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Towards an accurate and systematic characterisation of persistently asymptomatic infection with SARS-CoV-2

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People with persistently asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection experience no symptoms throughout the course of infection, and pre-symptomatic individuals become infectious days before they report symptoms. Transmission of SARS-CoV-2 from individuals without symptoms contributes to pandemic spread, but the extent of transmission from persistently asymptomatic individuals remains unknown. We describe three methodological issues that hinder attempts to estimate this proportion. First, incomplete symptom assessment probably overestimates the asymptomatic fraction. Second, studies with inadequate follow-up misclassify pre-symptomatic individuals. Third, serological studies might identify people with previously unrecognised infection, but reliance on poorly defined antibody responses and retrospective symptom assessment might result in misclassification. We provide recommendations regarding definitions, detection, documentation, and follow-up to improve the identification and evaluation of people with persistently asymptomatic SARS-CoV-2 infection and their contacts. Accurate characterisation of the persistently asymptomatic fraction of infected individuals might shed light on COVID-19 pathogenesis and transmission dynamics, and inform public health responses.

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Introduction

Among the immense challenges of the COVID-19 pandemic are mitigating viral spread and understanding the spectrum of illness severity, both of which depend on accurate descriptions of the diverse clinical presentations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Control of spread in particular has been limited by the variable incubation period,[1] well documented pre-symptomatic transmission,[2] with approximately 25–40% of transmission occurring before the onset of symptoms,[3] and heterogeneous transmission dynamics, whereby clusters and superspreading events have a major role in propagating the pandemic, even though many infections lead to no subsequent cases.[4–6] Although there have been more than 75 000 peer-reviewed and preprint publications on SARS-CoV-2 and COVID-19 since January, 2020, the size and characteristics of the persistently asymptomatic subpopulation remain poorly understood.

An asymptomatic person has laboratory-confirmed SARS-CoV-2 infection with no symptoms at all throughout the duration of infection. Defining the proportion of SARS-CoV-2 infections that is truly asymptomatic will help to better characterise the COVID-19 illness severity spectrum, pathogenesis, transmissibility, and immunity, and will inform control policies. Two systematic reviews that only included studies with sufficient time to exclude pre-symptomatic infection have estimated the proportion of SARS-CoV-2 infections that remain completely free of symptoms to be 20% (95% CI 17–25%)[7] and 17% (95% CI 14–20%).[8] The individual studies included in these reviews rarely estimated an asymptomatic fraction greater than 50%. The range of estimates of asymptomatic SARS-CoV-2 infection reported in studies that used a wider variety of study designs goes from as low as 4% to more than 80% (table).[9,10]

There are three main reasons for ongoing confusion about the proportion of asymptomatic infections. First, investigators have not yet developed a consistent case definition, meaning that symptom assessments differ substantially between studies and over time, with minor or atypical symptoms almost certainly missed in the earliest descriptions of COVID-19. Second, cross-sectional studies that assess symptoms at a single timepoint or studies with a short follow-up period might incorrectly categorise individuals as asymptomatic when they are actually pre-symptomatic or post-symptomatic.[21,22] Third, the time course and durability of the SARS-CoV-2 antibody response remain poorly understood, so there might be major limitations when using serological surveys, particularly when they are coupled with retrospective clinical history, to estimate the proportion of asymptomatic infections.

This Personal View summarises these limitations, using examples from studies that have reported on people with asymptomatic SARS-CoV-2 infections (table), and gives recommendations for future studies that will describe this important subset of individuals.

Inconsistent reporting of symptoms

Our understanding of the possible clinical presentations of SARS-CoV-2 infection has evolved since the beginning of the pandemic, and many studies that report on the asymptomatic proportion of individuals have not completely described or assessed COVID-19 symptoms on the basis of current knowledge. The first large descriptive studies of hospitalised patients with COVID-19 from China in January, 2020, used information extracted from medical records and reported that the most common symptoms were fever, cough, fatigue, and myalgia.[23,24] Gastrointestinal symptoms were uncommon in those case series, although now these symptoms are more widely recognised, and some reports suggest that they might occur in up to half of infected individuals.[25,26] Anosmia and dysgeusia were first documented in

	Asymptomatic proportion reported	Follow-up period	Symptom assessment	Notes
Incomplete symptom reporting or restrictive symptom assessment				
Diamond Princess cruise ship[11]	311 (44%) of 712 individuals	>14 days	Cough, dyspnoea, chest pain, sore throat, nasal discharge	Symptoms prospectively assessed
Skilled nursing facility in the USA[12]	13 (39%) of 33 individuals	30 days	Typical (fever, cough, shortness of breath, hypoxia) and atypical (sore throat, nasal congestion, diarrhoea, decreased appetite, chills, myalgias, headaches, new onset confusion) symptoms	Authors note that memory impairment might have resulted in an overestimation of the asymptomatic rate
Call centre in South Korea[9]	4 (4%) of 97 individuals	14 days	Not defined	Face-to-face interviews for symptom assessment
Vo, Italy[13]	34 (42%) of 81 individuals	12 days	Fever or cough or at least two of the following symptoms: sore throat, headache, diarrhoea, vomit, asthenia, muscle pain, joint pain, loss of taste or smell, or shortness of breath	Mix of prospective and retrospective symptom assessment
Pregnant women presenting for delivery in New York City, NY, USA[14]	26 (79%) of 33 individuals	Variable, median follow-up 2 days	Fever or other symptoms of COVID-19	Symptom screen on admission; unclear how symptoms were assessed during follow-up period
Cross-sectional studies or inadequate follow-up				
Homeless shelters in Boston, MA, USA[15]	129 (88%) of 147 individuals	None	Cough, shortness of breath, other symptoms optional	Single timepoint symptom screen
Iceland[16]	525 (43%) of 1221 individuals	None	"cough, fever, aches, and shortness of breath"	Single timepoint symptom screen
Nursing home in the USA[17]	3 (6%) of 48 individuals	7-day prospective follow-up	Comprehensive	Nurse-administered symptom assessments on days 1 and 7
Antarctic-bound cruise ship[10]	104 (81%) of 128 individuals	None	Not described	Mechanism of symptom assessment not clear
Long-term care facilities in the USA[18]	257 (41%) of 631 individuals	14 days before testing	Comprehensive	Symptom assessments by case reports
USS Theodore Roosevelt aircraft carrier[19]	44 (18%) of 238 individuals	Not well defined	Comprehensive	Convenience sample; retrospective symptom assessment
Serological study				
Spain[20]	680 (29%) of 2390 participants (of 51 958 participants screened with immunoassay)	Single timepoint but serological survey	Fever, chills, severe tiredness, sore throat, cough, shortness of breath, headache, anosmia or ageusia	Antibody responses of asymptomatic individuals with SARS-CoV-2 infection currently poorly defined

Table: **Assessment of selected studies reporting on the asymptomatic fraction**

March, 2020; they might be more prevalent in mild cases[27,28] and are strongly associated with SARS-CoV-2 infection.[19] A large study using a symptom-tracking smartphone application found that it became more common for individuals with COVID-19 to report anosmia or dysgeusia in the UK after the association of these symptoms with infection was reported widely in the media.[19,27]

Many studies have used an unclear or uncomprehensive method of symptom ascertainment, making it difficult to interpret the reported frequency of symptoms. Information extracted retrospectively from medical records or reports that rely on spontaneous reporting by study participants will probably underestimate the frequency of mild or atypical symptoms. In a cohort of 147 individuals diagnosed with PCR-confirmed SARS-CoV-2 infection at homeless shelters in Boston, MA, USA, 129 (88%) were classified as asymptomatic when asked only about a narrow range of symptoms that included a history of cough and shortness of breath.[15] They were also invited to report other symptoms, a strategy that does not reliably capture a complete clinical picture. A large study of infections in Iceland considered only cough, fever, aches, and shortness of breath as symptoms compatible with COVID-19.[16] A report of individuals infected on the *Diamond Princess* cruise ship omitted commonly reported symptoms, including anosmia and gastrointestinal complaints, which might have led to an overestimated asymptomatic proportion of 44% (311 of 712 participants).[11] Additionally, it is not clear how potential language barriers were addressed, since symptom assessment occurred in Japan from a presumably multinational and multilingual cohort. Other studies of the *Diamond Princess* outbreak have estimated different proportions of asymptomatic infections, including a modelling study that estimated 17·9% (credible interval 15·5–20·2%)[29] and another study of the early phase of the outbreak that reported 14% (24 of 172 participants),[30] but only tested suspected cases (defined as those with fever or respiratory symptoms) that might have biased the outcome.

Two detailed investigations of outbreaks at nursing facilities, one in Washington State, USA,[17,31] and one in Illinois, USA,[12] from March, 2020, did not include assessment for changes in smell or taste, because these symptoms were not widely recognised at that time. A study of an outbreak associated with a call centre in South Korea found that just four of 97 cases were persistently asymptomatic, although the list of symptoms enquired about is not described in the report.[9] Details about case definition and manner of symptom assessment are required to interpret study results, and incomplete symptom assessment probably leads to an overestimation of the proportion of asymptomatic individuals.

In describing the outbreak of SARS-CoV-2 infection in the town of Vo, Italy, investigators reported a persistently asymptomatic proportion of 43%.[13] Study participants were tested for SARS-CoV-2 by nasopharyngeal swab and completed a survey with symptom assessment on Feb 24, and again on March 7, an interval of 12 days. Symptomatic patients were defined as those who "required hospitalization and/or reported fever (yes/no or a temperature above 37°C) and/or cough and/or at least two of the following symptoms: sore throat, headache, diarrhoea, vomit, asthenia, muscle pain, joint pain, loss of taste or smell, shortness of breath". Although reported symptom assessment was systematic and comprehensive, requiring at least two minor symptoms to be present in cases confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) might have led to misclassification of some individuals with mild symptoms as asymptomatic.

Inadequate follow-up time

An absence of symptoms at the time of a positive RT-PCR test is insufficient to determine whether an individual has persistently asymptomatic infection because an RT-PCR test result can be positive before symptom onset.[3,32,33] Cross-sectional studies can therefore assess the proportion of people with and without symptoms at the time of testing but cannot distinguish pre-symptomatic from asymptomatic infection.

The duration of follow-up needed to capture pre-symptomatic infections is the maximum duration of the incubation period, and more than 95% of infected individuals who develop symptoms will do so within 14 days, making this a reasonable length of follow-up to detect most pre-symptomatic cases.[1] Two examples show the importance of follow-up time in studies with different contexts and inclusion criteria. Among residents of a nursing home in the USA who were tested after a healthcare worker was found to be infected, 48 tested positive for SARS-CoV-2, of whom 21 (44%) had symptoms and 27 (56%) were asymptomatic at the time of testing.[17] Over the next 7 days, 24 (89%) of the initial 27 residents without symptoms developed symptoms and were therefore pre-symptomatic at the time of testing.[17] In South Korea, 110 (36%) of 303 individuals were initially asymptomatic at a clinical treatment centre, a setting designed for individuals with mild or no symptoms, and 21 (19%) of these 110 individuals eventually developed symptoms indicating a persistently asymptomatic fraction in this cohort of 29% (ie, 89 of 303 participants stayed asymptomatic) .[34]

Three publications including pregnant women in New York City, NY, USA, show the importance of accurate reporting of symptoms and adequate follow-up.[14,35,36] The first report,[14] stating that "29 of the 33 patients who were positive for SARS-CoV-2 at admission (87·9%) had no symptoms of COVID-19 at presentation", had a median follow-up time of 2 days post-partum, an insufficient period to exclude pre-symptomatic infection. In fact, two subsequent publications, which had an overlapping cohort of obstetric patients with RT-PCR-confirmed SARS-CoV-2 infection and a longer follow-up, found that the proportion of asymptomatic women was much lower, including one study[35] in which just 46 (29%) of 158 participants remained asymptomatic throughout follow-up (63 [40%] were asymptomatic at diagnosis), and another study[36] with at least 2 weeks of follow-up time, in which four (9%) of 43 participants remained asymptomatic (12 [28%] were asymptomatic at diagnosis).

Several other cross-sectional studies in different contexts have at times been interpreted inappropriately as reporting the asymptomatic proportion of infected individuals, including the study in Boston homeless shelters,[15] a report of an outbreak on a cruise ship off South America,[10] and the study of infections in Iceland,[16] among others.[37] Additionally, an RT-PCR test might remain positive after the period of infectiousness, since the median duration of nasopharyngeal swab shedding for immunocompetent adults with mild disease has been shown to be 22 days.[22] It is therefore also important to assess for previous symptoms if the timing of infection is unknown.

Issues with assessment of symptom status in seroprevalence studies

Antibody test characteristics are defined by comparison with RT-PCR as a reference standard and their performance is not fully understood for individuals who had a negative RT-PCR test (or were not tested) with previous asymptomatic infection. Antibody durability in these individuals is another concern, with one study finding that among individuals who previously had a positive RT-PCR test, 12 (40%) of 30 were asymptomatic, but only four (13%) of 31 symptomatic individuals became seronegative after about 8 weeks.[38]

A large seroprevalence study in Spain reported that nearly a third of people with SARS-CoV-2 antibodies were asymptomatic.[20] Symptom assessment was comprehensive and systematic, and although there was no follow-up period, those with positive IgG titres would have been out of the pre-symptomatic period.[39] In the study, IgG antibodies were found in 8·0% (95% CI 6·0–10·6) of participants with a previous negative

RT-PCR test and in 4·2% (95% CI 3·8–4·5) of those who never had an RT-PCR test. To interpret these results properly, it would be important to understand this subpopulation (ie, participants with a negative RT-PCR test and positive IgG test) better: were these individuals tested because they indeed had a compatible syndrome or a close contact, or both? Individuals with a compatible syndrome with negative RT-PCR testing many days after symptom onset are likely to have had previous SARS-CoV-2 infection. However, it is important to consider the possibility that some or many of these individuals might have falsely positive serologic testing.

The importance of understanding the persistently asymptomatic subpopulation

Gaps in understanding limit development of optimal public health strategies to control the pandemic. For instance, it is not known whether people with persistently asymptomatic SARS-CoV-2 infection have demographic, clinical, immunological, or virological characteristics that differ from those who develop symptoms, or how their transmission potential differs. Studies reporting on asymptomatic individuals with SARS-CoV-2 infection often include few participants, without detailed descriptions of baseline characteristics or comparison with participants with symptoms. This evidence gap precludes analyses of how asymptomatic individuals might differ from those who develop symptoms. More detailed descriptions would allow for a richer understanding of differences between these populations, and pooled analyses would be possible if individual patient data were available. In future research studies, meticulous description of methods used to enrol participants and assess the persistently asymptomatic subpopulation will also make it easier to investigate study heterogeneity in systematic reviews of this topic,[7] and better inform modelling studies that make assumptions about viral transmission dynamics on the basis of estimates of the persistently asymptomatic subpopulation.[40] This information would improve pandemic control strategies.

Detailed follow-up of people with persistently asymptomatic SARS-CoV-2 infection will also allow a definitive understanding of viral dynamics and antibody responses in these individuals, which could help to determine whether they develop a sufficiently robust and durable antibody response after infection and how they might respond to vaccines. Furthermore, the characteristics of this group might help to explain the wide spectrum of illness severity and COVID-19 pathogenesis. Lastly, thanks to the growing understanding that mild symptoms could be associated with SARS-CoV-2 infection, coupled with reduced barriers to diagnostic testing, more cases could be readily identified, which would help to reduce community transmission.

Recommendations to help define the persistently asymptomatic fraction

We make six recommendations to allow for accurate ascertainment of asymptomatic infection status and to eventually comprehensively identify the proportion of asymptomatic individuals.

Define persistently asymptomatic infection clearly

First, the term persistently asymptomatic SARS-CoV-2 infection should be reserved for people who have no known COVID-19 symptoms, including no atypical or mild symptoms, throughout the course of infection. Cross-sectional studies should report proportions without symptoms as asymptomatic at the time of testing.

Use a standard, broad-symptom definition

Second, there are numerous clinical case definitions with emphasis on different symptoms from various groups including WHO,[41] the European Centre for Disease Prevention and Control,[42] the US Centers for Disease Control and Prevention,[43] and the Canadian Ministry of Health and Long-Term Care[44,45,46] (panel). We recommend standardisation of clinical definitions, and we favour the symptom list in the Canadian case definition at this time, which is the most comprehensive. This definition allows documentation of the most common symptoms, and characterisation of cases as typical, atypical, mildly symptomatic, or persistently asymptomatic.

Assess symptoms prospectively and retrospectively for the minimum appropriate follow-up period

Third, a minimum follow-up period of 14 days from last possible exposure (or first positive test if exposure is unknown) will differentiate pre-symptomatic from persistently asymptomatic individuals. Investigators should report the follow-up period, together with baseline characteristics of individuals with all clinical presentations, including age, sex, and ethnic group as a minimum.

An investigation of non-hospitalised household contacts of individuals with SARS-CoV-2 infection in Wisconsin and Utah, USA, did an assessment consistent with our recommendations, including systematic, detailed symptom assessment and an adequate follow-up period, and might be a model for similar studies moving forward.[47]

Clearly report testing protocols used for SARS-CoV-2 detection

Fourth, details of testing, including timing, site, and test platform, are necessary to interpret results from studies reporting on asymptomatic cases. Timing of testing should reflect the SARS-CoV-2 viral load dynamics and incubation period and should not be done before day 5 after exposure for those without symptoms.[48] The optimal site of testing is actively being studied but in clinical practice to date, nasopharyngeal or oropharyngeal testing is most common. Salivary testing might be less sensitive and might have

other handling constraints (ie, rapid time to processing) that require further study.[49] Poor sampling could yield false negative results. This possibility was suggested in the report of four symptomatic individuals from Italy who initially had negative nasopharyngeal RT-PCR tests taken by non-otolaryngologists, which were positive when a repeat sample was obtained by an otolaryngologist 6–72 hours later.[50] In another study, suspected false negative RT-PCR tests had significantly lower amounts of human DNA than other samples.[51] Although RT-PCR-based platforms are most commonly used now, less sensitive rapid antigen testing is likely to become much more common.[52] The sensitivity of antigen tests for individuals with persistently asymptomatic SARS-CoV-2 infection is unknown at this time.

Report serologic studies in detail to understand asymptomatic infection

Fifth, serologic testing could become a helpful adjunct to identify the persistently asymptomatic subpopulation. To interpret results, researchers should clearly report the time window between suspected infection and antibody testing. Symptom recall bias might be worse with longer delays. In a follow-up of the Iceland study,[16,53] researchers clearly reported the timing of exposures and antibody testing. They found that 142 (10%) of the 1421 individuals who quarantined after a COVID-19 exposure had detectable antibodies without previous symptoms and without reported PCR testing.[53] The pre-test probability for infection is higher in individuals who are in quarantine than in a random population sample and, although this study did not estimate the population-wide prevalence of asymptomatic infections, it improves on previous serologic studies' assessment of asymptomatic cases. Serial testing can help to define antibody decay trajectories, an important variable for estimating the asymptomatic proportion of individuals in serological studies.

Design studies to minimise biases that affect ascertainment of the asymptomatic fraction

Finally, research studies to measure the persistently asymptomatic proportion of SARS-CoV-2 infections need to be designed so that the absence or presence of symptoms does not affect selection into the study. The ideal study design would screen a population and prospectively follow individuals infected with SARS-CoV-2. Clinical and demographic data would be collected at baseline, with frequent (even daily) comprehensive symptom assessments, serial RT-PCR testing from multiple body sites, and intermittent measurements of antibody titres and immune response. Detailed contact-tracing studies in unbiased populations should also be done so that secondary attack rates can be compared between people with persistently asymptomatic and symptomatic infection, and the duration of their period of infectiousness can be identified.

Panel: **Symptoms considered to be consistent with COVID-19 according to various case definitions**

WHO[41]

- Fever AND cough
- OR three or more of the following symptoms: fever, cough, general weakness or fatigue, headache, myalgia, sore throat, coryza, dyspnoea, anorexia or nausea or vomiting, diarrhoea, altered mental status
- OR recent onset anosmia or ageusia without another explanation

European Centre for Disease Prevention and Control[42]

- At least one of the following symptoms: cough, fever, shortness of breath, or sudden onset of anosmia, ageusia, or dysgeusia

US Centres for Disease Control and Prevention[43]

- At least two of the following symptoms: fever, chills, rigors, myalgia, headache, sore throat, nausea or vomiting, diarrhoea, fatigue, congestion or runny nose
- OR any one of the following: cough, shortness of breath, difficulty breathing, new olfactory disorder, new taste disorder

Government of Canada[44-46]

- At least one of the following symptoms:
  - Common symptoms: fever, new or worsening cough, shortness of breath
  - Other symptoms: sore throat, difficulty swallowing, new olfactory disorder, nausea or vomiting, diarrhoea, abdominal pain, runny nose or nasal congestion (in the absence of underlying reason for these symptoms [eg, seasonal allergies, postnasal drip])
  - Atypical symptoms: unexplained fatigue or malaise, myalgia, delirium, unexplained or increased number of falls, acute functional decline, exacerbation of chronic conditions, chills, headaches, croup, conjunctivitis

The distinction between asymptomatic and pre-symptomatic individuals should not distract from the overwhelming evidence that individuals without symptoms can transmit the virus, usually when they are pre-symptomatic; this evidence emphasises the need to continue implementing non-pharmaceutical interventions such as physical distancing, universal masking, and handwashing.[2] In addition, testing policy in outbreak settings and high-risk environments such as long-term health-care facilities needs to reflect this crucial fact: individuals without symptoms in close contact with an index case will need to be tested as part of the outbreak investigation to identify cases and allow for effective control measures.

To date, absence of comprehensive understanding of asymptomatic SARS-CoV-2 infection makes it difficult to inform public health strategies on the best way to control the pandemic. Uncertainty about the existence, characteristics, prognosis, and role of asymptomatic SARS-CoV-2

infection in this pandemic will continue unless we have systematically and accurately collected data.

Contributors

EAM, AR, and MC conceptualised the manuscript and wrote the first draft. IIB and NL contributed substantially to the methods and reviewed and edited the manuscript. All authors contributed substantially to the writing and editing of the final submission.

Declaration of interests

IIB has consulted for BlueDot, a social benefit corporation that tracks the spread of emerging infectious diseases. All other authors declare no competing interests.

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