cases transmitted SARS-COV-2 to their family members.	NR
(TONG ET AL., 2020)	This report describes 2 family clusters that had contact with a pre-symptomatic traveller (at a conference) in Zhoushan, China. Transmission would have occurred 2-3 days before the index case developed symptoms. Contacts developed symptoms 5-7 days post exposure.	Last 2-3 days of the incubation period
(P. WANG ET AL., 2020)	(China CDC weekly) This study describes the case of Wuhan traveller that transmitted SARS-COV-2 while asymptomatic to her parents and boyfriend, but not a number of social contacts during her preclinical period.	NR
(TANG ET AL., 2020)	A single asymptomatic case hypothesized to have been exposed Jan 9 and 15 and is thought to have transmitted the virus Jan 12-15 (3-6 days after initial exposure) to a contact.	NR

(COVID-19 NATIONAL EMERGENCY RESPONSE CENTER, EPIDEMIOLOGY, CASE MANAGEMENT TEAM, KOREA CENTERS FOR DISEASE CONTROL, & PREVENTION, 2020)	Describes the relationship and close contacts of the first 28 Korean cases. Many examples of transmission likely occurring in the few days before symptom onset.	NR
(LU ET AL., 2020)	Index patient was asymptomatic and came from Wuhan Jan 21. Family tests were done Feb 8-11, 1 symptomatic and 2 asymptomatic positives. There is no additional information.	NR
(LUI, WU, LUI, & ET AL., 2020) <i>FULL MANUSCRIPT IS NOT AVAILABLE.</i>	Cluster of 11 people, 6 became positive and 1 had IgG antibodies at the time of the cluster identification. Thus, seropositive case is thought to be an asymptomatic index cases.	NR
(LI ET AL., 2020)	Zhoushan China familial cluster and pre-symptomatic transmission is described. In this case, a plausible exposure time for the index patient is not provided. So we only know that familial exposure occurred 2-6 days before the index patient was tested initially, he developed symptoms 2 days later. So 4-8 days after the secondary cases were exposed.	Last 4-8 days of the incubation period
(QIAN ET AL., 2020)	Asymptomatic transmission occurred among a cluster of three families that had interactions prior to anyone becoming clinical. Index exposure is thought to be Jan 19, secondary transmission Jan 20-23 (days 1-4 after exposure) and on Jan 23 (day 4 after exposure).	Last 1-4 days of the incubation period.

5. A range of the proportion of asymptomatic cases upon initial presentation that eventually develop symptoms is reported in the literature. Few studies provide this estimate as they rarely follow cases through recover from infection. The studies in Table two suggest this range is 25% and 90%. Further research is needed to better define the proportion of asymptomatic cases that occur.

*Table 2: Listed below are a few studies that followed asymptomatic cases and provide evidence that a proportion of asymptomatic cases never develop symptoms.*

REFERENCE	DETAILS
(LING ET AL., 2020)	49 cases that originally presented RT-PCR positive, but symptom negative eventually had a positive CT (n=15, within 3-6 days), presented few clinical symptoms (30, after negative CT 3-14 days) or recovered without any symptoms (4).

(Y. WANG ET AL., 2020)	Describes 55 asymptomatic cases at time of testing – testing due to being a close contact- 70.9% became symptomatic. Time from hospitalization to illness onset was 1-7 days.
(TABATA ET AL., 2020)	Diamond Cruise ship cohort of patients treated at a military base. On arrival 43/104 confirmed cases were asymptomatic. During observation 10 of these cases developed symptoms (7 mild and 3 severe). Data is not provided on length of time to developing symptoms from positive test/enrollment

6. Table 3 lists studies that report asymptomatic cases, at least upon initial presentation, identified during cluster investigations and contact tracing. These numbers are not necessarily a good representation of the proportion of infected cases that are asymptomatic or in a pre-symptomatic phase and viral RNA positive, but they do demonstrate that at any give time there are infected asymptomatic cases in the population where active transmission is occurring. At this time asymptomatic transmission is incorporated into many predictive models, however there are still uncertainties around the extent of transmission that is attributable to exposure to asymptomatic cases.

*Table 3: Studies that identified asymptomatic cases during cluster investigations and/or contact tracing.*

REFERENCE	DETAILS	OUTCOMES
(TAO ET AL., 2020) <b>MEDRXIV PREPRINT</b>	Retrospective medical chart review of cases identified due to being a case or close contact to a case. N=167	20/167 were asymptomatic at diagnosis. Table 3 has details by age of asymptomatic patients. Mean latency (def unknown): 7-20.5 days 7-20.5 days hospital stay 6-22 days
(TIAN ET AL., 2020) <b>JOURNAL OF INFECTION</b>	Retrospective medical chart review of cases identified due to being a case or close contact in Beijing, china N=262	13/262 were asymptomatic.
(Tabata et al., 2020)	Diamond Cruise ship cohort of patients treated at a military base. On arrival 43/104 confirmed cases were asymptomatic	43/104 asymptomatic at initial testing
(DONG ET AL., 2020) <b>PEDIATRICS</b>	Pediatric cases in China, reported to China CDC, N=2143	94/2143 (4.4%) were asymptomatic.
(PANG, 2020) <b>SSRN PREPUBLICATION</b>	Testing of close contacts during cluster investigations in Suzhou. N=37	5/37 were asymptomatic at the time of testing.
(LING ET AL., 2020) <b>EUROPEAN JOURNAL OF RADIOLOGY</b>	Retrospective medical chart review of cases identified due	42/295 (17%) were asymptomatic on initial

	to being a case or close contact in Beijing, china N=295	presentation. 4/295(1%) never developed symptoms or positive CT scan.
(LUO ET AL., 2020) <b>CHINESE JOURNAL OF MEDICINE</b>	Cluster investigations in Anqing identified asymptomatic cases among 83 cases.	8/83 were asymptomatic on initial presentation. 1/83 remained asymptomatic after 17 days hospitalization.
(COVID-19 NATIONAL EMERGENCY RESPONSE CENTER, EPIDEMIOLOGY ET AL., 2020) <b>OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES</b>	The first 28 cases identified in Korea, 16 travel related, 10 close contacts.	3/28 were asymptomatic.
(YAN ET AL., 2020) <b>IN CHINESE</b>	Zhejiang province cases and contacts tested for SARS-COV-22. N=391	54/391 were asymptomatic on initial presentation.
(QIU ET AL., 2020) <b>MEDRXIV PREPRINT</b>	Hunan province 104 cases and close contracts, N=104	5/104 asymptomatic on initial presentation.
(BI ET AL., 2020) <b>MEDRXIV PREPRINT</b>	Shenzhen CDC: 1286 close contacts to cases tested positive.	20% were asymptomatic on initial presentation.
(D. WANG ET AL., 2020) <b>CHINESE J PEDIATRICS</b>	31 pediatric cases from several Chinese provinces were described.	4/31 were asymptomatic for the duration of their infection.
(HONGJUN ET AL., 2020) <b>PREPUBLICATION</b>	Cross-sectional study of cases in Whenzhou identified by contact tracing. N=459	4.4% were asymptomatic
(KI & -NCOV, 2020) <b>EPI AND HEALTH</b>	South Korea, analysis of the first 24 cases. N=24	2/24 were asymptomatic
(KANG ET AL., 2020) <b>MEDRXIV PREPRINT</b>	Guangdong Province cluster investigations. N-84	2/84 asymptomatic on initial presentation.
(NISHIURA ET AL., 2020) <b>MEDRXIV PREPRINT</b>	Evacuees from Wuhan to Japan. N=8 cases	4/8 were asymptomatic on initial presentation.

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