

Asymptomatic SARS-CoV-2 infection: the tip or the iceberg?

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Cruise ships, with their unique enclosed environment, have provided valuable insights into the dynamics of viral transmission during the COVID-19 pandemic. On the Diamond Princess cruise ship in Yokohama, Japan, approximately 21% of those on board tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with 51.7% of these representing asymptomatic infections at the time of testing.¹ In this month's edition of *Thorax*, Ing *et al* describe an outbreak on a cruise ship departing Argentina for the Antarctic peninsula with 223 members, all of whom were screened with temperature and symptom check prior to embarkation in mid-March 2020. At day 8, the first member developed symptoms. Despite immediate imposition of cabin isolation of all passengers and strict personal protective equipment use by crew, 128 (59.0%) of those on board tested positive for SARS-CoV-2 on day 20, when everyone was screened with an RT-PCR-based test. Of those testing positive, only 24 (18.8%) developed symptoms and 104 (81.2%) remained asymptomatic until day 28, when the first cohort of passengers disembarked. Some caution is required in interpreting this figure as the follow-up period is not long enough to be confident that all individuals remained truly asymptomatic. Nevertheless, it is striking that despite rigorous attempts to limit spread, such widespread transmission occurred on board. The enclosed environment may be the major driver of the high transmission rate; however, the possibility that transmission from asymptomatic cases contributed significantly must also be considered.

Asymptomatic infection is often understood as detection of SARS-CoV-2 by RT-PCR, in the absence of a clinical illness compatible with COVID-19. In practice, reported asymptomatic infections encompass a heterogeneous mixture

of paucisymptomatic infection (where symptoms are present but are mild or non-specific), presymptomatic infection (where RT-PCR is positive and symptoms emerge shortly afterwards), missed infection (where RT-PCR is positive in a person who retrospectively reports symptoms) and true asymptomatic infection (those actively monitored for 14 days for symptom development). Regardless of how these cases are categorised, any case where there is an infection without recognition, and therefore without behaviour change, risks onward transmission.

Understanding the nature and role of asymptomatic SARS-CoV-2 infection is crucial to inform public health strategies to tackle COVID-19. Three key steps are required: the proportion of asymptomatic SARS-CoV-2 infection must be characterised, the role of asymptomatic infection in onward transmission in different settings must be established, and interventions to recognise and limit the spread from asymptomatic cases must be evaluated.

It is increasingly clear that the context of the investigation likely accounts for the wide-ranging estimates of asymptomatic infection prevalence and proportion reported to date. A systematic review, currently in preprint, identified five studies with a clearly defined sampling frame and adequate follow-up to distinguish true asymptomatic from presymptomatic infection. The pooled proportion of asymptomatic infection was 16% (95% CI 12% to 20%).² Community RT-PCR testing of the entire village of Vo in Italy, at two time points, demonstrated an overall infection prevalence of 2.6% at the start of lockdown and 1.2% at the end of lockdown, with 43% of all infections being asymptomatic.³ Data from screening healthcare workers (HCWs), where unrecognised infection may have significant consequences for nosocomial transmission, suggest a low overall prevalence of asymptomatic infection. Asymptomatic HCW screening in a London hospital showed a prevalence of 7% in late March, reducing to 1% in late April.⁴ In Cambridge, UK, screening of 1032 HCW in April revealed 30 (3%) positive cases, of whom only 5 were considered truly asymptomatic.⁵ Perhaps more comparable to the contained environment of cruise ships are data from residential home outbreaks,

revealing a high prevalence of infection. In a residential home in Washington, USA, with 89 residents, 55 (62%) tested positive over 3 weeks.⁶ Although 27 (49%) were asymptomatic at the time of testing, only 3 (5%) remained asymptomatic throughout the observed follow-up period of at least 7 days. Furthermore, during follow up of 96 asymptomatic cases from the Diamond Princess cruise ship, 11 individuals subsequently developed symptoms, with a greater risk of illness in older patients.⁷

Onward transmission from asymptomatic infection was first described in China, where an index case transmitted infection to all five members of a family despite remaining asymptomatic throughout.⁸ Investigation of 30 patients in Vietnam revealed lower viral loads in those who were asymptomatic, with epidemiological investigation revealing at least 3 cases which had been acquired through contact with asymptomatic sources.⁹ In Guangzhou, China, 4950 contacts of 129 confirmed cases, including 8 asymptomatic cases, were serially screened with RT-PCR every 2 days.¹⁰ A single infection (0.3%) occurred in 305 contacts of the asymptomatic cases compared with 116 infections (5%) in 2305 contacts of symptomatic cases.

The cruise ship outbreak described by Ing *et al* raises another interesting question relating to the variability in risk of onward transmission from infected cases (the overdispersion parameter), where sometimes a high number of secondary cases arise from a presumed single source.¹¹ Mathematical modelling has estimated that 80% of secondary transmissions may occur from as few as 10% of cases.¹² If asymptomatic cases are demonstrated to contribute to these so-called 'superspreading' events, then any intervention in the assessment of an outbreak must be able to recognise and manage such cases.

The wider implications of screening for asymptomatic infection as part of effective interventions to reduce transmission of SARS-CoV-2 are particularly relevant as governments implement strategies to release lockdown measures. The current mainstay of intervention relies on identification of infection, case isolation, implementation of infection control measures and contact tracing. Mass indiscriminate RT-PCR testing of asymptomatic groups requires careful consideration of laboratory testing capacity and interpretation of test results in the context of non-infectious, prolonged RT-PCR positivity in convalescence.¹³ However, in outbreak scenarios,

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where a high prevalence of asymptomatic infection from point prevalence data has been repeatedly demonstrated, mass screening represents a valuable tool to identify asymptomatic (including paucisymptomatic, and presymptomatic) cases, that would otherwise go unrecognised. This could be employed in care homes, in cruise ships, in hospital outbreaks or other community clusters, in order to promptly and completely interrupt chains of transmission. Determining whether transmission from asymptomatic cases is a rare event or a significant driver of SARS-CoV-2 spread must be a research priority, allowing both cruise ships and governments to safely navigate a path out of this pandemic.

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