Australian Government
National Health and Medical Research Council

NHMRC

National COVID-19 Health and Research Advisory Committee*

Date of report: 27 August 2020

Advice 11: Incubation period, serial interval and transmissibility

Focus

The National COVID-19 Health and Research Advisory Committee (NCHRAC) was requested to provide advice to the Chief Medical Officer (CMO) on whether there is evidence that:

- the incubation period or the serial interval of COVID-19 is shortening
- the transmissibility of SARS-CoV-2 is increasing.

This report was developed by an NCHRAC working group (see membership at **Attachment 1**).

A glossary of key terms is provided in **Attachment 2**.

Notes

This advice is point in time and may need further review as more evidence becomes available. NCHRAC's conclusions are outlined below. The conclusions represent the expert interpretation of relevant evidence as at 26 August 2020.

This report may be published at www.nhmrc.gov.au/nchrac.

* NHMRC is providing secretariat and project support for the Committee, which was established to provide advice to the Commonwealth Chief Medical Officer on Australia's health response to the COVID-19 pandemic. The Committee is not established under the NHMRC Act and does not advise the NHMRC CEO.

Conclusions

The following conclusions are based on the working group's consideration of a range of literature (including peer-reviewed articles and pre-prints), drawing on relevant systematic reviews and meta-analyses where possible.

Incubation period

NCHRAC conclusion 1: There is no available evidence to suggest that the incubation period of COVID-19 has changed.

The incubation period is the time between exposure to the virus and symptom onset (see Glossary and **Figure 1, Attachment 3**). The current estimate for the incubation period of COVID-19, reported by the World Health Organisation (WHO) and the Communicable Diseases Network Australia (CDNA) *National Guidelines for Public Health Units, Coronavirus Disease 2019 (COVID-19)* is on average 5-6 days, with a range of 1 to 14 days.[1,2]

There is no current evidence that indicates a shortening of the incubation period, with estimates of the incubation period in the recent literature remaining within the current range reported by the WHO and CDNA.[3,4,5,6,7,8,9]

A synthesis of incubation period estimates from 106 pre-prints and peer-reviewed publications for four key epidemiological parameters of COVID-19 in China (the basic reproduction number, incubation period, infectious period, and case-fatality-rate) demonstrated that the mean incubation period reported from 23 January to 12 February 2020 (5.14 days, 95% CI 4.63–5.63, p<0·05) was slightly shorter than that reported from 13 February to 20 March 2020 (5.63 days, 95% CI 5.00–6.50); however, this difference was not statistically significant.[10]

Recent studies also highlight factors that may affect the reported estimates of SARS-Cov-2 incubation period including:

- Dose of exposure
    - For example, a systematic review (pre-print) analysing studies of asymptomatic and pre-symptomatic transmission reported that exposure to a higher dose of SARS-CoV-2 may be associated with a shorter incubation period.[11]
- Age
    - There are conflicting reports about the incubation period in different age groups. For example, a systematic review reported that older adults have a longer incubation period than younger adults.[9] However, it was acknowledged that older adults tend to have more health complications such as respiratory issues and chronic diseases; thus, pre-existing symptoms may mask the onset of COVID-19 symptoms, which could bias the measurement of incubation period. The underlying mechanism is unclear and warrants further investigation.[9] An analysis of 178 cases and 131 transmission chains in Hubei province, China outlined no difference between age groups.[12]

Serial interval

NCHRAC conclusion 2: There is evidence that the serial interval of COVID-19 is shortening, but this is considered a measure of the positive impact of public health interventions.

The serial interval of an infectious disease, also known as the generation time, is defined as the time between analogous phases in successive cases of a chain of infection.[13] The 'transmission serial interval', or the time between the infection events of the primary case patient (infector) and the secondary case patient (infectee), is an important serial interval as it determines how rapidly the disease can spread in the community and provides a time window for its containment. However, this interval is difficult to measure as times of infection (transmission events) are often unknown. A commonly used alternative is the 'clinical onset serial interval', which is defined as the time between symptom onset of a primary case patient (infector) and symptom onset of a secondary case-patient (infectee).[13,14] Unless otherwise specified, the term 'serial interval' in this document is taken to refer to the 'clinical onset serial interval'.

The serial interval varies depending on many factors. Ali et al[15] reported that these factors include:

- Incubation period, which tends to follow a similar distribution from one location to another, with minor differences resulting from social or cultural differences in how symptoms are perceived or reported.
- The profile of infectiousness over time that can vary because of human behaviour.
- Changes in contact patterns within a population and the use of public health measures, which can reshape the timing of infection events by limiting successful contacts overall (e.g. social distancing) or after illness onset (e.g. case isolation).

A reduction in the serial interval is considered a measure of the effectiveness of public health control measures such as effective test, trace and quarantine/isolation processes.[13,15,16] These measures not only reduce the total number of secondary infections. They also reduce cases that are infected after the primary case patient has developed symptoms (that is, those with a longer serial interval), thereby reducing the mean/median serial interval overall (see **Figure 2, Attachment 3**).[13]

Recent literature provides evidence for a reduction in the serial interval for COVID-19 due to public health measures. A study examining 677 transmission pairs for COVID-19 cases in mainland China found that the serial interval shortened substantially from 7.8 days to 2.6 days within a month (9 January to 13 February 2020). The study also reported that this change was driven by intensive non-pharmaceutical interventions, in particular, a reduction of the delay in isolation of suspected and confirmed cases.[15]

An analysis of 1,178 SARS-CoV-2 infected individuals and their 15,648 close contacts based on detailed contact tracing data from Hunan, China did not identify any significant effects of the age of infectors on serial interval.[13]

NCHRAC conclusion 3: The 'diagnostic serial interval' based on the date of diagnosis of cases may be a better and more objective measure compared to 'clinical onset' serial interval, which relies on the subjective self-reporting of symptoms.

As described previously, the 'clinical onset serial interval' is dependent on the symptom onset date. Reports of the limitations of this measure[11,17] include the following:

- It does not account for infectors or infectees who are asymptomatic or pre-symptomatic, which is not uncommon in COVID-19 cases.
- The time of symptom onset is not always documented.
- As highlighted above, it does not provide information about the timing of transmission of infection to the infectee, which may occur before or after symptom onset in the infector.
- It relies on subjective perception and accurate reporting of the onset of symptoms by individuals. Factors that can influence the reporting of symptom onset include:
  - public communication about the pandemic and individual knowledge of the changing definitions of symptoms. For example, in February 2020, the WHO advised that symptoms of COVID-19 included fever, dry cough, fatigue, sputum production, shortness of breath, sore throat, headache, myalgia or arthralgia, chills, nausea or vomiting, nasal congestion, diarrhoea, haemoptysis and conjunctival congestion.[18] On 17 April 2020, the WHO added loss of smell or taste, as well as rash and skin discolorations of fingers and toes as additional symptoms of COVID-19.[19]
  - differing levels of chronic illness and varying levels of symptom awareness; for example, an older person with chronic illness may attribute muscle and joint pain to age, whereas a younger person may describe the same signs as symptoms of COVID-19.
  - recall bias and inherent inaccuracy of memory that leads to errors in the date reported as the onset of symptoms.

Use of the 'diagnostic serial interval' has been proposed to address these limitations.[17] The 'diagnostic serial interval' is defined as the time between the diagnosis dates of the infector and the infectee[17], and would be easier to determine than the 'clinical onset serial interval', since dates of diagnosis are routinely recorded and less subjective than the onset of symptoms. Moreover, in contrast to the 'clinical onset serial interval', it is defined for those with asymptomatic infection with SARS-CoV-2.

Transmissibility of SARS-CoV-2

NCHRAC conclusion 4: During the course of a viral pandemic, an increase in transmissibility of a virus and reduced mortality in the host is theoretically expected due to the natural selection of the virus to favour increased transmission.

Biological features of viruses that have achieved sustained human transmission include selection of viral mutations that favour increased transmission and a briefer interval between exposure and infectiousness, and mutations that keep infected individuals in the infectious stage longer, including reduced virulence and reduced mortality in the host.[20,21,22]

Based on these normal biological features and natural selection of viruses, the working group considered that an increase in transmissibility of SARS-CoV-2 may be expected during the COVID-19 pandemic.

NCHRAC conclusion 5: Although the biology of the current predominant G614 variant of SARS-CoV-2 has some differences compared to other variants, there is currently no evidence that this leads to variation in clinical or epidemiological features of COVID-19.

A SARS-CoV-2 variant with Spike G614 (identified in February 2020) has replaced the D614 variant as the dominant pandemic form globally and is the predominant variant seen in Australia. [23,24,25] The shift occurred even in local epidemics where the original D614 form was well established prior to introduction of the G614 variant, suggesting that the G614 variant may have a fitness advantage and that the change may enhance viral transmission.[23,24] There have been peer-reviewed and pre-print reports examining experimental and clinical evidence showing that the G614 variant appears to grow faster/to higher titre levels *in vitro* [23,24], and that both the G614 and D614 were neutralised with comparable efficiencies by convalescent plasma.[25] While the G614 variant is reported to be associated with lower RT-PCR cycle thresholds in infected individuals, suggestive of higher upper respiratory tract viral loads, there was no significant association between G614 status and disease severity as measured by hospitalisation outcomes (p=0.66).[23]

These findings highlight the need for continued monitoring of the evidence around the transmissibility of SARS-CoV-2 mutations.

NCHRAC conclusion 6: There is to date little available evidence to suggest that there is a change in the transmissibility of SARS-CoV-2. However, there are circumstances that could increase transmissibility.

The working group considered that there is still little available evidence to suggest an increase in the transmissibility of SARS-CoV-2. Despite the genomic change noted in conclusion 5 above, this has not yet translated to evidence that new strains of SARS-CoV-2 are intrinsically more transmissible. In addition, various epidemiological factors can impact on transmission, with evidence that the risk of transmission of SARS-CoV-2-can be increased by the following factors. Such epidemiological circumstances can potentially result in higher transmissibility which is independent of intrinsic virus transmissibility:

- duration of exposure.[13,26] While there is little high quality data about the effect of exposure time, a recently published analysis of exposure position (seat rows) and time (1-8 hours in blocks of 1 hour) based on data from 2,334 index patients and 72,093 close contacts who had co travel times of 0–8 hours on high speed trains from the 19 December 2019–6 March 2020 in China indicates that the attack rate increased on average by 0.15% (p=0.005) per hour of co-travel.[26]
- contact setting, with the risk of transmission reported to be highest in household contacts with decreasing transmission risk in extended family, social groups and then in the community (see **Figure 3, Attachment 4**)[13,27,28]
- closeness of social interactions within a contact setting; for example, increased risk between spouses compared to non-spouse family members in a household.[13,28]

- the number of contacts for an infector; for example, the secondary attack rate was higher in households with one contact than households with three or more contacts.[28]
- lower generation within a cluster. Hu et al[27] classified epidemiologically linked cases according to the generation time of SARS-CoV-2 transmission, with primary cases considered to be generation 1. Higher generations within a cluster had lower risk relative to generation 1 (second generation: odds ratio=0.13, p-value<0.001; generations 3–4: odds ratio=0.05, p-value<0.001, relative to generation 1).[27]
- age. There is little available evidence to suggest differences in infectiousness due to age.[27,29] However, studies have reported significantly higher secondary transmission of SARS-CoV-2 to adult contacts than children contacts suggesting reduced susceptibility with young age.[27,28] Nevertheless, infectiousness can be high for adolescents and young adults: a prospective contact-tracing study of a cluster of eight young patients (16–23 years) originating from an asymptomatic index case reported rapid transmission with a median incubation period of 2 days (range 1–4 days) and a median serial interval of 1 day (range 0–4 days).[30]

Background

The request from the CMO for advice on the evidence for a shorter incubation period or an overall reduction in serial interval of COVID-19, and the transmissibility of SARS-CoV-2, followed anecdotal reports from health care workers of extremely short incubation periods, very short exposure resulting in transmission and apparent increase of cases amongst young people during current outbreaks in Australia.

Other considerations

In the course of developing this advice, NCHRAC identified that advice about transmission from asymptomatic and pre-symptomatic COVID-19 cases was out of scope, but may be an important and related considerations.

Attachments

Attachment 1: NCHRAC Working Group members and consulted experts

Attachment 2: Glossary

Attachment 3: Figures

References

Note: Research papers shared before peer review are identified as pre-prints in this reference list. Accordingly, they should be interpreted with caution.

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Attachment 1

About the Committee and the Working Group

About the National COVID-19 Health and Research Advisory Committee

The National COVID-19 Health and Research Advisory Committee (NCHRAC) was established in April 2020 to provide advice to the Commonwealth Chief Medical Officer advice on Australia's health response to the COVID-19 pandemic. NCHRAC provides rapid and evidence-based advice (or expert advice in the absence of evidence) on Australia's health response to the COVID-19 pandemic with the aim of preventing new cases, optimising the treatment of current cases, and assisting in optimising overall health system readiness to deal with the pandemic as it progresses.

Further information on the terms of reference and membership of the Committee is available at: www.nhmrc.gov.au/nchrac. NHMRC is providing secretariat and project support for the Committee. The Committee is not established under the NHMRC Act and does not advise the NHMRC CEO.

Working Group Membership

NCHRAC convenes working groups of its members and external experts to deliver its reports. The following NCHRAC members were involved in the development of this advice:

Committee Members

Professor Jonathan Carapetis AM (Chair)

Professor Bart Currie

Dr Michael Freelander MP

Professor Michael Good AO

Professor Raina McIntyre

Additional experts

Professor Paul Glasziou, Director, Centre for Research in Evidence Based Practice, Bond University

Professor Ben Howden, Chair, Public Health Laboratory Network

Professor Bill Rawlinson AM, Senior Medical Virologist, Director of Serology, Virology and OTDS Laboratories, NSW Health Pathology

Dr Christine Selvey, Communicable Diseases Network Australia

Attachment 2

Glossary

Term	Meaning as applied in the NCHRAC report
Asymptomatic	A person infected with COVID-19 who does not develop symptoms.[1]
Clinical onset serial interval	The time between symptom onset of a primary case-patient (infector) and symptom onset of a secondary case-patient (infectee).[2] (See also 'serial interval'.)
Cluster	The term 'cluster' in relation to COVID-19 refers to two or more cases (who do not reside in the same household) that are epidemiologically related in time, place or person where a common source (such as an event or within a community) of infection is suspected but not yet established.[3]
Contact tracing	The process of identifying, assessing, and managing people who have been exposed to a disease to prevent onward transmission.[4]
Convalescent plasma	The liquid part of blood that contains the antibodies.
COVID-19	The coronavirus disease caused by the virus SARS-CoV-2.[5]
Cycle threshold (ct)	A relative and semi-quantitative measure of the concentration of a RNA/DNA target in a quantitative PCR test, which can be used to estimate the level of virus in a sample. Lower cycle threshold = higher amount of RNA/DNA.[6]
Generation time	A modelling term describing the time duration from the onset of infectiousness in a primary case to the onset of infectiousness in a secondary cases infected by the primary case. The generation time is a non-observable period which, depending on the disease, may be described by the term 'serial interval' (see definition).
Generation within a cluster	Epidemiologically linked cases according to the generation time of SARS-CoV-2 transmission, with primary cases considered to be generation one.[7]
Incubation period	The time between exposure to the virus and symptom onset.[8]
Infectee	Secondary case patient
Infectious	Transmitting or capable of transmitting infection.[9]
Infector	Primary case patient.
In vitro	Process performed or taking place in a test tube, culture dish, or elsewhere outside of a living organism.

Term	Meaning as applied in the NCHRAC report
Isolation	The separation of ill or infected persons from others to prevent the spread of infection or contamination.[5] of virus
PCR	Polymerase Chain Reaction; a test by which RNA is made into complementary DNA (cDNA) then is repeatedly copied. This is the core test for COVID-19 virus as it is very sensitive and specific and directly measures the virus itself. There is a risk of PCR contamination resulting in falsely positive results, because of the highly sensitive nature of the test.[10]
Quarantine	The restriction of activities of, or the separation of, persons who are not ill but who may have been exposed to an infectious agent or disease, with the objective of monitoring their symptoms and ensuring the early detection of cases.[11]
SARS-CoV-2	Severe acute respiratory symptom coronavirus 2. The formal name of the coronavirus that causes COVID-19.[12]
Serial interval	The time between analogous phases in successive cases of a chain of infection.[2] • The commonly used serial interval is the 'clinical onset serial interval', which is the time between symptom onset of a primary case-patient (infector) and symptom onset of a secondary case-patient (infectee). • The 'transmission serial interval' is the time between the infection events of the infector and the infectee.
RT-PCR	Reverse transcriptase Polymerase Chain Reaction – see *PCR*.
Symptomatic	A person who develop symptoms of COVID-19.
Transmission serial interval	Time between the infection events of the primary case patient (infector) and the secondary case patient (infectee).

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Figures

Figure 1: Schematic of the relation between different time periods in the transmission of infectious disease.[1]

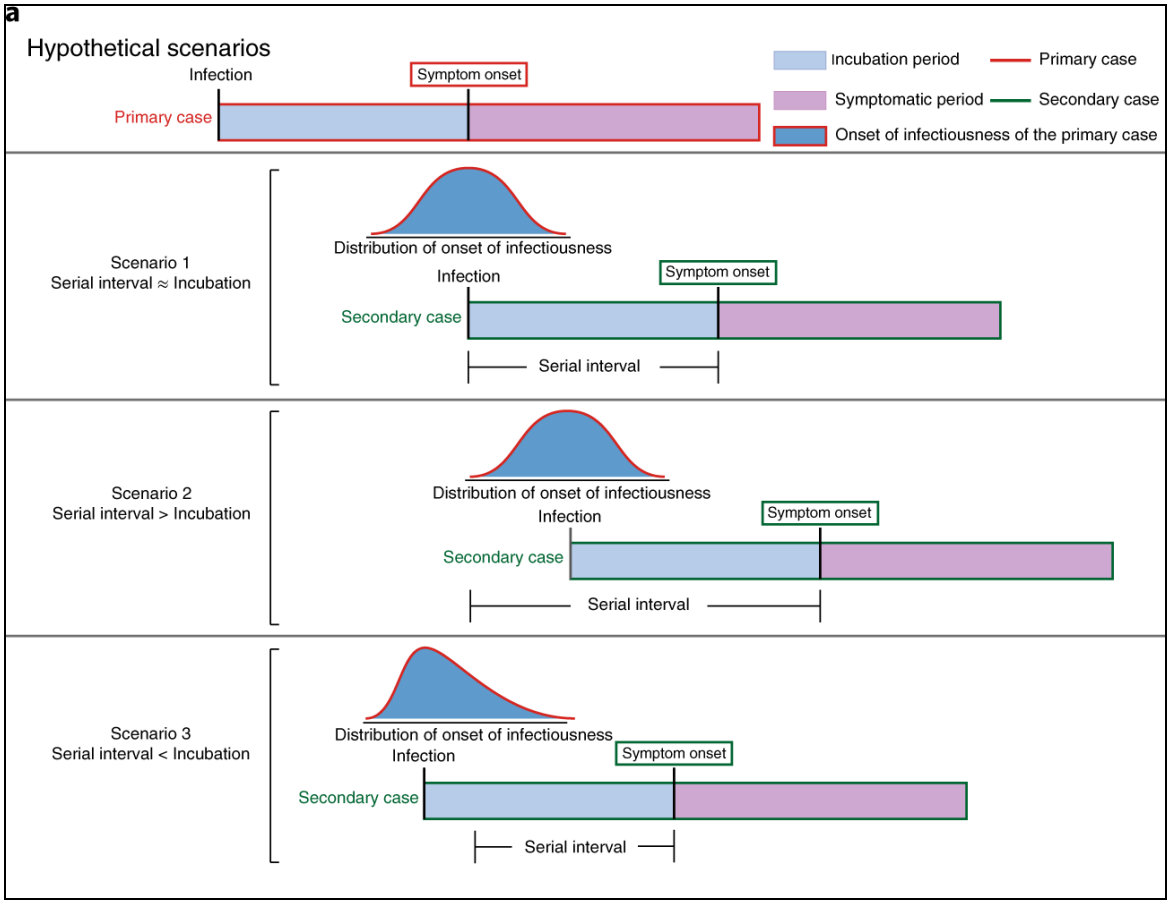
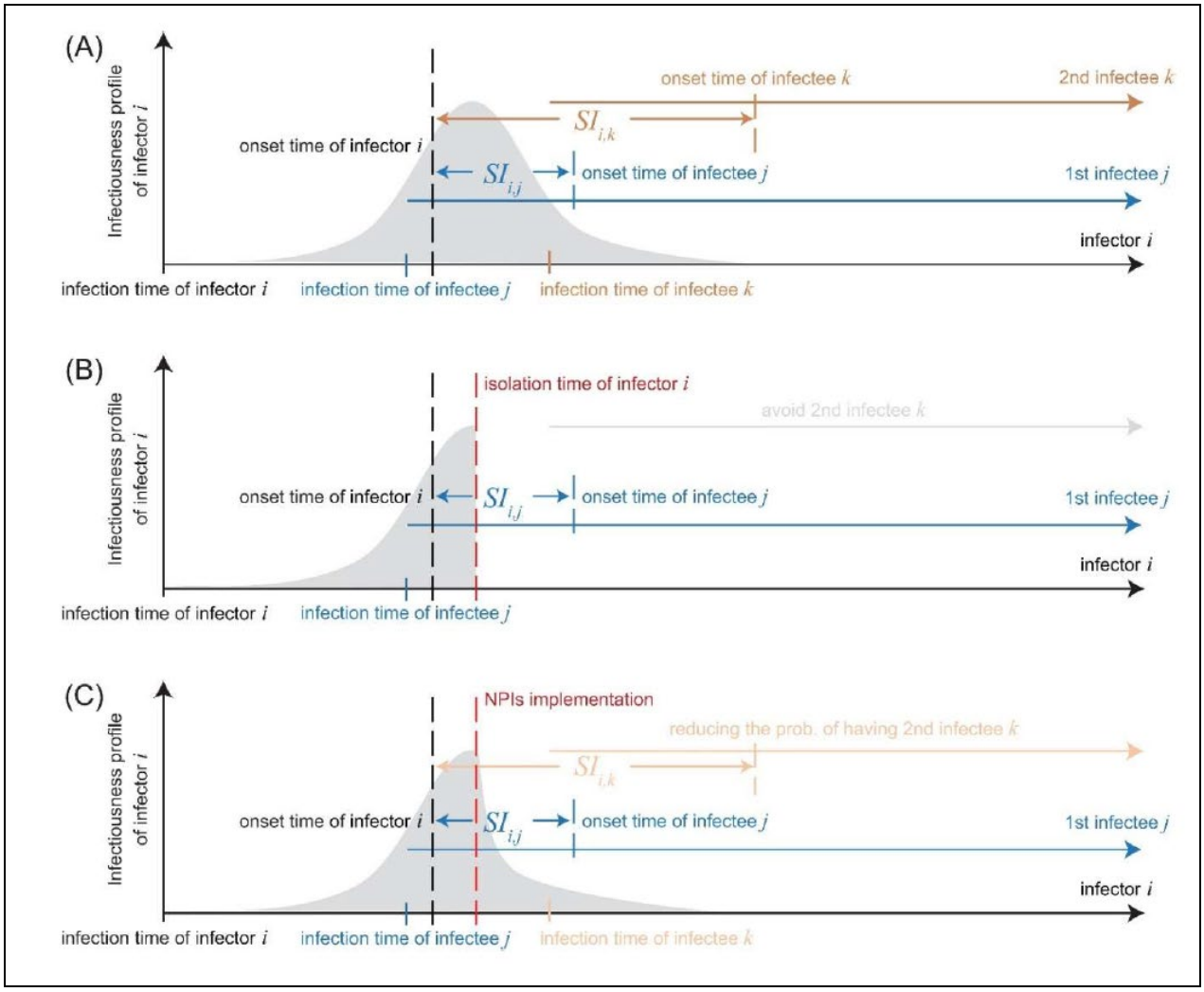
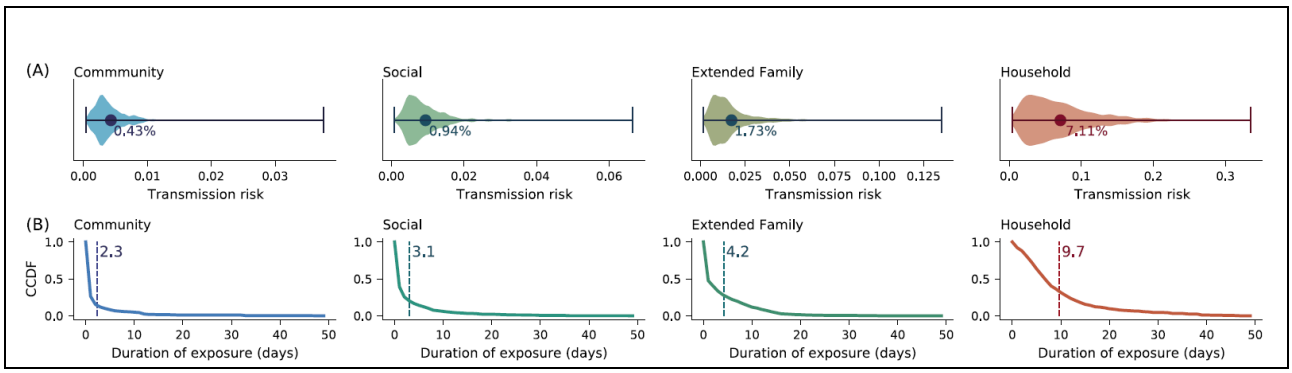


Figure 2: The influence of non-pharmaceutical intervals (NPIs) on changing serial interval distribution.[2]



(A) Without NPIs, the distribution of serial intervals depends on the properties of contacts (e.g., contact patterns, structure of contacts) and properties of transmission pair (e.g., infectiousness profile, incubation period). (B) Rapid case identification and isolation can abruptly truncate the infectiousness profile of an infector, avoiding the generation of some secondary cases thereon. (C) Other NPIs (e.g., lockdown, confinement, travel restrictions) may reduce overall infectiousness but some were triggered by symptoms and hence have a larger effect on infectiousness after symptom onset. The overall effect narrows the infectiousness profile of an infector, lowering the probability in generating secondary cases.[2]

Figure 3: Transmission risk by setting[3]



Columns from left to right represent community contacts (public transportation, food & entertainment), social contacts, extended family contacts, and household contacts.
(A) Distribution of the transmission risk by setting, adjusted for all other covariates.
(B) Cumulative distribution function of the duration of exposure (i.e. the probability that exposure is longer or equal to a certain value). Dashed vertical lines indicate average values.[3]

References

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[2] Ali ST, Wang L, Lau EHY, et al. Serial interval of SARS-CoV-2 was shortened over time by nonpharmaceutical interventions. Science. 2020; eabc9004 [published online 21 Jul 2020]. doi: https://doi:10.1126/science.abc9004. Figure S1.

[3] Sun K, Wang W, Gao L, et al. Transmission heterogeneities, kinetics, and controllability of SARS-CoV-2. medRxiv. 2020.08.09.20171132. 13 Aug 2020 [cited 20 Aug 2020]. Available from: https://doi.org/10.1101/2020.08.09.20171132 **[Pre-print]**. Figure 2(A).