VIEWPOINT: COVID-19

SARS-CoV-2 transmission without symptoms

Symptomless transmission silently drives viral spread and is key to ending the pandemic

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a potentially long incubation period and spreads opportunistically among those who are unaware they are infected. Asymptomatic COVID-19 cases are those that do not develop symptoms for the duration of infection, whereas presymptomatic cases develop symptoms later in the course of infection, but both are crucial drivers of transmission (*1*). Transmission without symptoms poses specific challenges for determining the infectious timeline and potential exposures. Early in the pandemic, most transmission was from undocumented cases, suggesting that spread was driven by people who were either asymptomatic or experiencing such mild disease that it was not recognized as COVID-19 (*2*). Contagious people without observable signs of illness make infection prevention efforts vulnerable to compliance with masking, distancing, hand hygiene, symptom screening, and ultimately, people staying home when possible. The lack of widespread testing in asymptomatic individuals further complicates COVID-19 mitigation and control efforts.

The true occurrence and transmission capacity of asymptomatic and presymptomatic infections are difficult to evaluate. Owing to insufficient surveillance testing (testing regardless of symptoms), presymptomatic cases lost to follow up, and unrecognized mild symptoms, symptomless cases are often undercounted or misclassified. It is virtually impossible to detect such cases without continuous community surveillance screening, which has not been widely implemented, or without effective contact tracing and testing. Beyond implementing general and often vague control measures, public health efforts have struggled to truly address symptomless transmission. Surveillance testing has predominantly been carried out in targeted populations such as long-term care facilities. Only certain industries, such as professional sports and entertainment, have implemented asymptomatic testing, but such data are not publicly available and these groups are not representative of the broader community. It is important to understand infectiousness and viral shedding, as well as the overall contribution of asymptomatic or presymptomatic cases to secondary cases.

The prevalence of symptomless cases is not precisely established. Early studies reported that asymptomatic cases accounted for 30 to 80% of infections (*3*), but more recent data point to a rate of asymptomatic cases between 17 and 30% (*4*). A recent systematic review of studies reporting SARS-CoV-2 diagnoses by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR, the standard molecular diagnostic test) and follow-up of symptoms found that the proportion of asymptomatic infections was 20% and that the rate of presymptomatic individuals could not be determined because of heterogeneity across studies (*4*). A limitation of such studies is measurement of asymptomatic status and selection bias. Often, large outbreaks driven by asymptomatic or presymptomatic transmission are restricted to specific populations or circumstances, such as in skilled nursing or long-term care facilities, where surveillance testing takes place (*5*). Because these are high-risk clinical environments, it is not surprising that symptomless transmission has been detected more frequently than in nonclinical settings, such as restaurants or offices, which lack access to testing or medically trained staff. The unknown prevalence of asymptomatic SARS-CoV-2 infections makes disease control and mitigation strategies inherently challenging.

Beyond assessing the prevalence of symptomless infections, it is vital to determine their risk for secondary transmission. Contact tracing is reliant on case identification, which generally involves testing of people with symptoms. This reliance on symptom-based testing, especially early in the pandemic, was also complicated by limited understanding of the full range of COVID-19 symptoms. The lack of surveillance testing makes analysis of secondary attack rates (the percentage of cases that result from one infected person within a defined group) for asymptomatic cases exceedingly difficult. In symptomatic COVID-19, infectiousness begins 2 days prior to symptom onset and for several days after, with reduced or undetectable viral shedding within the first week of symptom onset (*5*, *6*). Viral shedding kinetics for asymptomatic COVID-19 is not well understood. Early in infection, individuals have similar viral loads regardless of eventual symptom severity, but asymptomatic cases have lower titers at peak replication, faster viral clearance, and thus a shorter infectious period (*6*).

Measuring the true impact of symptomless infections on transmission can be extremely confounding. Data on asymptomatic and presymptomatic cases who had close contacts but did not result in transmission are limited. Some studies found that asymptomatic cases were 42% less likely to transmit the virus, and observed lower secondary attack rates, whereas others have noted that regardless of a shorter infectious period, there is similar transmissibility for those with presymptomatic or asymptomatic COVID-19 in the first days of infection (*6*). Studies of presymptomatic transmission suggest that higher secondary attack rates are likely compared with asymptomatic cases (*7*). Moreover, analyses of contact tracing data indicated that at least 65% of transmission occurs prior to symptom onset (*8*). Another study found that only 12.6% of cases resulted from symptomless transmission (*9*). These discrepancies can be explained by several factors, including the misclassification of cases that were not followed up (*4*), but also that many are identified as a result of specific settings, such as superspreading events on cruise ships or in choir practice that result in rigorous investigations, and may not be representative of typical transmission events.

Determining the true transmission capability of asymptomatic and presymptomatic cases is inherently complex, but knowledge gaps should not detract from acknowledging their role in the spread of SARS-CoV-2. Those with symptoms appear to have higher secondary attack rates, but these cases are also more likely to present for testing and practice isolation because of obvious illness (*10*). The public health and infection prevention challenges rely on those without symptoms to self-quarantine and implement a suite of interventions, such as masking, social distancing, ventilation, and hand hygiene. However, emphasis on the degree of contagiousness rather than the knowledge that people without symptoms are generally contagious detracts from the public health threat that

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asymptomatic and presymptomatic infections pose and the need for continuous community-based surveillance and interventions.

The 2003 outbreak of the related SARS-CoV was eventually contained by using standard epidemiological approaches of isolating cases and tracing and quarantining contacts. This was effective because contagious patients could be easily identified through temperature and symptom screening. A major distinction from SARS-CoV is viral shedding of SARS-CoV-2 in the absence of observable clinical symptoms. Unlike SARS-CoV, SARS-CoV-2 viral loads are highest at symptom onset and up to a week after (*6*), which suggests substantial presymptomatic shedding. Therefore, people are likely contagious for a relatively long period and when they are unaware they have been infected or exposed. The minimum infectious dose required for transmission is also not known and likely varies depending on individual exposure and susceptibility. Although viral loads decline over the course of infection, the exact point at which someone stops being contagious is unclear, but probably occurs within 10 days of infection in most cases, provided symptoms are resolving.

Testing provides limited clarity on whether a person is likely to be contagious on the basis of estimated viral loads. Although people who have fully recovered from COVID-19 can continue to shed viral RNA and test positive by qRT-PCR in the absence of recoverable infectious SARS-CoV-2, as assessed by culture (*1, 5, 6, 11–14*), these cases have not been associated with new clusters of transmission (*12*, *13*). qRT-PCR detects viral RNA but not infectious virus particles. PCR cycle thresholds can be used to estimate viral load in nasal swabs, but do not always directly correlate with the quantity of infectious virus shed in respiratory particles. These particles are highly heterogeneous depending on various factors, including where in the respiratory tract cells are secreting infectious virus, breathing rate, and symptoms such as coughing (*15*). Not all exhaled particles contain infectious virus, and the amount of time that virus remains infectious after exhalation in respiratory particles can vary substantially depending on environmental conditions such as temperature and humidity, as well as the quantity of infectious particles being shed. Assays that measure infectious titer must be performed in biosafety level 3 (BSL-3) containment, so this cannot be routinely measured in clinical settings. Furthermore, qRT-PCR and rapid antigen tests can be performed in hours or minutes, compared to several days for determining infectious titer. Viral loads determined by qRT-PCR are, at best, a crude measure of actual infectious virus shedding, so further research is needed to establish viral loads in asymptomatic and presymptomatic cases (see the figure).

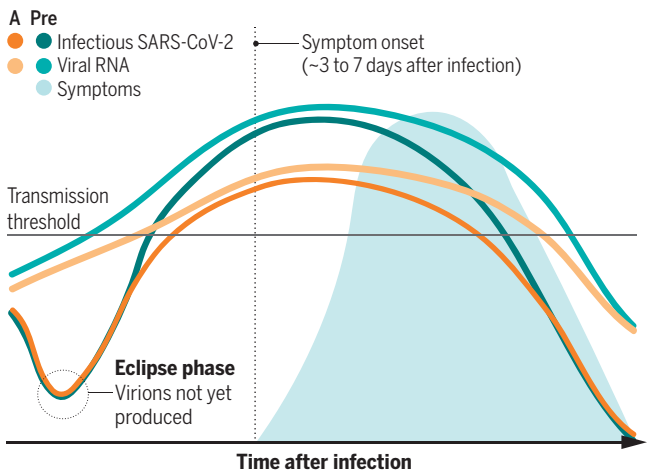
The biological basis for transmission without symptoms is poorly understood, even though it is common for respiratory viruses, including "common cold" pathogens such as rhinoviruses and other coronaviruses, to be spread by both contact and inhalation. Symptomless transmission is influenced by the timing and magnitude of the host response to infection, which is a major determinant of pathogenicity. Delayed or reduced host antiviral immune responses are closely linked to COVID-19 severity, suggesting a relationship between host response and symptom onset. This includes suppressed interferon-induced cytokine expression, which is linked to symptoms. As a gateway between the body and the environment, the upper respiratory tract is regularly exposed to external antigens. Thus, the nasal mucosa is a niche immune site in which antiviral responses are modulated by external factors (such as temperature or humidity) and host susceptibility (mucus, receptor distribution, and host response to infection) and may explain why symptomless spread is common for respiratory viruses.

With many contagious people experiencing no symptoms and in the absence of robust surveillance testing for asymptomatic or presymptomatic infections, it is critical to maximize efforts to reduce transmission risk in the community. Academic debates about the frequency of different transmission routes reframe exposure risk reduction as a dichotomy rather than a spectrum, confusing rather than informing guidance. Rather than targeting transmission by either inhalation or contact, infection prevention efforts should focus instead on the additive nature of risk reduction and the need for continued vigilance in community-based infection prevention measures, including masks, distancing, avoiding enclosed spaces, ventilation, hand hygiene, and disinfection.

Transmission without symptoms critically contributes to the unabated spread of SARS-CoV-2 and presents a considerable infection prevention challenge. Although asymptomatic individuals appear to be contagious for a shorter period of time and may pose a lower transmission risk, they still pose a substantial public health risk as they are more likely to be out in the community. It is unclear how vaccination will affect the number of asymptomatic cases, although preliminary data suggest that mass immunization will reduce infection overall, thus reducing transmission. For presymptomatic cases, research has shown that viral shedding is highest just before and for a few days after symptoms begin, which is a critical time to ensure that individuals who may not realize they have been exposed stay home when possible and practice risk reduction efforts when in the community. Until there is widespread implementation of robust surveillance and epidemiological measures that allow us to put out these smokeless fires, the COVID-19 pandemic cannot be fully extinguished. ■

Viral replication and symptom onset

The titer of infectious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the amount of viral RNA are generally lower in asymptomatic (A) than presymptomatic (Pre) COVID-19. There is likely to be a threshold at which a person becomes contagious, but this is not known. In presymptomatic patients, symptoms usually begin when viral load peaks, so there is a period of infectiousness when a person has no symptoms.



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