Australian Government
National Health and Medical Research Council

NHMRC

National COVID-19 Health and Research Advisory Committee*

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Differentiation between asymptomatic and pre-symptomatic transmission, and the period of time persistent positive cases are infectious

Focus

The focus of this report is on the evidence for, and implications of, infectivity and transmission from asymptomatic and pre-symptomatic positive cases, as well as on the period of time persistently RNA-positive cases are infectious (i.e. capable of transmission to others).

Limitations

- lack of high quality evidence about infectivity and pre-symptomatic and asymptomatic transmission
- current limitations on the usefulness of serology during acute phases of an outbreak/cluster situation.

This report is evidence-informed and based on expert advice. It is point in time and may need further review as more evidence is available.

This report was developed by the NCHRAC Asymptomatic Working Group (see membership at **Attachment 1**). A glossary of key terms is provided in **Attachment 2**.

Conclusions

NCHRAC conclusion 1: Both pre-symptomatic and asymptomatic people infected with SARS-CoV-2 can transmit the virus to other people but cannot be easily distinguished from each other at the time of identification.

Current evidence[1,2,3,4,5] suggests the following: that, in settings with active case-finding and testing accompanied by isolation of cases and contact tracing with quarantining, approximately 45% of COVID-19 cases have been found to be acquired from pre-symptomatic or asymptomatic cases. Where there is little or slow contact tracing and quarantining, the number of identified cases acquired from pre-symptomatic or asymptomatic cases is found to reduce to approximately one-third of all COVID-19 cases. Although there are no definitive studies differentiating the transmission potential of

* 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.

asymptomatic and pre-symptomatic cases, the weight of current evidence (based on epidemiological as well as viral shedding data) suggests that truly asymptomatic individuals are approximately 40% less likely than pre-symptomatic individuals to transmit virus to others. Assuming this is the case:

- In places with more active management, where it is found that 45% of cases are acquired from people without symptoms, it is estimated that around 30% come from pre-symptomatic cases and 10–15% from asymptomatic transmission.
- In places with little or no active case management, where 33% of cases are acquired from people without symptoms, it is estimated that about 23% of these are acquired from pre-symptomatic transmission and less than 10% from asymptomatic transmission.

There is considerable uncertainty around these estimates and they will need to be updated as new evidence becomes available.

A recent study investigating persistent asymptomatic people identified different immunological signatures (inflammatory cytokines) between asymptomatic and symptomatic people.[6] Research about immunological signatures in pre-symptomatic people may also demonstrate early signs of inflammation. Other unknowns include whether there is a difference in age (particularly children versus adults), sex and underlying comorbidities that differentiate asymptomatic from pre-symptomatic cases; development of long-term immunity; and whether asymptomatic cases take longer to develop active disease or remain silent.[3]

Robust evidence is required to provide a better understanding of the level and extent of transmission potential from truly asymptomatic people and how this contributes to driving the spread of the pandemic. This information will help optimise the public health response.

NCHRAC conclusion 2: Estimates of the prevalence of asymptomatic cases vary between populations, with the current reported estimate being approximately 15% of all cases.

The reported prevalence estimate for asymptomatic cases is approximately 15% of all cases (range 5–25%).[3,7]

This figure represents the proportion of positive cases that are asymptomatic. However, many studies do not make it clear whether they include only cases that are asymptomatic at the time of identification or whether prevalence is adjusted for cases that subsequently develop symptoms and are reclassified as ‘pre-symptomatic’. Variables that affect reported prevalence also include: type of test used to confirm COVID-19, sampling method, timing(s) of test(s), age, sex, co-morbidities, changing definitions of confirmed cases.

Increased testing of asymptomatic contacts and sentinel populations with higher risk of infections (e.g. health care workers, others in higher-risk occupations, local areas of resurgence) is likely to reveal more asymptomatic cases.

NCHRAC conclusion 3: The public health response with respect to pre-symptomatic and asymptomatic cases is similar.

Identifying asymptomatic and pre-symptomatic COVID-19 cases in the community is difficult as individuals are not likely to seek testing or medical attention if they do not have symptoms. These cases can only be detected if they are tested, which in most situations will only occur if they are identified as a contact of a case and there is a protocol for contact testing of asymptomatic contacts, or in certain other circumstances such as research studies or broader sentinel population testing.

Individuals who develop symptoms (symptomatic) are tested and if positive, are isolated with contact tracing performed to interrupt the transmission chain. However, as there is insufficient evidence to accurately estimate the infectious period of COVID-19[8], it is often difficult to ascertain when a contact of a confirmed case may have been exposed, and contacts who are asymptomatic or pre-symptomatic may go undetected. Current estimates of the infectious period suggest that it may begin between 1–3 days before the onset of symptoms and persist for around 7–10 days after the onset of symptoms, with infectivity decreasing over time.[1,9,10]

If an asymptomatic case subsequently develops symptoms, it is then re-classified as pre-symptomatic. However, the practical implication for management of pre-symptomatic and asymptomatic cases should not differ as both types of cases do not display symptoms, both are infectious and both cannot be identified without testing. Testing, tracing and isolation can capture many of the pre-symptomatic and asymptomatic cases and remove them from transmission chains.

Given that transmission can occur from both asymptomatic and pre-symptomatic cases, all contacts of confirmed COVID-19 cases should be tested, regardless of whether or not they display symptoms.

NCHRAC conclusion 4: Additional testing of people in quarantine may facilitate early detection of a greater number of positive cases and enhanced contact tracing and testing.

As outlined above (Conclusion 3), the infectious period of COVID-19 is still being determined.[8] The infectious period in symptomatic individuals may begin around 1–3 days before the onset of symptoms, and persists for about 7–10 days after the onset of symptoms. PCR testing during the first 3–5 days of quarantine (both within the community as well as returned travellers in hotels) will likely detect the majority of cases.[11] Serology testing is a rapidly evolving area and may be useful in some circumstances. Currently, it is most useful where an upstream contact may have been the source of the infection for the reported case, and only if at least a week has elapsed since that upstream contact was themselves an active but undetected case (e.g. asymptomatic). Such people may be NAT (PCR) negative at the time of quarantine but seropositive, which will assist with the epidemiological investigation. If assays currently under development, such as surrogate neutralisation assays, are able to confirm that an individual is non-infectious, that person may not need to remain in quarantine.

Increased testing frequency of those in quarantine — particularly during the early phases — combined with testing of all contacts regardless of whether they show symptoms, results in:

- earlier detection of positive cases, including pre-symptomatic and asymptomatic cases, who may have been infected and infectious prior to entering quarantine
- earlier and more effective contact tracing and testing, with earlier removal of new cases from transmission chains.

A key benefit is a reduction in the potential risk of transmission in the community and the number of tests required in the longer term.

NCHRAC conclusion 5: Australia is currently in a fortunate position due to excellent disease control. The cornerstone of ongoing efforts in Australia to control COVID-19 will be identifying new cases and preventing undetected chains of transmission.

Australia has been very successful in controlling the spread of SARS-CoV-2, with the result that infection rates are low and most of our population is non-immune. Until an effective vaccine is provided to the majority of our population, the cornerstone of control efforts in Australia will be to identify new cases and prevent transmission that results in large outbreaks. That requires intensive contact tracing, testing and appropriate isolation of cases and quarantining of contacts and other high-risk individuals (e.g. returned travellers) until they are no longer infectious.

NCHRAC recognises that contact tracing and testing protocols in each jurisdiction are rapidly evolving and responsive to emerging situations (e.g. *Hotspot Intervention Plan* implemented in Melbourne during the development of this advice[12]). Nevertheless, NCHRAC believes that current approaches can be augmented with enhanced contact tracing and additional testing of contacts. This will help maintain the gains that Australia has made by stopping undetected chains of transmission. Identifying every infection requires testing of contacts in outbreak settings who are asymptomatic at the time. The provision of appropriate resources for enhanced contact tracing and additional testing should be provided and evaluated against the benefits outlined above, noting that access to large numbers of tests and the speed of results becoming available are critical determinants of outbreak control.[13] It is also recognised that under surge conditions, the priority will be to focus on symptomatic cases, and the capacity for enhanced contact tracing, testing and rapid turnaround of test results may be limited unless significant resources (people, equipment) can be mobilised quickly. The current outbreaks in greater Melbourne highlight the need for advanced preparation for such surge capacity.

NCHRAC conclusion 6: There are a number of different potential methods for measuring the infectivity of COVID-19 cases.

NCHRAC conclusion 7: Results from evaluations of current and emerging assays are required to inform recommendations about their use for assessment of the infectiousness of a specific individual.

Understanding the infectivity of COVID-19 cases is critical for the effective management of a person who tests positive to reduce the risk of transmission of the virus to other people; for

example, recommendations about when a person who tests positive may be released from quarantine and isolation or return to the workplace.

Currently, there are no routine assays known to correlate well with infectivity in a clinical setting due in part to the characteristics of the assays themselves, but also virus sampling. The current reference method for measuring infectivity is virus culture, but this is not a practical technique for informing a public health response because it is not widely available, it does not give rapid results, and the correlation between this biomarker assay (culture *in vitro*) and actual infectivity is unproven. Other relevant and emerging assays that may be correlated with infectivity include neutralisation assays, and surrogates for neutralisation assays that are currently being developed and validated.[14,15]

Lung lesions on chest x-ray or CT (computer tomography) scans have been detected in people who are pre-symptomatic but PCR negative.[16,17] Whether radiological evidence of pathogenesis in the lungs relates directly to the degree of potential infectiousness is unknown.

This area is rapidly evolving. To inform recommendations about how the infectivity of a person who tests positive for SARS-CoV-2 should be measured and how a positive case should be managed, a coordinated approach is urgently required for the evaluation of current and emerging assays. Evaluation studies should involve systematic protocols for longitudinal testing of cases and contacts, including the collection and storage of appropriate samples (e.g. nasal, pharyngeal, deep respiratory such as bronchoalveolar lavage [BAL] fluid, sputum, blood, faeces and/or urine) and epidemiological data.

NCHRAC acknowledges that until there is greater certainty around infectivity and transmission, it will be challenging for specialists/clinicians to declare someone as definitively non-infectious without more accurate and reliable information.

NCHRAC conclusion 8: The period of time that persistent positive cases are infectious is uncertain.

A persistent positive case is a person who continues to test positive after clinical recovery. The majority of studies reporting on persistent positive cases are based on PCR analysis, with reports of PCR positive tests for more than one month after onset of symptoms or the first positive PCR test, and for patients who have previously tested PCR negative.[18,19,20,21,22,23,24] However, viral RNA detection by PCR does not equate to infectiousness or viable virus.[9,25,26]

A small number of studies based on viral culture have reported negative viral cultures 8–11 days after onset of symptoms.[18,27,28] This is despite ongoing detectable viral load reported using PCR.[27] In re-positive cases identified in Korea, where confirmed cases took on average 44.9 days (range 8–82 days) from initial symptom onset to re-testing PCR positive after their discharge or release from isolation after recovery, viral culture was negative in all cases tested (108 of 284), and 96% were positive for neutralising antibodies where appropriate samples were collected (23 of 108).[24]

There is currently insufficient high-quality evidence to support a recommendation about the period of time persistent positive cases are infectious.

NCHRAC conclusion 9: To obtain an understanding of the epidemiology of asymptomatic and pre-symptomatic transmission and the time that persistent positive cases are infectious in the Australian context, relevant data related to clusters and outbreaks of COVID-19 in each jurisdiction is required.

Given the relatively low prevalence rates of COVID-19 in Australia, it is an ideal time to increase efforts to identify cases and their contacts, undertake intensive longitudinal surveillance and standardise the collection of information and samples. Longitudinal studies of symptomatic, pre-symptomatic and asymptomatic cases will facilitate a better understanding of the epidemiology of such cases, identify where secondary cases occur, and allow the virological and immunological correlates of transmissibility to be determined. This will improve our understanding of how pre-symptomatic and asymptomatic transmission contribute to the pandemic in the Australian context and how this can be addressed.

Data related to cases and their contacts, clusters and outbreaks of COVID-19 in each jurisdiction that should be routinely collected and analysed includes:

- number of confirmed COVID-19 cases
- criteria for identification of contacts (close contacts and source contacts)
- which contacts of confirmed COVID-19 cases were tested (e.g. all contacts? only symptomatic contacts?)
- number of contacts tested
- when contacts were tested (symptomatic and asymptomatic)
- what tests were used for contacts (serology, PCR)
- duration of follow-up period
- number of contacts that tested positive and were symptomatic
- number of contacts that tested positive and were asymptomatic.

Biorepositories of samples from these cases and contacts can then be used for a range of viral and immunological assays in order to correlate biological markers with infectivity.

Background

Many people infected with SARS-CoV-2 show varying degrees of symptoms (symptomatic) ranging from very mild symptoms to severe symptoms requiring hospitalisation of the patients. People infected with the virus can transmit the virus to other people before the onset of symptoms (pre-symptomatic) as well as after the onset of symptoms (symptomatic). There is also evidence of people who are infected with SARS-CoV-2, and are transmitting the virus to other people, but never show symptoms (asymptomatic).

For an effective public health response to the COVID-19 pandemic, it is important to identify and isolate confirmed cases regardless of whether or not they show symptoms, to trace, test and manage their relevant contacts, and to be able to say with confidence when a person is no longer infectious and can be released from quarantine or isolation and can safely return to their workplace. However, there is still significant uncertainty around the infectious period and the extent of transmission of SARS-CoV-2, particularly among those who are

pre-symptomatic or asymptomatic, to provide definitive advice at this stage. Advice on this issue will change over time as evidence emerges.

Other considerations

In the course of developing this advice, NCHRAC identified the following considerations that were out of scope for this advice, but are important and related considerations:

- factors that affect seroconversion
- methods for test sampling, noting for instance the large range of serology assays of variable quality[29]
- protocols for release from isolation or quarantine
- benefits of the outcomes from enhanced testing protocols and improved assessment of infectivity for mental health and wellbeing.[30]

Attachments

Attachment 1: NCHRAC Asymptomatic Working Group members and consulted experts

Attachment 2: Glossary

References

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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

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Dr Christine Selvey, Communicable Diseases Network Australia

Professor Davina Ghersi, Senior Principal Research Scientist, NHMRC

Glossary

Term	Meaning as applied in the NCHRAC report
Antibody	A protein made in the body to combat infection by a pathogen such as SARS-CoV-2.
Asymptomatic	A person infected with COVID-19 who does not develop symptoms.[1]
Close contact	As defined in the CDNA National Guidelines for Public Health Units: Coronavirus Disease 2019 (COVID-19).[2] Version 0.3 (22 June 2020) defines a close contact as requiring: • face-to-face contact in any setting with a confirmed or probable case, for greater than 15 minutes cumulative over the course of a week, in the period extending from 48 hours before onset of symptoms in the confirmed or probable case, or • sharing of a closed space with a confirmed or probable case for a prolonged period (e.g. more than 2 hours) in the period extending from 48 hours before onset of symptoms in the confirmed or probable case.
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]
Confirmed case	As defined in the CDNA National Guidelines for Public Health Units: Coronavirus Disease 2019 (COVID-19).[2] Version 0.3 (22 June 2020) defines a confirmed case of COVID-19 as a person who: • tests positive to a validated specific SARS-CoV-2 nucleic acid test, OR • has the virus isolated in cell culture, with PCR confirmation using a validated method, OR • undergoes a seroconversion to or has a significant rise in SARS-CoV-2 neutralising or IgG antibody level (e.g. four-fold or greater rise in titre).
Contact tracing	The process of identifying, assessing, and managing people who have been exposed to a disease to prevent onward transmission.[4]
COVID-19	The coronavirus disease caused by the virus SARS-CoV-2.[5]

Term	Meaning as applied in the NCHRAC report
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]
IgG	The smallest and most abundant circulating antibody. It usually appears later in infections and is the most significant antibody for immunity after an infection. Different subtypes of IgG exist and mediate different types of immune response.[7]
Infectious period	The period of time that an individual with disease can spread the disease to others encompassing both a pre-symptomatic infectious period and the symptomatic infectious period.[8]
Infectious	Transmitting or capable of transmitting infection.[9]
Infectivity	The ability of a pathogen, such as the SARS-CoV-2 virus, to establish an infection.
Isolation	The separation of ill or infected persons from others to prevent the spread of infection or contamination.[5]
Microneutralisation	A highly specific reference assay for detecting virus-specific antibodies that prevent (neutralise) virus growth.
Molecular testing	Molecular testing, nucleic acid testing (NAT), or PCR testing, detects genetic material (RNA) of the virus and so can detect if a person is currently infected with (or less frequently has been previously infected with residual RNA from) SARS-CoV-2.[10]
Neutralising antibodies (Nab)	A subset of antibodies produced against a virus that independently block viral entry into host cells and are primarily of the IgG isotype.
Outbreak	The term 'outbreak' in relation to COVID-19 refers to two or more cases (who do not reside in the same household) among a specific group of people and/or over a specific period of time where illness is associated with a common source (such as an event or within a community). Some states and territories may report a single case associated with a residential aged care facility as an outbreak.[3]
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.[11]
Persistent positive case	A person who continues to test positive to having SARS-CoV-2 virus by PCR after clinical recovery.[12]
Positive case	See 'confirmed case'.

Term	Meaning as applied in the NCHRAC report
Pre-symptomatic	A person who has no symptoms when testing positive for COVID-19, but later develops symptoms.
Prevalence	The proportion of a particular population confirmed to have COVID-19 infection at a specific time.[13]
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.[14]
SARS-CoV-2	Severe acute respiratory symptom coronavirus 2. The formal name of the coronavirus that causes COVID-19.[15]
RT-PCR	Reverse transcriptase Polymerase Chain Reaction – see *PCR.*
Sentinel population testing	Testing people across the community, including those who are apparently well, in order to discover unseen transmission.[16]
Seroconversion	The development of detectable antibodies in the blood against SARS-CoV-2.[7]
Serology	Tests that measure the antibody response in an individual. Antibodies to COVID-19 are produced over days to weeks after infection with SARS-CoV-2.[10]
Symptomatic	A person who develop symptoms of COVID-19.

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