COVID-19 LITERATURE REPOSITORY

What is the transmission risk of asymptomatic or pre-symptomatic carriers of SARS-CoV2?

Author(s)
A/Professor Pamela Palasanthiran[1], Dr Adam Bartlett[1], Professor William Rawlinson [2] and Dr Meghan Gunst[1]

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1. Department of Immunology & Infectious Disease, Sydney Children's Hospitals Network, Randwick
2. Head of Medical Virology, NSW Health Pathology Service, Randwick

Discussion

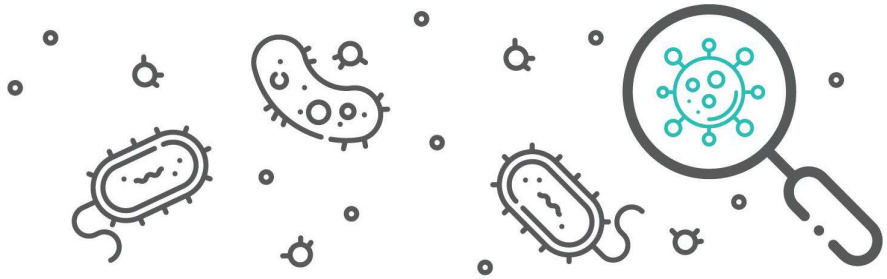
After successful flattening of the epidemic curve in Australia, there has been renewed discussion of active case finding in the community including screening for asymptomatic carriage of SARS-CoV2 (1), the virus causing COVID-19. Thorough understanding of community prevalence is particularly important for public health response planning and the confident relaxation of current social distancing and associated restrictions on population movement. At present, there are several aspects of viral screening that remain controversial or unknown, causing confusion and conflicting opinions on the best way forward.

Asymptomatic carriage or pre-symptomatic detection of SARS-CoV2?

Current understanding of asymptomatic SARS-CoV2 infection relies on case studies (2, 3, 4) and small cluster cohort studies from contact tracing of symptomatic patients (5) (6) (4), with inconsistency in case definitions such as combining asymptomatic patients (who never develop disease) from pre-symptomatic patients (who do not show symptoms at the time of testing then develop symptomatic illness) (8), as well as accuracy of community prevalence rates reflecting the varying testing rates and approaches. The confusion of case definition is highlighted in Bai's report (9) on a family cluster of 5 SARS-CoV2 infections, presumably from an asymptomatic Wuhan relative visiting them in Anyang, adds to current reports on presumed transmission from 'asymptomatic' individuals (10-13).

The diagnosis of SARS-CoV2 in the Wuhan relative (patient 1) without clinical, laboratory or radiological evidence of infection rests on a single positive SARS-COV2 RT PCR, amidst a negative RT-PCRs 2 days *before*, and on re-testing 8 and 11 days after. The authors imply that the first PCR may be a false negative. The time line suggests that patient 6 may be the potential source for the other symptomatic family members as she was the first with symptoms, 4 days after all 6 met up, with the others showing symptoms within the expected incubation period (14 days) (13). Patient 1's positive RT PCR was 18 days after she first arrived in Anyang; if truly positive, it is plausible she was not the carrier but was infected by one in the cluster of 5 with symptoms. The start period of patient 1's isolation was not stated, nor, importantly, whether she had further contact after January 13 (the day they all met) with patients 2 – 6. This of course acknowledges that patient 6 had no other epidemiological risk factors aside from the Wuhan visitor but the clarity of patient 1 being an asymptomatic carrier is raised.

Determining whether asymptomatic SARS-CoV2 individuals are transmission risks is important as the information significantly impacts infection prevention & control practice. Similarly, accurate understanding of asymptomatic transmission is vital for disease modelling in the general community and healthcare worker populations (14). Distinction should be made between the truly asymptomatic individual and the "pre-symptomatic" individual. The asymptomatic individual is virus positive on testing e.g. by RT-PCR but never exhibits symptoms during the incubation period (IP) which is estimated to be a median of 5.1 days (95% CI, 4-5 to 5.8 days). Only ~1% fall



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outside this window period (15). The 'pre-symptomatic' individual is the infected individual who becomes symptomatic. The other reports of presumed asymptomatic transmission involved asymptomatic individuals who were pre-symptomatic. (12, 13, 15, 16) In this report, patient 1 was completely asymptomatic, and questions are raised as to whether she was truly RT PCR positive, and if so, whether she could have been infected by one in the cohort instead. One study of 94 patients and 77 infector-infectee transmission pairs modelled the dynamics of viral shedding and its effect of transmissibility, finding almost half of secondary cases were infected in the pre-symptomatic phase of infection (2-3 days prior to symptom onset) with SARS-CoV2 (14).

A retrospective study of 26 asymptomatic, SARS-CoV2 PCR positive people who were identified as contacts of COVID-19 patients (either diagnosed or suspected), then hospitalised for the purpose of isolation found that asymptomatic cases were mostly infected by symptomatic cases with only two exceptions (17). The authors postulate that asymptomatic carriers may be capable of transmitting disease but are less infectious than symptomatic patients. Similarly, a surveillance study of 14,000 quarantined individuals in Vietnam found people in quarantine in Vietnam found 0.3% SARS-CoV2 PCR positivity from nasopharyngeal throat swabs (18). Of the 30 individuals who participated in the study (from a total of 49 who tested positive), 43% were asymptomatic while 57% either had, or developed, symptoms. Through repeat testing they found only two asymptomatic individuals transmitted the infection to others and had a significantly faster viral clearance compared to symptomatic patients ($P<0.001$ for difference over the first 19 days of surveillance).

Does the detection of viral RNA through PCR testing correlate with transmission potential?
Complicating the discussion of symptomatic, pre-symptomatic and asymptomatic cases of COVID-19 is the unknown significance of viral RNA being detected through screening samples including rectal swabs and stool PCR testing. Several case studies and small cohort studies discuss the persistent PRN positivity on stool or rectal swab samples in cases where the respiratory samples were equivocal but never positive, had been positive days or weeks earlier but were subsequently negative (19), or where respiratory samples were never positive at all. Several theories include the increased ACE-2 receptor presence in GIT epithelial cells (20) resulting in a comparatively increased viral load in the GIT and/or prolonged colonisation and viral shedding for the GIT following respiratory infection; as is seen in similar respiratory viral infections such as adenovirus. There are no studies yet investigating the viability and therefore infectivity of SARS-CoV2 in stool, however several groups postulate that this may prove to have public health significance as a route of transmission as previously observed for MERS and SARS (21).

Conclusions

Transmission by asymptomatic individuals is an important infection control issue and clarity is essential, especially given the implications for healthcare workers, PPE availability and public health control measures for the wider community.

It is essential to consider the distinction between asymptomatic and pre-symptomatic individuals when interpreting literature on the topic.

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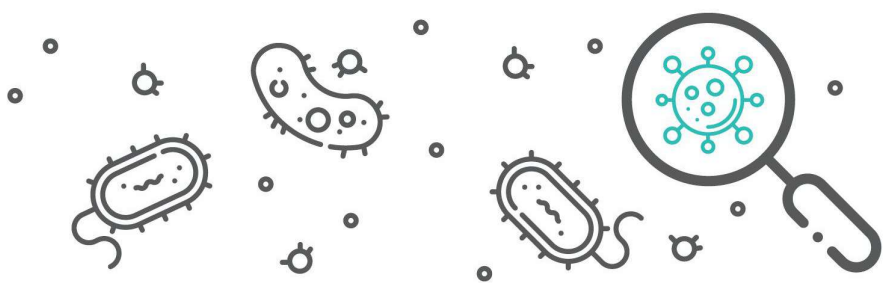

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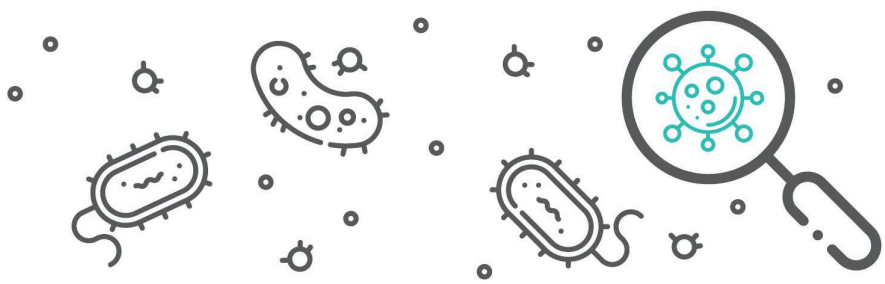

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