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Evidence for pre-symptomatic and asymptomatic transmission of SARS-CoV-2 - A rapid review of the evidence

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04/04/2020

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Suggested Citation: Kirk L., (04/04/20). *Evidence for pre-symptomatic and asymptomatic transmission of SARS-CoV-2 - A rapid review of the evidence*. ANU College of Health and Medicine COVID-19 Evidence Team, Canberra, Australia.

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COVID19 Canberra Health Service and ANU College of Health and Medicine – Pre-symptomatic and asymptomatic transmission

4/4/20, L KIRK

Acronyms:

- WHO: World Health Organization, CDNA: Communicable Diseases Network Australia, PPE: Personal protective equipment, HCW: Healthcare worker, NPIR: Negative pressure isolation room, AGP: Aerosol-generating procedure (including CPR, manual ventilation, intubation, bronchoscopy, suctioning)

Summary:

- Evidence from epidemiological case studies, viral load studies, and modelling, that suggest **evidence of pre-symptomatic and asymptomatic transmission**.
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- **Viral load studies**
 - o A study of 19 patients, including one asymptomatic patient, showed that the viral load in the asymptomatic patient were similar to that of symptomatic, suggesting possible capability for transmission¹
 - o Viral load studies included two individuals under active surveillance, had a positive PCR one day before symptom onset²
- **Epidemiological case studies**
 - o A study of 243 cases from Singapore suggests evidence for pre-symptomatic transmission 1-3 days before symptoms occur³
 - o An outbreak in a long-term care facility in the US showed 57% (n=13) of residents screened were initially asymptomatic
 - **10 of those 13 went on to develop symptoms**⁴
 - o A number of case series in China show evidence of pre-symptomatic or asymptomatic transmission of SAR-CoV-2⁵⁻¹¹
- **Modelling**
 - o Modelling from the Diamond Princess cruise ship estimated that 17.9% (95CI:15.5-20.2) of individuals onboard were asymptomatic cases¹²
 - o Pooled data from Singapore and Tianjin (China) was used to calculate the mean incubation period and serial interval, and suggested that on average, infection was transmitted 2.55 (Singapore) and 2.89 (Tianjin) days before symptom onset¹³

EVIDENCE BASE AND SOURCE**SUMMARY – RELATING TO PRE-SYMPTOMATIC AND ASYMPTOMATIC TRANSMISSION**

01/04/20, Research article:
Presymptomatic transmission of SARS-CoV-2 – Singapore, January 23–March 16, 2020³

https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e1.htm?s_cid=mm6914e1_w#suggestedcitation

- Study of 243 cases in Singapore between Jan 23–16 identified **seven case clusters which are likely explained by presymptomatic transmission**
- Evidence of presymptomatic transmission **occurring 1-3 days before symptom onset**
 - o Recommendation for contact tracing to include period before symptom onset, and to continue social distancing measures
- Limitations of this study:
 - o Unknown source may have been cause of clusters
 - o Recall bias of symptom onset dates, particularly if symptoms were mild

12/03/20, Rapid communication:
Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020¹²

<https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.10.2000180>

- Used modelling to estimate the proportion of asymptomatic individuals onboard
- 634 people had tested positive by RT-PCR two days after the end of the two week quarantine → 3,063 tests were conducted
- Estimated **asymptomatic proportion is 17.9% (95CI:15.5-20.2)**
 - o Alongside the reported similar viral loads between asymptomatic and symptomatic patients, there may be the possibility of asymptomatic transmission.
- The high proportion of asymptomatic cases holds significant public health implications

06/03/20, Preprint: **Transmission interval estimates suggest pre-symptomatic spread of COVID-19¹³**

<https://www.medrxiv.org/content/10.1101/2020.03.03.20029983v1.full.pdf>

- Study of incubation period and serial intervals in Singapore and Tianjin, China
- Mean incubation period of 7.1 days (95CI:6.1,8.3) for Singapore and 9 days (7.92,10.2) for Tianjin
 - o Mean serial interval of 4.56 (2.69,6.42) for Singapore and 4.22 (3.43,5.01) for Tianjin
- This suggests that **on average infection was transmitted 2.55 and 2.89 days before symptom onset** (Singapore and Tianjin respectively)

03/03/20, Research article:
Asymptomatic and presymptomatic SARS-CoV-2 infections in residents of a long-term care skilled nursing facility – King Country, Washington, March 2020⁴

<http://dx.doi.org/10.15585/mmwr.mm6913e1>

- Following a case of COVID19 in a HCW, 76 residents (of 82) at the health facility were tested for SARS-CoV-2
 - o 23 (30.3%) of the residents tested positive
- Of the 23 that tested positive
 - o 10 (43%) had symptoms on the date of testing
 - o **13 (57%) were asymptomatic**
- **Seven days after testing, 10 of the 13 previously asymptomatic cases developed symptoms**
- The RT-PCR minimal threshold value indicates that there are large quantities of viral RNA in asymptomatic, presymptomatic and symptomatic cases – suggesting transmission by pre-symptomatic or asymptomatic cases could occur.
- Suggests that one a facility has a confirmed case of COVID19, all residents should be cared for using PPE as recommended by CDC – considerations should be made for extended use, or reuse of PPE

27/03/20, Preprint: **Epidemiology and transmission of COVID-19 in Shenzhen China: Analysis of 391 cases and 1,286 of their close contacts**¹⁴

<https://doi.org/10.1101/2020.03.03.20028423>

- Analysis of 391 cases of COVID19 in Shenzhen and their close contacts (lived in the same apartment, meal, travel, social)
 - o Casual contacts (other clinic patients) and close contacts wearing a mask were not included
 - o Close contacts were isolated and monitored for 14 days, with PCR tests at the beginning and end of isolation
 - o Compared to symptom surveillance at travel hubs and homes
- Median incubation 4.8 days, 95% who develop symptoms, will do so in 14 days
- Median time to recover 22 days in 50-59 yr age group
- Secondary attack rate for household contacts of 15.8% (95%CI12.9,19.4), and 10.3% (8.4,12.6) overall
 - o Rate of infection for those under 10yrs was similar to the general cohort population (7.4 vs. 7.9%)
- Contact-based surveillance reduced days from symptom onset to isolation 2.2 days (95%CI:1.7,2.6), compared to 3.4 days for symptom-based surveillance (3.1,3.7)
- Using data from contact-based surveillance, 19.5% were asymptomatic, and 28.7% were afebrile at time of the positive PCR
- **“This work further supports the picture of COVID-19 as a disease with fairly short incubation period (4-6 days) but a long clinical course...”**

16/03/20, Article: **SARS-CoV-2 and COVID-19: The most important research questions**¹⁵

05/03/20, Comment: **Can we contain the COVID-19 outbreak with the same measures as for SARS?**¹⁶

[https://doi.org/10.1016/S1473-3099\(20\)30129-8](https://doi.org/10.1016/S1473-3099(20)30129-8)

<https://dx.doi.org/10.1186%2Fs13578-020-00404-4>

19/03/20, Correspondence: **SARS-CoV-2 viral load in upper respiratory specimens of infected patients**¹

<https://www.nejm.org/doi/full/10.1056/NEJMc2001737>

- Absence of fever in SARS-CoV2 infection is more common (~12%) compared to SARS (1%) and MERS (2%)
 - o Changes effectiveness of fever surveillance
 - o Also unclear viral load and shedding meaning timeline of infectious is unknown
- For COVID19 → concerns regarding asymptomatic or pre-symptomatic transmission
 - o Mild disease, and potential asymptomatic spread makes control more difficult

- Study of SARS-CoV-2 viral load in 19 patients in Guangdong, China
- One patient was never symptomatic but was a close contact of a known case
 - o Remained asymptomatic but had positive nasal and throat swabs on days 7, 10 and 11 after contact
 - o CT of the asymptomatic case was also unremarkable
- Viral load in the nose > throat
- **The viral load detected in the asymptomatic patient was similar to that of the symptomatic patients, suggesting transmission potential of asymptomatic, or minimally symptomatic patients.**

24/03/20, Correspondence: **Viral load of SARS-CoV-2 in clinical samples**²

[https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30113-4/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30113-4/fulltext)

28/02/20, Correspondence: **A family cluster of SARS-CoV-2 infection**

- Study of viral load in 82 infected individuals – two patients for serial samples, and 80 at different stages of infection
- **Two individuals under active surveillance due to an exposure history, showed positive RT-PCR one day before onset**
- Suggests may become infectious before becoming symptomatic

- Index patient travelled through Wuhan before arriving at family home in Nanjing.
- Had contact with a number of relatives on Jan 21st and 23rd, before becoming symptomatic on Jan 28.
 - o Tested positive on Jan 29

<p>involving 11 patients in Nanjing, China⁶</p> <p>https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30147-X/fulltext</p>	<ul style="list-style-type: none"> ○ Three patients who lived with the index patient also tested positive ○ Three relatives who had contact with the index case on the 23rd (whilst asymptomatic) also tested positive for SARS-CoV-2 ○ Two of the patients also appeared to transmit SARS-CoV-2 whilst asymptomatic
<p>19/02/20, Correspondence: Asymptomatic cases in a family cluster with SARS-CoV-2 infection⁷</p> <p>https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30114-6/fulltext</p>	<ul style="list-style-type: none"> - Report on a family cluster (n=3) which included one asymptomatic man, and two asymptomatic cases - The two asymptomatic cases had two lots of positive RT-PCR, but not signs or symptoms of COVID19, and a normal chest CT
<p>09/03/20, Letter: Potential presymptomatic transmission of SARS-CoV-2, Zhejiang Province, China, 2020⁸</p> <p>https://wwwnc.cdc.gov/eid/article/26/5/20-0198_article</p>	<ul style="list-style-type: none"> - Report of two-family cluster infected with SARS-CoV-2 in Zhoushan, China - Contact tracing identified two confirmed cases of symptomatic COVID19, after exposure to a likely presymptomatic index patient, who was later diagnosed with COVID19 <ul style="list-style-type: none"> ○ Two of these patients transmitted SARS-CoV-2 to three family members, who did not report symptoms at the time of detection of SARS-CoV-2
<p>09/03/20, Preprint: Transmission of COVID-19 in the terminal stage of incubation period: a familial cluster⁹</p> <p>https://www.ijidonline.com/article/S1201-9712(20)30146-6/pdf</p>	<ul style="list-style-type: none"> - Report of a familial cluster of COVID19 with evidence for potential transmission in the incubation period (pre-symptomatic) - Five family members had close contact with the index patient in the presymptomatic incubation period <ul style="list-style-type: none"> ○ Index patient travelled from Hunan to stay with relatives – no symptoms during this time. ○ Returned to Wuxi city in Hunan. Relative was diagnosed with SARS-CoV-2 ○ Testing of the index patient revealed SARS-CoV-2 infection, but was still asymptomatic ○ Later developed symptoms and CT changes
<p>23/03/20, Article: A COVID-19 transmission within a family cluster by presymptomatic infectors in China¹⁰</p> <p>https://doi.org/10.1093/cid/ciaa316</p>	<ul style="list-style-type: none"> - Report of a family cluster of COVID19 - Two asymptomatic patients, and evidence of transmission of SARS-CoV-2 during the incubation period (pre-symptomatic)
<p>04/03/20, Research paper: Clinical characteristics of 24 asymptomatic infections with COVID-19 screened</p>	<ul style="list-style-type: none"> - Study of close contacts of COVID-19 patients in Nanjing, China – identified 24 asymptomatic carriers - Five of the 24 went on to develop symptoms during hospitalisation (all developed a fever, +/- other symptoms) <ul style="list-style-type: none"> ○ Five other patients had symptoms that were considered reactions or side effects of IVIg, lopinavir/ritonavir or darunavir/cobicistat.

among close contacts in Nanjing, China⁵

<https://link.springer.com/article/10.1007%2Fs11427-020-1661-4#citeas>

21/02/20, Letter: Presumed asymptomatic carrier transmission of COVID-19¹¹

<https://jamanetwork.com/journals/jama/fullarticle/2762028>

- All 24 had a chest CT – 12 (50%) showed typical findings of COVID-19 (ground-glass opacity or patchy shadows)
 - o Five (21%) had atypical findings
 - A range of abnormalities on blood test was detected among the cases (lymphopaenia 16.7%, leukopaenia 16.7%, elevated LFTs, elevated CRP and D-dimer)
 - Seven (29.2%) of the cases had normal CT images and developed no symptoms during hospitalisation
 - o These cases on average younger (med 14.0, P=0.012)
 - One case appeared to have caused transmission to her family, despite being asymptomatic.
 - Five of the initially asymptomatic cases developed symptoms, however 50% of cases had atypical CT findings
 - There is evidence for asymptomatic transmission
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- Study of a familial cluster in Anyang, China
 - o Five symptomatic patients, one asymptomatic patient
 - Patient 1 is the presumed asymptomatic carrier – she returned three negative RT-PCR, and one positive, and initially a normal chest CT with her CRP and WCC within normal limits.

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